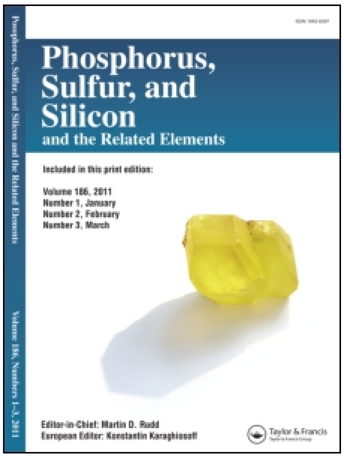

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NEIGHBORING GROUP PARTICIPATION IN ORGANIC REDOX REACTIONS. 13. INTRAMOLECULAR INTERACTION OF THE β-PHOSPHONIC ACID GROUP IN THE AQUEOUS IODINE OXIDATION OF THIOETHERS AND DISULFIDES.[1] GENERATION OF A PHOSPHONIC-PHOSPHORIC ANHYDRIDE

Joyce Takahashi Doi[a]; W. Kenneth Musker[a]
[a] Department of Chemistry, University of California, Davis, CA

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NEIGHBORING GROUP PARTICIPATION IN ORGANIC REDOX REACTIONS. 13. INTRAMOLECULAR INTERACTION OF THE β-PHOSPHONIC ACID GROUP IN THE AQUEOUS IODINE OXIDATION OF THIOETHERS AND DISULFIDES.[1] GENERATION OF A PHOSPHONIC–PHOSPHORIC ANHYDRIDE

JOYCE TAKAHASHI DOI† and W. KENNETH MUSKER
Department of Chemistry, University of California, Davis, CA 95616

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The oxidation of the phosphonic acid-thioether, 2-methylthioethanephosphonic acid (MTEP) and the oxidative-cleavage of the phosphonic acid-disulfide (PED) by aqueous iodine are accelerated by neighboring-group participation. The pH profiles indicate that in both cases it is the dianionic form of the phosphonate group which is responsible for accelerations of 10^6 and 10^2 in the reactions of MTEP and PED, respectively, compared to analogs without neighboring groups. The oxidative cleavage of PED in the presence of phosphate buffer generates ca. 30% of a hydrolytically stable, mixed phosphonic-phosphoric anhydride, which makes the proposed cyclic sulfenic-phosphonic anhydride intermediate one of the more efficient phosphate-coupling agents in aqueous solution. In contrast, no mixed anhydride is generated during the oxidation of MTEP in phosphate buffer.

INTRODUCTION

The formation of the high-energy P—O—P bond of polyphosphates is an essential part of living cells. Although the chemiosmotic theory of polyphosphate formation satisfactorily accounts for the biological process, there is continuing interest in chemical coupling processes in which phosphorus-containing anhydrides are formed.[2] Previous workers had shown that ATP formation could be coupled with a redox system involving the oxidation of a thioether, disulfide or thiol in a non-aqueous solvent in the presence of phosphate,[3] but we thought that a more logical route to the formation of phosphorus-containing anhydrides would involve a reaction which proceeds in dilute, aqueous solution.

We recently reported that the aqueous iodine oxidation of the carboxylic acid-thioether, 3-methylthiopropanoic acid[1b] is anchimerically assisted. Some carboxylate buffer catalysis was observed and we postulated that the buffer anion was attacking an intermediate cyclic acyloxysulfonium ion, $R\overline{S^{+}\text{—}O\text{—}C}(O)$, either at the sulfur atom to give an acyclic acyloxysulfonium ion or at the carbonyl carbon to give an carboxylic acid anhydride. In our previous study of the oxidative cleavage of the carboxylic acid-disulfide, 3,3′-dithiodipropanic acid,[4] we proposed the formation of a cyclic mixed sulfenic-carboxylic acid anhydride. There was no buffer catalysis of the rate, however, we thought that the buffer

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† Author to whom correspondence should be sent.

might be involved in the mechanism after the rate-determining step in which case it would not contribute to the rate law. We thought that if we oxidized a thioether or a disulfide having a neighboring phosphonic acid group, similar cyclic intermediates, $R\overline{S^{+}-O-P}(O_2)^{-}$ or a cyclic sulfenic-phosphonic anhydride, would form. Subsequent attack of phosphate buffer on the phosphorus atom of either intermediate would give a hydrolytically stable phosphonic-phosphoric anhydride which could be observed using ^{31}P NMR.

