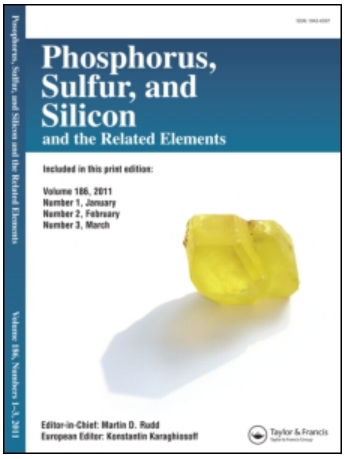

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STEREOELECTRONIC EFFECTS IN THE HYDROLYSIS OF PHOSPHONIUM IONS FROM ACYCLIC AND BICYCLIC PHOSPHOROTHIONATES

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STEREOELECTRONIC EFFECTS IN THE HYDROLYSIS OF PHOSPHONIUM IONS FROM ACYCLIC AND BICYCLIC PHOSPHOROTHIONATES

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The alkaline hydrolysis of the bicyclic phosphonium ion 1-methyl-3,5,8-trioxabicyclo-[2.2.2]octane-4-methylthiophosphonium ion **1** proceeds mainly with P—O bond cleavage as shown by hydrolysis in ^{18}O labeled water to form the cyclic epimers *cis*- and *trans*-2-methylmercapto-2-oxo-5-hydroxymethyl-1,3,2-dioxaphosphorinane (**2/3**) in addition to the bicyclic phosphate, 1-methyl-4-phospha-3,5,8-trioxabicyclo-[2.2.2]octane-4-oxide, **4**. The *trans* epimer **3** is formed after pseudorotation of the triagonal bipyramid (tbp) intermediate and is the predominant initial product. This could be explained by deprotonation of the initial neutral tbp intermediate **5** followed by fast pseudorotation to give the more stable anionic tbp **5'** in which the negatively charged oxygen is placed in the equatorial position of the intermediate. In contrast, the acyclic analogue triethoxy(methylthio)phosphonium ion undergoes alkaline hydrolysis with 100% P—S bond cleavage. It is very unusual to observe P—O bond cleavage competitive with P—S bond cleavage as we have demonstrated for the hydrolysis of the bicyclic thiophosphonium ion, **1**. These results are supportive of the stereoelectronic effect hypothesis.

Key words: Phosphonium; 1-methyl-3,5,8-trioxabicyclo-[2.2.2]octane-4-methylthiophosphonium ion; stereoelectronic effect; hydrolysis; mechanism.

INTRODUCTION

Thiophosphonium salts are quite reactive intermediates and readily hydrolyze in aqueous solution.[1,2] Hydrolysis mainly proceeds through P—S rather than P—O bond cleavage (reaction 1).[1–7]

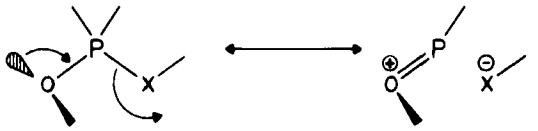
$$(R'O)_3P^+—SR + {}^-OH \rightarrow (R'O)_3P{=}O + RS^- \qquad (1)$$

This preference for P—S bond cleavage is reasonable since an alkylthio group is a better leaving group (less electronegative) than an alkoxy group. Thus 100% P—S cleavage is observed[5–7] in the alkaline hydrolysis of alkoxy(alkylthio)methylphenylphosphonium ions such as methoxy(methylthio)-methylphenylphosphonium hexachloroantimonate and methoxy-(methylthio)t-butylphenylphosphonium hexachloroantimonate.

However, consideration of the stereoelectronic effect[9–12] would lead to the prediction that if there are electron lone pairs antiperiplanar (app) to the P—O bond, then this bond may instead be favored to break compared to a P—S bond

with no app lone pairs. Ab initio molecular orbital calculations[12–16] and experiments[10,12–22] have suggested that the orientation of lone pairs on directly bonded oxygen or nitrogen atoms can significantly affect the reactivity of organophosphorous compounds.

The stereoelectronic effect is attributed to $n_0 \leftrightarrow \sigma^*_{P-X}$ orbital mixing (n_0, oxygen lone pair; σ^*_{P-X}, P—X antibonding orbital) which will facilitate P—X bond formation (or cleavage)[8–11] (Scheme I). Stereoelectronic interactions should facilitate P—X bond cleavage in phosphate ester[10] or phosphonium ion hydrolysis. In our present work, we show how stereoelectronic effects may contribute to the specificity of bond cleavage in the hydrolysis of the bicyclic thiophosphonium ion **1**. In addition evidence is presented for pseudorotation[23,24] of pentacovalent intermediates in the hydrolysis of **1**.



SCHEME I

EXPERIMENTAL SECTION

^{1}H and noise decoupled-^{31}P NMR spectra were recorded on either Bruker WP-80 or Nicolet NT-200 spectrometers at 80 (^{1}H) or 200 (^{1}H) MHz, respectively and ^{13}C NMR spectra were recorded on a IBM WP-200 SY spectrometer at 200 (^{1}H) MHz. Chemical shifts in parts per million for ^{1}H NMR spectra are referenced to Me_4Si and for ^{31}P spectra are referenced to 85% H_3PO_4. Melting points were obtained on a Thomas Hoover apparatus and are uncorrected.

