Phosphorothiolate Sulfoxides and Sulfones: NMR Characteristics and Reactivity†

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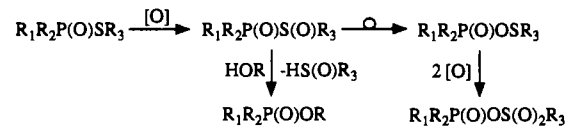
Phosphorothiolate sulfoxides and sulfones are the initial and sequential products observed in yields of up to 53 and 68%, respectively, on treatment of variously substituted phosphorodiamidothiolates, phosphoramidothiolates, and phosphorotrithiolates with *m*-chloroperoxybenzoic acid in dry chloroform. They are not observed on peracid oxidation of methamidophos and acephate. The assignments are based on two types of NMR evidence: diastereomer formation and three-bond P–S–C–H coupling constants for the sulfoxides; ^1H and ^{13}C chemical shift relationships for the SCH_3, $S(O)CH_3$, and $S(O)_2CH_3$ substituents of the phosphorodiamidothiolate derivatives. Reactions of the phosphorodiamidothiolate sulfoxides and sulfones with nucleophiles generated during the course of peracid oxidation are of interest in two respects: they account for the formation of phosphinyloxysulfonates, phosphinyloxychlorobenzoates, pyrophosphates, and phosphoric acids; they serve as a model for the bioactivation of phosphorothiolate pesticides. The sulfur-containing oxidation products from selected *S*-methyl phosphorothiolates include $CH_3S(O)_2SCH_3$ and smaller amounts of $CH_3S(O)SCH_3$, $CH_3S(O)_2S(O)CH_3$, and $CH_3S(O)_2OH$.

INTRODUCTION

Phosphorothiolate sulfoxides are proposed as the toxicologically relevant bioactivation products of many phosphorothiolate pesticides, but they have not been characterized from biological systems (Eto et al., 1977; Wing et al., 1983). The oxidative bioactivation of phosphorothiolates may reflect their conversion to more potent phosphorylating agents on treatment with peracids (Casida, 1984; Eto et al., 1977; Segall and Casida, 1981). Formation of the corresponding sulfoxides was reported from peracid oxidation of methamidophos [$CH_3O(NH_2)P(O)SCH_3$] (Eto et al., 1977; Thompson et al., 1984) and $C_2H_5O(CH_3)P(O)SC_2H_5$ (Yang et al., 1990). We, however, have been unable to directly observe the sulfoxides of these and closely related compounds by ^{31}P or ^{13}C NMR, which we attribute to their known instability and exceptional reactivity as phosphorylating agents (Segall and Casida, 1983). On this basis, the major terminal products in the peracid oxidation of phosphorothiolate pesticides and related compounds are solvent dependent. For example, when the oxidations are carried out in nonhydroxylic solvents, the phosphinyloxysulfonates predominate, whereas in a primary alcohol there is near quantitative conversion to the corresponding alkyl phosphate (Segall and Casida, 1981, 1982, 1983; Bielawski and Casida, 1988). The general mechanism first proposed for these reactions is as follows:



In an attempt to clarify the spectroscopic properties and reactivities of phosphorothiolate sulfoxides, and in particular to delineate their toxicological role as possible bioactivation products of phosphorothiolate pesticides, we selected phosphorodiamidothiolates as the starting point for study since the substituted nitrogen functionalities are expected to stabilize the purported sulfoxides by electron donation to the phosphorus center (Wu et al., 1991). This approach proved to be successful since the desired intermediate products were observed and thereby provided a basis for defining the NMR spectral properties and reactions of these species.

MATERIALS AND METHODS

Spectroscopy. NMR spectra were recorded with a Bruker WM-300 spectrometer at 300 (^1H), 75 (^{13}C), or 121.5 MHz (^{31}P NMR) for solutions in $CDCl_3$. Chemical shifts (parts per million) were referenced to either internal tetramethylsilane (^1H and ^{13}C) or external trimethyl phosphate in $CDCl_3$ (^{31}P). Coupling constants were quoted in hertz. Product distributions were based on integration of the resonances in the ^{31}P NMR spectra obtained on direct analyses of the reaction mixtures with an appropriate inverted gate delayed acquisition pulse sequence to minimize nuclear Overhauser effects. Spectroscopic data for known compounds were consistent with those reported in the literature.

Chromatography. Thin-layer chromatography (TLC) utilized silica with fluorescent indicator and a layer thickness of 0.25 mm for analysis and 2.0 mm for preparative isolations. Aromatic compounds were visualized with UV light and phosphorothioates with $PdCl_2$ spray reagent.

Chemicals. *m*-Chloroperoxybenzoic acid (MCPBA) (99%) was prepared by washing a dichloromethane solution of the commercial material (85%) with pH 7.5 buffer (Fieser and Fieser, 1967) to remove *m*-chlorobenzoic acid. Dry $CDCl_3$ was obtained on distillation from P_2O_5.

Phosphorodiamidothiolates **1–5**, **8**, **9**, and **11–14** were synthesized as follows. The corresponding alkyl phosphorodichlorothionates were treated with 4 molar equiv of the appropriate amines in dry CH_2Cl_2 and then the resulting phosphorodiamidothionates rearranged to the corresponding thiolates by heating with the desired alkyl halide in dimethylformamide containing KCl. [*S*-$^{13}CH_3$]-**3** and -**14** were prepared in a similar manner using $^{13}CH_3I$. [$^{13}CH_3$]-**16** was made according to the procedure of Thompson et al. (1984). Compounds **6**, **7**, **10**, and **15** were synthesized by reacting phosphorus oxychloride with 1 equiv each of the appropriate thiol and triethylamine, followed by 4

† This study was supported in part by National Institute of Environmental Health Sciences Grants RO1 ES04863 and PO1 ES00049 and the Health Effects Component of the University of California Toxic Substances Research and Teaching Program.

