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Singlet Oxygen Promoted Carbon−Heteroatom Bond Cleavage in Dibenzyl Sulfides and Tertiary Dibenzylamines. Structural Effects and the Role of Exciplexes

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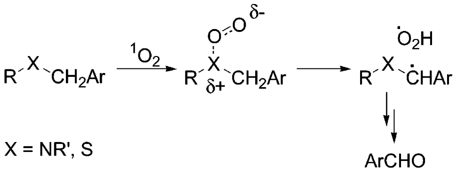

The C−heteroatom cleavage reactions of substituted dibenzyl sulfides and substituted dibenzylcyclohexylamines promoted by singlet oxygen in MeCN have been investigated. In both systems, the cleavage reactions (leading to benzaldehyde and substituted benzaldehyde) were slightly favored by electron-withdrawing substituents with ρ values of +0.47 (sulfides) and +0.27 (amines). With dibenzyl sulfides, sulfones were also obtained whereas sulfoxide formation became negligible when the reactions were carried out in the presence of a base. Through a careful product study for the oxidation of dibenzyl sulfide, in the presence and in the absence of Ph_2SO, it was established that sulfone and cleavage product (benzaldehyde) do not come by the same route (involving the persulfoxide and the hydroperoxysulfonium ylide) as required by the generally accepted mechanism (Scheme 1) for C−heteroatom cleavage reactions of sulfides promoted by singlet oxygen. On this basis and in light of the similar structural effects noted above it is suggested that dibenzyl sulfides and dibenzylamines form benzaldehydes by a very similar mechanism. The reaction with singlet oxygen leads to an exciplex that can undergo an intracomplex hydrogen atom transfer to produce a radical pair. With sulfides, collapse of the radical pair leads to an α-hydroperoxy sulfide than can give benzaldehyde by an intramolecular path as described in Scheme 3. With amines, the radical pair undergoes an electron-transfer reaction to form an iminium cation that hydrolyzes to benzaldehyde. From a kinetic study it has been established that the fraction of exciplex converted to aldehyde is ca. 20% with sulfides and ca. 7% with amines.

Introduction

It is well-known that in the reaction of sulfides with singlet oxygen ($^1\Delta_g$), hereafter indicated as $^1O_2$, products of C−S bond cleavage can be formed in addition to the normal S-oxidation products, viz., sulfoxides and sulfones.[1] The C−S bond cleavage reaction, eq 1, can become particularly important (and represent the major reaction pathway) in aprotic solvents and when the α-CH bond in the sulfide is relatively weak (e.g., when R = Ph).[1]

$$RCH_2SR' + {}^1O_2 \rightarrow RCHO + \text{S-oxidation products} \quad (1)$$

Reaction 1 is receiving increasing attention and is generally discussed in the framework of the widely accepted mechanism of the $^1O_2$-promoted sulfoxidation of sulfides. According to the most recent mechanistic studies,[1f−h] the key step is the conversion of the first formed persulfoxide **1** into the *S*-hydroperoxysulfonium ylide **2** (Scheme 1, path a). The latter compound can lead to sulfoxide and sulfone but it may also undergo a Pummerer rearrangement to form the α-hydroperoxy sulfide **3**

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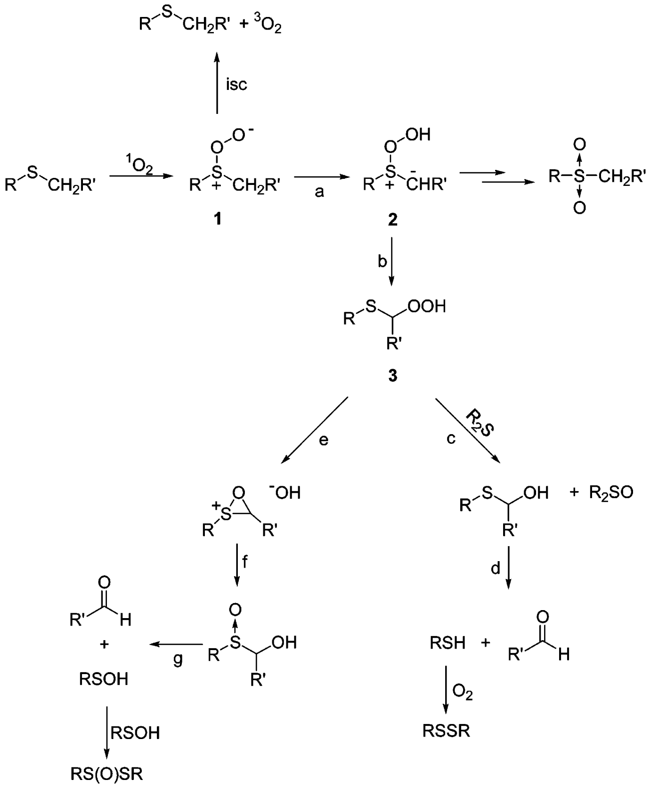
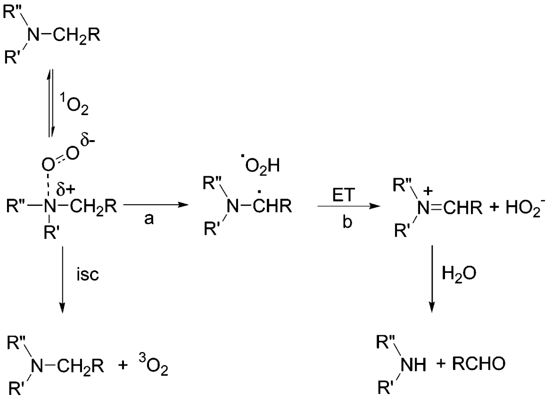
SCHEME 1



(path b) that can react with another molecule of sulfide forming a sulfoxide and an α-hydroxy sulfide (path c). The hydrolysis of the latter generates the cleavage products (path d) that, however, can also be formed from **3** by a unimolecular mechanism that does not produce sulfoxide (path e).