Trimethyl Phosphorothionate, **10**. Sulfur (2.64 g; 0.0825 mol) was added slowly to trimethyl phosphite (10.0 g; 0.0806 mol) at 0° and after 1½ h of stirring, the trimethyl phosphorothionate was distilled, at a temperature below 25°C under ca. 0.1 mm pressure [Lit.[25] bp 95–100°C (11 mm)]; ^{1}H NMR ($CDCl_3$): δ 3.68 ppm (d, J = 13.5 Hz); ^{31}P NMR ($CHCl_3$): δ 72.9 ppm.

Triethyl phosphorothionate, **11** was prepared as described above from triethyl phosphite and sulfur; bp 45/50°C (ca. 0.2 mm) [lit[26] bp 100°C (16 mm)]; ^{1}H NMR ($CDCl_3$): δ 4.06 (d of q, J_{P-CH_2} = 10 Hz, $J_{CH_2-CH_3}$ = 7 Hz); ^{31}P NMR ($CDCl_3$): δ 67.6 ppm.

1-methyl-4-phospha-3,5,8-trioxabicyclo-[2,2,2]octane, bicyclic phosphite (**8**) was prepared by the method of Verkade and Reynolds.[27] To effect purification the crude product was sublimed three times at 50°C (2 mm); mp 96.5–98°C (lit.[27] mp 97–98°C after 3 sublimations); ^{1}H NMR ($CDCl_3$): δ 3.95 (d, J_{P-H} = 2 Hz, 6 H), 0.73 ppm (s, 3H); ^{31}P NMR ($CDCl_3$): δ 91.4 ppm (lit.[27] δ 9.15 ppm).

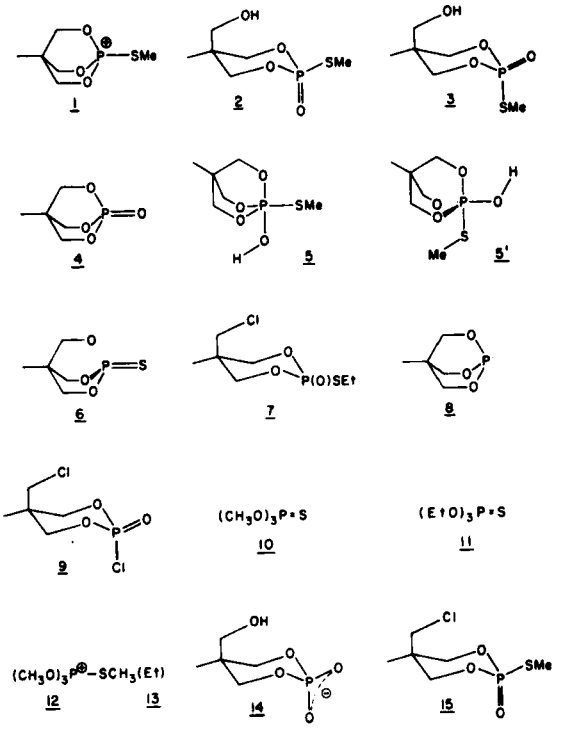
1-methyl-4-phospha-3,5,8-trioxabicyclo-[2.2.2]octane-4-oxide, bicyclic phosphate (**4**). Bicyclic phosphite (**8**) was oxidized with 30% hydrogen peroxide by the method of Verkade and Reynolds.[27] The product after crystallization from absolute ethanol melted at 245–248°C. This melting point improved to 249.5–250°C after several sublimations. (Lit.[27] mp after three sublimations: 249–250°C); ^{31}P NMR ($CDCl_3$): δ −7.8 ppm, ^{13}C NMR (CD_3OD): δ 80.50 (d, $^2J_{PC(2)}$ = 5 Hz), 35.40 (d, $^2J_{PC(1)}$ = 38 Hz, 12.30(s).

1-methyl-4-phospha-3,5,8-trioxa-bicyclo[2.2.2]octane-4-sulfide, bicyclic phosphorothionate (**6**) was prepared by the method of Verkade and Reynolds[27] from the reaction of bicyclic phosphite (**8**) with sulfur. The product was purified by several sublimations; mp 224–225°C (lit.[27] mp 224–225°C); ^{1}H NMR (CH_2Cl_2): δ 4.43 (d, J = 6 H), 0.85 ppm (s, 3 H); ^{31}P NMR (CD_3NO_2): δ 59.607 ppm.

Attempted Alkylation of Bicyclic Phosphate **4**. No alkylation was observed, as monitored by ^{31}P NMR, with a seven-fold excess of the following alkylation reagents in the indicated solvents

(Me_3OBF_4 in SO_2, FSO_3CH_3 in CH_2Cl_2, FSO_3CH_3 in SO_2). This result is consistent with Finley, *et al.*'s finding.[28]

Alkylation of bicylic phosphorothionate, **6**; *formation of bicyclic phosphonium ion,* **1**. The bicyclic phosphorothionate, **6** (52.4 mg, 0.291 mmol) and trimethyloxonium hexachloroantimonate (384.9 mg, 0.973 mmol) were mixed in ca. 3.0 mL of CD_3NO_2. In the ^{31}P NMR spectrum, besides the starting ester, **6**, new peaks at δ 66.94 (phosphonium ion, **1**), −1.87 (monocyclic ester, **14**), and −4.66 ppm (bicyclic phosphate, **4**) were observed confirming the formation of the phosphonium ion (δ 66.94 ppm). Addition of 3 equivalents of trimethyloxonium hexachloroantimonate was necessary to force the methylation to completion.



