could be reverted to MH^+_{trans} by the mechanism delineated above, thus "resetting" the system to the initial state.

Especially the potential biological model character of the merocyanine phototropism seems to us to warrant a more detailed investigation of how the individual steps of the reaction cycle depend upon both medium polarity and aryl substituents.

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Monomeric Methyl Metaphosphate. 3. Electrophilic Aromatic Substitution in Solution

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Abstract: Monomeric methyl metaphosphate can be generated either by the pyrolysis of methyl 2-butenylphostonate in the gas phase or by warming solutions of methyl hydrogen *threo*- or *erythro*-1-phenyl-1,2-dibromopropylphosphonate in the presence of triethylamine. The monomeric methyl metaphosphate produced by either pathway will react by electrophilic aromatic substitution, albeit in low yield, with either diethyl aniline or with tetraethyl-*m*-phenylenediamine. The fragmentations of the phenyldibromopropylphosphonates are strictly stereospecific, and correspond to trans elimination. The dianion of phenyldibromopropylphosphonic acid fragments much more rapidly than does the monoester monoanion, which in turn fragments much faster than does the diester. These facts, and the formation of electrophilic substitution products during the fragmentation process, are indicative of a monomeric metaphosphate mechanism.

Many reactions of phosphates have been postulated to take place by way of monomeric metaphosphates as intermediates.[1] Recently two new lines of evidence have supported such a mechanism: the results of pyrolysis of methyl 2-butenylphostonate[2] and the results of the "three-phase test" with reagents designed to produce metaphosphate.[3] In addition, compounds analagous to metaphosphates have actually been isolated.[4]

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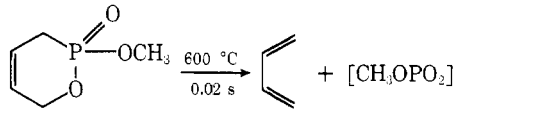
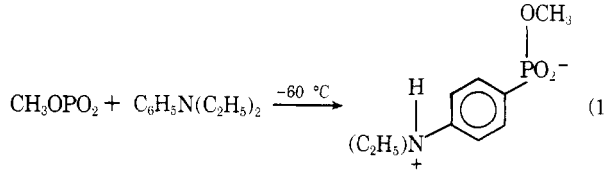
The argument that the pyrolysis of methyl 2-butenylphostonate in the gas phase produces free monomeric methyl metaphosphate rests most securely on the observation that some product in the gas stream from pyrolysis reacts with diethylaniline, stirred in *n*-butylbenzene at −60 °C, to yield the zwitterion of methyl hydrogen *p*-diethylaminobenzenephosphonate.[2] Only a powerful electrophile could be responsible for substitution under these experimental conditions. On the other hand, most of the product consisted of polymeric methyl metaphosphate, and the low yield of electrophilic substitution at least requires discussion.





(1)

The present paper reports that tetraethyl-*m*-phenylenediamine, like diethylaniline, undergoes electrophilic attack by the monomeric methyl metaphosphate generated by pyrolysis. Furthermore, it is here shown that monomeric methyl metaphosphate can be generated in solution at moderate temperatures (70 °C) from the fragmentation of β-bromophosphonates. Previous investigations of the decomposition of the dianions of β-halophosphonates[5-10] had suggested the hypothesis that the fragmentation occurs by way of monomeric metaphosphate ion. Since monomeric methyl metaphosphate is expected, on electronic grounds, to be a much more powerful electrophile than PO_3^-, a way to generate the former particle was needed. Previous attempts to eliminate alkyl esters of monomeric metaphosphoric acid from simple β-halophosphonates have led to dehydrohalogenation instead;[6,8] reactions giving displacement of halogen have also been observed.[6,9,10] Since 1-phenyl-1,2-dibromopropylphosphonate dianion rapidly undergoes fragmentation to produce a conjugated olefin[7] (along with bromide ion and a phosphate residue), we synthesized methyl hydrogen 1-phenyl-1,2-dibromopropylphosphonate; when this compound is heated to 70 °C in diethylaniline or in tetraethyl-*m*-phenylenediamine, in the presence of acetonitrile and water, it undergoes fragmentation. The products (obtained in low yield) include those expected for electrophilic substitution of monomeric methyl metaphosphate into the aromatic amines; these experiments are then diagnostic for monomeric metaphosphates. The relative rates of decomposition of the diester, monoester monoanion, and dianion of the phosphonic acid are also consistent with the monomeric metaphosphate mechanism.

Experimental Section

Materials. 1-Phenyl-1-chloropropylphosphonic acid (A), prepared according to Conant and Coyne,[5] melted at 182.5-184.5 °C: ^{1}H NMR (CD_3OD) δ 0.91 (t, J = 7.1 Hz, 3 H), 2.2-2.9 (multiplet, 2 H, diastereotopic CH_2), 7.30-7.46, 7.61-7.75 (multiplets, 5 H, phenyl); ^{31}P NMR (20% CD_3OD in CH_3OH) δ −17.21 (s).

***(E)*-1-Phenyl-1-propenylphosphonic acid** (formerly designated as trans) was prepared from 65 g of A as previously described,[7] except that the crude product while still hot was dissolved in water and neutralized with sodium hydroxide, and the alkaline solution freed from propenylbenzene by extraction with ether. After the water had been removed by rotary evaporation, the resulting white solid was extracted for 30 min with 1.1 L of boiling 95% ethanol and filtered hot; the insoluble residue was combined with a second crop (see below) to yield disodium salt. It was acidified with 200 mL of 3 N hydrochloric acid, the water removed by rotary evaporation, and the phosphonic acid extracted into a comparable volume of acetone. After the solvent had been removed, the product was crystallized from chloroform, mp 157-161 °C, yield 19.0 g (33%). The ^{1}H NMR spectrum in CD_3OD shows δ 1.67 (d of d, J_{H-H} = 7, J_{H-P} = 4 Hz, 3 H), 6.8 (d of q, J_{H-H} = 7, J_{H-P} = 22 Hz, 1 H), and 7.3 (5 H). Impure **(*Z*)-1-phenylpropenylphosphonic acid** (formerly designated as cis) was isolated as a mixture (78% *Z*/22% *E*) from the ethanol extract obtained in the synthesis of the *E* isomer. Solvent was removed by rotary evaporation to leave a white solid that was extracted with 200 mL of 90% boiling ethanol; the white, crystalline insoluble solid was combined with the crude disodium salt of the *E* acid, above. After the ethanol solution had been cooled to room temperature, the disodium salt of the *Z* acid, still contaminated with *E*, was precipitated with ether and crystallized from 95% ethanol. This crude product was used for the preparation of the erythro dibromo acid; see below.

