A New Mechanism for Oxidative C−S Bond Cleavage during Reactions of Singlet Oxygen with Organic Sulfides: Electronically Dictated Reaction Selectivity in the Persulfoxide Intermediate

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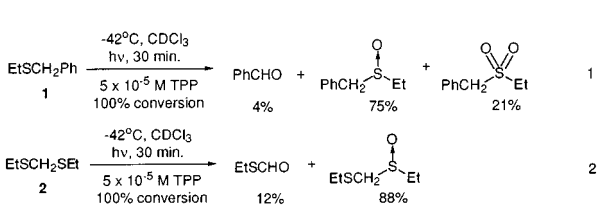
Oxidative cleavage of carbon−sulfur bonds during reactions of organic sulfides with singlet oxygen was first reported by Corey and Ouannes in 1976.[1] Cleavage products are formed in substantial amounts in the photooxidations of benzylic sulfides and in five-membered rings[2] but are only formed in trace amounts, or are completely absent, in the photooxidations of other sulfides.[3] We report here the results of a study of the effect of anion stabilizing groups (−CO_2R) and radical stabilizing groups (−SR) on the photooxidations and subsequent cleavage reactions of sulfides **1**−**8**. These results suggest that the cleavage reactions occur via both radical- and anion-mediated Pummerer rearrangements (Scheme 1) and that the Pummerer product, the α-hydroperoxy sulfide, **C**, decomposes by both unimolecular and bimolecular processes. In addition, our results provide the first insight into the structural and environmental factors which dictate the choice, by the hydroperoxy sulfonium ylide, **B,** of reaction channel (a, b, or c in Scheme 1).

Photooxidations were conducted by irradiation of $CDCl_3$ solutions[4] 0.05 to 0.06 M in the α-substituted sulfide and 10^{-4} M in tetraphenylporphyrin (TPP) under a constant stream of O_2 with a 600 W tungsten lamp at 23 °C through a saturated 12 M $NaNO_2$ filter solution for 10−20 min. The reactions were monitored by ^{1}H NMR and the products isolated by chromatography and identified by spectroscopic comparison to independently synthesized materials. Identical results were obtained in the reactions of 0.1 M solutions of the sulfides with 3 equiv of 1,4-dimethylnaphthalene endoperoxide as a chemical source of singlet oxygen. Control reactions also demonstrated that the product ratios (Table 1) were essentially independent of conversions between 20 and 70%.

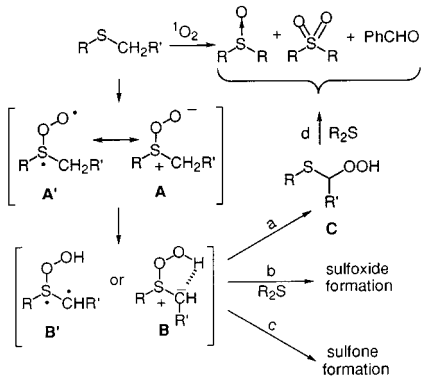
Pummerer cleavage products were observed in the reactions of singlet oxygen with all eight of the sulfides examined. (Table 1) The sulfides can be placed into one of three groups based upon the identities of their sulfur containing fragmentation products: (1) those that give exclusively thiosulfinate (**1** and **2**), (2) those that give exclusively disulfide (**3**, **4**, **5**, and **6**), and (3) those that give a mixture of thiosulfinate and disulfide products (**7** and **8**).

The sulfides which give exclusively thiosulfinate fragmentation products, **1** and **2**, also give large amounts of both the cleavage and sulfide oxidation products (sulfoxides and sulfones). Suppression of the Pummerer and enhancement of the sulfide oxidation products are observed when these substrates are photooxidized at low temperature. (eqs 1 and 2)

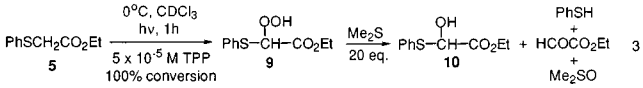


(1) Corey, E. J.; Ouannes, C. *Tetrahedron Lett.* **1976**, 4263−4266.
(2) Takata, T.; Ishibashi, K.; Ando, W. *Tetrahedron Lett.* **1985**, *26*, 4609−4612.

