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Dimethyldioxirane Hydroxylation of a Hypersensitive Radical Probe: Supporting Evidence for an Oxene Insertion Pathway

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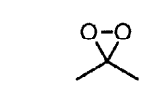
Abstract: Dimethyldioxirane oxidation of the hypersensitive radical probe (*trans*-2-phenylcyclopropyl)ethane gave non-rearranged hydroxylation products consistent with an oxene insertion mechanism for the reaction.

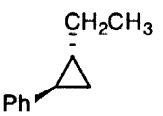
The facile oxidation of hydrocarbons at ambient temperature is a continuing challenge. Dioxiranes are powerful oxidants that can hydroxylate hydrocarbons in the absence of metal ions by pathways that might be similar to those of the iron-containing enzymes cytochrome P450 and methane monooxygenase.[1] The mechanism of dimethyldioxirane (DMDO) hydroxylation has been considered to involve either electrophilic oxygen insertion or a hydrogen abstraction to give a radical pair followed by a fast, in-cage rebound step.[2] Recently, the mechanistic question has become somewhat controversial. Minisci and co-workers hold that available evidence indicates that hydroxylation occurs via a radical pair pathway,[3] while Adam and Curci and co-workers state that the available evidence supports an electrophilic insertion reaction.[4]

The results of mechanistic studies of DMDO hydroxylations are not disputed. Under typical reaction conditions, the absence of diffusively free radicals is clearly indicated by, for example, stereospecific and 100% stereoselective hydroxylations of *cis*- and *trans*-1,2-dimethylcyclohexane,[5] the failure of ring opening to occur in hydroxylation of isopropylcyclopropane,[6] and the absence of detectable amounts of epimerization in hydroxylation of (*R*)-2-phenylbutane.[4] It is also clear that radical chain reactions of DMDO are possible; such reactions emerge when oxygen is purged from the system.[3,7,8] The radical chain sequence, which must involve diffusively free radicals, leads to acetate products rather than alcohols, and there is no question that this pathway is suppressed by oxygen under typical reaction conditions. The crux of the mechanistic issue revolves around whether or not the induced radical chain process implicates a radical pair mechanism for the "typical" hydroxylation reaction.

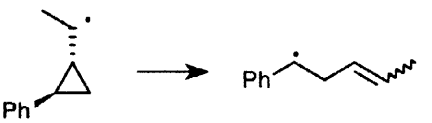
In this Letter, we report studies of the hydroxylation of hypersensitive probe **1** with DMDO. The radical formed by H-atom abstraction from the cyclopropylcarbinyl position of **1** (*i.e.* **2**) rearranges to radical **3** with a rate constant of 1×10^{11} s^{-1} at ambient temperature,[9] a reaction fast enough to time events in the transition state for a concerted insertion. Our results verify the absence of diffusively free radicals from DMDO hydroxylations under a variety of conditions and indicate that the mechanism of the hydroxylation reaction involves oxygen atom insertion instead of radical pair formation.



dimethyldioxirane (DMDO)



1



2 **3**

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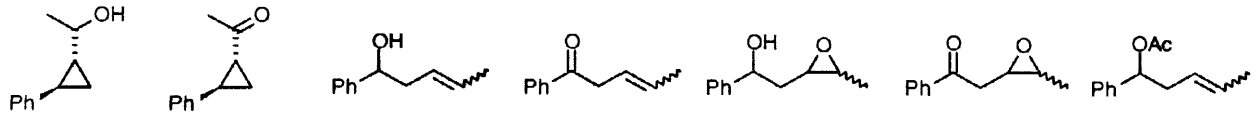

