Mechanism of the Conant–Swan Fragmentation and the Formation of Monomeric Metaphosphate Ion

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Abstract: The decomposition of $PhCH(PO_3^{2-})CHBrCOPh$ (I) to yield bromide ion, chalcone, and monomeric metaphosphate ion, PO_3^-, occurs cleanly in methanol at 25 °C with a rate constant of 69 s^{-1}. Only in the presence of strong base are phosphonic acids fully ionized in methanol, but the reaction is shown to be that of the dianion, and the rate is unaffected by additional nucleophiles. Substitution of a *p*-methoxyl group into the first phenyl group of I increases the rate about 25-fold and indicates that the formation of the double bond occurs in the rate-limiting step of the overall process; this and additional data rule out the formation of a phostone as intermediate. The reaction thus appears to be a simple fragmentation, where free monomeric metaphosphate is formed.

For almost 30 years, monomeric metaphosphates have been postulated as intermediates in the hydrolysis of phosphate esters and have been suggested as the essential phosphorylating agents in the reactions of intermediary metabolism.[1-3] Both monomeric metaphosphate ion,[4] PO_3^-, and methyl metaphosphate,[5] CH_3OPO_2, have been formed free in the gas phase, and excellent evidence has been accumulated that metaphosphates, or something very similar to them, act as phosphorylating agents in solution.[3]

In some instances, however, the phosphorylations appear to occur by borderline mechanisms,[6] where a small amount of bond forming accompanies bond breaking, so that the monomeric metaphosphate is not only solvated, but never entirely free. For example, Skoog and Jencks[7] studied the transfer of the monomeric metaphosphate residue from pyridinium phosphonate to substituted pyridine. In sharp contrast to the results of our investigation (vide infra), they found that their reaction is kinetically second order (first order in pyridinium phosphonate and first order in the attacking pyridines) and further that the second-order rate constants are not quite independent of the p*K* of the attacking pyridine. Bourne and Williams[8] carried out a similar study with quinolinium phosphonate. A rate-limiting dissociation of the monomeric metaphosphate ion from pyridinium or quinolinium phosphonate would have been first order (as is our fragmentation); if the reaction involved preassociation, then the second-order rate constants would have been independent of the p*K* of the nucleophile or would have shown a break in the plot of the rate constants against the p*K* of the nucleophile. Such a break was either absent or at least not prominent. Presumably, in these cases, bond formation accompanied bond breaking.

We chose for study bromophosphonates that yield chalcones as product,[13] since the strong long-wavelength absorption of the α,β-unsaturated ketones formed as product makes it easy to follow the course of the reaction by UV spectroscopy.

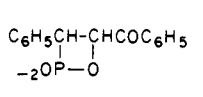
$$\underset{\text{I–VI}}{XC_6H_4CH(PO_3^{2-})CHBrCOC_6H_5} \rightarrow XC_6H_4CH{=}CHCOC_6H_5 + Br^- + PO_3^- \quad (1)$$

$$PO_3^- + ROH \rightarrow HPO_3(OR)^-$$

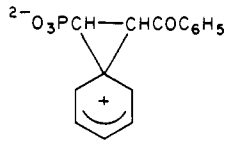
I, X = H; II, X = *p*-OCH_3; III, X = *p*-CH_3; IV, X = *m*-CH_3; V, X = *p*-Cl; VI, X = *p*-NO_2

Our study of the fragmentation of these β-halophosphonates (the Conant–Swan reaction[9-12]) does not reveal any of the effects noted by Jencks or by Williams and their collaborators. The reaction proved to be first order, is not accelerated by added nucleophiles, and appears to be a simple fragmentation that produces monomeric metaphosphate ion. This statement, however, is not made easily. The question of what is meant by "free" monomeric metaphosphate ion is postponed to the Discussion. The possibility that the reaction proceeds by way of a phostone is considered below.

In his original treatment of the decomposition of β-halophosphonates, Conant[13] suggested that the reaction proceeds by way of a phostone (structure VII below) as intermediate. Although some earlier work from this laboratory[11] had cast doubt upon that idea, we thought it necessary finally to confirm or eliminate it. In the course of the experiments directed to that objective, we found that the rate of fragmentation is accelerated strongly by the *p*-methoxy substituent in II. This introduced the possibility that the reaction might proceed by way of the phenonium ion(VIII),



VII



VIII

rather than by either a simple fragmentation, or by way of Conant's phostone. In the accompanying paper,[14] we present evidence that a phenonium ion is not involved; in this paper we show that the reaction does not proceed by way of a phostone. The way was then open to investigate whether the reaction is a simple fragmentation.

$$I + \text{base} \rightarrow VII + Br^- \rightarrow C_6H_5CH{=}CHCOC_6H_5 + PO_3^- \quad (2)$$

In order to determine whether the reactions in methanol are strictly those of the dianions of the phosphonic acids, we needed to determine the ionization constants, in our solvent, of the phosphonic acids we used. In 1924, Goldschmidt[15] showed that the ionization constants in methanol of electrically neutral acids,

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such as benzoic acid, are decreased by a factor of about 10^4 compared to the corresponding constants in water, presumably because of the increased energy of separation of ions in a solvent of lower dielectric constant. One could reasonably expect that the difference in the electrostatic energy of separation of oppositely charged ions in methanol, as compared to that in water, would be even greater for the second ionization constant than for the first. It is not therefore surprising that Semiokhin and Andreen[16] found that the first pK of methylphosphonic acid in methanol is 6.77, as compared to 2.38 in water, and that they found the second pK inaccessible. We could not, of course, measure the pK's of the specific β-bromophosphonic acids with which we were concerned, since the dianions decompose with half-lives of the order of 0.01 s. But we were successful at least in estimating the pK's of various substituted benzylphosphonic acids that can serve as surrogates for our compounds and found these values essential in interpreting our data.