***threo*-1-Phenyl-1,2-dibromopropylphosphonic acid** was prepared as previously described.[7] It was best crystallized by dissolving the bromination product in a little diethyl ether, adding alcohol-free chloroform, and removing most of the ether by rotary evaporation. The resulting crystalline product was extensively dried at 50 °C under vacuum; only then was the melting point[7] of 180.5-181.5 °C achieved. ^{1}H NMR, (CD_3OD): δ 2.13 (d of d, J_{H-H} = 6.4, J_{H-P} = 0.8 Hz, 3 H), 5.16 (d of q, J_{H-H} = 6.4, J_{H-P} = 2.9 Hz, 1 H), 7.23-7.38, 7.72-7.87 (aromatic multiplet, 5 H). Proton decoupled ^{31}P NMR (20% CD_3OD in CH_3OH); δ −11.85 (s). **Methyl hydrogen *threo*-1-phenyl-1,2-dibromopropylphosphonate** was prepared by demethylating crude dimethyl *threo*-1,2-dibromo-1 phenylpropylphosphonate. The latter was made by methylating the corresponding phosphonic acid (5 g, 0.014 mol) with a slight excess of diazomethane in anhydrous ether. After removal of the ether by rotary evaporation it was identified by ^{1}H NMR ($CDCl_3$); δ 2.11 (d of d, J_{H-H} = 6.4, J_{H-P} = 0.9 Hz, 3 H), 3.40 (d, J_{H-P} = 10.7 Hz, 3 H), 3.81 (d, J = 10.8 Hz, 3 H), 5.09 (d of q, J_{H-H} = 6.5, J_{H-P} = 3.0 Hz, 1 H), 7.27-7.45, 7.70-7.86 (5 H). Note that the separate doublets of δ 3.40 and 3.81 arise from the diastereotopic methoxyl groups of the diester.

The dimethyl phosphonate prepared from 5 g of the acid was dissolved with lithium bromide (1.22 g, 0.014 mol) in 10 mL of dry acetone; after 40 h at room temperature, a product (2.5 g) crystallized; it was recrystallized from 15 mL of methanol by adding 250 mL of benzene. The recrystallized product was acidified with 10 mL of 1 N hydrochloric acid, and the organic acid extracted into two 10-mL portions of chloroform. After the chloroform had been removed by rotary evaporation, the product was dissolved in 5 mL of benzene and crystallized by the addition of 80 mL of hexanes to yield methyl hydrogen *threo*-1-phenyl-1,2-dibromopropylphosphonate (1.3 g, 25% of theory): mp 148-149.5 °C; ^{1}H NMR (CD_3OD) δ 2.11 (d of d, J_{H-H} = 6.4, J_{H-P} = 0.7 Hz, 3 H), 3.50 (d, J_{H-P} = 10.9 Hz, 3 H), 5.17 (d of q, J_{H-H} = 6.4, J_{H-P} = 2.8 Hz, 1 H), 7.27-7.41, 7.73-7.87 (m, 5 H); proton decoupled ^{31}P NMR (20% CD_3OD in CH_3OH) δ −13.55 (s). Anal. Calcd for $C_{10}H_{13}Br_2PO_3$: C, 32.29; H, 3.52; Br, 42.96; P, 8.33. Found: C, 32.12; H, 3.58; Br, 42.86; P, 8.48.

***erythro*-1-Phenyl-1,2-dibromopropylphosphonic acid** was prepared essentially according to the previously published procedure.[7] In order to carry out the synthesis, the crude mixture of disodium 1-phenyl-1-propenylphosphonate (24.1 g, 78% *Z*/22% *E*) was converted into a mixture of the corresponding dry diacids by acidifying with aqueous hydrochloric acid, removing water by rotary evaporation, and azeotroping with ethanol. The product, redissolved in ethanol, was separated from sodium chloride by filtration and then thoroughly dried by evaporation and azeotroping with benzene: mp of the dibromo acid, 187-188.5 °C (lit.[7] 185.5-187.5 °C); ^{1}H NMR δ 1.57 (d, J = 6.6 Hz, 3 H), 5.06 (d of q, J_{H-H} = 6.5, J_{H-P} = 5.5 Hz, 1 H), 7.26-7.41, 7.85-7.97 (m, 5 H); proton-decoupled ^{31}P NMR (20% CD_3OD in CH_3OH) δ −13.67 (s).

Methyl hydrogen *erythro*-1-phenyl-1,2-dibromopropylphosphonate was prepared by demethylating crude dimethyl *erythro*-1-phenyl-1,2-dibromopropylphosphonic acid, following the same procedures outlined for the threo isomer. The crude dimethyl ester was identified by its ^{1}H NMR spectrum ($CDCl_3$); δ 1.51 (d, J = 6.6 Hz, 3 H), 3.45 (d, J_{H-P} = 10.5 Hz, 3 H), 3.89 (d, J_{H-P} = 11.0 Hz, 3 H), 4.99 (d of q, J_{H-H} = 6.6, J_{H-P} = 5.3 Hz, 1 H), 7.26-7.44, 7.77-7.93 (m, 5 H). After demethylation with lithium bromide and acidification, the product was dissolved in 10 mL of chloroform and 70 mL of hexanes added to give 3.2 g (61% of theory) of methyl hydrogen *erythro*-1-phenyl-1,2-dibromopropylphosphonate: mp (after crystallization) 156-159 °C; ^{1}H NMR (CD_3OD) δ 1.52 (d, J = 6.5 Hz, 3 H), 3.57 (d, J_{H-P} = 10.6 Hz, 3 H), 5.07 (d of q, J_{H-H} = 6.5, J_{H-P} = 5.2 Hz,

1 H), 7.29–7.43, 7.78–7.94 (m, 5 H); proton decoupled ^{31}P NMR (20% CD_3OD in CH_3OH) δ −15.26. Anal. Calcd for $C_{10}H_{13}Br_2PO_3$: C, 32.29; H, 3.52; Br, 42.96; P, 8.33. Found: C, 32.12; H, 3.58; Br, 42.86; P, 8.48.