Dialkylphosphonates have shown to act as neighboring nucleophiles in the iodocyclization of dialkyl 4-pentenylphosphonates[5a] and in the substitution-cyclization of 1,3-dibromopropane with triethylphosphite[5b] to give 2-alkoxy-2-oxo-1,2-oxaphosphacycloalkanes. However, we have been unable to locate any reports of the use of phosphonic acid anions as neighboring nucleophiles.

For this study we have prepared the thioether, 2-methylthioethanephosphonic acid (MTEP), and the disulfide, bis(2-phosphonoethyl)disulfide (PED), and have examined the effect of phosphate buffer on the kinetics and products of their reactions with aqueous iodine.

EXPERIMENTAL SECTION

Equipment and Chemicals

All ^{31}P NMR spectra were run on a Nicolet NT-200 FT spectrometer with the variable temperature 12-mm probe thermostated at 25°C. All broad band ^{1}H-decoupled chemical shift values are reported relative to an external 85% H_3PO_4 reference standard. Spectral Parameters: $P_2 = 10.00\ \mu s$, $D_5 = 2.5$ s, SW = 6000 Hz.

^{1}H NMR spectra were run on a Varian EM-390 spectrometer. The infrared spectra were obtained on a Perkin–Elmer IR 32 FTIR spectrometer.

The diethyl 2-bromoethylphosphonate was obtained from Aldrich Chemical Company, Inc.

Kinetics

The kinetic procedures have been described previously.[6]

2-*Methylthioethanephosphonic Acid, MTEP*

Diethyl 2-methylthioethanephosphonate was prepared from diethyl 2-bromo-ethylphosphonate and sodium methanethiolate in diethylether/1,2-dimethoxyethane, as reported previously.[7] The distilled phosphonate (1.2 g, 5.7×10^{-3} mol) was heated with $(CH_3)_3SiCl$ (2.6 g, 24×10^{-3} mol, added in portions over 5 days) at 72° for 7 days.[8] The reaction mixture was evaporated under vacuum and 4 mL of H_2O added. The aqueous portion was extracted four times with 4 mL of diethyl ether and the aqueous layer was evaporated to dryness under vacuum. The residue was dissolved twice in a few mL of ethanol and then evaporated to dryness. The residue was dissolved in diethyl ether and reprecipitated by addition of hexane. The solvent was decanted and the precipitate (0.27 g, 30% yield) was dried under vacuum for several hours; m. 85–88°C. Anal. Calcd. for $C_3H_9PO_3S$; C, 23.08; H, 5.81. Found: C, 23.48; H, 5.91: ^{1}H NMR (D_2O) δ 2.6 (m, 2), 2.0 (m and s, 5); ^{31}P NMR (D_2O) δ 26.8. Attempts to use more efficient dealkylation reagents[9] yielded substantial amounts of side products.

bis(2-*Phosphonoethyl*)*disulfide, PED*

The Bunte salt was prepared from diethyl 2-bromoethylphosphonate and oxidized with iodine to bis(diethyl 2-phosphonoethyl)disulfide according to the method of Dirscherl.[10] The disulfide was purified by chromatography on silica gel using 5% ethanol in chloroform and isolated in 60% yield. ^{1}H NMR ($CDCl_3$) δ 4.05 (p, 8), 2.8(m, 4), 2.1(m, 4), 1.3(t, 12); ^{31}P NMR ($CDCl_3$) δ 28.8.

The bis(diethyl 2-phosphonoethyl)disulfide (1.5 g, 4.1×10^{-3} moles) was treated with $(CH_3)_3SiCl$(2.4 g, 0.022 moles) at 72°C for 7 days. The $(CH_3)_3SiCl$ was added in portions over 5 days. The resulting *tetra*trimethylsilyl ester was hydrolyzed in 4 mL of H_2O and the aqueous solution was washed four times with 5 mL portions of diethylether. The aqueous layer was evaporated to dryness under vacuum. The crude phosphonic acid (0.850 g, 3.86×10^{-3} mol, m 174–8°) was treated with isobutylamine (0.56 g, 7.7×10^{-3} mol) in ethanol. The salt,

$(C_4H_9NH_3)_3[HOP(O)_2(CH_2)_2SS(CH_2)_2(PO_3)]$ precipitated on addition of an equal volume of diethyl ether. The product was triturated three times with diethyl ether and dried (0.5 g salt, 40% yield). ^1H NMR (D_2O) δ 2.9(d, m, 10H), 2.0–1.7 (m, 7), 0.95 (d, 18H); ^{31}P NMR (D_2O) δ 20.1.