Experimental Section

Materials. Methanol and methanol-d_1 (Stohler Isotope Chemicals) were distilled from magnesium methoxide (generated in situ) under nitrogen. Diisopropyl- and diisopropylethylamines were distilled from calcium hydride under nitrogen. Acetone (Mallinckrodt) was distilled from anhydrous calcium sulfate. Tetrabutylammonium hydroxide was obtained from Aldrich Chemical Co. Other chemicals were reagent grade. Analyses were performed by the Galbraith Laboratories, Knoxville, TN.

(2-Bromo-1,3-diphenyl-3-oxo-1-propyl)phosphonic acid (I)[13] melted at 205–206 °C. Substituted derivatives of (I) were prepared by the same procedure as that for I but using the appropriate chalcones as starting materials.[17-20] In all cases a mixture of diastereomeric products was obtained. The major diastereomer selectively crystallized from this mixture from the same solvent system that was used for recrystallization. For the *p*-methoxy derivative II this was shown[14] to be the 1*R*,2*S* (and 1*S*,2*R*) diastereomer. On the basis of the coupling constants between the phosphorus atom and the C-2 hydrogen atom in the NMR spectra, apparently the diastereomer of the same configuration preferentially crystallized for all of the compounds here prepared.

(2-Bromo-1-(4-methoxyphenyl)-3-phenyl-3-oxo-1-propyl)phosphonic acid (II) (yield 55%), recrystallized from acetone/petroleum ether, melted at 185–186 °C. ^{1}H NMR (acetone-d_6) δ 8.25–6.23 (m, 9 H), 6.12 (dd, J_1 = 12, J_2 = 8.3 Hz, 1 H), 4.20 (dd, J_1 = 12, J_2 = 22 Hz, 1 H), 3.81 (s, 3 H); ^{31}P NMR (acetone-d_6) δ 16.38 (s). Anal. Calcd for $C_{16}H_{16}BrO_5P$: C, 48.14; H, 4.05; P, 7.76. Found: C, 48.45; H, 4.02; P, 7.92.

(2-Bromo-1-(4-methylphenyl)-3-phenyl-3-phenyl-3-oxy-1-propyl)-phosphonic acid (III) (yield, 45%), recrystallized from acetone/petroleum ether, melted at 211–212 °C. ^{1}H NMR (acetone-d_6) δ 8.26–7.09 (m, 9 H), 6.15 (dd, J_1 = 12, J_2 = 8.4 Hz, 1 H), 4.24 (dd, J_1 = 12, J_2 = 22 Hz, 1 H), 2.33 (d, J = 1.8 Hz, 3 H); ^{31}P NMR (acetone-d_6) δ 16.98 (s). Anal. Calcd for $C_{16}H_{16}BrO_4P$: C, 50.19; H, 4.19; P, 8.29. Found: C, 49.91; H, 4.19; P, 8.29.

(2-Bromo-1-(3-methylphenyl)-3-phenyl-3-oxo-1-propyl)phosphonic acid (IV) (yield, 55%), recrystallized from acetone/petroleum ether, melted at 194–195 °C. ^{1}H NMR (acetone-d_6) δ 8.30–7.12 (m, 9 H), 6.18 (dd, J_1 = 12, J_2 = 8.2 Hz, 1 H), 4.26 (dd, J_1 = 12, J_2 = 22 Hz, 1 H), 2.34 (s, 3 H); ^{31}P NMR (acetone-d_6) δ 16.07 (s). Anal. Calcd for $C_{16}H_{16}BrO_4P$: C, 50.19; H, 4.21; P, 8.09. Found: C, 49.96; H, 4.27; P, 8.28.

(2-Bromo-1-(4-chlorophenyl)-3-phenyl-3-oxo-1-propyl)phosphonic acid (V) (yield 50%), recrystallized from acetone/petroleum ether, melted at 197–198 °C. ^{1}H NMR (acetone-d_6) δ 8.26–7.29 (m, 9 H), 6.19 (dd, J_1 = 12, J_2 = 8.3 Hz, 1 H), 4.31 (dd, J_1 = 12, J_2 = 22 Hz, 1 H); ^{31}P NMR (acetone-d_6) δ 16.48 (s). Anal. Calcd for $C_{15}H_{13}BrO_4P$: C, 44.63; H, 3.25; P, 7.68. Found: C, 44.63; H, 3.32; P, 7.83.