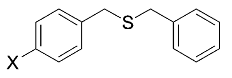
In many respects, the C−S bond cleavage of sulfides presents a close analogy to the C−N bond cleavage (N-dealkylation) that is the main outcome of the reaction of tertiary trialkylamines with $^1O_2$.[2] In this case, however, the cleavage is thought to take place by a simple mechanism involving a hydrogen abstraction reaction occurring inside the charge-transfer complex (exciplex) formed by interaction of the amine lone pair with $^1O_2$ (Scheme 2).[2j,k] A radical couple is formed (path a) that can undergo an electron transfer from the carbon radical to $HO_2^\bullet$ to form an iminium cation (path b). The latter can easily hydrolyze with cleavage of the C−N bond to form an aldehyde and a secondary amine. In the amines case, no evidence, either theoretical or experimental, has been ever found for intermediates en route from the charge-transfer complex to the radical couple. Thus, two very similar processes, both induced by the same species, appear to involve completely different mechanisms.[3]

SCHEME 2

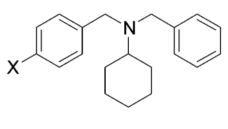


In this context, it seems of interest to study structural effects in the $^1O_2$-promoted C−heteroatom bond cleavage reactions of dibenzyl sulfides and dibenzylamines with the aim of investigating whether and how these effects are influenced by the mechanistic differences noted above for the two systems. The structural effects could be quite different in the hydrogen transfer step that in both cases should be the key step leading to the heteroatom−carbon cleavage. According to the mechanisms displayed in Schemes 1 and 2, the hydrogen transfer step for dibenzyl sulfides is the one where the persulfoxide intermediate is converted into the hydroperoxysulfonium ylide (Scheme 1, path a), whereas for dibenzylamines it is the one where the exciplex is converted into the radical pair (Scheme 2, path a).

Thus, we have studied the reaction of a series of arylmethyl benzyl sulfides (**4**) and arylmethyl(benzyl)cyclohexylamines[4] (**5**) with $^1O_2$ in MeCN. Structural effects on the C−heteroatom bond cleavage can be easily evaluated by measuring the 4-X-C_6H_4CHO/benzaldehyde ratio in the products mixture.



4: X = H
4a: X = OMe
4b: X = Me
4c: X = CN



5a: X = OMe
5b: X = Me
5c: X = CN

To gain a better mechanistic understanding of the sulfoxidation reaction, a careful determination of the sulfoxidation products in the reaction of dibenzyl sulfide with $^1O_2$ was also carried out. Moreover, the study was completed with kinetic measurements for the determination of the rates of total and chemical quenching of $^1O_2$ by dibenzylamines and dibenzyl sulfides.

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(1) (a) Corey, E. J.; Ouannes, C. *Tetrahedron Lett.* **1976**, *17*, 4263. (b) Takata, T.; Ishibashi, K.; Ando, W. *Tetrahedron Lett.* **1985**, *26*, 4609. (c) Akasaka, T.; Sakurai, A.; Ando, W. *J. Am. Chem. Soc.* **1991**, *113*, 2696. (d) Sheu, C.; Foote, C. S.; Gu, C.-L. *J. Am. Chem. Soc.* **1992**, *114*, 3015. (e) Bonesi, S. M.; Mella, M.; d'Alessandro, N.; Aloisi, G. G.; Vanossi, M.; Albini, A. *J. Org. Chem.* **1998**, *63*, 9946. (f) Toutchkine, A.; Clennan, E. L. *J. Am. Chem. Soc.* **2000**, *122*, 1834. (g) Toutchkine, A.; Aebisher, D.; Clennan, E. L. *J. Am. Chem. Soc.* **2001**, *123*, 4966. (h) Bonesi, S. M.; Fagnoni, M.; Monti, S.; Albini, A. *Tetrahedron* **2006**, *62*, 10716.

(2) (a) Fisch, M. H.; Gramin, J. C.; Olesen, J. A. *Chem. Commun.* **1970**, 13. (b) Fisch, M. H.; Gramin, J. C.; Olesen, J. A. *Chem. Commun.* **1971**, 663. (c) Bellus, D.; Lind, H.; Wyatt, J. F. *Chem. Commun.* **1972**, 1199. (d) Smith, W. F. *J. Am. Chem. Soc.* **1972**, *94*, 186. (e) Tsubomura, H.; Yagishita, T.; Toi, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3051. (f) Gollnick, K.; Lindner, J. H. E. *Tetrahedron Lett.* **1973**, 1903. (g) Inoue, K.; Saito, I.; Matsuura, T. *Chem. Lett.* **1977**, 607. (h) Haugen, C. M.; Bergmark, W. R.; Whitten, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 10293. (i) Cocquet, G.; Rool, P.; Ferroud, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, *14*, 2277. (j) Baciocchi, E.; Del Giacco, T.; Lapi, A. *Org. Lett.* **2004**, *6*, 4791. (k) Baciocchi, E.; Del Giacco, T.; Lapi, A. *Helv. Chim. Acta* **2006**, *89*, 2273. (l) Baciocchi, E.; Del Giacco, T.; Lanzalunga, O.; Lapi, A.; Raponi, D. *J. Org. Chem.*, **2007**, *72*, 5912.

(3) The similar outcome of the reactions of benzyl sulfides and tertiary benzylamines with $^1O_2$ has been already noted by Albini and co-workers, who have considered whether the analogy could imply a similar structural dependence.[1h] They have concluded negatively, but on the basis of a general comparison between sulfides and amines, i.e., not strictly limited to those systems that undergo carbon−heteroatom scission.

(4) (a) The cyclohexyl group was chosen as alkyl substituent since it does not show any reactivity with $^1O_2$.[2k,4b] (b) Baciocchi, E.; Del Giacco, T.; Lapi, A. *Org. Lett.* **2006**, *8*, 1783.

TABLE 1. $^1O_2$ Total Quenching Rate Constants (k_T) by Dibenzyl Sulfides 4a−c and Dibenzylamines 5a−c in MeCN at 22 °C

X	compd	k_T (M^{-1} s^{-1})^a	compd	k_T (M^{-1} s^{-1})^a
H	**4**	1.06×10^7		
OMe	**4a**	1.34×10^7	**5a**	4.04×10^6
Me	**4b**	1.37×10^7	**5b**	4.05×10^6
CN	**4c**	7.34×10^6	**5c**	3.05×10^6

[a] Errors are ±10%.

Results

Kinetic Study. The rate constants (k_T) for the total quenching (physical and chemical) of $^1O_2$ by dibenzyl sulfides **4** and **4a−c** and dibenzylcyclohexylamines **5a−c** were measured in MeCN by laser flash photolysis experiments following the decay rate of the singlet oxygen luminescence at 1270 nm. The results are reported in Table 1 and it can be immediately noted that in both systems the rate of total quenching is little influenced by the substituent in the ring.