Scheme 1



Photooxidations of the sulfides, which give exclusively the disulfide fragmentation products, **3**, **4**, **5**, and **6**, also give substantial amounts of cleavage products at room temperature. (Table 1) The α-hydroperoxy sulfides, **C** in Scheme 1, were directly observed in the reaction mixtures from photooxidations of sulfides **5** and **6**.[5−7] In these cases the large phenyl and *tert*-butyl groups in the substrates sterically obstruct reduction of **C** (vide infra). Photooxidations of **3**, **5**, and **6** at low temperatures completely suppressed both sulfide oxidation and cleavage product formation to give a 100% yield of the α-hydroperoxy sulfide, **C**, in stark contrast to the low-temperature photooxidations of **1** and **2**. (eq 3) In addition, **9** formed in the photooxidation of **5** could be quantitatively reduced to the α-hydroxy sulfide, **10**.[8]



These results suggest that there are two competing pathways for decomposition of the α-hydroperoxy sulfide as depicted in Scheme 2. The intermolecular process involves reduction of the α-hydroperoxy sulfide with a molecule of starting material, formation of the α-hydroxy sulfide, **D**, cleavage to the thiol and carbonyl compound, and subsequent air oxidation of the thiol to the disulfide. The intramolecular process involves formation of an oxothiiranium ion, **E**, which, in analogy to thiiranium ions, can collapse to a α-hydroxy sulfoxide, **F**, by hydroxide attack at either carbon or sulfur.[9] The α-hydroxy sulfoxide decomposes to a sulfenic acid, **G**, and the carbonyl fragmentation product. The sulfenic acid can either react with another sulfenic acid to form its anhydride, the thiosulfinate, or with a thiol formed in the intermolecular process to form the disulfide.[10]

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(4) $CDCl_3$ used in this study was protected from contact with the atmosphere by storage under nitrogen at 10 °C, and the reaction mixtures were stirred with Na_2CO_3 (approx. 100 mg/2 mL $CDCl_3$) prior to irradiation.
(5) The isolation of an α-hydroperoxy sulfide during photooxidation of a thiazolidene derivative was previously reported by Ando, W.; Ito, K.; Takata, T. *Tetrahedron Lett.* **1982**, *23*, 3909−3912.
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(8) **9**: ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 1.28 (t, J = 7.1 Hz, 3H, CH_3CH_2), 4.23 (q, J = 7.1 Hz, 2H, CH_3CH_2), 5.68 (s, 1H, *CH*OOH), 7.36−7.60 (m, 5H, Ph), 9.54 (bs, 1H, OOH). **10** ($CDCl_3$, 400.13 MHz) δ 1.26 (t, J = 7.3 Hz, 3H, CH_3CH_2), 3.58 (d, J = 9.5 Hz, 1H, OH), 4.20 (q, J = 7.3 Hz, 2H, CH_3CH_2), 5.40 (d, J = 9.5 Hz, *CH*OH), 7.31−7.51 (m, 5H, Ph).
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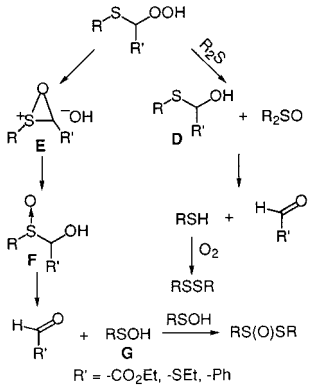
Table 1. Product Ratios in the Photooxidations of Sulfides 1−8[a]

sulfide	carbonyl fragmentation/sulfur oxidation	sulfur fragmentation
$EtSCH_2Ph$ **1**	PhCHO (50), $PhCH_2S(O)Et$ (41), $PhCH_2SO_2Et$ (9)	$EtS(O)SEt$ (100)[e]
$EtSCH_2SEt$ **2**	EtSCHO (67), $EtS(O)CH_2SEt$ (33)	$EtS(O)SEt$ (100)[e]
$EtSCH_2CO_2Et$ **3**	$HC(O)CO_2Et$ (52), $EtS(O)CH_2CO_2Et$ (37) $EtSO_2CH_2CO_2Et$ (11)	EtSSEt (100)
$EtSCH(CH_3)CO_2Me$ **4**	CH_3COCO_2Me (30), $EtS(O)CH(CH_3)CO_2Me$ (62)[b] $EtS(O)_2CH(CH_3)CO_2Me$ (8)	EtSSEt (100)
$PhSCH_2CO_2Et$ **5**	$HC(O)CO_2Et$ (20), $PhS(O)CH_2CO_2Et$ (23) $PhSCH(OOH)CO_2Et$ (57)	PhSSPh (100)
t-$BuSCH_2CO_2Et$[c] **6**	$HC(O)CO_2Et$ (35), t-$BuSCH_2CO_2Et$ (41) *t*-$BuSCH(OOH)CO_2Et$ (24)	tBuSStBu(100)
$(EtS)_2CHCOCH_3$[d] **7**	$EtSC(O)C(O)CH_3$ (100)	$EtSS(O)Et$ (67) EtSSEt (33)
$(EtS)_2CHCO_2CH_3$[d] **8**	$EtSCOCO_2CH_3$ (100)	$EtSS(O)SEt$ (75) EtSSEt (25)