Anal: Calcd. for $C_{16}H_{45}N_3O_6S_2P_2$, C 38.3; H, 9.06: N, 8.38. Found: C, 39.09; H, 9.36; N, 8.69.

Products of Iodine Oxidation

From 2-Methylthioethanephosphonic Acid, MTEP: To a solution of MTEP (0.055 g, 3.5×10^{-4} mol) in 5 mL of 0.875 M phosphate buffer, pH 5.8, was added I_2 (0.089 g, 3.5×10^{-4} mol). The reaction was monitored by ^{31}P NMR and was complete in 10 min at 26°C. Only one product (^{31}P NMR (pH 5.8) δ 2.07) was formed on oxidation of MTEP (^{31}P NMR (pH 5.8) δ 22.4) under these conditions. The product was freeze-dried and identified as 2-methylsulfinylethanephosphonic acid. IR(KBr pellet): 1029 cm^{-1}, S—O; ^1H NMR (D_2O) 3.15 (m, 2), 2.75 (d, 3), 1.95(m, 2); ^{31}P NMR (D_2O) δ 26.8.

From bis(2-Phosphonoethyl)disulfide, PED, in the Absence of Buffer: The triisobutylammonium salt of PED (0.97×10^{-3} mol) was dissolved in water. Over the course of two hours, a KI-I_2 solution (38 mL of 0.096 M solution, 3.6×10^{-3} mol) was added to the solution and 2 M aqueous KOH was delivered by an autotitrator such that the solution was maintained at pH 8. The solution was freeze-dried and the anion characterized as $(O_3SCH_2CH_2PO_3)^{3-}$. ^1H NMR (D_2O) δ 2.95 (m, 2), 1.75 (m, 2). IR(KBr pellet): 1206 ($—SO_3^-$), 1048 (SO_3^-, $—PO_3^{2-}$), 972 ($—PO_3^{2-}$); ^{31}P NMR (pH 6.8, D_2O, as $(O_3SCH_2CH_2PO_3H)^{2-}$) δ 19.5.

From bis(2-Phosphonoethyl)disulfide, PED, with Phosphate Buffer: PED (0.175 g, 3.5×10^{-4} mol) and iodine (0.45 g, 17.7×10^{-4} mol) were added to 4.0 mL of a pH 6.1 (0.58 M) phosphate buffer solution at ambient temperature. After 30 min, the ^{31}P NMR spectrum displayed signals at δ 17.2 (s), δ 14.1 (*d*, $J = 26$ Hz), δ 11.29 (*d*, $J = 20$ Hz), δ ≈ −6.4 (two *d*, unresolved) in addition to $(SCH_2CH_2PO_3H)_2^{2-}$ (δ 20.4) and $(O_3SCH_2CH_2PO_3H)^{2-}$ (δ 19.3).

Two weeks later, the ^{31}P NMR spectrum displayed signals at δ 19.7(s), δ 13.9 (*d*, $J = 24$ Hz) and δ − 6.0 (*d*, $J = 24$ Hz) (Figure 1). When the sample was hydrolyzed at pH 0.3,[11] at 90°C for 3 h, the ^{31}P NMR spectrum showed only one signal due to an organophosphorus compound at δ 21.5 which is assigned to $(O_3SCH_2CH_2PO_3H)^{2-}$.

