Phosphoramidate Solvolysis[1]

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Abstract: The solvolytic properties of mono- and dimethyl esters of phosphoramidic acid are reported and compared with previously published data on unsubstituted phosphoramidate. The similarity of the rate constants for the hydrolysis (0.58 hr^{-1}) and solvolysis in 50% v/v methanol–water (0.296 hr^{-1}) of neutral monomethyl phosphoramidate at 36.8° to those for neutral phosphoramidic acid suggest a common (bimolecular) mechanism for both compounds. Solvolysis of monomethyl phosphoramidate in 50% methanol gives 65 and 21% methanolysis in the reactions of the neutral and cationic species. The yield of trimethyl phosphate in the corresponding solvolysis of the dimethyl phosphoramidate cation is 12%. Dimethyl phosphoramidate undergoes ready P–O bond cleavage in dilute alkali (k_{OH} = 5.0 M^{-1} min^{-1}); substitution of methyl groups into the amine moiety depresses the rate by a factor of *ca.* 10^4. It is proposed that the reaction of the former compound proceeds *via* a metaphosphate-like intermediate. The reaction of formate with phenyl phosphoranilide, which has been reported to proceed by a four-center type mechanism, has been subjected to kinetic analysis. The formation of formanilide, which is the basis of the previously proposed mechanism, has been found to be readily reversible and the equilibrium constant for formanilide hydrolysis has been determined.

Phosphoramidates and their esters have been of considerable value in the recent past as phosphorylating agents especially in the synthesis of pyro- and polyphosphate linkages.[2] They undergo displacement reactions with amines and alcohols as well as carboxylic acids[3] to give transphosphorylation products, some of which are isolable, others existing only as transient intermediates. These reactions have been the subject of mechanistic studies, their molecularity being a problem with which various workers have repeatedly concerned themselves.[3d,4] It is now generally accepted that substitution reactions with certain ionic species of simple phosphate esters take place not by direct attack on the phosphorus atom, but by a unimolecular elimination mechanism involving a hypothetical metaphosphate intermediate.[5] The possibility of a unimolecular mechanism for the reactions of unsubstituted phosphoramidic acid ($(HO)_2P(O)NH_2$) in its various forms has been assessed by Chanley and Feageson,[4a] who examined activation parameters as well as product distribution in mixed hydroxylic solvents to derive arguments for direct nucleophilic attack on all ionic species of this compound, not totally excluding, however, the coexistence of a unimolecular pathway in the reactions of the neutral molecule. Results of parallel studies with N-*p*-chlorophenylphosphoramidate also pointed to a bimolecular mechanism for the solvolyses of the monoanionic and neutral forms of this derivative. In this case it was the acid-catalyzed breakdown, which, by its product distribution pattern, seemed to be unimolecular. It has been pointed out, however, that this need only mean that the cationic species of N-*p*-chlorophenylphosphoramidate itself is nonselective toward the nucleophiles used by the above workers.[6]

We chose to look further into this question of molecularity by studying the effect that the substitution of an alkoxyl group for a hydroxyl function might have on the solvolytic properties of phosphoramidate. The introduction of a second ester group into phosphate monoesters and anhydrides greatly reduces their hydrolytic rates, presumably by eliminating the unimolecular pathway. Thus, the rate of P–O bond cleavage in the acetyl phenyl phosphate monoanion is more than 2000 times slower than that of the corresponding ionic form of acetyl phosphate.[7] There is independent evidence that the former undergoes direct solvent attack, while the latter reacts *via* a metaphosphate intermediate. The differential stabilities of mono- and dibenzyl phosphates,[8] mono- and dimethyl phosphates,[9] phosphoromono- and dichloridates,[10] P^1,P^1-diethyl- and P^1,P^1,P^2-trimethyl pyrophosphates,[11] and free and esterified phosphonates[12] are other cases in point. It would be expected, therefore, that if unsubstituted phosphoramidate reacts through a metaphosphate intermediate, its reactions would be much faster than those of its esterified derivatives. The studies reported below have been carried out with the monomethyl ester of phosphoramidate in an effort to minimize steric and inductive effects. The solvolytic behavior of dimethyl phosphoramidate, as well as its

(1) Supported by a grant from the National Institutes of Health (GM 11820). I. Ö. was the recipient of the Blatherwick Fellowship of Yale University.

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(4) (a) J. D. Chanley and E. Feageson, *J. Am. Chem. Soc.*, **85**, 1181 (1963); (b) V. M. Clark and S. G. Warren, *Proc. Chem. Soc.*, 178 (1963); (c) N. K. Hamer, *J. Chem. Soc.*, 46 (1965); (d) N. K. Hamer, *ibid.*, 2731 (1965); (e) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **86**, 1410 (1964).

(5) J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).

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(10) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press Inc., New York, N. Y., 1965, p 270.

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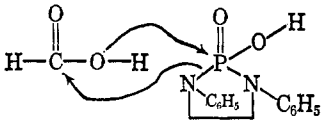
basic hydrolysis and that of its N,N-dimethyl-substituted analog, were also studied.

In a study of the hydrolysis of cyclic phosphorodiamidates in formate buffer, Kutzbach and Jaenicke[13a] reported high yields of N-formyl-N,N′-diarylethylenediamine in the pH range 3–7. Similarly high yields 50%) of formanilide were reported in the solvolysis of phenyl phosphoranilide in 1 *M* formate buffer at pH 4. To account for these reactions the authors proposed a four-centered mechanism involving nucleophilic attack on the formate carboxyl group by the amide nitrogen concerted with hydroxyl transfer from formate to the phosphoryl moiety of the substrate.[13b] This mecha-



nism closely resembles one proposed for several enzymatic reactions in which a C–N bond is formed, as in the synthesis of N-formylglycinamidine ribonucleotide[14a] and N-carboxybiotin.[14b,c] The concerted reaction proposed by Kutzbach and Jaenicke apparently provides the first example of a nonenzymatic reaction in which electrophilic catalysis by the phosphoryl group is concerted with nucleophilic attack, and we were, therefore, interested in obtaining further information concerning this reaction.

Experimental Section

Materials. Dimethyl Phosphoramidate. Dimethyl phosphite was prepared by the dropwise addition of PCl_3 (1 mole) to a cooled solution of methanol (3 moles) and quinoline (2 moles) in 350 ml of ether with constant stirring. The ether layer was decanted and saved; the quinoline·HCl precipitate was further extracted with 300 ml of ether. The combined extracts were reduced in volume by preliminary distillation at atmospheric pressure, and dimethyl phosphite was isolated by vacuum distillation of the remaining fraction, bp 36–38° (1–1.5 mm). Dimethylphosphoryl chloride was obtained from dimethyl phosphite by reaction of the latter with N-chlorosuccinimide (mole ratio 1:1) in dry benzene at room temperature overnight. The product was recovered by vacuum distillation of the benzene layer, bp 45° (~2 mm), and showed only minor impurities under gas chromatography. Ammonolysis of the chloride was carried out by the simultaneous slow addition of dimethylphosphoryl chloride and dry ammonia to chilled ether until precipitation of ammonium chloride was complete. After removing the ether layer the precipitate was extracted with chloroform, and the combined solvents were removed by evaporation at reduced pressure. The product is a low-melting solid crystallizable from ether (lit.[15a] mp 40–42°). *Anal.* Calcd: N (from determination of acid-labile ammonia), 11.19. Found: N, 11.02.

