[Contribution from the Department of Chemistry, The Mount Sinai Hospital]

A Study of the Hydrolysis of Phosphonamides. I. Aromatic Phosphonamides[1]

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The synthesis and hydrolysis of N-(phenyl)- I, N-(*p*-chlorophenyl)- II, and N-(*p*-methoxyphenyl)- III amidophosphoric acid has been investigated. The rates of hydrolysis in water and water–dioxane mixture over the *p*H range 1–10 were determined; the hydrolysis of compound II has been investigated in strong acid (0.3–2.0 *M* HCl). Rate equation 1 which describes the hydrolysis at any *p*H is $k_{obs} = k_H[H^+][M_0] + k_0[M_0] + k_1[M_1]$, where M_0 and M_1 are the mole fractions of the neutral and singly negatively charged species and k_H, k_0 and k_1 are their associated specific rate constants. In water k_0 is larger than k_1; in 50% dioxane–water mixture the reverse is found to be the case. The heats and entropies of activation in water and water–dioxane mixture have been evaluated. The similarities and differences in the *p*H dependency of the hydrolysis of amidophosphate and phosphate esters are noted and the effect of dioxane on the hydrolysis is discussed.

In contrast to the extensive investigations which have been pursued in various laboratories on the mechanism of hydrolysis of simple phosphoric acid esters, $R-OPO_3H_2$, there are but few studies on the hydrolysis of the related monoamidophosphoric acid derivatives, $R-NHPO_3H_2$.[2a,b,c] A study of the hydrolysis, over the *p*H range 1.1–10, of the following phosphonamides: N-(phenyl)- (I), N-(*p*-chlorophenyl)- (II) and N-(*p*-methoxyphenyl)- (III) amidophosphoric acid has been made (Fig. 1) The similarities and differences in the *p*H dependency of the hydrolysis of amidophosphates and phosphate esters are noted. The effect of dioxane on the hydrolysis of N-(*p*-chlorophenyl)-amidophosphoric acid has been investigated (Fig. 2) and has served to make understandable the observed difference in the *p*H dependency of the hydrolysis for the two classes of phosphates. The energies and entropies of activation in both water and the mixed solvent dioxane–water have been evaluated. The acid-catalyzed hydrolysis of compound II has been studied (Fig. 3). A discussion of the findings of this investigation is given.

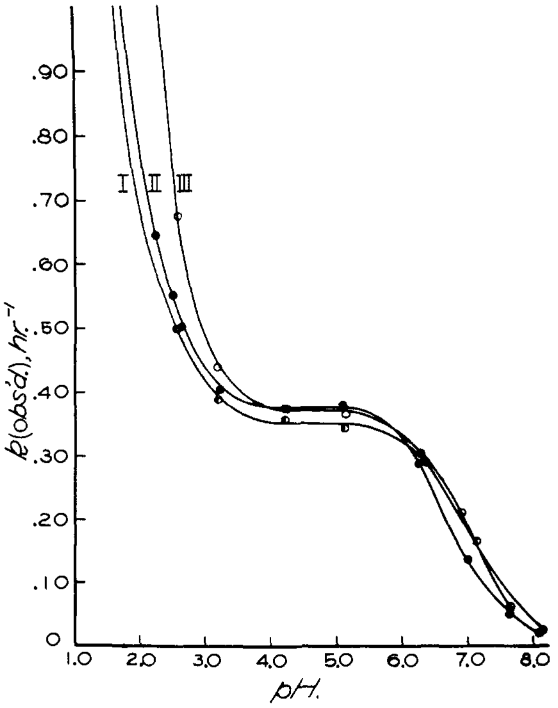

Fig. 1.—The observed hydrolysis rate as plotted against *p*H for N-(*p*-phenyl)-I, ◑; N-(*p*-chlorophenyl)- II, ●; and N-(*p*-methoxyphenyl) III, O.

