Reaction of Singlet Oxygen with *trans*-4-Propenylanisole. Formation of [2 + 2] Products with Added Acid

Alexander Greer, Georgios Vassilikogiannakis, Kun-Chun Lee, Telly S. Koffas, Keepyung Nahm, and Christopher S. Foote*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095

foote@chem.ucla.edu

Received October 11, 1999

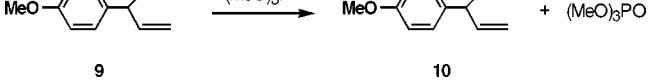
We report the effects of added acid in the reaction of singlet oxygen with *trans*-4-propenylanisole (**1**). We provide evidence that solvent acidity modifies the behavior of the transient intermediates. Relative to reactions in aprotic solvent, enhanced dioxetane concentrations are observed in MeOH and in nonprotic solvents with acid. We suggest a new mechanism that invokes a proton transfer from MeOH and benzoic acid to perepoxide (**2**) and zwitterion (**3**) intermediates.

Several research groups have observed that alcoholic solvents promote the formation of [2 + 2] products (dioxetanes) relative to ene or [2 + 4] products in the reaction of singlet oxygen ($^1\Delta_g$) with indenes,[1,2] indoles,[3] furans,[4,5] pyrans,[4] and polyolefins.[5−8] To rationalize the enhanced dioxetane concentrations, polar solvent effects and hydrogen bonding between the alcohol and the intermediates formed from singlet oxygen have been proposed. Despite the intense interest in olefin photooxidations, no attempt to investigate solvent acidity has been reported. Recently, Albini et al. demonstrated that solvent acidity can change the reactivity of singlet oxygen with sulfides.[9] We report here the effects of added benzoic acid in nonpolar solvents on the reaction of singlet oxygen with *trans*-4-propenylanisole (**1**). We provide the first evidence that solvent acidity can modify the behavior of the transient intermediates in an olefin photooxidation. Relative to reactions in aprotic solvent, enhanced dioxetane concentrations are observed in MeOH and in nonprotic solvents with trace acid. We suggest a new mechanism for the reaction of **1** with singlet oxygen that invokes a proton transfer from MeOH and benzoic acid to perepoxide (**2**) and zwitterion (**3**) intermediates.

Singlet oxygen reacted with **1** (0.1 M) in CD_3OD, C_6D_6, $CDCl_3$, and CD_3CN at 25 °C. Benzoic acid was added to the nonpolar solvents in catalytic (0.01 M) and stoichiometric (0.1 M) amounts. Singlet oxygen was generated by chemical (room-temperature decomposition of 1,4-dimethylnaphthalene-1,4-endoperoxide)[10] and photochemical methods (irradiating aluminum(III) phthalocyanine tetrasulfonate chloride or *meso*-tetraphenylporphyrin in O_2-saturated solutions with a 300-W Xenon lamp through a 0.05 M $K_2Cr_2O_7$ filter). The products were observed by NMR spectroscopy. Products from [2 + 4] cycloaddition (endoperoxides, **5** and **6**) and [2 + 2] cycloaddition (dioxetane, **7**) are formed in ∼95% yield. Isomerization of the starting material (*cis*-4-propenylanisole, **8**) was also observed (∼4%). Only in preparative scale reactions were "ene" products (hydroperoxides) observed (less than 1%).[11] The experimental evidence provided below supports the mechanism depicted in Scheme 1.

