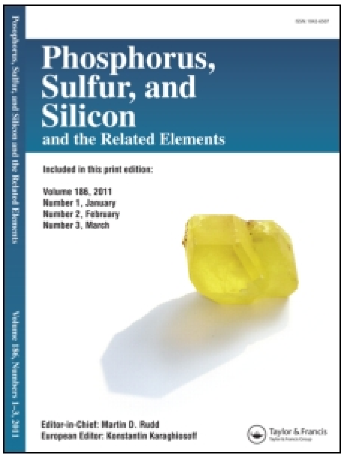

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THIONO COMPOUNDS. 9. USE OF SPECTRA TO STUDY INTERMEDIATES IN THE OXIDATION OF THIONO PHOSPHORUS, COMPOUNDS

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THIONO COMPOUNDS. 9. USE OF SPECTRA TO STUDY INTERMEDIATES IN THE OXIDATION OF THIONO PHOSPHORUS COMPOUNDS[1,2]

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Intermediates in the oxidation by *m*-chloroperoxybenzoic acid (MCPBA) of 13 structurally different thiophosphoramides and phosphorothioates were studied at −25°C to 0°C using NMR, EPR, UV, IR and Raman spectra. The lifetimes of intermediates ascertained by NMR varied from a few minutes to many hours at the same temperature and were longer for thiono esters than for amides, for aryl than for alkyl constituents, and for electron-donating substituents on aryl groups than for electron-withdrawing groups. The major ^{31}P NMR peaks for all intermediates appeared in the same region, about midway between the resonances of the $\geqslant P(S)$ starting materials and the $\geqslant P(O)$ products, indicating close structural similarity to one another for the intermediates; the range of 13–33 ppm for the major peaks indicates that the intermediates are tetracoordinate and supports phosphonium polysulfide structures for them of the type R_3PS_x (**26**, Scheme 1), or perhaps R_3POS_x. UV spectra also afforded support for polysulfide structures, since typical absorption develops and then disappears. Raman, ^{31}P NMR, and UV spectra are consistent with longer-term presence of bisphosphonium species (e.g. **25**, from reactions of **26**; Scheme 1). EPR spectra gave no indication of homolysis.

Key words: Phosphorothioates, Raman Spectra, Infrared Spectra, Thionophosphorus, NMR Spectra, Thiophosphoramides

INTRODUCTION

Phosphorothioates, such as the insecticide parathion (**1**, R = Et, Ar = 4-$NO_2C_6H_4$), are widely used. Intermediates formed in the oxidation of these phosphorothioates are important, since they evidently are responsible for producing adverse biological effects encountered with phosphorothioates.[3a] Neal and co-workers have proposed Equation (1) for oxidation both by enzyme systems and peroxy acid models.[3a] Phosphoxathiiranes with a structure like that of **3** have been suggested as intermediates in other circumstances.[3] One phosphoxathiirane has been reported,[4] but a correction appeared,[5] and so far as we are aware no intermediates actually have been observed in reactions like that shown by Equation (1); indeed, the oxidation of phosphinothioates,

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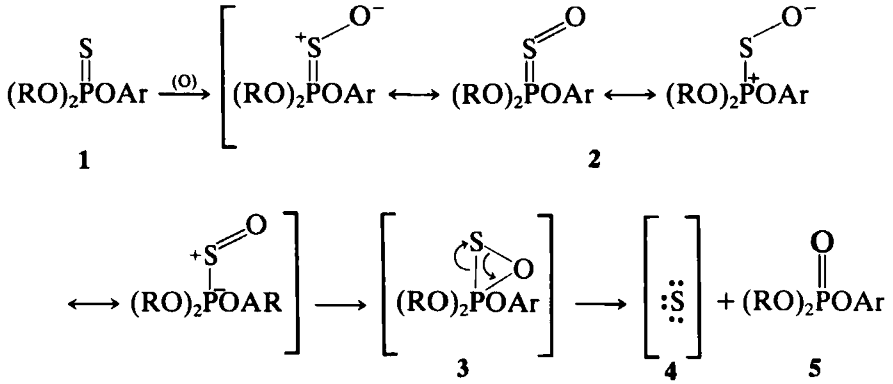
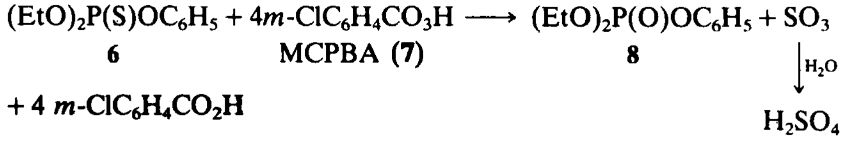


(1)

$R^1R^2P(S)OR^3$, by peroxy acids at 0°C "was complete within 20 sec with no NMR signals other than starting materials and products being detected".[6] The improbability that singlet sulfur (**4**) was extruded (Equation (1)) was demonstrated, at least in model oxidations, earlier by our failure to trap it with cyclohexane, or with the double bond in an alkenyl phosphorothioate (which also excluded triplet sulfur).[7]

Our studies of the oxidation of thiono compounds have been focused on three points. The first was whether intermediates might in fact be detected. We answered this question affirmatively in a preliminary communication.[7] We reported that oxidation of O,O-diethyl O-phenyl phosphorothioate (**6**) with *m*-chloroperoxybenzoic acid, **7** (hereafter MCPBA), at 25°C revealed no intermediates detectable by NMR in the formation of the phosphate **8** (Equation (2)).