For the preparation of the N,N-dimethyl-substituted analog an ethereal solution of dimethylamine was substituted for ammonia in the final step, and the chloroform extraction was omitted. The product, purified by vacuum distillation, boils at 51° (~2 mm) (lit.[15b] 78–79° (15 mm)).

Monomethyl Phosphoramidate, Monosodium Salt. This material was obtained from the dimethyl ester by saponification (49 mmoles of ester:50.5 mmoles of NaOH in final volume of 10 ml) at 30° overnight. The slightly turbid hydrolysate was filtered after 1:1 dilution with water, then taken to dryness *in vacuo* to give a glassy liquid which eventually solidified after repeated trituration with ether and vacuum drying. Recrystallization was not attempted in view of the hygroscopic nature of the product. Elemental analysis at this stage is consistent with that of a hemihydrate; hydrates have been reported for monobenzyl phosphoramidate[16] and monomethyl N-cyclohexylphosphoramidate.[4c] *Anal.* Calcd for hemihydrate: C, 8.45; H, 4.23; N, 9.85; P, 21.80. Found:[17] C, 8.83; H, 3.90; N, 9.62; N (determined from ammonia assay following acid hydrolysis), 9.64; P, 20.80.

$(^{14}CH_3O)P(O)(ONa)NH_2$, $(^{14}CH_3O)_2P(O)NH_2$, and $(C^3H_3O)_2P(O)N(CH_3)_2$ were prepared by the appropriate substitution of $^{14}CH_3OH$ and C^3H_3OH in the synthesis of dimethyl phosphite.

Phenyl Phosphoranilide. Phenyl phosphoryl dichloride was prepared by a published procedure[18] and had bp 96–98° (3.7 mm) (lit.[18] 106–107.5° (7 mm)). Phenyl phosphoranilide was obtained from the dichloride by the method of Michaelis[19] and was recrystallized from acetonitrile, mp 140–140.5° (lit.[19] 134°). *Anal.* Calcd: C, 57.80; H, 4.85; N, 5.61. Found: C, 57.75; H, 4.95; N, 5.76.

Formanilide and acetanilide were obtained from commercial sources and were recrystallized from water and ethanol–water, respectively. Acetyl phenyl phosphate was prepared according to the method of Jencks.[20]

Organic solvents were distilled before use; dioxane was refluxed with sodium for 2 hr prior to distillation. Reagent grade inorganic salts and buffer components were used as commercially obtained. Glass-distilled water was used throughout.

Methods. Rates of P–N bond cleavage for dimePA[21] in water and for monomePA in water and mixed solvents were followed by assaying release of ammonia either by Nesslerization, or, in the cases of monomePA methanolysis and hydrolysis in mixed solvents, where this procedure was complicated by turbidity, by the Conway microdiffusion technique. Agreement between the two assays was checked and found to be satisfactory. Alkaline hydrolysis of dimePA was followed on a Radiometer SBR 2/SBU 1/TTA 31 pH-Stat assembly equipped with a Metrohm EA 121 H combination electrode and an air-tight, water-jacketed titration vessel (Metrohm EA 662), by recording the uptake of NaOH necessary to keep the reaction mixture at a preset pH. The basic hydrolysis of $(dime)_2PA$ was found to be very slow in the pH and temperature range where this titrimetric method can be used and a chromatographic assay procedure was therefore devised employing substrate tritiated in the methoxy moieties. P–O bond cleavage gives two radioactive products, monomethyl N,N-dimethylphosphoramidate and methanol. Owing to the presence of an ionizable hydroxyl group, the former is separable from the rest of the reaction mixture on a Dowex-1-Cl anion-exchange column, so that its appearance can be used to monitor the reaction. In a typical experiment 0.13 mmole of substrate (2×10^5 cpm) was dissolved in 5.0 ml of 1 *M* NaOH; 0.25-ml aliquots were dealt into ampoules, sealed, and put in a boiling water bath. At various intervals the ampoules were removed from the bath and immediately chilled in ice. The contents were brought to pH 7 by the addition of appropriate amounts of 1 *M* KH_2PO_4 and quantitatively transferred to a 1×12 cm Dowex-1-Cl column, which was then washed with water until the radioactivity of the effluent (containing neutral starting material and methanol) returned to background. Monomethyl N,N-dimethylphosphoramidate was subsequently eluted with 0.1 *N* HCl and quantitated by counting aliquots of the effluent. Preliminary experiments using as eluent an 0.01 *M* imidazole buffer of pH 6.5 and total chloride concentration of 0.05 *M* had shown the nonwater-elutable counts to consist of only one peak. Radioactivity was determined using a Beckman CPM 100 liquid scintillation counter and a dioxane–naphthalene–PPO–POPOP (500 ml:

(13) (a) C. Kutzbach and L. Jaenicke, *Ann. Chem.*, **692**, 26 (1966); (b) The mechanism given in ref 13a involves the dipolar forms of the phosphoryl and carbonyl substrates.

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(17) Analysis by the Mikroanalytisches Laboratorium im Max Planck Institut für Kohlenforschung, Mülheim, West Germany. Acid-labile ammonia and phosphate analyses by I. Ö. using the Nessler ammonia and ammonium phosphomolybdate methods.

(18) V. V. Katyshkina and M. Ya. Kraft, *Zh. Obshch. Khim.*, **26**, 3060 (1956); *Chem. Abstr.*, **51**, 8028*c* (1957).

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(20) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272 (1959).

(21) Abbreviations used: monomePA, sodium monomethyl phosphoramidate; dimePA, dimethyl phosphoramidate; $(dime)_2PA$, dimethyl N,N-dimethylphosphoramidate; PPA, phenyl phosphoranilide; APP, acetyl phenyl phosphate; PA, phosphoramidic acid.

100 gm:5 gm:0.125 gm) scintillating fluid with Cab-O-Sil M 5 as the gelling agent. The extent of quenching by the water and acid eluents was the same, as determined by the identity of quench ratios obtained with 0.2 ml of water or 0.1 *N* HCl per 10 ml of scintillating fluid, so that the total number of counts recovered in the water and acid fractions could be compared directly. The sum of the water- and acid-elutable counts was found to be reproducible within ±6%.

