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Novel solvent hydrogen-bonding effects in the singlet oxygen ene reaction: a comparison of α,β-unsaturated esters and acids

Kristina L. Stensaas,* Jason A. Payne, Alexa N. Ivancic and Anisha Bajaj

Department of Chemistry, Millsaps College, 1701 N. State Street, Jackson, MS 39210, USA

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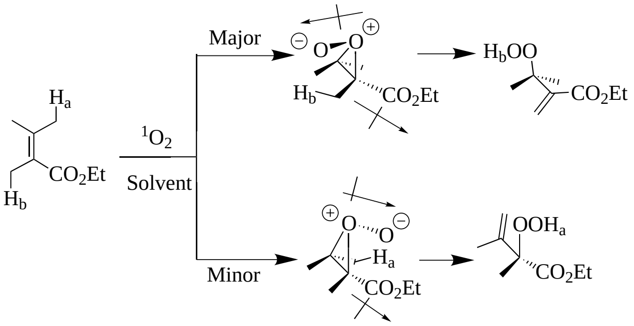
Abstract—The photooxidations of tiglic acid, angelic acid, 2,3-dimethyl-2-butenoic acid and their corresponding methyl esters using singlet oxygen were investigated in methanol and methanol/water solvent mixtures and compared to non-hydrogen-bonding solvents with different dielectric constants. The major and minor ene allylic hydroperoxide products were quantified and this ratio for the acids was found to be dependent on a hydrogen-bonding interaction between the solvent and substrate. © 2001 Elsevier Science Ltd. All rights reserved.

The ene reaction of singlet oxygen ($^1O_2$) has received considerable mechanistic[1] attention and much of this evidence indicates that the reaction proceeds through a perepoxide intermediate.[2] Previous studies on the effects of non-hydrogen-bonding solvents on the ene reactions of α,β-unsaturated esters[3] and acids[4] with singlet oxygen have been reported. Our interest in the aqueous reactions of singlet oxygen has led us to consider the ene reaction and the effects of hydrogen-bonding solvents including methanol and water. We would like to report the first example of side selectivity dependence in the singlet oxygen ene reaction of α,β-unsaturated acids in hydrogen-bonding solvents.

In 1991 Orfanopoulos and Stratakis[3] studied the photooxidation of ethyl 2,3-dimethyl-2-butenoate with singlet oxygen (Scheme 1) and reported a decrease in the major ene product from 95% to 80% in switching from CCl_4 to DMSO as the reaction solvent. They attributed this decrease in major product to an increased stabilization[5] of the transition state with the higher net dipole moment by the polar solvent, consequently producing more minor product.

In order to determine if hydrogen-bonding solvents also exhibit this trend of increased production of minor product with increasing solvent polarity, we utilized methanol (CD_3OD) and methanol/water (CD_3OD/D_2O) solvent mixtures and compared the major and minor allylic hydroperoxide product distributions to photooxidations[6] conducted in benzene-d_6 (C_6D_6) and acetonitrile-d_3 (CD_3CN). Deuterated solvents were chosen because of the longer singlet oxygen lifetimes and, therefore, decreased photooxidation times. Table 1 shows the percentage of allylic hydrogen abstraction leading to the minor (**a**) and the major (**b**) allylic hydroperoxide products during the photooxidations of methyl tiglate (**1**), methyl angelate (**2**), and methyl 2,3-dimethyl-2-butenoate (**3**).



Scheme 1. Perepoxide Intermediates leading to the major and minor ene products.

In all of the solvents tested methyl tiglate (**1**) displayed a geminal[7] regioselectivity; allylic hydrogen **b** on the methyl group geminal to the ester functional group is preferentially abstracted. This result is expected because **1** only has one possible perepoxide intermediate (**I**) which leads to ene products and, therefore, abstraction at this site leads to the preferred conjugated major product. This intermediate is further stabilized by the

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Keywords: singlet oxygen; ene reactions; aqueous solvent; hydrogen bonding.

