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Solvent Effects in the Stereoselectivity of the Ene Reaction of Singlet Oxygen with Allylic Alcohols

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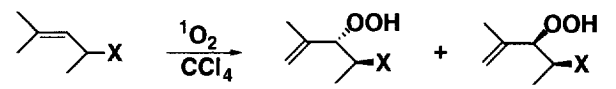
Abstract: The stereoselectivity of the ene reaction of singlet oxygen with *E*-2,4-dimethylpent-3-en-2-ol-5,5,5-d_3 depends on solvent; polar solvents favor hydrogen abstraction from the methyl anti to the alcohol; nonpolar solvents favor the opposite. Copyright © 1996 Elsevier Science Ltd

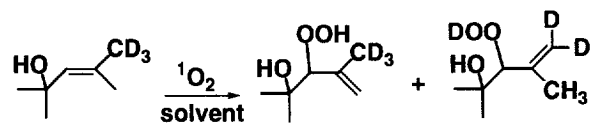
The stereochemistry of singlet oxygen ($^1O_2$) reactions with alkenes bearing allylic hydrogens (ene reaction) has received recent attention both because of its interesting mechanism and also because of its synthetic applications.[1] Singlet oxygen affords a variety of regio[2] and diastereoselective[3] ene reactions. The initial ene products are useful precursors[4] to mono- or polyoxofunctionalized compounds. Among the more valuable applications is the diastereoselective photooxygenation of chiral allylic alcohols[5] and amines[6] examined by Adam and coworkers.



1-X
X = OH, NH_2, NH_3^+

~ 95% **~5%**

They proposed that $^1O_2$ forms an exciplex with **1-X** in which oxygen can coordinate to the allylic functionality X, providing high selectivity (~95%) to give threo allylic hydroperoxides in nonpolar solvents. The exciplex is equivalent to the "perepoxide" mechanism suggested by many authors in its stereochemical predictions. We sought a similar effect on the syn/anti stereoselectivity of the ene reaction, and synthesized *E*-2,4-dimethylpent-3-en-2-ol-5,5,5-d_3[7] (**2E**) in 90% geometric purity to examine this question.



2E **3-syn** **3-anti**

For **2E**, singlet oxygen can interact with only one allylic hydrogen or deuterium on each side of the alkene. Simultaneous interaction of the perepoxide with two allylic hydrogens on the same side of the double bond was used by many authors to explain the higher reactivity of the more substituted side ("cis effect") in the reaction with trisubstituted alkenes.[8] No analogous cis-effect would be expected with **2E** since the number of allylic hydrogens is the same on both sides. Reaction of $^1O_2$ with **2E** in the presence of 10^{-3} M 2,6-di-*tert*-butyl phenol as free radical scavenger proceeds smoothly in a variety of solvents at 20 °C, affording only ene products with H ("syn") or D ("anti") abstraction. The lamp output was filtered to remove wavelengths below 588 nm. The results are summarized in Table I.

Table I. Stereoselectivity of photooxygenation of 2E in a variety of solvents

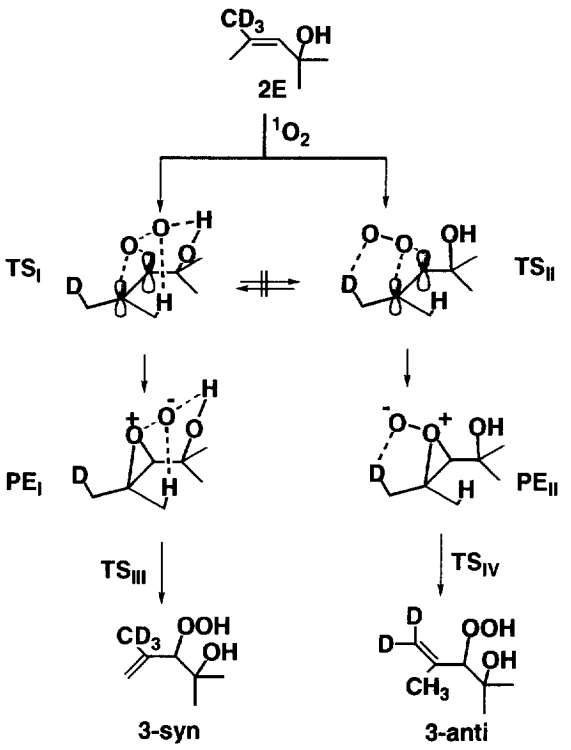
Solvent	sensitizer[a]	3-syn/3-anti[b,c]
CCl_4	TPP	75/25
benzene	TPP	73/27
$CHCl_3$	MB	66/34
acetone	MB	42/58
CH_3CN	MB	41/59
MeOH	MB	33/67

