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Fluorous Biphasic Singlet Oxygenation with a Perfluoroalkylated Photosensitizer

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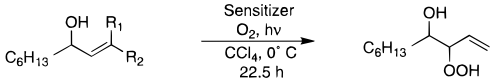
Singlet oxygen ($^1O_2$) is a versatile reagent for the selective oxidation of organic substrates.[1] The most common method for generation of $^1O_2$ involves visible irradiation of a dye sensitizer in oxygenated ($^3O_2$) solutions of a substrate. Decomposition of the sensitizer is a deleterious side reaction that is particularly acute with reluctant substrates (simple alkenes and allylic alcohols), or in preparative scale reactions run at high concentrations of substrate.[2] For example, the singlet oxygenation of **1** and related substrates under the typical reaction conditions employed in our laboratories[3] was accompanied by extensive degradation of the tetraphenylporphyrin (TPP) sensitizer (Scheme 1). Successful reaction required periodic recharging with TPP, and the presence of large quantities of degraded sensitizer complicated product purification. These practical concerns limit the utility of singlet oxygenation as a preparative method. Two possible means for mitigating sensitizer degradation are (1) increasing the chemical stability of the sensitizer toward oxidative degradation and (2) physical separation of the sensitizer from the other components of the reaction.[4,5] These two experimental techniques can be simultaneously employed with *meso*-perfluoroalkylporphyrins, which are both extremely electron-deficient and soluble in perfluoroalkane solvents. We now report that visible irradiation of 5,10,15,20-tetrakis(heptafluoropropyl)porphyrin (TPFPP)[6] in a fluorous biphasic medium[7,8] is an effective protocol for preparative photooxygenations and can be applied to the singlet oxygenation of electron-poor substrates.

A series of experiments was designed to compare the stability of TPFPP to that of TPP in the presence of $^1O_2$. As an initial test, continuously oxygenated CCl_4 solutions of the sensitizers were subjected to visible irradiation for 9 h. The concentration of TPFPP was virtually unchanged, whereas less than 4% of the TPP remained at the conclusion of the experiment. A similar study comparing the stability of TPFPP and TPP in the presence of singlet oxygen and added cumyl hydroperoxide found 98% of the TPFPP and 7% of the TPP remaining after 10 h.

Scheme 1



1E: $R_1 = H, R_2 = CH_3$
1Z: $R_1 = CH_3, R_2 = H$

2

Sensitizer	Porphyrin Recovered, %	Porphyrin Remaining by Absorbance, %	Yield, %
TPP	<10	11	53
TPFPP	70	86	57

Table 1. Results of Cyclohexene Oxidations

entry	sensitizer	solvent	time, h	yield, %	porphyrin remaining, %
1	TPP	CCl_4	8.0	35	<1
2	TPFPP	CCl_4	8.0	25	6
3	TPFPP	C_6F_{14}/CD_3CN	8.0	23	>99
4	TPFPP	C_6F_{14}/CD_3CN	32.0	84	94
5	TPFPP	C_6F_{14}/CD_3CN	46.0	96	83

Having demonstrated the superior chemical stability of TPFPP toward singlet oxygen and a generic hydroperoxide, we now examined the relative stabilities of TPFPP and TPP under typical photooxygenation conditions.[3] A 0.1 M solution of allylic alcohol **1E** in CCl_4 was photolysed for 22.5 h. The remaining porphyrin was assayed by absorbence.[9] The isolated yield of hydroperoxide **2** and the amount of recovered sensitizer were determined following chromatography. Although the yield of **2** was nearly identical for the two sensitizers, TPFPP was considerably more stable than TPP under the reaction conditions (Scheme 1). Furthermore, the extremely nonpolar nature of TPFPP, coupled with its solubility in hexane, greatly simplified its chromatographic separation from both **1E** and **2**.[10]

The results in Scheme 1 indicate that the substrate plays a crucial role in the chemical processes leading to sensitizer destruction, therefore sensitizer lifetime should be inversely correlated with substrate concentration. This prediction is borne out by the results of reactions conducted at high concentrations of substrate. The relative stabilities of TPFPP and TPP were compared during singlet oxygenations of 1.0 M solutions of cyclohexene in CCl_4. Both sensitizers were found to undergo extensive decomposition under these conditions and only modest conversions were obtained (entries 1 and 2, Table 1). Similar observations have been reported for photooxygenations involving other electron-deficient porphyrins.[2]

The preliminary experiments implied that increased longevity of the sensitizer might best be achieved through physical segregation from the reaction substrate and products. The use of fluorous biphasic mixtures seemed particularly appropriate given that TPFPP and O_2, but not most organic molecules, are quite soluble in readily available and environmentally benign fluorocarbons such as perfluorohexanes.[7] Furthermore, the generated $^1O_2$ has a relatively long lifetime (~100 ms) in perfluoroalkanes.[11] Several solvents were examined for the organic phase. Acetonitrile was chosen on the basis of both the favorable partition coefficient of the TPFPP sensitizer and the reasonable $^1O_2$ lifetime ($\tau = 54.4$ μs) in this solvent.[12] Photooxygenations were conducted in CD_3CN ($\tau = 600$ μs) to permit rapid assay of reaction mixtures by ^{1}H NMR.[13] A solution of cyclohexene in CD_3CN was layered on top of a solution TPFPP in perfluorohexanes and photooxygenated. As predicted, the fluorous biphasic system dramatically reduced

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[1] *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Ed.; Academic Press: New York, 1979; Vol. 40.

