{2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H -naphtho[1,2-b]-pyran-6-yl} phosphate (VII, 452 mg.) was dissolved in 15 ml. of glacial acetic acid and was reduced and debenzylated over 750 mg. of 10% Pd-on-Darco. The theoretical consumption of hydrogen was essentially complete in about 3 hr.; the catalyst was removed by filtration and washed with 10 ml. of glacial acetic acid. The combined filtrate and washings was concentrated *in vacuo*, and a 242-mg. portion of the residual glassy residue was adsorbed on 10 g. of silica gel from Skellysolve B solution. Elution of the column with Skellysolve B gave a purified fraction which on crystallization from petroleum ether yielded 3,4-dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H -naphtho-[1,2-b]pyran-6-yl phosphate (VIII), m.p. 146–147.5°; equiv. wt. (50% aqueous acetone) 558 ($pH^{1/2}$ 3.8), 516 ($pH^{1/2}$ 8.6); λ_{max}^{EtOH} 242.5 mμ ($E1_{m}^{\%}$ 750), $\lambda_{max}^{CHCl_3}$ 2.8–3.9 μ.

Anal. Calcd. for $C_{31}H_{49}O_5P$ (532.69): C, 69.90; H, 9.27; P, 5.82. Found: C, 69.57; H, 9.12; P, 5.80.

Nuclear Magnetic Resonance Spectroscopy.—All the n.m.r. data were obtained through the use of a Varian Associates model

4300B high resolution spectrometer equipped with superstabilizer and phase detector and operating at 60 megacycles. All spectra were run using 5–10% solutions in carbon tetrachloride placed in a spinning Wilmad precision bore tube. The resonance positions were determined relative to a benzene capillary as an external reference and scaled by the use of side bands[22] generated by a Hewlett–Packard audioösscillator model 200 CD calibrated by frequency counting. The shielding numbers τ were calculated using the equation $\tau = (\Delta\nu/\nu_0) + 3.50$ in which $\Delta\nu$ is the observed resonance displacement from benzene in cycles per second and ν_0 is the spectrometer frequency in megacycles.[23] In the one instance where $(CD_3)_2CO$ was used as a solvent for VIII, the constant used in the above equation was 2.85 instead of 3.50.

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A Study of the Hydrolysis of Phosphoramides. II. Solvolysis of Phosphoramidic Acid and Comparison with Phosphate Esters[1]

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The solvolysis of phosphoramidic acid ($NH_2PO_3H_2$) in water and various solvent mixtures has been investigated. Our studies of the solvolysis of aromatic phosphoramides and phosphate esters have been extended. The *p*H *vs.* hydrolysis rate curve (Fig. 1) (*p*H 2–8) for phosphoramidic acid, in water and methanol–water mixture (50%), is described by the rate equation (1), $k_{obsd} = k_h(H)(M_0) + k_0(M_0) + k_1(M_1)$, where M_0 and M_1 are the mole fractions of the neutral and singly negatively charged species (monoanion) and k_b, k_0 and k_1 are their associated specific rate constants for the particular medium. The variation in product composition, monoalkyl phosphate/phosphoric acid, derived from the solvolysis of both phosphoramidic and N-(*p*-chlorophenyl)-amidophosphoric acid in various ethanol and methanol–water mixtures over the acidity range 3 *M* HCl to *p*H 7 (Fig. 2) has been investigated and correlated with the solvolysis of the ionic species present. For the monoanionic species the ratio alkyl phosphate/phosphoric acid is significantly larger than the ratio alcohol/water present in the reacton mixture. In the case of phosphoramidic acid the two-term bimolecular rate equation (2), $k_{obsd} = k_{H_2O}(H_2O) + k_{CBO_3B}(CH_3OH)$, correctly predicts the rate and product composition for the solvolysis in methanol–water mixture (0–60%). Similar studies with the simple aromatic phosphate esters, monophenyl and mono-*p*-nitrophenyl phosphate, show that the ratio monomethyl phosphate/phosphoric acid is very nearly the same as the ratio methanol/water in the reaction mixture, while for ethanol–water mixtures it is smaller. The solvolysis of phosphoramides is catalyzed by heterocyclic tertiary nitrogenous base (pyridine, nicotinic acid); that of phosphate esters is not. The strict steric requirement imposed on the base as exemplified by the absence of catalysis with 2-methylpyridine, is noted and the catalytic constant for a number of bases has been evaluated. These observations, coupled with other considerations presented in the text, strongly favor the conclusion that the solvolysis of the monoanionic species of phosphoramides is bimolecular in nature proceeding by way of direct attack of the solvent (H_2O, CH_3OH) on the phosphorus. On the other hand, as has been postulated by many investigators, in the solvolysis of the monoanionic species of simple phosphate esters metaphosphoric acid is formed. Evidence is presented supporting the contention that the zwitterion of the monoanionic species of the phosphoramides is the reactive form. Again in the solvolysis of the neutral species, its zwitterion appears to be the reactive form. The acid-catalyzed solvolysis of phosphoramidic and N-(*p*-chlorophenyl)-amidophosphoric acid proceed by different mechanisms. The results of product distribution studies in methanol and ethanol–water mixtures support the view that the protonated species of N-(*p*-chlorophenyl)-phosphoramidic acid decomposes unimolecularly to give metaphosphoric acid, while the solvolysis of phosphoramidic acid is bimolecular involving preferential attack by water.

Introduction

We have reported[2] on the solvolysis of a few aromatic monoamidophosphoric acid derivatives. The evident structural similarity between these compounds and simple monoalkyl and aryl phosphates suggested that for their respective monoanions $(RNHPO_3H)^-$ and $(ROPO_3H)^-$, the same mechanism obtained in the cleavage of the N–P and O–P bonds. It has been reported,[3] however, that heterocyclic tertiary nitrogenous bases, *e.g.*, pyridine and imidazole, catalyze the hydrolysis of phosphoramidic acid $NH_2PO_3H_2(PA)$,[4] the simplest monoamidophosphate. No base catalysis, as reported herein, was noted with aryl phosphates. The possibility that the solvolysis of amidophosphates may proceed by direct attack of the solvent molecule

(1) This work was supported in part by a grant from the U. S. Public Health Service, Grant No. C-2336.
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(3) T. Rathlev and T. Rosenberg, *Arch. Biochem. Biophys.*, **65**, 319 (1956).
(4) The following abbreviations are used: PA, phosphoramidic acid; ClPhPA, N-(*p*-chlorophenyl)-amidophosphoric acid.

on the phosphorus, and metaphosphoric acid need not be formed, was indicated. Of particular significance in this connection is the broad body of evidence[5a,b,6,7] strongly favoring the view that in the hydrolysis of the monoanion of simple phosphate esters the unstable hypothetical monomeric metaphosphoric acid is formed and cleavage of the O–P bond (although involving hydrogen bonded intermediates with solvent)[5a,b] does not proceed by direct attack of solvent on the phosphorus atom. The evidence does not necessarily exclude the aforementioned alternate interpretation.[6–8] To gain a better understanding of the hydrolysis of amidophosphates as well as phosphate esters, a study

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(6) (a) C. A. Vernon, "The Mechanisms of Hydrolysis of Organic Phosphates," Phosphoric Esters and Related Compounds, Special Publication No. 8, pp. 17–32, The Chemical Society, London, 1957; (b) Dr. P. A. T. Swoboda, *ibid.*, Discussions, pp. 41–42.
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was made of the effect of various bases, solvent mixtures and pH on both the rate and product composition in the solvolysis of phosphoramidic acid and N-(p-chlorophenyl)-amidophosphoric acid (ClPhPA).[4] Parallel studies were made with two simple aromatic phosphates, monophenyl and p-nitrophenyl phosphate, with particular attention paid to the product composition derived from alcohol–water mixtures. This communication reports and discusses our findings.

Experimental

Materials.—Phosphoramidic acid, monopotassium salt, was prepared essentially according to procedure of Klement and Becht.[9] The crude product was twice recrystallized from ethanol–water mixtures. One gram of crude material was dissolved in 12 ml. of cold water, ethanol was added (*ca.* 17 ml.) until turbidity and the mixture cooled in ice. The crystalline salt was filtered, washed with alcohol, ether, and dried *in vacuo* over P_2O_5.

Anal. Calcd. for NH_4PO_3K: N, 10.37; P, 22.95; K, 28.93. Found: N, 10.11; P, 22.91; K, 28.19.

N-(p-Chlorophenyl)-amidophosphoric acid,[2] monoanilinium salt, and monophenyl phosphate[8] were prepared as previously described. p-Nitrophenyl phosphate, disodium salt, was obtained from California Biochemical Research Co., Los Angeles. The material proved to be a hydrated mixture of the sodium salts of p-nitrophenyl phosphate and phosphoric acid. This was demonstrated by analysis for phosphate and p-nitrophenol before and after complete hydrolysis of the salt. No free p-nitrophenol ($<1\%$) was present in the original material. On hydrolysis, equimolecular quantities of p-nitrophenol and phosphoric acid were produced. Nicotinic acid, m.p. 232–234°, picolinic, m.p. 138°, and isonicotinic acid, m.p. 320°, were recrystallized from water. Reagent grade pyridine, 2- and 3-methylpyridine were dried over KOH and redistilled before use; 2,6-lutidine was purified according to Brown.[10] Redistilled reagent grade absolute methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol and dioxane purified according to Scatchard and Benedict[11] were used. The compositions of the solvent mixtures are expressed as per cent by volume. They were prepared by adding a measured volume of the non-aqueous component to a volumetric flask and diluting to the mark with distilled water. The molar composition of the methanol–water and ethanol–water mixtures were calculated from data relating density to volume per cent.[12] The calculated mole per cent alcohol for the various mixtures employed are given in Table VI.