4 5 6 7 8 9 10

Possible products from oxidation of the cyclopropylcarbinyl position of **1** include the unrearranged products alcohol **4** and ketone **5** and the ring-opened products **6** and **7**, the ketones would arise from overoxidations of the corresponding alcohols. Epoxidation of the ring-opened products would give **8** and **9**. Authentic samples of both diastereomers of **4**, **5**, *trans*-**6**, *trans*-**7**, *trans*-**8**, and the conjugated isomer of **7** were prepared. Epoxide *trans*-**9** was prepared from mcpba oxidation of **7** and characterized by GC and GC-mass spectrometry, but this compound was not isolated. In order to identify possible products from the radical chain reactions of DMDO, samples of the isomeric acetates **10** and the acetates from both diastereomers of alcohol **4** were prepared by reaction of the appropriate alcohol with acetic anhydride and pyridine; the acetates were characterized by NMR spectroscopy and HRMS.

Control reactions demonstrated that putative products **4**, **6** and **7** were adequately stable to the reaction conditions to permit detection. Thus, small amounts of each (comparable to the observed amounts of products from oxidation of **1**, see below) were allowed to react under the same conditions and concentrations of DMDO as used in the oxidations of **1**. The average results from triplicate reactions were as follows: Alcohol **4** was oxidized to ketone **5** in 83% yield. Reaction of alcohol **6** gave **6**, **7**, and **8** in 40%, 5%, 25% yields, respectively. Reaction of **7** returned **7** in 35% yield. The detection of products **6**-**8** in 70% overall yield from reactions of **6** with DMDO indicates that rearranged products would be detected if **6** was formed in substantial amounts in the oxidation of **1**.

DMDO oxidations of probe **1** were run under low conversion conditions in an attempt to minimize secondary reactions.[10,11] The results are collected in Table 1. The only clearly identifiable products by GC and GC-mass spectrometry were the two diastereomers of alcohol **4** and ketone **5**. Minor products with GC retention times the same as those of compounds **6**-**8** and acetates **10** were formed in the reactions, but the amounts of these products were not sufficient for GC-mass spectral characterization. In Table 1, we have listed yields for **6**-**8** and **10** based on the assumption that the small peaks observed in the GC traces were from these compounds; that is, the listed yields for these compounds are maximum values.

Table 1. Percent Yields of Products from Reactions of Probe **1** with DMDO.[a]

Conditions	**4**	**5**	(**6** + **7** + **8**)[b]	**U/R**[c]	**10**
normal[d]	0.3	2.1	nd[e]		nd[e]
normal[d]	0.3	1.7	0.05	40	0.14
oxygen[f]	0.3	2.2	0.08	30	0.01
argon[g]	0.3	1.7	0.05	40	0.09

[a]Percent yields based on DMDO. [b]Sum of products **6**-**8**. [c]Ratio of products (**4** + **5**) to (**6**-**8**). [d]Normal reactions (averages of triplicate runs) were exposed to atmosphere. [e]nd = not determined. [f]Oxygen reactions (average of duplicate runs) were purged with oxygen as described in ref 3. [g]Argon reactions (average of duplicate runs) were purged with argon as described in ref 3.

The ratios of unrearranged to rearranged alcohol products (**U/R**) in Table 1 are likely to represent minimum values because we were generous in estimating the yields of products **6-8**. On the other hand, the control reactions suggest that some ring opened product **6** will be lost in subsequent reactions. In any event, the consistency of the ratio of unrearranged to rearranged products (**U/R**) under the various conditions is satisfying and provides some assurance that we are not analyzing artifactual species. From the ratios of **U/R** and the rate constant for ring opening of radical **2**, one calculates that the "capture" process for **2** has a rate constant of about 4×10^{12} s^{-1} at ambient temperature or the "lifetime" of **2** is only 0.2 ps. This value is indistinguishable from that for the lifetime of a transition state calculated from transition state theory (0.17 ps) due to uncertainties in the determination of the rate constant for ring opening of **2**, the quantitation of **6-8**, and the stability **6**.