[2] Quast, H.; Dietz, T.; Witzel, A. *Liebigs Ann.* **1995**, 1495−1501.

[3] Oxidations were carried out in a 0 °C cooled jacketed Pyrex cell, into which was placed substrate (0.1 M) and sensitizer, TPP, (2×10^{-4} M) in CCl_4. The solution was aspirated with oxygen and photolyzed with a 200 W illuminator (Dolan-Jenner Industries) at a distance of 10 cm. The reaction was followed by TLC and stopped after the disappearance of the alkene. Fluorous biphasic reactions were carried out as above with a solution of substrate (3 M) and a solution of TPFPP (2×10^{-4} M) in perfluorohexanes placed in cell and photooxygenated with vigorous stirring.

[4] Midden, W. R.; Wang, S. Y. *J. Am. Chem. Soc.* **1983**, *105*, 4129−4135.

[5] Eisenberg, W. C.; Anand, J.; Wang, S.; Stevenson, R. J. *Photochem. Photobiol.* **1992**, *56*, 441−445.

[6] DiMagno, S. G.; Williams, R. A.; Therien, M. J. *J. Org. Chem.* **1994**, *59*, 6943−6948.

[7] Horváth, I. T.; Rabái, J. *Science* **1994**, *266*, 72−75.

[8] Horváth, I. T.; Rabái, J. U.S. Patent 5,463,082, 1995.

[9] Sensitizer decompostion was measured by the absorbance spectroscopy. Changes in the Soret band absorption of the porphryin (419 nm for TPP and 405 nm for TPFPP) were monitored using an OLIS UV/vis/NIR system that is based on the optics of a Carey 14 spectophotometer. Withdrawn aliquots were diluted approximately 20-fold with $CHCl_3$ before spectra were taken, and concentrations were corrected for solvent loss.

[10] Procedures for the preparation of **1E** and **1Z**, along with spectral data for compound **2**, are contained in supporting information.

[11] Schmidt, R. *J. Am. Chem. Soc.* **1989**, *111*, 6983−6987.

[12] Ogilby, P. R.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 3423−3430.

[13] Yield was determined by integration of peaks of 500 MHz ^{1}H NMR spectra taken on aliquots withdrawn from the reaction.

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the rate of TPFPP degradation. After 8 h the concentration of sensitizer was virtually unchanged (entry 3, Table 1). After 46 h, a point at which the reaction had nearly run to completion (96% yield),[13] 83% of the sensitizer remained (entries 4 and 5).

To illustrate the synthetic utility of the fluorous biphasic system, a photooxygenation was performed on 5 mL of a 3 M solution of **1Z** in acetonitrile. After 10 days, the acetonitrile layer was separated from the sensitizer solution, concentrated, and subjected to chromatography to afford **2** in 59% yield. Spectroscopic analysis of the perfluorohexanes layer indicated 57% of the sensitizer remained. The sensitizer solution could be reused directly. Alternatively, the sensitizer and perfluorohexanes could be individually recovered following simple distillation.

The TPFPP/fluorous biphasic protocol is shown to be a simple and effective preparative method for singlet oxygenation of organic compounds. The principal advantages of this procedure include (1) the use of inexpensive, reusable, and environmentally benign reagents, (2) the ability to conduct preparative scale reactions or prolonged oxygenations of reluctant substrates without significant loss of sensitizer, and (3) the ability to separate sensitizer from reactants and products without chromatography. The last characteristic makes the use of TPFPP in a fluorous biphasic medium potentially attractive for continuous preparative oxygenations.

Caution: As in any work involving peroxides, standard precautions (use of safety shields, avoidance of heat, light, or metal salts, performance of reactions on minimal scale) should be faithfully observed.[14−16]

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Supporting Information Available: Preparation of **1E** and **1Z**, spectral data for compound **2**, and procedure for fluorous biphasic reaction (2 pages). Ordering information is given on any current masthead page.

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(14) Patnaik, P. *A Comprehensive Guide to the Hazardous Properties of Chemical Substances*; Van Nostrand Reinhold: New York, 1992; pp 763.

(15) Medard, L. A. *Accidental Explosions: Types of Explosive Substances*; Ellis Horwood Limited: Chichester, 1989; Vol. 2.

(16) Shanley, E. S. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. 3, pp 341−369.

(17) **Note Added in Proof.** After acceptance of this manuscript, a description of the use of fluorocarbon media for TPP-sensitized oxygenation was reported: Chambers, R. D.; Sanford, G. *Synth. Commun.* **1996**, *26*, 1861−1866.