Buffers.—In general, the potassium salts of the buffer material were used, since the monosodium salt of PA is quite insoluble in water. Below pH 2.5 glycine, in the pH range 2.5–6 phthalate or acetate, and for pH 6–9 phosphate and Veronal buffers were employed.[13] The ionic strength was adjusted by the addition of KCl.

Ionization Constants and Mole Fractions (M_0, M_1).—The semi-classical ionization constants of phosphoramidic acid at 25°, $\mu = 0.2$ M, were determined for the various solvent mixtures used in the rate and product composition experiments by the method previously described.[14] The mole fractions of the ionic species of PA present in a particular solvent mixture were then evaluated[14] from the relevant ionization constants and the measured pH. For the temperature range 20–37° the

IONIZATION CONSTANTS OF PHOSPHORAMIDIC ACID AT 25° ($\mu = 0.2$ M)

Vol., %	Methanol pK_1	Methanol pK_2	Ethanol pK_1	Ethanol pK_2	Dioxane pK_1	Dioxane pK_2	*tert*-Butyl alcohol pK_1	*tert*-Butyl alcohol pK_2	2-Propanol pK_1	2-Propanol pK_2
0	3.00	8.15								
20	3.47	8.34	3.42	8.31	3.45	8.45				
30					3.65	8.59				
40	3.85	8.54	3.76	8.50						
50	4.05	8.63	3.91	8.57	4.08	8.80	3.55	8.28	3.67	8.49

In D_2O, $pK_2 = 8.84$, where $pD = $ "meter pH" $+ 0.40$.[15]

anticipated variation in ionization constants would hardly affect the mole fractions calculated at 25°.[14]

Kinetic Procedures.—Phosphoramidic acid: The rate of solvolysis of PA was followed by analysis for liberated ammonia; PA is too unstable in the presence of molybdate to permit the determination of inorganic phosphate. The ammonia was determined by one of three procedures: by titration, either directly in the reaction flask, "pH-Stat" method[16] (A), or after it had been collected by an aeration procedure[17] (B), and by a Nesslerization procedure according to Buchi[18] (C). The choice of method was dictated by the particular reaction conditions. Wherever feasible, the "pH-Stat" procedure was used, as it was found to be the most accurate. It was employed over the pH range 3–7.3 for all solvent mixtures and also for those reactions catalyzed by nicotinic acid, isonicotinic acid and picolinic acid. Below pH 3, the aeration procedure B was used; and in the pH range 7–8 for the base-catalyzed reactions (pyridine, etc.), with the exceptions mentioned above, the Nesslerization procedure C was used. For the non-base-catalyzed reactions in the pH range 7–8 method B was employed. A few solvolyses were followed by each of the methods, A, B, and C, and excellent agreement was obtained.

"**pH-Stat**" **Procedure.**—The assembly consisted of a TTT1A Radiometer automatic titrator and a three-neck glass-jacketed reaction flask (100 ml.) snugly fitted with a glass electrode, calomel cell and buret with capillary tip extending below the surface of the liquid. The temperature was controlled ($\pm0.02°$) by circulating water from a thermostat through the jacket, and the reaction mixture was stirred by a bar magnet. A 40.00-ml. aliquot of the reaction mixture, *ca.* 10^{-2} M in PA, adjusted to $\mu = 0.20$ M with KCl, was delivered into the reaction chamber. (For the base-catalyzed reaction the potassium salt of the pyridine carboxylic acids was added.) Titrant, usually 0.05 M in HCl, and of the same solvent composition and ionic strength as the reaction mixture, was introduced in slight excess of the amount needed to achieve the desired pH. This ensured that subsequent automatic addition of titrant kept pace with the rate of formation of ammonia. At appropriate intervals the volume of acid delivered was recorded. The final readings were checked on a separate aliquot. This was particularly necessary for the slow reactions, since over extended time periods (2–3 days) meter drift was sometimes encountered. For the independent final measurement an equivalent aliquot of the reaction mixture was mixed with a measured volume, slightly less than the necessary amount of titrant (as estimated from trial runs) and allowed to hydrolyze to completion at 40° in a stoppered flask, brought to reaction temperature and titrated to the same pH as used in the rate run. Final values obtained in the rate runs were considered acceptable when they corresponded to the independently determined values within 1.5%. The pseudo-first-order rate constants calculated from the first-order expression $k_{obsd} = \ln (V_\infty - V_0/V_\infty - V_t)/t$ showed less than 1% deviation and a $\pm2\%$ reproducibility.

Aeration Procedure (B).—A solution of PA, *ca.* 0.01 M, of the desired acidity, solvent composition and ionic strength was prepared in the cold and placed in a constant temperature bath. At suitable intervals aliquots were delivered with a chilled volumetric pipet into urea tubes containing either cold buffer or alkali to bring the pH to *ca.* 7, and these were quickly frozen by immersion in a Dry Ice–acetone-bath and reserved until completion of the run. The tubes were connected in a typical "aeration-train," strong alkali was added to each of the aliquots, and as soon as the solution thawed, aeration was begun and continued for *ca.* 2.5–3 hours. The ammonia liberated from each aliquot was collected in a boric acid–mixed indicator solution[19] and titrated with 0.01 M HCl. The pseudo-first-order constants were determined as above or by plot of log ($V_\infty - V_t$) *vs. t.*

Nesslerization Procedure (C).—A buffered solution of PA (*ca.* 0.01 M) containing the nitrogenous base (0–0.09 M) was incubated in a constant temperature bath. At appropriate intervals, 1.00-ml. aliquots were pipetted into a fivefold volume of ice-cold buffer (pH 7), followed by addition of 3.00 ml. of Nessler reagent; the mixture was diluted to 50.00 ml. and allowed to stand at room temperature for 1 hour. The optical density of these solutions was measured at 420 mμ employing a Klett colorimeter. The pseudo-first-order rate constants were determined from the first-order rate equation

$$k_{obsd} = \ln (D_\infty - D_0/D_\infty - D_t)/t$$

The measured pH of the initial and final solution did not differ by more than 0.04 pH unit.

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N-(p-Chlorophenyl)-amidophosphoric Acid.—The solvolysis rate of ClPhPA was determined by the method previously described[2] and also by measuring the change in optical density[20] at 245 and 250 mμ, employing a Beckman spectrophotometer. In a typical run a 4.00-ml. aliquot of a solution of ClPhPA (prepared from 31 mg. of the anilinium salt + 2.10 ml. of 0.10 M NaOH diluted to 10.00 ml.) was diluted to 25.00 ml. with acetate buffer and placed in a constant temperature bath. At appropriate intervals 2.00-ml. aliquots were pipetted into a chilled alkaline solution (3.00 ml. of 0.10 M NaOH + 10 ml. of H₂O), the mixture diluted to 100.00 ml. and the optical density measured at 250, 245 mμ. The pseudo-first-order rate constants were either calculated or obtained from the plot of log (O.D.$_\infty$ − O.D.$_t$) vs. t. The measured, initial and final pH's agreed within ±0.03 unit.

Aromatic Phosphates.—The rates of solvolysis of the mono-anions of monophenyl phosphate and mono p-nitrophenyl phosphate were obtained by measuring the release of phenol, employing the Folin-Ciocalteu reagent[21] (O.D. in Klett units, at 660 mμ), and p-nitrophenol (O.D. at 400 mμ, Beckman spectrophotometer) according to the method of Sturtevant,[22] respectively. The rates in water also were determined by measurement of inorganic phosphate with Fisk-SubbaRow reagent, as previously described,[8,14] were in agreement. To ensure that only the monoanionic species was present, the solvolyses were done in phthalate buffer. The measured pH's were 3.0–3.2 in water, 3.8–4.0 in 50% methanol–water. As anticipated, no change in solvolysis rate was observed on changing the pH of the medium to 5.0. Aliquots of the same solution were used for the determination of both rate and product distribution. A more detailed description is incorporated under product distribution (cf. below).

Products of Solvolysis.—A buffered[23] methanol–water solution (30–70%) of PA (5.3 × 10⁻² M) was allowed to hydrolyze to completion at 37°. The hydrolysate, ca. 8 μl., after shaking with Dowex-50 resin (acid form) was spotted on S and S No. 589 orange ribbon paper and chromatographed (descending) for 17 hours with Ebel acid solvent mixture according to Kroupa.[24] A mixture containing Na₄P₂O₇, KH₂PO₄ and monomethyl phosphate (obtained from K and K Laboratories, Inc., Long Island City 1, N. Y.) was similarly treated and spotted alongside the hydrolysate. The air dried chromatogram was sprayed with Haynes–Isherwood molybdate reagent,[25] heated 14 minutes at 75° and exposed to ultraviolet light according to Axelrod.[26] Phosphoric acid and monomethyl phosphate were identified as the sole products of solvolysis. No pyrophosphate was detected.[27]

Product Composition.—The percentage phosphoric acid or monoalkyl phosphate is the ratio of the moles of phosphoric acid or alkyl phosphate formed to the moles of compound solvolyzed, times 100. The moles of compound solvolyzed is equal to the molar sum of the products phosphoric acid + alkyl phosphate. This ratio should be invariant with time. Thus for any time (t)

$$(\% \text{ inorganic phosphate})_t = \frac{100 \times (\text{H}_3\text{PO}_4)_t}{(\text{H}_3\text{PO}_4 + \text{alkyl phosphate})_t}$$

At all temperatures and pH's investigated the solvolysis of PA or the aromatic phosphate is so much faster than either the solvolysis of products (methyl or ethyl phosphate)[6] or the esterification of phosphoric acid[28] that these factors need not be considered. While the product distribution for the aromatic phosphates may be ascertained at any point in the solvolysis, the instability of phosphoramidic acid in the presence of molybdate precludes such a determination. Necessarily in the latter case the percentage inorganic phosphate was obtained after complete solvolysis.