0021-8561/92/1440-1425$03.00/0

equiv of pyrrolidine or piperidine. The R_p and S_p diastereomers of (1*R*,2*S*)-(−)-ephedrine derivative **19** were prepared according to the method of Hall and Inch (1979). Phosphorotrithiolate **22** was synthesized by reaction of phosphorus oxychloride with 2 equiv each of *tert*-butyl mercaptan and triethylamine in $CHCl_3$ followed by 1 equiv of sodium thiomethoxide. Phosphinothiolate **25**, which could not be prepared by rearrangement of the thiono analog, was made by coupling diphenylphosphinic chloride (commercial) with sodium thiomethoxide. Phosphoramidothiolate **18** was a minor byproduct in the synthesis of **5**. Compounds **16**, **17**, **20**, **21**, **23**, and **24** were available from commercial sources or earlier syntheses in this laboratory. All of the final products were subjected to preparative TLC to obtain a purity of >97% as determined by ^1H and ^{31}P NMR.

The ^1H spectral data for the phosphorothiolates synthesized and the ^1H and ^{31}P data for some of their thiono precursors are as follows.

Compound **1**: 0.93 (t, J = 7.4, 6 H, $CH_2CH_2CH_3$), 1.54 (m, J = 7.4, 4 H, $CH_2CH_2CH_3$), 2.24 (d, J = 13.5, 3 H, $PSCH_3$), 2.86 (2 H, $NHCH_2CH_2CH_3$), and 2.95 (m, 4 H, $CH_2CH_2CH_3$).

Thiono precursor of **1**: 0.92 (t, J = 7.4, 6 H, $CH_2CH_2CH_3$), 1.52 (m, J = 7.2, 4 H, $CH_2CH_2CH_3$), 2.64 (2 H, $NHCH_2CH_2CH_3$), 2.87 (m, 4 H, $CH_2CH_2CH_3$), 3.65 (d, J = 14.0, 3 H, $POCH_3$), and 71.65 (P).

Compound **2**: 2.24 (d, J = 13.1, 3 H, $PSCH_3$) and 2.71 [d, J = 11.3, 12 H, $N(CH_3)_2$].

Thiono precursor of **2**: 2.63 [d, J = 11.9, 12 H, $N(CH_3)_2$], 3.60 (d, J = 13.9, 3 H, $POCH_3$), and 82.60 (P).

Compound **3**: 1.85 [m, 8 H, $N(CH_2CH_2)_2$], 2.26 (d, J = 12.7, 3 H, $PSCH_3$), and 3.23 [m, 8 H, $N(CH_2CH_2)_2$].

Thiono precursor of **3**: 1.84 [m, 8 H, $N(CH_2CH_2)_2$], 3.14 [m, 8 H, $N(CH_2CH_2)_2$], 3.62 (d, J = 13.7, 3 H, $POCH_3$), and 72.50 (P).

Compound **4**: 1.33 (t, J = 7.4, 3 H, $PSCH_2CH_3$), 1.84 [m, 8 H, $N(CH_2CH_2)_2$], 2.85 (2q, J = 7.4, 11.9, 2 H, $PSCH_2CH_3$), 3.21 [m, 8 H, $N(CH_2CH_2)_2$].

Compound **5**: 1.38 [d, J = 6.7, 6 H, $CH(CH_3)_2$], 1.85 [m, 8 H, $N(CH_2CH_2)_2$], 3.21 [m, 8 H, $N(CH_2CH_2)_2$], and 3.49 [m, 1 H, $PSCH(CH_3)_2$].

Compound **6**: 1.76 [m, 8 H, $N(CH_2CH_2)_2$], 3.18 [m, 8 H, $N(CH_2CH_2)_2$], and 7.29, 7.62 (2 m, 3 H, 2 H, aromatic).

Compound **7**: 1.81 [m, 8 H, $N(CH_2CH_2)_2$], 3.24 [m, 8 H, $N(CH_2CH_2)_2$], and 7.84, 8.13 (2 d, 2 H, 2 H, aromatic).

Compound **8**: 1.54 [m, 12 H, $N(CH_2CH_2)_2CH_2$], 2.24 (d, J = 13.1, 3 H, $PSCH_3$), and 3.14 [m, 8 H, $N(CH_2CH_2)_2CH_2$].

Thiono precursor of **8**: 1.54 [m, 12 H, $N(CH_2CH_2)_2CH_2$], 3.04 [m, 8 H, $N(CH_2CH_2)_2CH_2$], 3.59 (d, J = 13.7, $POCH_3$), and 76.86 (P).

Compound **9**: 1.34 (t, J = 7.4, 3 H, $PSCH_2CH_3$), 1.54 [m, 12 H, $N(CH_2CH_2)_2CH_2$], 2.81 (2 q, J = 7.4, 11.5, 2 H, $PSCH_2CH_3$), and 3.13 [m, 8 H, $N(CH_2CH_2)_2CH_2$].

Thiono precursor of **9**: 1.28 (t, J = 7.1, 3 H, $POCH_2CH_3$), 1.53 [m, 12 H, $N(CH_2CH_2)_2CH_2$], 3.04 [m, 8 H, $N(CH_2CH_2)_2CH_2$], 3.99 (m, 2 H, $POCH_2CH_3$), and 74.51 (P).

Compound **10**: 1.53 [m, 21 H, $C(CH_3)_3$, $N(CH_2CH_2)_2CH_2$], 3.12 [m, 8 H, $N(CH_2CH_2)_2CH_2$].

Compound **11**: 2.29 (d, J = 13.4, 3 H, $PSCH_3$), 3.22 [m, 8 H, $O(CH_2CH_2)_2N$], and 3.67 [m, 8 H, $O(CH_2CH_2)_2N$].

Thiono precursor of **11**: 3.11 [m, 8 H, $O(CH_2CH_2)_2N$], 3.66 [m, 11 H, $O(CH_2CH_2)_2N$, $POCH_3$], and 75.76 (P).

Compound **12**: 1.71, 2.09 (2 m, 2 H, $P[N(CH_3)CH_2]_2CH_2$), 2.28 (d, J = 12.1, 3 H, $PSCH_3$), 2.70 [d, J = 11.8, 6 H, $P[N(CH_3)CH_2]_2CH_2$], and 3.00, 3.08 [2 m, 4 H, $P[N(CH_3)CH_2]_2CH_2$].