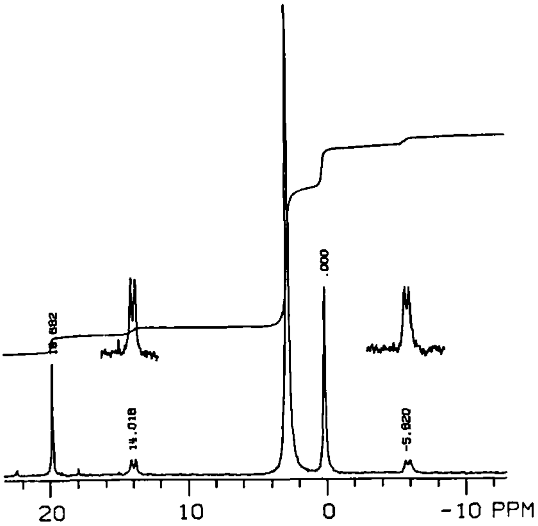


FIGURE 1 Phosphorus NMR spectra (200 MHz, in 0.6 M phosphate buffer, pH 6.1) of the products of the reaction between PED and iodine (taken after the solution was left at ambient temperature for two weeks): The signals have been assigned as follows: δ 19.7, $(O_3SCH_2CH_2PO_3H)^{2-}$; δ 14.0 ($J = 24$ Hz), $(O_3SCH_2CH_2PO_3PO_3H)^{3-}$; δ −5.8 ($J = 24$ Hz), $(O_3SCH_2CH_2PO_3PO_3H)^{3-}$; δ 2.7, phosphate buffer; δ 0.0, 85% H_3PO_4 reference.

RESULTS

Synthesis

Diethyl 2-methylthioethanephosphonate was prepared as described by Mikolajczyk[7] and converted to MTEP by treatment with chlorotrimethylsilane[8] followed by hydrolysis of the trimethylsilyl esters. The tetraethyl ester of PED was prepared from diethyl 2-bromoethylphosphonate by displacement of the bromide with thiosulfate and oxidation of the Bunte salt with iodine.[10] The tetraethyl ester was converted to PED *via* hydrolysis of the trimethylsilyl ester. The PED was purified as its triisobutylammonium salt and further characterized by NMR and IR.

^{31}P NMR Analysis

The only product of the iodine oxidation of MTEP either in the presence or absence of phosphate buffer is 2-methylsulfinylethanesulfonic acid. There is only a single signal in the ^{31}P NMR. The only product formed in the iodine oxidation of PED in the absence of buffer is 2-sulfoethanephosphonic acid. However, in the presence of phosphate buffer, the ^{31}P NMR spectrum taken when ~50% of PED has been oxidized, exhibits several signals in addition to PED ($\delta = 21.4$ in pH 6.6 buffer) and the final product, 2-sulfoethanephosphonic acid $(O_3SCH_2CH_2PO_3H)^{2-}$ ($\delta = 19.3$). We have tentatively assigned the signals as follows[12]: $\delta = 17.2$ (s) $(O_2SCH_2CH_2PO_3H)^{2-}$; $\delta = 14.1$ (d, $J = 26$ Hz) $(O_3SCH_2CH_2\underline{P}O_3PO_3H)^{3-}$; $\delta = 11.2$ (d, $J = 20$ Hz) $(O_2SCH_2CH_2\underline{P}O_3PO_3H)^{3-}$; $\delta = -6.4$ (m) $(O_nSCH_2CH_2PO_3\underline{P}O_3H)^{3-}$, ($n = 2$ or 3).

When the reaction mixture is allowed to stand in air for two weeks at room temperature, the sulfinic acid is oxidized and the only products observed are $(O_3SCH_2CH_2PO_3H)^{2-}$ and $(O_3SCH_2CH_2PO_3PO_3H)^{3-}$. After acid hydrolysis the only product observed is $(O_3SCH_2CH_2PO_3H)^{2-}$.

Kinetics

The rate constants for the iodine oxidation of MTEP are listed in Table I. When [MTEP] is varied, the pseudo first-order rate constant, k_{obsd}, is linear with [MTEP]; the slope is 1.04 and the coefficient of correlation is 0.997. Thus, the second-order rate constant $k_2 = k_{obsd}/[MTEP]$. The dependence of k_{obsd} vs $[I^-]$ is complex at both pH 5.5 and 6.2 ranging from −2.5 at lower $[I^-]$ to −3 at higher $[I^-]$. Plots of $10^4 k_{obsd} \times [I^-]^2$ vs $g/(g + [I^-])$ at pH 5.5, gave a coefficient of correlation of 0.995 when $g = 0.1$, and at pH 6.2, gave a coefficient of correlation of 0.997 when $g = 0.2$. A plot of pH (in the range 4.6 to 6.2) against log k_2 has a slope of 1.32 and a coefficient of correlation of 0.999. The non-integral dependence of k_2 on $[H^+]$ could arise from a combination of an inverse first-order dependence of the rate on $[H^+]$ and an inverse dependence of the value of g, which occurs in the iodide expression, on $[H^+]$. The observed rate was independent of phosphate buffer at pH 6.2 and of acetate buffer at pH 4.6. The