Products of Solvolysis of Mono- and Dimethyl Phosphoramidate. For monomePA the product distribution in 50% v/v methanol was studied under two different conditions: at pH 2.5 where the neutral form of the substrate is the sole reacting species, and in 0.2 *N* HCl where the acid-catalyzed reaction constitutes 80% of the observed rate. dimePA solvolysis was studied in 0.2 *N* HCl. For these studies 0.05–0.2 mmole of radioactive substrate was dissolved in 5.0 ml of the methanol–water mixture at 36.8° and then incubated at this temperature for at least six half-lives. A 4–5-ml portion of the reaction mixture was brought to approximately pH 5 with NaOH and then applied to a 1 × 22 cm Dowex-1-Cl column. The column was washed with water and then eluted with 0.01 *M* imidazole buffer at pH 6.5 (with a total chloride concentration of 0.05 *M*) until 120 ml of effluent was collected. The elution volume of dimethyl phosphate is 28–73 ml under these conditions. For the elution of monomethyl phosphate an additional 130 ml was collected using an identical eluent adjusted to pH 5.1. With sodium monomePA two peaks were obtained from the solvolysis reactions, their positions corresponding to those of mono- and dimethyl phosphate. dimePA gave one peak (dimethyl phosphate) elutable with pH 6.5 buffer, the rest of the radioactivity coming off with the water wash as expected of neutral trimethyl phosphate. dimePA hydrolyzed in 0.2 *N* HCl and chromatographed using the same procedure gave no water-elutable counts, thus establishing the absence of water-elutable radioactive impurities and any parallel reactions involving C–O cleavage generating radioactive methanol, which would interfere with the determination of the trimethyl phosphate yield in the methanolysis reactions. The recovery from the column was quantitative (99.0%) and the extent of quenching of radioactivity by the two eluent buffers was again comparable. Per cent methanolysis for mono- and dimePA was calculated from the ratio, respectively, of pH 6.5 and water-elutable counts to total radioactivity recovered from the column. Mono-, di-, and trimethyl phosphate are stable under the assay conditions.[9,22]

P–N Cleavage in Phenyl Phosphoranilide. Hydrolysis of phenyl phosphoranilide was studied in formate and acetate buffers in the pH range 3.55–5.0. The rate of breakdown of 5×10^{-3} *M* PPA in 1 *M* formate buffer, pH 3.55 at 50°, was determined spectrophotometrically at 275 mμ in a stoppered cuvette with a Zeiss PMQ II spectrophotometer. The stabilities of aniline and formanilide at 50° in the same buffer system (pH 3.7) were checked by incubating solutions of aniline·HCl and formanilide in sealed ampoules and periodically assaying for aniline by the Bratton–Marshall diazotization method.[23] Hydrolysis of PPA in 1 *M* acetate buffers, pH 4.0 and 5.0, at 100° was carried out in sealed ampoules and monitored by assaying for aniline. The reactions at pH 5.0 were carried out under an argon atmosphere.

Results

Mono- and Dimethyl Phosphoramidate P–N Cleavage. The pH–rate profiles for the solvolysis of monomePA in water and in 50% v/v methanol–water are given in Figure 1. The rates of hydrolysis were obtained in dilute buffer solutions (0.05 *M*) using the Nessler ammonia assay. Higher substrate and hence higher buffer concentrations were required in the methanolysis reactions where release of ammonia had to be followed by the Conway microdiffusion technique. However, a study using chloroacetic acid at pH's 2.2–2.8 indicated the rate to be independent of buffer concentration to 0.5 *M*. The pH dependence of the rate can be analyzed in terms of the uncatalyzed and acid-catalyzed reactions of undissociated methyl phosphoramidate with solvent according to the rate law

$$\text{rate} = k_{obsd}(\text{MePA})^{total} = k_0(\text{MePA})^0 + k_{H^+}(H^+)(\text{MePA})^0 \quad (1)$$

Expressing $(\text{MePA})^0$ in terms of total substrate concentration, this rate law becomes

$$\text{rate} = k_{obsd}(\text{MePA})^{total} = [k_0 + k_{H^+}(H^+)]\left[\frac{(H^+)}{(H^+) + K_a}\right](\text{MePA})^{total} \quad (2)$$

where K_a is the acid dissociation constant of neutral monomePA. The curves given in Figure 1 are drawn according to this rate law using the values for k_0 and k_{H^+} given in Table I, and 2.51×10^{-3} and 6.31×10^{-4} for K_a in water and methanol–water, respectively. The pK_a values of 2.60 and 3.20 obtained from this kinetic analysis agree well with those determined by direct titration (Table II), and with the value reported for monomethyl N-cyclohexylphosphoramidate in water (3.1).[4c] The corresponding constant for ethyl hydrogen N,N-diethylphosphoramidate is reported at 7.2.[24] The monoanion of monomePA is stable; less than 2% cleavage was observed at the end of 26 hr in a reaction at pH 6.58. Experiments conducted with ^{14}C-labeled substrate showed monomethyl phosphate to be the only

Table I. Rates of Solvolysis of Phosphoramidates in Water and Mixed Solvents at 36.8° [a]

Reaction	Substrate	k_0, hr^{-1}	k_{H^+}, $M^{-1}\,hr^{-1}$
Hydrolysis in water	$(CH_3O)(OH)P(O)NH_2$	0.58	5.60
	$(OH)_2P(O)NH_2$	0.42[b]	33.3[b]
	$(O^-)(OH)P(O)NH_2$	0.25[b,d]	
Hydrolysis in water, $\mu = 1.0$ *M*	$(CH_3O)(OH)P(O)NH_2$	0.55	8.40
Solvolysis in 50% methanol–water	$(CH_3O)(OH)P(O)NH_2$	0.296	5.99
	$(OH)_2P(O)NH_2$	0.52[b]	9.34[b]
Hydrolysis in 50% dioxane–water	$(CH_3O)(OH)P(O)NH_2$	0.32	4.34
	$(O^-)(OH)P(O)NH_2$	0.315[b,d]	
Hydrolysis in 50% acetonitrile–water	$(CH_3O)(OH)P(O)NH_2$	0.174	5.60
Hydrolysis in water, $\mu = 0.8$ *M*	$(CH_3O)_2P(O)NH_2$	0	5.55
Solvolysis in 50% methanol–water	$(CH_3O)_2P(O)NH_2$		1.3[c]

[a] Ionic strength 0.2 *M* unless otherwise indicated. [b] Data from ref 4a. [c] Approximate value. [d] First-order rate constant for hydrolysis of the monoanion.

Table II. Dissociation Constants for Neutral Monomethyl Phosphoramidate in Various Solvent Systems[a]

Solvent system	pK_a[b]
Water	2.50
50% methanol–water	3.04
50% dioxane–water	3.13
50% acetonitrile–water	3.07

[a] Ionic strength 0.2 *M*, 36.8°. [b] Calculated by the logistic treatment of Reed and Berkson described in W. M. Clark, "Oxidation–Reduction Potentials of Organic Systems," Williams & Wilkins Co., Baltimore, Md., 1960, p 150.

(22) P. W. C. Barnard, C. A. Bunton, D. R. Llewellyn, K. G. Oldham, B. A. Silver, and C. A. Vernon, *Chem. Ind.* (London), 760 (1955).

(23) The Bratton–Marshall assay was modified as described by G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, 87, 5692 (1965).

(24) E. W. Crunden and R. F. Hudson, *J. Chem. Soc.*, 3591 (1962).

