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# Trapping of Peroxidic Intermediates with Sulfur and Phosphorus Centered Electrophiles

Edward L. Clennan,* Kristina L. Stensaas, and Sally D. Rupert

*Department of Chemistry, University of Wyoming, Laramie, WY 82071*

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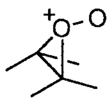
## ABSTRACT

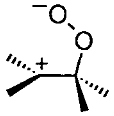
*The trapping ability of a new peroxidic trapping agent relative to several well-established trapping agents was measured. Two different methods for this measurement were utilized. It was shown that adamantylidene adamantane reacts under the trapping conditions to give adamantylidene adamantane epoxide via a more complicated process than previously recognized and is consequently an inappropriate system to make this measurement. In contrast, the use of diethyl sulfide is straightforward and gives reliable values.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem **9**:51–56, 1998

## INTRODUCTION

The reactions of singlet oxygen with organic and biological substrates have been exhaustively examined [1–3]. With the possible exception of singlet oxygen 4 + 2 cycloadditions to form endoperoxides [4], these reactions invariably occur in a stepwise fashion via transient intermediates that include perepoxides, **1**, zwitterions, **2**, ion pairs, **3**, persulfoxides, **4**, thiadioxiranes, **5**, hydroperoxy sulfonium ylides, **6**, sulfuranes, **7**, exciplexes, **8**, and possibly diradicals, **9**.



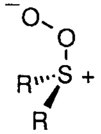
**1**



**2**

$R_2S^{\cdot +}\ O_2^{\cdot -}$

**3**



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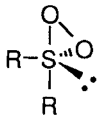

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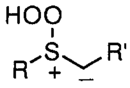

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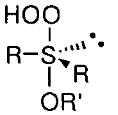

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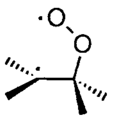
**8**



**9**

The presence of these intermediates have often been detected by the use of trapping agents that are converted to oxidized products that serve as a signature for the intermediate. A suitable trapping agent and its oxidized products must be inert to singlet oxygen, and the products must be stable under the reaction conditions. In addition, the trapping agent must be very reactive, allowing it to compete effectively with other reactions of the intermediate. A variety of trapping agents including alcohols [5,6], olefins [7], phosphites [8,9], sulfoxides and sulfides [10], and sulfenate and sulfinate esters [11] have been shown to meet these stringent requirements. Never the less, a need exists for additional trapping agents that exhibit enhanced selectivity for the various peroxidic intermediates and that are stable under a variety of conditions, including biological media. In this article, we introduce a new trapping agent, sulfinamide (**10**), and we discuss the advan-

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Dedicated to Prof. William E. McEwen on the occasion of his seventy-fifth birthday.

*To whom correspondence should be addressed.

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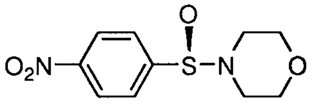
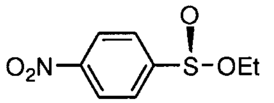
tages and disadvantages of two different methods to determine its trapping efficiency relative to well-established trapping agents, **11–13.**



**10**



**11**

$P(OPh)_3$

**12**

$Ph_2SO$

**13**

## *RESULTS AND DISCUSSION*

The two substrates most often used to determine the relative efficiencies of trapping agents are diethyl sulfide, **14**, and adamantylidene adamantane, **15**. The established mechanisms for the photooxidations of these substrates are depicted in Figures 1a and 1b, respectively. The intermediates sequestered in these reactions by the electrophilic trapping agents used in this study are the nucleophilic persulfoxide, **16**, and the perepoxide, **17**.

*Diethyl Sulfide.* The photooxidations of oxygen-saturated benzene solutions of **14** containing 2 × $10^{-4}$ M TPP (meso-tetraphenylporphyrin) in the presence of various amounts of trapping agents, **10–13**, were monitored at low conversions (<18%) by gas chromatography and the [$Et_2SO$]/[trapO] product ratio measured using calibration curves. The rate constant ratio $k_x/k_{Trap}$ (Figure 1a) were determined by plotting [$Et_2SO$]/[trapO] versus the inverse of the trapping agent concentration, 1/[trap], according to Equation 1, which was derived from the mechanism depicted in Figure 1a by steady-state treatment of both the persulfoxide, **16**, and thiadioxirane intermediates. The trapping efficiencies relative to diphenyl sulfoxide, **13**, were derived by dividing the $k_X/k_{trap}$ for **13** by the corresponding ratio for each of the trapping agents. These values $k_{trap}$ (rel) and the $k_X/k_{trap}$ for each of the trapping agents are compiled in Table 1. These data reveal that the trapping efficiencies increase in the order **10** < **13** < **11** < **12**.