Thiono precursor of **12**: 1.70, 2.02 [2 m, 2 H, $P[N(CH_3)CH_2]_2CH_2$], 2.74 [d, J = 13.5, 6 H, $P[N(CH_3)CH_2]_2CH_2$], 2.97, 3.16 [2 m, 4 H, $P[N(CH_3)CH_2]_2CH_2$], 3.59 (d, J = 13.1, 3 H, $POCH_3$), and 78.21 (P).

Compound **13**: 1.13 [t, J = 7.1, 6 H, $N(CH_2CH_3)_2$], 2.24 (d, J = 13.2, 3 H, $PSCH_3$), 2.72 [d, J = 11.1, 6 H, $N(CH_3)_2$], and 3.13 [m, 4 H, $N(CH_2CH_3)_2$].

Thiono precursor of **13**: 1.10 [t, J = 7.1, 6 H, $N(CH_2CH_3)_2$], 2.55 [d, J = 12.8, 6 H, $N(CH_3)_2$], 3.17 [m, 4 H, $N(CH_2CH_3)_2$], 3.59 (d, J = 13.8, 3 H, $PSCH_3$), and 81.10 (P).

Compound **14**: 1.55 [m, 6 H, $N(CH_2CH_2)_2CH_2$], 1.85 [m, 4 H, $N(CH_2CH_2)_2$], 2.25 (d, J = 13.0, 3 H, $PSCH_3$), and 3.20 [m, 8 H, $N(CH_2CH_2)_2CH_2$, $N(CH_2CH_2)_2$].

Thiono precursor of **14**: 1.53 [m, 6 H, $N(CH_2CH_2)_2CH_2$], 1.83 [m, 4 H, $N(CH_2CH_2)_2$], 3.11 [m, 8 H, $N(CH_2CH_2)_2CH_2$, $N(CH_2CH_2)_2$], 3.62 (d, J = 13.7, 3 H, $POCH_3$), and 75.57 (P).

Compound **15**: 1.85 [m, 4 H, $N(CH_2CH_2)_2$], 3.27 [m, 6 H, $N(CH_2CH_2)_2$,$NHCH_2$], 3.44 (m, 2 H, SCH_2), and 3.76 (m, 1 H, NH).

Compound **18**: 1.35, 1.36 [2 d, J = 6.2, 6.2, 6 H, $OCH(CH_3)_2$], 1.87 [m, 4 H, $N(CH_2CH_2)_2$], 2.24 (d, J = 14.0, 3 H, $PSCH_3$), and 4.79 [m, 1 H, $OCH(CH_3)_2$].

Compound **22**: 1.62 [s, 18 H, $C(CH_3)_3$] and 2.45 (d, J = 15.5, 3 H, $PSCH_3$).

Compound **25**: 2.30 (d, J = 14.6, 3 H, $PSCH_3$) and 7.48, 7.97 (2 m, 6 H, 4 H, aromatic).

Thiono analog of **25**: 3.72 (d, J = 13.7, 3 H, $POCH_3$), 7.44, 7.87 (2 m, 6 H, 4 H, aromatic), and 81.44 (P).

Oxidation Reactions. A 5-mm NMR tube containing the phosphorothiolate (0.2 mmol) in dry $CDCl_3$ (0.5 mL) was cooled in acetone–dry ice (−60 °C) for 10 min, MCPBA (1.0–4.0 molar equiv) was added, and then the tube was removed from the coolant and shaken vigorously to dissolve the remaining solid MCPBA. NMR spectra were recorded at 10 min (by which time the reaction mixture had warmed to 20 °C) or at regular intervals between 5 and 70 min and then at 24 h after addition of the oxidant.

RESULTS

Relation of Phosphorothiolate Structure to Detection of Phosphorothiolate Sulfoxides and Sulfones (Table I). Twenty-five thiolates were each treated with 1.5 molar equiv of MCPBA in cold $CDCl_3$ as above and examined by ^{31}P NMR 10 min later. Sixteen of the product mixtures gave ^{31}P NMR signals associated with two oxidation products assigned as the sulfoxides and sulfones on the basis of the criteria discussed later. This included 12 of 15 phosphorodiamidothiolates, 2 of 4 phosphoramidothiolates, and 2 of 3 phosphorotrithiolates but not any of the phosphorothiolates or phosphinothiolate examined. In a variation of the normal procedure, the NMR probe was maintained at −50 °C for the reaction of **3** and **8** with 1.5 molar equiv of MCPBA; this resulted in the same oxidation products but with slightly longer lifetimes for the intermediates.

Relation of Phosphorothiolate Sulfoxide and Sulfone Yields to Reaction Time and Oxidant Amount. Bis(pyrrolidyl) and bis(piperidyl) phosphorodiamidothiolates **3** and **8**, respectively, were examined for optimal observable sulfoxide and sulfone yields by varying the amount of oxidant and time of reaction. About 80% of bis(piperidyl) derivative **8** reacted with 1.5 molar equiv of MCPBA within 10 min to give two major initial products. The more stable one (46% yield) was designated the sulfoxide and the less stable one (26% yield) the sulfone (Figure 1). The products from bis(pyrrolidyl) derivative **3** were also related to the reaction time (5 vs 50 min) and amount of MCPBA (Table II). The maximum sulfoxide yield observed was 53% at 5 min with 1.5 molar equiv of MCPBA. Above 1.5 molar equiv of peracid the sulfoxide decreased as the sulfone increased; with 3 molar equiv of MCPBA the latter appeared in 68% yield at 5 min. The levels of sulfoxide and sulfone were both always reduced in amount at 50 relative to 5 min. Other products that dominated at later times and with more peracid (Figure 1; Table II) are discussed below.