$$\underset{\mathbf{6}}{(EtO)_2P(S)OC_6H_5} + \underset{\text{MCPBA }(\mathbf{7})}{4m\text{-}ClC_6H_4CO_3H} \longrightarrow \underset{\mathbf{8}}{(EtO)_2P(O)OC_6H_5} + SO_3 \xrightarrow{H_2O} H_2SO_4 \qquad + 4\,m\text{-}ClC_6H_4CO_2H \tag{2}$$

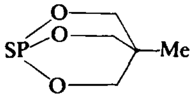
However, oxidation of **6** at −25°C led to an intermediate with a ^{31}P-NMR peak at δ 29.8 (cf. Expts 1 and 2 of Table I). This peak was found between those of the $\geqslant$P(S) starting material (**6**, δ 65.9) and the $\geqslant$P(O) product (**8**, $\delta = -4.1$). As one would expect if it were due to an intermediate, the peak disappeared at −25°C in ca. 2 h (Expt 2, Table I) or when the mixture was warmed (Expt 3).[7]

The second point to be addressed was the delineation of factors that would prolong the lifetime of intermediates and thus facilitate their study. This question is the principal focus of the present paper. The third point, details of the structures and reactions of intermediates that could account for the adverse biological effects, will be addressed in a later paper.

In our earlier work,[7] at 25°C with excess MCPBA where no intermediate was seen, the phosphate **8** was the sole phosphorus-containing product isolated. The sulfur balance of 83% of sulfate ion and 6% of elemental sulfur, along with peracid consumption of 4.02 molar proportions were consistent with Equation (2) for the oxidation. A plot of peracid consumption vs. time indicated that in acetone three molar proportions of MCPBA were consumed rapidly and the

TABLE I

Intermediates in the oxidation of phosphorothioates and thiophosphoramides[a]

Expt. no.	Structure	Compound no.	Temp., °C	Conc'n. (M)	NMR instrument[b]	Chemical shift of intermediate peaks[c] (lifetime, h; max. intensity, %[d]) major peak	minor peak(s)[e]	Max. intensity of product, %[f]
1[g]	$(EtO)_2P(S)OC_6H_5$	**6**	25	1.00	A	none	none	100
2[g]			−25	1.00	A	29.8 (2.0 h, 13%)	26.5 (1.0 h, <5%)	22
3[g]			−25 to 0	1.00	A	29.8 (1.6 h, 12%)	26.5 (1.0 h, <5%)	22
4			−15	0.25	B	29.8 (7.0 h, 14%)	26.5 (6.0 h, 5%)	Ca. 25
5	$(EtO)_2P(S)NHC_6H_5$	**9**	−25	0.25	B	32.9 (1.0 h, <5%)	31.0 (0.8 h, <5%) 55.0 (0.6, <5%)	45
6			−15	0.25	B	32.9 (0.5 h, <5%)	31.0 (0.1 h, <5%) 55.0 (0.3, <5%)	129
7	$SP(NHC_6H_3\text{-}2,4\text{-}Me_2)_3$	**10**	−15	0.25	B	26.7 (3.3 h, 40%)	37.0 (0.5 h, 8) 25.0 (0.5 h, 7)	48
8	$SP(NHC_6H_5)_3$	**11**	−15	0.25	B	24.9 (0.3 h, 5%)	39.0 (0.1 h, <5%)	48
9	$SP(NHC_6H_3\text{-}2,4\text{-}Cl_2)_3$	**12**	−15	0.25	B	28.8 (1.5 h, 11%)	none	[h]
10	$SP(OC_6H_5)_3$	**13**	−5	0.25	B,C	20.0 (>15.5 h, 12%)		36
11	$SP(OMe)_3$	**14**	−25	1.00	C	30.0 (2.0 h, <5%)		20
12	$(EtO)_2P(S)(OC_6H_4\text{-}4\text{-}NO_2)$	**15**	−5	0.125[i]	C	30.8 (10 h, <5%)		22
13	$SP(OC_6H_4\text{-}4\text{-}Me)_3$	**16**	−5	0.25	B	20.5 (≫8–10 h, 17%)[j]		36
14	$SP(OC_6H_4\text{-}4\text{-}NO_2)_3$	**17**	−5	0.25	B B	13 (8.0 h, ≪5%)		25
15		**18**	0	0.25	C	15.5 (1.0 h, ≪5%)		20

[a] One molar proportion of *m*-chloroperoxybenzoic acid was used. Acetone-d_6 was used as a solvent in all experiments.

[b] For Instrument A, see reference 7; for B and C, see Experimental.

[c] Relative to 85% H_3PO_4.

[d] "Lifetime" reports the approximate total time (h) during which the peak could be seen, and "max. intensity" reports the highest intensity observed as an approximate percentage of the intensity for the starting material.

[e] Other minor peaks sometimes seen never diminished and were attributed to hydrolysis or other side reactions.