Similarly, trimethyloxonium tetrafluoroborate and alkyl triflates could be used for the alkylation of the bicyclic phosphorothionate. The bicyclic phosphorothionate **6** (0.158 mmol) was completely methylated in about 130 min. by 0.5 mmol trimethyloxonium tetrafluoroborate at rt in nitromethane. 0.23 mmol of the bicyclic phosphorothionate in nitromethane with two equivalents of methyl triflate at rt produced about 30% phosphonium ion in one hour and about 45% in 5 h. On the other hand, ethyl triflate, under identical conditions, produced only 15% phosphonium ion in 5 h. The phosphonium ion derived from trimethyloxonium hexachloroantimonate appeared in the ^{31}P NMR spectrum at δ 66.94 ppm, and that from the trimethyloxonium tetrafluoroborate reaction appeared at δ 66.88 ppm. The phosphonium ion derived from the reaction of the bicyclic phosphorothionate and ethyl triflate appears in the ^{31}P NMR spectrum at δ 64.4 ppm and with methyl triflate at 64.7 ppm.

The alkylation could also be monitored by ^1H NMR. Thus 65.2 mg (0.362 mmol) of bicyclic phosphorothionate **6** was mixed with 54.6 mg (0.369 mmol) of trimethyloxonium tetrafluoroborate in *ca.* 0.5 mL of sulfur dioxide. In the ^1H NMR new peaks at δ 5.02 (d, $J = 6$ Hz, CH_2–), 2.78 (d, $J = 19$ Hz, SCH_3) and 1.12 (s, CCH_3) ppm were observed for the phosphonium ion. Under these conditions about 50% phosphonium ion was formed. The reaction could be forced to completion by using 3 equivalents of trimethyloxonium tetrafluoroborate.

Alkylation of triethyl phosphorothionate. Triethyl phosphorothionate could easily be alkylated under identical concentrations utilized for the bicyclic phosphorothionate (2 equivalents of alkylating

reagents), with various alkylating reagents such as Et_3OSbCl_6/CH_3NO_2, Et_3OBF_4/CH_2Cl_2, and $CF_3SO_3CH_3/CH_2NO_2$. Alkylation was complete within $\frac{1}{2}$ h. S-methyl phosphonium ion appeared in the ^{31}P NMR spectrum at δ 46.6 ppm in nitromethane. The S-ethyl phosphonium ion appeared at δ 46.0 ppm in nitromethane with triethyloxonium hexachloroantimonate and at 45.7 ppm in methylene chloride with triethyloxonium tetrafluoroborate.

Alkylation of trimethyl phosphorothionate. Alkylation of trimethyl phosphorothionate, in general, did not lead to a stable phosphonium ion, but instead to a rearranged S-alkyl isomer (T. Fanni and K. Taira, unpublished observations). The thiophosphonium ion derived from the trimethyl ester was not used in further hydrolysis studies.

2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane, **9** was prepared by the method of Wadsworth *et al.*[29] The bicyclic phosphite **8** (1 g, 6.757 mmol) in 6 mL of carbon tetrachloride was added dropwise to a solution of sulfuryl chloride (0.913 g, 6.763 mmol) in 6 mL of carbon tetrachloride. ^1H NMR (CD_3CN): δ 0.96 ppm (s), 3.83 ppm (s), 4.50 ppm (m). ^{31}P NMR (CH_3CN, D_2O external): δ −3.5 ppm. ^{13}C NMR (CD_3CN): δ 75.47 ppm (d, $^2J_{P-O-C} = 7.5$ Hz), 47.2 ppm (s, CH_2Cl), 37.25 ppm (d, $^3J_{P-O-C-C} = 5.5$ Hz), 15.1 ppm (s, CH_3).

cis- and trans-2-thioethyl-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinate, **7** was prepared by the method of Wadsworth *et al.*[29] To the phosphorochloridate **9** (0.4 g, 1.83 mmol) in 6 mL acetonitrile/tetrahydrofuran (1:1 v/v) in a dry-ice bath, solid sodium thioethoxide (0.154 g, 1.83 mmol) was added with stirring. After 4 h at room temperature the solvent was removed under vacuum. The solid product was recrystallized from carbon tetrachloride to yield a mixture of the *cis* and *trans* esters, **7**. ^{31}P NMR (CD_3CN): δ 21.9 and 20.51 ppm (assignment of the stereochemistry for the two ester signals was not made). ^{13}C NMR (CD_3CN): δ 74.5 ppm (d, $^2J_{P-O-C} = 7$, Hz), 46.0 ppm (s, CH_2Cl), 37.5 ppm (d, $^3J_{P-O-C-C} = 5.3$ Hz), 24.6 ppm (d, $^2J_{P-S-C} = 4$ Hz), 17.6 ppm (d, $^3J_{P-S-C-C} = 11$ Hz), 16.0 ppm (s, CH_3) (only small differences were observed in the ^{13}C chemical shifts of the two epimers).