(2-Bromo-1-(4-nitrophenyl)-3-phenyl-3-oxo-1-propyl)phosphonic acid (VI) (prepared at 45 °C, rather than at room temperature; yield, 20%), recrystallized from methylene chloride/petroleum ether, melted at 188–190 °C. ^{1}H NMR (acetone-d_6) δ 8.29–6.80 (m, 9 H), 6.28 (dd, J_1 = 12, J_2 = 8.1 Hz, 1 H), 4.48 (dd, J_1 = 12, J_2 = 22 Hz, 1 H); ^{31}P NMR (acetone-d_6) δ 18.34 (s). Anal. Calcd for $C_{15}H_{13}BrNO_6P$: C, 43.50; H, 3.16; P, 7.48. Found: C, 43.86; H, 3.40; P, 7.24. **Benzylphosphonic acid** melted at 170–172 °C (lit.[21] 169–170 °C). ^{1}H NMR (acetone-d_6) δ 7.30 (m, 5 H), 3.09 (d, J = 22 Hz, 2 H); ^{31}P NMR (acetone-d_6) δ 23.50 (s). **(4-Methoxybenzyl)phosphonic acid** melted at 208–210 °C (lit.[22] 204–206 °C). ^{1}H NMR (acetone-d_6) δ 7.35–6.84 (m, 5 H), 3.09 (d, J = 22, 2 H), 3.81 (s, 3 H); ^{31}P NMR (acetone-d_6) δ 24.34 (s). **(4-Nitrobenzyl)-phosphonic acid** melted at 226–228 °C (lit.[22] 232–234 °C). ^{1}H NMR (acetone-d_6) δ 8.35–7.35 (m, 5 H), 3.50 (d, J = 22 Hz, 2 H); ^{31}P NMR (acetone-d_6) δ 21.39 (s).

Products. The chalcones derived from the fragmentation of the phosphonic acids I and II were isolated by extraction of the reaction mixtures with chloroform and identified by their melting points and proton NMR spectra; in addition, the chalcones from I and II were shown by their UV spectra to be the trans isomers. In reactions in methanol, the phosphorus product was identified as methyl dihydrogen phosphate by comparing the ^{31}P NMR spectrum of the product with that of an authentic sample. Similarly, when the fragmentations were conducted in acetone 0.1–0.75 M in ethanol in the presence of various amines, the product was identified by ^{31}P NMR spectroscopy as ethyl dihydrogen phosphate; in no case was a signal from a phosphoramide observed.

The products from the partial decomposition of I in acetone were determined as follows: Two syringes were connected to a Y-shaped mixing chamber, which emptied through tubing of various lengths into a stirred solution of 6 N sulfuric acid. One syringe was filled with 10 mM I and the other with 1 M diisopropylamine/1.25 M methanol, both in acetone as solvent. In several successive experiments using different lengths of tubing after the Y, the reaction mixtures obtained by mixing the solutions were quenched; this resulted in different time intervals. Although the absolute times were unknown, the relative times were proportional to the lengths of tubing after the Y. The products after quenching were identified and their quantities estimated by measurement of the ^{31}P NMR spectrum of the solution and measuring it again after the addition of a known quantity of I. A portion of the quenched mixture was also diluted 5-fold with methanol, and the concentration of chalcone was determined by the absorbance at 360 nm, where the extinction coefficient is 1000 cm^{-1} M^{-1}.

NMR Spectra. The ^{1}H NMR spectra were obtained with a Varian FT80 spectrometer, in acetone-d_6 as solvent unless otherwise specified. The results are reported in parts per million relative to tetramethylsilane as an internal standard. The ^{31}P NMR spectra were obtained with a Varian XL-100 spectrometer, equipped with a 40.5-MHz phosphorus probe, and the results reported in parts per million relative to 85% phosphoric acid, which was used as an external standard.

Kinetics. The kinetics were performed by using a thermostated Durrum-Gibson 13701 stopped-flow spectrometer modified to use a Zeiss PMQ II monochrometer and a deuterium lamp. The Zeiss was set to 360 nm, which proved convenient even though it does not correspond to the maximum in the absorption curve for the chalcone. The power supply for the tungsten lamp was a Hewlett-Packard 6281A, operated at 6 V and 5 amps. The power supply for the phototube was a Hewlett-Packard 6515A, operated at 500 V, dc, and the tube's output was displayed on a Tektronix 564 storage oscilloscope and photographed with a Tektronix-Polaroid C-30 oscilloscope camera. The output of the oscilloscope, in percent transmission, was converted into kinetic data by the method of Lonzetta.[23]

Potentiometric Titrations. Potentiometric titrations were carried out in methanol as solvent with a Radiometer TTTlb titrator, using 1.124 M tetrabutylammonium hydroxide as titrant. The output from a cell with a standard glass electrode and a reference calomel electrode (filled with 0.01 tetrabutylammonium bromide in methanol[24]) was recorded on a Texas Instruments strip-chart recorder. The pK_a's of the benzylphosphonic acids were determined relative to benzoic acid as standard; the pK of benzoic acid in methanol[25] had previously been found as 9.1. The total volume of the solution used for titration was 4.5 mL, and the average ionic strength was 0.018 M.

The results of potentiometric titrations were confirmed by NMR measurements. Relative pK_a's of the benzylphosphonic acids were determined by adding small aliquots of 0.889 M sodium methoxide in methanol to an NMR tube containing 3 mL of a mixture of 10.8 μM benzylphosphonic acid and of (*p*-nitrobenzyl)phosphonic acid or 13.2 μM

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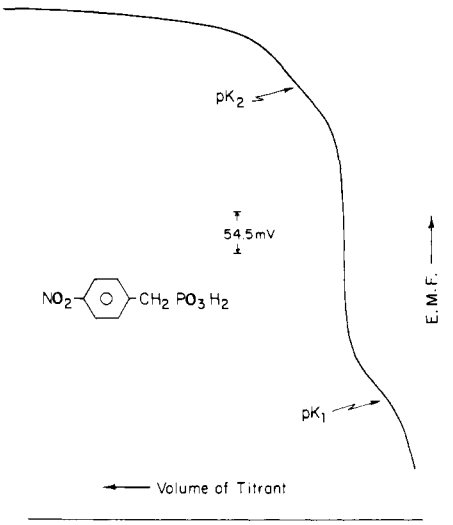