(a) Aromatic Phosphates.—Equal aliquots (5.00 ml.) of a stock solution containing 110–170 mg. of aromatic phosphate in 25.00 ml. of 0.1 M aqueous phthalate buffer were pipetted into volumetric flasks (50.00 ml.) and diluted to the mark with the requisite amount of alcohol and H₂O, and H₂O only. The water solution, usually heated at 100°, served to establish the maximum amount of inorganic phosphate that could be realized on complete hydrolysis, and further gave a check on the final phenol or p-nitrophenol reading obtained in the run. Separate aliquots of the solutions were sealed in Pyrex tubes and heated in a constant temperature bath. At appropriate intervals a

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(28) Unpublished observations.

sealed tube was withdrawn, the reaction quenched by immersion in an ice-bath and equal aliquots (5.00 ml.) were withdrawn and diluted exactly fivefold with water. Phosphate was determined using a 2.00-ml. aliquot of the above, phenol[21] on a 1.00-ml. aliquot and p-nitrophenol[22] was measured after adding a 2.00 ml. aliquot to 5.0 ml. of 10% Na₂CO₃ and diluting to 100.00 ml. The rate of solvolysis was calculated from the first-order equation. The results of a typical experiment showing the calculated specific rate constant and the product composition calculation for solvolysis in mixed solvent is given below.

SOLVOLYSIS OF p-NITROPHENYL PHOSPHATE (MONOANION) AT 54.8°

In CH₃OH–H₂O(70%), phthalate buffer, μ = 0.15

t, hr.	0	69.5	115.0	119.5	Final[a]
H₃PO₄ (Klett units)	95	115	123	125	(190) H₂O
p-Nitrophenol (O.D.)	0.003	0.193	0.259	0.265	0.369
k_{obsd} × 10², hr.⁻¹		1.0₆	1.0₅	1.0₅	
Phosphoric acid,[b] %	42.0	42.0	45.4		Av. = 43.0

[a] The final p-nitrophenol reading, 0.369 was obtained by heating at 100° for 4 hr.; phosphate reading obtained from water hydrolysis at 100°. [b] (% phosphoric acid)$_t$ =

$$\frac{(\% \text{ hydrolysis according to phosphate reading})}{(\text{actual } \% \text{ hydrolysis})} =$$

$$\left(\frac{\text{Klett}_t - \text{Klett}_0}{190 - \text{Klett}_0}\right)\left(\frac{0.369 \times 100}{\text{O.D.}}\right)_t$$

(b) Phosphoramides.—Aliquots (1.00 ml.) of an aqueous stock solution of the phosphoramide (ca. 2.5 × 10⁻² M) prepared in the cold were delivered into volumetric flasks (10.00 ml.) containing the requisite amount of buffered H₂O or alcohol–water mixtures. The mixture was solvolyzed at the desired temperature for a sufficient period to ensure complete hydrolysis (99%), diluted exactly fivefold, and phosphate determined on a 2.00-ml. aliquot. The percentage phosphoric acid produced is 100 times the ratio of the phosphate reading observed in the alcohol–water mixtures and water alone. The percentage alkyl phosphate formed in each solvent mixture is (100 − % phosphoric acid).

Results

Phosphoramides. pH Dependency and Rates.—First-order kinetics were observed for the solvolysis of phosphoramidic acid in all the solvent mixtures and at the pH's studied. The rate vs. pH profiles for water and 50% methanol–water mixture over the pH range 2–8 at 36.8° and μ = 0.2 M are illustrated in Fig. 1 from data collected in Table I; PA is not decomposed

TABLE I

SOLVOLYSIS RATES OF PHOSPHORAMIDIC ACID AT VARIOUS pH'S AT 36.80°, μ = 0.2 M, IN WATER AND METHANOL–WATER (50%)

\---H₂O\---		\---CH₃OH–H₂O (50%)\---	
pH	k_{obsd},[a] hr.⁻¹	pH	k_{obsd},[a] hr.⁻¹
2.00	0.79	1.93	0.81
2.12	.72	2.08	.69
2.23	.60	2.55	.565
2.71	.35	3.20	.520
3.15	.33	4.04	.520
3.20	.29	5.77	.522
4.13	.255		
4.63	.251[b]		
5.14	.245[c,d]		
6.13	.256[c]		
7.32	.229[d]		
7.63	.203[f]		
7.92	.150[e]		

[a] Method A for pH 3–7.32; method B for pH's below 3. [b] Same rate obtained in acetate or phthalate buffer employing method B. [c] No change in rate at μ = 0.015 M. [d] Addition of potassium acid phosphate (0.05–0.1 M) left rate unchanged (method B and method C). [e] Same rate obtained in phosphate buffer (method C) or in Veronal buffer (method B). [f] In phosphate buffer (method C).

at 60° above pH 10, demonstrating the stability of its completely ionized form (NH₂PO₃)⁻. The S-shaped curve[2] in water is analogous to that found for N-(p-chlorophenyl)-amidophosphoric acid and the rate equation used to analyze the latter adequately described the hydrolysis of PA over the pH range investigated (eq. 1).
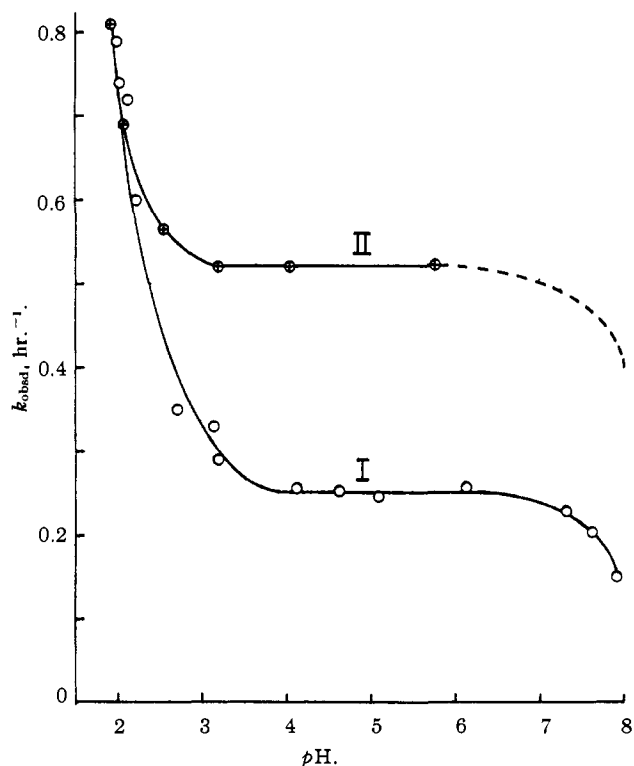
Fig. 1.—The observed solvolysis rate at 36.80°, $\mu = 0.2M$, as plotted against pH for phosphoramidic acid: in water, I; in 50% methanol-water, II. The solid lines are the theoretical curves; the symbols $\bigcirc$ and $\oplus$ represent the experimental points.

$$k_{obsd} = k_h(H)(M_0) + k_0(M_0) + k_1(M_1) \qquad (1)$$

Here M_0 and M_1 are the mole fractions of the neutral $(NH_2PO_2H_2)^0$ and monoionic species $(NH_2PO_2H)^-$, respectively, and k_h, k_0 and k_1 are their associated specific rate constants. The specific rate constants were evaluated as previously described.[2,8] Inspection of the hydrolysis rate vs. pH curve and pK's of PA in water and 50% methanol-water indicated that above pH 3 acid catalysis is insignificant and only the monoanionic and neutral species participate in the hydrolysis. In the pH range 4.5–6.5 and 5.5–7.5, in water and 50% methanol-water, respectively, PA exists exclusively as the monoanion. The observed rate of hydrolysis at these pH's is the specific rate constant k_1 associated with the monoanionic species. The specific rate constant k_0 was evaluated from the observed rates of hydrolysis at those pH's where the calculated concentrations of the monoanion (M_1) and neutral species (M_0) were nearly equivalent; for water, pH ca. 3.0, and 50% methanol-water, pH ca. 4.0. Substitution of the relevant data in eq. 1 gave $k_1 = 0.25$ hr. $^{-1}$, $k_0 = 0.42$ hr. $^{-1}$ for water, and $k_1 = k_0 = 0.52$ hr. $^{-1}$ for 50% methanol-water. As with aromatic phosphoramides the fast rate of hydrolysis of the neutral species in water may be ascribed to its easily hydrolyzable zwitterionic form $(H_3N^+PO_3H^-)^0$. The hydrolysis of phosphoramidic acid is catalyzed by acid. The catalysis becomes evident at pH 2 in water and below pH 3 in 50% methanol-water. The specific rate constant $k_h = 33.3$ l. mole^{-1} hr.$^{-1}$ was evaluated from hydrolysis in water at pH 2.5 from appropriate substitution in eq. 1 as

$$k_{obsd} = 0.46 = k_h(0.0032)(0.76) + 0.42(0.76) + (0.25)(0.24)$$

The reasonableness of this analysis is illustrated at pH 2, where $k_{calcd} = 33.3(0.01)(0.91) + 0.42(0.91) + 0.25-(0.09) = 0.71$ hr.$^{-1}$; $k_{found} = 0.75$ hr.$^{-1}$. Analogous calculation for 50% methanol-water at pH 2.55 (the
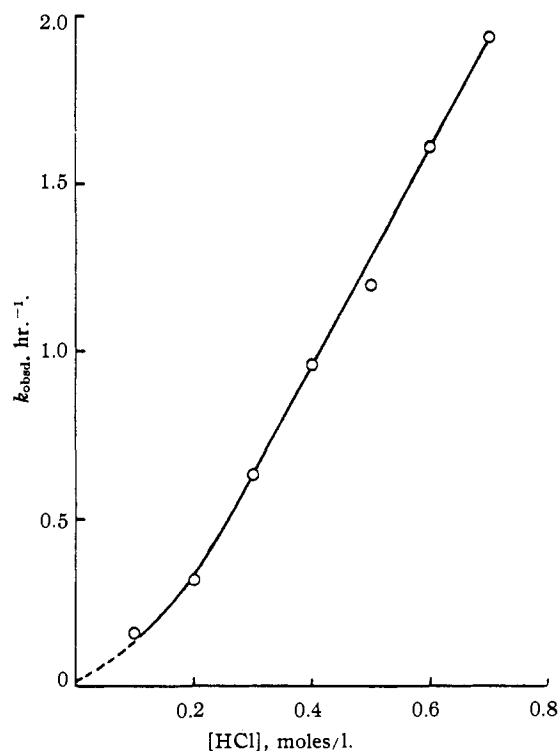