Products of the hydrolysis of the bicyclic phosphonium ion, **1**. The thiophosphonium ion **1** (produced from the reaction of 52.4 mg (0.291 mmol) of bicyclic phosphorothionate, **6** and 0.974 mmol of trimethyloxonium hexachloroantimonate in 3 mL CD_3NO_2) was added to 0.5 mL of 1.2 M sodium hydroxide solution in D_2O and 2.0 mL dimethylsulfoxide previously cooled in acetone-dry-ice bath with vigorous stirring. ^{31}P NMR of the above reaction mixture: δ 25.3 ppm, 24.96, and −5.4 ppm (in CD_3NO_2/DMSO-d_6/D_2O (6:4:1, v/v) δ 25.14 ppm, 24.70, and −4.26 ppm.

Unsuccessful attempts were made to separate and purify the hydrolysis products. To support our product assignments a sample of a structurally related thio ester **7** was independently synthesized. Epimeric analogs **7** (*cis* and *trans*) showed similar ^{31}P chemical shifts, 21.9 and 20.5 ppm (in CD_3CN), as the mixture of thiophosphate epimers, *cis*- and *trans*-2-methylmercapto-2-oxo-5-hydroxymethyl-1,3,2-dioxaphosphorinane (**2/3**), (δ 25.14 ppm and 24.70 ppm; in CD_3NO_2/DMSO-d_6/D_2O) from the hydrolysis of **1**.

To further confirm the structures of the products **2** and **3**, a ^{13}C NMR spectrum was taken of the reaction mixture which showed the presence of the two epimers in addition to the bicyclic phosphate **4**. ^{13}C NMR (CD_3OD) (see below for discussion of the presumed assignment of the stereochemistry of the two epimers): **3**, 76.69 ppm (d, $^2J_{P-O-C} = 7.4$ Hz), 63.5 ppm (s, CH_2OH), 34.85 ppm (d, $^3J_{P-O-C-C} = 4$ Hz), 24.5 ppm (d, $^2J_{P-S-C} = 4$ Hz), 15.6 ppm (S, CH_3). **2**: δ 75.17 ppm (d, $^2J_{P-O-C} =$ 7.3 Hz), 64.9 ppm (s, CH_2OH), 31.5 ppm (d), 24.8 ppm (d, $^2J_{P-S-C} = 4$ Hz), 15.5 ppm (s, CH_3). The ^{13}C spectra of the structurally related chloridate **9** and thioethyl phosphorinane ester, **7** were quite similar to that of the mixture of thiomethyl phosphorinane esters **2/3** except for —CH_2Cl which is shifted upfield relative to —CH_2OH.

Products of the strong alkali hydrolysis of bicyclic phosphonium ion, **1**. To the bicyclic thiophosphonium ion, **1** (synthesized in situ from the reaction of 11.1 mg (0.062 mmol) of bicyclic phosphorothionate, **6**, and 0.20 mmol of trimethyloxonium hexachloroantimonate in 2.5 mL CD_3NO_2) was added in steps with vigorous stirring either 2.4 mL of 1.2 M sodium hydroxide in D_2O and 1.5 mL DMSO previously cooled in an acetone-dry-ice bath or 0.5 mL of 1.2 M sodium hydroxide in D_2O and 2.0 mL DMSO.

Hydrolysis of triethyl methylthiophosphonium ion, **13**. To the phosphonium ion (ca. 2 mmol) produced by the reaction of triethyl phosphorothionate with methyl triflate was added either 0.1 or

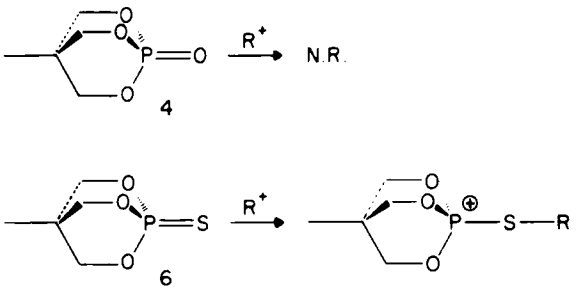
0.5 mL of 1.2 M sodium hydroxide solution in D_2O and 0.5 mL dimethyl sulfoxide previously cooled in acetone-dry-ice bath with vigorous stirring. ^{31}P NMR: −0.68 ppm (Lit.[28] δ −1.0 ppm in methylene chloride).

Hydrolysis of the bicyclic phosphonium ion **1** *in* ^{18}O *labeled water.* The phosphonium ion **1**, produced from trimethyloxonium tetrafluoroborate and hydrolyzed as described above except that 0.25 mL ^{18}O-labeled water and 0.25 mL D_2O was substituted for the D_2O.