$$\frac{[Et_2SO]}{[trapO]} = 1 + \frac{2k_x}{k_{trap}[trap]} \qquad (1)$$

For comparison, the relative trapping abilities of

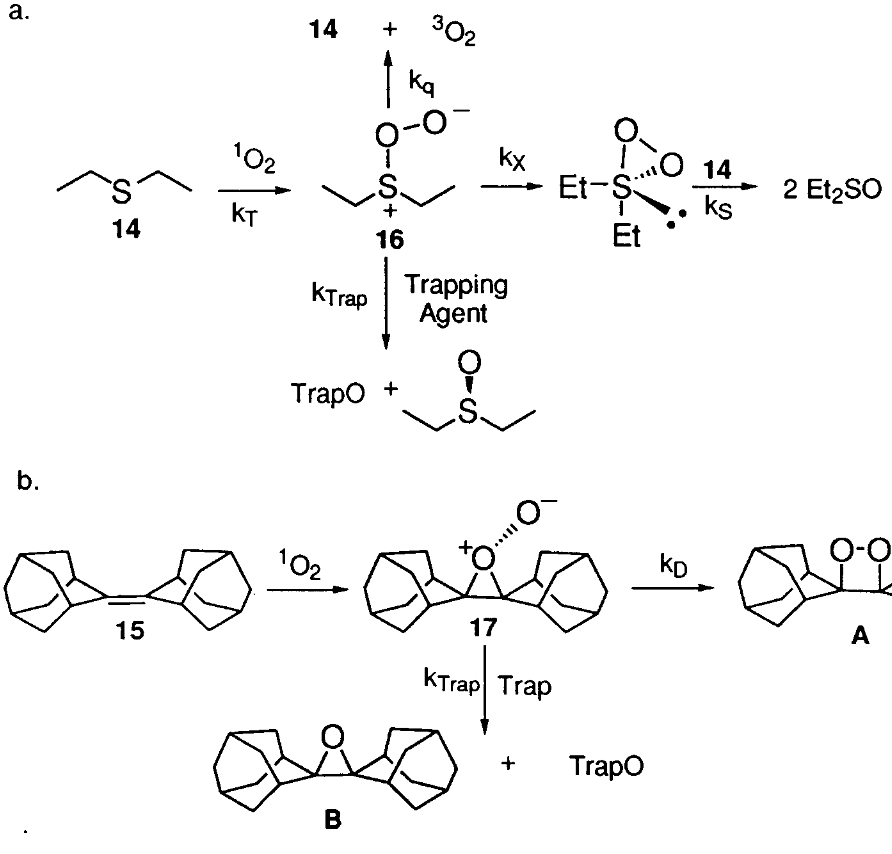


**FIGURE 1** Mechanisms for the photooxidations of **14** and **15**.

**11–13** were also measured by direct competition. Mixtures of **11** and **13** and of **12** and **13** in oxygen-saturated benzene solutions were irradiated on a merry-go-around, and aliquots were taken and analyzed for the concentrations of the oxidized traps at various time intervals. The product concentration ratios were extrapolated to time = 0 to give $[\text{trapO1}]_0/[\text{trapO2}]_0$ that were used in conjunction with Equation 2 to give the relative trapping rate constants. The values $k_{\text{trapO1}}/k_{\text{trapO2}}$ obtained for **11/13** of 2.6 and for **12/13** of 19.1 are in reasonable agreement with the noncompetitive persulfoxide trapping results shown in Table 1.

$$\frac{[\text{trapO1}]_0}{[\text{trapO2}]_0} = \frac{k_{\text{trapO1}}[\text{trapO1}]}{k_{\text{trapO2}}[\text{trapO2}]} \tag{2}$$

*Adamantylidene Adamantane.* In principle, determination of trapping efficiencies using the adamantylidene adamantane probe requires measurements of the dioxetane, **A**, and epoxide, **B**, concentrations and plotting them according to Equation 3, which was derived from the mechanism depicted in Figure 1b using the steady-state approximation on the perepoxide **17**. In practice, however, the use of this probe system is complicated by the fact that substantial amounts of epoxide form even in the absence of a trapping agent.