Benzylamines. Singlet oxygen was both photochemically and thermally generated. In the former case tetraphenylporphyrin (TPP) was used as the photosensitizer, whereas in the latter process, singlet oxygen was generated by thermal decomposition of 1,4-dimethylnaphthalene endoperoxide.[5] In the photochemical reactions, the substrate (10^{-2} M) was irradiated (400−600 nm) in O_2-saturated dry acetonitrile in the presence of TPP (10^{-4} M) at 25 °C with an irradiation time ranging from 15 to 30 min. During the reaction, further TPP was added at 5-min intervals due to its degradation in the reaction medium. In all cases, no product formation was observed when irradiations were performed in the absence of TPP or O_2. Thermal reactions were carried out by heating (40 °C) a solution of the amine (10^{-2} M) in the presence of 1,4-dimethylnaphthalene endoperoxide (2×10^{-2} or 0.1 M) in dry MeCN for 4 h in the dark. Blank experiments carried out under the same conditions in O_2-saturated MeCN but in the absence of 1,4-dimethylnaphthalene endoperoxide showed the absence of reaction products. Product analysis was carried out by GC, GC-MS, and ^1H NMR. In both photochemical and thermal reactions, substrate conversion was kept below 20% and the mass balance was always greater than 95%, with respect to benzaldehydes.

From the dibenzylamines **5a−c,** 4-substituted and unsubstituted benzaldehydes were obtained together with the corresponding secondary amines. Moreover, benzylidene cyclohexylamines were also observed, which likely derive from the further oxidation of the secondary amines.[6] As previously found in the oxidation of *N*,*N*-dimethylbenzylamine with $^1O_2$,[2j] it was observed that H_2O_2 is formed in a molar amount very close to the sum of the substituted and unsubstituted benzaldehydes.[7]

The yields of substituted and unsubstituted benzaldehydes, as well as the 4-X-C_6H_4CHO/PhCHO molar ratios, are reported in Table 2. It can be noted that there is an excellent agreement between the ratios obtained in the photochemical and thermal experiments.

TABLE 2. Benzaldehydes Yields in the Oxidation of Dibenzylamines 5a−c by Photochemically and Thermally Generated $^1O_2$

		benzaldehydes yields (%)^a		4-X-C_6H_4CHO/ PhCHO
X		PhCHO	4-X-C_6H_4CHO	
OMe	$h\nu^b$	6.4 ± 0.3	5.0 ± 0.3	0.79
	Δ^c	3.7 ± 0.2	3.0 ± 0.2	0.82
Me	$h\nu^b$	7.5 ± 0.4	6.7 ± 0.3	0.89
	Δ^c	3.9 ± 0.2	3.5 ± 0.2	0.89
CN	$h\nu^d$	3.1 ± 0.2	4.9 ± 0.3	1.5
	Δ^e	5.7 ± 0.3	8.0 ± 0.4	1.4

[a] Referred to the initial amount of substrate and determined by GC analysis. Average of at least four determinations. [b] 15 min irradiation. [c] Endoperoxide/substrate ratio = 2:1. [d] 30 min irradiation. [e] Endoperoxide/substrate ratio = 10:1.

TABLE 3. Benzaldehydes Yields in the Oxidation of Dibenzyl Sulfides 4a−c by Photochemically and Thermally Generated $^1O_2$

		benzaldehydes yields (%)^a		4-X-C_6H_4CHO/ PhCHO
X		PhCHO	4-X-C_6H_4CHO	
OMe	$h\nu^b$	5.8 ± 0.4	4.3 ± 0.3	0.74
	Δ^c	3.3 ± 0.2	2.1 ± 0.1	0.64
Me	$h\nu^b$	5.3 ± 0.4	4.4 ± 0.3	0.83
	Δ^c	2.9 ± 0.2	2.2 ± 0.2	0.77
CN	$h\nu^b$	4.0 ± 0.3	7.6 ± 0.5	1.9
	Δ^c	1.8 ± 0.1	3.6 ± 0.3	2.0

[a] Referred to the initial amount of substrate and determined by ^1H NMR analysis. Average of at least four independent determinations. [b] 15 min irradiation. [c] Endoperoxide/substrate ratio = 1:3.

The results obtained with 1,4-dimethylnaphthalene endoperoxide allow us to calculate the rate constant for benzaldehydes formation, $k_{R(ArCHO)}$, in the reaction of a dibenzylamine with $^1O_2$. Since it is known that in MeCN the endoperoxide generates $^1O_2$ in a 70% yield,[4b] from the $^1O_2$ self-decay rate constant in MeCN (1.4×10^4 s^{-1})[8] and the k_T values (Table 1) it is possible to calculate the molar amount of $^1O_2$ that actually reacts with the dibenzylamine under our conditions (see the Supporting Information). From this amount and the molar amount of benzaldehydes formed in the reactions with thermally generated $^1O_2$, the fraction of exciplex converted to benzaldehydes, in competition with intersystem crossing (see Scheme 2), can be calculated (e.g., 7% in the case of **5b**). The $k_{R(ArCHO)}$ value can then be obtained from the k_T value reported in Table 1 (details in the Supporting Information). This analysis, in the case of **5b**, gave a $k_{R(ArCHO)}$ value of 2.8×10^5 M^{-1} s^{-1}. In view of the small substituent effects on the aldehyde yields as well as on the k_T values, similar values of $k_{R(ArCHO)}$ are obtained for the other compounds (Supporting Information).

Benzyl Sulfides. Dibenzyl sulfides **5a−c** were also reacted with both photochemically (TPP) and thermally (1,4-dimethylnaphthalene endoperoxide) generated $^1O_2$. In both cases, C−S bond cleavage products (4-X-C_6H_4CHO and PhCHO) were the main reaction products accompanied by S-oxidation products and sulfur-containing cleavage products (see later). No formation of H_2O_2 was observed.

The X-C_6H_4CHO/PhCHO molar ratios, determined as in the benzylamines case, resulted very similar in photochemical and thermal oxygenation and are displayed in Table 3. In this case too, the results of the reaction with thermally generated $^1O_2$ allow us to calculate the rate constant for benzaldehyde formation following the procedure described above for the benzylamines (details in the Supporting Information). For **4b**, $k_{R(ArCHO)}$ is 3.0×10^6 M^{-1} s^{-1}. Very similar values are obtained for the other sulfides.

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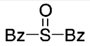
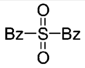
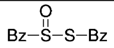
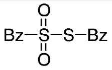
(5) Turro, N. J.; Chow, M. F. *J. Am. Chem. Soc.* **1981**, *103*, 7218.

(6) After 5 min of irradiation under the same reaction conditions, it was observed that *N*-benzylcyclohexylamine (10^{-2} M) was converted to benzylidene cyclohexylamine in 65% yield.