RESULTS AND DISCUSSION

Phosphate ester alkylation

As reported by Finley *et al.*[28] the bicyclic phosphate, 1-methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]-octane-4-oxide, **4** is unreactive towards a variety of alkylating reagents such as trialkyloxonium tetrafluoroborate, trialkyloxonium hexachloroantimonate, and alkyl trifluoromethanesulfonate (Scheme II). In contrast, the



SCHEME II

bicylic phosphorothionate, 1-methyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane-4-sulfide, **6** readily undergoes alkylation with these reagents (Figure 1). The difference in nucleophilic reactivity of the phosphoryl oxygen and of phosphorothionyl sulfur may be explained by the hard and soft acid/base concept; according to which oxygen is a "hard base" and so reacts preferentially with "hard acids" (protons, carbonyl carbon, phosphoryl phosphorus), whereas sulfur

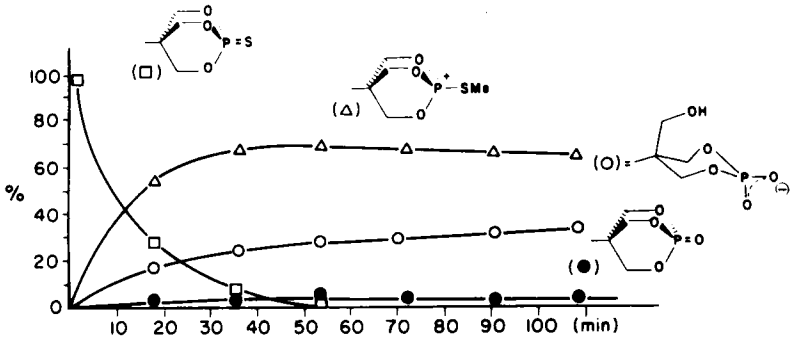
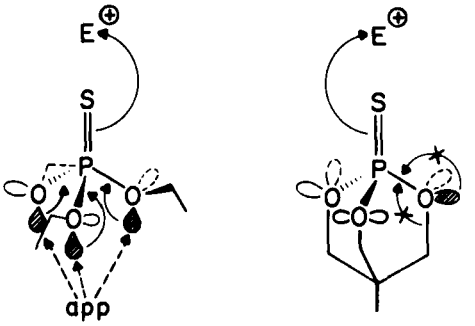


FIGURE 1 Time course for the reaction of 0.291 mM bicyclic phosphorothionate **6** (□) with trimethyloxonium hexachloroantimonate to yield thiophosphonium ion **1** (△), bicyclic phosphate ester **4** (●) and phosphate diester **14** (○), in CD_3NO_2, room temperature, as monitored by ^{31}P NMR.

is a "soft base" and reacts mainly with "soft acids" (tetrahedral carbon, halogens).

Although the bicyclic phosphorothionate can be alkylated, its reactivity is less than that of an acyclic phosphorothionate such as triethyl phosphorothionate. Thus, 0.23 M triethyl triethyl phosphorothionate in nitromethane can be 50% methylated in 10 minutes at rt when it is treated with two equivalents of methyltriflate. However, under the identical condition, the bicyclic phosphorothionate undergoes 50% methylation in 114 minutes.

The stereoelectronic effect provides the most satisfying explanation for the 11-fold poorer nucleophilicity of the bicyclic phosphorothionate relative to the acyclic phosphorothionate.[19,20,23] Thus, in the case of triethyl phosphorothionate, assuming free rotation about the P—O bonds, a maximum of three lone-pair orbitals on oxygens are antiperiplanar (app) to the P=S bond (Scheme III). However, the oxygen lone pairs in the bicyclic phosphorothionate cannot be oriented app to the P=S bond because of ring constraints (all lone pairs are locked gauche to the P=S bond). In the resonance description of the stereoelectronic effect (Scheme I), the atom which is app to the lone pairs will have a higher electron density. Indeed our earlier molecular orbital calculations support this interpretation.[12,14,15] Because of ring constraints in the bicyclic esters **4**/**6**, this stereoelectronic lone pair interaction is not feasible; and thus, the electron density on the oxygen or sulfur atom of the P=X bond (X = O, S) will be substantially decreased.



SCHEME III

This factor of 11, however, is considerably smaller than other stereoelectronic effects that our laboratory has observed; thus the bicyclic phosphate **4** and phosphorothionate **6** hydrolyze 10^2–10^3-fold faster than their acyclic analogues.[10,21] In many chemical reactions, steric effects also play an important role and, as can be expected, methyl triflate reacts faster than ethyl triflate. Thus, 0.23 M of the bicyclic phosphorothionate in nitromethane produces 45% phosphonium ion in 5 h at rt when 2 equivalents of methyl triflate is used. However, under the identical condition, ethyl triflate produces only 15% phosphonium ion.

Hydrolysis of bicyclic phosphonium ion 1-methyl-3,5,8-trioxabicyclo-[2.2.2]octane-4-methylthiophosphonium hexachloroantimonate, **1**. When bicyclic phosphonium ion **1** was added to a 1.2 M sodium hydroxide solution (concentra-