(*E*)- and (*Z*)-1-bromo-1-propenylbenzene (previously[7] designated as cis and trans, respectively) were prepared by the published procedure.[7] The ^1H NMR spectrum ($CDCl_3$) of the *E* isomer: δ 1.64 (d, J = 10 Hz, 3 H), 6.62 (q, J = 10 Hz, 1 H), and 7.40 (s, 5 H); that of the *Z* isomer ($CDCl_3$) δ 1.94 (d, J = 10 Hz, 3 H), 6.25 (q, J = 10 Hz, 1 H), 7.35 (m, 5 H).

***N,N,N′N′*-Tetraethyl-*m*-phenylenediamine.** Twice recrystallized *m*-phenylenediamine dihydrochloride (61.2 g) was neutralized with sodium hydroxide (27.2 g) in 300 mL of water, and 114.3 g of sodium bicarbonate added. Diethyl sulfate (209.7 g) was dripped into the solution with stirring at room temperature during 1 h; the carbon dioxide produced was vented through a bubbler. Stirring was continued for 5 h. The reaction mixture was then stirred at 50 °C for 5 h with an additional 57.2 g of sodium bicarbonate and 105 g of diethyl sulfate. The warm reaction mixture was saturated with sodium chloride and filtered; the products were extracted into two 300-mL volumes of chloroform. After the chloroform had been removed by rotary evaporation, the products were partitioned between 150 mL each of carbon tetrachloride and water. (The water removed a salt tentatively identified as *m*-diethylaminotriethylanilinium monoethyl sulfate). The carbon tetrachloride layer was reduced by rotary evaporation and dried over calcium chloride and the product was vacuum distilled: yield 56 g (75% of theory); bp 90 °C (0.1 mm).[11] The compound was stirred with 1/4 (v/v) pivaloyl chloride (to remove traces of secondary amine) and redistilled: ^1H NMR ($CDCl_3$) δ 1.23 (t, J = 7.0 Hz, 12 H), 3.40 (q, J = 7.0 Hz, 8 H), 6.10–6.20, 7.05–7.25 (m, 4 H). Anal. Calcd for $C_{14}H_{24}N_2$: C, 76.31; H, 10.98; N, 12.71. Found: C, 76.27; H, 11.02; N, 13.07.

Dimethyl 2-Diethylamino-4-diethylaminobenzenephosphonate. Redistilled phosphorus trichloride (6.9 g) was added with stirring to dry tetraethyl-*m*-phenylenediamine (11.0 g) and left under argon for 1 h at room temperature to give a solid cake. The cake was broken up under anhydrous ether (50 mL) and triethylamine (7.6 g), and solids were removed by filtration. Solvent was rotary evaporated, and an ice-cold solution of triethylamine (15.2 g) and methanol (4.8 g) was added to the remaining fuming oil. The mixture was treated with 50 mL of ether and filtered, and the filtrate was reduced by rotary evaporation to leave an oil (presumably the aryl phosphonite) with a sickeningly sweet odor. Exposure to the vapors from this compound produced headaches and nausea; it should be handled only with great care. The oil was immediately added to Goldman's activated manganese dioxide (100 g) in benzene (300 mL); the mixture was stirred overnight and then filtered. Evaporation of the solvent left 5.25 g of dimethyl 2-diethylamino-4-diethylaminobenzenephosphonate as an oil which was separated from a small quantity of tetraethyl-*m*-phenylenediamine and purified by molecular distillation at 94 °C (3–4 × 10^{-6} mm). The compound could also be purified by chromatography on Florisil with ethyl acetate as eluent. ^1H NMR ($CDCl_3$); δ 1.04, 1.15 (overlapping triplets, J = 7.1, 7.0 Hz, 12 H), 3.03 (q, J = 7.1 Hz, 4 H), 3.34 (q, J = 7.0 Hz, 4 H), 3.71 (d, J_{H-P} = 11.2 Hz, 6 H), 6.34–6.44, 7.51–7.74 (m, 3 H); proton decoupled ^{31}P NMR (20% CD_3OD in CH_3OH) δ −24.0 (s). Anal. Calcd for $C_{10}H_{13}Br_2PO_3$: C, 32.29; H, 3.52; Br, 42.96; P, 8.33. Found: C, 32.10; H, 3.63; Br, 43.02; P, 8.24.

Methyl hydrogen 2-diethylamino-4-diethylaminobenzenephosphonate was prepared by heating the dimethyl ester above (1.0 g) with sodium iodide (0.9 g) in dry acetonitrile (10 mL) for 4 days. The reaction was carried out in a round-bottom flask equipped with a Vigreux column to vent the methyl iodide as it was formed. Solvent was removed by rotary evaporation, and the product purified by column chromatography on 110 g of Florisil, with acetonitrile/methanol/water (8.8/0.85/0.35) as eluent; 30-mL fractions were collected every 10 min. An unidentified compound eluted in fractions 6–8; the zwitterionic product eluted in the 1 L of solvent following fraction 33. (Apparently Florisil protonates the expected lithium salt.) The solvent was removed by rotary evaporation and the product crystallized by dissolving it in a minimum amount of methanol and adding about 100 mL of ether. The crystals (0.27 g, 29% of theory) melted at 182 °C. The product, on titration with aqueous base, showed a pK (25 °C, μ = 0.25) of 11.1 and a neutralization equivalent of 311 ± 10 (calcd 315). The high pK suggests that the compound exists as a zwitterion, with the proton presumably bonded at the 2-diethylamino group; electrostatic and steric effects would then raise the pK above that for typical aromatic ammonium salts. ^1H NMR (D_2O), pD 4: δ 1.09, 1.22 (overlapping triplets, J = 7.1, 7.2 Hz, 12 H), 3.23–3.78 (quartets, partially obscured by a doublet, 11 H), 6.65 (d of d, $J_{H-H} \simeq 2$, $J_{H-P} \simeq 4$ Hz, 1 H), 6.88 (d of d of d, $J_{H_3-H_5} = J_{H-P} \simeq 2.0$, $J_{H_6-H_5} = 9.0$ Hz, 1 H), 7.51 (d of d, $J_{H-H} = 9.0$, $J_{H-P} = 12.0$ Hz, 1 H); proton-decoupled ^{31}P NMR (D_2O, pH 4) δ −15.3 (s).