(7) For example, in the reaction of **5b**, H_2O_2 was formed in a 13% yield, very close to that of the two benzaldehydes (14%).

(8) Wilkinson, F.; Helman, W. P.; Ross, A. B. *J. Phys. Chem. Ref. Data* **1995**, *24*, 663.

TABLE 4. $^1O_2$-Promoted Oxidation of 4 Photosensitized by Rose Bengal

Entry	Additive	Time	Product yields (%)[a]				
			PhCHO	 $\mathrm{Bz{-}\overset{\overset{O}{\|}}{S}{-}Bz}$	 $\mathrm{Bz{-}\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}{-}Bz}$	 $\mathrm{Bz{-}\overset{\overset{O}{\|}}{S}{-}S{-}Bz}$	 $\mathrm{Bz{-}\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}{-}S{-}Bz}$
1		1 min	10 ± 1	1.2 ± 0.1	2.5 ± 0.1	0.6 ± 0.1	1.0 ± 0.1
2		5 min	18 ± 1	6.6 ± 0.3	3.0 ± 0.1	1.5 ± 0.1	0.7 ± 0.1
3		15 min[b]	44 ± 3	27 ± 2	6.2 ± 0.3	2.9 ± 0.1	1.9 ± 0.1
4	*i*-Pr$_2$NEt[c]	10 min[d]	18 ± 2	1.0 ± 0.1	4.2 ± 0.2	1.5 ± 0.1	0.8 ± 0.1

[a] Referred to the initial amount of substrate and determined by HPLC analysis. Average of at least two determinations. [b] Rose bengal was added at 5-min intervals due to its bleaching during the irradiation. The final RB concentration was 6×10^{-4} M. [c] 5×10^{-3} M. [d] Because of the $^1O_2$ quenching property of ethyl diisopropylamine, a longer irradiation time has been used to achieve the same benzaldehyde yield as in the reaction carried out in the absence of the amine (see entry 2).

Product Study in the Reaction of Dibenzyl Sulfide. A detailed product study was carried out for the photochemical reaction of dibenzyl sulfide **4** with $^1O_2$, with the aim of obtaining further mechanistic information on the oxygenation of this substrate.

The irradiation (400−600 nm) of a solution of **4** (10^{-2} M) in the presence of rose bengal[9] (10^{-4} M) as the photosensitizer in O_2-saturated dry MeCN afforded benzaldehyde, benzyl sulfoxide, benzyl sulfone, benzyl benzylthiosulfinate, and benzyl benzylthiosulfonate. No dibenzyl disulfide was detected in the reaction mixture. From the results reported in Table 4 (entries 1−3), it can be readily noted that the products distribution changes with the reaction time. In particular, the amount of dibenzyl sulfoxide formed, relative to that of benzaldehyde, increases with the progress of photooxidation (the benzaldehyde/benzyl sulfoxide ratio decreasing from 8.3 to 1.6 on going from 1 to 15 min of irradiation). An important observation, however, was that under our reaction conditions, a rapid bleaching of rose bengal took place, the solution appearing colorless after only 2 min of irradiation. A further observation was that the rose bengal color was not restored after addition of another aliquot of the sensitizer even in the dark. We suspect that an acidic compound is formed during the oxidation (presumably benzylsulfenic acid, as reported in Scheme 1, or other acids derived therefrom)[1c,f−h] and accordingly it was found that the addition of an amine (*N*-methylpiperidine, *N*,*N*-dimethylbenzylamines, or ethyl diisopropylamine) restored the original rose color of the solution.[10]

Since it is well-known that the presence of acid species catalyzes the sulfoxide formation in the $^1O_2$-promoted oxidation of sulfides,[1e,11] the relative increase in the yield of benzyl sulfoxide shown in entries 1−3 of Table 3 can be easily explained. Indeed, when the oxygenation reaction was performed in the presence of ethyl diisoproplyamine (5×10^{-3} M)[12] no bleaching of the rose bengal was observed and only a very small amount of benzyl sulfoxide was found among the reaction products (Table 4, entry 4; compare with entry 2). With use of the substituted dibenzyl sulfides, it was verified that the 4-X-C_6H_4CHO/PhCHO molar ratios (Table 3) are not influenced at all by the presence or absence of the base in the reaction medium.

The mass balance with respect to the starting material was excellent (≥95%) when benzaldehyde and sulfoxidation products (sulfone and sulfoxide) are considered. On the other hand, a poor mass balance was observed for the sulfur-containing products coming from the cleavage reaction (benzyl benzylthiosulfinate and benzyl benzylthiosulfonate). Probably under these reaction conditions the main cleavage product, sulfenic acid, is oxidized in large part to acid products that are difficult to identify and isolate.[13]

Since the pioneering work by Foote and co-workers,[14] experiments of $^1O_2$-promoted sulfoxidation in the presence of diphenyl sulfoxide have allowed considerable insight into the reaction mechanism as this species functions as an excellent trap for the persulfoxide, the key reaction intermediate. Thus, it is of interest to look at the effect of adding diphenyl sulfoxide during the oxidation of dibenzyl sulfide. In particular, we were concerned with the effect of diphenyl sulfoxide on the benzaldehyde/dibenzyl sulfone ratio. According to the mechanism in Scheme 1, trapping the persulfoxide should lower the yields of aldehyde and sulfone, but leave their ratio unchanged. Substantial formation of dibenzyl sulfoxide should also be observed.[14]

When the oxidation of dibenzyl sulfide was carried out under the usual reaction conditions but in the presence of 0.5 M diphenyl sulfoxide, a significant amount of benzyl sulfoxide was formed, as expected (Table 5, entry 2). However, the presence of diphenyl sulfoxide does not seem to significantly affect the amount of benzaldehyde formed whereas a significant decrease of benzyl sulfone is observed (the aldehyde/sulfone

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[9] For this product study, rose Bengal was preferred to TPP since it allowed us to use shorter irradiation time.

[10] The same behavior was exhibited by TPP when it was used as the photosensitizer in the photooxidation of **4**. A rapid change in color of the solution (from purple to green) was observed and the original color was restored after addition of a base.

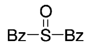
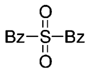
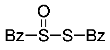
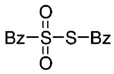
[11] (a) Clennan, E. L.; Greer, A. *J. Org. Chem.* **1996**, *61*, 4793. (b) Bonesi, S. M.; Albini, A. *J. Org. Chem.* **2000**, *65*, 4532. (c) Bonesi, S. M.; Fagnoni, M.; Monti, S.; Albini, A. *Photochem. Photobiol. Sci.* **2004**, *3*, 489.