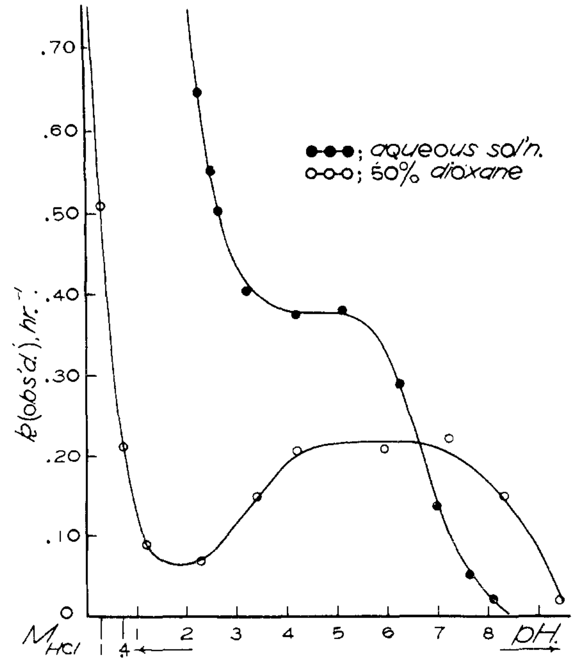

Fig. 2.—The observed hydrolysis rate as plotted against *p*H for N-(*p*-chlorophenyl)-amidophosphoric acid: in water, ●; in 50% dioxane–water mixture, O.

Although the syntheses of compounds II and III have been claimed, the previously reported properties of N-(*p*-chlorophenyl)[3a] and N-(*p*-methoxyphenyl)-amidophosphoric acids[3b] are at complete variance with what has been found in this investigation and what might have been anticipated from earlier findings on the stability of amidophosphates.[2a,b,c] The authors feel that the prior claims to the synthesis of these compounds are to be discounted, while in the case of N-(phenyl)-amido-

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[2] (a) T. Winnick and E. M. Scott, *Arch. Biochem. and Biophys.*, **12**, 201, 209 (1947); (b) K. M. Moller, *Biochim. et Biophys. Acta*, **16**, 162 (1955); (c) T. Rathler and T. Rosenberg, *Arch. Biochem. and Biophys.*, **65**, 319 (1956).

[3] (a) Si-Oh Li, *Acta Chem. Scand.*, **4**, 610 (1950); (b) H. Holter and Si-Oh Li, *Compt. rend. Lab. Carlsberg*, **27**, 393 (1951).

phosphoric acid[4] we have shown that the compound originally claimed to be the latter is in fact its anilinium salt (see Experimental).

Experimental

The instability of the aromatic amidophosphoric acid compounds precluded their isolation in their free form. They were obtained easily from the reaction mixtures as the crystalline pure monoanilinium salts. The synthesis of and isolation of the amidophosphates was carried out in the following manner: (a) the appropriate amine was condensed with dibenzyl chlorophosphonate in the presence of excess base (amine or triethylamine), (b) hydrogenation of the dibenzyl derivative, (c) precipitation of the amidophosphate from the hydrogenation mixture by the addition of aniline. The anilinium salts are but slightly soluble in water or alcohol. The amidophosphates gave no test for free phosphoric acid, when examined by the procedure described below. The melting points given are essentially decomposition points. The neutralization equivalents were obtained by suspending the material in a mixture of methanol–water and employing thymolphthalein as indicator. The anilinium salts of compounds I and II are quite stable in the dry state when kept away from direct sunlight. The *p*-methoxy derivative slowly decomposes even under the most favorable conditions.

Anilinium Salt of N-(Phenyl)-amidophosphoric Acid (I).—Dibenzyl chlorophosphonate[5] prepared from dibenzyl phosphite[6] (40 g.) was condensed with aniline (60 ml.) according to the procedure described by Todd, *et al.*,[5] to give crude dibenzylanilinophosphonate. Two recrystallizations from cyclohexane gave the pure material, 36 g., m.p. 88–90°, reported[5] 91–92°, which was satisfactory for hydrogenation. A mixture of 5 g. of the anilino derivative in 150 ml. of 95% ethanol was hydrogenated at room temperature (25°) and atmospheric pressure in the presence of 300 mg. of a 5% Pd/C catalyst. Two moles of hydrogen was absorbed after 2.5 hr., at which time the uptake practically ceased. The catalyst was removed by filtration and, to the filtrate cooled in ice, aniline (1.29 ml.) was added with vigorous handswirling. Immediate precipitation ensued. The microcrystalline precipitate was removed by filtration and washed successively with cold absolute alcohol (two 5-ml. portions), ether (three 10-ml. portions) and dried *in vacuo* over KOH; yield 3.48 g., m.p. *ca.* 250° dec.