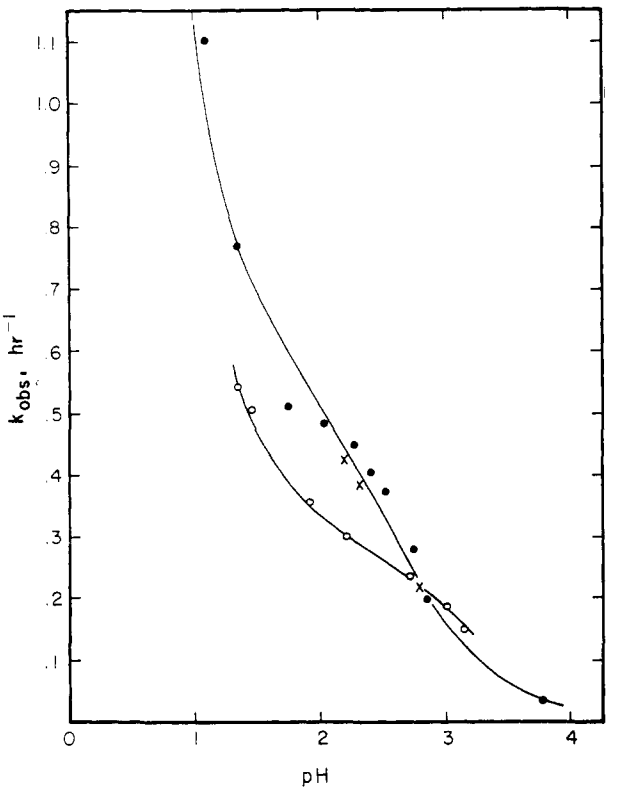

Figure 1. pH–rate profile for the solvolysis of monomethyl phosphoramidate at 36.8°: ●, hydrolysis in water with HCl or 0.05 *M* trichloroacetate or chloroacetate buffers, ionic strength 0.2 *M*, 2×10^{-3} *M* substrate, Nessler ammonia assay; ×, hydrolysis in water with 0.5 *M* chloroacetate buffer, 2×10^{-2} *M* substrate, Conway microdiffusion assay; ○, solvolysis in 50% methanol–water with 0.2 *M* trichloroacetate, phthalate, or chloroacetate buffers, 2×10^{-2} *M* substrate, Conway microdiffusion assay.

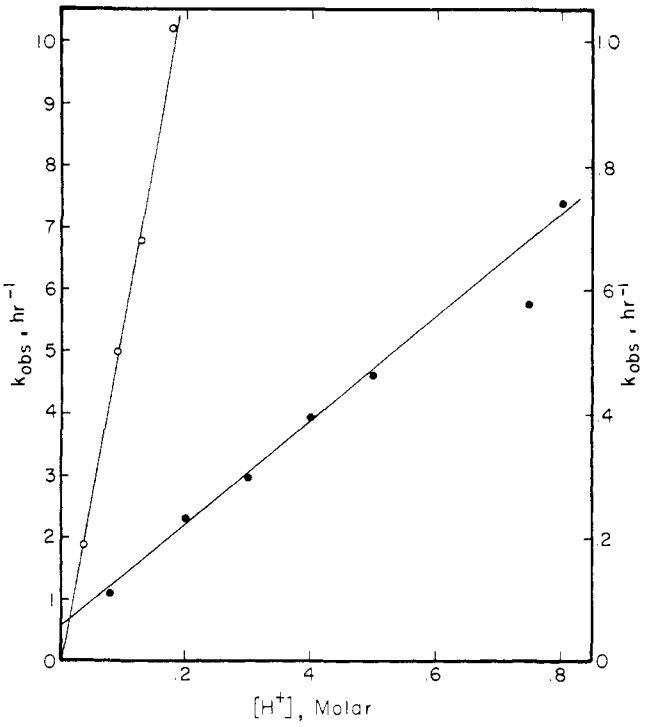

Figure 2. Hydrolysis of mono- and dimethyl phosphoramidate in aqueous HCl at 36.8°: ●, monomethyl phosphoramidate, left ordinate, ionic strength 1.0 *M*; ○, dimethyl phosphoramidate, right ordinate, ionic strength 0.8 *M*.

product of hydrolysis at acid pH as evidenced by the presence of a single peak under Dowex column chromatography of the hydrolysate, accounting for the total radioactivity originally in the reaction mixture. This excludes the possibility of C–O cleavage in the range studied, since such cleavage would have given radioactive methanol as a product. The absence of C–O bond cleavage and the displacement of a group with a pK_a of 9 (NH_4^+) rather than one with a pK_a of less than 1 ($^+NH_3P(O)(OH)_2$) is contrary to what one might have expected judging from the results obtained in the neutral hydrolysis of monomethyl and dimethyl phosphate where the more acidic group is displaced *via* C–O bond cleavage.[9]

The dependence of the observed rate of hydrolysis on hydrogen ion concentration in the pH range where the acid-catalyzed reaction predominates is depicted in Figure 2; the slope of the line gives a value of 8.4 M^{-1} hr^{-1} for the second-order rate constant (k_{H^+}) in the rate law (1) above. Extrapolation to zero [H$^+$] gives an intercept of 0.55 hr^{-1} as k_0 in the same rate law. These constants, obtained at $\mu = 1.0$ *M*, are to be compared to 5.6 M^{-1} hr^{-1} (based on hydrogen ion activity) and 0.58 hr^{-1}, respectively, calculated from pH–rate data obtained at $\mu = 0.2$ *M* (Figure 1). Acid-catalyzed hydrolysis appears to be subject to a positive salt effect in line with similar effects reported for dimethyl phosphate.[9] Also shown in Figure 2 is the dependence of the rate of hydrolysis of dimePA on hydrogen ion concentration. The slope of this curve gives 5.55 M^{-1} min^{-1} for k_{H^+} and the extrapolation to the origin indicates that the rate of hydrolysis of the neutral compound is negligible. Only P–N cleavage occurs since ^{14}C-labeled dimethyl phosphoramidate gave dimethyl phosphate as the only radioactive product. Any parallel C–O cleavage would have resulted in a mixture of mono- and dimethyl phosphate and methanol which are easily differentiable in the column chromatographic procedure described above.

Addition of methanol, dioxane, or acetonitrile decreases the rate of hydrolysis of neutral monomePA slightly, but has no effect on the acid-catalyzed rate, except in the case of dioxane, where a small decrease is observed. The decrease in the rate of the acid-catalyzed breakdown of dimePA is more pronounced, amounting to approximately threefold if we extrapolate from ionic strength 0.8 *M*, in which the reaction in water was carried out, to ionic strength 0.2 *M*, which was the condition for the methanolysis experiment. The results, together with earlier data for the solvolysis of unsubstituted phosphoramidic acid,[4a] are given in Table I.

Products of Solvolysis. Figure 3 shows the chromatographic resolution of mono- and dimethyl phosphate standards and the products of solvolysis of monomePA in methanol–water, 0.2 *N* with respect to HCl. A similar pattern was obtained from methanolysis at pH 2.5, differing only in the ratio of the radioactivities recovered in the individual peaks. The yields of dimethyl phosphate at pH 2.5 and in 0.2 *N* HCl were 65 and 30%, respectively. With dimethyl phosphoramidate 12% of the total radioactivity in the products was elutable with water. This figure represents the amount of trimethyl phosphate formed in the solvolysis of dimePA. The remaining 88% of the counts ap-

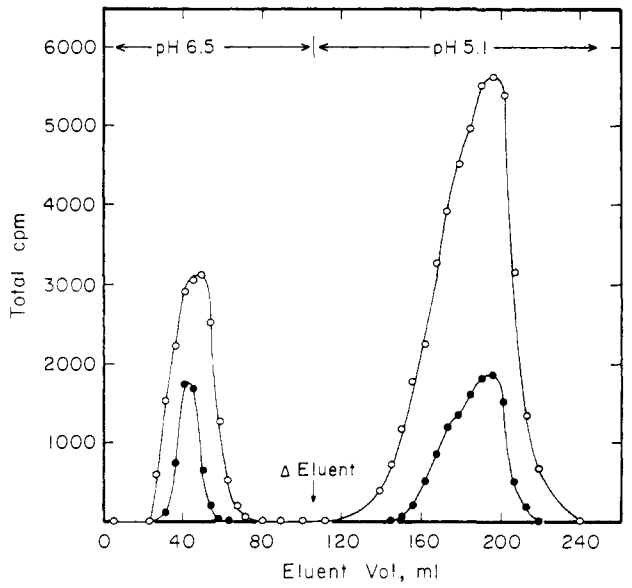

Figure 3. Chromatographic resolution of the products of the solvolysis of monomethyl phosphoramidate in 0.2 M HCl and 50% methanol, ○; and of mono- and dimethyl phosphate, ●, under pH regions 5.1 and 6.5, respectively.