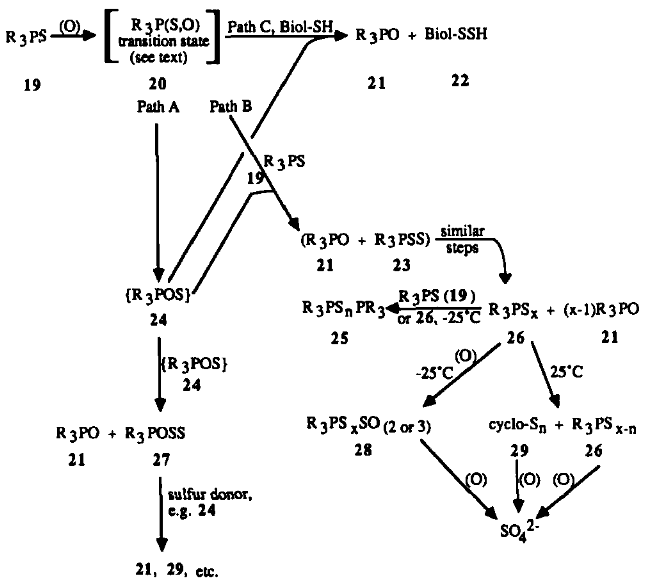
[f] Intensity of the ^{31}P signal for the $\geqslant$P(O) product relative to that of the $\geqslant$P(S) starting material.

[g] Reported in reference 7.

[h] The thiophosphoramide **12** was converted in 100% yield to the phosphoramide.

[i] Done at low concentration both because of sparing solubility and toxicity.

[j] The peak for **16** *began* to disappear in ca. 10 h vs. 6–8 h for **13**; **16** so clearly led to a longer lifetime that **16** was allowed to warm to 25°C, where the peak even then persisted for ca. 8 h.



SCHEME 1
(Where R = the various combinations of OAlk, OAryl, and N(H)Aryl shown in Table I)

fourth relatively slowly. At −25°C, ca. two proportions were consumed rapidly and a total of three was consumed in 72 h.[7] In experiments at −25°C with only *one* molar proportion of MCPBA (Table I, Expt 2), the peak at 29.8 ppm reached a maximum intensity of only 12–13% of that for the $\geqslant$P(S) function of the starting material (**6**),[7] suggesting that much of the MCPBA must have been consumed in oxidation of intermediates; this inference was confirmed by maximum intensities for the concomitant $\geqslant$P(O) product (**8**) of ca. 22% of that for **6** (at 25°C, where the intermediates did not survive long enough to consume much MCBPA, the intensity for **8** rose to ca. 100% of that for **6**; Table I, Expt 1). Our conclusions from the earlier work,[7] now expanded in Scheme 1, were that an oxygenated form of the phosphorothioate **19** (cf. **20** and **24**) on the one hand could lead to phosphorus species containing growing polysulfide chains (e.g. **26**), which could lose elemental sulfur (**29**). Good precedent exists for a stepwise accretion of sulfur atoms on a growing chain, as suggested for the growth of **23** or **27**, followed by cyclization to liberate sulfur as shown in Scheme 1.[8] On the other hand, in the presence of a biomacromolecule containing an SH group, the oxygenated phosphorus species reasonably was expected to produce a hydrodisulfide (**22**), as proposed in the metabolism of thionophosphorus compounds;[3a] hydrodisulfides can be reasonably stable species.[9]

RESULTS AND DISCUSSION

Studies with NMR Spectra

As a first step in ascertaining factors that would maximize the lifetimes of intermediates, the principal purpose of the present paper, the earlier results with

6 first were confirmed with a different instrument (cf. Expts 2 and 3 with 4, Table I). In Expt 4, however, the concentration was only 0.25 M instead of 1 M as in Expts 2 and 3; even though the temperature was 10°C higher, the survival time of the intermediate was much longer in Expt 4, implying by the concentration dependence that loss of the intermediate occurred by a reaction order higher than one.

The effect of different structural features on the lifetime of intermediates was explored by using ^{31}P NMR to study the oxidation of representative thionophosphorus compounds at low temperatures. Table I gives the lifetimes of the intermediates observed, along with other pertinent data.

Phosphorothioamides. Because of the prospect that internal hydrogen bonding might stabilize intermediates from the oxidation of thiophosphoramides, relative to esters, the amidothioate **9** was compared with the ester counterpart **6** (Expts 4 and 6 of Table I). The amide led to far less stable intermediates. The conclusion that thioamides as a class would give much more rapidly formed and much less stable intermediates was borne out in Expts 8 and 10 where the ester **13** gave a much longer lived intermediate than its amide counterpart **11** despite oxidation of **13** at −5°C instead of at −15°C for **11**. After a study of thioamides **9–12** all pointed to shorter lifetimes than for esters, we therefore concentrated on phosphorothioate esters (Expts 10–15). Several other features observed with the thioamides also warrant comment; these will be discussed in the sequence of the thioamides **9–12**.

In the oxidation of **9** at −25°C, the major peak was accompanied by two smaller peaks, one of which was the farthest downfield of any in Table I; these persisted for varying lengths of time (Expt 5). At −15°C with **9** (Expt 6), the same peaks were observed, but they never became as intense as at the lower temperature of Expt 5. That the peaks also disappeared more quickly at −15°C than at −25°C signifies that they were indeed produced by intermediates and not by stable by-products. Since the maximum intensity of the phosphoramide peak in Expt 5 was 45% of that for **9** after only 7 min, the low amplitude of the intermediate signals probably is attributable to near completion of the oxidation in 7 min, with intermediates rapidly giving the $\geqslant$P(O) product instead of persisting long enough to give more highly oxidized intermediates (e.g. **28** of Scheme 1). With all of the thioamides (**9–12**) three characteristics seem to exist, relative to the esters, viz. shorter lifetimes and lower intensities of peaks for intermediates, and higher yields of $\geqslant$P(O) products.