Anal. Calcd. for $C_{12}H_{15}O_3N_2P$: C, 54.13; H, 5.68; N, 10.52; P, 11.65; neut. equiv., 133.1. Found: C, 54.20; H, 5.85; N, 10.78; P, 11.50; neut. equiv., 133.0.

The hydrogenation mixture, when allowed to stand in the cold overnight, yielded the same product as obtained above. The anilinium salt is formed by the hydrolysis of the phosphonamide to aniline and ethyl phosphate and the subsequent precipitation of the anilinium salt of the amidophosphate. Previously[4] it had been assumed that the crystalline product that resulted from the hydrogenation, after standing, was the free acid.

The anilinium salt of N-(*p*-chlorophenyl)-amidophosphoric acid (II) was prepared essentially as described above with the following modifications. To a solution of dibenzyl chlorophosphonate (prepared from 15 g. of dibenzylphosphite) in 150 ml. of carbon tetrachloride, cooled to −10°, a solution of *p*-chloroaniline (9.12 g., 0.072 mole) and triethylamine (16 ml.) in chloroform (200 ml.) was added dropwise over a period of 45 min. After allowing the mixture to stand overnight, the precipitated triethylamine hydrochloride was removed. The filtrate was washed successively with ice-cold 1 *N* HCl (two 100-ml. portions), water (three 250-ml. portions), saturated salt solution and dried overnight over anhydrous sodium sulfate. Evaporation of the dried chloroform extract yielded a crystalline residue (21 g.), which after crystallization from 95% alcohol gave the pure dibenzyl *p*-chloroanilinophosphonate, m.p. 89°, rept.[3a] 89°. Five grams of the above derivative was dissolved in absolute ethanol and hydrogenated in the presence of 5% Pd/C catalyst. Proceeding as previously described, the anilinium salt of N-(*p*-chlorophenyl)-amidophosphoric acid was obtained; yield 3.3 g., m.p. 268° dec.

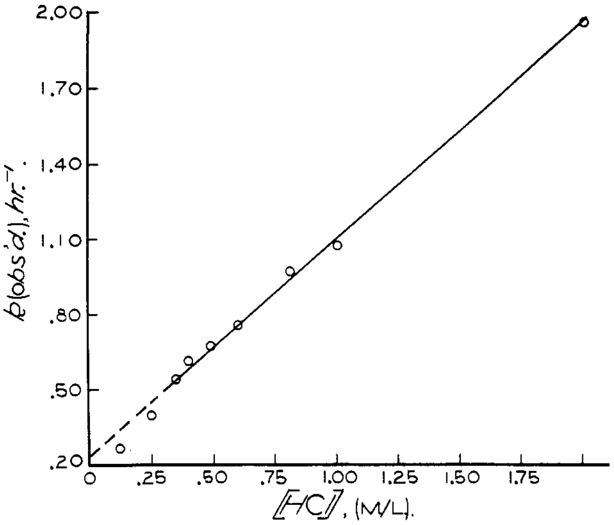

Fig. 3.—The observed hydrolysis rate as plotted against molarity of HCl for N-(*p*-chlorophenyl)-amidophosphoric acid.

Anal. Calcd. for $C_{12}H_{14}O_3N_2PCl$: C, 47.93; H, 4.69; N, 9.32; P, 10.31; Cl, 11.79; neut. equiv., 150. Found: C, 48.20; H, 4.71; N, 9.52; P, 10.24; Cl, 11.56; neut. equiv., 148.

The anilinium salt of N-(*p*-methoxyphenyl)-amidophosphoric acid (III) was prepared as described for the *p*-chloro compound. The insolubility of dibenzyl *p*-methoxyanilinophosphonate necessitated the use of 5 times the volume of chloroform given above. From dibenzyl phosphite (15 g.) there was obtained dibenzyl *p*-methoxyanilinophosphonate (17 g.), m.p. 115–116°, reported[3b] 115–116°, after recrystallization from chloroform. Hydrogenation of 5 g. of the above gave, after addition of aniline, the anilinium salt of N-(*p*-methoxyphenyl)-amidophosphoric acid; yield 3.3 g., m.p. *ca.* 260° dec.

Anal. Calcd. for $C_{13}H_{17}O_4N_2P$: C, 52.70; H, 5.78; N, 9.46; P, 10.47; neut. equiv., 148. Found: C, 52.64; H, 5.72; N, 9.57; P, 10.22; neut. equiv., 147, 149.