[a] All photooxidations in $CDCl_3$ to approximately 20% conversion. The products are formed quantitatively with only traces of byproducts and the material balances were >95% in all cases. The product ratios in parentheses are an average of 2 or 3 ^1H NMR determinations using acetone or fluorene as internal standards and are good to ±1−2%. The sulfur fragmentation products and the carbonyl compounds were formed in the anticipated stoichiometric ratios. [b] Formed in a diastereomer ratio of 2.1/1.0. [c] Isobutylene and presumably a sulfinic acid ($HOS(O)CH_2SEt$) also formed in this reaction.[18] [d] A small amount of unidentified products were also formed which were not sulfoxide, mono-sulfone, or bis-sulfoxide. [e] $EtSO_2SEt$, the product of further oxidation of EtS(O)SEt, was present in reaction mixtures at high conversions.

Scheme 2



The choice of inter- or intramolecular cleavage of the α-hydroperoxy sulfide appears to be electronically dictated. Electron-withdrawing groups, such as the carbonyl groups in **3**, **4**, **5**, and **6**, destabilize the oxothiiranium ion, **E**, and direct the cleavage along the intermolecular pathway and give only disulfide fragmentation products. The phenyl group in **1** and the −SEt group in **2** promote the intramolecular process, giving the thiosulfinate exclusively, while both the carbonyl and −SEt groups in **7** and **8** allow both reaction pathways to occur concurrently.

The dramatically different temperature dependence exhibited by sulfides with radical-stabilizing substituents, **1** and **2**, in comparison to those with anion-stabilizing substituents, **3**, **5**, and **6**, can be rationalized if hydroperoxy sulfonium ylide formation can occur by two competitive pathways; hydrogen abstraction and proton transfer. Both pathways are reasonable since the persulfoxide precursor of the hydroperoxy sulfonium ylide can be depicted as either a zwitterion, **A**, or as a diradical, **A′**, and in fact is most likely a hybrid of these two limiting resonance forms.[11] Most of the chemistry of the persulfoxide is dominated by the dipolar form (i.e., nucleophilic oxygen transfer),[12] although the reactivities of benzyl ethyl sulfides have recently been attributed to their diradical forms.[13,14] We suggest (Scheme 1) that only proton transfer occurs in sulfides with anion stabilizing substituents to give **B**, while both proton transfer and hydrogen abstraction to give **B** and **B′** occurs in sulfides with radical-stabilizing substituents.

Extensive delocalization of the negative charge in **B** with anion-stabilizing groups, weakens the hydrogen bond, allowing the Pummerer rearrangement (path a) to occur with exclusion of sulfoxide formation via path b (Scheme 1). Consequently, the effect of decreasing temperature in the reactions of **3**, **5**, and **6** is to suppress sulfoxide formed by the reaction of **C** with substrate (path d in Scheme 1). In sulfides with radical-stabilizing substituents the transition state from **A** leading to the hydrogen bonded **B** has a lower energy of activation than that from **A′** leading to **B′** and is preferred at lower temperatures. However, **B** containing radical-stabilizing groups has a more localized negative charge than when substituted with anion-stabilizing groups and a stronger hydrogen bond and prefers to react via path b in Scheme 1. Consequently, the increase in the population of **B** relative to **B′** with decreasing temperatures is accompanied by enhanced sulfoxide formation.

A high level ab initio computational study provides corroborating evidence for this new Pummerer rearrangement mechanism.[15] (Scheme 1) The lowest-energy conformer of dimethylhydroperoxy sulfonium ylide was located and shown to adopt a hydrogen-bonded structure with a O−H−α-carbon distance of 3.15 Å at the MP2/6-311+G(2df) computational level.[15] In addition, a transition state connecting the hydroperoxy sulfonium ylide, **B**, to the α-hydroperoxy sulfide, **C**, was also located. We envision hydroperoxy sulfonium ylide, **B′**, as an *isomer* of **B**, without the hydrogen bond and with a different structural arrangement of the hydroperoxy proton.

In conclusion, substituents at the α-positions of sulfides dictate the choice of reaction pathway available to the hydroperoxy sulfonium ylide (a, b, or c in Scheme 1) and also play a critical role in the selection of either an inter- or intramolecular pathway for decomposition of the Pummerer products. In addition, for the first time two different hydroperoxy sulfonium ylides have been invoked, which can react by Pummerer rearrangement, undergo reduction with sulfide to give sulfoxide,[16] or rearrange by a 1,2-hydroxy shift to ultimately give a sulfone.[17]

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