[12] The sterically encumbered ethyl diisopropylamine was used to minimize the $^1O_2$ quenching by the amine ($k_T = 7.56 \times 10^7$ M^{-1} s^{-1} in MeCN at 22 °C; lower than the values generally shown by tertiary aliphatic amines).[8]

[13] Davis, F. A.; Billmers, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 7016.

[14] (a) Gu, C.-L.; Foote, C. S.; Kacher, M. L. *J. Am. Chem. Soc.* **1981**, *103*, 5949. (b) Liang, J.-J.; Gu, C.-L.; Kacher, M. L.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 4717.

TABLE 5. **$^1O_2$-Promoted Oxidation of Dibenzyl Sulfide in the Presence of Ethyl Diisopropylamine**

Entry	PhCHO	Product yields (%)[a]				Aldehyde/sulfone
		 $\mathrm{Bz{-}\overset{O}{\overset{\|}{S}}{-}Bz}$	 $\mathrm{Bz{-}\underset{O}{\underset{\|}{\overset{O}{\overset{\|}{S}}}}{-}Bz}$	 $\mathrm{Bz{-}\overset{O}{\overset{\|}{S}}{-}S{-}Bz}$	 $\mathrm{Bz{-}\underset{O}{\underset{\|}{\overset{O}{\overset{\|}{S}}}}{-}S{-}Bz}$	
1	15 ± 1	0.8 ± 0.1	3.6 ± 0.3	1.3 ± 0.1	0.7 ± 0.1	4.0 ± 0.2
In the presence of diphenyl sulfoxide (0.5 M)						
2	14 ± 1	11 ± 1	2.7 ± 0.1[b]	1.7 ± 0.1	0.9 ± 0.2	4.9 ± 0.1

[a] Referred to the initial amount of substrate and determined by HPLC analysis. Average of seven independent determinations. [b] Determined by GC analysis due to peak overlapping (Ph_2SO) in HPLC analysis.

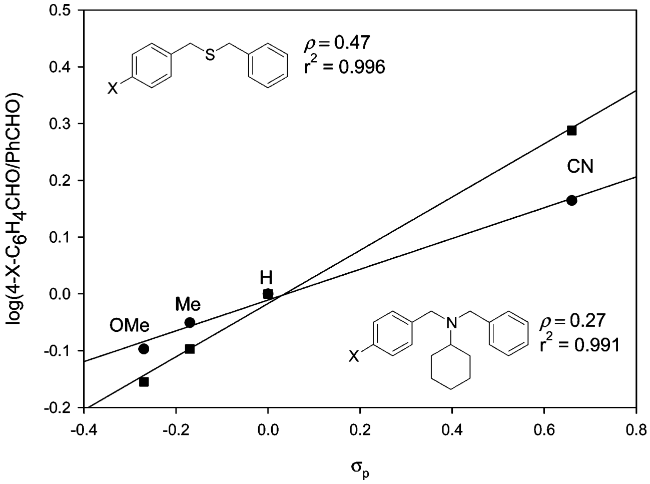


FIGURE 1. Plot of the logarithms of the molar ratios of 4-X-C_6H_4-CHO/PhCHO (average of data from both thermal and photochemical reactions) vs Hammett σ_p in the oxidation of benzyl sulfides **4a**−**c** (squares) and dibenzylcyclohexylamines **5a**−**c** (circles) with $^1O_2$.

ratio increases from 4.0 to 4.9, largely outside experimental error; compare entries 1 and 2 in Table 5).

Discussion

For the reaction of dibenzylamines with $^1O_2$, the 4-X-C_6H_4-CHO/PhCHO ratios shown in Table 2 indicate that the C−N bond cleavage reaction is favored, even though to a very small extent, by electron-withdrawing group on the aromatic ring. When the log of these ratios (average values of photochemical and thermal experiments) are plotted against the substituent Hammett σ_p values, a nice plot is obtained (Figure 1) from which a positive ρ value (+0.27) can be calculated. These results are in line with the mechanism suggested in Scheme 2. The key step in the formation of PhCHO or substituted PhCHO is the hydrogen atom transfer inside the exciplex leading to the radical couple. Since in the exciplex there is a partial transfer of charge, the hydrogen atom transfer might have some character of proton transfer, which may account for the observed positive ρ value. Collapse of the radical pair by an intracomplex electron-transfer reaction is consistent with the observation of almost identical yields of benzaldehydes and H_2O_2.

The 4-X-C_6H_4CHO/PhCHO ratios for the substituted dibenzyl sulfides are displayed in Table 3. Clearly, the C−S bond cleavage reactions of dibenzyl sulfides exhibit a structure dependence that is very close to that observed for the tertiary benzylamines. In this case too, the cleavage reaction is favored by electron-withdrawing substituents and from the Hammett plot a positive ρ value (+0.47) can be calculated, slightly larger than that found for tertiary benzylamines.[15]

According to the mechanism in Scheme 1, the key step in the oxidation leading to the C−S bond cleavage products should be the one involving the conversion of the persulfoxide into the hydroperoxysulfonium ylide (path a). If this hypothesis is correct (see later, however), it would seem that steps a in Schemes 1 and 2 are characterized by quite similar transition state structures.

Whereas this situation is certainly possible (for the persulfoxide **1** a diradical structure has also been considered[1e,16,17] and path a of Scheme 1 might have substantial hydrogen atom transfer character and exhibit a small sensitivity to electronic effects), it does not seem, however, probable on the basis of the product study carried out with dibenzyl sulfide, whose results are reported in Tables 4 and 5. Accordingly, this study provides us with two pieces of important mechanistic information. The first information is that the α-hydroperoxy sulfide (**3**), in whatever way formed, *must* produce the aldehyde exclusively by the intramolecular mechanism (Scheme 1, paths e−g). Accordingly, the other mechanism leading to the aldehyde from **3** (paths c and d) appears not to be operating to a significant extent since dibenzyl sulfoxide and dibenzyl disulfide, which should accompany the formation of the aldehyde,[1f,g] are not formed (dibenzyl disulfide) or are formed in negligible amounts (dibenzyl sulfoxide).