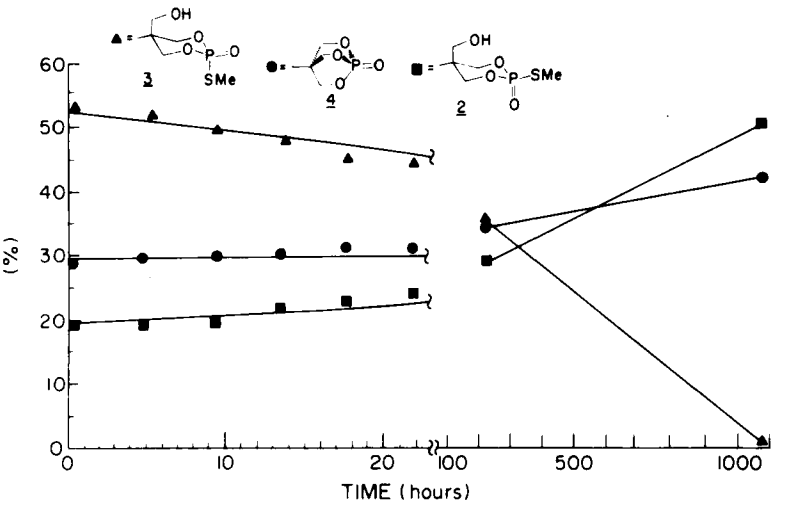
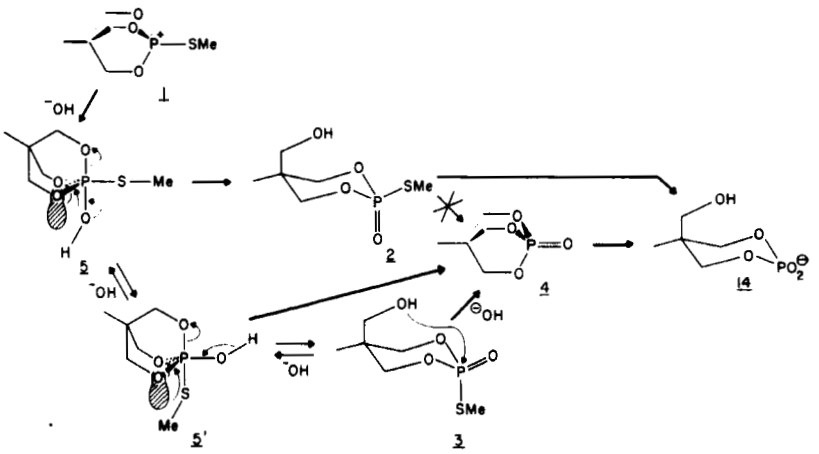


FIGURE 2 Time course for the reaction of the products of hydrolysis of bicyclic phosphonium ion **1** as monitored by ^{31}P NMR. The bicyclic phosphonium ion **1** (0.20 mmol), prepared as described in Figure 1 (ca. 70–80% pure, the remainder consisting of hydrolysis products, bicyclic phosphate ester **4** and phosphate diester **14**), is added to 0.5 mL of NaOD (1.2 M in D_2O) and 2.0 mL dimethylsulfoxide to yield bicyclic phosphate **4**(●), and thiophosphate esters **2**(■) and **3**(▲). Initially the NaOD/D_2O/DMSO solution gave a "pH" ~13 (uncorrected pH meter reading). During the first hour of reaction the pH dropped to 1.4.

tions are reported only for the added aqueous portion of the solvent mixture) and the reaction was followed by ^{31}P NMR, three product peaks appeared immediately at 25.14 ppm, 24.70 ppm, and −4.26 ppm. All of the phosphonium ion **1** was consumed during the base addition period and none remained in the first ^{31}P NMR spectrum acquired immediately after mixing. The time course for the hydrolysis of the initial reaction products is shown in Figure 2. Because of the rapid consumption of the alkali (2:1 molar ratio) due to the hydrolysis of both the phosphonium ion and the hexachloroantimonate, the pH dropped to 1.4 during the course of the subsequent reaction. The peak at −4.26 ppm was identified as the bicyclic phosphate **4** by adding an authentic, separately prepared sample of **4** to the reaction mixture which resulted in the increase in its intensity without the appearance of a new peak. The peaks at 25.14 ppm and 24.70 ppm were assigned to epimers **2/3** by comparison of the ^{31}P and ^{13}C NMR spectra of the epimeric 5-chloromethyl analogs **7**, as described in the experimental section.

Stereochemical assignments for **2/3** were tentatively made by assuming that only one of the thioester products can readily undergo direct recyclization to yield bicyclic ester **4** (see Scheme IV; these and additional arguments are further discussed below). Thus assignment of the peak at 24.70 ppm to the *trans* epimer **3** is based upon the observation that initially this peak represented 54% of the reaction products and that this peak decreased over the course of the reaction to 0%, while the peak at 25.14 ppm (assigned to the *cis* epimer **2**) *increased* from 18% to 54% at pH 1.4 over the course of seven days; the peak at −4.26 ppm (bicyclic ester **4**) increased from 28% to 46% during this reaction period.