TABLE I

Rate constants of aqueous iodine oxidation of $(HO)_2P(O)CH_2CH_2SCH_3$,[a] MTEP

10^4[MTEP]	[KI]	[buffer]	pH	10^4k_{obsd}, s^{-1}	k_2 M^{-1} s^{-1}
9.2	0.10	0.050	5.5	2030 ± 40	221
9.2	0.20	0.050	5.5	350 ± 8	38
9.2	0.40	0.050	5.5	47.0 ± 0.8	5.1
9.2	0.80	0.050	5.5	8.5 ± 0.2	11
9.2	0.20	0.050	6.2	1740 ± 40	190
6.15	0.20	0.050	6.2	1260 ± 80	205
3.07	0.20	0.050	6.2	570 ± 60	186
6.15	0.80	0.050	6.2	31.9 ± 0.1	5.2
6.15	0.60	0.050	6.2	76 ± 8	12
6.15	0.40	0.050	6.2	219 ± 1	36
6.15	0.40	0.25	6.2	237 ± 3	39
6.15	0.40	0.15	6.2	287 ± 1	47
9.2	0.40	0.025	4.6	3.5 ± 0.3	0.38
9.2	0.40	0.05[b]	4.6	2.5	0.27
9.2	0.40	0.10[b]	4.6	2.37 ± 0.01	0.26

[a] 26.0°C, all concentrations in molarity, $[I_3^-]_0 = (3–9 \times 10^{-5}$ M), phosphate buffer, [KI] + [KCl] = 1.0 M; [b] acetate buffer; [c] pH < 4, the reaction is reversible.

rate law for the aqueous iodine oxidation of MTEP is given in equation (1)

$$-d[I_3^-]/dt = k[\mathrm{MTEP}][H^+]^{-1}[I_3^-][I^-]^{-2}\{g/(g+[I^-])\} \qquad (1)$$

The rate constants for the iodine oxidation of PED are listed in Table II. When [PED] is varied, the pseudo first-order rate constant, k_{obsd}, is first-order in [PED]

TABLE II

Rate constants of aqueous iodine cleavage of $(HO)_2P(O)CH_2CH_2SSCH_2CH_2P(O)(OH)_2$,[a] PED

10^4[PED]	[KI]	[buffer]	pH	10^4k_{obsd}, s^{-1}	k_2 M^{-1} s^{-1}
8.35	0.050	0.050	7.59	67 ± 3	8.0
8.35	0.050	0.050[b]	7.76	77 ± 4	9.2
8.35	0.050	0.050[b]	8.45	96 ± 5	11.4
8.35	0.050	0.050	6.63	25.9 ± 0.9	3.1
8.35	0.050	0.050	5.60	4.96 ± 0.04	0.59
8.35	0.050	0.050	6.72	22.5 ± 0.8	2.7
5.51	0.050	0.050	6.80	14.9 ± <0.1	2.7
2.76	0.050	0.050	6.80	9.3 ± 0.2	3.4
8.35	0.050	0.033	6.81	25.7 ± 0.4	3.1
8.35	0.050	0.0166	6.72	22.7 ± 0.1	2.7
8.35	0.20	0.050	6.8	5.3 ± 0.2	0.63
8.35	0.10	0.050	6.8	10.8	1.29
8.35	0.025	0.050	6.73	61 ± 2	7.3
8.35	0.025	0.050	6.73	70.6 ± <0.1	8.5
8.35	0.0125	0.050	6.73	187.8 ± 0.4	22
8.35	0.20	0.050	7.8	15.6 ± 0.8	1.9
8.35	0.10	0.050	7.8	31.9 ± 0.4	3.8
8.35	0.050	0.050	7.8	67 ± 4	8.0
8.35	0.025	0.050	7.8	162 ± 2	19.4
8.35	0.0125	0.050	7.8	450 ± 20	54

[a] 26.0°C, all concentrations in molarity, $[I_3^-]_0 = (3–9 \times 10^{-5}$ M), phosphate buffer, [KI] + [KCl] = 1.0 M;
[b] borate buffer.