The second, more crucial, information is that, in the presence of 0.5 M Ph_2SO, benzaldehyde yield remains substantially constant, whereas the aldehyde/sulfone ratio increases significantly from 4.0 to 4.9, largely outside experimental error. This result is not in line with the mechanism described in Scheme 1. Accordingly, since Ph_2SO should trap the intermediate persulfoxide,[14] we would expect, as already mentioned, that the presence of Ph_2SO should lead to lower yields of both aldehyde and sulfone, whereas the aldehyde/sulfone ratio is unchanged, which is not observed. Clearly, the effect of Ph_2SO indicates that persulfoxide is an intermediate for the formation of sulfone, but *not* for the formation of the aldehyde, the C−S bond

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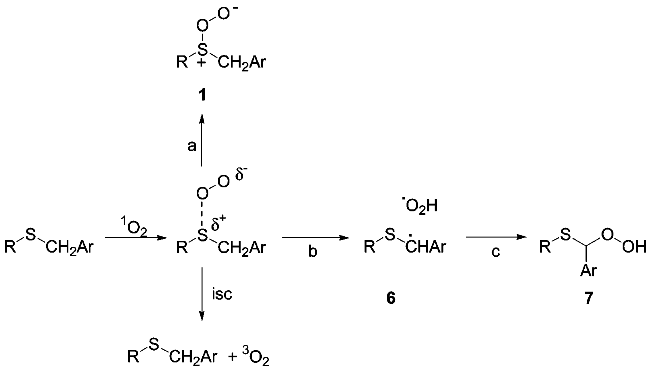
[15] In principle, also the sulfone yield should be influenced by the substituents. However, the substituent effect on the yield of sulfone can be reasonably neglected given the small yield of this product with respect to that of the aldehyde. Thus, the effects are probably within experimental error.

[16] Bonesi, S. M.; Torriani. R.; Mella, M.; Albini, A. *Eur. J. Org. Chem.* **1999**, 1723.

[17] (a) Calculations, however, favor the zwitterionic structure.[17b,c] (b) Greer, A.; Jensen, F.; Clennan, E. L. *J. Org. Chem.* **1996**, *61*, 4107. (c) Clennan, E. L. *Acc. Chem. Res.* **2001**, *34*, 875.

SCHEME 3



cleavage product. In other words, sulfone and the aldehyde *must* come from different routes.[18]

This conclusion together with the already noted strong similarity of dibenzyl sulfide structural effects with those observed for tertiary benzylamines[19] led us to suggest that the two systems react with $^1O_2$ to form benzaldehydes by a similar mechanism. Thus, as shown in Scheme 3, with sulfides too an exciplex might be formed that, in addition to undergoing intersystem crossing and being converted to persulfoxide, can also undergo an intracomplex hydrogen transfer to form the radical couple **6**, analogous to that formed from tertiary alkylamines (Scheme 2).[20]

The absence of H_2O_2 formation in the reaction of sulfides (see Results), however, suggests that the collapse of **6** does not occur by an electron-transfer reaction as proposed in the case of amines (Scheme 2, path b).[2j] Since α-alkylthio carbon radicals are much less easily oxidizable than α-dialkylamino carbon radicals, a reasonable hypothesis is that this radical is not oxidized by $HO_2^\bullet$, but undergoes a coupling reaction to form the α-hydroperoxy sulfide **7** (Scheme 3, path c). The latter may then be converted to PhCHO by the intramolecular path shown in Scheme 1 (path e).[1f,g]

The possible involvement of exciplexes in the oxygenation of sulfides by $^1O_2$ has received very scarce attention, even though these species have been called into play on several occasions, particularly by Gorman.[21,1e] The probable reason is that the most common situation in these reactions is the one where the only fate of the exciplex (in addition to undergoing intersystem crossing) is that of being converted into the persulfoxide intermediate from which all sulfoxidation chemistry generally observed ensues. It is, however, possible that with systems where a relatively weak C−H bond is adjacent to sulfur as in benzyl sulfides, an additional route (namely, path b in Scheme 3) becomes available to the exciplex that can favorably compete with conversion to persulfoxide (Scheme 3, path a).[22]

The formation of dibenzyl sulfone in the reaction of dibenzyl sulfide with $^1O_2$ shows that the exciplex, as already mentioned, can also be converted to the persulfoxide from which the sulfone is formed through the hydroperoxysulfonium ylide, as shown in Scheme 1.[23] The hydroperoxysulfonium ylide might also undergo the Pummerer rearrangement, but this process seems to be, at most, a very minor route. Accordingly, as already noted, dibenzyl sulfoxide is formed in very small amounts and the yield of aldehyde is almost insensitive to the presence of Ph_2SO.

The rate constant values for formation of benzaldehydes also deserve some comment. Considering the *p*-methyl derivatives **4b** and **5b**, $k_{R(ArCHO)}$ turns out to be about 10 times larger for the sulfide than for the amine (3.0×10^6 vs 2.8×10^5 M^{-1} s^{-1}). When the rates for total quenching of $^1O_2$ (k_T) of the two substrates are considered, 1.37×10^7 and 4.05×10^6 M^{-1} s^{-1}, respectively, it turns out that the fraction of exciplex leading to benzaldehyde is 22% for dibenzyl sulfide **4b** and 7% for dibenzylcyclohexylamine **5b**. The difference is not very large and a role might be played by steric and stereoelectronic effects that are probably different in the two systems.

Summary and Conclusions

The reactions of $^1O_2$ with dibenzyl sulfides and dibenzylcyclohexylamines in MeCN have been investigated. With dibenzylamines, the reaction leads to the formation of benzaldehyde and the secondary amine as the exclusive reaction products. Benzaldehyde is formed as the major product with dibenzyl sulfides, accompanied by the formation of S-oxidation products. Our investigation has led to the following main observations. First, a careful product study of the reaction of dibenzyl sulfide with $^1O_2$ has shown that, when the reaction is carried out in the presence of a base, dibenzyl sulfoxide is formed in almost negligible amounts with respect to benzaldehyde and sulfone. Most interestingly, addition of Ph_2SO does not significantly modify the benzaldehyde yield, whereas that of sulfone is significantly lowered. Moreover, no dibenzyl disulfide is present among the sulfur-containing cleavage products. Clearly, these results do not fit the mechanism generally accepted (Scheme 1) to explain the formation of cleavage products in the oxidation of sulfides by $^1O_2$, but force us to suggest that dibenzyl sulfone and benzaldehyde are formed by different routes. The second observation comes from a study of the reactions of *p*-substituted dibenzyl sulfides (**4a**−**c**) and dibenzylcyclohexylamines (**5a**−**c**), which shows that the cleavage reactions in the two systems respond in a similar way to electronic effects, the cleavage being favored by electron-withdrawing substituents in both cases. The effects are, however, very small as indicated by the ρ values

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(18) (a) A rewiewer has suggested that the presence of 0.5 M diphenyl sulfoxide (molar fraction <0.05) might significantly vary the polarity of the medium, thus influencing the partition of the hydroperoxysulfonium ylide **2** between benzaldehyde and benzyl sulfone (Scheme 1). This possibility, however, appears very unlikely when it is considered that the $E_T(30)$ polarity value of solutions of DMSO in MeCN remains practically the same as that of pure MeCN up to 0.1 DMSO molar fraction.[18b,c] (b) Bosch, E.; Rosés, M. *J. Chem. Soc., Faraday Trans.* **1992**, *88*, 3541. (c) Rosés, M.; Ràfols, C.; Ortega, J.; Bosch, E. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1607.