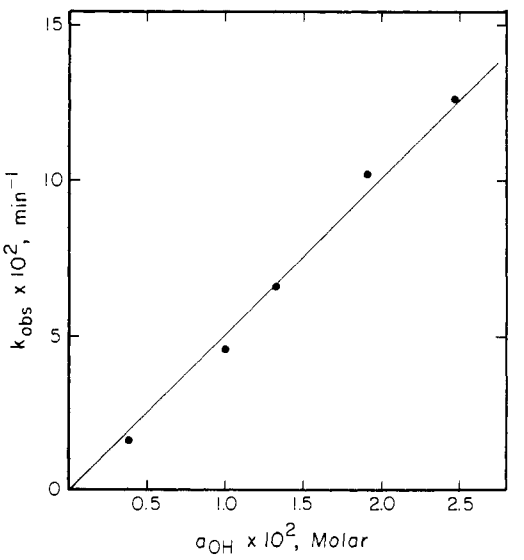

Figure 4. Alkaline hydrolysis of dimethyl phosphoramidate at 36.8° and ionic strength 0.2 M.

peared as dimethyl phosphate, the product of hydrolysis. From these results the methanol and water components (k_0^m, k_0^w and $k_{H^+}^m$, $k_{H^+}^w$) of the rate constants in Table I were calculated from eq 3 and are given in Table III.

rate increases linearly with pH in the range 11.20–12.01 (Figure 4) and the second-order rate constant for hydroxide catalysis is 5.0 M^{-1} min^{-1}, based on hydroxide activity calculated from pH and an interpolated $pK_w^{37°}$ of 13.62. The values of k_{OH} for the breakdown of dimethyl N,N-dimethylphosphoramidate obtained at 100° and two hydroxide concentrations (0.15 and 1.0 M, μ = 1.0 M) were 1.1 × 10^{-2} M^{-1} min^{-1} and

Table III. Solvolysis of Mono- and Dimethyl Phosphoramidate in 50% Methanol–Water[a]

Conditions	Substrate	% methanolysis	k_0, H_2O/CH_3OH	k_{H^+}, H_2O/CH_3OH
0.2 M chloroacetate buffer, pH 2.5	monomePA	65.5 ± 0.5	0.104/0.192	
0.2 N HCl	monomePA	29.6 ± 0.8		4.74/1.25
0.2 N HCl	dimePA	12.2 ± 0.4		1.14/0.16[b]
pH 5.0[c]	PA (monoanion)	72		
pH 3.0[c]	PA (neutral compound	44	0.133/0.389	
0.2–0.7 M HCl[c]	PA (cation)	8[b]		9.34/0[b]

[a] 36.8°, μ = 0.2 M with KCl except for the reaction of PA cation. [b] Approximate values. [c] Reference 4a.

monomePA

$$k_0 = k_0^m + k_0^w$$

$$k_{H^+} = k_{H^+}^m + k_{H^+}^w$$

$$\% \text{ methanolysis (pH 2.5)} = (k_0^m/k_0)100$$

$$\% \text{ methanolysis (in 0.2 } N \text{ HCl)} = (k_{H^+}^m[H^+] + k_0^m)100/k_{obsd} \quad (3)$$

dimePA

$$k_{H^+} = k_{H^+}^m + k_{H^+}^w$$

$$\% \text{ methanolysis (in 0.2 } N \text{ HCl)} = (k_{H^+}^m[H^+])100/k_{obsd}$$

Using the rate constants so derived, a 21% yield of methanolysis product is calculated for cationic monomePA.

P–O Bond Cleavage in Alkali. The hydrolysis of dimePA to the corresponding monomethyl compound occurs readily in relatively dilute base. The observed 1.64 × 10^{-2} M^{-1} min^{-1}, respectively. Correction of these values to 36°, assuming an activation energy of 16.2 kcal/mole (the value for trimethyl phosphate[5]) shows that the basic hydrolysis of the N,N-dimethyl-substituted compound is some 38,000 times slower than that of the parent dimethyl phosphoramidate.

P–N Cleavage in Phenyl Phosphoranilide. The four-center reaction proposed by Kutzbach and Jaenicke[13] for the formolysis of cyclic phosphorodiamidates and phenyl phosphoranilide predicts that the extent of aniline formylation in the latter compound will be independent of substrate concentration. If, however, the reaction proceeds by a stepwise pathway in which the initial products are formyl phenyl phosphate and aniline, and formanilide is formed by the subsequent reaction of aniline with the acyl phosphate, the per cent yield of formanilide should decrease with substrate concentration as the concentration of aniline becomes low enough for hydrolysis of the acyl phosphate to predominate. Studies by Di Sabato and Jencks[7] of the

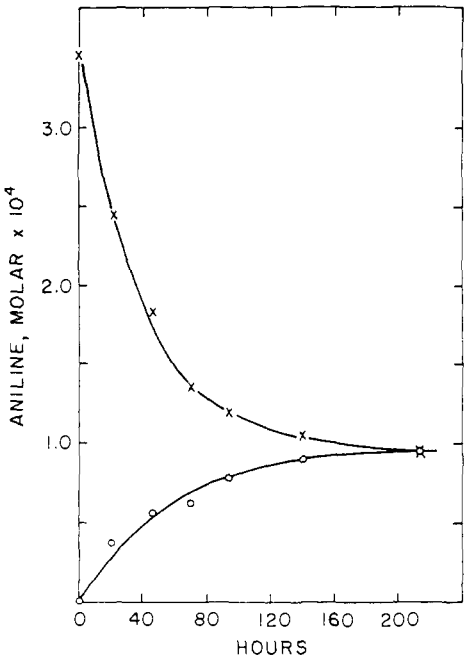

Figure 5. Approach to equilibrium of formic acid, aniline, and formanilide at pH 3.7, 50°, and ionic strength 1.0 *M*. The initial concentrations were 1.0 *M* formate, and 3.5×10^{-4} *M* formanilide (○), or aniline (×).

