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Solvent Effects on the Side Selectivity of Singlet Oxygen with α,β Unsaturated Esters. New Evidence for a Perepoxide Intermediate.

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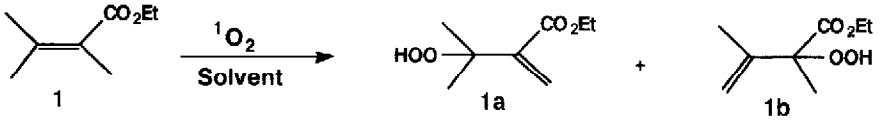
Abstract: *The side selectivity of the ene reaction of singlet oxygen with α, β-unsaturated esters depends on solvent polarity. These results are consonant with the formation of a perepoxide intermediate in the limiting step, of the title reaction.*

The ene reaction of singlet oxygen with α,β-unsaturated ketones[1], esters[2], carboxylic acids[3] and sulfoxides[4] has recently received considerable mechanistic attention. With all these substrates it was found that the major ene product was formed regioselectively by preferential hydrogen abstraction from the alkyl group which is geminal to the electron-withdrawing functionality. A number of intermediates and mechanisms has been reported, namely: zwitterions; perepoxides; [4+2] adducts; and trioxenes. Furthermore, extensive mechanistic work has shown that there is negligible solvent effect on the ene reaction of $^1O_2$ with α,β-unsaturated ketones[1a], olefins, and dienes[5].

We wish to report here the first case[6] of substantial dependence of side selectivity of the ene addition of singlet oxygen to α,β-unsaturated esters on solvent polarity[8]. In an earlier report we described the ene geminal selectivity of the photooxygenation of a variety of α,β-unsaturated esters[2]. In this communication we report the effect of solvent on the photosensitized oxidation of α,β-unsaturated ester **1**. This reaction proceeds smoothly at 25°C to give the allylic hydroperoxides **1a** and **1b** as the only products.



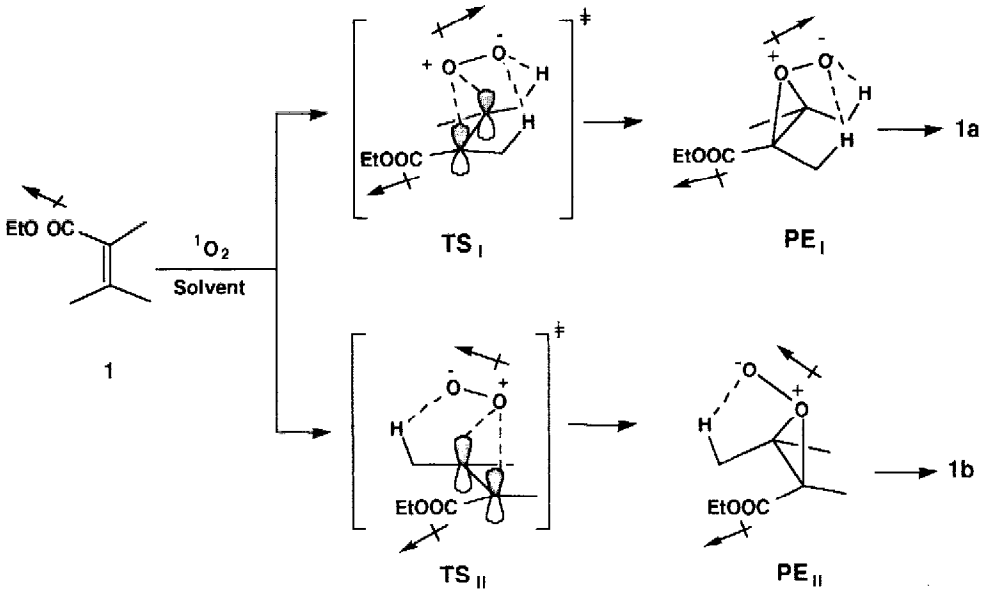
As seen from Table 1 , the hydrogen abstraction from the methyl group which is geminal to the ester functionality, producing adduct **1a**, decreases substantially as the solvent polarity increases. For example, the ratio of ene products **1a/1b** decreases by a factor of 5, in going from carbon tetrachloride to the most polar solvent used in this series, DMSO.