Diffusively free radicals are unequivocally excluded as intermediates in the hydroxylation of probe **1** because even a diffusion-controlled bimolecular trapping reaction by a reagent at 0.1 M concentration would intercept only 1% of radical **2** before rearrangement, but diffusively free radicals were already excluded by previous studies. The mechanistic issue revolves around whether hydroxylation occurs by an oxenoid insertion reaction or by singlet radical pair formation and subsequent collapse. The distinction between the two is real. In an insertion, the oxygen atom would be positioned within bonding distance of carbon at the instant of reaction such that the ensemble proceeds to product in the time frame of a bond vibration giving rise to the subpicosecond transition state "lifetime". One assumes that hydrogen atom abstraction by DMDO to give a radical pair would involve a linear C–H–O arrangement similar to those computed for the transition structures for H–atom abstractions in reactions of hydrocarbons with alkoxyl radicals where the distance between carbon and oxygen is about 2.5 Å.[12] Even if radical-radical recombination occurs with no barrier, atomic translation over 1 Å necessary to produce the C–O bond would require a few picoseconds.

The observation that no epimerization is found in oxidation of 2-phenylbutane[4] already established a maximum lifetime for a "radical" (ca. 1 ps) that probably was too short to be accommodated by a radical-pair reaction. Our results set an even shorter maximum lifetime for the "radical", about 200 fs. These results definitely are not consistent with production of a radical pair.

Reactions conducted with argon purging did not give good yields of acetate products. The difference between our results and those reported by Minisci's group is likely due to the large difference in concentrations of DMDO in the two studies. The DMDO concentrations in the previous study were about 50 times greater than those we employed.[3] Even then, the radical chain reaction of hydrocarbons was the minor process in three of the four examples reported, and acetate products averaged about 50% relative yield.[3] A logical conclusion from the molecule induced decomposition reaction of DMDO and the differences in DMDO concentrations is that, with exactly the same argon purging conditions leaving the same amount of residual oxygen as in the previous studies, we should have obtained acetate products in 1% relative yield as appears to be the case. Nevertheless, because the rearranged products from our probe are unstable towards further oxidation, they are poorly suited for studying the induced decomposition pathway, and studies with saturated hydrocarbons as reported[3] are more meaningful.

Although we did not obtain good yields of acetates with argon purging, there is no reason to doubt that one can express radical chain reactions of DMDO under appropriate conditions. However, we question the logic that demonstration of an induced radical chain reaction implicates radical pair formation in the predominant reaction of DMDO with hydrocarbons.[3] The argument contends that by definition an insertion reaction precludes "leakage" of small amounts of radicals as proposed by Curci[8] and Adam.[4] However, transition states have finite, albeit short, lifetimes, and the possibility of branching processes existing after the transition state is widely accepted despite the claim[3] to the contrary. As for the application of Occam's razor to exclude an insertion pathway,[3] the demonstrated lack of epimerization in hydroxylation of 2-phenylbutane[4] and

the probe results reported here clearly require an alternative to radical pair formation in our opinion. In addition, recent high level computational results indicate that dioxirane hydroxylations occur by insertion-type transition states and that bifurcation after the transition state to give either a collapse product (alcohol) or a radical pair is energetically reasonable;[13] essentially, this is the "leakage" model of Curci and Adam.[4,8] In total, the evidence appears to weigh heavily in favor of the insertion mechanism in the predominant reactions of DMDO.

The results with DMDO have been compared to those obtained in studies with other oxidants to illustrate the generality of the duality of oxidation mechanisms, concerted versus radical.[3] In that context, it is noteworthy that hypersensitive probe **1** and analogs have been used in studies of several oxidants including cytochrome P450 isozymes,[14] methane monooxygenase hydroxylase enzymes,[15] and Gif conditions,[16] and the results suggest that clear mechanistic differences can be discerned. Studies of enzyme-catalyzed hydroxylation reactions gave mainly unrearranged products, as seen with DMDO, and implicated concerted processes with "radical lifetimes" in the range of 70-150 fs.[14,15] On the other hand, Gif oxidations of hypersensitive probes including **1** gave rearranged products requiring that diffusively free radicals were produced.[16]

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