The compound required hard burning in the presence of V_2O_5 catalyst to give the correct combustion analysis. Anal. Calcd for $C_{15}H_{27}N_2O_3P$: C, 57.11; H, 8.63; N, 8.88; P, 9.82. Found: (different samples) C, 57.24, 57.02; H, 8.66, 8.76; N, 8.65, 8.82; P, 9.82, 9.74.

***sym*-Dimethylpyrophosphoric acid** was purchased from Pfaltz and Bauer. The ^{31}P NMR spectrum showed that it was a complex mixture but predominantly methyl phosphate and the desired *sym*-dimethyl pyrophosphate. The latter could be obtained 95% pure by the procedure of Glonek and VanWaser:[12] ^{31}P NMR (D_2O) 9.90 (s).

Pyrolyses. Pyrolyses of 70–200 mg of methyl 2-butenylphostonate were conducted as previously described.[2] The pyrolysis products were trapped in a magnetically stirred mixture of 1.0 g of *N,N,N′,N′*-tetraethyl-*m*-phenylenediamine in 1.7 g of *n*-butylbenzene cooled in a dry ice–isopropyl alcohol bath. Following the reaction, either $CDCl_3$ and 0.3 mL of triethylamine or toluene-d_8 was added to the reaction mixture, and proton-decoupled ^{31}P NMR spectra were obtained. Methyl hydrogen 2-diethylamino-4-diethylaminobenzenephosphonate was identified at δ −12.7 by adding synthetic compound to the product mixture in toluene-d_8. The absolute yield of product is unreliable because of difficulties with mechanical transfer. Nevertheless, the yield seemed variable, and the best yields (approximately 5%) were obtained when the hot zone (600 °C) of the pyrolysis tube was close to the outlet.

Isolation. The aromatic substitution product was isolated by washing the pyrolysis trap with 10 mL each of methylene chloride and barium hydroxide and shaking this mixture with the trapping solution in 3 mL of $CDCl_3$. The aqueous layer was separated by centrifugation from the copious precipitate and the organic solvent, and then neutralized with carbon dioxide. Barium carbonate was removed by further centrifugation, the aqueous layer evaporated, and the resulting solid extracted with methanol (7 mL). After the methanol was removed, the residual solid was dissolved in 0.2 mL of water and purified by high-pressure liquid chromatography, using a Waters Associates ALC Model 202 apparatus equipped with a 24 × 1/8 in. Bondapak C-18/Porasil B column (35–50 μ); the progress of the chromatography was monitored at 254 nm with a UV detector. Products were eluted with acetonitrile/methanol/water (1.2/0.8/8.0) at a flow rate of 0.37 mL/min and 1000 psi. The aromatic substitution product emerged in the fractions collected between 43 and 54 min, and after concentration by rotary evaporation was rechromatographed at a flow rate of 0.15 mL/min. It then emerged between 150 and 220 min, well separated from contaminants. After the solvent was removed by rotary evaporation, the product was dissolved in D_2O (0.25 mL). Its NMR spectrum was identical with that of a similarly purified synthetic sample. The best yields of purified aromatic substitution product actually isolated from pyrolysis experiments were about 1–3%.

Elimination Experiments. Samples of methyl hydrogen *erythro*- and *threo*-1-phenyl-1,2-dibromopropylphosphonate (100 mg) were placed in dry 180 × 12 mm NMR tubes, closed with rubber serum caps, and dried overnight at 70 °C under vacuum; the tubes were evacuated through hollow needles inserted through the caps. Then either diethylaniline (1.5 mL) or *N,N,N′,N′*-tetraethyl-*m*-phenylenediamine (1.5 mL), plus acetonitrile (1.5 mL) and water (0.06 mL) was added. The solid acid dissolved promptly. The reaction mixtures, under argon, were warmed to 70 °C. Although the fragmentations were 75% complete after 1 h, the tubes were heated for 6–10 h to ensure complete reaction. Acetonitrile-d_3 (1 mL) was then added to each sample to provide a lock for Fourier transform NMR, and proton-decoupled ^{31}P NMR spectra obtained (see Figure 1).

Purified compounds from the elimination were isolated as follows. The reaction products were partitioned between 10 mL each of methylene chloride and saturated barium hydroxide. The saturated barium hydroxide solution was treated as already described under the pyrolysis experiments. The aromatic substitution products separated by HPLC emerge quite pure after one pass. That from diethylaniline eluted with water between 2 and 3 h at a pressure of 1000 psi and a flow rate increasing from 0.35 to 0.50 mL/min; that from tetraethyl-*m*-phenylenediamine eluted in acetonitrile/methanol/water

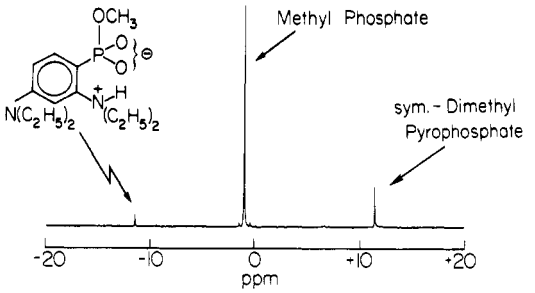


Figure 1. The 40.5-MHz ^{31}P spectrum of products from the elimination of methyl hydrogen *threo*-1-phenyl-1,2-dibromopropylphosphonic acid in tetraethyl-*m*-phenylenediamine, acetonitrile, and 2% water at 70 °C.