Fig. 2.—The observed hydrolysis rate as plotted against molarity of HCl for phosphoramidic acid, at 10.1°.

actual hydrogen ion concentration in 50% methanol-water mixtures was interpolated from a graph of measured pH vs. hydrogen ion concentration) gives $k_h = 9.34$ l. mole^{-1} hr.$^{-1}$. The correspondence at pH 2.08 in 50% methanol-water between $k_{calcd} = 0.66$ hr.$^{-1}$ and $k_{found} = 0.69$ hr.$^{-1}$ is good. The proportionality between rate and acidity was further shown by a study of the hydrolysis of PA in water at 10° over the range 0.1–0.7 M HCl. At these high acidities the acid-catalyzed rate predominates and above 0.2 M HCl the contribution of the neutral species to the hydrolysis is insignificant. The plot of k_{obsd} vs. hydrogen ion concentration yields a straight line with $k_h = 3.3$ l. mole^{-1} hr.$^{-1}$ (see Table II; Fig. 2).

TABLE II

HYDROLYSIS OF PHOSPHORAMIDIC ACID AT 10.1° IN AQUEOUS HCl

HCl, M	0.10	0.20	0.30	0.40	0.50	0.60	0.70
k_{obsd},[a] hr.$^{-1}$	0.16	0.32	0.63	0.96	1.14	1.61	1.94

[a] Rates were measured by method B, ionic strength brought to $\mu = 0.5$ M with KCl for all acidities below 0.5 M HCl.

Solvent Effects on Rates.—A comparison of the effect of various solvent mixtures and D_2O on the solvolysis rate of the monoanionic species of phosphoramidic and N-(p-chlorophenyl)-amidophosphoric acid is given in Table III. While these changes are small, they are in the opposite direction for the two compounds. Methanol, ethanol and dioxane increase and D_2O decreases the solvolysis rate of PA; the opposite is true for N-(p-chlorophenyl)-amidophosphoric acid.

Energies and Entropies of Activation.—The rates of hydrolysis of phosphoramidic acid in water were determined at a few additional temperatures and appropriate pH's, so that the specific rate constants k_0 and k_1 could be evaluated and the heats, $\Delta H^{\ddagger}$, and entropies, $\Delta S^{\ddagger}$, of activation associated with the ionic species could be calculated. The results are given in Table IV. Similar studies were made in 50% methanol-water and dioxane-water mixtures. It should be noted at this point that one cannot properly refer to a heat and entropy of

TABLE III

SOLVOLYSIS OF THE MONOANION OF PHOSPHORAMIDIC ACID AT 36.80°, $\mu = 0.2\ M$, AND N-(p-CHLOROPHENYL)-AMIDOPHOSPHORIC ACID AT 25.00°, $\mu = 0.2\ M$, IN VARIOUS SOLVENT MIXTURES AND D_2O

Solvent	Vol. %	pH^a	k_{obsd}, hr.$^{-1}$
	Phosphoramidic acid		
H_2O		5.11	0.252
D_2O	99.8	5.13	.209
C_2H_5OH–H_2O	30	5.30	.270
	50	5.63	.283
Isopropyl alc.–H_2O	50	5.37	.222
$tert$-Butyl alc.–H_2O	50	5.26	.222
Dioxane–H_2O	20	5.15	.276
	40	5.55	.305
	50	5.80	.315
	N-(p-Chlorophenyl)-amidophosphoric acid		
H_2O		4.64	$0.691,^b\ 0.688^c$
D_2O	99.8	4.75	$.913^b$
CH_3OH–H_2O	50	5.44	$.500^b$
Dioxane–H_2O	50	6.56	$.404^c$

^{a} pH so chosen that the concentration of monoanionic species was ca. 99%. ^{b} Rates determined by spectrophotometric method. ^{c} Molybdate procedure (cf. ref. 2).

the alcohol–water solvent mixture. For both PA and ClPhPA the product distribution from 30 and 50% ethanol and methanol–water mixture over the acidity range 3 M HCl to pH 7.66 was determined. The results are illustrated in Fig. 3 from the data given in Table V. The product composition is concerned with the mode of breakdown of the particular ionic species present in the reaction mixture. Over that pH range where only the monoanionic species contributes to the hydrolysis of PA and ClPhPA a flat maximum is observed. As the pH decreases, the concentration of the neutral species increases and a change in the product distribution is observed. In strongly acidic alcohol–water mixtures the hydrolysis proceeds primarily by way of acid catalysis and the curves for both the aromatic and aliphatic phosphoramides flatten. For ClPhPA in CH_3OH–H_2O (50%) from 0.3–3.0 molar HCl there is little change in product composition (29% methyl phosphate). For PA, formation of alkyl phosphate is small, approaching 8% as a limit. It is the zwitterionic form of the neutral species of phosphoramides which is unstable. In the pH range 2.5–4.0 for methanol–water (50%) the prevalent neutral species exists primarily as zwitterion for PA and as non-zwitterion for ClPhPA

TABLE IV

SPECIFIC RATE CONSTANTS, HEATS AND ENTROPIES OF ACTIVATION FOR THE VARIOUS IONIC SPECIES OF PHOSPHORAMIDIC ACID

Solvent	pH	T, °C.	k_{obsd}, hr.$^{-1}$	k_h, l. mole^{-1} hr.$^{-1}$	$\Delta H^{\ddagger,a}$ kcal./mole	$\Delta S^{\ddagger,a}$ e.u.
			$[H_3NPO_3H_2]^+$			
H_2O	0.2–0.7 M HCl	10.10			3.30^b	14.5	-21.1
	2.50	36.80	0.46		33.3		
CH_3OH–H_2O (50%)	2.55	36.80	3.565		9.34		
			$[H_2NPO_3N_2]^0$			
				k_0, hr.$^{-1}$		
H_2O	3.03	10.10	0.0144	0.0237^c	18.1	-18.2
	3.03	36.80	.335	.420		
CH_3OH–H_2O (50%)	4.04	36.80	.520	.520		
			$[H_2NPO_3N]^-$			
				k_1, hr.$^{-1}$		
H_2O	5.15	20.00	0.0265	0.0265	23.6^e	-1.6^e
	4.6–6.1	36.80	$.252^d$	.252		
CH_3OH–H_2O (50%)	5.77	20.00	.0592	.0592	$(22.8)^f$	$(-2.6)^f$
	7.20	25.00	.116	.120		
	5.77	36.80	.522	.522		
Dioxane–H_2O (50%)	5.83	20.00	.0306	.0306	24.5	$+1.8$
	5.83	36.80	.315	.315		

^{a} The heats and entropies of activation were calculated from the Eyring equation. See S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw–Hill Book Co., Inc., New York, N. Y., 1941; estimated error $= \pm 0.5$ kcal./mole, ± 1.5 e.u. ^{b} Evaluated from the slope of the plot of k_{obsd} vs. [H$^+$] over acidity 0.2–0.7 M HCl; cf. Experimental. ^{c} Calculated from eq. 1. For the monoanion, $k_1 = 0.0093$ hr.$^{-1}$ as evaluated from $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. ^{d} Average value (± 0.002). The rate remains sensibly invariant over pH range 4.6–6.1, as concentration of monoanion is ca. 99%. ^{e} Calculated on the basis of a bimolecular reaction, $\Delta S^{\ddagger} = -9.4$ e.u. ^{f} See text.

activation for a reaction which is bimolecular (as appears to be the case for the alcohol–water mixtures; see below) with respect to each of several components of a mixed solvent. If the values of the activation parameters for the separate reactions with each component of the solvent mixture are of not too different magnitude, the customarily derived energy and entropy terms may be regarded as the average of the over-all reaction. These values are given in parentheses in Table IV.

Product Composition.—The phosphorus-containing products from the solvolyses were identified by paper chromatography. Only phosphoric acid and the monoalkyl phosphate, derived from the particular alcohol used, were formed; no pyrophosphoric acid could be detected. A striking variation in product composition (phosphoric acid/alkyl phosphate) is observed in the solvolysis of phosphoramidic acid and N-(p-chlorophenyl)-amidophosphoric acid with change in acidity of

(discussed below). Thus, the solvolysis of the neutral species of PA contributes substantially to the over-all rate and product distribution. A gradual change in % alkyl phosphate with pH is observed. On the other hand, the solvolysis of ClPhPA is primarily attributable to the breakdown of the monoanionic species and to acid catalysis, resulting in the extension of the maximum into the region of high acidity (see Fig. 3).