^1H, ^{13}C, and ^{31}P NMR Assignments of Phosphorothiolate Sulfoxides and Sulfones. Characterization studies focused on the phosphorodiamidothiolates which gave the most stable intermediate oxidation products, i.e., *N*,*N*-dimethyl and *N*,*N*-diethyl compounds **2** and **13**, and particularly the pyrrolidyl and piperidyl compounds **3**, **8**, and **14**. In comparing the sulfoxides and sulfones with parent compounds **2**, **3**, **8**, **13**, and **14**, and ^{31}P NMR signals

Table I. ^{31}P NMR Assignments for Phosphorodiamidothiolates and Related Compounds and Their Sulfoxide and Sulfone Derivatives

	$R_1R_2P(O)SR_3$			^{31}P NMR chemical shift, ppm		
no.	R_1	R_2	R_3	thiolate	sulfoxide	sulfone
			Phosphorodiamidothiolates			
1	n-C_3H_7NH	n-C_3H_7NH	CH_3	31.01		
2	$(CH_3)_2N$	$(CH_3)_2N$	CH_3	40.19	35.12	26.03
3	$(CH_2)_4N$	$(CH_2)_4N$	CH_3	30.91	26.88	20.01
4	$(CH_2)_4N$	$(CH_2)_4N$	C_2H_5	30.26	26.25	20.58
5	$(CH_2)_4N$	$(CH_2)_4N$	i-C_3H_7	29.33	26.39	21.13
6	$(CH_2)_4N$	$(CH_2)_4N$	C_6H_5	28.03	26.72	18.87
7	$(CH_2)_4N$	$(CH_2)_4N$	C_6H_4-4-NO_2	24.93		
8	$(CH_2)_5N$	$(CH_2)_5N$	CH_3	35.67	30.77	21.19
9	$(CH_2)_5N$	$(CH_2)_5N$	C_2H_5	34.88	29.82	21.51
10	$(CH_2)_5N$	$(CH_2)_5N$	t-C_4H_9	32.34	29.68	23.61
11	$O[(CH_2)_2]_2N$	$O[(CH_2)_2]_2N$	CH_3	35.07	28.82	18.11
12	$CH_3NCH_2CH_2CH_2NCH_3$		CH_3	32.29	25.34	17.19
13	$(CH_3)_2N$	$(C_2H_5)_2N$	CH_3	38.84	36.07 34.39	25.40
14	$(CH_2)_4N$	$(CH_2)_5N$	CH_3	32.71	29.64 28.04	20.82
15	$(CH_2)_4N$		$HNCH_2CH_2$	47.21		
			Phosphoramidothiolates			
16	H_2N	CH_3O	CH_3	34.04		
17	$CH_3C(O)NH$	CH_3O	CH_3	27.53		
18	$(CH_2)_4N$	i-C_3H_7O	CH_3	29.01	19.41 16.52	7.75
19	$CH_3NCH(CH_3)CH(C_6H_5)O$		C_2H_5 S_p	39.31	33.22	18.87
			R_p	37.96	33.87 32.97	18.97
			Phosphorotrithiolates			
20	n-C_4H_9S	n-C_4H_9S	n-C_4H_9	62.42	59.29	52.05
21	$C_6H_5CH_2S$	$C_6H_5CH_2S$	$C_6H_5CH_2$	59.62	56.63	49.52
22	t-C_4H_9S	t-C_4H_9S	CH_3	54.86		
			Phosphorothiolates			
23	C_2H_5O	C_2H_5O	C_6H_5	20.89		
24	C_6H_5O	C_6H_5O	n-C_5H_{11}	19.37		
			Phosphinothiolate			
25	C_6H_5	C_6H_5	CH_3	63.61		

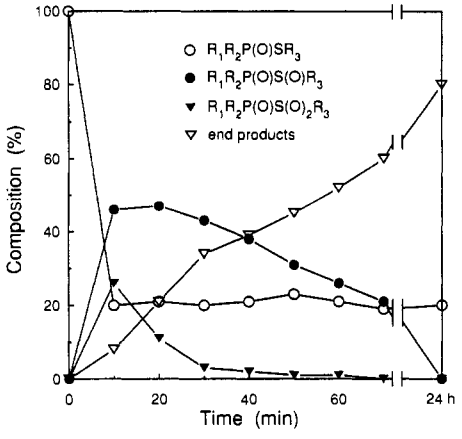


Figure 1. Phosphorothiolate sulfoxide and sulfone and end products [$R_1R_2P(O)OR_4$; R_4 = H, $S(O)_2R_3$, $C(O)C_6H_4$-3-Cl or $P(O)R_1R_2$] at various times after treatment of phosphorodiamidothiolate $R_1R_2P(O)SR_3$ [R_1 = R_2 = $(CH_2)_5N$, R_3 = CH_3] (compound 8) with 1.5 molar equiv of MCPBA in $CDCl_3$.

for the sulfoxides appeared 3–5 ppm upfield of those for the thiolates, and the signals for the sulfones appeared 7–11 ppm upfield of those for the sulfoxides (Table I). In addition, and as anticipated, the ^{13}C signals of the methyl substituents of **3** and **14** were shifted downfield by ~21 and ~31 ppm on conversion to the sulfoxides and sulfones, respectively (Tables III and IV). The ^1H chemical shifts of the analogous *S*-methyl groups of the sulfoxides and sulfones derived from **2**, **3**, **13**, and **14** were ~0.7 ppm downfield of the corresponding thiolates (Tables III and IV). The coupling constants between phosphorus and the methyl protons in ^1H NMR ranged from 12.7 to 13.1 Hz with the thiolates and from 8.9 to 14.5 Hz with the sulfoxides (Table III). Evidence that the P–S–C–H linkage remained intact in the sulfoxides was based on the ^{31}P chemical shifts and the three-bond coupling constants which were observed between phosphorus and the methyl protons consistent with the normal 10–15-Hz range for P–O–C–H or P–S–C–H (Gorenstein, 1983); this also ruled out rearrangement to the P–O–S–CH_3 moiety of the phosphinyloxysulfenates. The progressive upfield shifts of the ^{31}P signals and downfield shifts of the ^{13}C signals on going from the thiolate to its first and second oxidation products are consistent with the increasing oxidation state of the sulfur center.

The diastereomeric sulfoxides derived from chiral phosphorodiamidothiolates **13** and **14** and chiral phosphoramidothiolates **18** and **19**-R_p showed the appropriate two ^{31}P signals (Table I) and the two ^1H and ^{13}C signals of the *S*-methyl moiety (only **13** and **14** were examined) (Table III). As expected, this phenomenon was not seen for the sulfones. The failure to observe two ^{31}P signals for the sulfoxides of **19**-S_p suggests that the oxidation may be stereospecific. This rationale is based on the presence of the bulky chiral substituted-oxazaphospholidine substituent.