reaction of aniline with acetyl phenyl phosphate indicate that both aminolysis and hydrolysis of APP proceed with C–O bond cleavage with relative rates of 2100:1 in 1 *M* aniline at 39°. A study was carried out in which the initial phenyl phosphoranilide concentration was varied from 0.5×10^{-4} to 25×10^{-4} *M* and the amount of formanilide formed was determined by the difference between the aniline found and that predicted from the initial substrate concentration. It was found, however, that considerable aniline disappeared in the absence of phenyl phosphoranilide, and that the formation of formanilide is readily reversible under the conditions employed. An equilibrium constant for formanilide hydrolysis was determined and the results are given in Figure 5. The value of the equilibrium constant (K = [anilinium]$^+$[formate]$^-$/[formanilide][H_2O]) is 0.134,[25] where the activity of water has been taken to be unity, giving values of 1.29 kcal/mole for the standard free energy of hydrolysis and −2.77 kcal/mole for the free energy of hydrolysis at pH 7 referred to 1 *M* solutions of the reactants and products as the standard state. The conclusions previously advanced for the formolysis of PPA are, therefore, subject to considerable doubt. Hydrolysis of PPA at pH 4.0 in 1 *M* acetate buffer was independent of buffer concentration and gave quantitative yields of aniline; acetanilide is stable under these conditions. Attention was directed to the reaction at pH 5.0, where the yield of aniline is not quantitative, and buffer catalysis of the breakdown of the substrate is observed. These observations suggested that the proposed four-center reaction might be demonstrable and a study of the effect of substrate concentration on the yield of acetanilide was, therefore,

(25) Based on pK_a's of 3.78 (50°) for formic acid ("Handbook of Chemistry and Physics," 46th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1965, p D-80), and 4.25 (50°) for aniline (extrapolated from the values reported for the temperature range 20–40° by A. I. Biggs, *J. Chem. Soc.*, 2572 (1961)).

Table IV. Effect of Substrate Concentration on the Yield of Acetanilide Formed in the Solvolysis of Phenyl Phosphoranilide in Acetate Buffer[a]

	Reaction	Free aniline detected (OD$_{545}$)[b] Time, hr 0	89	136	Acetanilide formed,[c] %
A	7.67×10^{-4} *M* An·HCl in 1 *M* acetate	0.400	0.372		7
B_1	1.55×10^{-3} *M* PPA in 1 *M* acetate		0.402		
	1.55×10^{-3} *M* PPA in 2.7×10^{-2} *M* acetate			0.437	8
B_2	1.55×10^{-4} *M* PPA in 1 *M* acetate		0.395		
	1.55×10^{-4} *M* PPA in 2.7×10^{-2} *M* acetate			0.440	10
B_3	1.55×10^{-5} *M* PPA in 1 *M* acetate		0.395		
	1.55×10^{-5} *M* PPA in 2.7×10^{-2} *M* acetate			0.441	10
B_4	3.2×10^{-6} *M* PPA in 1 *M* acetate		0.390[d]		
	3.2×10^{-6} *M* PPA in 2.7×10^{-2} *M* acetate			0.483[d]	19
C	7.67×10^{-4} *M* An·HCl and 10.0×10^{-4} *M* APP in 1 *M* acetate	0.400	0.302		24
	7.67×10^{-6} *M* An·HCl and 10.0×10^{-6} *M* APP in 1 *M* acetate	0.400	0.354		12

[a] Ionic strength maintained at 1.0 *M* with KCl, 100°, pH (measured at room temperature) 5.0. [b] Optical densities measured following Bratton–Marshall diazotization after 89 and 136 hr, which correspond to *ca.* six half-lives for PPA cleavage in 1.0 and 0.01 *M* acetate buffers, respectively. Appropriate dilutions were made to bring absorbance values to a readable range. [c] Calculated from the optical density ratios $(t_{136} - t_{89})/t_{136}$ or $(t_0 - t_{89})/t_0$. [d] The low aniline concentrations required a slightly different assay procedure and these values are less reliable than those given above.

carried out under these conditions. The complex of experiments is summarized in Table IV. The rate of acetanilide hydrolysis at this pH is again low and contributes less than a 3% error into the quantitation of acetanilide yield in the various reaction mixtures. The yields of acetanilide from the breakdown of PPA were found to be consistently higher than accountable for in terms of spontaneous reaction of aniline with acetate. These differences (B_1, B_2, B_3, and B_4 compared to A) are undoubtedly less than the true ones since acetanilide formation in reaction A begins at zero time while the corresponding reaction in B requires prior cleavage of PPA. The yield of acetanilide (Table IV) is independent of the substrate concentration over a 500-fold range. Calculation of this yield, however, requires a subtraction of large numbers and the resulting uncertainty makes us reluctant to interpret these results in terms of either mechanism. The results with acetyl phenyl phosphate and aniline in acetate (Table IV, reactions C) suggest that nucleophilic attack on phenyl phosphoranilide by acetate to give acetyl phenyl phosphate as an intermediate does not take place to a significant extent, since this would have led to higher yields

of acetanilide than observed. The majority of the catalysis of PPA breakdown by acetate ion[26] (k_{H_2O} = 3.0×10^{-2} hr^{-1}; $k_{Ac^-} = 2.7 \times 10^{-2}$ M^{-1} hr^{-1} at 100° and μ = 1.0 M) is quite likely due to a general base-catalyzed pathway.

Discussion

Hydrolysis of Phosphoramidates. Consistent with the patterns for unsubstituted PA[4a] and most phosphate monoesters[27] the pH–rate profile for the hydrolysis of monomethyl phosphoramidate reflects the necessity either for the presence of an undissociated hydroxyl group in the phosphate moiety, which will facilitate the departure of the leaving group by proton transfer to the latter, or for the occurrence of the substrate in a zwitterionic form where the protonation of the leaving group occurs in a preequilibrium. The latter alternative has been proposed for phosphoramidate on the basis of the high pK_a values of 3.0 and 8.0 for the ionization of the neutral and monoanionic species of this compound as compared to those of oxygen esters.[4a] However, it has also been suggested that this may be the result of the different electronegativities of nitrogen and oxygen.[6] X-Ray crystallographic data[28] cited as evidence for the zwitterionic state of the phosphoramidate monoanion again are not conclusive; infrared studies show benzyl hydrogen phosphoramidate to be zwitterionic in the crystalline state, while parallel studies of this compound in dimethyl sulfoxide and dimethylformamide provide evidence for the existence of a neutral molecule.[29] Further evidence on this point comes from our observation that the monomethyl phosphoramidate anion and neutral dimethyl phosphoramidate are stable indicating that zwitterion formation is required for phosphoramidate hydrolysis.[30] Hamer[4c] has previously arrived at a similar conclusion on the basis of the results of Moffatt and Khorana[31] in which the reactivity of adenosine-5′ hydrogen-N-substituted phosphoramidates has been demonstrated to increase with increasing basic strength of the parent amine.

The kinetically indistinguishable reactions involving attack of water on the PA monoanion or hydroxide with the neutral form of PA can be resolved in favor of the former mechanism by analysis of the results obtained with monomethyl phosphoramidate. The stability of the monoanion of this compound under conditions where the unsubstituted derivative is hydrolyzed indicates that the monomePA monoanion is not subject to attack by water *and* the reaction of hydroxide with the neutral form of monomePA is not significant. This suggests that reaction of hydroxide ion with the neutral form of unsubstituted PA is also insignificant. A similar ambiguity can be resolved in the cleavage of neutral PA where solvolysis might involve either the reaction of water with the neutral compound, or hydroxide with the cationic species. The former mechanism is implicated from the results indicating that neutral dimePA is stable under conditions where the neutral unsubstituted compound is cleaved. Again this stability reflects the absence of a reaction of hydroxide with the cationic form of dimePA, and by inference the absence of a reaction of hydroxide with cationic unsubstituted PA.