(1.2/0.8/8.0) after only 0.9–2 h. The products were identified by their ^1H NMR spectra.

The methylene chloride extract containing 1-bromo-1-propenylbenzene was extracted twice with 25-mL portions of 1 N hydrochloric acid to remove aromatic amines. Methylene chloride was then removed by rotary evaporation, and contaminating water by azeotropic distillation at 35 °C with two 20-mL portions of benzene. The resulting oil was dissolved in $CDCl_3$ for ^1H NMR analysis. The absolute yields of isolated (*E*)- and (*Z*)-1-bromo-1-propenylbenzene, formed respectively from the erythro and threo monoacids of the dibromophosphonate, were 66 and 71%.

The following data show that the reactions are almost stereospecifically clean. First, the threo and erythro starting materials are pure by crystallization (mp threo, 148–149.5 °C; erythro, 156–159 °C). More significantly, their NMR spectra are distinct (Figure 2). The doublet for the terminal methyl group of these acids appears at δ 1.52 for the erythro isomer and at δ 2.11 for the threo isomer; even a trace of diastereomeric contaminant would have been plainly visible, since these signals are entirely separate from one another. Similarly, the isomers of 1-bromopropenylbenzene can be distinguished not only by IR spectra (as previously[7]) but also from the NMR spectra. The signal from the terminal methyl group of the *E* isomer appears as a doublet centered at δ 1.64, whereas that from the *Z* isomer appears at δ 1.94. Although these signals are not separated as widely as those for the starting materials, they are nevertheless far enough apart to provide a baseline from which to estimate isomeric impurities. Further, the aromatic regions of the ^1H NMR spectra are entirely different: the *E* isomer shows a singlet at δ 7.34, whereas the *Z* isomer shows a complex multiplet; since, however, these signals are in the same area, they do not offer as good an analytical probe of product purity as do the signals from the methyl groups.

The NMR spectra, shown in Figure 2, show that each of the isomeric olefins is, however, contaminated with a trace of the other; perhaps 1–2% of the *Z* isomer is present in the *E* isomer, and vice versa. Incidentally, the crude *E* product obtained from the decomposition of the erythro methyl ester in tetraethyl-*m*-phenylenediamine shows evidence, in the NMR spectrum, of a trace of some additional impurity; whatever it is, however, it is not the corresponding *Z* isomer.

Elimination experiments with methyl hydrogen *threo*- and *erythro*-1-phenyl-1,2-dibromopropylphosphonate in tetraethyl-*m*-phenylenediamine and in diethylaniline were also carried out in the absence of water. The yields of aromatic substitution products (1–3%) isolated from reactions with tetraethyl-*m*-phenylenediamine were similar to those obtained with diethylaniline; the major product was of course polymeric material.

Rates of Elimination. Rates of elimination were crudely estimated. The compound to be tested, together with 1.5 mL of tetraethyl-*m*-phenylenediamine, 1.5 mL of acetonitrile-d_3, and 0.06 mL of water, was placed in an NMR tube and the disappearance of starting material monitored by ^{31}P NMR. A small loss of *erythro*-1-phenyl-1,2-dibromopropylphosphonic acid (0.10 g) had occurred at room temperature by the time its spectrum was recorded; addition of 0.15 mL of triethylamine which converts starting compound to the dianion caused its complete disappearance in less than 1.5 min ($k_{obsd} > 0.5$ min^{-1}), the time it took to record a signal; it had previously been shown that the reaction is essentially instantaneous in aqueous 0.1 M KOH.[7] Elimination from the monomethyl esters (0.10 g) at 70 °C was followed by withdrawing samples from the temperature bath at 15-min intervals, quenching in ice, and recording integrated spectra; pseudo-first-order rate plots were linear for 3–5 half-times. The rate for the erythro isomer was 0.022 min^{-1} ($t_{1/2}$ = 31 min); addition of 0.15 mL of triethylamine caused no difference in rate, demonstrating that the ester is completely ionized. The threo monomethyl ester gave k_{obsd} = 0.032 min^{-1} ($t_{1/2}$ = 22 min) with 0.15 mL of added triethylamine. After 1 h at 70 °C the erythro dimethyl ester (~0.1 g) showed <5% reaction ($k_{obsd} < 10^{-3}$ min^{-1}); continued heating for 24 h gave demethylation as did the addition of 0.15 mL of triethylamine (10% reaction in 1 h). No detectable level of aromatic substitution product was formed from the dimethyl ester after 1 h at 70 °C under either condition.

Methods. NMR spectra were obtained with Varian A-60 and XL-100 spectrometers. The latter instrument is equipped for Fourier transform, and has a phosphorus probe at 40.5 MHz. The phosphorus chemical shifts are reported relative to external 85% phosphoric acid