Figure 1. Titration of 12.7×10^{-3} M (4-nitrobenzyl)phosphonic acid. The output of the pH meter (mV) is plotted against the volume (in mL) of 1.124 M tetrabutylammonium hydroxide in methanol. With benzoic acid in methanol as standard, the two pK's indicated are 5.6 and 13.2.

benzylphosphonic acid and of (*p*-methoxybenzyl)phosphic acid in methanol/methanol-d_4 (6/1 v/v) at an ionic strength of approximately 0.04 M. The shift in the ^{31}P NMR resonances of the respective acids was observed. A similar analysis compared the fraction of ionization of benzyl- and of (*p*-nitrobenzyl)phosphonic acids in the presence of diisopropylamine in acetone as solvent. The chemical shift of the NMR signal from the dianions in acetone was found by addition of a small excess of tetrabutylammonium hydroxide in methanol to a solution of the corresponding acids in acetone.

Results

Ionization Constants. The first ionization constants of benzylphosphonic acid and of its *p*-methoxy and *p*-nitro analogues were easily determined; their pK_a's in methanol are around 6, and the variation in pK_a with substitution is quite similar to that observed for substituted phenylacetic acids in water. The (*p*-nitrobenzyl)phosphonic acid is 0.60 pK units more acidic than the unsubstituted acid, as compared to 0.46 units for the phenylacetic acids, whereas (*p*-methoxybenzyl)phosphonic acid is 0.07 pK units less acid than the unsubstituted member of the series, in almost exact agreement with the acidity difference for the phenylacetic acid series.[26]

In accord with the earlier work of the Russian investigators,[16] we found the second ionization constants scarcely accessible. (*p*-Nitrobenzyl)phosphonic acid, which is a little stronger than the others, gave a noticeable break in the titration curve and an observable end point, so that it proved possible to get a crude measure of its ionization constant. The titration curve is presented as Figure 1. (A blank, from titration of the solvent, introduced no correction.) We estimate its pK_2 as about 13.2. Since pure methanol has a self-ionization constant[27] at 25 °C of 10^{-18}, the value for the nitro acid is well within measurable limits. The titration curves for the other acids, although clearly distinguishable from those of control experiments when only tetrabutylammonium hydroxide was added to the solvent, scarcely allowed a determination of their pK's. An estimate of the difference in pK between these acids and (*p*-nitrobenzyl)phosphonic acid was made by the NMR method described in the Experimental Section. These pK differences proved quite similar to those derived from the first ionization constants; since the electrostatic effects for the two ionizations should be similar, this result is heartening. The second pK's for the unsubstituted and *p*-methoxy acids were therefore estimated by adding the appropriate differences obtained from the NMR spectra to the measured pK of (*p*-nitrobenzyl)-phosphonic acid. These data appear in Table I. Since the pK's of substituted phenylacetic acids follow a Hammett relationship

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Table I. Potentiometrically Determined Approximate pK_a Values for Para Substituted Benzylphosphonic Acids in Methanol at 25 °C

X[a]	pK_1[b]	pK_2	ΔpK_1[c]	ΔpK_2[c]
H	6.20	13.9[d]	0.0	0.0
p-CH_3O	6.27	13.9[d]	−0.07	−0.05
p-NO_2	5.60	13.2	0.62	0.68

[a] Acid concentrations were 13×10^{-3} M. [b] Based on the pK_a of benzoic acid of 9.1 in methanol.[25] [c] Determined from the ^{31}P NMR titration. [d] Calculated from the potentiometrically determined pK_a of (4-nitrobenzyl)phosphonic acid and the relative pK_a's determined from the ^{31}P NMR titration.

Table II. Rates of Decomposition of I in Methanol at 25 °C

base	10^3[base], M	k, s^{-1}	base	10^3[base], M	k, s^{-1}
$NaOCH_3$	3.00	2.3×10^{-3} [a]	$NaOCH_3$	60	21.6[b]
				80	46.5
	5.00	2.3×10^{-3}		100	60.8
				140	69.6
	6.84	13.8			
	7.45	23.6	diisopropyl-	10	4.16
	8.06	34.5	amine[c]	50	12.3
	8.99	42.6		100	23.2
	9.59	54.6		250	33.0
	10.6	62.0		500	32.6
	12.4	66.0		1000	27.0
	23.9	69.0		2000	25.0
	37.7	68.6			

[a] [I] = 4.55×10^{-3} M. [b] [I] = 4.0×10^{-2} M. [c] [I] = 5.69×10^{-3} M.