Electron donation from the methyl groups in **10** increased the lifetime and intensity of the major peak considerably, relative to the phenyl counterpart **11** (cf. Expts 7 and 8). As with the thioamides in general, however, the major peak for the major intermediate even with **10** both developed and disappeared more rapidly than with most esters (40% as intense as the peak of **10** after ca. 4 min but only 24% after 10 min more; Expt 7). The stabilizing effect inferred for the electron donation in **10** was confirmed by the shorter lifetime and lower intensity seen for the major peak from the dichloro counterpart (**12**) of the dimethyl amide (**10**); **12** reacted very rapidly, mostly within 5 min; as one therefore would expect, the yield of $\geqslant$P(O) product was unusually high (100%), with only one intermediate being detected (Expt 9).

Phosphorothioates. With **6** as a model, oxidants other than MCPBA conferred no advantages:[2] *p*-nitroperoxybenzoic acid led to less intense peaks for intermediates, *t*-butyl hydroperoxide was inconveniently slow (as was H_2O_2 with **13**), and trifluoroperoxyacetic acid led to more by-products.

Among the phosphorothioates, the dialkyl aryl ester **6** and trialkyl ester **14** gave similar results (cf. Expt 2 with 11). However, a much greater stabilizing effect of aryl than of alkyl is reflected when one compares Expt 4 with Expt 10, where the major intermediate from **6** clearly was much less stable than that from the triaryl ester **13** even at 10°C lower. Parathion, **15**, apparently also gave a less stable intermediate than **13**, even at twice the dilution (cf. Expt 12 with 10), although the *p*-NO_2 group no doubt is partly responsible. As with the thioamides, electron donation stabilized intermediates, since the peak from the tri-*p*-tolyl ester (**16**, Expt 13) was more intense and survived considerably longer than that from the triphenyl ester (**13** in Expt 10). This conclusion was confirmed by comparing the 4-nitro counterpart **17** with **13** and **16** (Expt 14 vs. 10 and 13), where the effect of the 4-nitro group of **17** contrasts with those of H and Me in leading to a marked decrease in the intensity and lifetime of the major peak.

The only ester of the seven in Table I that produced no clearly detectable intermediate was the cage phosphorothioate **18** (Expt 15). No reaction was observed below −5°C, and reaction seemed very sluggish at −5°C. At 0°C, a faint signal for an intermediate was seen, but at room temperature no intermediate could be detected. These results were surprising, since low proportions of intermediates in the only other such instances, with the thioamides, were attributable to so rapid a reaction that reaction was nearly complete when the first spectrum was obtained. Again in contrast to the thioamides, phosphate formation from **18** was relatively low. The apparent anomalous reactivity of **18** as a thiono ester may be a consequence of orientation of the oxygen atoms in such a way that poor overlap occurs with phosphorus, thus decreasing the nucleophilicity of the thiono moiety. Verkade has proposed that decreased π-bonding capability caused by restricted POC bond angles leads to negative charge concentration on the oxygen at the expense of nucleophilicity of the phosphorus atom;[10a] the results also may be influenced by a stereoelectronic feature that leads to more rapid hydrolysis of the caged structure **18** than of acyclic counterparts.[10b]

Oxidation of two other triaryl phosphorothioates, the 2,4,6-trimethylphenyl (**30**) and the 3,5-dichlorophenyl (**31**), was attempted but was precluded by too low

$(2,4,6\text{-}Me_3C_6H_2O)_3P(S)$ $(3,5\text{-}Cl_2C_6H_3O)_3P(S)$

30 **31**

a solubility of **30** and **31** in acetone-d_6. Other solvents dissolved **30** and **31**, but it seemed undesirable to add another variable to the studies, and ^{31}P NMR studies of **30** and **31** were not pursued.[2]

In light of the foregoing, the esters most amenable to further study seemed to be the triphenyl (**13**) and tri-*p*-tolyl (**16**). Rigorous kinetic conclusions could not be expected from ^{31}P NMR studies because of the likelihood of multiple reaction pathways and intermediates. Nevertheless, the rapidity of oxidation of the

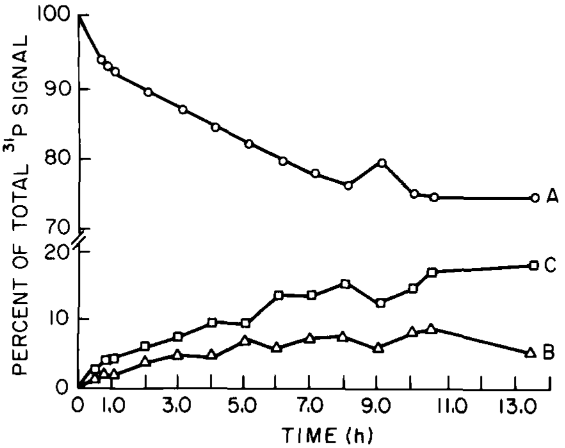


FIGURE 1 Relative abundancies (%) of phosphorus species during the oxidation at −5°C of triphenyl phosphorothioate (**13**), from integration of the ^{31}P NMR spectrum: Curve A, unconsumed **13**; B, intermediate (δ 20.0); C, triphenyl phosphate.

triphenyl ester (**13**) by MCPBA could be at least approximated at −5°C. Figure 1 shows a plot of the percentage of the total signal for ^{31}P which was attributable to still unconsumed **13** (Curve A), to the intermediate (Curve B), and to the phosphate product (Curve C). Several intriguing references are possible from Figure 1: (1) The brief upturn at ca. 9 h in the concentration of **13** may reflect merely unavoidable experimental error (Curve A); however, since it was reproducible and since UV spectra showed a similar discontinuity (vide infra), it may signify decomposition of an accumulated polysulfide intermediate (e.g. **26** of Scheme 1) to give sulfur and regenerate **13**. (2) The rather regular variations in Curve B also may reflect cyclical formation and collapse of an intermediate like **26** (although experimental error caused by unavoidably low concentrations could be responsible). (3) The residual signal in Curve B after ca. 13 h is attributable to a relatively stable intermediate such as a bisphosphonium polysulfide (e.g. **25**, Scheme 1).