The observed solvent effect on the stereoselectivity of singlet oxygen with ester **1** can be rationalized by examining the possible transition states of this reaction. In transition state TS_{II}, leading to the minor perepoxide intermediate PE_{II} in a limiting step, the oxygen is placed *syn* to the ester group, and the net dipole moment is expected to be larger than that in transition state TS_I where the oxygen has an *anti* orientetion with respect to the ester group. TS_{II} is therefore more polar than TS_I, and expected to be stabilised better by polar solvents than TS_I. Consequently, the ratio **1a/1b** decreases with increase in solvent polarity. We wish to point out here that although the present results are consonant with either the first or second (product forming) step being the rate determining step of the reaction, we consider the first step, the one producing the perepoxide intermediate, as the limiting step of the reaction. Recently we have shown that in the ene reaction of singlet oxygen with tetrasubstituted[9] and trisubstituted[10] olefins, the rate dedermining step is the formation of a perepoxide intermediate, followed by a fast rearangement to the ene products.

Table 1. Solvent Effect on Regioselectivity of Singlet Oxygen Addition to **1** to Give **1a** and **1b.**

Solvent	Sensitizer[a]	1a/1b[b]	Dielectric Constant[c]
CCl_4	TPP	95/5	2.2
benzene	TPP	94/6	2.3
acetone	TPP or RB[d]	88/12	20.0
CH_3CN	MB	85/15	37.5
DMSO	TPP or RB[d]	80/20	48.9

[a]The photooxygenations were carried out with 1.5×10^{-4} tetraphenylporphyrine (TPP) or rosebengal (RB) or methylene blue (MB) as sensitizers. [b] The product ratio was determined by ^1H NMR of the allylic hydroperoxides (integration of peaks at δ 5.93-5.70, 2H of **1a** and 5.03 ppm, 2H of **1b**) and, after reduction to the corresponding allylic alcohols, by GC analysis. Each value is the average of three consequent GC measurements. [c] From reference 8a. [d]Variation of sensitizers does not cause any change to 1a/1b ratio.



If the dipole interactions arguement of the *anti* and *syn* perepoxide-like transition states TS_I and TS_{II} with the solvents are responsible for the changes in side selectivity, then one would expect an increase of the ene product formed from hydrogen abstraction from one side of the double bond to be followed by an equal decrease of ene product, produced from the other side of the double bond. Although in ester **1** the hydrogen abstraction from the methyl group geminal to the ester functionality can be easily determined by ^1H NMR analysis, the results do not permit assessment of the relative contributions (and subsequently the side selectivity) of each of the geminal methyl groups to the formation of the new double bond in the ene product **1b**. To overcome this problem and clarify the solvent effect on the side selectivity of this reaction, we prepared the ester **2E** in high stereochemical purity[11]. This substrate is ideally suited for this purpose. It bears two ene reactive methyl groups on each side of the double bond in a trans configuration, while the allylic methylene hydrogens of the n-butyl group are totally unreactive under the photooxygenation conditions. As seen in Table 2, the sensitized oxidation of ester **2E** in a series of solvents produced two ene adducts **2a** and **2b**.