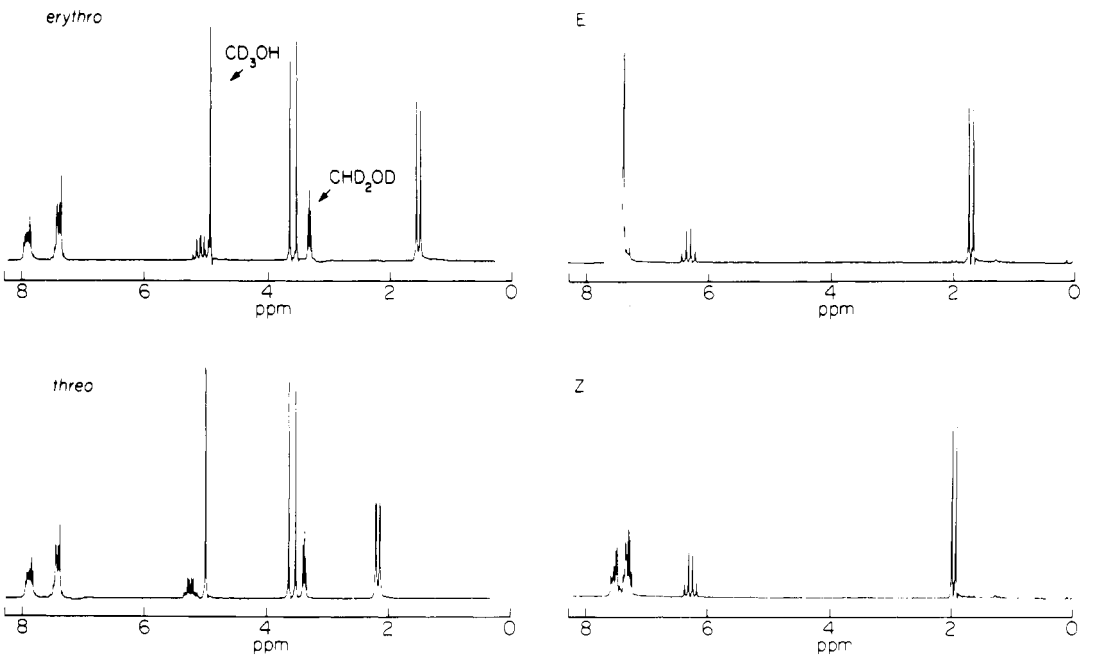


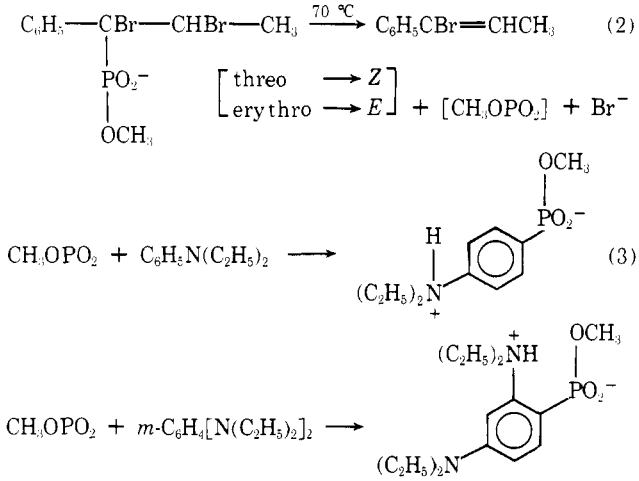
Figure 2. The 100-MHz ^1H NMR spectra of methyl hydrogen *erythro*- and *threo*-1-phenyl-1,2-dibromopropylphosphonic acid in methanol-d_4 and of their respective elimination products, (*E*)- and (*Z*)-1-bromo-1-propenylbenzene in chloroform-d_1.

as standard; proton shifts are relative to tetramethylsilane. In order to determine the P-H coupling constants, the spectra were simplified by irradiating the samples at the frequency appropriate to the nearby methyl group; this left only the splitting caused by the spin of the ^{31}P on the methine proton. Similarly, coupling constants of protons of the aromatic ring were determined by irradiating appropriate adjacent protons, and so simplifying the spectra. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points are corrected. Deuterium oxide was obtained from BioRad and Stohler, methanol-d_4 from Merck Sharpe and Dohme, and chloroform-d_1 from Norell Chemical Co.

Results

The chemistry of the gas-phase pyrolysis process is shown in eq 1 in the Introduction and in ref 2.

The chemistry of the fragmentation reactions in solution is shown in eq 2 and 3.

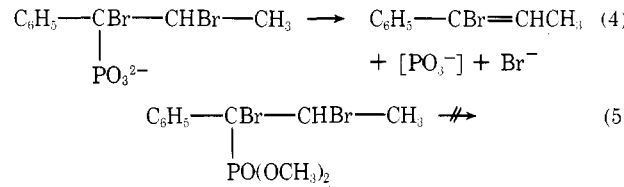


The identification of the products of electrophilic aromatic substitution was made in all cases by (a) ^{31}P NMR spectroscopy of the crude reaction mixtures and (b) purification of the aromatic product by HPLC and subsequent comparison of its ^1H NMR spectrum with that of a synthetic sample. Since the yield of the aromatic substitution product is in all cases low (about 5%), most of the products seen in the ^{31}P NMR spectra of crude reaction mixtures are those of dimeric and polymeric materials and of other reaction products. When methyl hydrogen *threo*- or *erythro*-1-phenyl-1,2-dibromopropylphosphonate is decomposed in dry diethylaniline or in dry tetraethyl-*m*-phenylenediamine solution/acetonitrile-d_3, the ^{31}P NMR spectrum is extraordinarily complex; in addition to the products of aromatic substitution (identified by addition of authentic materials to the NMR tubes and by isolation) at least 25–35 other NMR signals can be seen. Of course, several signals may be attributed to a single product, e.g., one that contains two dissimilar phosphorus atoms; such a compound may present opportunities for diastereomerism as well as for P-P splitting of the signals. Such products would arise if monomeric methyl metaphosphate were added to the phosphonic acid residue of a molecule of starting material. Although the pattern of NMR signals can be accounted for, speculatively, on such a basis, proper analysis of the system is all but precluded by its complexity. On the other hand, a remarkable simplification in the spectrum has been achieved by the addition of 2% water (60 mg of water to 100 mg of phosphonate, or a tenfold molar excess) to the reaction mixture. Under these circumstances (Figure 1) three major products, accounting for >98% of the phosphorus, were observed, and were identified by adding authentic samples of each in separate experiments to the NMR tubes. These products are either methyl hydrogen *p*-diethylaminobenzenephosphonate (δ −16.6) or methyl hydrogen 2-diethylamino-4-diethylaminobenzenephosphonate (δ −11.5), plus (in all cases) methyl phosphate (δ −0.73) and *sym*-dimethylpyrophosphate (δ +12.02). The yield of aromatic substitution product determined from these spectra by comparison of the integrals with those of known quantities of authentic material was about 5 ± 1% from either the erythro or the threo isomer; the yield of methyl phosphate was 81% and that of the pyrophosphate 14%. The large tendency of monomeric metaphosphates to transfer to phosphate is clear from the rather substantial yield of the pyrophosphate, even in the presence of a large molar excess of water.