$$\frac{[\text{dioxetane, }\mathbf{A}]}{[\text{epoxide, }\mathbf{B}]} = \frac{[\text{dioxetane, }\mathbf{A}]}{[\text{trapO}]} = \frac{k_D}{k_{\text{trap}}[\text{trapping agent}]} \tag{3}$$

Bartlett reported that photoooxidation of **15** in benzene resulted in formation of an epoxide/dioxetane (**B**/**A**) ratio of 35/65 [12]. We have also observed that photooxidation of an oxygen-saturated benzene solution $4.01 \times 10^{-2}$ M in **15**, $6.46 \times 10^{-4}$ M in the internal standard dodecane, and $2.15 \times 10^{-4}$ M in the sensitizer meso-tetraphenylporphyrin (TPP) gives a 30/70 epoxide/dioxetane ratio at 1.7% conversion of **15**. In addition, we have noted that this ratio is dependent on the % conversion of **15** and therefore a function of irradiation time as shown in Figure 2. The dioxetane becomes increasingly important as the photolysis proceeds, and at 12% conversion, the **B**/**A** ratio is only 14/86. In addition, the extent of epoxide formation is also a sensitive function of the solvent sensitizer combination (Table 2).

An additional complicating factor is seen upon photolysis of oxygen-saturated benzene solutions containing various amounts of trapping agent **11**, 3.21 mM **15**, $5.28 \times 10^{-4}$ M biphenyl, and $2.05 \times$

**TABLE 1** Kinetic Data for Trapping of Diethyl Persulfoxide[a]

| *Trapping Agent* | $k_X/k_{Trap}$ | $k_{rel}$[b] |
|---|---|---|
| $p\text{NO}_2\text{C}_6\text{H}_4\text{SO}_2\text{Et}$, **11** | 0.0098 (±0.0005) | 2.35 |
| $\text{Ph}_2\text{SO}$,[c] **13** | 0.023 | 1.0 |
| $(\text{PhO})_3\text{P}$, **12** | 0.0011 | 20.91 |
| $p\text{NO}_2\text{C}_6\text{H}_4\text{S}$-morph,[d] **10** | 0.1269 (±0.003) | 0.18 |

[a] In benzene.
[b] Relative to diphenyl sulfoxide.
[c] Ref. [10].
[d] Morph-morpholinyl, $\text{N(CH}_2\text{CH}_2)_2\text{O}$.

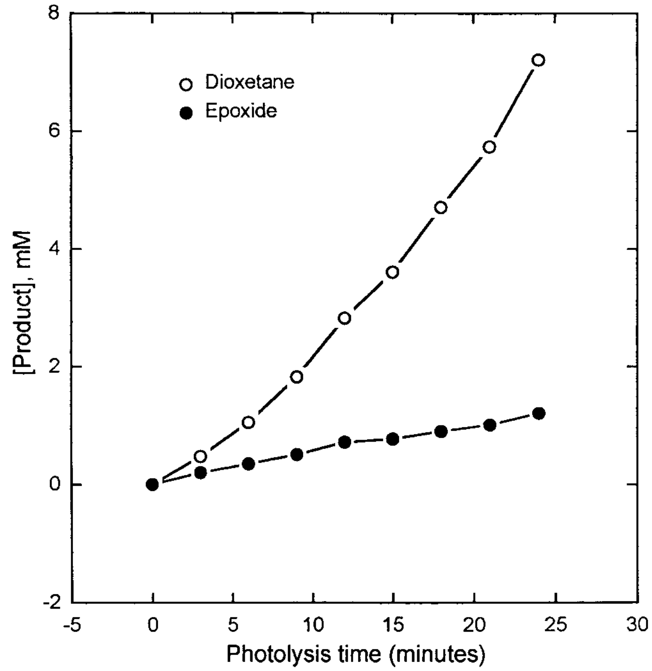


**FIGURE 2** Dioxetane, **A**, and epoxide, **B**, concentration as a function of photolysis time in oxygen-saturated benzene containing **15** ($4.01 \times 10^{-2}$ M), dodecane ($6.46 \times 10^{-4}$ M), and TPP ($2.15 \times 10^{-4}$ M).

**TABLE 2** Epoxide/Dioxetane Ratios in the Photooxidations of **15**

| *Solvent* | *Sensitizer* | *Epoxide/Dioxetane* |
|---|---|---|
| Chloroform | TPP[a] | 20/80[b] |
| Acetone | eosin B | 10/90[c] |
| Benzene | TPP[a] | 36/64[d] |
| Benzene | $\text{C}_{60}$ | 80/20[e] |
| Acetone | Rose Bengal | 54/46[f] |

[a] Meso-tetraphenylporphine.
[b] 51.7% conversion.
[c] 6.5% conversion.
[d] 10.6% conversion.
[e] 10.0% conversion.
[f] 18.8% conversion.