($\log k_{\mathrm{obsd}}$ vs log [PED], coefficient of correlation = 0.995, slope = 0.79). The second-order rate constants, k_2, were calculated by dividing k_{obsd} by [PED]. The rate constants are independent of the concentration of buffer but are dependent on $[\mathrm{H}^+]$. In 0.05 M KI, $k_2 = 0.43 + 11.4\ (6\times10^{-8}/(6\times10^{-8}+[\mathrm{H}^+]))\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$, $r = 0.998$. The rate constants increase when the concentration of iodide is decreased, following an equation of the form $k_2 = (a\,[\mathrm{I}^-]^{-1} + b\,[\mathrm{I}^-]^{-2})\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$; at pH 6.8, $a = 0.12$, $b = 8.7\times10^{-4}$, $r = 0.989$; at pH 7.8, $a = 0.34$, $b = 4.1\times10^{-3}$, $r = 0.993$.

DISCUSSION

Oxidation of MTEP

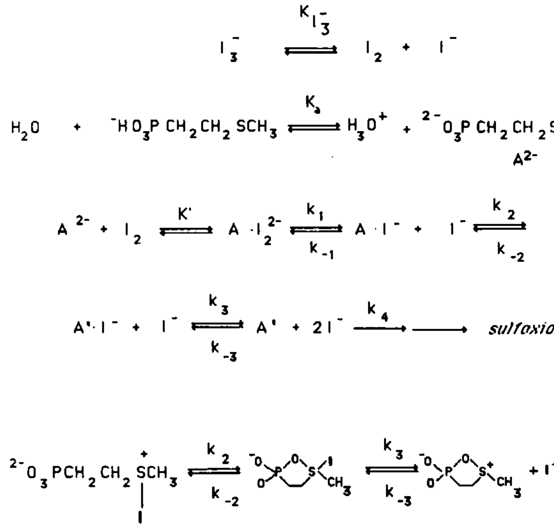
The aqueous iodine oxidation of MTEP to the sulfoxide occurs very rapidly and is buffer independent. The pK values of phosphonic acids are $\mathrm{pK}_1 = 2.4$ and $\mathrm{pK}_2 = 8.2$,[13] therefore, the predominant species in the pH range from 4.6 to 6.2 is the monoanion, $\mathrm{CH_3SCH_2CH_2PO_3H^-}$, the inverse first-order dependence on $[\mathrm{H}^+]$ indicates that the rate increase is directly proportional to the concentration of the dianion, $\mathrm{CH_3SCH_2CH_2PO_3^{2-}}$. Then if

$$[\mathrm{CH_3SCH_2CH_2PO_3^{2-}}][\mathrm{H^+}]/[\mathrm{CH_3SCH_2CH_2PO_3H^-}] = \mathrm{K}_2$$

Equation (1) becomes

$$-d[\mathrm{I_3^-}]/dt = k[\mathrm{CH_3SCH_2CH_2PO_3^{2-}}]\mathrm{K}_2^{-1}[\mathrm{I_3^-}][\mathrm{I^-}]^{-2}\{g/(g+[\mathrm{I^-}])\} \qquad (2)$$

A mechanism which is consistent with this rate law is shown in Scheme I. It is similar to the mechanism which we proposed previously for the oxidation of the carboxylic acid-thioether, 3-methylthiopropanoic acid.[1b] The lack of any buffer dependence on the rate of the oxidation and the absence of any P—O—P



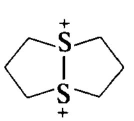
SCHEME 1 Aqueous $\mathrm{I_2}$ oxidation of MTEP

grouping in the ^{31}P NMR spectrum of the reaction mixture suggests that the phosphate buffer is not involved in the reaction either before or after the rate-determining step.

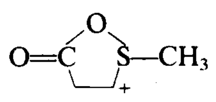
In the mechanism proposed in Scheme I, iodine and the phosphonate-thioether dianion form a complex, $A \cdot I_2^{2-}$, which cyclizes to an iodosulfurane, A'-I^- with loss of iodide ion. Subsequent loss of iodide from $A' \cdot I^-$ gives the phosphonyloxysulfonium ion, A'. A steady-state concentration of A' is suggested by the iodide dependence in the rate law in which factor "g" is equal to k_4/k_{-3}. This ratio is increased when the $[H^+]$ is decreased. This trend suggests that OH^- reacts with intermediate A' either as a nucleophile or as a base and in a manner which increases k_4/k_{-3}.

It is useful to compare the mechanism of the oxidation of a simple thioether in the presence of phosphate buffer with the oxidation of a thioether having a neighboring phosphonate. If, in a simple thioether, the rate law contains a phosphate buffer dependence and has an order in iodide of from −2 to −3, the mechanism involves an attack of the phosphate buffer on an iodosulfonium ion to give an acyclic phosphoryloxysulfonium ion.[14] In the case of the oxidation of MTEP, the order in iodide also varies from −2 to −3, but in this case, the internal phosphonate dianion takes the place of the external phosphate and attacks the iodosulfonium ion ($A \cdot I^-$) to give a cyclic phosphonyloxysulfonium ion (A').

