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MECHANISTIC IMPLICATIONS OF THE STEREOCHEMISTRY OF SINGLET OXYGEN-OLEFIN REACTIONS

Lawrence B. Harding and William A. Goddard III*

Contribution No. 5669 from the Arthur Amos Noyes Laboratory of Chemical Physics,
California Institute of Technology, Pasadena, California 91125, USA

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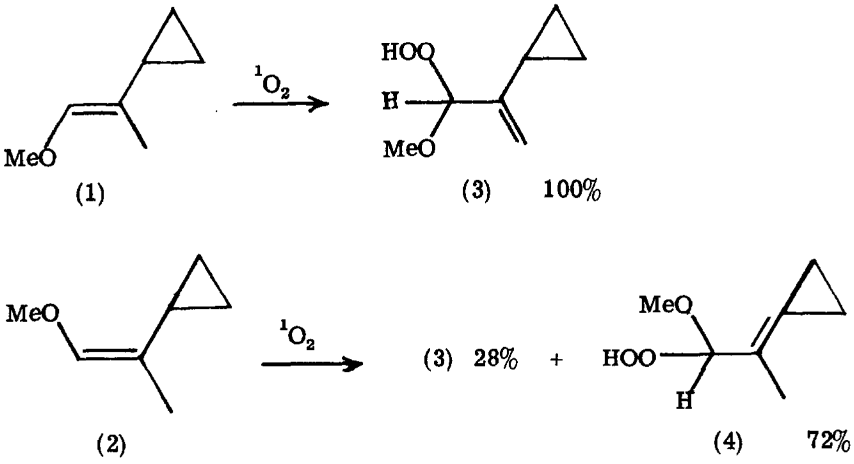
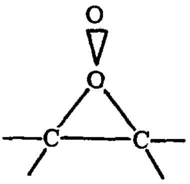
We analyze the stereoselectivity of singlet oxygen-olefin reactions, concluding that a biradical peroxyl intermediate is involved and that experimental results are inconsistent with perepoxide intermediates.

Recently Conia et al.[1] have reported the results of a series of experiments on the reaction of singlet oxygen with methoxy-substituted olefins. They found the methoxy group to play a surprising role in directing the course of these reactions. For example, the regiospecific nature of the following reactions,

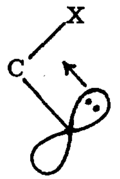


show clearly a strong preference for H-abstraction cis to the methoxy group. These results, and similar unpublished results of Foote, have been interpreted by Fukui et al.[2] to offer strong support for the intermediacy of a peroxirane or perepoxide species (5) in these reactions.

We have recently reported[3] the results of accurate ab initio (GVB-CI) calculations that indicate perepoxide structures are extremely unstable (in the parent case, the perepoxide is found to be 7 kcal above the •CCOO• biradical). In this communication we show that the results of Conia et al.[1] are completely consistent with a biradical mechanism and in fact are counter to that expected of perepoxide intermediates.



(5)



Before discussing the details of the proposed mechanism, we review briefly the nature of the anomeric effect.[4,5] The anomeric effect results from a delocalization of a heteroatom lone pair into the region of an adjacent polar bond, as shown here. The result is an increased stability ($\sim$ 5 kcal each) of configurations in which a lone pair is in the same plane as an adjacent polar bond. Thus, for example, the lowest energy conformation of methanediol is one in which the two O-H bonds are approximately perpendicular to the O-C-O plane.[6] This effect has also been invoked to explain differences in the reactivities of aldehyde acetals toward ozone.[7]

Our proposed mechanism for the $^1O_2$ reaction is shown in Figure 1. Considering first the reaction with compound (1), initial attack of the singlet oxygen will be directed toward the methoxy-substituted carbon (anomeric effect). We estimate (using the group additivity approach of Benson[8]) the resulting biradical (6) to be 6 kcal/mole more stable than the biradical (8) arising from attack at the other end of the C-C double bond.[9] Again, as a result of the anomeric effect, biradical (6) will have two preferred conformations, shown in Figure 2, with a 3-5 kcal barrier to rotation about the C-O bond. Of these two conformations, B will be unreactive (there are no abstractable hydrogens adjacent to the radical center). Conformation A, however, would be expected to abstract a hydrogen from the adjacent methyl group, leading to the observed *cis* abstraction product.