$10^{-4}$ M TPP (Figure 3). Addition of 1.12 mM of **11** (point 2 in Figure 3a) and photolysis to low conversions (12–15%) of **15** enhances the epoxide formation increasing its concentration by $3.33 \times 10^{-4}$ M (points 2 and 1; Figure 3a). Epoxide formation from trapping of perepoxide **17** must be equal to the decrease in dioxetane **A** (Figure 1b) and therefore accounts for only 5% of the total increase in epoxide formation (100 × [points 3 − 4]/[points 2 − 1]). In contrast, at higher conversions (29–33%) of **15**, trapping of the perepoxide accounts for 51% of epoxide formation (100 × [points 3 − 4]/[points 2 − 1]; Figure 3b).

Plotting of the data at the low (12–15%) or higher conversions (29–33%) according to Equation 3 gives straight lines (Figures 4a and 4b). However, the slopes are not $k_D/k_{\text{trap}}$ (Equation 3) especially at low conversions since mechanism b in Figure 1 is not the

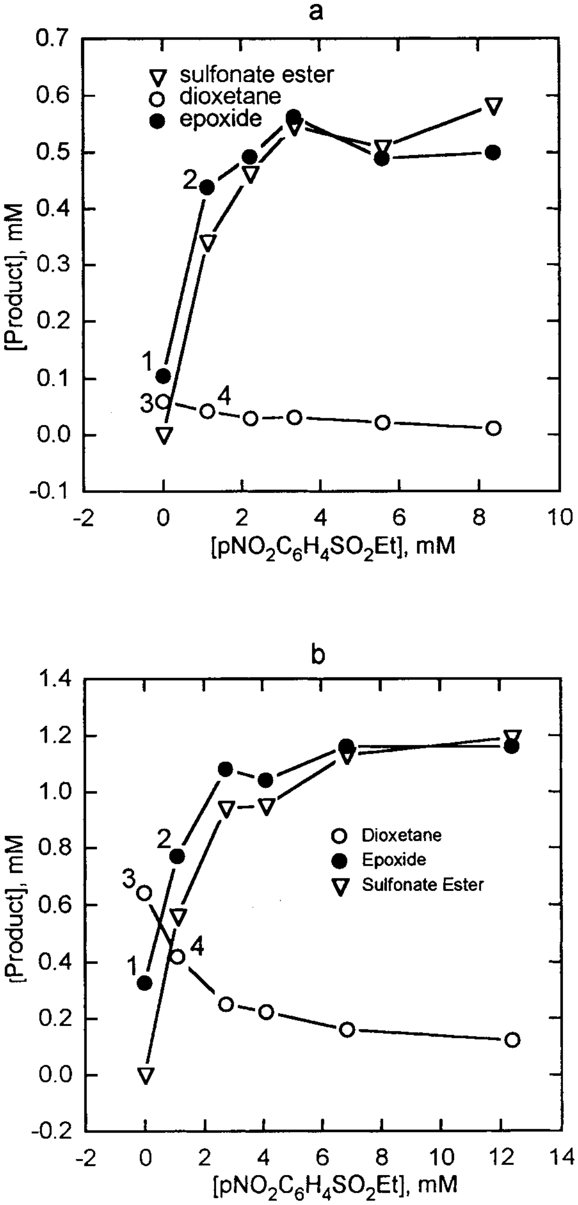


**FIGURE 3** Product concentrations as a function of ethyl *p*-nitrophenylsulfonate ester, **11,** in oxygen saturated benzene containing **15** ($4.0 \times 10^{-3}$ M), dodecane ($6.46 \times 10^{-4}$ M), and TPP ($2.24 \times 10^{-4}$ M) after (a) 10 minutes and (b) 25 minutes of irradiation.