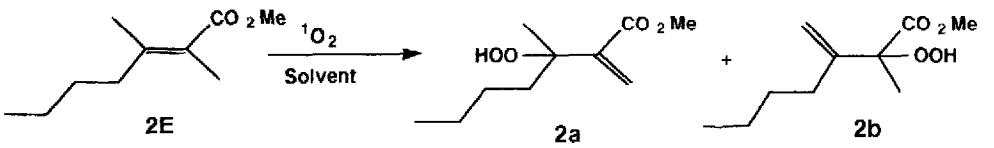


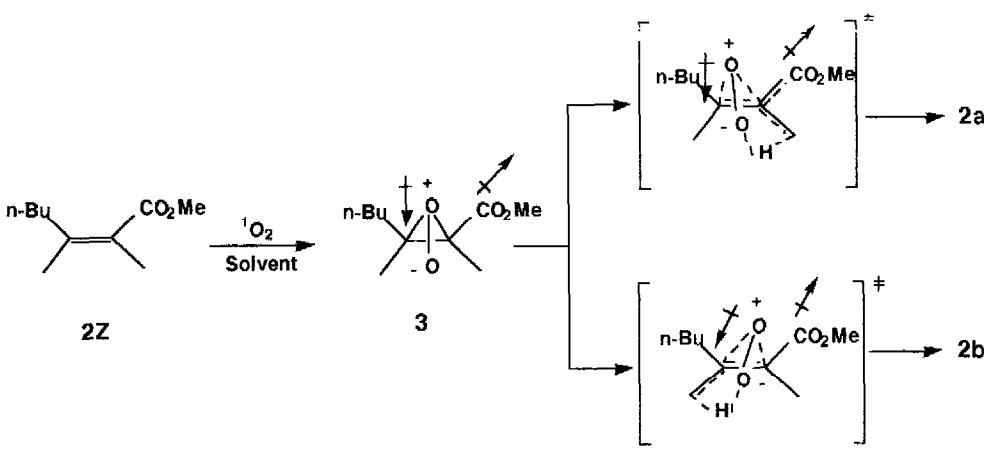
Table 2. Solvent Effect on Side selectivity of Singlet Oxygen Addition to **2E** and **2Z** to Give **2a** and **2b**.

Solvent	2a/2b[a] with **2E**	with **2Z**
CCl_4	85/15	95/5
benzene	83/17	95/5
acetone	80/20	
CH_3CN	75/25	92/8
DMSO	70/30	93/7

[a]Corrected for maximum isomeric purity of **2E** and **2Z** The product ratio was determined by ^{1}HNMR of the allylic hydroperoxide (integration of peaks at δ 6.09-5.84, 2H of **2a** and 5.16-4.96, 2H of **2b**) and, after reduction to the corresponding allylic alcohols, by GC analysis. Each value is the average of three consequent GC measurements.

Again as the solvent polarity increases the ene adduct **2a** with the double bond conjugated to the ester group decreases while the ene product **2b**, produced by hydrogen abstraction from the methyl group placed on the other side of the double bond, increases. In going from carbon tetrachloride to DMSO, the product ratio **2a/2b** changes by a factor of 2.5. These results are consonant with the proposed *syn* (polar) and *anti* (less polar) perepoxide-like transition states similar to TS_I and TS_{II} whose relative stabilities change with solvent polarity.

It is constructive to note that the ene product distribution is insensitive to solvent polarity when the two sides of the double bond do not compete for the ene product. This is demonstrated with substrate **2Z** where the only reactive side of the double bond is the one opposite to the ester functionality. In the photooxygenation of **2Z** ester both the **2a** and **2b** ene products are formed by hydrogen abstraction from the two *cis* methyl groups, and their ratio is insensitive to solvent polarity. These results are also summarized in Table 2.



These results indicate that the ene adducts **2a** and **2b** are produced from the same *anti* perepoxide intermediate **3.** In this case, in the product determining step, the two transition states have rather similar net dipole moments and therefore should experience similar solvent effects.

All these solvent effects are consonant with the formation of a perepoxide or a structurally equivelant exciplex intermediate in the limiting step, followed by a fast ene rearrangement to produce the observed products. Our recent reports on the stereochemistry and isotope effects of the ene reaction of singlet oxygen with alkenes[12] provide strong support to the perepoxide intermediate. The dipolar and nucleophilic nature of this intermediate has been demostrated by trapping experiments with phosphites in the presence of adamantylideneadamantane and singlet oxygen[13]. A perepoxide intermediate has been also suggested in the reaction of singlet oxygen with allyltin compounds[14].

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11. Isomers **2E** and **2Z** were prepared in 88% and 81% isomeric purity by a known method. See: Sum, F.; W., Weiler L. *Can. J. Chem.* **1979**, *57* 1431-41. ^{1}HNMR data for **2E**: $\{(CD_3)_2CO\}$ δ 0.91 (t, J=5 Hz, 3H), 1.25-1.35 (m, 4H), 1.82 (bs, 3H), 1.94 (d, J=1Hz, 3H), 3.65 (s, 3H). and **2Z**:$\{(CD_3)_2CO\}$ δ 0.88 (t, J=6Hz, 3H), 1.28-1.38 (m, 4H), 1.80 (bs, 6H), 3.65 (s, 3H).
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