Conclusions from the studies of ^{31}P NMR spectra can be summarized as follows: (1) In every instance, the appearance of signals between those for the initial $\gtrdot$P(S) and the ultimate $\gtrdot$P(O) groups, followed by the loss of these signals with relatively brief standing or gentle warming, shows that the new signals correspond to intermediates.

(2) In each of the Expts 1–15, the major signals of intermediates appeared between the signals for the $\gtrdot$P(S) and $\gtrdot$P(O) compounds, about midway (13–33 ppm downfield from 85% H_3PO_4), pointing to the same type of intermediate in each instance. That the intermediates are likely to be tetracoordinate is indicated by a range of about 82 to −5 ppm for tetracoordinate compounds like those in Scheme 1 in tabulations of ^{31}P chemical shifts.[11] And the likelihood that these tetracoordinate intermediates are phosphonium polysulfides such as **25**–**28** of Scheme 1 is supported by the similarity of the chemical shifts

(13–33 ppm) to those for such sulfur-containing quaternary phosphonium species as **32**[12] and **33**.[13]

$$(EtO)_3\overset{+}{P}SC_6H_5\,Cl^- \qquad (EtO)_3\overset{+}{P}SEt\,SbCl_6^-$$

32; 40.4 ppm **33**; 46.4 ppm

(3) The lifetimes of intermediates from thiophosphoramides usually are significantly smaller than for intermediates from phosphorothioates. Moreover, the thioamides are oxidized to $\geqslant$P(O) products more rapidly and in higher yield.

(4) Aryl groups stabilize the intermediates more than do alkyl groups.

(5) Electron-donating substituents on aryl groups of either thioamides or thioesters increase the lifetimes and intensities of intermediates, and electron withdrawal usually decreases both.

(6) Although the significance is not clear, the thioamides (**9–11**) usually gave two or three peaks for intermediates (hydrogen bonding effects ?) in contrast to only one or two for the thioesters (**6**, **13–18**).

(7) Those $\geqslant$P(S) compounds that reacted fastest usually led to the highest yields of $\geqslant$P(O) products.

(8) Triphenyl (**13**) and, especially, tri-*p*-tolyl phosphorothioate (**16**) gave the most stable intermediates and are considered the best choices for further studies.

Studies with Electron Paramagnetic Resonance Spectroscopy

There was no reason to believe that formation or reaction of the intermediates discussed above involved free radicals, but confirmation of this improbability by EPR spectra seemed prudent. Accordingly, aliquots from a mixture of equimolar amounts of the triphenyl ester (**13**) and MCPBA in acetone-d_6 at ca. −10°C were monitored by EPR spectroscopy after one and after six hours (for the maximum amount of intermediate). Neither spectrum showed any signal whatever; 2,2-diphenyl-1-picrylhydrazyl, a positive control, produced a strong signal. For confirmation, the experiment was repeated with introduction of N-*t*-butyl-α-phenylnitrone, *t*-BuN(O)=CHPh (**34**), as a spin trap. Since **34** reacts with free radicals to produce a relatively persistent radical, even minute quantities of a free radical should be detectable.[14] However, EPR spectra acquired 3.5 and 7 hours after mixture again showed no signal, although again the hydrazyl gave a strong signal. The lack of any significant quantity of free radicals agrees with earlier findings that the reaction of a phosphorothioate with H_2O_2 was not affected by UV light.[15]

Studies with Ultraviolet Spectra

With sulfanes of the type $R^1S_nR^2$, the greater the number of sulfur atoms the longer the wavelength of UV absorption and the greater the molar extinction coefficient (for examples, see references 16 and 17). Polysulfides such as **25–28** (Scheme 1) thus would be expected to absorb above 300 nm. The starting materials (MCPBA and triphenyl phosphorothioate, **13**) and final products (*m*-chlorobenzoic acid and triphenyl phosphate) absorbed between 260 and 285 nm, but none of them absorbed significantly above 300 nm.

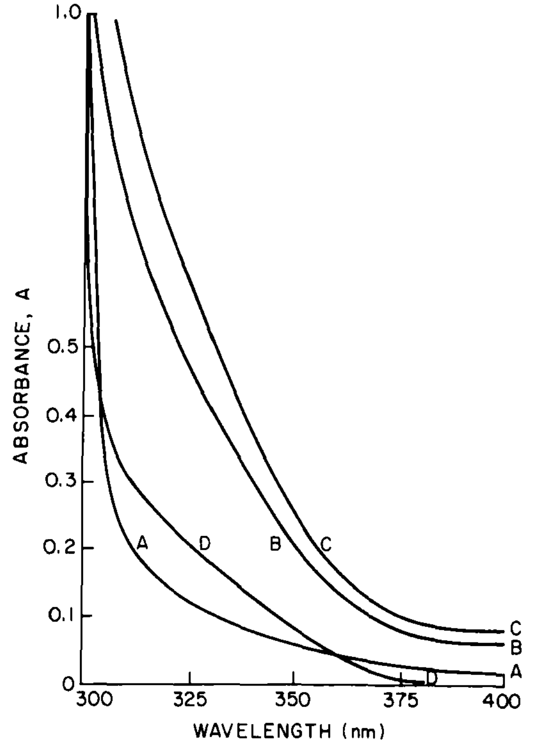


FIGURE 2 UV spectra during the reaction of equimolar amounts of triphenyl phosphorothioate (**13**) and MCPBA (**7**) at −10°C in CH_2Cl_2 (2.5×10^{-3} M in **13**) at various times after mixing (0 min, negligible absorption): Curve A, 2 min; B, 2 h; C, 4 h; D, 30 h.