Comparison of ^{13}C and ^1H NMR Chemical Shifts for the *S*-Methyl Substituents of Two Thioethers, One Disulfide, One Thiocarbamate, and Selected Phosphorodiamidothiolates and Their Sulfoxide and Sulfone Derivatives (Table IV). The relationships

Table II. Phosphorothiolate Sulfoxide and Sulfone and Other Products at 5 and 50 Min after Treatment of Phosphorodiamidothiolate $R_1R_2P(O)SR_3$ [$R_1 = R_2 = (CH_2)_4N$, $R_3 = CH_3$] (Compound 3) with 1.0–4.0 Molar Equivalents of MCPBA in $CDCl_3$

MCPBA, molar equiv	min	composition, %						
		$R_1R_2P(O)S(O)_nR_3$			R_4 of $R_1R_2P(O)OR_4$			
		thiolate	sulfoxide	sulfone	SO_2CH_3	$C(O)C_6H_4Cl$	$P(O)R_1R_2$	H
1.0	5	47	43	10	0	0	0	0
	50	48	32	2	1	2	3	12
1.5	5	19	53	22	0	1	2	3
	50	20	34	1	4	8	10	23
2.0	5	18	32	37	1	2	2	8
	50	16	22	1	6	9	14	32
2.5	5	5	22	56	3	2	2	10
	50	3	6	6	9	11	27	38
3.0	5	0	0	68	10	6	8	8
	50	0	0	0	28	15	26	31
4.0	5	0	0	0	44	21	21	14
	50	0	0	0	44	22	21	13

Table III. ^{13}C and ^1H NMR Assignments for *S*-Methyl Substituents of *S*-Methyl Phosphorodiamidothiolates and Their Sulfoxide and Sulfone Derivatives

no.	$R_1R_2P(O)SCH_3$		NMR chemical shift, ppm, and coupling constant, Hz		
	R_1	R_2	thiolate	sulfoxide	sulfone
			^{13}C NMR		
3	$(CH_2)_4N$	$(CH_2)_4N$	12.20 (3.7)	33.85	43.67 (25.9)[a]
14	$(CH_2)_4N$	$(CH_2)_5N$	12.34 (3.5)	34.10 33.48	43.11 (26.9)[a]
			^1H NMR		
2	$(CH_3)_2N$	$(CH_3)_2N$	2.24 (13.1)	3.02 (9.1)	
13	$(CH_3)_2N$	$(C_2H_5)_2N$	2.23 (13.1)	3.05 (8.9) 2.91 (10.2)	2.99 (1.7)[a]
3	$(CH_2)_4N$	$(CH_2)_4N$	2.27 (12.7)	2.96 (14.1)	2.99 (1.7)[a]
14	$(CH_2)_4N$	$(CH_2)_5N$	2.25 (12.9)	2.96 (14.4) 2.92 (14.5)	2.99 (1.6)[a]

[a] It is interesting to note the large P–S–C two-bond carbon–phosphorus coupling constants (25.9–26.9 Hz) and the small P–S–C–H three-bond phosphorus–proton coupling constants (1.6–1.7 Hz) in the sulfones because they are much beyond the normal range of 0–5 and 16–20 Hz, respectively (Gorenstein, 1983). The unusual P–S–CH_3 bond coupling constants for the sulfones may be due to the effects of two oxygens on sulfur.

between the ^{13}C and ^1H chemical shifts of the methyl groups through the oxidation states $RSCH_3$, $RS(O)CH_3$, and $RS(O)_2CH_3$ for two thioethers, one disulfide, and one thiocarbamate were very similar to those for the phosphorodiamidothiolate oxidation series.

^{31}P NMR Assignments for Phosphorodiamidates Derived from MCPBA Oxidation of Six Phosphorodiamidothiolates. Products other than the sulfoxides and sulfones derived from **3** and **8** increased with amount of MCPBA and time of exposure to this peracid (Figure 1; Table II). There were four phosphorus-containing products from **3** and **8** in $CDCl_3$, with no observed intermediates other than the sulfoxides and sulfones, under the reaction conditions studied. Comparable products were also formed from **4**, **5**, **9**, and **10** (Table V). The products from **3** were identified as the phosphinyloxysulfonate (by its ^{31}P NMR chemical shift) and the phosphinyloxychlorobenzoate (isolated) and pyrophosphate (isolated) and phosphoric acid (analyzed after methylation) by their ^1H and ^{31}P NMR spectra (Figure 2). The ratio of these products did not change greatly with time, but it did depend on the amount of MCPBA added initially. The phosphoric acid was favored when MCPBA was limiting and the phosphinyloxysulfonate when a large excess of MCPBA was used (Table II). The ^{31}P signals of the phosphinyloxysulfonate shifted upfield with increasing bulk of the *S*-alkyl groups (Table V). Differences in the chemical shifts of the phosphoric acids (Table V) were attributable to changes in concentration and acidity.

The potential high reactivity of the intermediate oxidation products and the origins of the end products were examined for **3** by carrying out the oxidations in the presence of a 20-fold molar excess of any one of $CH_3S(O)_2OH$, *m*-chlorobenzoic acid, bis(pyrrolidyl)phosphorodiamidic acid, or water added to the reaction mixture before or immediately after the MCPBA; the resulting major ^{31}P NMR signal in each case was for the product that incorporated the added acid or water (Figure 2). This experiment also verified the identity of each of the four end products. With a 20-fold excess of methanol, methyl bis(pyrrolidyl)phosphorodiamidate was the major product, and this ester was the only product with methanol as the solvent.