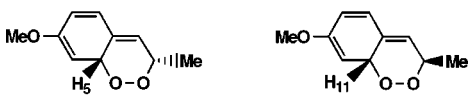
Endoperoxide and Dioxetane Products. In aprotic solvents (C_6D_6, $CDCl_3$, and CD_3CN), **1** reacted with $^1O_2$ to give predominantly [2 + 4] adducts, along with small amounts of the [2 + 2] product (Table 1). Endoperoxide **5**, whose stereochemistry was shown to be trans,[12] reacted further with $^1O_2$ to give a 1:1 mixture of diendoperoxide diastereomers **6**. At 10% conversion the ratio of **5**:**6** is 9:1, while at 60% conversion the ratio is 3:1. Compounds **5** and **6** are stable in solution at room temperature, but attempts to isolate and purify them resulted in their decomposition. Compound **7** decomposed under the reaction conditions to anisaldehyde and ac-

(1) Burns, P. A.; Foote, C. S. *J. Am. Chem. Soc.* **1974**, *96*, 4339−4340.
(2) Burns, P. A.; Foote, C. S.; Mazur, S. *J. Org. Chem.* **1976**, *41*, 899−907.
(3) Zhang, X.; Foote, C. S.; Khan, S. I. *J. Org. Chem.* **1993**, *58*, 47−51.
(4) Gollnick, K.; Knutzen-Mies, K. *J. Org. Chem.* **1991**, *56*, 4017−4027.
(5) Lissi, E. A.; Encinas, M. V.; Lemp, E.; Rubio, M. A. *Chem. Rev.* **1993**, *93*, 699−723.
(6) Manring, L. E.; Kanner, R. C.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 4707−4710.
(7) Manring, L. E.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 4710−4717.
(8) (a) Wilson, S. L.; Schuster, G. B. *J. Am. Chem. Soc.* **1983**, *105*, 679−681. (b) Hasty, N. M.; Kearns, D. R. *J. Am. Chem. Soc.* **1973**, *95*, 3380−3381.
(9) Bonesi, S. M.; Mella, M.; d'Alessandro, N.; Aloisi, G. G.; Vanossi, M.; Albini, A. *J. Org. Chem.* **1999**, *63*, 9946−9955.
(10) Wasserman, H. H.; Larsen, D. L. *J. Chem. Soc. Chem. Commun.* **1972**, 253.
(11) The allylic hydroperoxide (**9**) was characterized as the allylic alcohol (**10**) in the photooxidation of 0.2 M **1** with 0.2 M $P(OMe)_3$ and 10^{-4} M sensitizer in CD_3OD and $CDCl_3$. The reaction was carried to high conversions and **10** was separated by column chromatography.



9 **10**

(12) A comparison was made between endoperoxides generated from the reaction of $^1O_2$ with trans- and *cis*-4-propenylanisole, which yielded reaction mixtures containing **5** and **11**, respectively. The endoperoxide methyl groups were irradiated (1.30 ppm for **5** and 1.25 ppm for **11**). A much larger NOE enhancement was observed for H_{11} (6−8%) than for H_5 (0−2%) confirming that endoperoxide **5** is trans.