As discussed above, disubstituted phosphate compounds have been found to solvolyze at greatly reduced rates as compared with related monosubstituted derivatives. Presumably this is caused by the lesser resonance stabilization available to a metaphosphate ester as compared with a metaphosphate ion. Although metaphosphate esters have been proposed as intermediates in phosphate transfer reactions,[32] these is little evidence supporting this pathway. In contrast, reactions that are apparently bimolecular are unaffected by methyl substitution, as indicated by the similarity of the rates of P–O bond cleavage in neutral dimethyl phosphate and phosphoric acid.[5] Based upon this criterion, we conclude from the similarity of the rates of hydrolysis of neutral monomethyl phosphoramidate and the unsubstituted compound that both reactions are bimolecular.

Solvolysis in Mixed Organic Solvents. Addition of organic solvents results in a marked decrease in the rate of *hydrolysis* of all of the ionic forms of the unsubstituted and methyl-substituted phosphoramidates. The sole exception is the phosphoramidate monoanion where dioxane increases the rate (Table I) suggesting that there is a significant difference in the mechanism for this compound, *vide infra*. Analysis of the effect of organic solvents on the rate of the hydronium ion catalyzed reaction is complicated by the fact that the second-order rate constants obtained for these reactions reflect the effect of solvent on the solvolysis rate as well as the equilibrium for substrate protonation. This complication may be resolved by assuming that the effect of the solvents on the equilibrium for protonation of the neutral compound are in the same direction as those observed for protonation of the monoanion (Table II), in which case the above correlation still holds. A possible explanation for the solvent effects is that the reaction involves considerable reorientation and "freezing" of solvent molecules and the degree of reorientation is greater in a mixture of water and a less polar organic component than in water alone.[33] Such an entropy effect in itself might account for the differential rates. An alternate explanation has been given for the observed decrease in the hydrolytic rate of neutral N-*p*-chlorophenyl phosphoramidate in dioxane.[4a] This decrease is such that the typically S-shaped pH–rate profile obtained in water (and attributed to the comparable reactivities of the monoanionic and neutral species) is replaced by one characteristic of phosphate mono-

(26) Obtained from the intercept and slope respectively of a plot of the observed rate of aniline release from PPA at pH 5 (25°) *vs.* the acetate concentration (0.1–1.0 *M*) which was calculated from the pH and a pK_a for acetic acid of 4.8.

(27) W. P. Jencks, *Brookhaven Symp. Biol.*, **15**, 134 (1962).

(28) E. Hobbs, D. E. C. Corbridge, and B. Raistrick, *Acta Cryst.*, **6**, 621 (1953).

(29) Lord Todd, *Proc. Chem. Soc.*, 199 (1962).

(30) The possibility of internal proton transfer in the nonzwitterionic forms cannot be ruled out. We consider this unlikely from consideration of the reaction of amines with the PA monoanion[3d] where symmetry requires proton transfer to and from the leaving and attacking amine. Since tertiary amines display normal reactivity in this reaction, it appears that this mechanism is not involved.

(31) J. G. Moffatt and H. G. Khorana, *J. Am. Chem. Soc.*, **83**, 649 (1961).

(32) (a) A. Todd, *Proc. Natl. Acad. Sci. U. S.*, **45**, 1389 (1959); (b) G. Weimann and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 4329 (1962); (c) V. M. Clark, D. W. Hutchinson, G. W. Kirby, and A. Todd, *J. Chem. Soc.*, 715 (1961); (d) D. M. Brown, J. A. Flint, and N. K. Hamer, *ibid.*, 326 (1964).

(33) R. G. Pearson, *J. Chem. Phys.*, 20, 1478 (1952).

esters, where the rate goes through a maximum in the region where the substrate is predominantly in the monoanionic form and goes down again with the protonation of the monoanion at lower pH. It has been suggested that the depressive effect of dioxane on the hydrolysis of neutral N-*p*-chlorophenyl phosphoramidate may be caused by a shift in the zwitterionic equilibrium of this compound such that the concentration of the substrate in the zwitterionic and reactive form is decreased. If this is the case, it is difficult to understand why the rate of hydrolysis of the monoanion is not similarly depressed (the observed rate decrease is 1.7-fold with the monoanion and 6.8-fold with the neutral compound).[34] It appears reasonable to expect that the equilibrium constant for formation of the zwitterion is more favorable with the neutral compound as compared with the monoanion from comparison of the relative pK's of the competing sites for protonation. Therefore, if organic solvents have a similar destabilizing effect on the zwitterion of both ionic species the equilibrium for the monoanion would be expected to be more sensitive to the resulting shift produced by dioxane.

Methanol–Water Competition with Phosphoramidates. Studies of the partitioning of phosphate compound between competing nucleophiles has been suggested as a means for determining the molecularity of solvolysis.[4a,35] In several reactions in which a metaphosphate intermediate is believed to exist, it has been found that the mole ratio of products closely parallels that of the nucleophiles. This has been attributed to the phosphonium ion character and hence high reactivity of the intermediate which makes its reactions nonselective. Recently, however, in studies of several solvolytic reactions in which there is good evidence for a unimolecular mechanism the relative reactivity of methanol and water have been found to vary with changes in the leaving group. Thus, the yield of methyl phosphate varies in the solvolysis of the dianions of *p*-nitrophenyl, 2,4-dinitrophenyl, and 2,6-dinitrophenyl phosphates.[36] Analysis of the results obtained in reactions that are apparently bimolecular reveals a complex pattern further undermining the use of partitioning data as a criterion of mechanism. For example, in displacement reactions with compounds with an identical leaving group the yield of methanolysis product is sensitive to methyl substitution in the phosphate moiety; 8, 21, and 12% methanolysis are observed in the cleavage of the cationic forms of unsubstituted, monomethyl, and dimethyl phosphoramidates. Effects of varying the leaving group are complex and methanol–water partitioning is identical with PA and the product of the reaction of PA with nicotinic acid.[4a] In another case, the yield of ethanolysis product goes from 8% with methyl hydrogen N-cyclohexylphosphoramidate to 40% with the corresponding phosphoramide formed by displacement of cyclohexylamine by pyridine.[4c]

The pattern observed in studies with nitrophenyl phosphates has recently been interpreted in terms of a selective solvation process in which alcohols are to varying degrees excluded from the inner reactive solvent shell surrounding the substrate.[36a,37] This interpretation does not, however, appear to be consistent with the decreasing per cent methanolysis with the monoanionic, neutral, and cationic forms of phosphoramidate. It might be expected that exclusion of methanol would be greatest with the two charged species. Furthermore, we have failed to observe a progressive increase in methanolysis in the acid-catalyzed solvolysis of phosphoramidates with substitution of alkoxyl for hydroxyl groups. Finally, Kirby[36a] has ascribed the low reactivity of 2-propanol, as compared to methanol, with the *p*-nitrophenyl phosphate dianion to exclusion of the 2-propanol from the solvent shell of the substrate. However, a similar effect is not observed in the reaction of amines with this substrate and the rates of reaction of methyl-, *n*-propyl-, isopropyl-, and *n*-butylamine are comparable.[36a,38] A complicating factor in interpreting these results is that the amine reactions appear to be at least partly bimolecular, from studies of the concentration dependence of the rate, while the molecularity of alcoholysis reactions is difficult to determine since it is necessary to study reaction of alcohols at such high concentrations that studies of the dependence of the rate on the alcohol concentration are subject to considerable uncertainty. Irrespective of this factor, one might still expect increases in the hydrocarbon nature of the amine to result in exclusion from the solvent sphere of the dianionic substrate.