If additional base is added to the hydrolysis reaction mixture to keep the



SCHEME IV

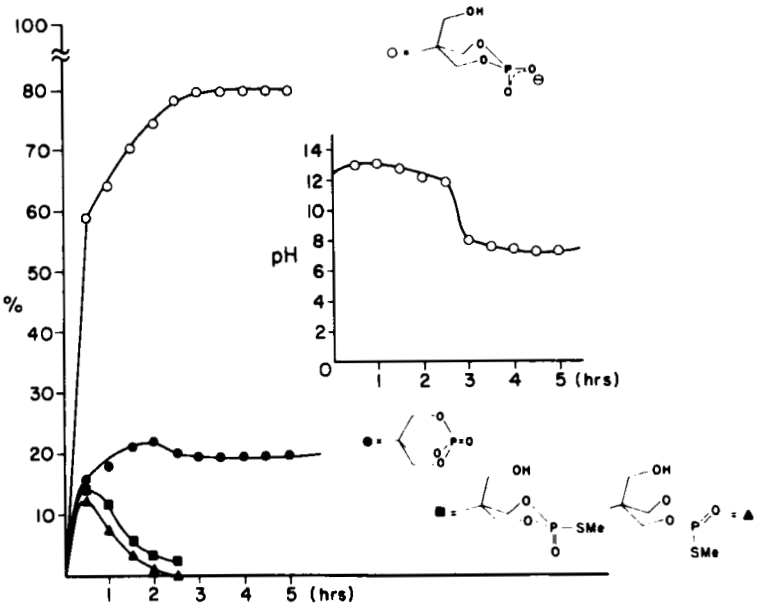


FIGURE 3 Time course for the basic reaction of the products of hydrolysis of bicyclic phosphonium ion **1** as monitored by ^{31}P NMR. The hydrolysis of the bicyclic phosphonium ion **1** (0.27 mmol) follows the experimental procedure described in Figure 2, and yields bicyclic phosphate **4** (●), thiophosphate esters **2**(■) and **3**(▲) and diester **14**(○). Initially the solution of 0.5 mL of 1.2 M $NaOH/D_2O$ and 2.0 mL DMSO gave a "pH" ~13. During the course of the ^{31}P NMR spectral block averaging, the pH gradually decreased and the pH was readjusted by addition of 1.2 M $NaOH/D_2O$ every 30 m. The pH of the NMR sample was measured before and after each block of spectra were acquired and after each readjustment of the pH and the initial pH of the sample prior to the NMR run is shown in the inset.

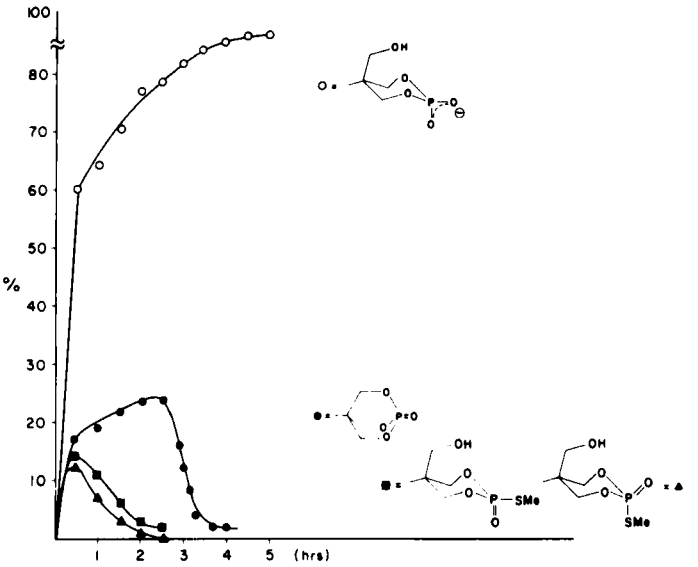


FIGURE 4 Time course for the basic reaction of the products of hydrolysis of bicyclic phosphonium ion **1** as monitored by ^{31}P NMR. The hydrolysis of the bicyclic phosphonium ion **1** (0.27 mmol) follows the experimental procedure described in Figures 2 and 3, and yield bicyclic phosphate **4**(●), thiophosphate esters **2**(■) and diester **14**(○). 1.2 M NaOH/D_2O was added in increments to keep the pH of the solution at ca. 12–13 during the entire reaction.

solution alkaline, further reactions of both thioesters **2** and **3** to **14** is observed (Figures 3 and 4). As shown in Figures 3 and 4, rapid hydrolysis of the phosphonium ion **1** yields within 0.5 hr not only the two epimeric thiophosphates **2/3** (12–14%) and 15–17% bicyclic **4**, but also ca. 60% of the phosphate diester **14** (pH ~12–13). Addition of alkali to keep the solution at pH ~13 for several hours, leads to a disappearance of the thiophosphates **2/3** and an increase in the amount of the final diester product **14**. Most importantly, during this period of time, the amount of the bicyclic phosphate **4** also increases. This suggests that at least some of the additional final product **14** that is formed derives from hydrolysis of the bicyclic phosphate **4**, which in turn is produced from the recyclization of **2** and/or **3** even under basic conditions. The analysis is complicated due to the concurrent synthesis (via recyclization) and hydrolysis of **4** under these basic conditions. Note that once all of **2** and **3** are consumed, the amount of **4** begins to decline as well. In Figure 3, the pH was allowed to decrease from ca. 12 to 8 at 2.5 hrs (inset Figure 3) and the proportion of bicyclic phosphate **4** remained constant at 20% (Figure 3). If the solution was kept at pH 12–13 during the entire reaction period (Figure 4), then once again **2** and **3** gradually decreased in the first 2.5 hrs with a gradual increase in **4** (besides a larger increase in **14**). After all of **2/3** is consumed (with an increase in **4**) then **4** rapidly hydrolyzes to **14** (during time period 3.0–4.0 hr; Figure 4). This shows that the 7–8% additional increase in the amount of bicyclic ester **4** during the 0.5–2.5 hr time period in the basic reaction is due to recyclization of **2** and/or **3**. Competing hydrolysis of **2**, **3** and/or **4** to **14** is also observed and very much complicates a more quantitative analysis.