The relationship between product composition and PH for any particular alcohol–water mixture may be expressed in terms of the ionic species present and their specific contributions to the product composition.

$$(\% \text{ MP})_{obsd} = \frac{k_h(H)(M_0)(MP)_{k_h}}{k_{obsd}} + \frac{k_0(M_0)(MP)_{k_0}}{k_{obsd}} + \frac{k_1(M_1)(MP)_{k_1}}{k_{obsd}} \quad (2)$$

TABLE V

VARIATION OF % ALKYL PHOSPHATE WITH pH FROM THE SOLVOLYSIS OF PHOSPHORAMIDIC ACID AT 37.15°, $\mu = 0.2$ M AND N-(p-CHLORO-PHENYL)-AMIDOPHOSPHORIC ACID AT 25.00°, $\mu = 0.15$ M, IN METHANOL AND ETHANOL–WATER MIXTURES[a]

CH₃OH-H₂O, 50%		CH₃OH-H₂O, 30%		C₂H₅OH-H₂O, 50%		C₂H₅OH-H₂O, 30%		CH₃OH-H₂O, 50%		C₂H₅OH-H₂O, 50%	
pH	% MP	pH	% MP	pH	% EP	pH	% EP	pH	% MP	pH	% EP
Phosphoramidic acid								N-(p-Chlorophenyl)-amidophosphoric acid			
1.0 M HCl	9.9	1.35	11.1	1.52	6.2	1.35	2.8	3.5 M HCl	27.9	3.5 M HCl	13.1
0.5 M HCl	12.6	1.69	11.9	1.95	8.0	1.76	2.2	1.0 M HCl	33.2	1.0 M HCl	15.0
.3 M HCl	14.8	1.95	16.1	2.30	15.1	2.07	6.9	0.2 M HCl	52.5	0.2 M HCl	23.8
.1 M HCl	19.3	2.07	19.5	3.10	19.1	2.81	10.6	1.45	58.1	1.55	29.7
1.42	20.5	2.81	30.1	3.91	29.2	3.55	21.9	2.25	65.3	2.31	33.2
1.76	25.8	3.55	42.6	5.00	40.5	4.50	22.6	3.49	67.0	3.61	33.8
1.84	31.4	4.38	46.2	5.98	40.5	4.60	25.1	3.99	68.4	4.07	33.1
2.18	30.5	4.50	52.0	6.55	36.5	5.45	24.9	5.27	68.3	5.45	33.0
2.30	37.0	4.60	48.6	7.66	36.3	5.85	20.6	5.68	69.5	6.58	33.7
3.10	46.3	5.45	56.7			7.00	19.9	6.31	69.0		
3.83	58.3	5.65	52.8								
3.91	64.4	6.80	53.5								
5.00	73.4										
5.85	73.2										
6.25	72.1										
7.40	70.2										

[a] MP and EP are methyl and ethyl phosphate, respectively. Over the pH range 1.4–7.0 at 10.1°, random determinations of % alkyl phosphate from PA varied but slightly from the values recorded above. For the strong acid solutions (0.1–3.5 M HCl), $t = 10.1°$. At 100° in 50% CH₃OH–H₂O at pH 6.4, % MP from phosphoramidic acid was reduced to 56%.

where $(MP)_{k_h}$, $(MP)_{k_1}$ are each the percentage methyl phosphate that would be formed if the total rate of solvolysis could be ascribed to the term in which it appears above, and the other symbols have the same meaning as in rate eq. 1. This relationship was examined
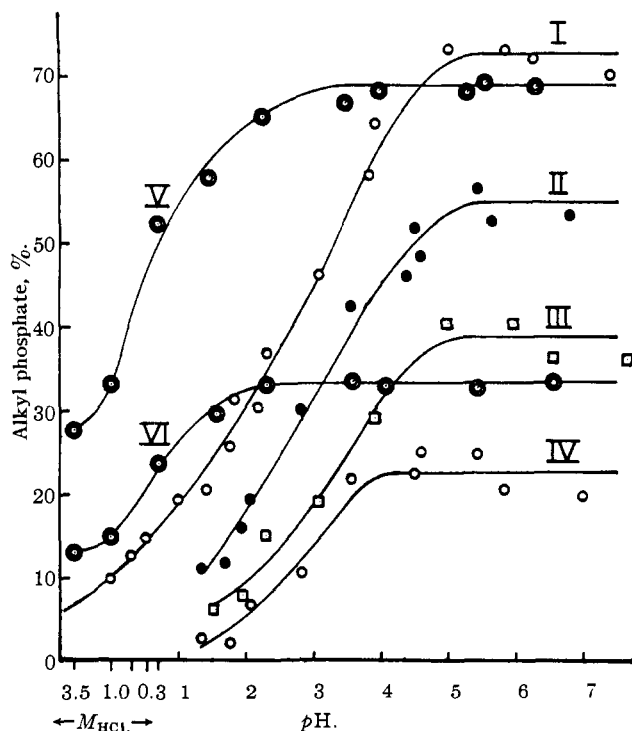

Fig. 3.—The observed % alkyl phosphate plotted against acidity for the solvolysis of phosphoramidic acid at 37°, $\mu = 0.2$ M, and N-(p-chlorophenyl)-amidophosphoric acid at 25°, $\mu = 0.2$ M, in various alcohol–water mixtures. Curves I and II refer to the solvolysis of PA in 50% and 30% methanol–water mixtures; III and IV refer to 50% and 30% ethanol–water mixtures, respectively. Curves V and VI refer to the solvolysis of ClPhPA in 50% methanol– and ethanol–water mixtures, respectively.

for the hydrolysis of PA in 50% methanol–water mixture over the pH range 2–8. The first term in the above equation may be neglected, since acid catalysis contributes slightly to the over-all rate and MP formed from

the latter is small. At pH ca. 5 the solvolysis involves only the monoanionic species; therefore the per cent methyl phosphate observed $= (MP)_{k_1} = 72\%$. $(MP)_{k_0} = 44\%$ was evaluated at pH 3, where hydrolysis proceeds in great measure by way of breakdown of the neutral species, by substitution into eq. 2.

$$(\% \text{ MP})_{obsd} = 45 = \frac{(0.52)(0.92)(MP)_{k_0} + (0.52)(0.08)(72)}{(0.53)}$$

The agreement between calculated and found values for various pH's in 50% methanol–water is good.

	Methyl phosphate, %	
pH	Calcd.	Found
4.0	58	65
2.5	41	37
2.08	33	30

The solvolysis of PA (monoanion) in isopropyl and tert-butyl alcohol–water mixtures (50%) gave only phosphoric acid. No alkyl phosphate ($<2\%$) was detected.

Aromatic Phosphates. Rates and Product Composition.—The rates and product distribution for the solvolysis of monophenyl phosphate and mono p-nitrophenyl phosphate in their monoanionic form were determined in various ethanol and methanol–water mixtures at the temperatures 37°, 54° and 100°. The results are given in Table VI. For the same alcohol–water mixtures these aromatic phosphate esters yield a significantly smaller amount of alkyl phosphate than the corresponding monoanionic form of phosphoramides. The solvolysis rates were unaffected by the addition of those heterocyclic tertiary nitrogenous bases which catalyze the solvolysis of phosphoramides. The solvolysis of the aromatic phosphates in isopropyl and tert-butyl alcohol–H₂O mixtures (50%) gave only phosphoric acid; no alkyl phosphate was detected (not included in table).

Discussion

The results imply that a different mechanism obtains in the solvolysis of the monoanions of phosphate esters and of the phosphoramides. An analysis of the mechanism of hydrolysis of phosphoramides must be concerned with the breakdown of the various ionic forms. Each ionic species will be treated separately and a comparison of the hydrolysis of phosphoramides and simple aryl and alkyl phosphates follows.

TABLE VI

PERCENTAGE ALKYL PHOSPHATE FORMED AND RATES OF SOL-
VOLYSIS OF AROMATIC PHOSPHATES (MONOANION) IN METHANOL
AND ETHANOL–WATER MIXTURES AT 37°, 54.8°, 100°[a]

Solvent	k_{obsd}, hr.$^{-1}$			Alkyl phosphate,[b] %			Mole % alcohol in solv. mixt.
	(× 1) 100°	(× 10²) 54.8°	(× 10¹) 37°	100°	54.8°	37°	
			p-Nitrophenyl phosphate				
H₂O	4.1	2.6					
30% CH₃OH–H₂O	3.7	1.8	1.7	16	23	22	15.5
50% CH₃OH–H₂O	2.6	1.2	1.3	29	34	38	29.2
70% CH₃OH–H₂O	2.1	1.1	0.98	47	57	55	48.0
30% C₂H₅OH–H₂O	3.8	1.8	1.7	8	14	9	11.3
50% C₂H₅OH–H₂O	2.8	1.3	1.4	12	12	15	22.4
70% C₂H₅OH–H₂O	2.5	1.2	1.1	23	22	24	40.4
			Phenyl phosphate				
	(× 1)	(× 10³)					
H₂O	1.00	5.2					
30% CH₃OH–H₂O	0.76	3.8		22	27		
50% CH₃OH–H₂O	.69	2.6		31	42		
70% CH₃OH–H₂O	.49	2.3		48	58		
30% C₂H₅OH–H₂O	.78	3.7		10	11		
50% C₂H₅OH–H₂O	.65	2.7		14	22		
70% C₂H₅OH–H₂O	.57	2.6		25	30		

[a] These experiments were carried out in phthalate buffer
(pH 3.1 in water). [b] Solvolysis at pH 5 with or without nico-
tinic acid anion (0.08 M) gave the same rate and percentage
alkyl phosphate.