[a]TPP: tetraphenyl porphine; MB: methylene Blue. [b]Determined by ^1H NMR, integrating the appropriate peaks at 5.16 and 5.08 ppm for two olefinic hydrogens and at 4.28 ppm for one allylic hydrogen next to OOH. [c]Corrected for purity of **2E**.

As seen from Table I, hydrogen abstraction from the syn methyl group decreases dramatically as the solvent polarity increases. For example, the ratio 3-syn/3-anti decreases by a factor of 6 on going from carbon tetrachloride to the polar solvent methanol. The "cis effect" selectivity in non polar solvents (CCl_4, benzene or $CHCl_3$) reverses in polar solvents with lone pairs that can accept hydrogen bonds (acetone, acetonitrile and methanol) preferentially producing the 3-anti adduct.[8c]

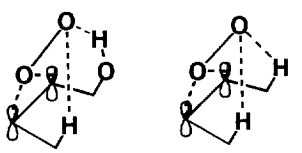
Examination of the possible transition states in scheme I may shed some light on the observed stereoselectivity. For trisubstituted alkenes,[9] it is established that formation of perepoxide is essentially irreversible, and we assume that this mechanism can be applied to the current system. In TS_I, where singlet oxygen approaches at the more crowded side of the olefin to form PE_I, it interacts simultaneously with both hydroxyl and allylic hydrogens. This interaction probably stabilizes transition state TS_I. In TS_{II}, oxygen interacts with only one allylic hydrogen and this transition state should be less favorable.[8]

Scheme I



Polar solvents which can hydrogen bond with the hydroxyl reduce the ability of OH to interact with oxygen and the selectivity trend is reversed. In methanol, the ratio endo/exo = 33/67 is a typical anti "cis effect" and very close to the 25/75 ratio observed in the photooxygenation of the structurally similar 2,4,4-trimethyl 2-pentene,[10] which is not surprising, since t-butyl is approximately the same size as 2-hydroxy-2-propyl.

The stabilizing interaction cannot arise from interaction between the lone pair on oxygen and the incoming electrophilic singlet oxygen, since replacement of OH by OMe causes a significant drop in the threo diastereoselectivity in the parent chiral allylic alcohol **1-OH**.[5] It is more likely that the OH interacts with the negative oxygen on the perepoxide/exciplex to control the stereoselectivity, an interaction similar to that causing the "cis effect". The effect of solvent could be either to lessen the internal hydrogen bond, or because of the additional steric effect caused by hydrogen bonding of the alcohol to the solvent. An interaction similar to that with the OH between silicon and perepoxides has been proposed to control the stereochemistry in the photooxygenation of allylsilanes.[11]



There are only a few examples of solvent dependencies in ene regioselectivity, usually very small[12] and only one proposed explanation in the photooxygenation of α,β-unsaturated esters.[12c] To the best of our knowledge the present results report the largest solvent dependence of ene products ever observed. Also, this is the first time that the anti "cis effect" selectivity has been found to depends not only on steric interactions (as recently reported[8c]), but on solvent polarity as well. Although a syn preference has been recognized in the photooxygenation of 3,3-dialkyl substituted primary allylic alcohols[13] and postulated for the chiral secondary allylic alcohols,[4] this is the first direct evidence for a net directing effect of hydroxyl in photooxygenations of allylic alcohols.