* Corresponding author. Tel.: (601) 974-1402; fax: (601) 974-1401; e-mail: stenskl@millsaps.edu

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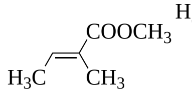
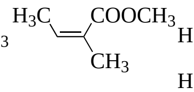
Table 1. % Hydrogen abstraction leading to minor (**a**) and major (**b**) ene products[a]

Esters



1



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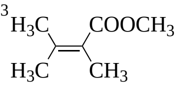


3

Solvent	ε[b]	**1a**	**1b**	**2a**	**2b**	**3a**	**3b**
C_6D_6	2.3	3	97	14	86	11	89
CD_3OD	33.0	0	100	21	79	15	85
CD_3CN	36.6	–	–	22	78	17	83
90/10[c]	37.7	0	100	30	70	18	82
80/20[d]	42.4	–	–	37	63	20	80

[a] Product ratios were determined by ^1H NMR of the allylic hydroperoxides. Average values from three runs are reported.

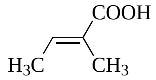
[b] Taken from *Handbook of Chemistry and Physics*, 81st ed.

[c] 90% CD_3OD/10% D_2O; the dielectric constant was calculated using a weighted average of the two solvents: H_2O 80.1, CH_3OH 33.0.

[d] 80% CD_3OD/10% D_2O.

Table 2. % Hydrogen abstraction leading to minor (**a**) and major (**b**) ene products[a]

Acids



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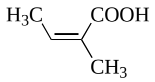

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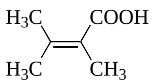


6

Solvent	ε[b]	**4a**	**4b**	**5a**	**5b**	**6a**	**6b**
C_6D_6	2.3	0	100	0	100	0	100
CD_3OD	33.0	0	100	13	87	9	91
CD_3CN	36.6	–	–	20	80	14	86
90/10[c]	37.7	0	100	19	81	10	90
60/40[d]	51.8	–	–	21	79	13	87

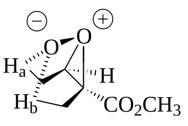
[a] Product ratios were determined by ^1H NMR of the allylic hydroperoxides. Average values from three runs are reported.

[b] Taken from *Handbook of Chemistry and Physics*, 81st ed.

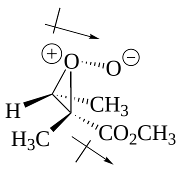
[c] 90% CD_3OD/10% D_2O.

[d] 60% CD_3OD/40% D_2O.

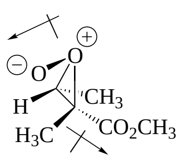
well established '*cis* effect'[8] which invokes stabilization of the negatively charged pendant oxygen by the six *cis* allylic hydrogens. In contrast, methyl angelate (**2**) has *trans* methyl groups and, therefore, cannot benefit from the *cis* effect but instead forms two competing intermediate perepoxides (**II** and **III**). In fact **2** forms substantial amounts of the minor hydroperoxide and as the polarity of the solvent is increased, so is the amount of minor product, 14% in C_6D_6 to 37% in 80% CD_3OD/20% D_2O.[9] It is interesting to note that the photooxidation of **2** in CD_3CN as compared to 90% CD_3OD/10% D_2O, which have similar dielectric constants, produced a significant 8% difference in minor product whereas CD_3OD gave approximately the same amount. This does not appear to be a hydrogen-bonding effect because CD_3OD and CD_3CN produce a similar result; therefore, we attribute this difference to the high polarity of D_2O and its specific stabilization of the transition state leading to the more polar perepoxide intermediate (**II**) which forms minor product. The photooxidation of methyl 2,3-dimethyl-2-butenoate (**3**) with singlet oxygen appears to be much less sensitive to solvent polarity effects than **2**, only a 9% change could be achieved covering a range of dielectric constants from 2.3 to 42.4. These results are again consistent with the *cis* effect and the subsequent stabilization of the transition state leading to the major product.