Sulfur-Containing Products from MCPBA Oxidation of $^{13}CH_3$-Labeled 3, 14, and 16. ^{13}C NMR studies clarified the fate of the thiomethyl group on MCPBA oxidation of phosphorodiamidothiolates **3** and **14** (Figure 3) and phosphoramidothiolate **16**. As noted above, the intermediate phosphorothiolate sulfoxides (b) and sulfones (c) were observed by ^{13}C NMR from **3** (Table III) and **14** (Figure 3) but not from **16**. Additional products were the corresponding phosphinyloxysulfonates (j) (40.91 ppm from **3**, 40.85 ppm from **14**, and 40.80 ppm from **16**). The major product in each case was $CH_3S(O)_2SCH_3$ (h) with ^{13}C signals (18.86, 49.40 ppm) identical to those of the standard. Other compounds were $CH_3S(O)SCH_3$ (g) (15.15, 43.04 ppm) and $CH_3S(O)_2S(O)CH_3$ (i) (38.71, 35.11 ppm) [identical with the first product from oxidation of CH_3SSCH_3 and $CH_3S(O)_2SCH_3$, respectively, with limiting MCPBA under dilute and cool conditions] and $CH_3S(O)_2OH$ (f) (~40 ppm) (identified by matching with authentic standard). The tentative assignments of products d and e as $CH_3S(O)H$ and $CH_3S(O)_2H$, respectively, were based on observation of signal d when CH_3SH was treated with <0.1 molar equiv of MCPBA in $CDCl_3$ and signal e when water was added to $CH_3S(O)Cl$.

DISCUSSION

The goal of this study was to clarify the NMR spectroscopic characteristics and reactivity of phosphorothiolate sulfoxides as intermediates in MCPBA oxidation of phosphorothiolate pesticides in $CDCl_3$. Phosphorodiamidothiolates derived from pyrrolidine and piperidine were the starting esters of choice since they were found in a preliminary survey (Wu et al., 1991) to yield products of enhanced stability which led to recognition not only of the phosphorothiolate sulfoxides but also of the corresponding sulfones.

Table IV. Comparison of ^{13}C and ^{1}H NMR Chemical Shifts for the *S*-Methyl Substituents of Two Thioethers, One Disulfide, One Thiocarbamate, and Selected Phosphorodiamidothiolates and Their Sulfoxide and Sulfone Derivatives

	NMR chemical shift, ppm			difference		
R	$RSCH_3$ *a*	$RS(O)CH_3$ *b*	$RS(O)_2CH_3$ *c*	*b* − *a*	*c* − *b*	*c* − *a*
			^{13}C NMR			
CH_3	18.63	41.37	43.13	22.74	1.76	24.50
$C_6H_5CH_2$	15.46	37.05	39.54	21.59	2.49	24.08
CH_3S	22.68	43.04	49.40	20.36	6.36	26.72
$(n\text{-}C_3H_7)_2NC(O)$	13.37	37.59	40.23	24.22	2.64	26.86
$[(CH_2)_4N]_2P(O)$	12.20	33.85	43.67	21.65	9.82	31.47
$(CH_2)_4N$	12.34	34.10	43.11	21.76	9.01	30.77
$P(O)$		33.48		21.14	9.63	
$(CH_2)_5N$						
			^{1}H NMR			
CH_3	2.13	2.63	3.00	0.50	0.37	0.87
$C_6H_5CH_2$	1.98	2.54	2.77	0.56	0.23	0.79
CH_3S	2.43	3.02	3.32	0.59	0.30	0.89
$(n\text{-}C_3H_7)_2NC(O)$	2.31	2.82	3.14	0.51	0.32	0.83
$[(CH_2)_4N]_2P(O)$	2.27	2.96	2.99	0.69	0.03	0.72
$(CH_2)_4N$	2.25	2.96	2.99	0.71	0.03	0.74
$P(O)$		2.92		0.67	0.07	
$(CH_2)_5N$						
$[(CH_2)_5N]_2P(O)$	2.23	2.93	3.00	0.70	0.07	0.72

Table V. ^{31}P NMR Assignments for Phosphorodiamidates Derived from MCPBA Oxidation of Six Phosphorodiamidothiolates

	$[(CH_2)_nN]_2P(O)SR$		^{31}P NMR chemical shifts, ppm, for $[(CH_2)_nN]_2P(O)OR'$ products with indicated R′ substituents				
no.	*n*	R	SO_2R	$C(O)C_6H_4$-3-Cl	$P(O)[N(CH_2)_n]_2$	H	CH_3
3	4	CH_3	5.66	6.96	1.25	2.68	11.99
4	4	C_2H_5	5.41	6.88	1.16	3.04	
5	4	$i\text{-}C_3H_7$	5.15	7.01	1.29	2.55	
8	5	CH_3	8.04	8.88	3.49	3.77	14.82
9	5	C_2H_5	7.57	8.81	3.58	3.91	
10	5	$t\text{-}C_4H_9$	6.63	8.74	3.67	4.04	

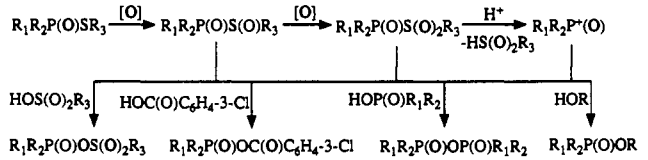


Figure 2. Phosphorothiolate sulfoxides and sulfones and other products formed on treatment of phosphorothiolates $R_1R_2P(O)SR_3$ with MCPBA in $CDCl_3$ (R = H or, when CH_3OH is added, CH_3 and H).

There are seven types of evidence for the intermediacy of phosphorothiolate sulfoxides and sulfones in peracid oxidation of phosphorothiolates: (1) The sulfoxide and sulfone are the first two products seen. (2) They are formed sequentially and in high yields with suitable levels of peracid. (3) The sulfones are less stable than the sulfoxides. (4) The sulfoxides show the expected three-bond P–S–C–H coupling constant. (5) Diastereomers are evident only for the sulfoxides. (6) The relationship between the relative chemical shifts of the SCH_3, $S(O)CH_3$, and $S(O)_2CH_3$ moieties in the phosphorus-containing series is the same as that in the corresponding oxidation series for thioethers, a disulfide, and a thiocarbamate. (7) Both oxidation products are very reactive with nucleophiles, yielding anhydrides or esters or acids (Figure 2).