An analogous argument leads to the prediction of *cis* abstraction products for the reaction of compound (2). In this case, however, the unfavorable thermochemistry (the *cis* abstraction product is $\sim$ 10 kcal higher than the *trans* abstraction product) leads to a mixture of *cis* and *trans* abstraction products (predominantly *cis*).[10]

Moreover, the observed isotope shifts[1,11] are consistent with the biradical mechanism but not with a concerted mechanism, the energetics of the biradical mechanism are consistent with the observed activation energy,[12] and the expected stereoselectivity agrees with experiment. Thus, we conclude that the formal ene reaction proceeds through a peroxyl biradical intermediate.

Analysis of the proposed perepoxide intermediate in terms of the anomeric effect leads us to conclude that the conformation in which the terminal oxygen is *trans* to the methoxy substituent will be more stable ($\sim$ 3-5 kcal) than the *cis* conformation (see Figure 3).[13] Assuming the *trans* perepoxide conformation to be more stable, then the perepoxide mechanism predicts *trans* products and hence the results of Conia *et al.*[1] can be interpreted as evidence *against* the intermediacy of perepoxides.[14]

In conclusion, we have shown the results of Conia *et al.* to be completely consistent with a biradical mechanism. In addition, we conclude that these results constitute persuasive evidence *against* the intermediacy of perepoxides.

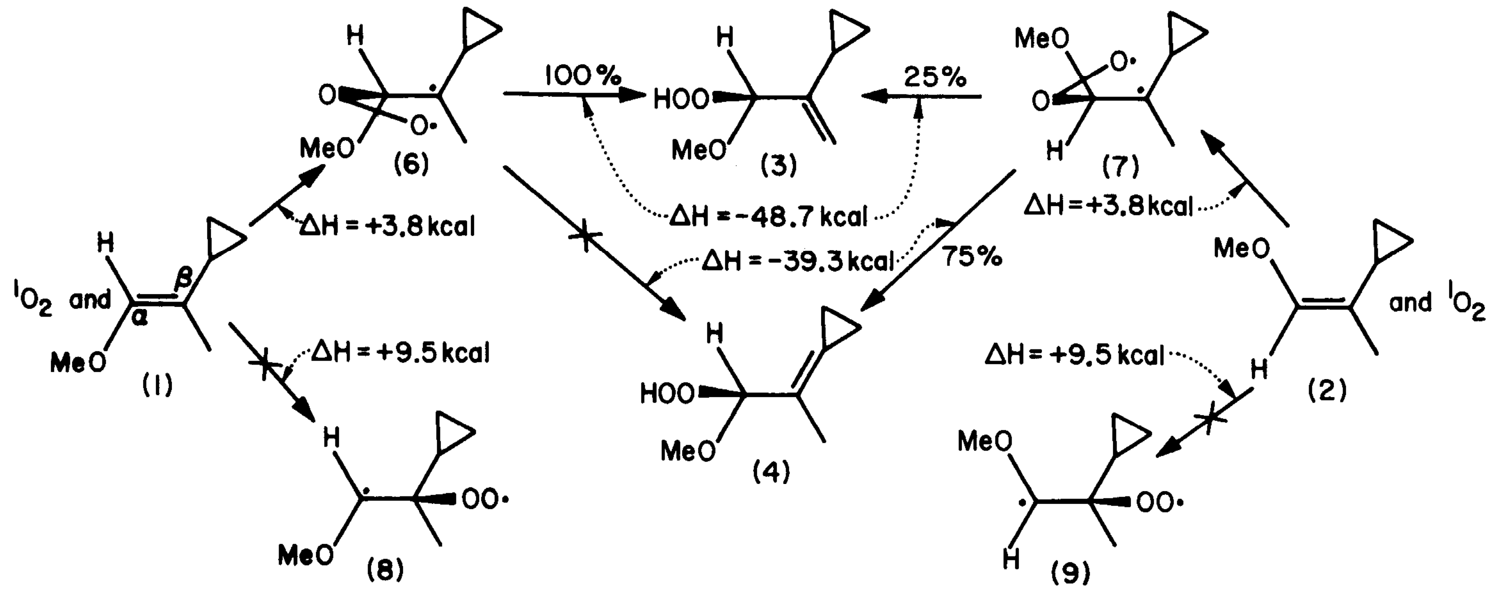


Figure 1. Proposed biradical mechanism for the stereospecific reaction of singlet O_2 with methoxy olefins. [Heats of reaction (kcal/mole) were estimated using the methods of Ref. 8.[9]]