The olefinic products from the elimination reaction are (*E*)- and (*Z*)-1-bromo-1-propenylbenzene, formed respectively from the erythro and threo dibromoester acids. The ^1H NMR spectra of these reactants and products, shown in Figure 2, are described in the Experimental Section.

The aromatic substitution products, after purification by HPLC, gave spectra that were identical, regardless of source, with that of the synthetic material. In Figure 3, we have compared the spectrum of synthetic methyl hydrogen 2-diethylamino-4-diethylaminobenzenephosphonate with those obtained from the products of electrophilic substitution with tetraethyl-*m*-phenylenediamine. The latter came from three sources: (a) high-temperature pyrolysis in the gas phase, and the reaction of the (b) *erythro*- and (c) *threo*-1,2-dibromophenylpropylphosphonates with tetraethyl-*m*-phenylenediamine in solution. The four spectra are obviously identical (Figure 3). The spectra from the reactions with diethylaniline similarly demonstrate the identity of the products obtained in the various reactions of the arylamine.

The rates of the decomposition of various β-bromophosphonates in the presence of tetraethyl-*m*-phenylenediamine were obtained only in the crudest fashion; they are, however, sufficiently different to make even these crude measurements mechanistically significant. The complete decomposition (eq 4) of the dianion of the diacid occurred at room temperature



before any NMR measurement could be made. By contrast, the half-time for the decomposition of the erythro monoester monoanion at 70 °C was 30 min, at least 1000 times longer (taking into account the difference in temperature) than for the dianion; perhaps the actual factor is much greater, since all we know now concerning the rate of fragmentation of the dianion is that it decomposes in less than 1.5 min. In fact, the elimination was previously shown to occur essentially instantaneously in 0.1 M aqueous potassium hydroxide.[7] The dimethyl ester of 1-phenyl-1,2-dibromopropylphosphonic acid (eq 5) was heated at 70 °C for 1 h with less than 5% reaction (although after heating for 1 day, demethylation occurred). Obviously, the fragmentation reaction is still much slower with the diester than with the monoester monoanion.

Discussion

The cleavage of β-bromophosphonates was discovered by Conant and his collaborators[5] in the 1920s, and rediscovered by Maynard and Swan in 1963. Swan,[6] and others,[7,13] considered the question of whether the reaction takes place by way of monomeric metaphosphate ion. Since the decomposition of β-chlorodecyl phosphonate in *tert*-butyl alchol as solvent[6] leads to the formation of *tert*-butyl phosphate, the metaphosphate pathway appears more probable than a displacement mechanism; certainly *tert*-butyl alchohol is not generally an effective nucleophile. The stereochemical nature of the fragmentation reaction has been established (ref 7 and this paper) as that of

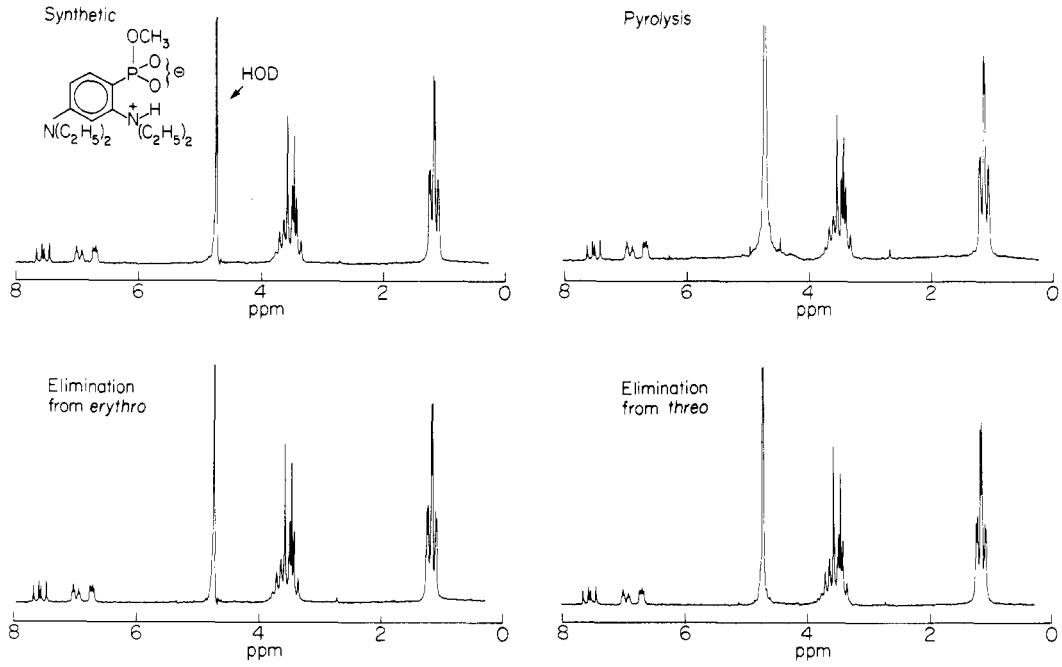


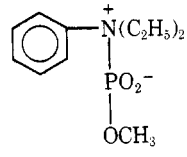
Figure 3. The 100-MHz ^1H NMR spectra of four samples of methyl hydrogen 2-diethylamino-4-diethylaminobenzenephosphonate in D_2O; the chemical shifts are given relative to that of sodium 2,2-dimethyl-2-silapentane-5-sulfonate. The spectrum at the upper left is that of product obtained by synthesis; the other three spectra are those of product produced on trapping monomeric methyl metaphosphate. The source of the monomeric methyl metaphosphate (pyrolysis or fragmentation in solution) is shown in the figure. The pyrolysis is that of methyl 2-butenylphostonate; erythro and threo refer to the diastereomers of methyl hydrogen 1-phenyl-1,2-dibromopropylphosphonic acid.

trans elimination from the preferred conformers of the dibromophosphinic acids, but this finding would be consistent either with a displacement concerted with loss of halide ion or with direct fragmentation to monomeric metaphosphate.