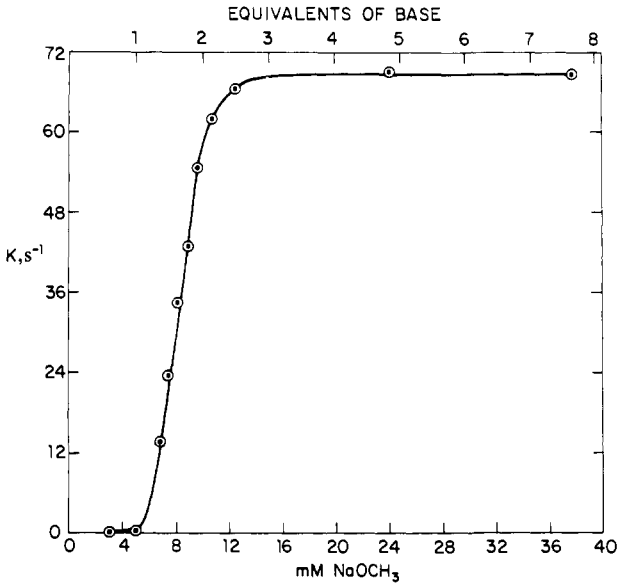

Figure 2. Plot of the rate constants (s^{-1}) for the formation of 1,3-diphenyl-2-propen-1-one from 4.55×10^{-3} M I as a function of the concentration of sodium methoxide. The ratio of moles of base to moles of I is plotted along the upper abscissa.

and since no resonance effects should complicate the pK's of either those acids or the benzylphosphonic acids, we are confident that we can estimate the first and second pK's of variously substituted benzylphosphonic acids. Although we do not, unfortunately, know the pK's of the acids I–VI with which we are here primarily concerned, presumably the bromine atom in the position β to the phosphonic acid group in our compounds will lower the pK's; we estimate that this effect will be in the range of 0.8 pK units, as it is for the difference between the pK of propionic and that of β-bromopropionic acid.[28]

Kinetics. The rate constants for the decomposition of compound I in the presence of sodium methoxide in methanol at 25 °C are

(28) "Dissociation Constants of Organic Acids in Aqueous Solution"; Kortum, G., Vogel, W., Andrussow, K., Eds.; Butterworths: London, 1961; pp 243, 296.

Table III. Effect of Added Nucleophiles on the Rate of Decomposition of I

amine	[amine], M	k, s^{-1}	amine	[amine], M	k, s^{-1}
none[a]	0.0	27.2	none[b]	0.0	69.1
pyridine[a]	0.05	26.3	triethylene-diamine[b]	0.25	68.3
pyridine[a]	0.10	27.5			
pyridine[a]	0.20	26.3	triethylene-diamine[b]	0.50	68.5
cyclohexyl-amine[a]	0.50	26.1			
			triethylene-diamine[b]	1.00	68.8

[a] In methanol/water (3/1, v/v, 0.2 M KCl), [I] = 5.12×10^{-3} M, [KOH] = 5×10^{-2} M. [b] In methanol, [I] = 7.43×10^{-3} M, [$NaOCH_3$] = 2.97×10^{-2} M.

Table IV. Solvent Kinetic Isotope Effect on the Decomposition of I at 25 °C[a]

k^H, s^{-1}	k^D, s^{-1}	k^H/k^D
70.4	67.8	1.04
67.1	66.3	1.01
		av 1.02

[a] [I] = 7.18×10^{-3} M, [$NaOCH_3$] = 29.8×10^{-3} M.

Table V. Effect of Salts on the Decomposition of I at 25 °C

salt	[salt], M	k, s^{-1}	salt	[salt], M	k, s^{-1}
none[a,b]	0.0	69.0	Bu_4N^+, ClO_4^-[a]	0.33	150
Bu_4N^+, Br^-[a]	0.33	160			
Bu_4N^+, Br^-[a]	1.00	270	KCl[b]	0.05	57.0
			KCl[b]	0.10	44.0

[a] In methanol, [I] = 6×10^{-3} M, [$NaOCH_3$] = 2.5×10^{-2} M. [b] In methanol/water (70/30, v/v), [I] = 9.5×10^{-3} M, [KOH] = 5.0×10^{-2} M.

shown in Table II, and the essential data are plotted in Figure 2. The rate constants obtained with increasing concentrations of methoxide trace a smooth titration curve, with a maximum rate constant of 69 s^{-1}. Addition of a moderate excess of tetrabutylammonium methoxide to the dianion has no effect on the rate.

The rate of fragmentation of I in methanol was also measured in the presence of diisopropylamine instead of sodium methoxide. The rate increased with concentrations of amine up to 0.25 M but then leveled off at a rate constant of about 33 s^{-1} and at even higher concentrations of amine actually declined. The data appear, along with those for the reaction in the presence of sodium methoxide, in Table III. The maximum rate constant in the presence of the amine is only about half that observed with sodium methoxide. ^{31}P NMR experiments showed that, in the presence of excess amine, benzylphosphonic acid is only about 50% ionized.

Solvent Isotope Effect. The solvent isotope effect upon the rate of fragmentation of I was measured by carrying out the reaction in CH_3OD. The data are shown in Table IV. The reaction was carried out with an excess of sodium methoxide, so that the phosphonic acid was completely ionized. The base was added to deuterated solvent as a concentrated solution in ordinary methanol, diluting the deuterium content of the solvent to 97%. The solvent isotope effect, k_H/k_D, is 1.02 ± 0.02, i.e., essentially unity.

Common-Ion Effect. The effects of salts, and specifically of bromide ion, on the rate of the fragmentation are presented in Table V. A 6 mM solution of I in methanol containing 0.0–1.0 M tetramethylammonium bromide or perchlorate was mixed in 1:1 ratio in the stopped-flow apparatus with 0.25 mM sodium methoxide in methanol that contained the same concentration of the same ammonium salt as did the solution of I. Alternatively, a 50 mM solution of I in 70/30 (v/v) methanol/water containing 0.0–0.1 M KCl was mixed in 1:1 ratio in the stopped-flow apparatus with a 50 mM solution of KOH in the same solvent and with the same salt concentration.