The stability conferred on the sulfoxides and sulfones in the phosphorodiamidothiolate and phosphoramidothiolate series appears to depend both on electron donation by the nitrogen-containing substituents and on steric factors. Thus, for the bis(amidate)s the stability decreases in the order $(CH_2)_4N$ or $(CH_2)_5N$ > $(CH_3)_2N$ or $(C_2H_5)_2N$ ≫ RNH and CH_3S > C_2H_5S or $i\text{-}C_3H_7S$ > $t\text{-}C_4H_9S$ or C_6H_5S. In comparison, the lack of an observable sulfoxide or sulfone of **7** may reflect the reactivity of the nitrophenyl substituent as the leaving group. Only two of the non-amidates gave detectable sulfoxides and sulfones (i.e., **20** and **21**), and these were minor products. Low yields or the absence of sulfoxides and sulfones with the

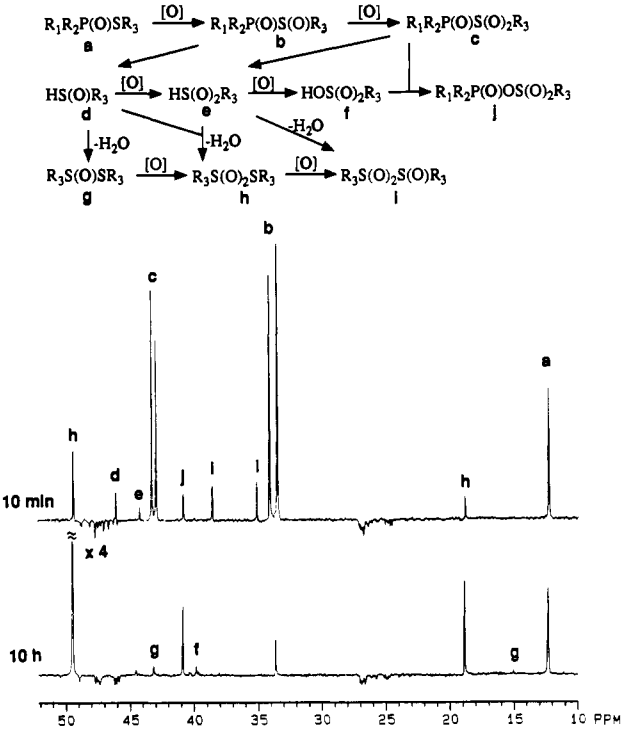


Figure 3. Sulfur-containing compounds formed on peracid oxidation of phosphorothiolates illustrated by ^{13}C NMR spectra for products at 10 min and 10 h after treatment of $R_1R_2P(O)SR_3$ [$R_1 = (CH_2)_4N$, $R_2 = (CH_2)_5N$, $R_3 = {}^{13}CH_3$] (compound **14**) with 1.5 molar equiv of MCPBA in $CDCl_3$. Criteria for structural assignments are given in the text.

trithiolates may be due to oxidation on other sulfur groups. The intermediate *S*-oxide is not sufficiently stabilized to be observed in the phosphinothiolate examined here; however, *S*-oxides have been reported for metal complexes of diphenylphosphinylthiolate (Effinger and Lorenz, 1990).

The present study and a preliminary paper (Wu et al., 1991) are the first reports of the direct observation of phosphorothiolate sulfones and of adequately characterized phosphorothiolate sulfoxides. They indicate that compounds examined earlier including $CH_3O(NH_2)P(O)SCH_3$ (**16**) and $C_2H_5O(CH_3)P(O)SC_2H_5$ do not have functionalities present which would confer sufficient stability on the sulfoxides and sulfones to allow their direct observation. The previous assignment for the sulfoxide of methamidophos was based on radiotracer and mass spectroscopic techniques, ^{13}C NMR studies, and a purported reversion of **16** sulfoxide to **16** on treatment with trimethyl phosphite (Eto et al., 1977; Thompson et al., 1984). We do not observe an oxidation product of **16** with a ^1H, ^{13}C, or ^{31}P NMR chemical shift appropriate for the sulfoxide [see also Segall and Casida (1981)]. Moreover, trimethyl phosphite would react with other sulfoxidized compounds including the major product $CH_3S(O)_2SCH_3$ (Eto et al., 1977; Michalski et al., 1960) in the complex reaction mixture. The description of $C_2H_5O(CH_3)P(O)S(O)C_2H_5$ by Yang et al. (1990) is based on ^{31}P NMR evidence, and our data suggest that the reported chemical shift is more characteristic of the phosphinyloxysulfonate than of the phosphorothiolate sulfoxide.

The ultimate products in the phosphorothiolate–peracid mixtures (Segall and Casida, 1983) can be rationalized in terms of the reactions attributable to the electrophilic character conferred on phosphorus by the oxidant, including the phosphorothiolate sulfoxide and sulfone described here and the phosphorus cation discussed by Wu et al. (1991), with nucleophiles generated during the course of the reaction (Figure 2). There are four major nucleophilic reactants: the sulfonic acids and water formed on oxidation or coupling reactions of the sulfenic and sulfinic acids (Figure 3); *m*-chlorobenzoic acid from reduction of MCPBA; phosphorus acids formed on reaction of the intermediates with water (Figure 2). The actual product distribution depends on the availability of the various nucleophiles, and the product ratio can be shifted to almost entirely any individual terminal compound by adding the appropriate nucleophile. Thus, as an example, on addition of excess methanol the phosphorylating reactivity of the phosphorothiolate sulfoxides and sulfones is evidenced by their quantitative conversion to the corresponding methyl phosphate.

Evaluation of the toxicological relevance of these findings requires three types of extrapolations: from model compounds to phosphorothiolate pesticides; from peracid to cytochrome P_{450} or flavin-containing monooxygenase; from nonnucleophilic solvents to aqueous medium. The substituent groups associated with the phosphorothiolate appear to influence the stability of the intermediate(s) more than the outcome of the reaction, thereby making the findings with a phosphorodiamidothiolate applicable to the pesticidal compounds. The shift from a peracid to the monooxygenase and from aprotic solvents to water is not likely to change the process of sulfoxide and sulfone formation but will alter further reactions. Thus, the high reactivity of the phosphorothiolate sulfoxides in all probability means that oxidative metabolism of the phosphorothiolates remote from their esterase targets leads to cleavage and therefore detoxification (Wing et al., 1983). The reactivity of the pesticidal phosphorothiolate sulfoxides is probably so high that sulfone formation is unlikely to proceed under biological conditions. Accordingly, in the bioactivation process, phosphorothiolate sulfoxides must be generated in close proximity to the AChE or other esterase or macromolecule with which they react.

ACKNOWLEDGMENT

We thank Neil Jacobsen of this laboratory for advice on the NMR studies.