Monoanionic Species.—When the solvolysis of
phosphoramidic acid was effected in methanol– and
ethanol–water mixtures, not only was the rate en-
hanced, but the proportion of alkyl phosphate formed
was considerably larger than the mole fraction of alcohol
in the reaction mixtures. For example, in a 50%
methanol–water mixture, the mole per cents of methanol
and water are 29 and 71, respectively; the percentage
methyl phosphate found in the hydrolysate was 72.5
and that of phosphoric acid 27.5. The rate of hydroly-
sis of the monoanionic species of phenyl and p-nitro-
phenyl phosphate was decreased by the addition of
methanol or ethanol (Table VI). Of greater significance
is the fact that at the three temperatures studied
the distribution of products for the methanol–water
mixtures varied slightly and closely approximated the
mole per cent of the solvent constituents. In the eth-
anol–water mixtures the percentage of ethyl phosphate
formed was smaller than the mole per cent of ethanol in
the reaction mixtures and corresponded to that re-
ported in the solvolysis of glycerol phosphate.[6] In the
unimolecular solvolysis of tert-butyl chloride in the
mixed solvents CH₃OH– and C₂H₅OH–H₂O, where the
rate-determining step is the ionization of the chloride
to the reactive tert-butyl cation, the ratio of products
alcohol to ether is as the mole fractions of water and
methanol, while in the ethanol–water mixtures tert-
butyl alcohol is formed in slight excess over the
ether.[29] The findings with the aryl phosphates are
consistent with the proposed mechanisms of hydrolysis
of phosphate esters where the formation of monomeric
metaphosphate is presumed. So reactive an intermedi-
ate as metaphosphate would be expected to react very
nearly as rapidly with methanol, ethanol or water, and
consequently the percentage of alkyl phosphate and
phosphoric acid would be as the mole per cent of alcohol
and water in the reaction mixture. Further support
for this conclusion was forthcoming by an examination
of the solvolysis[28] at 37° of acetyl phosphate (diionic
form), N-benzoylphosphoramidic acid, N-acetylphos-
phoramidic acid (monoanions), and the equilibration at

(29) C. K. Ingold, "Structure and Mechanism in Organic Chemistry,"
Cornell University Press, Ithaca, N. Y., 1953, pp. 351–352.

100° of the monoanion of phosphoric acid in various
methanol–water mixtures. We have invariably found
that the product distribution monomethyl phosphate/
phosphoric acid is in all cases very nearly the same as
the mole per cent of the constituents of the solvent mix-
tures. These results are best explained by assuming the
formation of metaphosphate in each instance. In the
hydrolysis of acetyl phosphate[30] and N-benzoylphos-
phoramidic acid[31,32] the formation of metaphosphate
has been postulated. In the former case the arguments
in favor of this presumption are particularly strong.
The results[28] with the monoion of phosphoric acid are
analogous to those obtained with $H_2^{18}O$ exchange ex-
periments where the formation of metaphosphate is
also indicated.[33] The obvious inference is that the
solvolysis of PA is bimolecular involving direct attack
of the solvent molecule on the phosphorus. In a mixed
solvent system, e.g., alcohol–water, one may expect a
rate equation in terms of the solvent constituents. As
pointed out by Ingold[29] "Supposing. . . .that the sum
of the terms does describe the total rate, then the test
of the mechanism consists in ascertaining whether the
ratio of the two terms describes the product ratio."
The hydrolysis of phosphoramidic acid was carried out
in methanol–water mixtures (0–60%) and the rate and
distribution of products were determined. The bi-
molecular rate expression given below was assumed.

$$k_{obsd} = k_{H_2O}(H_2O) + k_{CH_3OH}(CH_3OH) \qquad (3)$$

In eq. 3, $k_{H_2O} = (k_1)/55.5 = 4.51 \times 10^{-3}$ l. mole^{-1} hr.$^{-1}$
is the second-order specific rate constant for the hy-
drolysis of phosphoramidic acid in water_and is assumed
to be invariant in all the methanol–water mixtures;
k_{CH_3OH} is the hypothetical second-order rate constant
that would be found if the hydrolysis were carried out
in absolute methanol. The assumption that k_{H_2O} and
by implication k_{CH_3OH} are not seriously affected over the
range of solvent mixtures investigated is supported by
the observation that in the solvolysis of PA in both 50%
tert-butyl– and isopropyl alcohol–water mixtures the
rate is slightly reduced (ca. 10–15%). This change cor-
responds closely to the reduction in water concentration
Neither of these alcohols appear to act as nucleophiles
since their corresponding phosphates are not formed.
The terms (H_2O) and (CH_3OH) refer to the molar con-
centrations of water and alcohol in the mixture.

Since the solvolysis is not feasible in absolute meth-
anol, k_{CH_3OH} was obtained from the observed rate in 50%
methanol–water by substitution of the appropriate data
in eq. 3; $k_{CH_3OH} = 3.17 \times 10^{-2}$ l. mole^{-1} hr.$^{-1}$. The
first and second terms in eq. 3 are proportional to the
amount of phosphoric acid and methyl phosphate,
respectively, formed in any particular solvent mixture.
The per cent methyl phosphate (MP) and phosphoric
acid may be calculated from the relationships

$$(\% \ MP)_{calcd} = \frac{k_{CH_3OH}(CH_3OH)}{k_{obsd}} \times 100$$

$$(\% \ H_3PO_4)_{calcd} = \frac{k_{H_2O}(H_2O)}{k_{obsd}} \times 100$$

The calculated rates and product distribution and those
found experimentally in the various solvent mixtures
are given in Table VII. Their correspondence is con-
sonant with the concept of attack of the solvent mole-
cules on the phosphorus. Similar treatment of the rate
and product data for the aryl phosphates showed no
such agreement. The observed product distribution in

(30) G. DiSabato and W. P. Jencks, J. Am. Chem. Soc., 83, 4393 (1961);
83, 4400 (1961).

(31) C. Zioudrou, Tetrahedron, 18, 197 (1962).

(32) M. Halmann, A. Lapidot and D. Samuel, J. Chem. Soc., 4672 (1960).

(33) C. A. Bunton, D. R. Llewellyn, C. A. Vernon and V. A. Welch,
ibid., 1636 (1961).

TABLE VII

RATES AND PRODUCT DISTRIBUTION OBSERVED AND CALCULATED ACCORDING TO EQUATION 3 FOR THE SOLVOLYSIS OF PHOSPHORAMIDIC ACID (MONOANION) AT 36.83°, μ = 0.2 M, IN METHANOL–WATER MIXTURES

% vol. CH₃OH	Contribution to rate		pH^a	k, hr.^-1		Alkyl phosphate, %		Mole % alcohol in solvent
	Hydrolysis $k_{H_2O}[H_2O]$	Alcoholysis $k_{CH_3OH}[CH_3OH]$		Obsd.	Calcd.^b	Obsd.	Calcd.	
0	(0.250)		5.14	0.250	(0.250)			
10	.226	0.078				23.1	25.6	4.7
15	.215	.117	5.09	.319	.332			
20	.203	.156				38.8	43.4	9.8
30	.181	.219	5.40	.400	.400	55.0	54.9	15.5
40	.157	.311				61.2	66.4	22.0
50	(.133)	(.389)	5.77	.522	(.522)	72.5	74.4	29.3
60	.109	.466	6.02	.593	.575			

^a pH's so chosen that compound exists 99% as monoanion. ^b Calculations based on figures in parentheses.

ethanol–water mixtures indicates that $k_{C_2H_5OH}$ is larger that k_{H_2O}. The increase in rate, however, in 50% ethanol–water is too small (12%) for any reliable calculation of $k_{C_2H_5OH}$.

The solvolysis of the monoanionic species of N-(p-chlorophenyl)-amidophosphoric acid is presumably also bimolecular. It yields for the same alcohol–water mixtures very nearly the same product distribution (alkyl phosphate/phosphoric acid) as phosphoramidic acid (Table V; Fig. 3). It was found, however, that in 50% methanol- and dioxane–water mixtures the rate of solvolysis is decreased 25 and 44%, respectively. Although these changes are small, they are in the opposite direction to that observed with phosphoramidic acid. The correspondence in product composition and opposite solvent effects for phosphoramidic vs. N-(p-chlorophenyl)-amidophosphoric acid cannot be reasonably ascribed to specific solvent effects which obtain for one compound and not the other. A likely qualitative explanation is forthcoming when one considers the equilibrium K_e between the two forms, non-zwitterion and zwitterion $(RNH-PO_3H)^- \rightleftarrows (RH_2N^+-PO_3^-)^-$ of the monoanionic species, and the solvolysis rates associated with each of these. If K_e is small ($< 10^{-1}$) in water, any lowering of its magnitude, as might be anticipated in changing to a less aqueous solvent, would primarily result in an equivalent percentage change in concentration of the zwitterionic form. Conversely, if K_e is relatively large in water, an equivalent percentage change in it would not substantially alter the concentration of zwitterion. The following observations suggest that K_e is large for phosphoramidic acid[34] and small for N-(p-chlorophenyl)-amidophosphoric acid. The monoanion of PA, as shown by X-ray crystallographic studies,[35] is zwitterionic in the solid state. The second ionization constant of PA (pK_2 8.2) is significantly smaller than that of N-benzoylphosphoramidic acid (pK_2 = 6.0,[28] 6.42,[31] 5.67[32]), and N-acetylphosphoramidic acid[28] (pK_2 6.0), where zwitterion formation is precluded. The second ionization constant pK_2 = 6.8 of N-(p-chlorophenyl)-amidophosphoric acid[2] appears to be normal. Presumably in the various ethanol-, methanol-, dioxane–water mixtures employed, the zwitterionic form of the monoanion of phosphoramidic acid and the non-zwitterionic form of N-(p-chlorophenyl)-amidophosphoric acid predominate. Other evidence indicates that the zwitterionic form is mainly responsible for the solvolysis of the monoanionic species. There is the analogy with the neutral species of ClPhPA, the hydrolysis[2] of which is associated with its zwitterionic form. The same distribution of products is