(19) In this respect, it can also be noted that very similar intramolecular kinetic deuterium isotope effects have been found in the $^1O_2$ promoted benzaldehyde formation from benzyldimethylamine (3.5)[2j] and benzyl ethyl sulfide (2.95)[1e] in MeCN.

(20) It must be acknowledged that the proposal that the C−S cleavage products, in the oxidation of benzyl sulfides, might come from a route parallel to that leading to sulfoxides and sulfones involving exciplexes formation has been already put forward by the Albini group.[1e] However, no consideration has been given later to this hypothesis in a work by the same group on the same subject.[1h] Apart from this, the mechanism following exciplex formation proposed by Albini and co-workers is different from that presented here.

(21) (a) Gorman, A. A. *Adv. Photochem.* **1992**, *17*, 218. (b) Clennan, E. L.; Oolman, K.; Yang, K.; Wang, D.-X. *J. Org. Chem.* **1991**, *56*, 4286.

(22) It cannot be excluded, however, that formation of the exciplex occurs in a parallel path along with the formation of persulfoxide. Generally, the exciplex undergoes intersystem crossing exclusively, but with substrates with relatively weak α C−H bonds, it might lead to products.

(23) The fact that in the presence of diphenyl sulfoxide the yield of benzyl sulfoxide becomes close to that of benzaldehyde (Table 5) shows that the conversion of exciplex to persulfoxide is, at least, as important as that leading to benzaldehyde.

(+0.47 for sulfides and +0.27 for amines). On the basis of the above results, it is suggested that the $^1O_2$-promoted C−S bond cleavage in benzyl sulfides occurs by the same mechanism as that already proposed for the corresponding C−N bond cleavage reactions in benzylamines: Formation of an exciplex between the substrate and $^1O_2$ which undergoes an intracomplex hydrogen transfer leading to a radical pair. With benzylamines the radical pair undergoes an ET process leading to an iminium cation from which benzaldehyde can be formed (Scheme 2). With sulfides, the radical pair instead can collapse to the α-hydroperoxy sulfide **3** (α-alkylthio carbon radicals are much less easily oxidizable than α-dialkylamino carbon radicals) from which benzaldehyde can be formed as described in Scheme 1, path e. Part of the exciplex can also be converted into the persulfoxide **1**, which leads to the sulfone through the hydroperoxysulfonium ylide **2**, as shown in Scheme 1. It also has been determined that the fraction of exciplex that is converted to aldehyde is quite close for the two systems (ca. 20% with sulfides and ca. 7% with amines).

Experimental Section

Materials. Commercially available benzyl sulfide (**4**) was purified by silica gel chromatography (hexane/ethyl acetate 9:1) and then recrystallized from hexane to eliminate traces of benzyl disulfide. Phenyl sulfoxide was commercially available and purified by recrystallization from hexane. Ethyl diisopropylamine was commercially available and distilled before use. The photosensitizers rose bengal disodium salt and tetraphenylporphyrin were commercially available and were used as received. 1,4-Dimethylnaphthalene endoperoxide was prepared according to a literature procedure.[5] Benzaldehyde, 4-methoxybenzaldehyde, 4-methylbenzaldehyde, 4-cyanobenzaldehyde, benzyl sulfoxide, and benzyl sulfone were commercially available whereas benzyl benzylthiosulfinate[24] and benzyl benzylthiosulfonate[25] were prepared according to literature procedures. Acetonitrile (HPLC plus grade) was refluxed (3 h) and then distilled over calcium hydride. CD_3CN (99.8% D atom) was distilled over calcium hydride and stored over molecular sieves.

General Procedure for the Synthesis of Benzyl Sulfides 4a−c. Benzyl sulfides **4a**−**c** were prepared by reaction of benzyl mercaptane with 4-methoxybenzyl chloride, 4-methylbenzyl chloride, and 4-cyanobenzyl bromide, respectively. A 20 mL solution of the 4-substituted benzyl halide (15 mmol) in EtOH was slowly added to a stirred solution of benzylmercaptane (2.0 g, 16 mmol) and KOH (1.0 g, 18 mmol) kept at 80 °C under Ar atmosphere. The mixture was then refluxed for 2 h, after which it was cooled to room temperature, poured into 200 mL of water, and extracted with three fractions (100 mL each) of chloroform. The combined organic layers were washed with 25% aqueous KOH, water, and brine and dried over anhydrous $MgSO_4$. After rotary evaporation, the residue was purified by flash chromatography.

General Procedure for the Synthesis of Dibenzylcyclohexylamines 5a−c. Dibenzylcyclohexylamines **5a**−**c** were prepared by reaction of benzylcyclohexylamine[26] with 4-methoxybenzyl chloride, 4-methylbenzyl chloride, and 4-cyanobenzyl bromide, respectively. The benzyl halide (8.3 mmol) in MeCN (5 mL) was slowly added to a stirred solution of benzylcyclohexylamine (1.0 g, 5.3 mmol) and K_2CO_3 in MeCN (20 mL) at room temperature. The mixture was then refluxed for 6 h, after which it was cooled to room temperature, poured into 40 mL of water, and extracted with three fractions (50 mL each) of diethyl ether. The combined organic layers were washed with water and brine and dried over anhydrous $MgSO_4$. After rotary evaporation, the residue was purified by flash chromatography (silica gel; gradient from hexane to hexane/ethyl acetate 4:1).