Phosphate Determination.—The rate of hydrolysis was obtained by analysis for free phosphoric acid. The determination of free phosphoric acid in the presence of unreacted amidophosphoric acid presented some difficulties. Analysis for free phosphate by the method of Fiske and SubbaRow, as modified by Sobel,[7] could not be employed. The aromatic amidophosphoric acids decomposed almost instantaneously and completely because of the high acidity of the medium. Preliminary experiments indicated that the method of Lowry–Lopez,[8] employing a *p*H of *ca.* 4 in the development mixture, was promising. Although at room temperature aromatic amidophosphoric acids are hydrolyzed by the Lowry–Lopez mixture, at 0–4°, the hydrolysis is so repressed as to make the determination of pre-existing free phosphate feasible. Employing Lowry–Lopez conditions with development of color at ice temperature, standard phosphate solutions gave maximum color development in *ca.* 23–25 min., after which time the intensity of color remained constant for at least an hour. Furthermore, Beer's law was found to hold. The hydrolysis of aromatic phosphonamides is catalyzed by the molybdate[2a,c] present in the development mixture. The percentage hydrolysis which occurs during development time is small, since there is but a small increase in free phosphate with prolonged development times. A reasonable correction for this latter hydrolysis, as well as for the release of free phosphate in the time needed to determine the phosphate concentration colorimetrically, was applied by noting the difference in free phos-

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[4] H. G. Cook, J. D. Klett, B. C. Saunders, G. J. Stacey, H. G. Watson, I. G. E. Welding and S. J. Woodcock, *J. Chem. Soc.*, 2921 (1949).

[5] F. R. Atherton, H. T. Openshaw and A. R. Todd, *ibid.*, 382 1945).

[6] O. M. Friedman, D. L. Klass and A. M. Seligman, THIS JOURNAL, **76**, 916 (1954).

[7] A. E. Sobel, *Ind. Eng. Chem., Anal. Ed.*, **17**, 242 (1945).

[8] T. H. Lowry and J. A. Lopez, *J. Biol. Chem.*, **162**, 421 (1946).

phate values for development time 25 and 50 min. and subtracting this difference from the 25-min. value. Obviously, the greater the total percentage hydrolysis, the smaller would be the correction. This was found to be the case. For the runs at high acidities (0.25–2 *M* HCl) (μ = 2 *M*), where the salt concentration was necessarily high in the development mixture (*vide infra*), the increase of color with prolonged development times was somewhat greater. Standard phosphate solutions at high salt concentration behaved similarly. A Klett–Summerson colorimeter with a 660 mμ filter was employed in evaluation of phosphate concentration.

Rate Run Procedures.—The anilinium salt of the phosphonamide (*ca.* 60 mg., 0.2 mmole) was dissolved in 25 ml. of an alkaline solution containing 2.1 equiv. of sodium hydroxide. One ml. of this stock was added to exactly 5 ml. of the appropriate buffer (μ = 0.2 *M*) and the solution diluted to 10 ml. The reaction flask was then heated at the desired temperature and 1-ml. aliquots removed at appropriate intervals. These aliquots were delivered into an ice-cold solution of an acetate buffer (*p*H 4.04); 1 ml. of the molybdate reagent and 1 ml. of the ascorbic acid solution (both ice-cold) were then added; the mixture was diluted to 10 ml. with ice-cold water, inverted and allowed to stand for 25 min. in an ice-bath. The intensity of color was read at 660 mμ and the solution returned to the ice-bath. The second reading was made 25 min. later. The difference between the second and first readings was subtracted from the initial reading. An example of the results of a particular run is furnished below. For the hydrolyses run at *p*H 1 and 2 the acetate buffer of *p*H 4.4 was employed in the development mixture. For the runs at high acidity (0.2–2.0 *M* HCl) the ionic strength was maintained at μ = 2 *M* by addition of the requisite quantity of KCl. In the later case the aliquots were removed with previously iced pipets and deliveries were made directly into an ice-cold mixture containing the stoichiometric quantity of 2 *N* NaOH as well as 5 cc. of acetate buffer.

The hydrolyses followed first-order kinetics, and the observed rates were calculated from the first-order equation

$$k_{\text{obsd}} = \frac{2.303}{t - t_0} \times \frac{\log (P_\infty - P_{t_0})}{(P_\infty - P_t)_{\text{cor}}}$$

where (P_∞) = final phosphate reading and P_t phosphate reading at time *t*.