found in the base- and non-base-catalyzed hydrolysis of both PA and ClPhPA in alcohol–water mixtures. For the base-catalyzed reaction, e.g., pyridine, the reactive intermediate is the zwitterionic species
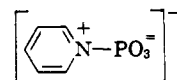
The structural analogy between it and the zwitterionic form of the monoanion is apparent. We surmise that the decrease in rate noted with the aromatic phosphoramides in the presence of methanol and dioxane is primarily associated with the decrease in zwitterion concentration (cf. Neutral Species). For PA the zwitterion concentration remains substantially unchanged in the alcohol– and dioxane–water mixtures used. The rate of solvolysis of PA is primarily determined by the relative nucleophilic power and concentration of the constituents of the alcohol mixture and eq. 3 applies.[36] We find that methanol and ethanol are nucleophiles superior to water.[37] The equivalence of product distribution for both phosphoramidic acid and the aromatic phosphoramide requires only that the ratio $k_{alcohol}/k_{H_2O}$ be the same in each instance. The solvolysis of the PA and ClPhPA monoanions proceeded 10^3–10^4 times faster than that of aliphatic or aromatic phosphates. The relative stability of the neutral species (non-zwitterion) and diionic species of phosphoramides as well as that of the anion of diamidophosphoramides[38] $(RNH-)_2-PO_2^-$ suggests that not only a protonation of the nitrogen is involved in the solvolysis, but that this proton is derived from the P–OH moiety. It is unlikely that this proton transfer is involved in the rate-determining step. The rate of solvolysis of phosphoramidic acid is decreased but 15% in D₂O, while that of N-(p-chlorophenyl)-amidophosphoric acid is increased ca. 30%. Here again an opposite effect of solvent on rate is noted. A small decrease in solvolysis rate is encountered in PA as in many diverse reactions[39] in D₂O. The increase in rate observed with ClPhPA may result from an increase in zwitterion concentration.[40] In analogy with the solvolysis of

(34) The same conclusion has been reached by Kumler in studies of acidities of various phosphate esters and amidophosphates. Cf. W. D. Kumler and J. J. Eiler, J. Am. Chem. Soc., 65, 2355 (1943); cf. E. W. Crunden and R. F. Hudson, J. Chem. Soc., 3592 (1962).

(35) E. Hobbs, D. E. C. Corbridge and B. Raistrick, Acta Cryst., 6, 621 (1953). See Lord Todd, Presidential Address, Proc. Chem. Soc., 199 (1962).

(36) In 50% dioxane–water mixture the solvolysis of PA is slightly enhanced (ca. 25%). This may be a specific solvent effect since the same percentage enhancement of rate is observed in the solvolysis of phenyl phosphate.

(37) I. Dostrovsky and M. Halmann, J. Chem. Soc., 502 (1953).

(38) D. F. Heath and P. Casapieri, Trans. Faraday Soc., 47, 1093 (1951).

(39) P. M. Laughton and R. E. Robertson, Can. J. Chem., 34, 1714 (1956); R. E. Robertson and P. M. Laughton, ibid., 35, 1319 (1957).

(40) It may be argued that since the zwitterionic form of the monoanion of ClPhPA is a stronger acid than its non-zwitterionic form, and since ΔpK = (pK_{D_2O} − pK_{H_2O}) increases with increasing pK of the acid, the latter would be relatively more favored in D₂O than in H₂O and consequently the rate of solvolysis should decrease rather than increase as found. However, two different types of acids are being compared, $(RN^+H_2-PO_3^-)^-$ and $(RNHPO_3H)^-$, and, as pointed out by Long, ΔpK values vary with acid type. For example, the ΔpK for the strong acids $R_2N^+H_2$ are larger than those found for the weaker carboxylic acids RCO₂H. Cf. E. Hogfeldt and J.

TABLE VIII

HYDROLYSIS OF PHOSPHORAMIDIC ACID ($Ca.$ 1×10^{-2} M) IN H_2O AT 25.0°, $\mu = 0.2$, IN PRESENCE OF VARIOUS BASES

pH	Base,[a] M	0.00	0.02	0.04	0.06	0.09	k_{cat} (Av.)	pK_a[k]
7.2	Pyridine[b]							
	k_{obsd}, hr.$^{-1}$	0.0474	0.409	0.764				5.17
	k_{cat}, l. mole^{-1} hr.$^{-1}$		20.1	19.9			20.0	
7.2	3-Methylpyridine							
	k_{obsd}	.0474	0.451	0.909				5.68
	k_{cat}		22.4	23.9			23.1	
7.2	4-Methylpyridine							
	k_{obsd}	.0474	0.522	0.972				6.02
	k_{cat}		26.4	25.7			26.0	
7.2	2-Methylpyridine							
	k_{obsd}	.0474			0.0471[i]			5.97
		.236[c]			.249[c,i]			
7.6	2,6-Dimethylpyridine							
	k_{obsd}	.202[c]		0.206[c]				6.75
6.74	Aniline							
	k_{obsd}	.241[d]			.255[d,e]	0.252[d,f]		4.70
7.2	Nicotinic acid							
	k_{obsd}	.0474		0.323		0.667		4.85
				0.329[g]				
	k_{cat}			7.65		7.65	7.65[h]	
6.75	Isonicotinic acid							
	k_{obsd}	0511		0.451	.641			
	k_{cat}			10.4	10.3		10.3	4.95
6.75	Picolinic acid							
	k_{obsd}	.0511		0.057				5.40
		.241[d]		0.216[d]				
7.2	Nicotinic acid							
	k_{obsd}[j]		.257			0.571	3.71	

[a] Pyridine, 3-methyl-, 4-methyl-, 2-methyl- and 2,6-dimethylpyridine rates done according to Nessler. All others done by pH-Stat method. [b] At pH 7.2, 37.15°, k_{obsd} in 0.01 M pyridine was 0.693 hr.$^{-1}$. [c] $t = 37.15°$. [d] $t = 36.8°$. [e] 0.055 M. [f] 0.11 M in aniline. [g] D_2O as solvent. [h] Reported $k_{cat} = 7.70$; cf. ref. 3. [i] 0.05 M in base. [j] Hydrolysis of N-(p-chlorophenyl)-amidophosphoric acid. [k] Values taken from the literature; cf. H. C. Brown, et al., J. Am. Chem. Soc., **77**, 1723 (1955); H. H. G. Jellinek and J. R. Urwin, J. Phys. Chem., **58**, 548 (1954).

dialkyl phosphochloridates, which proceeds in water without oxygen exchange,[41] we assume as most likely a one-stage displacement reaction with the approach of the nucleophilic reagent being simultaneous with the release of the phosphate ion or, in the case of alcoholic solvents, of alkyl phosphate. A second bimolecular mechanism which involves the rapid reversible formation of an intermediate complex, which then slowly decomposes into products, is not contradicted by our findings. A choice between these alternatives awaits experiments with $H_2^{18}O$. The postulated mechanism of solvolysis is shown below. Path I is considered the primary course of solvolysis of the phosphoramides PA and ClPhPA. However, for reasons discussed below (cf. Neutral Species), path II may be of some significance, at least in the solvolysis of ClPhPA.

$$[RHN-PO_3H]^- \rightleftarrows [RH_2\overset{+}{N}-PO_3^-]^-$$

II ↓R'OH   ↓R'OH I

$$\begin{bmatrix} H-O \\ \downarrow \\ RH\overset{\downarrow}{N}-PO_2 \\ \vdots \\ R'-O-H \end{bmatrix}^- \quad \begin{bmatrix} RH_2\overset{+}{N}-PO_3^- \\ \vdots \\ R'-O-H \end{bmatrix}^-$$

$$\longrightarrow RNH_2 + R'OPO_3H^-$$

$R = H$ or p-C_6H_4Cl-; $R' = CH_3$, C_2H_5 or H
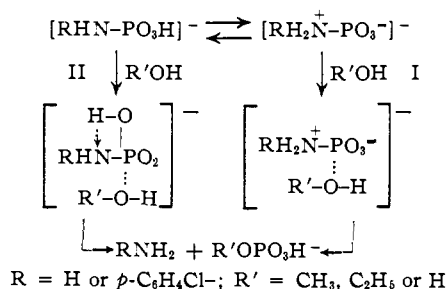
Base Catalysis of Phosphoramides.—The solvolysis of the monoanion of phosphoramidic acid, but not the dianion,[3] is catalyzed by and proportional to the concentration of the bases: pyridine, 3- and 4-methylpyridine, and the anions of nicotinic and isonicotinic

acid. The hydrolysis of N-(p-chlorophenyl)-amidophosphoric acid is also catalyzed by the anion of nicotinic acid, the only base investigated. No catalysis of solvolysis was noted with either of the aromatic phosphates. Kinetically, no deviation from first order was found even when the concentration of base was but twice that of the phosphoramidic acid. The catalytic constants k_{cat} were evaluated from the rate equation

$$k_{obsd} = [k_1 + k_{cat}(B)](M_1) \qquad (4)$$

where k_1 refers to the specific rate constant of the uncatalyzed reaction, (B) the concentration of the particular base and M_1 the mole fraction of monoanionic species present. The catalysis by nicotinic acid anion was also studied in various methanol–water mixtures and D_2O. The catalytic constant decreased with increasing proportions of methanol, but was unaffected by D_2O. The results are given in Tables VIII and IX. No catalysis of hydrolysis of phosphoramidic acid was observed on the addition of 2-methylpyridine, 2,6-dimethylpyridine, aniline, the anion of picolinic acid, or the diion of phosphoric acid. The ineffectiveness of the α-substituted pyridine bases of comparable base strength to the catalytic bases emphasizes the strict steric requirement imposed on the nucleophile. These results parallel those of Brown,[42] who has demonstrated the inhibitory effect of α-substituents in the bimolecular displacement reaction involving alkyl halides and substituted pyridines. It is perhaps for this reason that, as mentioned previously, neither isopropyl nor $tert$-butyl phosphate are formed when the solvolysis of phosphoramidic acid is carried out in the presence of their corresponding alcohols. The base catalysis, as illustrated below for pyridine, may be reasonably interpreted as a two-step reaction. The first step, rate

Bigeleisen, J. Am. Chem. Soc., **82**, 15 (1960); P. Ballinger and F. A. Long, ibid., **82**, 795 (1960); ref. 15.