We had previously[2] established that the gas-phase pyrolysis reaction produced a fragment capable of electrophilic substitution into the aromatic nucleus of arylamines, and had concluded that this fragment must be monomeric methyl metaphosphate. Aromatic substitution into an activated ring then served (as does the three-phase test introduced by Rebek and Gaviña)[3] to identify a monomeric metaphosphate. These considerations led naturally to the experiments here described.

The question must be answered as to whether this aromatic substitution could still represent an S_N2-type attack at phosphorus, i.e., a nucleophilic attack at phosphorus by the aromatic amine. This unlikely hypothesis is essentially ruled out by the wide discrepancy in rates of fragmentation for the dianion (most active), the monoanion (active), and the diester (essentially inert) of dibromophenylpropylphosphonic acid (eq 4, 2, and 5, respectively). In other words, aromatic substitution occurs within 1 h with the monoester monoanion; none was observed on heating the diester with aromatic amine for a similar time. A displacement reaction should proceed most readily by attack of a nucleophile on the neutral diester,[14] and least readily by attack of a nucleophile at the phosphorus atom of an electron-rich dianion; the fragmentation, by contrast, should proceed most readily from the dianion, where the concentrated negative charge of the reactant is finally distributed between the two monoanionic products. The identification of the mechanism as that of fragmentation to monomeric methyl metaphosphate is then relatively secure.

A major mechanistic problem nevertheless remains: why is the yield so low (5%) for electrophilic substitution into the ring? No explanation has yet been established. A possible, hypothesis, however, is that monomeric metaphosphate is generally trapped by addition to the unshared electron pair of the amine nitrogen, to form zwitterionic structures such as B. This, in turn, could react with water and methyl phosphate to give



B

methyl phosphate and *sym*-dimethyl pyrophosphate, respectively; kinetic studies suggest that a similar reaction is bimolecular.[15] Despite the low yield of aromatic substitution product, two lines of reasoning suggest that the electrophilic intermediate (presumably monomeric methyl metaphosphate) shows little selectivity. First, the yield of aromatic substitution product is about the same from diethylaniline as from tetraethyl-*m*-phenylenediamine, although the latter is probably much more easily attacked at carbon;[16] this is true regardless of whether monomeric methyl metaphosphate is generated in the gas phase or in solution. Second, the solution is nearly equimolar in good nucleophiles (water, amines, phosphate) and aromatic sites; a selective reagent would react essentially exclusively with the former.

Some question has been raised as to how "free" metaphosphates can possibly be in solution; like the proton or primary carbonium ions, monomeric metaphosphates may not exist as independent particles except in the gas phase.[2] Although Rebek's three-phase test provides evidence for reactive phosphorylating intermediates in solution, these intermediates might be dioxane–metaphosphate complexes rather than "free" monomeric metaphosphates. A parallel possibility has been discussed for the reaction of 2,4-dinitrophenylphosphate dianion in aqueous dioxane.[17] Similarly, perhaps Gerrard and Hamer's[18] stereochemical evidence for the formation of planar metaphosphate might be complicated by the involvement of a dimethoxyethane–metaphosphate complex; in any event, dioxane rapidly racemizes secondary carbonium ions through complex formation.[19] The metaphosphate–amine complex, suggested above as one product of our fragmentation reactions, is again similar.

The experiments reported here show, however, that a

phosphorylating agent of unusual nonselectivity can be formed in basic solution and, prior to its reaction with amino nitrogen or aromatic ring, is probably as "free" as any metaphosphate in solution.

Acknowledgments. This paper is dedicated to Professor Edgar Lederer, in honor of his seventieth birthday. The research was supported by the National Science Foundation under Grant CHE 77-05948. The authors also wish to thank Professor G. L. Kenyon for helpful discussions.

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Biosynthesis of Cyclonerodiol

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Abstract: Sodium [2-^{14}C]mevalonate was incorporated into the cyclopentanoid sesquiterpene cyclonerodiol by cultures of *Gibberella fujikuroi*. Chemical degradation located the label equally at C-4, C-8, and C-12. A biosynthetic pathway consistent with the observed labeling pattern involves cyclization of nerolidyl pyrophosphate by addition of water across the vinyl and central double bonds.

Iridoid and derivative classes of cyclopentanoid monoterpenes are found in a large variety of higher plants and some insect species.[1] Typical structures are those for loganin (**1**),[2] the demonstrated precursor of the nontryptamine portion of the indole alkaloids,[3] and iridomyrmecin (**2**), a secretory component of the ant, *Iridomyrmex humilis*.[4]

In contrast to the widespread occurrence of these 1,2,3-substituted cyclopentane monoterpenes, only a handful of structurally related sesquiterpene metabolites is known, the majority being produced by higher fungi. Best studied are cyclonerodiol (**3**)[5-7] and two closely related substances, cyclonerodiol oxide (**4**)[5a] and cyclonerotriol (**5**).[5c,7] These metabolites are distinguished from the cyclopentanoid monoterpenes by oxygenation pattern and by having trans,trans ring stereochemistry.[8]

The biosynthesis of cyclonerodiol and cyclonerotriol has been studied by Hanson who fed [4,5-$^{13}C_2$]mevalonate to cultures of *Fusarium culmorum*.[9] The ^{13}C NMR spectra of each of the derived metabolites **3** and **5** showed 3 pairs of enhanced and coupled doublets corresponding to C-9 and C-10, C-1 and C-2, and C-5 and C-6 in cyclonerodiol and cyclonerotriol, respectively. These results established the intact incorporation of three molecules of mevalonate and were supported by feedings of various $^{3}H/^{14}C$-labeled mevalonates. In the latter experiments no significant changes were observed in $^{3}H/^{14}C$ ratio in going from precursor to product. Finally, feeding of biosynthetically labeled **3** to *F. culmorum* gave a 15% incorporation into cyclonerotriol.

In connection with our own interest in the stereochemistry of biosynthetic processes we have been studying the biosynthesis of cyclonerodiol. As a first step we have incorporated ^{14}C-labeled mevalonate and devised a degradation sequence

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