HYDROLYSIS OF N-(*p*-CHLOROPHENYL)-AMIDOPHOSPHORIC ACID (II)

20.0° ± 0.03°, μ = 0.1 *M*, *p*H 4.20.

t, min.	1st reading	2nd reading	Cor.	$(P_\infty - P_t)_{\text{cor.}}$	*k*, hr.$^{-1}$, obsd.
0	48	51	(−3)	128	. . .
40	76	79	(−3)	100	0.376
80	99	102	(−3)	77	.380
120	116	114	(−2)	59	.383
165	129	131	(−2)	46	.376
213	141	142	(−1)	35	.370
262	147	147	(0)	26	.364
∞	173	173	(0)		. . .
(*ca.* 30 hr.)				k_{obsd} av. = 0.375 ± 0.005	

The same procedure was followed for the hydrolysis of N-(*p*-chlorophenyl)-amidophosphoric acid in the 50% dioxane–water mixture (prepared by mixing equal volumes of the appropriate buffer and dioxane). The observed rates are the average of at least two determinations, each of which was done in duplicate. The variation in results (*ca.* 2–3%) was no greater than the deviation in any run.

Solutions.—(a) Buffers employed for hydrolysis: *p*H 2–4 prepared according to W. M. Clark from 0.2 *M* KH-phthalate and 0.2 *M* HCl; *p*H 4–6 prepared according to W. M. Clark from 0.2 *M* KH-phthalate and 0.2 *M* NaOH; *p*H 7–9 prepared according to L. Michaelis from sodium veronal and 0.1 *M* HCl; the *p*H 1.15 was obtained from 0.1 *N* HCl + KCl. All buffers brought to ionic strength μ = 0.2 *M* by addition of KCl. The *p*H's of the hydrolysis solutions, determined with a Cambridge *p*H meter, were measured before and after hydrolysis and did not vary by more than 0.05 *p*H unit.

Color Development Reagents.—Buffers: (a) equal volumes of 0.1 *N* acetic acid and 0.025 *N* sodium acetate were mixed to give *p*H 4.04; (b) equal volumes of 0.2 *N* acetic acid and 0.127 *N* acetate were mixed to give *p*H 4.41; a 1% solution of ascorbic acid in acetate buffer of *p*H 4.04 was prepared fresh for each run; in 20 ml. of a 2.5% ammonium molybdate solution 0.05*N* in sulfuric acid was diluted to 50 ml. with acetate buffer (*p*H 4.04).

Results

First-order kinetics were observed in the hydrolysis of each of the compounds investigated over the *p*H range 2–10. Table I and Fig. 1 give the observed specific rates of hydrolysis in hr.$^{-1}$ ($k_{\text{obsd.}}$) for each of the *p*H's studied. The phosphonamides are stable in alkali, while the rate of hydrolysis is constant over *ca.* a 100-fold change in hydrogen ion concentration (*p*H *ca.* 3–5). There appears to be but little difference in rate, in the flat region, for the three compounds investigated. The hydrolyses of the phosphonamides studied are acid catalyzed. Figure 3 illustrates the dependence of hydrolysis of N-(*p*-chlorophenyl)-amidophosphoric acid on the hydrogen ion concentration. Above 0.4 *M* HCl a straight line relationship is found to hold. In 50% dioxane–water as solvent, first-order kinetics were observed at each *p*H. The most striking difference between the hydrolysis in water as compared to that in dioxane is in the shape of the *p*H *vs.* hydrolysis rate curve (see Fig. 2). The *p*H *vs.* hydrolysis rate curve in water is S-shaped and completely analogous to that reported for amidophosphoric acid ($NH_2PO_3H_2$),[2b,c] while in the dioxane–water mixture the shape is completely analogous to that observed in the hydrolysis of simple aliphatic phosphoric acid esters. A small decrease in rate of hydrolysis is observed in the flat region of the curves in passing from the water to the mixed solvent; while at *p*H *ca.* 3 and below a very large difference in the rate is observed. This point will be discussed subsequently. A comparison of the energy and entropies of activation and the rates from which the latter quantities were obtained both in water and 50% dioxane–water are given in Table II and Fig. 4.