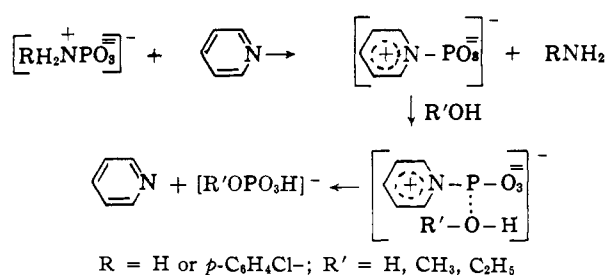(41) I. Dostrovsky and M. Halmann, J. Chem. Soc., 1004 (1956).

(42) H. C. Brown and A. Cahn, J. Am. Chem. Soc., **77**, 1715, 1723, 1727 (1955).

TABLE IX

SOLVOLYSIS OF PHOSPHORAMIDIC ACID $(ca.\ 1 \times 10^{-2}\ M)$ IN CH$_3$OH–H$_2$O MIXTURES AT 25.00°, pH 7.2, $\mu = 0.2\ M$, IN PRESENCE OF NICOTINIC ACID

% vol. CH$_3$OH	Base, M	0.00	0.02	0.04	0.06	0.09	k_{cat} (av.), l. mole^{-1} hr.$^{-1}$
0	k_{obsd}[a]	0.0474		0.323		0.667	7.65
15	k_{obsd}	.0677	0.181	0.370[c]	0.458[b]		
	k_{cat}		6.20	6.64	6.85		6.56
30	k_{obsd}	.0922	0.200	0.299	0.413	0.562	
	k_{cat}		5.86	5.63	5.82	5.68	5.75
50	k_{obsd}	.116	0.260[d]		0.402	0.527	
	k_{cat}		5.10		5.07	4.86	5.01
50	k_{obsd}		0.395[e]				9.90

[a] k_{obsd} expressed in hr.$^{-1}$ [b] 0.0625 M.   [c] 0.05 M.   [d] 0.03 M in nicotinic acid.   [e] 0.03 M in pyridine. The pK_a found for nicotinic acid at 25°, $\mu = 0.2\ M$, was 4.68 in water, 4.56 in 50% methanol–water and 5.32 in D$_2$O $(cf.$ ref. 15).

determining, is the attack of base on the phosphoramide; the second, the rapid bimolecular solvolysis of the intermediate.

$$\left[\text{RH}_2\overset{+}{\text{N}}\text{PO}_3\right]^{\equiv]^-} + \left\langle \text{N}\right\rangle \rightarrow \left[\left\langle\overset{+}{\text{N}}\right\rangle\text{N} - \text{PO}_3\right]^- + \text{RNH}_2$$

$$\downarrow \text{R'OH}$$

$$\left\langle\text{N}\right\rangle + [\text{R'OPO}_3\text{H}]^- \leftarrow \left[\left\langle\overset{+}{\text{N}}\right\rangle\text{N} - \overset{\equiv}{\text{P}} - \text{O}_3 \atop \text{R'}-\text{O}-\text{H}\right]^-$$

R = H or p-C$_6$H$_4$Cl–; R' = H, CH$_3$, C$_2$H$_5$

As previously mentioned, the product distribution found in the solvolysis of phosphoramidic acid is unchanged by the addition of base (see Table X). This result can only obtain if the relative rate of attack of the alcohol and water (k_{ROH}/k_{H_2O}) on the reactive intermediate is the same as that found for the uncatalyzed reaction.

TABLE X

EFFECT OF BASE ON PRODUCT DISTRIBUTION IN THE SOLVOLYSIS OF PHOSPHORAMIDIC ACID MONOANION IN METHANOL AND ETHANOL–WATER MIXTURES
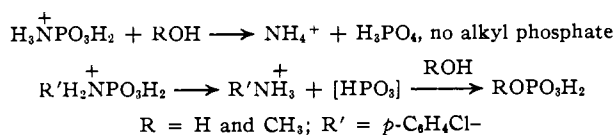
	Alkyl phosphate, %		
	CH$_3$OH–H$_2$O		C$_2$H$_5$OH–H$_2$O,
Nicotinic acid, M	30%	50%	50%
0	55	72	37
0.09	56	70	32
0.18	52		

Neutral Species and Acid-catalyzed Reaction.—In analogy with aromatic phosphoramides, the fast rate of hydrolysis of the neutral species of phosphoramidic acid may be ascribed to its zwitterionic form (H$_3$N$^+$–PO$_3$H$^-$)^0. The non-zwitterionic form probably corresponds in stability to un-ionized monoalkyl or aryl phosphates. The relatively small first ionization constant ($pK_1 = 3.00$ in water and $pK_1 = 4.05$ in 50% methanol–water) of phosphoramidic acid as compared to N-acetyl- and N-benzoylphosphoramidic acid (pK_1 1.3,[28] 1.99,[31] respectively) and the fact that its monoanion exists as a zwitterion $(cf.$ above) suggests that in water and methanol–water (50%) the neutral species exists primarily as a zwitterion.[34] The hydrolysis of the neutral species is enhanced in 50% methanol–water. The increase in rate is smaller than that observed for the monoanionic species and correspondingly the percentage alkyl phosphate formed in all alcohol–water mixtures studied is also smaller; see Table V. The

percentage alkyl phosphate formed, however, is larger than the mole per cent of alcohol in the reaction mixtures (Table V). We infer from these observations that the solvolysis of the neutral species is also bimolecular, although the incursion of an alternative breakdown of zwitterion by a unimolecular process with the formation of metaphosphate cannot be excluded.

The first ionization constant of N-(p-chlorophenyl)-amidophosphoric acid[2] ($pK\ ca.\ 1.6$) is significantly larger than that of phosphoramidic acid. In dioxane–water (50%) mixtures the solvolysis of its neutral species is drastically reduced, so that a minimum (as with alkyl phosphates) is observed at pH $ca.\ 2$ in the pH $vs.$ hydrolysis rate curve.[2] In this solvent mixture the pH $vs.$ hydrolysis rate curve (0.1 M to pH 7) may be accounted for by the rate terms associated with the monoanionic species and the acid-catalyzed hydrolysis of the neutral species. This decrease in rate of solvolysis of the neutral species in 50% dioxane–water has been ascribed to the repression of zwitterion formation.[2] Of interest in this connection is the observation that the solvolysis rate of the monoanion of ClPhPA is reduced to a lesser extent than the neutral species in the dioxane–water mixture. A rationale for this is found in the assumptions that dioxane substantially enhances[36] only the solvolysis of the monoanion (zwitterionic form), thus partially compensating for the reduction in zwitterion concentration, and/or that the solvolysis of the non-zwitterionic form of the monoanion also contributes to the over-all rate of decomposition. Assuming the same factors to be operative in the solvolysis of N-(p-chlorophenyl)-amidophosphoric acid in 50% methanol–water as in dioxane–water, one may anticipate the same type of pH $vs.$ hydrolysis rate curve as found for the dioxane–water mixture. This conjecture has not yet been tested experimentally. The product distribution $vs.$ pH curve for the solvolysis of N-(p-chlorophenyl)-amidophosphoric acid in alcohol–water mixtures (50%) exhibits a flat maximum region extending as low as pH 2 (Fig. 3), followed by a precipitous fall and subsequent flattening of the curve. Just such a relationship between percentage alkyl phosphate and pH would be anticipated if the solvolysis of the neutral species was insignificant.

Acid catalyzes the hydrolysis of both phosphoramidic and N-(p-chlorophenyl)-amidophosphoric acid. There appears, however, to be a difference in the mechanism of their hydrolyses. Phosphoramidic acid in acidified methanol–water (50%) systems yields practically no methyl phosphate $(ca.\ 8\%)$. On the other hand, for N-(p-chlorophenyl)-amidophosphoric acid the percentage alkyl phosphate formed in the various strongly acidified alcohol–water mixtures is the same as the mole per cent of alcohol present (Table V). It seems likely that solvolysis of N-(p-chlorophenyl)-amidophosphoric acid proceeds by way of a unimolecular breakdown of the protonated species with formation of metaphosphate, while protonated phosphoramidic acid is preferentially attacked by water as shown below.

$$\text{H}_3\overset{+}{\text{N}}\text{PO}_3\text{H}_2 + \text{ROH} \longrightarrow \text{NH}_4^+ + \text{H}_3\text{PO}_4, \text{ no alkyl phosphate}$$

$$\text{R'H}_2\overset{+}{\text{N}}\text{PO}_3\text{H}_2 \longrightarrow \text{R'}\overset{+}{\text{N}}\text{H}_3 + [\text{HPO}_3] \xrightarrow{\text{ROH}} \text{ROPO}_3\text{H}_2$$

R = H and CH$_3$; R' = p-C$_6$H$_4$Cl–