5 **11**

10.1021/jo991576d CCC: $19.00
Published on Web 09/27/2000

Scheme 1

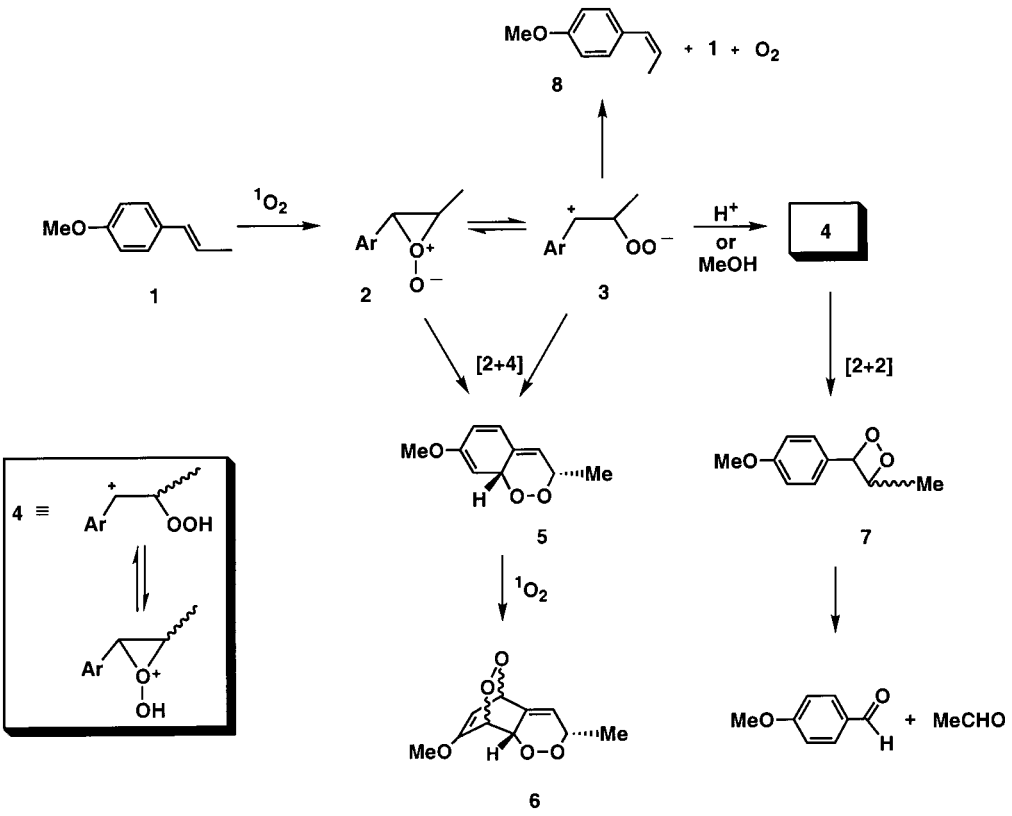


Table 1. Product Distributions

solvent	products,[a,b] % [2 + 4]	[2 + 2]
C_6D_6	73	24
$CDCl_3$	80	18
CD_3CN	70	29
C_6D_6 + acid(cat.)	10	86
C_6D_6 + acid (stoic.)	10	87
$CDCl_3$ + acid (cat.)	4	93
$CDCl_3$ + acid (1:3)	10	88
$CDCl_3$ + acid (stoic.)	3	96
CD_3CN + acid (stoic.)	18	78
CD_3OD	0	97

[a] Minor products are the "ene" products (~1%) and *cis*-4-propenylanisole **8** (~4%). Benzoic acid, cat. = 0.01 M, 1:3 = 0.03 M, stoic. = 0.1 M.

etaldehyde. In CD_3OD and in C_6D_6, $CDCl_3$, and CD_3CN with added benzoic acid, **1** reacted with $^1O_2$ to give mostly the [2 + 2] product. We believe that benzoic acid and MeOH serve as proton donors to the transient intermediate(s) since solvent polarity variations give no detectable change (Table 1) and since control experiments show that the products are inert to benzoic acid and MeOH under the reaction conditions. However, proton transfer is not a requirement for [2 + 2] product formation since small concentrations are observed in nonpolar solvents.

Isomerized Products. The amount of isomerized starting material **8** observed in these reactions (~4%) allowed for a mechanistic study by GC/MS. Small amounts of isomers of **5**−**7** are probably formed concomitantly, but these peroxides are unstable to GC/MS detection. A quantitative study of the reaction of **1** (0.2 M) with added trimethyl phosphite $P(OMe)_3$ (0.002−0.10M) with $^1O_2$ in CD_3OD showed that the isomerization **1** → **8** is suppressed (Table 2). This suppression is consistent with trapping by $P(OMe)_3$ or inhibition of the formation of a

Table 2. Trapping Transient Intermediates with $P(OMe)_3$

[$P(OMe)_3$] added, M	[**8**] produced, M
0.002	0.0060
0.01	0.0025
0.03	0.0015
0.06	0.0002
0.10	0.0003

zwitterionic intermediate **3**, which can rotate around the former double bond and return to starting material. Trimethyl phosphite is an effective trap for intermediate(s) in singlet oxygen reactions but reacts slowly with $^1O_2$ itself.[13,14]