Determination of $^1O_2$ Total Quenching Rate Constants (k_T). $^1O_2$ was produced in MeCN by energy transfer to O_2 from the triplet state of phenalenone (7.0×10^{-5} M), generated by excitation at 355 nm from a Nd:YAG laser (pulse width ca. 7 ns and energy <3 mJ per pulse). The phosphorescence emission of $^1O_2$ emerging from the cuvette passed through a cutoff filter at 1050 nm and three pieces of gelatin cutoff filter at 870 nm and was detected by a germanium diode detector (5 mm diameter). After amplification with a two-stage homemade amplifier (ca. 100 MHz bandwidth, 14 dB), the output of the diode was fed into a digital signal analyzer and computer stored and analyzed.[27] Rate constants for the total quenching of $^1O_2$ (k_T) were determined from the decrease of $^1O_2$ emission lifetime in O_2-saturated solvent, in the presence of various amounts of substrates ($0-8 \times 10^{-3}$ M). All measurements were carried out at 22 ± 2 °C (some examples are reported in the Supporting Information).

Oxidation of Amines 5a−c by Photochemically Generated Singlet Oxygen. Photooxygenation reactions were carried out in a photoreactor equipped with ten 4500−6000 Å fluorescence lamps (14 W each). A 4-mL sample of a solution containing the dibenzylcyclohexylamine (10^{-2} M) and TPP (10^{-4} M, added as 0.2 mL solution in chloroform) in dry MeCN was irradiated at 25 °C in a thermostated jacketed tube for 15 (**5a**,**b**) or 30 min (**5c**) under slight oxygen bubbling. Further aliquots of TPP (each equal to the initial amount) were added in order to replace the bleached photosensitizer. An internal standard (4-methylbenzophenone) was added. Products analysis was carried out by GC and GC-MS (comparison with authentic specimens). Blank experiments, carried out under the same reaction conditions but in the absence of TPP or O_2, showed the absence of reaction products.

The amount of H_2O_2 was quantitatively determined by titration with iodide ion; the solution was treated, after dilution, with an excess of KI and a few drops of AcOH. The amount of I_3^- formed was determined from UV spectra ($\epsilon = 2.50 \times 10^4$ M^{-1} cm^{-1} at $\lambda_{max} = 361$ nm).[28] Blank experiments, performed in the absence of the substrate, showed no formation of H_2O_2.

Oxidation of amines 5a−c by Thermally Generated Singlet Oxygen. A 2-mL sample of amine (10^{-2} M) and 1,4-dimethylnaphthalene endoperoxide (2×10^{-2} M for **5a**,**b** and 0.1 M for **5c**) in dry MeCN was heated at 40 °C (water bath) in the dark for 4 h. An internal standard (4-methylbenzophenone) was added, and the mixture was analyzed by GC and GC-MS. No product formation was observed in blank experiments, carried out in the absence of 1,4-dimethylnaphthalene endoperoxide and in oxygen-saturated solutions.

Oxidation of Sulfides 4a−c by Photochemically Generated Singlet Oxygen. Photooxygenation reactions were carried out in a photoreactor equipped with ten 4500−6000 Å lamps (14 W each). A 2-mL sample of a solution containing the sulfide (10^{-2} M) and TPP (10^{-4} M, added as 0.1 mL solution in $CDCl_3$) in dry O_2-saturated CD_3CN was irradiated at 25 °C in a thermostated jacketed tube for 15 min. An internal standard (bibenzyl) was added. Product analysis was carried out by ^1H NMR spectroscopy (by GC analysis, the products benzyl benzylthiosulfinate and benzyl benzylthiosulfonate undergo thermal degradation forming a substantial amount of benzaldehyde making this analytical method inappropriate). When benzyl 4-methylbenzyl sulfide (**4b**) was irradiated for 30 min under the same reaction conditions but in the presence of ethyl diisopropylamine (5×10^{-3} M), the 4-methylbenzaldehyde/

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[24] Furukawa, N.; Morishita, T.; Akasaka, T.; Oae, S. *J. Chem. Soc., Perkin Trans. 2* **1980**, 432.

[25] Boekman, K.; Voegtle, F. *Chem. Ber.* **1981**, *114*, 1048.

[26] Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595.

[27] Elisei, F.; Aloisi, G. G.; Lattarini, C.; Latterini, L.; Dall'Acqua, F.; Guiotto, A. *Photochem. Photobiol.* **1996**, *64*, 67.

[28] Fukuzumi, S.; Kuroda, S.; Tanaka, T. *J. Am. Chem. Soc.* **1985**, *107*, 3020.

benzaldehyde molar ratio appeared to be unaffected by the presence of the amine. Blank experiments, carried out under the same reaction conditions but in the absence of TPP or O_2, showed the absence of detectable products.

Oxidation of Sulfides 4a−c by Thermally Generated Singlet Oxygen. A 1-mL sample of sulfide (10^{-2} M) and 1,4-dimethylnaphthalene endoperoxide (6.7×10^{-3} M) in CD_3CN was heated at 40 °C (water bath) in the dark for 4 h. An internal standard (bibenzyl) was added, and the mixture was analyzed by ^1H NMR spectroscopy. Blank experiments, carried out in the absence of 1,4-dimethylnaphthalene endoperoxide and in oxygen-saturated solutions, showed the absence of reactivity.

Oxidation of Benzyl Sulfide (4) by Photochemically Generated Singlet Oxygen. Photooxygenation reactions were carried out in a photoreactor equipped with four 4500−6000 Å lamps (14 W each). A 4-mL sample of a solution containing the sulfide (10^{-2} M) and rose bengal (10^{-4} M) in dry O_2-saturated MeCN was irradiated at 25 °C in a thermostated jacketed tube for 1, 5, and 15 min. An internal standard (4-methylbenzophenone) was added. Product analysis was carried out by HPLC (C18 column, solvent gradient from MeOH/H_2O 75:25 to MeOH). Photoreactions in the presence of ethyl diisopropylamine (5×10^{-3} M) alone or with phenyl sulfoxide (0.5 M) were carried out under the conditions reported above by irradiating the solution with six lamps for 5 min. In the reactions with diphenyl sulfoxide the intense peak of this compound superimposed with that of dibenzyl sulfone, therefore the quantitative analysis of the latter was carried out by GC. Blank experiments, carried out under the same reaction conditions but in the absence of RB or O_2, showed the absence of detectable products. Irradiation of ethyldiisopropylamine under the same reaction conditions but in the absence of **5** showed the absence of any detectable reaction product.

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Supporting Information Available: Characterization and spectral properties of compounds **4a−c** and **5a−c**, determination of $k_{r(ArCHO)}$ rate constants, and dependence of observed rate constants of $^1O_2$ quenching on concentration of **4**, **4a**, **5a**, and i-Pr_2NEt in MeCN. This material is available free of charge via the Internet at http://pubs.acs.org.

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