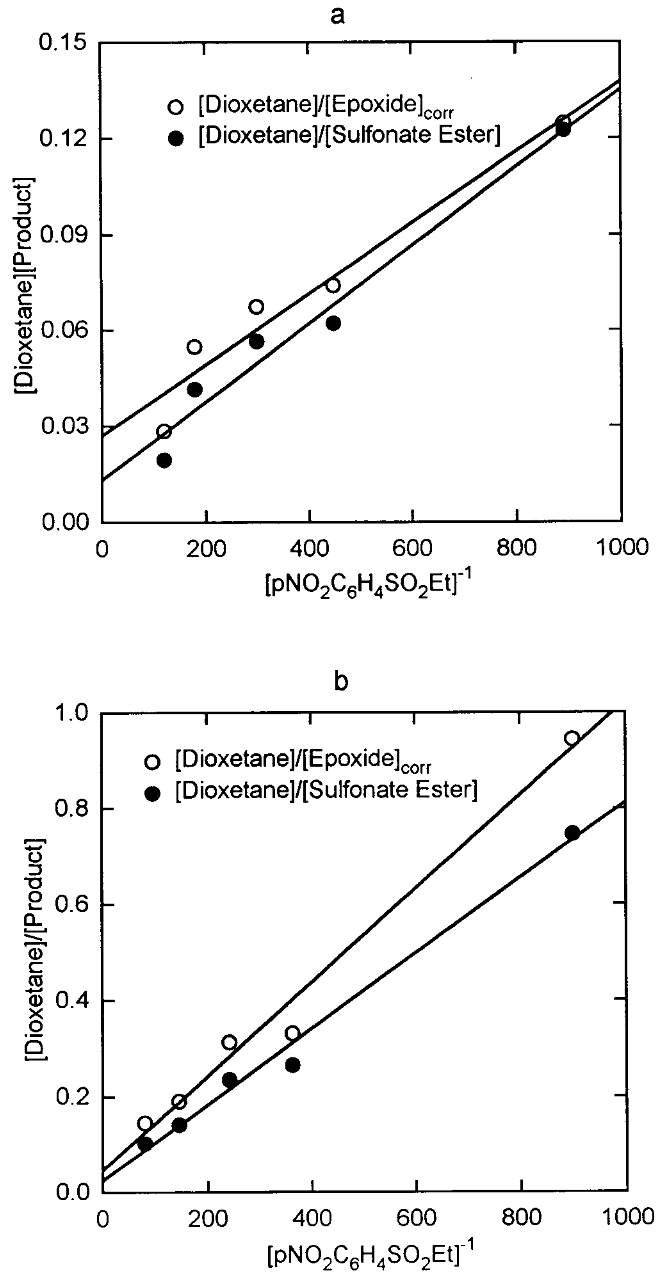


**FIGURE 4** Data in (a) Figure 3a and (b) Figure 3b plotted according to Equation 3.

only mechanism contributing to epoxide formation. Consequently, previous studies using this technique gave erroneous trapping efficiencies [11].

## *CONCLUSION*

The sulfur- and phosphorus-based electrophiles **10–13** are capable of trapping both the persulfoxide in the photooxidation of diethyl sulfide and the perepoxide in the photooxidation of adamantylidene adamantane, **15.** The oxidized trapping agent, trapO, in the photooxidation of diethyl sulfide is formed exclusively via process $k_{\text{trap}}$ (Figure 1a), and as a consequence, Equation 1 can be used to determine relative trapping efficiencies. This probe reveals that the new trapping agent, sulfinamide **10,** is less effective than **11, 12,** or **13.** The greater trapping ability of the sulfinate ester **11** is that anticipated based upon the electron-withdrawing ability of nitrogen versus oxygen.

The use of adamantylidene adamantane, **15,** to measure relative trapping efficiencies is complicated by the fact that the mechanism shown in Figure 1b cannot explain the experimental results. It is possible that there are at least two mechanisms for epoxidation of **15** and for formation of the oxidized trap, trapO; however, more experimental data will need to be collected in order to verify this suggestion. Consequently, this system is inappropriate for the quantitative measurements of trapping efficiencies.

## *EXPERIMENTAL*

*General Aspects.* All photooxidations were carried out in capped Pyrex test tubes using a merry-go-round apparatus equipped with a 450 W medium-pressure Hanovia lamp through a 0.1% aqueous w/v $K_2CrO_4$ filter solution (filters out light below 460 nm). The concentrations of reaction products were quantified using a Perkin-Elmer Autosystem capillary gas chromatograph equipped with a HP-5 [30 m × 0.25 mm × 0.25 $\mu$m (length × inside diameter × film thickness)] capillary column. The GC conditions were as follows: injection temp., 250°C; detector temp., 250°C; and oven initial temp., 75°C (3 min). The oven temperature was ramped at a rate of 8°C/min until it reached 200°C, where it was held for 2 minutes, and then increased a second time at a rate of 10°C to a final temperature of 250°C, where it was held for 15 minutes.