Rate Constant Determinations. Flash photolysis and competitive kinetic studies revealed details about the solvent effects on the overall and relative rate processes. The total rate constant (k_T) measured in O_2-saturated solvents by monitoring the induced quenching of the luminescence (1270 nm) of $^1O_2$ ($^1\Delta_g \rightarrow {}^3\Sigma_g^+$)[15] by **1** increased by a factor of 3.9 from benzene to acetonitrile (Table 3). Such increases in k_T due to solvent polarity have been observed previously.[16] The effects from added acid on k_T are insignificant. The chemical reaction rate constant (k_r) measured by competition[17] between 2-methyl-2-pentene and **1** with $^1O_2$ depended on the solvent and added acid. The physical quenching of $^1O_2$ to $^3O_2$ by **1** is

(13) Nahm, K.; Foote, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 1909−1910.
(14) Poon, T. H. W.; Pringle, K.; Foote, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 7611−7618.
(15) Ogilby, P. R.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 3423−3430.
(16) Gollnick, K.; Griesbeck, A. *Tetrahedron Lett.* **1984**, *25*, 725−728.
(17) Higgins, R.; Foote, C. S.; Cheng, H. *ACS Adv. Chem. Ser.* **1968**, *77*, 102.

Table 3. Rate Constants for the Reaction of 1 with Singlet Oxygen

solvent	$k_T \times 10^{-5}$ (M^{-1} s^{-1})	$k_r \times 10^{-4}$ (M^{-1} s^{-1})	$k_q \times 10^{-4}$ (M^{-1} s^{-1})	physical quenching (%)
MeCN	4.3	7.5	35.3	82
MeCN + acid (stoic.)	4.3	25.0	11.8	42
MeOH	1.7	9.9	7.3	42
C_6H_6	1.2	3.7	8.3	69
C_6H_6 + acid (cat.)	1.1	4.3	6.7	61
C_6H_6 + acid (stoic.)	1.1	5.0	5.9	54

diminished when acid is added to nonpolar solvents and in MeOH compared to nonpolar solvents alone. When stoichiometric amounts of benzoic acid are added to benzene, physical quenching decreases by 27%, for acetonitrile the decrease is 40%. Protonation of intermediate(s) apparently favors the chemical processes compared to physical quenching.

These data show that solvent acidity plays a critical role in the reaction of singlet oxygen with **1**. We rationalize these effects by the mechanism depicted in Scheme 1 where protonated intermediates **4** originate from the perepoxide **2** and the zwitterion **3**. The [2 + 2] product is expected to form from protonated intermediates **4** in acidic solvents and from unprotonated intermediates in nonpolar solvents. Product distribution and quenching depend on the solvent acidity; while solvent polarity is much less significant. While direct spectral evidence for the intermediates does not exist, the phosphite trapping studies indicate that at least one intermediate is on the reaction surface. Proton transfer to the intermediate(s) in the reaction of **1** with $^1O_2$ can explain why the reaction is strikingly similar in MeOH and in nonprotic solvents with small amounts of added acid.

Experimental Section

General Methods. Compound **1** (Aldrich, 99%), trimethyl phosphite (Aldrich, 97%), biphenyl (Aldrich, 98%), 1,4-dimethyl-1,4-naphthalene (Aldrich), and deuterated solvents (Cambridge Isotope Laboratories) were used as received. Methanol was purified by distillation over KOH.

Singlet oxygen reactions were carried out in 5- or 10-mm NMR tubes at room temperature with periodic oxygen bubbling and irradiation with a 300-W Cermax Xenon lamp through a 0.05 M $K_2Cr_2O_7$ filter solution or by stirring with 0.5 M dimethylnaphthalene 1,4-endoperoxide. TPP was the sensitizer in benzene, acetonitrile and chloroform; rose bengal (RB) and aluminum(III)-Pc tetrasulfonate chloride in methanol. A typical experiment contained 0.10 M **1** and 2×10^{-5} M sensitizer in a 1-mL O_2-saturated solution. Relative concentrations of **1** and **8** were determined by reference to calibration curves with GC/MS using the single ion (SIM) and SCAN (with extract ion) modes.