Added Nucleophiles. The effect of added amines as nucleophiles on the rate of the decomposition of I was investigated. A solution of 5 mM I in 3/1 methanol/water (v/v) with 0.2 M KCl was mixed with 50 mM KOH in the same solvent with the same salt concentration but with the addition of various concentrations of pyridine and cyclohexylamine (0.0–1.0 M). The data are presented in Table VI. The products from the decomposition in the presence of cyclohexylamine were investigated by adding D_2O to the reaction mixture after the reaction was complete and examining the ^{31}P NMR spectrum. Two peaks, corresponding to HPO_4^{2-} and $CH_3OPO_3^{2-}$, were present; no peak for the phosphoramidate of cyclohexylamine was observed. To eliminate any concern with the effects of the K^+ ion, the rate of decomposition of a 7.43 mM solution of I in methanol was observed when decomposed in the presence of 29.7 mM sodium methoxide in methanol with 0.0–2.0 M 1,4-diazabicyclo[2.2.2]octane. The resulting data are presented in Table III.

Table VI. Effect of Temperature on the Rate of Decomposition of I in Methanol[a]

T, °C	k, s^{-1}	T, °C	k, s^{-1}
1	6.96	27.5	84.2
11.5	18.1	36.5	184
18.5	38.3	46.5	435

[a] [I] = 7.28×10^{-3} M, [$NaOCH_3$] = 6.47×10^{-2} M.

Table VII. Rates of Decomposition of I in Acetone

amine	[ethanol], M	[ethanol], M	k, s^{-1}	T, °C
diisopropyl	0.1	0.1	2.58	25
diisopropyl	0.3	0.1	3.40	25
diisopropyl	0.5	0.1	9.58	25
diisopropyl	1.0	0.1	10.2	25
diisopropylethyl	0.1	0.1	0.59	25
diisopropylethyl	0.3	0.1	1.32	25
diisopropylethyl	0.5	0.1	1.56	25
diisopropylethyl	1.0	0.1	2.17	25
diisopropylethyl	0.5	0.1	0.87	22
diisopropylethyl	0.5	0.2	0.95	22
diisopropylethyl	0.5	0.39	1.09	22
diisopropylethyl	0.5	0.75	1.24	22

Table VIII. Substituent Effect on the Rate of Decomposition of the Dianions of I–VI in Methanol at 14 °C

X	k, s^{-1}	X	k, s^{-1}
p-CH_3O	600	H	24.7
p-CH_3	86.3	p-Cl	18.0
m-CH_3	59.8	p-NO_2	6.6

Finally, we have presented in Table VII the rates of fragmentation of I in acetone as solvent in the presence of diisopropylamine and of diisopropylethylamine. The reactions were carried out with various small amounts of added ethanol; as recorded in the Experimental Section, the phosphorus product of the reaction was ethyl dihydrogen phosphate.

Temperature Coefficient. The effect of temperature on the rate of decomposition of I in methanol is presented in Table VI. The calculated enthalpy and entropy of activation for the fragmentation are 17.2 kcal/mol and 7.4 cal/mol degree, respectively.

Substituent Effect. The rates of fragmentation of the compounds I–VI, that is to say, the effects of substitution on the rates, are presented in Table VIII. For these measurements, the concentrations of I–VI were 4 mM, and the concentration of sodium methoxide was 14.7 mM. These reaction conditions ensured that the reaction would take place via the dianion. The data are plotted as the logarithm of the rate constants against Hammett's σ in Figure 3. The curvature in this plot will be discussed later.

Discussion

Monomeric Metaphosphate Ion. The data of Tables II and III and of Figure 2 show unambiguously that the dianion of I undergoes unimolecular decomposition without nucleophilic assistance. The rate of decomposition of the monoanion is less than that of the dianion by a factor of more than 10^4. As previously pointed out,[3] this large rate factor is consistent with a fragmen-

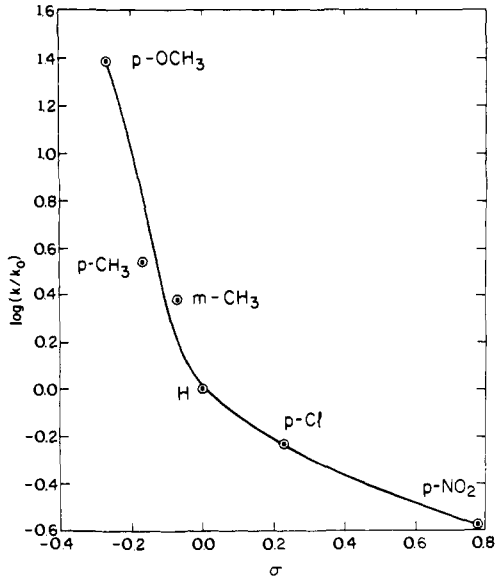

Figure 3. Hammett plot for the rate constants for the decomposition of 4.1×10^{-3} M I–VII in methanol, with 14.7×10^{-3} M sodium methoxide as base. The σ values are from ref 32.

tation but inconsistent with a process of displacement at phosphorus. In the presence of more than 1 equiv of sodium methoxide relative to I, the rate of the reaction is strictly proportional to the concentration of dianion present in solution; the data of Figure 2 trace an almost perfect titration curve. Furthermore, the rate of decomposition of the dianion is unaffected by the addition of a large excess of sodium methoxide, pyridine, cyclohexylamine, or triethylenediamine.