*Materials.* Diethyl sulfide (97%, Aldrich) was refluxed over Na metal and distilled prior to use. Adamantylidene adamantane (AdAd) was synthesized and purified according to a literature procedure [13]. 4-Morpholinyl *p*-nitrophenyl sulfide was synthesized by a known procedure [14]. **10** and the corresponding sulfonamide were prepared by 1 and 2 equivalent oxidations of the sulfide using mCPBA (Acros). Ethyl 4-nitrophenylsulfenate, sulfinate **11,** and sulfonate esters were synthesized according to literature methods [15]. Phenyl sulfoxide **13** (97%, Aldrich) was recrystallized with hexane-ethyl acetate prior to use. Triphenyl phosphite, morpholine (gold label), 2-adamantanone (99%), 4-nitrobenzenesulfenyl chloride, meso-tetraphenylporphine (TPP, 99%+), Rose Bengal, eosin B, and $C_{60}$ were purchased from Aldrich and used without further purification. Biphenyl (Aldrich) was recrystallized from hexanes. Benzene (Spectrum) was distilled over $P_2O_5$ prior to use. Acetone (J. T. Baker) was refluxed and distilled over $KMnO_4$. Chloroform (J. T. Baker) was dried over $CaCl_2$ and distilled.

## *METHODS*

### *Trapping of Diethyl Persulfoxide* (*Foote Method*)

A typical experiment consists of taking oxygen-saturated benzene solutions containing 0.10 M $Et_2S$, $2.02 \times 10^{-4}$ M TPP, $5.88 \times 10^{-4}$ M biphenyl (internal standard), $4.0 \times 10^{-3}$ to $4.0 \times 10^{-2}$ M $p$-$NO_2C_6H_4SO_2Et$ and irradiating for 20–30 minutes. The concentrations of $Et_2SO$ and $p$-$NO_2C_6H_4SO_3Et$ were quantified using recently constructed calibration curves. The $[Et_2SO]/[p\text{-}NO_2C_6H_4SO_3Et]$ ratio was plotted vs. $[p\text{-}NO_2C_6H_4SO_2Et]^{-1}$. The % conversion of the trapping agent was kept below 17% in all cases except for $(PhO)_3P$, which was below 30%.

### *Trapping of Diethyl Persulfoxide* (*Direct Competition*)

An oxygen-saturated benzene solution containing 0.10 M $Et_2S$, $6.46 \times 10^{-4}$ M dodecane (internal standard), $2.32 \times 10^{-4}$ M TPP, $3.07 \times 10^{-2}$ M $Ph_2SO$, and $1.56 \times 10^{-2}$ M $p$-$NO_2C_6H_4SO_2Et$ was irradiated for 5–35 minutes at which time aliquots were removed for GC analysis. The trapO concentrations were calculated and their ratio plotted vs. time of irradiation. The trap conversions were maintained below 15%.

### *Trapping of AdAd Perepoxide* (*Foote Method*)

A typical experiment consists of taking oxygen saturated benzene solutions containing $4.0 \times 10^{-3}$ M AdAd, $2.24 \times 10^{-4}$ M TPP, $6.46 \times 10^{-4}$ M dodecane, and $1.10 \times 10^{-3}$ to $1.24 \times 10^{-2}$ M $p$-$NO_2C_6H_4SO_2Et$ and irradiating for 20–25 minutes. Dioxetane is quantitatively cleaved under the GC conditions to adamantanone, and its concentration and that of the epoxide were calculated. A plot of [dioxetane]/[epoxide]$_{corr}$ vs. [$p$-$NO_2C_6H_4SO_2Et$]$^{-1}$ provided $k_d/k_{trap}$ as the slope. The % conversion of AdAd was from 30–33%.

## ACKNOWLEDGMENTS

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[4] 4 + 2 Cycloadditions of singlet oxygen have often been referred to as concerted reactions; however, suggestions have been made that these reactions might proceed via exciplexes ([E. L. Clennan, M. E. Mehrsheik-Mohammadi, *J. Am. Chem. Soc., 106,* 1984, 7112–7118) or even perepoxide intermediates (K. M. Davis, B. K. Carpenter, *J. Org. Chem. 61,* 1996, 4617–4622; G. Delogu, D. Fabbri, F. Fabris, F. Sbrogiò, G. Valle, O. De Lucchi, *J. Chem. Soc. Chem. Commun.* 1995, 1887–1888).

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