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References

1. Foote, C. S.; Clennan, E. L. In *Active Oxygen in Chemistry*; Foote, C. S.; Valentine, J. S.; Greenberg, A. Liebman, J. F., Eds.; Chapman and Hall, London, 1995; pp 105-140.
2. a) Clennan, E. L.; Chen, X. *J. Org. Chem.* **1988**, *53*, 3124-25. b) Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *Tetrahedron Lett.* **1989**, *30*, 4875-78. c) Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6417-19. d) Clennan, E. L.; Chen, X.; Koola, J. J. *J. Am. Chem. Soc.* **1990**, *112*, 5193-99. e) Adam, W.; Richter, J. M. *Tetrahedron Lett.* **1993**, *34*, 8423-26 and references cited therein.
3. Prein, M.; Adam, W. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 477-494.
4. a) Adam, W.; Griesbeck, A. *Synthesis* **1986**, 1050-52. b) Adam, W.; Braun, M.; Griesbeck, A.; Lucchini, V.; Staab, E.; Will, B. *J. Am. Chem. Soc.* **1989**, *111*, 203-12. c) Stratakis, M.; Orfanopoulos, M. *Syn. Comm.* **1993**, *23*, 425-30. d) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1993**, *115*, 7226-31. e) Linker, T.; Frohlich, L. *J. Am. Chem. Soc.* **1995**. *117*, 2694-97. f) Adam, W.; Brunker, H.-G. *Synthesis* **1995**, 1066-68.
5. a) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1992**, *114*, 6549-50. b) *ibid* **1993**, *115*, 5041-49.
6. a) Adam, W.; Brunker, H.-G. *J. Am. Chem. Soc.* **1993**, *115*, 3008-09. b) Brunker, H.-G.; Adam, W. *J. Am. Chem. Soc.* **1995**, *117*, 3976-82.
7. Allylic alcohol **2E** was prepared by ethyl tetrolate addition[14] to $(CD_3)_2CuMgI$ in THF at -78 °C, giving (E)- ethyl 4-methyl but-2-enoate-4,4,4-d_3 in 91% geometric purity. Addition of 2.5 eq. MeMgI gave **2E** (90% geometric purity). The labile[15] alcohol was kept in the presence of pyridine to avoid dehydration. HRMS, calcd. for $C_7D_3H_{11}O$ 117.1233, found 117.1234. ($M^+ - H_2O$) calcd. 99.1127, found 99.1132.
8. a) Stephenson, L. M.; Grdina, M. B.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419-25. b) Hurst, J. R.; Wilson, S. L.; Schuster, G. B. *Tetrahedron* **1985**, *41*, 2191-97. c) Stratakis, M.; Orfanopoulos, M. *Tetrahedron Lett.* **1995**, *36*, 4291-94.
9. Stratakis, M.; Orfanopoulos, M.; Chen, J.; Foote, C. S. *Tetrahedron Lett.* in press.
10. Orfanopoulos, M.; Stratakis, M.; Elemes, Y.; Jensen, F. *J. Am. Chem. Soc.* **1991**, *113*, 3180-81.
11. a) Dubac, J.; Laporterie, A.; Iloughmane, H.; Pillot, J. P.; Deleris, G.; Dunogues, J. *J. Organom.etall Chem.* **1985**, *281*, 149. b) Adam W.; Schwarm, M. *J. Org. Chem.* **1988**, *53*, 3129-30.
12. a) Manring, L. E.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 4710-17. b) Rautenstrauch, V.; Thommen, W.; Schulte-Elte, K. H. *Helv. Chim. Acta* **1986**, *69*, 1638-43. c) Orfanopoulos, M.; Stratakis, M. *Tetrahedron Lett.* **1991**, *49*, 7321-24.
13. Schulte-Elte, K. H.; Muller, B. L.; Pamingle, H. *Helv. Chim. Acta* **1979**, *62*, 816-29.
14. Anderson, R. J.; Corbin, V. L.; Cotterrell, G.; Cox, G. R.; Henrick, C. A.; Schaub, F.; Siddall, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 1197-204.
15. Vathke-Ernst, H.; Hoffman, H. M. R. *Chem. Ber.* **1981**, *114*, 1464-75.

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