Rate Constant Determinations. In an O_2-saturated solution, the sensitizer was irradiated with 532 nm light from a Quanta-Ray DCR-2 Nd:YAG laser and the luminescence of $^1O_2$ was monitored at 1270 nm using a cryogenic germanium photodetector (North Coast). The k_r determinations were conducted in 1-mL benzene-d_6 and MeOH-d_4 solutions containing 1×10^{-4} M sensitizer, 0.06−0.22 M 2-methyl-2-pentene and concentrations of **1** ranging from 0.11 to 0.19 M. The rate constant of product formation of **1** relative to 2-methyl-2-pentene was determined from equations derived by Higgins, Foote, and Cheng.[17] The k_r(**1**) was determined by multiplying the slope of these plots by the known k_r value for 2-methyl-2-pentene (7.59×10^5 M^{-1} s^{-1}).

Singlet Oxygen Reactions with Trimethyl Phosphite. The phosphite trapping studies were conducted in 1.0 mL of NMR grade MeOH-d_4 or spectral grade MeOH in 5-mm NMR tubes or 5-mL Pyrex test tubes containing 2×10^{-5} M sensitizer, 0.20 M **1**, and various concentrations of $P(OMe)_3$. Oxygen was bubbled into the solutions during the irradiation of the samples with a 300-W Xenon lamp through a 0.05M $K_2Cr_2O_7$ filter solution or the solutions were stirred with 0.5 M 1,4-dimethyl-1,4-naphthalene endoperoxide. Aliquots were removed at times selected so that less than 10% conversions of **1** were maintained.

Endoperoxide 5 was prepared in NMR grade C_6D_6 in 5-mm NMR tubes containing 1×10^{-4} M TPP and various concentrations of **1**. Oxygen was bubbled periodically during the irradiation of the sample with a 300-W Xenon lamp through a 0.05 M $K_2Cr_2O_7$ filter solution. Compound **5** was identified in the reaction mixture by NMR, but attempts to isolate and purify it by column chromatography resulted in its decomposition. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.30 (d, J = 5.9 Hz, 3H), 3.63 (s, 3H), 4.68 (m, 2H), 5.16 (m, 2H), 5.49 (m, 2H). ^{1}H NMR 400 MHz (C_6D_6): δ 1.02 (d, J = 6.5 Hz, 3H), 2.91 (s, 3H), 4.23 (dq, J_1 = 6.5 Hz, J_2 = 1.8 Hz, 1H), 4.46 (t, J = 2.9 Hz, 1H), 4.64 (d, J = 7.3 Hz, 1H), 4.81 (s, 1H), 4.86 (dd, J_1 = 7.3 Hz, J_2 = 2.7 Hz, 1H), 5.28 (s, 1H).

Allylic alcohol 10 was prepared in 5-mL solutions containing 0.2 M **1** with 0.2 M $P(OMe)_3$ and 1×10^{-4} M sensitizer in MeOH-d_4 and $CDCl_3$. Samples were irradiated with a 300-W Xenon lamp through a 0.05 M $K_2Cr_2O_7$ filter solution until ≥60% conversions were obtained. Compound **10** was collected in small amounts (1%) upon separation with column chromatography. ^{1}H NMR 360 MHz ($CDCl_3$) **10**: δ 3.8 (s, 3H), 5.32 (d with allylic coupling, J = 5.8 Hz, 1H), 5.36 (m, 2H), 6.06 (m, 1H), 7.11 (AA′MM′, J_1 = 8.7 Hz, J_2 = 2.9 Hz, J_3 = 2.0 Hz, 4H). ^{13}C NMR 400 MHz ($CDCl_3$): δ 55.32 (1 C), 88.36 (1 C), 114.08 (2 C), 119.26 (1 C), 129.06 (2 C), 130.14 (1 C), 135.57 (1 C), 159.87 (1 C). High-resolution MS: 164.0836, calcd 164.0837.

Acknowledgment. Supported by the National Science Foundation NSF (CHE97-03086).

JO991576D