TABLE I

HYDROLYSIS RATES OF COMPOUNDS I–III

20°, ionic strength 0.1 *M*

Compound	I	II	III	II	
*p*H	k_{obsd}, hr.$^{-1}$	k_{obsd}, hr.$^{-1}$	k_{obsd}, hr.$^{-1}$	*p*H	k_{obsd}, hr.$^{-1}$
	Solvent, H_2O			Solvent, 50% dioxane[a]	
1.10	1.53	1.53	2.40	1.0 *M* HCl	0.510
2.55	0.500	0.552	0.677	0.40 *M* HCl	.212
3.20	.389	.404	.440	1.18	.0894
4.20	.358	.374	.374	2.29	.0690
5.10	.345	.381	.367	3.40	.149
6.23	. . .	.289	.279	4.20	.207
6.35	.291	. . .	. . .	5.93	.209
6.91	. . .	. . .	.212	7.22	.222
6.99	. . .	.137	. . .	8.37	.149
7.12	.166	. . .	. . .	9.41	.0207
7.64	. . .	.0517	.0631		
8.09	.0255	.0211	. . .		

[a] Prepared by mixing equal volumes of H_2O and dioxane.

Discussion

An analysis of the observed dependency of the rate on the *p*H of the medium must of necessity take into consideration the hydrolysis of the various

TABLE II

REACTION RATES, HEATS AND ENTROPIES OF ACTIVATION,[a] COMPOUND II

Solvent	pH	t, °C.	$k_{\text{obsd.}}$, hr.$^{-1}$	$\Delta H^{\ddagger}$, kcal./mole[a]	$\Delta S^{\ddagger}$, e.u.[a]
H_2O	5.10	24.98	0.688		
		20.00	.381	19.8	− 6.3
		14.96	.207		
50% dioxane	6.56	30.01	.727		
		24.98	.404	20.8	− 6.9
		20.00	.216		
50% dioxane	2.28	20.00	.069		
		24.96	.130		
		30.01	.232	20.4	−12.6
		37.14	.456		

[a] Calculated from the Eyring equation; see S. Glasstone, K. T. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941.

ionic species present at the particular pH. Since the compounds are stable in alkali, the completely ionized form of the phosphonamide is stable. The relevant ionic forms which exist in the range of pH 2–8 and may break down to the parent amine and phosphoric acid are the neutral moiety $[M_0]$ and the monoionic form $[M_1]$. At high acidities, the positively charged form $[M]^+$ must be considered.

$$\begin{array}{ccc} [\mathrm{RNH_2{-}PO_3H_2}]^+ & \left[\begin{array}{c}\text{(a) }\mathrm{RNH{-}PO_3H_2}\\ \text{and/or}\\ \text{(b) }\mathrm{RNH_2{}^+{-}PO_3H^-}\end{array}\right] & [\mathrm{RNH{-}PO_3H}]^- \\ [\mathrm{M^+}] & [\mathrm{M_0}] & [\mathrm{M_1}] \end{array}$$

R = p-phenyl, p-chlorophenyl, p-methoxyphenyl

The shape of the pH *vs.* hydrolysis rate curve and the acid catalysis encountered at high acidities are accounted for adequately by rate equation equivalent to that given for the hydrolysis of simple phosphoric acid esters.[9–13b]

$$k_{\text{obsd}} = k_{\text{H}}[\text{H}^+][M_0] + k_0[M_0] + k_1[M_1] \qquad (1)$$