Figure 2 shows UV spectra obtained at different times during the reaction of equimolar amounts of the triphenyl ester **13** with MCPBA in CH_2Cl_2 at −10°C (2.5×10^{-3} M). *m*-Chlorobenzoic acid began to precipitate within a few minutes, and strong absorption quickly developed with a tail that extended well beyond 300 nm (Figure 2, Curve A). The absorbance increased markedly up to 2 h (Curve B), and still more up to 4 h (Curve C) but decreased greatly by 30 h (Curve D). With 325 nm as an arbitrary reference point, variations in absorbance with time are shown in Table II. The absorbance gradually increased over the first four hours to a maximum absorbance of 0.65 and then decreased for a few hours (to 0.40), as one would expect for formation and disappearance of polysulfide species such as **26**. Interestingly, the absorbance later rose to a second maximum absorbance of 0.54 at eight hours; as remarked above, this discontinuity at ca. 8 h resembles that at ca. 9 h in the NMR Curve A of Figure 1 (the difference may be ascribed to faster oxidation in CH_2Cl_2 than in acetone). These results strongly point to the generation of polysulfide species such as **25**–**28** which then disappeared, except for residual absorption attributed (as with Figure 1) to fairly stable species like **25** and **28**. The NMR signal for the intermediate from **13** (Figure 1) and the UV absorbance (Figure 2) follow much the same pattern, consistent with generation by the same intermediary species, i.e. growth, decline,

TABLE II

Absorbance (A) at 325 nm in the oxidation of triphenyl phosphorothioate (**13**) by MCBPA (**7**) at −10°C[a]

Time (h)	A	Time (h)	A	Time (h)	A
0.03	0.14	2.00	0.52	8.00	0.54
0.25	0.35	3.00	0.53	10.00	0.40
0.40	0.46	4.00	0.65	12.00	0.37
0.75	0.49	6.25	0.50	24.00	0.33
1.00	0.43	7.00	0.40	30.00[b]	0.22

[a] Equimolar amounts of **7** and **13** were used in CH_2Cl_2 at a concentration of **13** = 2.5×10^{-3} M.

[b] The last 6 h were at ca. 25°C.

growth, and final decline to a residual value. Strong confirmatory evidence that polysulfides indeed are responsible for the UV absorbance will be discussed in a later paper (e.g. that trimethyl phosphite destroys the polysulfide chain and hence the associated absorbance).[2] That the absorption evident in Figure 2 and Table II is not caused by S_6, S_8, or other forms of polysulfur can be argued convincingly from the insufficient intensities of such species;[2] it seems improbable, however, even by the simpler argument that most such species should change rapidly to S_8, which as a saturated solution in CH_2Cl_2 at −10°C was found to have an absorbance (A) of only 0.06 at 325 nm.

Studies with Infrared and Raman Spectra

Equimolar amounts of triphenyl phosphorothioate (**13**) and MCPBA were allowed to react in chloroform or acetone while Fourier-transformed IR spectra were acquired periodically; the spectrum from 900 to 460 cm^{-1} appeared to be monitored best with acetone-d_6 as a solvent and that from 900 to 1800 cm^{-1} with chloroform. The reactants were cooled as much as possible without precipitation (ca. 0°C) before mixing and transfer to an IR cell. Reaction was complete after 4–5 min. The IR results down to 460 cm^{-1} revealed no changes other than those for the phosphorothioate to phosphate and of the MCPBA to *m*-chlorobenzoic acid. Even when the reactants were cooled to −78°C in acetone-d_6 before mixture, no signals were discernible for intermediates by FTIR. Acetone seemed to play no active role in the conversion of $\gtrdot$P(S) to $\gtrdot$P(O), except apparently to reduce the strength of MCPBA as an oxidant by complexation.[2]

Laser Raman spectroscopy was performed similarly, but with more significant results. Acetone was used as the solvent because it seemed to permit slower reaction than less polar solvents and because it dissolved the reactants even at −78°C. Solutions of the ester **13** and MCPBA were cooled to −78°C, mixed (0.25 M), and allowed to warm while spectra were acquired. Unfortunately, laser-induced precipitation (sulfur ?) led to severe problems in that Rayleigh scattering particularly obscured the important range of ca. 1000–400 cm^{-1}. In the last of several experiments,[2] the oxidation was carried out at −10°C to −6°C for six hours (as a time for considerable intermediate, by NMR; cf. Fig. 1). The cloudy mixture then was treated with carbon and centrifuged while cold (dry ice).

A Raman spectrum (by difference from MCBPA) of the resultant clear colorless solution showed new (weak) bands at 523, 568, 608, 646, and 707 cm^{-1}; the band at 646 cm^{-1} probably was associated with P═S stretching,[18] but we had not previously detected the others. After four days at 25°C, the new bands were weaker but still present. This result is consistent with the view that the new bands were not from intermediates but were from at least moderately stable products such as the sulfanes **25** or **28**. The bands at 523 and 568 cm^{-1} were in the range expected for P—S stretching,[18] although they were weak.

