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OXIDATION OF DISULFIDES
WITH THE TRIPHENYL PHOSPHITE OZONIDE

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Sensitized photooxidation reactions in biological systems, termed photodynamic action, have received considerable attention from biological scientists. Recently chemists have turned their attention to these reactions with primary emphasis on the mechanistic aspects of the reactions. Foote[2] and Hastings and Wilson[3], among others have suggested that some of these reactions may involve singlet oxygen.

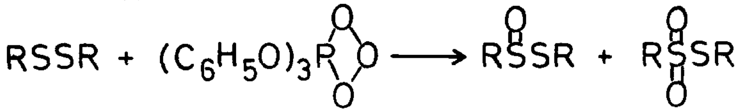
We have shown that triphenyl phosphite ozonide[4] is capable of giving singlet oxygen and that it is a convenient reagent for accomplishing this type of oxygenation.[5-7] This reagent offers the added advantage that the conditions for its use are extremely mild and no photochemical process is involved, thus reducing the possibility that first-produced materials are further transformed under the reaction conditions. The triphenyl phosphite ozonide is thus an attractive reagent for studying the possible involvement of singlet oxygen in photodynamic action.

A number of biologically important molecules containing the disulfide bond are known to be suceptible to photodynamic action. Weil et al[8] have shown that cystine and insulin[9] are photooxidized in the presence of methylene blue. Likewise, the photolysis of α-lipoic acid (1,2-dithiolane-3-valeric acid), which is believed to be responsible for the oxidative decarboxylation of α-keto acids[10-13] and has also been assigned an important role in photosynthesis[14-16], has also been studied.[14,17]

We have sought to determine whether singlet oxygen plays a role in these important oxidations by studying initially the reaction of the triphenyl phosphite ozonide with simple alkyl disulfides. In fact very little work on photosensitized oxidation of simple non-cyclic disulfides has been reported.

The observation[18] that diphenyldisulfide is inert to photosensitized oxidation seems to be the only report in this area. In separate experiments, to be reported elsewhere, we have found that photosensitized oxidation of these disulfides leads to the same products as described below from the triphenyl phosphite ozonide reaction.

We have found that treatment of dimethyl disulfide and diethyldisulfide with the triphenyl phosphite ozonide leads to oxidation of the disulfides. The initially observed reaction product contains both the thiolsulfinate and the thiolsulfonate in an approximately 10:1 ratio, respectively. Upon standing at room temperature, the reaction mixture changes composition until after 5-6 days the ratio becomes approximately 10:1 in favor of the thiolsulfonate.



$$RSSR + (C_6H_5O)_3P\overset{O}{\underset{O}{<}}O \longrightarrow R\overset{O}{S}SR + R\overset{O}{\underset{O}{S}}SR$$

In a typical experiment the ozonide was prepared by adding a CH_2Cl_2 solution of triphenyl phosphite to a saturated solution of ozone in CH_2Cl_2 at -78°C. The solution was then purged of excess ozone and a solution of the disulfide in CH_2Cl_2 added rapidly. The products were identified by comparing GPC retention times and NMR τ values with those of authentic samples. Control runs indicated that the oxidations were not caused by residual ozone. In a typical oxidation using diethyldisulfide, the reaction mixture, sampled at -30°C, showed a 55% yield of the thiolsulfinate and a 5% yield of the thiolsulfonate. At room temperature, the yield distribution was 37% thiolsulfinate and 13% thiolsulfonate. After standing at room temperature for six days the distribution was 2% thiolsulfinate and 48% thiolsulfonate.

In a separate experiment, using low temperature NMR, it was determined that dimethyldisulfide is converted to thiolsulfinate in appreciable yield at the lowest temperature achieved, namely -52°C. Beginning at -30°C the thiolsulfonate is also present.

While thiolsulfinates have been observed to undergo thermal disproportionation reactions, the rate at which thiolsulfinate is converted to thiolsulfonate in the reaction described appears to be faster than the usual thermal rate of disproportionation.[19] In separate experiments we have found that the observed rate of thiolsulfinate loss is not caused by ozonized CH_2Cl_2, triphenyl phosphate or phenol. Phenol was tested since the triphenyl phosphite is known to slowly hydrolyze to give phenol. Thiolsulfinate is not itself appreciably oxidized by the triphenyl phosphite ozonide or the singlet oxygen produced in the decomposition of the ozonide.

The preparative value of this reaction is shown by the oxidation of di-*tert*-butyl disulfide to the corresponding thiolsulfinate. Using the procedure described above the disulfide was converted to the thiolsulfinate in 48% isolated yield. The thiolsulfinate was identified by comparing its physical constants with literature[20] values. The resistance of di-*tert*-butyl disulfide to oxidation to the thiolsulfinate is shown by the report[21] that this disulfide is not oxidized by peracetic acid, a reagent which readily converts other disulfides to their corresponding thiolsulfinates.

Two possibilities need to be considered for the mechanism of the oxidation. The oxidation could be due to singlet oxygen liberated from the triphenyl phosphite ozonide as reported earlier for olefin substrates.[5-7] The similarity to photosensitized oxidation results would tend to support this view. A singlet oxygen mechanism has been suggested for the photosensitized oxidation of sulfides to sulfoxides.[22] On the other hand the appearance of oxidation products below the normal temperature of decomposition of the ozonide indicates that a direct bimolecular reaction of the ozonide and disulfide also needs to be considered. A direct donation of oxygen from the ozonide to tetramethylethylene has been reported by Bartlett and Mendenhall.[23] It is also possible that the disulfide could catalyze the decomposition of the ozonide permitting singlet oxygen oxidation at a lower temperature. We have measured the oxygen evolved when a CH_2Cl_2 solution of dimethyldisulfide is added to the ozonide at -78°C. While only 11% of the theoretical amount of oxygen was evolved at -78°C, the ozonide is stable at this temperature in the absence of added substrate. The possibility of induced decomposition of the ozonide needs to be considered further.

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