In the two other thioether oxidations which occur with similar iodide dependences[1b,6a] $[I^-]^{-2}$ $\{g/(g + [I^-])\}$, the slight buffer dependence which is observed is attributed to the involvement of either buffer mono- or dianion in the decomposition step (k_4 in Scheme I). However, in the oxidation of MTEP no buffer intervention is observed at all. If the structures of the three steady-state intermediates which have been proposed for reactions having this iodide dependence are examined, a progression of charge types is noticeable; +2 for the 1,5-dithiacyclooctane dication[6a] (1,5-DTCO^{2+}), +1 for 2-methyl-5-oxo-1,2-oxathiolanium cation,[1b] and 0 for the 5,5-dioxo-2-methyl-1,2,5-oxathiophospholane, A'.



1,5-dithiacyclooctane
dication



2-methyl-5-oxo-1,2,oxathiolanium
cation

To the extent that the overall charge of the steady-state intermediate is important with respect to the ease of attack by a nucleophile, a smaller buffer dependence would be expected for the phosphonate-thioether since the net charge is zero.

Since the three compounds have similar rate laws (with the exception of their pH dependence) their relative rates may be compared. For 1,5-DTCO, MTEP and 3-methylthiopropanoic acid at pH 6 and 0.4 M KI, the relative rates are 300: 40: 1 respectively, and about 10^6 times faster than a simple thioether. The difference in rates between the neighboring carboxylate and phosphonate may be explained by the higher basicity of the phosphonate.

Oxidation of PED

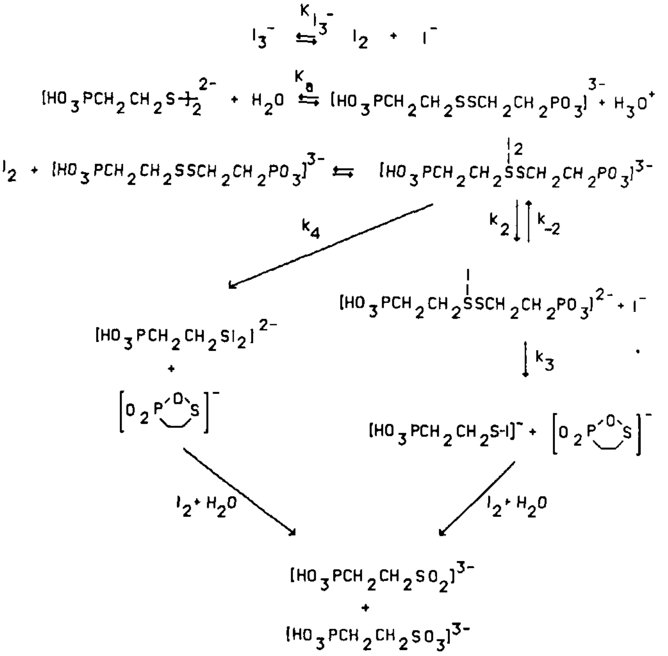
The final product of the oxidation of PED in the absence of buffer is 2-sulfoethanephosphonic acid and no intermediates are observed in the ^{31}P NMR. In the presence of phosphate buffer, when ~50% of the PED has been oxidized, there are now two intermediate species in the ^{31}P NMR spectrum; the sulfinic acid $(O_2SCH_2CH_2PO_3H)^{2-}$ and the mixed anhydride, $(O_nSCH_2CH_2PO_3PO_3H)^{3-}$, $n = 2$ or 3. After the sulfinic acids are air oxidized and the anhydride is hydrolyzed in strong acid, only 2-sulfoethanephosphonic acid, $(O_3SCH_2CH_2PO_3H)^{2-}$, and inorganic phosphate remain.