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Received for review January 6, 1992. Accepted April 23, 1992.

Registry No. 1, 141930-73-6; 1 thiono precursor, 141930-74-7; 2, 18545-49-8; 2 thiono precursor, 63385-24-0; (±)-2 sulfoxide, 141930-75-8; 2 sulfone, 141930-76-9; 3, 137090-14-3; 3 thiono precursor, 141930-77-0; (±)-3 sulfoxide, 141930-78-1; 3 sulfone, 141930-79-2; 4, 137090-17-6; (±)-4 sulfoxide, 141930-80-5; 4 sulfone, 141930-81-6; 5, 141930-82-7; (±)-5 sulfoxide, 141930-83-8; 5 sulfone, 141930-84-9; 6, 141930-85-0; (±)-6 sulfoxide, 141930-86-1; 6 sulfone, 141930-87-2; 7, 141930-88-3; 8, 137090-15-4; 8

thiono precursor, 141930-89-4; (±)-**8** sulfoxide, 141930-90-7; **8** sulfone, 141930-91-8; **9**, 137090-18-7; **9** thiono precursor, 141930-92-9; (±)-**9** sulfoxide, 141930-93-0; **9** sulfone, 141930-94-1; **10**, 141930-95-2; (±)-**10** sulfoxide, 141930-96-3; **10** sulfone, 141930-97-4; **11**, 141930-98-5; **11** thiono precursor, 141930-99-6; (±)-**11** sulfoxide, 141931-00-2; **11** sulfone, 141931-01-3; **12**, 141931-02-4; **12** thiono precursor, 141931-03-5; (±)-**12** sulfoxide, 141931-04-6; **12** sulfone, 141931-05-7; (±)-**13**, 141931-06-8; (±)-**13** thiono precursor, 141931-07-9; (±)-**13** sulfoxide (isomer 1), 141931-08-0; (±)-**13** sulfoxide (isomer 2), 141931-09-1; (±)-**13** sulfone, 141931-10-4; (±)-**14**, 137090-16-5; (±)-**14** thiono precursor, 141931-11-5; (±)-**14** sulfoxide (isomer 1), 141931-12-6; (±)-**14** sulfoxide (isomer 2), 141931-13-7; (±)-**14** sulfone, 141931-14-8; (±)-**15**, 141931-15-9; (±)-**16**, 115182-35-9; (±)-**17**, 115096-11-2; (±)-**18**, 141931-16-0; (±)-**18** sulfoxide (isomer 1), 141931-17-1; (±)-**18** sulfoxide (isomer 2), 141931-18-2; (±)-**18** sulfone, 141931-19-3; *R* p-**19**, 65960-96-5; *R* p-**19** sulfoxide (isomer 1), 141931-20-6; *R* p-**19** sulfoxide (isomer 2), 142033-88-3; *R* p-**19** sulfone, 141931-21-7; *S* p-**19**, 66007-25-8; *S* p-**19** sulfoxide, 142033-89-4; *S* p-**19** sulfone, 142033-90-7; **20**, 78-48-8; (±)-**20** sulfoxide, 141931-22-8; **20** sulfone, 141931-23-9; **21**, 14974-76-6; (±)-**21** sulfoxide, 141931-24-0; **21** sulfone, 141931-25-1; **22**, 141931-26-2; **23**, 1889-58-3; **24**, 88873-93-2; **25**, 3096-03-5; **25** thiono analog, 15288-70-7; C_6H_5SH, 108-98-5; 4-$NO_2C_6H_4SH$, 1849-36-1; *t*-C_4H_9SH, 75-66-1; $H_2NCH_2CH_2SH$, 60-23-1; $(CH_2)_4NH$, 123-75-1; $(CH_2)_5NH$, 110-89-4; $[(CH_2)_4N]_2P(O)OSO_2CH_3$, 137090-21-2; $[(CH_2)_4N]_2P(O)OC(O)C_6H_4$-3-Cl, 141931-27-3; $[(CH_2)_4N]_2P(O)OP(O)[N(CH_2)_4]_2$, 51833-62-6; $[(CH_2)_4N]_2P(O)OH$, 141931-28-4; H_3CSCH_3, 75-18-3; $C_6H_5CH_2SCH_3$, 766-92-7; CH_3SSCH_3, 624-92-0; $(n\text{-}C_3H_7)_2NC(O)SCH_3$, 55852-80-7; $CH_3S(O)CH_3$, 67-68-5; (±)-$C_6H_5CH_2S(O)CH_3$, 26547-94-4; (±)-$CH_3SS(O)CH_3$, 85085-08-1; (±)-$(n\text{-}C_3H_7)_2NC(O)S(O)CH_3$, 141931-29-5; $CH_3S(O)_2CH_3$, 67-71-0; $C_6H_5CH_2S(O)_2CH_3$, 3112-90-1; $CH_3SS(O)_2CH_3$, 2949-92-0; $(n\text{-}C_3H_7)_2NC(O)S(O)_2CH_3$, 141931-30-8; $[(CH_2)_4N]_2P(O)OSO_2C_2H_5$, 137090-22-3; $[(CH_2)_4N]_2P(O)OSO_2C_3H_7$-*i*, 141931-31-9; $[(CH_2)_5N]_2P(O)OSO_2CH_3$, 137090-23-4; $[(CH_2)_5N]_2P(O)OSO_2C_2H_5$, 137090-24-5; $[(CH_2)_5N]_2P(O)OSO_2C_4H_9$-*t*, 141931-32-0; $[(CH_2)_5N]_2P(O)OC(O)C_6H_4$-3-Cl, 141931-33-1; $[(CH_2)_5N]_2P(O)OP(O)[N(CH_2)_5]_2$, 141931-34-2; $[(CH_2)_5N]_2P(O)OH$, 6913-00-4; $[(CH_2)_4N]_2P(O)OCH_3$, 141931-35-3; $[(CH_2)_5N]_2P(O)OCH_3$, 91250-05-4; (±)-$CH_3S(O)_2S(O)CH_3$, 141931-36-4; $CH_3S(O)_2OH$, 75-75-2; phosphorus oxychloride, 10025-87-3; sodium thiomethoxide, 5188-07-8; diphenylphosphinic chloride, 1499-21-4.