Mechanism. As shown in the reaction Scheme IV, a trigonal bipyramid intermediate **5** is suggested to be initially formed by ^{-}OH attack at phosphorus on the bicyclic thiophosphonium ion **1**. ^{-}OH attack at carbon is ruled out because we do not observe any C—O bond cleavage, as evidenced by carrying the hydrolysis of phosphonium ion **1** in ^{18}O labeled water where the ^{31}P NMR of the hydrolysis product mixture **2/3** showed the appearance of new ^{18}O-isotope shifted ^{31}P peaks: δ 25.20 ppm (epimer **2**-^{16}O), 25.161 ppm (epimer **2**-^{18}O, 24.829 ppm (epimer **3**-^{16}O), 24.784 ppm (epimer **3**-^{18}O), −5.491 ppm (**4**-^{16}O), and −5.536 ppm (**4**-^{18}O). The intensity of the unlabeled and ^{18}O-labeled **2**–**4** product signals is found to be in the expected ratio based upon the amount of ^{18}O labeled water in the reaction mixture).

The trigonal bipyramid intermediate **5** could break down through P—S bond cleavage which is usually favored for acyclic systems[4–6] or through P—O bond cleavage. The unusual product distribution showing considerable P—O ring cleavage and the subsequent isomerization of the hydrolysis product **3** into the other hydrolysis product **4**, is consistent with the mechanism shown in Scheme IV. Immediate breakdown of the trigonal bipyramid intermediate **5** is shown to yield **2**, consistent with the required cleavage of the axial P—O bond of the trigonal bipyramid **5** (assuming applicability of the principle of expanded microscopic reversibility[23]).

The cyclic intermediate **5** can also undergo rapid pseudorotation[23] to form **5'** which can break down to yield **3** with apical cleavage of the P—O bond or **4** with apical cleavage of the P—S bond. In acid, **3** can recyclize to regenerate the trigonal bipyramid intermediate which can then break down again to yield **2**, **3** or **4**. This ring closure is permissible for the *trans* epimer **3** which places the OR and SMe groups in the apical positions of the tbp. Ring closure should not be readily possible for **2** since this would require placing the phosphoryl oxygen into the apical position. If it is unprotonated, then the tbp will have a very unfavorable O^{-} group in the apical position. Indeed the recyclization of **3** and the lack of reaction of **2** provides further support for the tentative assignment of the stereochemistry of the two thiophosphate esters.

In base (Figures 3/4) both epimeric thioesters **2** and **3** undergo further reaction with approximately the same half-life (~0.8–1 h). Presumably this reflects concurrently recyclization and direct hydrolysis of **3** and direct hydrolysis only of **2**. However there is no direct evidence that thioester **2** does not undergo recyclization in base. Recall again that *only* **3** undergoes recyclization and isomerization in acid.

Stereoelectronic Effect. These results are supportive of the stereoelectronic effect hypothesis.[8–10] It is very unusual to observe P—O bond cleavage competitive with P—S bond cleavage as we have demonstrated for the hydrolysis of the bicyclic thiophosphonium ion, **1**. Thus the acyclic triethyl methylthiophosphonium ion **13** hydrolyzes with complete P—S bond cleavage under the same conditions (either acid or base) to only yield triethyl phosphate. Since thioalkoxide is a much better leaving group than alkoxide (the pK's of the parent alcohols differ by >5 pK units), loss of alkoxide is expected. Ring cleavage (loss of alkoxide) in the

hydrolysis of bicyclic phosphonium ion **1** is thus unexpected if analyzed solely in terms of the leaving-group ability of $^{-}$OR vs. $^{-}$SR.

However, ring cleavage in the bicyclic system appears to be favored due to a stereoelectronic effect: since the electron lone pairs on the equatorial oxygens are antiperiplanar (app) to the breaking endocyclic P—O bond, this P—O bond cleavage results in the formation of compound **2**. (Note thioalkoxide loss is not stereoelectronically favored since none of the lone pairs of the equatorial ring oxygens are app to the SMe leaving group). It could be argued that the formulation of ring cleavage product **2** is initially favored over ring retention product **4** because the rate of pseudorotation of tbp intermediate **5** to yield tbp intermediate **5′** is slow relative to its breakdown. However, the observation of recyclization and breakdown of the tbp intermediate to phosphate ester **4** and the epimer thioester **3** shows that rate-limiting pseudorotation of the tbp intermediate **5′** is not responsible for the breakdown of **5** to the stereoelectronically favored ester **2**. The recyclization results also demonstrates that release of ring strain in the intermediate and transition states is not responsible for the unusual P—O vs. P—S bond cleavage. Whether **5** and **5′** further ionize to yield anionic intermediates[23,24] is not known and could be a contributing factor in the pseudorotation since placement of a negatively charged oxygen in anionic **5** into a equatorial position of **5′** is favored.[24]

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