I

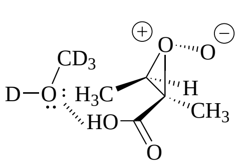


II

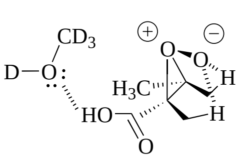


III

The results from the photooxidations of tiglic acid (**4**), angelic acid (**5**), and 2,3-dimethyl-2-butenoic acid[10] (**6**) with singlet oxygen are shown in Table 2. Due to the increased solubility of the acids in D_2O, a wider range of dielectric constants could be tested. Again, as expected, in all solvents tiglic acid (**4**) produced only the major hydroperoxide. However, the results for **5** and **6** show that increasing the solvent polarity does not necessarily increase the amount of minor product formed with these acids. We contend that the non-hydrogen-bonding CD_3CN values are misleading. When comparing the CD_3CN minor product values for **5** and **2**, 20 and 22%, the numbers are consistent. This indicates another factor must be operating within the hydrogen-bonding solvent systems. We submit that hydrogen bonding between the solvent and the carboxyl group stabilizes the transition state leading to perepoxide **IV** which produces the major product. **IV** appears to be favored for both steric and electronic reasons. Placing the negatively charged pendant oxygen away from the side of the perepoxide with the hydrogen bonded carboxyl group minimizes electronic interactions and steric interference with the hydrogen bonded solvent molecules. With **6** the *cis* effect and the hydrogen-bonding interaction (**V**) contribute to the formation of 91% major product. The increase from 80% major product in **5** to 86% in **6** using CD_3CN reflects the dramatic *cis* effect operating versus only the solvent polarity stabilization.



IV



V

It is significant to note that all of the acids in C_6D_6 formed 100% major product. This result is a reflection of the increased polarity of the acids compared to the esters and the subsequent increased stabilization of the transition state leading to the less polar perepoxide intermediate (**III**) by C_6D_6, a non-polar solvent. Furthermore, this result makes it conceivable that because the acids are more polar, they would be more susceptible to solvent polarity and a greater solvent effect with larger amounts of minor product could be expected.

While the results indicate that increasing the polarity of the solvent increases the minor product, this effect is not nearly as pronounced in the acids. For example, the photooxidation of **5** in 60% CD_3OD/40% D_2O (dielectric 51.8) produced only 21% of the minor hydroperoxide, whereas **2** in 80% CD_3OD/20% D_2O (dielectric 42.4) produced 37% of the minor hydroperoxide. Also, the amount of minor product increases for **5** as the dielectric of the hydrogen-bonding solvent is increased but not as much as in **2**. We propose that the hydrogen-bonding interaction between the solvent and the acid contributes more to the stabilization of the transition state leading to the major product than the polarity contribution by the acid.

In conclusion, it appears that several factors dictate the product distribution of singlet oxygen ene reactions of α,β-unsaturated esters and acids in hydrogen-bonding solvents: the polarity of the solvent and substrate, the *cis* effect, and the most important for biological systems, hydrogen-bonding interactions between the solvent and substrate. We are currently extending the scope of these photooxidations to include the salts of acids **4**–**6** and the specific polarity and hydrogen-bonding characteristics of water.

Acknowledgements

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5. The actual energy difference between the transition states leading to the intermediate perepoxides is expected to be relatively small but is evidenced by the change in product distribution.
6. The photooxidations were carried out with 2.0×10^{-4} M tetraphenylporphine, rose bengal, methylene blue, or aluminum(III) phthalocyanine tetrasulfonate chloride sensitizers depending on solvent solubility. Variation of sensitizer does not affect the product ratio.
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9. Higher concentrations of D_2O led to solubility problems with the esters.
10. Cyclization of the major hydroperoxide formed from **3** and **6** occurred under our conditions in several solvents. The acid has been previously noted to undergo this cyclization under highly acidic conditions by Adam and Griesbeck in Ref. 4.