Perhaps the most convincing evidence that nucleophilic assistance is absent in this method of forming metaphosphate comes from the solvent isotope effect. Essentially, there is none. The rate in methanol is only 1.02 ± 0.02 times that in CH_3OD. The product of the reaction in methanol is the dianion of methyl dihydrogen phosphate; if the reaction involved nucleophilic assistance, the proton (or deuteron) of the solvent should be in flight in the transition state. This should create a measurable solvent isotope effect; the absence of such an effect argues for free monomeric metaphosphate ion. The lifetime of this intermediate is another matter. In the S_N1 reactions, many carbonium ions have been found that are reasonably stable in solution;[29] by contrast, free monomeric metaphosphates have been unambiguously proven only in the gas phase.[4,5] Nevertheless, the species that results from fragmentation in the present investigation arises without nucleophilic assistance and apparently without significant bond forming to accompany bond breaking. Whether the PO_3^- should be regarded as free is perhaps a matter of definition. If one demands that an intermediate survive collision with nucleophilic solvent to be categorized as free, then we still do not know whether or not our PO_3^- warrants this description. If one regards the ion as free if it is formed without assistance (except, of course, for the solvation that characterizes all ions in solution), then the monomeric metaphosphate produced here should be regarded as free. At any rate, reactions that proceed as does this fragmentation must be sharply differentiated from S_N2 processes.

The decomposition of I in the presence of amines requires discussion. In methanol as solvent, an increase in the concentration of diisopropylamine increases the rate, but even at high concentrations the rate is only about half of that observed with excess methoxide ion. In fact, the rate even falls off at the highest concentrations (1–2 M) of amine. These facts are entirely consistent with the explanations here offered. Since the second ionization constants of phosphonic acids in methanol are so small, full ionization can be achieved only with strong base; NMR measurements show that benzylphosphonic acid is only about half-ionized in the presence of excess diisopropylamine. The maximum rate expected with amine, then, will be considerably lower than that with methoxide ion. Presumably the decrease in rate at the highest amine concentrations is a solvent effect; 2 M diisopropylamine in methanol is approximately 28% amine by volume.

Even more interesting, perhaps, are the data shown in Table VII for the fragmentation of I in acetone as solvent and with amines as promoters. (Alkoxide cannot be used for kinetic experiments in acetone, as it rapidly induces aldolization and introduces colored materials that interfere with our spectrophotometric analysis.) The rate of reaction increases, although not linearly, with the concentration of amine, and the rates are about 5 times greater with diisopropylamine than with diisopropylethylamine. Furthermore, the rates increase with increasing concentrations of added ethanol, although the rate is less than 50% greater for 0.75 M alcohol than for 0.10 M alcohol. If one had not realized that the second ionization constants of phosphonic acids are severely depressed in solvents of low ionizing power, one might erroneously have concluded that the fragmentation process proceeds with nucleophilic assistance, i.e., that the amine attacked the proton of ethanol and the incipient ethoxide ion attacked the phosphorus atom.

Only in the light of the work here reported is it clear that this interpretation is completely wrong. The lack of a solvent deuterium isotope effect shows that the proton is not in motion during the rate-limiting step. Further, the second ionization constant of phosphonic acids in methanol are so small that the acids are incompletely ionized, even in the presence of excess amine; in acetone the solution must contain ion pairs, and these cannot be formed stoichiometrically from acid and amine. ^{31}P NMR spectroscopy shows that, in the presence of excess diisopropylamine in acetone, only 20% of benzylphosphonic acid is present as the dianion. The reaction in acetone presumably follows the same pathway as in methanol, but the role of the dianion is obscured because the second ionization constant of the phosphonic acid is so severely depressed in the relatively nonpolar solvent.

Absence of a Phostone as Intermediate in the Fragmentation. The experiments presented above provide reasonable evidence for the formation of free monomeric metaphosphate ion as an intermediate in the Conant–Swan fragmentation provided that, as stated in the introduction, the reaction does not proceed by way of a four-membered phostone as intermediate or by way of a phenonium ion. In other words, the formation of free monomeric metaphosphate is secure provided that the reaction does not proceed by eq 2 or by way of a compound such as VIII. (Of course, even if eq 2 were correct, monomeric metaphosphate would presumably be involved in the decomposition of the phostone, but we would then have no evidence as to whether it had been formed with or without nucleophilic assistance, i.e., whether or not it was "free".) The stereochemistry[11] of the reaction is consistent either with a standard backside displacement to yield a phostone, or with an antiperiplanar fragmentation, as we had previously postulated;[11] the stereochemistry is not consistent with the formation of a phenonium ion intermediate.[14] Some doubt had already been thrown on the phostone pathway. In early work, Conant had carried out the decomposition of (2-bromo-1-styryl)phosphonic acid to yield phenylacetylene.[9d] Since displacements do not occur readily with vinyl halides, one might infer that no phostone is formed. However, the formation of phenylacetylene, contrary to Conant's report, is slow at 25 °C and occurs rapidly[11] only at 100 °C, so this evidence is not conclusive.