The apparent failure of an analysis based solely upon considerations of ground-state solvation suggests that it might be more reasonable to consider medium effects on the transition state. In the reactions of the relatively unreactive compounds studied the transition state can be expected to resemble the products of the reaction, *i.e.*, phosphoric acid or an alkyl phosphate.[39] The relative stabilities of these alternate solvolysis products are apparently highly sensitive to medium effects which is reflected in the greater dissociation constants for alkyl phosphates as compared with phosphoric acid[40] (also compare methoxylamine with hydroxylamine). This has been attributed to the absence of hydrogen bonding of the solvent with the hydroxyl group in the alkylated compound resulting in an increase in the electropositive character to the adjacent phosphoryl group.[40b] Hydrogen bond stabilization, which is only available to the products of hydrolysis, should be reflected in the transition state and thereby facilitate hydrolysis relative to methanolysis. The actual partitioning of a phosphoryl donor would, however, depend upon the amount of product character of the transition state. This can be illustrated with the various forms of phosphoramidate. The near identity of the rates of hydrolysis of the neutral and monoanionic species suggests that the latter compound reacts by a pathway which is predominantly unimolecular since it is difficult to explain the absence of electrostatic repulsion without assuming that ionization provides a greater

(34) J. D. Chanley and E. Feageson, *J. Am. Chem. Soc.*, 80, 2686 (1958).
(35) P. A. T. Swoboda, Special Publication No. 8, The Chemical Society, London, 1957, pp 41–42.
(36) (a) A. J. Kirby and A. G. Varvoglis, *J. Am. Chem. Soc.*, **89**, 415 (1967); (b) C. A. Bunton, E. J. Fendler, and J. H. Fendler, *ibid.*, **89**, 1221 (1967).
(37) C. A. Bunton and H. Chaimovich, *Inorg. Chem.*, **4**, 1763 (1965).
(38) A. J. Kirby and W. P. Jencks, *J. Am. Chem. Soc.*, **87**, 3209 (1965).
(39) G. S. Hammond, *ibid.*, 77, 334 (1955).
(40) (a) Statistical corrections result in magnification of the apparent differences in dissociation constants. (b) W. D. Kumler and J. J. Eiler, *J. Am. Chem. Soc.*, **65**, 2335 (1943).

driving force for an elimination pathway.[41] The transition state for the reaction of the monoanion is, therefore, similar to either the starting material or a metaphosphate intermediate and differences in the product stability are relatively unimportant. The high yield of methyl phosphate apparently reflects the greater nucleophilicity of methanol as compared with water. Increases in the unimolecular character of the reaction, as in the hypochlorous acid catalyzed cleavage of the monoanion,[4e] decrease the importance of the driving force of nucleophilic attack by methanol and the per cent methanolysis is decreased. This pattern continues with the *p*-nitrophenyl phosphate monoanion and dianion where the significance of nucleophilic attack is still less and the per cent methanolysis is further decreased.[36] Finally, the decreasing yields of methyl phosphate observed with the neutral and cationic forms of phosphoramidate reflect the progressive increasing molecularity of the reaction with concomitant increasing product character of the transition state.

Basic Hydrolysis. Studies of the basic hydrolysis of dimethyl phosphoramidates were suggested from earlier results with phosphorodiamidic halides.[42] In these studies the rates were found to be critically dependent upon the number of substituents on the amino moiety; recent studies with the sterically similar N,N′-dipropyl- and N,N,N′,N′-tetramethylphosphorodiamidic chlorides have shown the former to react with hydroxide some four million times faster than the fully substituted analog.[43] The mechanism proposed to account for this pronounced difference in rates involves a metaphosphate-like intermediate which requires the presence of an ionizable hydrogen on one or both of the nitrogens. The present study shows a comparable, though less spectacular, difference in the second-order rate constants for hydroxide attack on dimePA and its N,N-dimethyl-substituted analog.[44] The difference cannot be solely accounted for in steric terms, which ordinarily cause order of magnitude increments,[42a] and suggests that dimePA may also be reacting by an ionization mechanism, although it has been previously stated that such a mechanism is not possible when an alkoxide is the leaving group.[45]

Finally, it is of interest to compare the observed alkaline rate constants with that of trimethyl phosphate. Statistically corrected for the number of potential methoxide leaving groups, these rate constants are 2.5, 6.5×10^{-5}, and 6.6×10^{-3} M^{-1} min^{-1} [46] for dimePA, $(dime)_2PA$, and trimethyl phosphate, respectively (35–36.8°). The 100-fold difference between the rates of N-substituted phosphoramidate and trimethyl phosphate closely parallels that observed for the neutral hydrolyses of diisopropyl phosphorofluoridate (1.2×10^{-4} sec^{-1}) and N,N′-diisopropyl phosphorodiamidic fluoride (1.3×10^{-6} sec^{-1}) in water at 25°,[47] and presumably reflects the greater tendency for d_π–p_π overlap between nitrogen and the phosphorus atom causing a decrease in the electrophilic character of the latter. Spectral evidence for such conjugation, as reflected in P–O stretch frequencies and polarizability, between nitrogen and phosphorus in phosphoramidates has been reported.[48]

(41) In contrast to the hydrolysis reaction, the rate constant for reaction of hydroxylamine with neutral PA (calculated from the results in ref 3d) is more than 100 times that for the reaction with the monoanion.

(42) (a) D. F. Heath, *J. Chem. Soc.*, 3796, 3804 (1956); (b) D. Samuel and F. H. Westheimer, *Chem. Ind.* (London), 51 (1959).

(43) P. S. Traylor and F. H. Westheimer, *J. Am. Chem. Soc.*, **87**, 553 (1965).

(44) Analysis of the rate constants for reactions of compounds in which nucleophilic displacement and ionization mechanisms are proposed is arbitrarily carried out by comparison of the second-order rate constants for hydroxide catalysis. The rate ratio obtained in this comparison is, in fact, dependent upon the acid dissociation constant of the ionizable substrate. The decreased rate enhancement associated with an ionization mechanism calculated for dimethyl phosphoramidate may, therefore, be related to a lesser dissociation constant for this compound as compared with phosphorodiamidic halides.

(45) Reference 10, p 280.

(46) P. W. C. Barnard, C. A. Bunton, D. R. Llewellyn, C. A. Vernon, and V. A. Welch, *J. Chem. Soc.*, 1636 (1961).

(47) R. F. Hudson and L. Keay, *ibid.*, 1859 (1960).

(48) (a) G. Asknes, *Acta Chem. Scand.*, **14**, 1485 (1960); (b) T. Gramstad, *Spectrochim. Acta*, **19**, 497 (1963).