The rate of the reaction of PED is pH dependent and the rate constant for the reaction in solutions containing 0.05 M KI can be calculated using the equation $k_2 = 0.43 + 11.4\ (6 \times 10^{-8}/(6 \times 10^{-8} + [H^+]))\ M^{-1}\,s^{-1}$ ($r = 0.998$). The unassisted oxidative cleavage of the disulfide proceeds with a rate constant of $0.43\ M^{-1}\,s^{-1}$. This value is comparable to the rate constant of $0.594\ M^{-1}\,s^{-1}$ which we had observed for the unassisted rate of oxidative cleavage of $[HO(CH_2)_3S]_2$ under similar conditions.[4] The anchimerically assisted portion of the rate is due to a species having an acid dissociation constant of 6×10^{-8} ($pK_2 = 7.2$). This species would correspond to the second acid dissociation constant for the phosphonic acid.

The iodide dependence, which was calculated at pH 6.8 and 7.8, is of the form

$$k_{obsd} = a[I^-]^{-1} + b[I^-]^{-2}$$

and shows that the reaction occurs by two paths. One path, k_4, involves the disulfide-iodine complex and the other path, k_3, involves the disulfide-iodonium complex. (Scheme II)

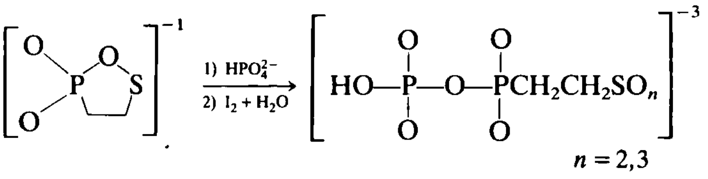


SCHEME 2 Aqueous I_2 oxidation of PED

The rate equation and the kinetic scheme reported here for the oxidative cleavage of the phosphonic acid-disulfide are similar to that which we have proposed for the oxidative cleavage of the carboxylic acid-disulfide 3,3′-dithiodipropanoic acid.[4] These two disulfides are the only ones which are required by the rate law to form disulfide-iodonium complexes.

The pH dependence of the rate was determined at 0.05 M KI and, at this iodide concentration, the reaction proceeds mainly *via* the path which has the rate constant k_4 and which is inverse first-order in iodide. Thus, the iodine complexes with one sulfur atom of the phosphonic acid-disulfide trianion and the cleavage occurs by attack of the dianionic phosphonate on the distal sulfur along an extension of the S—S bond axis, as shown by the path which has the rate constant, k_4. The involvement of the distal dianionic phosphonate in the cleavage reaction is indicated by the fact that the rate of reaction is accelerated by a group having a kinetic pK_a of 7.2 which corresponds to the pK_a of the dianionic form of the phosphonate group. The alternate path (with rate constant k_3) becomes increasingly important when the iodide concentration is decreased. The loss of iodide ion, as required by path k_3, may be facilitated by a stabilization of the positively charged disulfide-iodonium complex by the negatively charged proximal phosphonate monoanion but we do not believe that this kind of interaction has the correct geometry to induce disulfide cleavage.

The phosphonic-phosphoric anhydride, which is formed in ~30% yield, is formed, most likely, by reaction of the phosphate buffer with the phosphorus atom of the cyclic intermediate after the rate-determining step as shown below. The remaining 70% of the reaction probably proceeds by



reaction of phosphate buffer at the sulfur atom or by reaction of water at either the phosphorus or sulfur. Alternatively, oxidation may precede nucleophilic attack. These results are noteworthy because many other phosphorylating agents are not as efficient: the yield of pyrophosphate from acetylphosphate[2] and aqueous phosphate is ~15% and the yield of ATP from the oxidation of thiols and disulfides using iodine with ADP and orthophosphate[3] in non-aqueous solvents is ~26%. Our phosphonic acid-disulfide, PED, which undergoes cleavage to the cyclic sulfenic-phosphonic anhydride, 5-hydroxy-5-oxo-1,2,5-oxathiaphospholane or its anion, is the aqueous counterpart of the esters of mixed phosphonic-sulfonic anhydrides which are efficient phosphorylating agents in non-aqueous solvents.[15]

When the rate of oxidation is maximized, cleavage of the S—S bond in PED at low iodide concentration at pH 8 occurs about 100 times faster than the cleavage of an isolated disulfide bond. The acceleration provided by the phosphonate dianion is about the same as the acceleration caused by the carboxylate anion. Thus, the relative effectiveness of neighboring groups in disulfide cleavage reactions is 1° amine[16] $>$ —COOH $>$ —PO_3H_2 $\sim$ —OH at pH 5–6 but 1° amine $>$ PO_3H_2 $\sim$ —COOH $>$ OH at pH 7–8.

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