We therefore investigated the effects of substituents on the reaction; see Table VII and Figure 3. The effects are considerable; in particular, a *p*-methoxy group increases the rate about 25-fold. If the rate-limiting step were a displacement reaction to close the four-membered phostone ring, no such substituent effect would be anticipated; the methoxyl group in the aromatic ring is too far removed from the site of reaction to exert a polar effect and cannot interact with that site through resonance; the previous paper[14] shows that the reaction does not proceed by way of a phenonium

(29) "Carbonium Ions"; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley: New York, 1968–1973; Vol. 1–5.

ion. Furthermore, the data of Table I suggest that the basicity of the dianion of the *p*-methoxy acid II should be only slightly (15%) different from that of the dianion of I; that difference must be totally inadequate to account for the observed rate factor. The conclusion that a methoxy group would have minimal effect on a displacement is reinforced by other data on the phenylethyl system. The solvolyses of phenylethyl tosylate and of anisylethyl tosylate in ethanol and in ethanol/water proceed in part by solvent displacement reactions and in part by way of phenonium ions. Total rates, rates of reaction by way of the phenonium ion, and internal return have all been measured for these systems.[30] The rates of displacement alone can then be obtained by correcting the total rate of hydrolysis for internal return and for the fraction of reaction that proceeds by way of the phenonium ions. The displacement reactions are found to be only slightly accelerated, or perhaps not accelerated at all, by the *p*-methoxy substituent.

On the other hand, if fragmentation of II is rate limiting, then the resonance interaction of a *p*-methoxyl group with the double bond and the carbonyl group of the incipient chalcone would stabilize the transition state relative to the starting materials and so enhance the rate. The rate would also be enhanced if the methoxy compound reacted by way of a phenonium ion, but that possibility has been eliminated by the work reported in the accompanying article.[14]

In order to complete the argument, we must still eliminate the unlikely possibility that the fragmentation of the phostone, rather than its formation, is rate limiting. This hypothesis demands that the phostone is formed with a rate constant large compared to 69 s^{-1} and that its formation is followed by a rate-limiting decomposition of the four-membered ring, in analogy with the decomposition of the four-membered intermediate of the Wittig reaction. In fact, in order to allow the decomposition of the fictional phostone to be rate limiting, the rate constant for its formation would have to be at least of the order of 500 s^{-1}. This follows because, if the rate constant were less, the reaction would not follow a good first-order course, as in fact it does. If the formation of the phostone were an extremely rapid irreversible reaction, then a reaction mixture from a decomposition that had been carried only partway to completion would nevertheless contain no starting material. Such is not the case. The rapid-quench experiments previously described showed that when 35% of the theoretical yield of chalcone had been formed from I (UV measurement), 65% of the starting material was still present (NMR measurement) in the quenched solution, and similarly when 65% of the chalcone had been formed, 35% of the starting material was present. If the phostone had been formed in times of the order of a thousandth of a second, our rapid-quench experiments would have shown no residual starting material.

An alternative possibility is that the phostone is formed rapidly but reversibly and then decomposes in the rate-limiting step of the process. If this were true, the rate would be depressed by the addition of large quantities of bromide ion. Although some salt effects are observed in the overall reaction (Table V), bromides do not produce effects different from those of perchlorates. The only real differences observed concern the effects of cations; potassium salts depress the rate, whereas tetrabutylammonium salts strongly increase the rate; similar chemistry has been observed in other reactions.[31] A rapid formation of a phostone has therefore been ruled out. The combination of these experiments eliminates the possibility of Conant's phostone as an intermediate in the reaction of I, and confirms our assignment of the reaction as the simple fragmentation shown in eq 1.

Entropy of Activation. The enthalpy of activation for the fragmentation is unexceptionable, and the entropy of activation, +7.9 eu, is positive, as anticipated. For a somewhat analogous case, the fragmentation of 2,4-dinitrophenyl phosphate, Kirby and Varvoglis[32] observed an entropy of activation of 6.6 eu, quite similar to that that we found. A unimolecular decomposition would be expected to have a positive entropy of activation, and this fragmentation (as well as that of Varvoglis and Kirby) might have been expected to have an especially large positive entropy of activation because of solvation effects. The phosphonate dianion should "freeze", or at any rate strongly orient, more solvent than the two singly charged ions—such as the bromide ion and the monomeric metaphosphate ion—that result from the Conant–Swan reaction. Solvent should be more nearly free in the transition state than in the starting material, with a positive contribution to the entropy of activation. In fact, although one cannot have more than a qualitative feeling in such matters, the entropy of activation might have been expected to be even more positive than that that was observed.

Substituent Effects. Finally, something must be said about the effect of substituents on the rates of the fragmentation reaction. As argued above, the relatively large substituent effect of the methoxyl group demonstrates that the double bond of the chalcone is formed during the rate-limiting step; i.e., the substituent effects confirm that the reaction is a fragmentation. But the logarithms of the rate constants do not fall on a straight line when plotted against σ, σ^+, σ^R, or any other single parameter we know.[33] Figure 3 shows the data plotted against σ, since the plot against this parameter is monotonic, but the curve suggests that the effect of a *p*-nitro group in depressing the rate of fragmentation is less than might have been expected. Although the data can be presented as a linear plot with the two-parameter Yukawa–Tsuno treatment,[34] the use of a multiparameter equation for so few data is hardly justified. Perhaps the mechanism shifts slightly with strongly electron-withdrawing substituents, such as the nitro group, and the fragmentation proceeds by way of a benzyl carbanion as an intermediate; this would allow VI to react more rapidly than would be expected from a simple Hammett plot. The exploration of this possibility remains for further investigation.

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