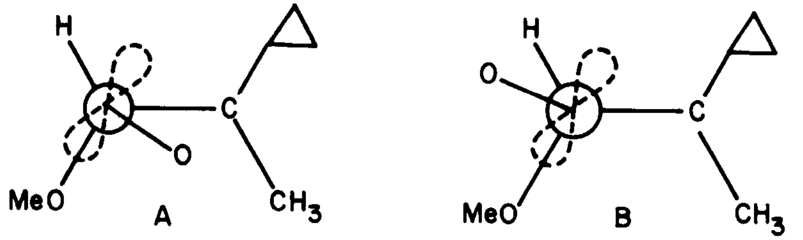


Figure 2. Preferred conformations of biradical (6). Dashed lines indicate the position of the oxygen lone pair orbital responsible for stabilizing these conformations (anomeric effect).

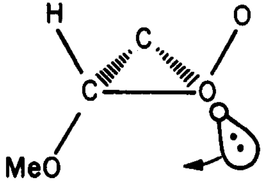


Figure 3. Preferred conformation of perepoxide, indicating stabilization due to anomeric effect.

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References and Footnotes:

1. G. Rousseau, P. LePerchec, and J. M. Conia, Tetrahedron Lett., 45, 2517 (1977).
2. S. Inagaki, H. Fujimoto, and K. Fukui, Chem. Lett., 749 (1976).
3. L. B. Harding and W. A. Goddard III, J. Am. Chem. Soc., **99**, 4520 (1977).
4. For a recent review of the anomeric effect, see N. S. Zefirov and N. M. Shekhtman, Russian Chem. Rev., **40**, 315 (1971).
5. R. U. Lemieux, in "Molecular Rearrangements," Vol. 2, Interscience, New York, 1964, p. 709.
6. G. A. Jeffrey, J. A. Pople, and L. Radom, Carbohyd. Res., **25**, 117 (1972).
7. P. Deslongchamps, C. Moreau, D. Frehel, and R. Chenevert, Can. J. Chem., **53**, 1204 (1975).
8. S. W. Benson, "Thermochemical Kinetics," J. Wiley and Sons, New York, 1976.
9. Our estimated heats of formation for compounds (1)-(4) and (6)-(9) are -15.6, -15.6, -37.9, -28.5, 10.8, 10.8, 16.5, and 16.5 kcal/mole, respectively.
10. An alternative explanation of the stereochemistry (using the biradical mechanism) would be to assume that steric interactions(between the methoxy group and the carbon substituents) force rotation at the β carbon, leading to cis H-abstraction. [M. J. S. Dewar has independently made a similar suggestion.] Although plausible, this explanation is inconsistent with the trans product observed[1] when the methoxy is replaced with a methyl group. [In the biradical mechanism this latter result is explained in terms of the favorable thermodynamics.]
11. A. Nickon, V. T. Chuang, P. J. L. Daniels, R. W. Denny, J. B. DiGiorgio, J. Tsunetsugu, H. G. Vilhuber, E. Werstiuk, J. Am. Chem. Soc., **94**, 5517 (1972).
12. R. D. Ashford and E. A. Ogryzlo, J. Am. Chem. Soc., **97**, 3604 (1975).
13. M.J.S. Dewar, using nonbonded repulsion arguments, has also suggested that the trans perepoxide conformation is the more stable one (private communication).
14. Fukui et al.[2] have interpreted similar unpublished results of Foote to support the intermediacy of perepoxide. They argue that the LUMO of singlet O_2 will be of the correct phase to interact favorably with the HOMO of the substituted olefin. Thus it is claimed that this intermolecular nonbonded attraction favors the formation of a perepoxide having the terminal oxygen cis to the methoxy group, leading to cis abstraction products. [This HOMO-LUMO analysis also predicts attack of the O_2 on the carbon β to the methoxy substituent, a prediction clearly at variance with Conia's results.] As discussed in the text, we disagree with these conclusions.