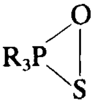
Raman spectra were sought of two model trisulfides, **35** and **36**, for comparison with the foregoing

$$RO\overset{O}{S}(CH_2)_4SSS(CH_2)_4\overset{O}{S}OR$$

35, R = Et; **36**, R = Na

results. The ester **35** in acetone unfortunately underwent generalized fluorescence and decomposition in the laser beam, and no spectrum could be obtained. The Raman spectrum of the salt **36** in D_2O showed weak bands at 482, 528, 630, 707, 949 and 1023 cm^{-1}. The two bands at 482 and 528 cm^{-1} were consistent with literature assignments for S—S stretching vibrations, which are strong in Raman spectra at 500–400 cm^{-1}.[9c,18] Comparison of the bands for **36** suggests that the bands at 523 and 568 seen when **13** was oxidized are consistent with polysulfide intermediates like those in Scheme 1.

Resulting Reaction Scheme (Scheme 1)

The studies reported herein support the general set of reactions presented in Scheme 1 (see the Introduction). There is of course no evidence as to the structure of the transition state(s) symbolized by the formula $R_3P(S,O)$ (**20**) in Scheme 1. Speculation suggests  or R_3PSO as possible transition states or, in Path A, R_3POS (**24**) as a possible intermediate (by an oxygen insertion into **19** or by rearrangement of **20**). Although in Path A, the R_3POS type of structure (e.g. **24**, **27**) is postulated as a possible intermediate, we have not characterized the ^{31}P NMR peaks of the observed intermediates sufficiently to support or rule out types such as **24** and **27**; obviously structure **27** is suspect, since it results from the reaction of two molecules of **24**. In Path B, the polysulfide intermediates **26** are consistent with the NMR and UV data, as well as with the observed formations of elemental sulfur (**29**) and sulfate ion. The structure **25** is invoked to account for the absorption mentioned in the NMR, UV, and Raman spectra that persisted after disappearance of the major absorptions; since **25** results from the reaction of either **19** or **26** itself with **26**, with loss of sulfide or polysulfide, n might have any value exceeding one in the various species present of **25**. The structure **28** is included to account for the clear brown solutions produced at ca. −25°C (where **26** persists long enough to be oxidized instead of cyclizing as at ca. 25°C). Path A accounts for the biochemical findings mentioned, which are not part of our studies.

EXPERIMENTAL

^1H NMR spectra were recorded on a JEOL-JNM-MH 100 or JEOL FX90Q spectrometer using as internal standards Me_4Si or the proton counterparts present of $CDCl_3$, or Me_2CO-d_6; ^{31}P NMR spectra were recorded on a Varian XL-100 (Instrument A),' Nicolet 300 (Instrument B), or Bruker AM400-NB (Instrument C) spectrometer with 85% H_3PO_4 as an external reference; all NMR spectra are reported in parts per million (^{31}P downfield from H_3PO_4). EPR spectra were obtained using a Varian E-3 spectrometer, UV spectra with a Cary Model 14 spectrometer, all IR spectra were FT-IR done with a Nicolet 6000 FT-IR instrument, and Raman spectra were obtained with a laser instrument assembled by P.L.P.

We thank Dr. Jack Uetrecht for the N-*t*-butyl-α-phenylnitrone used in the EPR studies. Commercially available MCPBA (**7**; Aldrich) either was purified to greater than 99% purity by a reported procedure,[19] or was titrated with aqueous $KI/Na_2S_2O_3$ solutions to determine purity. Peroxytrifluoroacetic acid (4 M) was prepared by a reported method.[20] *t*-Butyl hydroperoxide and H_2O_2 (30%) were used as obtained commercially. The following known compounds as prepared by us had appropriate NMR spectra and properties that agreed with reported values: **6**,[7] **9**,[2,21] **11**,[2,21] **13**,[22] **30**,[22] **31**,[22] **35**,[23] and **36**.[23] Also in agreement with reports were the properties of **14**, **17** and **18**, all known.[2] Meeting expectation were the properties of the new compounds **10**[2,21] and **12**.[2,21] Compound **15** was kindly provided by the Environmental Protection Agency, Pesticide Repository Program, Las Vegas, Nev. Except for **16** (below), all other compounds were commercial. Other general experimental details were essentially as described elsewhere.[23]

Tri(p-tolyl) phosphorothioate (**16**). The ester **16** had a different mp from the reported value, presumably because it was a different crystalline form. It is therefore reported as follows: Recrystallized *p*-cresol (10.71 g, 99 mmol) was allowed to react with NaH (4.46 g of a ca. 50% oil dispersion; 95 mmol) in dioxane (25 mL) under Ar for 45 min. When H_2 evolution ceased, 3.1 mL (30 mmol) of $PSCl_3$ in 15 mL of dioxane was added during 30 min. The mixture was stirred for 0.5 h, then heated under reflux for 4 days. Since NMR then showed presence of a little *p*-cresol, 0.45 g (10 mmol) of NaH dispersion was added, and the mixture was heated for 24 h more. Excess NaH then was destroyed with MeOH, and a $CHCl_3$ extract was washed with H_2O, 0.1 M base, and H_2O. Part of the product (4.6 g of 8.6 g) was chromatographed on 160 g of Si gel in a 50-mm id column with 1:9 EtOAc-hexane; yield, 3.93 g of **16** (64% overall) as greenish yellow solid, mp 46–46.5°C (lit.[24] 87–88°C); ^1H NMR (Me_2CO-d_6) δ 7.06 (s, 4H), 2.30 (*d*, 3H); ^{31}P NMR (Me_2CO-d_6) δ 54.0 (lit.[25] 54.0, 53.5).

Anal. Calcd. for $C_{21}H_{21}O_3PS$: C, 65.61; H, 5.51; S, 8.34. Found: C, 65.75; H, 5.60; S, 8.37.

Studies with ^{31}P NMR. Typically, the thiono compound of interest was dissolved in Me_2CO-d_6 in a NMR tube and cooled to the desired temperature. After a spectrum was obtained, the tube was removed and placed in a dry ice/Me_2CO bath. An equivalent amount of MCPBA in enough Me_2CO-d_6 (also chilled) was added to produce the concentrations reported in Table I for MCPBA and the substrate. The chilled mixture then was reinserted into the NMR probe and warmed to the reported temperature by passing N_2 gas through a cold bath and into the probe. Spectra were obtained as soon as instrumental requirements permitted (typically ca. 5 min). When no reaction was observed at lower temperatures, the temperature was raised in increments of 5°C until reaction occurred at the reported temperature (Table I).

EPR studies. Solutions containing 0.5 mmol of triphenyl phosphorothioate (**13**) and of MCPBA in 1 mL each of Me_2CO-d_6 at −10°C were mixed and kept at −10°C to −7°C. EPR spectra of aliquots acquired after 1 h and 6 h showed no peaks. When the expt. was repeated with addition of 2 mg of *N*-*t*-butyl-α-phenylnitrone, aliquots removed after 3.5 and 7 h also showed no ESR signal. A spectrum of 2,2-diphenyl-1-picrylhydrazyl obtained separately after each EPR study showed a strong signal.

Ultraviolet (UV) spectroscopy. Solutions containing 1.0 mmol of triphenyl phosphorothioate (**13**) in 1 mL of CH_2Cl_2 and 1.0 mmol of MCPBA in 3 mL of CH_2Cl_2, both at −10°C, were mixed and kept at −10°C. Aliquots of 20 μL were removed periodically, transferred to a 1-cm quartz UV cell (2-mL volume), and diluted to the mark with cold CH_2Cl_2 (hence solutions used were 2.5×10^{-3} M in **13**). UV spectra, each at 400–250 nm, were acquired during 30 h, with the results shown in Table II and Figure 2 (the mixture was at room temperature during the last 6 h).

Infrared spectroscopy. A solution of 1.0 mmol each of the triphenyl ester (**13**) and of MCPBA in a total of 4 mL of solvent was cooled as much as possible without precipitation and placed in an IR cell.

Spectra were acquired in regions from 1800 to 460 cm^{-1} (including difference spectra) until changes ceased (except for effects of evaporation) by starting at 0°C and allowing the temperature to rise. Solutions in $CHCl_3$ or $CDCl_3$ could not be cooled much below 0°C without precipitation and were mixed at 0°C; all changes seen in the IR spectrum occurred within the first 3.7 min, and no signals appeared that later disappeared (as we had hoped, for an intermediate). When the expt. was repeated in Me_2CO-d_6 at 0°C, all changes occurred within 4.6 min, but again no signals were observed to appear and then disappear.

In order to investigate an at-first suspected trapping reaction of Me_2CO by an intermediate,[2] the latter expt. was repeated in $CHCl_3$ containing enough Me_2CO to give $A_{1702\,cm^{-1}} = 0.3$. All changes occurred in 3.8 min, but the only significant observations were consistent with loss of MCPBA, formation of triphenyl phosphate, and a shoulder (1754 cm^{-1}) on a peak at 1734 cm^{-1} (C=O stretch of MCPBA) that we now attribute to H-bonding between the Me_2CO and MCPBA (which we believe slows the oxidation in acetone). Although the C=O stretches of *m*-chlorobenzoic acid and Me_2Co overlapped, the combination never showed the changes expected if Me_2CO were first consumed by an intermediate and later liberated.

Raman spectroscopy. Initially, Raman spectra of 0.25 M solutions showed peaks for Me_2CO at 523, 783, 1059, 1219, 1360, 1429 and 1703 cm^{-1}, small peaks at 992 and 1590 cm^{-1} for MCPBA, and a weak peak at 646 cm^{-1} for the triphenyl ester (**13**); *m*-chlorobenzoic acid showed weak bands at 825, 1157, and 1593 cm^{-1}. Spectra could not be obtained below ca. 480–500 cm^{-1} because of instrumental cutoff; unfortunately, during several expts., Rayleigh scattering soon obscured the region below 1000 cm^{-1} because of a turbidity that developed.

To minimize the Rayleigh scattering, precipitate was removed before spectra were taken. Thus after 6 h at −10 to −6°C, the mixture of **13** and MCPBA in Me_2CO was treated with decolorizing carbon and centrifuged in dry ice for ca. 5 min. A Raman difference spectrum of the clear colorless solution showed several new bands at 523, 568, 608, 646, and 707 cm^{-1}. After 4 days at ca. 25°C, the new signals still were present but were weaker. These results are consistent with the formation of a bisphosphonium polysulfide such as **25** (Scheme 1).

A Raman spectrum of disodium 4,4′-trithiobis(butanesulfinate) (**36**, 0.25 M in D_2O) used as a model showed weak bands at 482, 528, 630, 707, 949, and 1023 cm^{-1}; of these, those at 482 and 528 seem attributable to —S—S—.[18] Attempts to obtain a spectrum of the corresponding diethyl ester **35** were unsuccessful because of decomposition in the laser beam; fluorescence was observed, a black spot appeared where the beam struck the sample, and a gas was evolved (H_2S?).

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