where M_0 and M_1 stand for the mole fraction[14] of the particular ionic species and k_{H}, k_0 and k_1 are the specific rate constants associated with the particular ionic species. The first term in the above expression is kinetically indistinguishable from the decomposition of the singly positive charged cation $[M^+]$.[14] The invariance of the rate over the pH range 3.5–5.5 both in water and dioxane mixture in conjunction with the fall off in rate at higher pH's indicates that the compound exists *ca.* 100% in the monoionic $[M_1]$ form in this pH range. The specific rate constant (k_1) may then be evaluated from the observed rate in the flat portion of the curve. The third ionization constant (pK_3)[14] in water may be obtained from the curve by noting the pH at which the observed rate is one-half that in the flat region. They fall between pH 6.8 and 7.0. The increase in the rate of hydrolysis observed in water from pH 3.5 to *ca.* 2 is very much smaller than the concomitant change in hydrogen ion concentration. This increase in rate cannot be attributed to acid catalysis alone (see below), but rather indicates that in the pH region (*ca.* 3.5–2) the un-ionized species $[M_0]$ is building up and the specific rate of hydrolysis (k_0) associated with it is larger than that (k_1) associated with a singly negatively charged species $[M_1]$. (The reversal observed in dioxane ($k_1 > k_0$) will be discussed subsequently.) The instability of the compounds at 20° in the acid region precluded the determination of the second ionization constant (K_2) necessary for the evaluation of k_0. The acid-catalyzed hydrolysis could be studied at 0°. The deduction that k_0 is larger than k_1 was verified by an evaluation of these two constants as well as k_{H} in the following manner. The variation in rate of hydrolysis of N-(p-chlorophenyl)-amidophosphoric acid (II) with molarity of HCl at 0° and μ = 2.0 M was shown to follow a straight line above molarity = 0.45 (see Fig. 3). The equation describing this dependence was found to be $k_{\text{obsd}} = k_{\text{H}}[\text{H}^+] + k_0$.[15] At high acidities it may be presumed that the amidophosphoric acid exists almost exclusively in the un-ionized form.[15] The two initial points of the graph (see Fig. 3) fall off the line, since at the lower acidities the compound exists to some extent

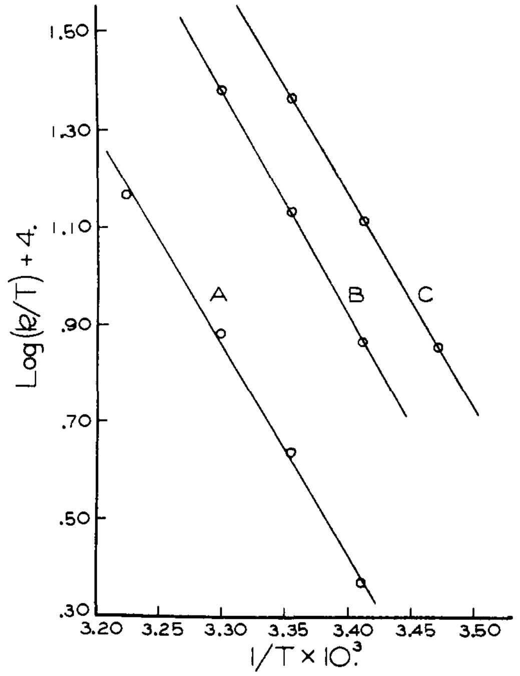

Fig. 4.—Plot of log k/T *vs.* $1/T$ for N-(p-chlorophenyl)-amidophosphoric acid, where k is the observed rate constant; A and B refer to rates obtained in 50% dioxane–water mixture at pH 2.28 and 6.56, respectively; C refers to rate obtained in water at pH 5.10.

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(9) M. C. Bailly, *Bull. soc. chim.*, [5] **9**, 421 (1942).

(10) A. Desjobert, *Compt. rend.*, **224**, 575 (1947); *Bull. scc. chim.*,]5] **14**, 809 (1947).

(11) W. W. Butcher and F. H. Westheimer, THIS JOURNAL, **77**, 2420 (1955); J. Kumamoto and F. H. Westheimer, *ibid.*, **77**, 2515 (1955).

(12) P. W. G. Bernard, C. A. Bunton, D. R. Llellyn, K. G. Oldham, B. L. Silver and C. A. Vernon, *Chemistry & Industry*, 760 (1955).

(13) (a) J. D. Chanley, M. Gindler and H. Sobotka, THIS JOURNAL, **74**, 4347 (1952); J. D. Chanley and E. M. Gindler, *ibid.*, **75**, 4035 (1953); J. D. Chanley and E. Feageson, *ibid.*, **77**, 4002 (1955); (b) S. S. Stein and D. E. Koshland, Jr., *Arch. Biochem. and Biophys.*, **39**, 229 (1952).

(14) The first ionization constant K_1 being defined as that related to the dissociation of the positively charged form $[\mathrm{RNH_2{-}PO_3H_2}]^+$, and $k_{\text{H}}[\text{H}^+][M_0] = k_{\text{H}}K_1[M^+]$; mole fraction [M] = [concn. of particular ionic species]/[total concn. of amidophosphate].

(15) Actually $k_{\text{obsd.}} = k_{\text{H}}[\text{H}^+][M_0] + k_0[M_0]$; however as Fig. 3 indicates from 0.4–2 M HCl, $M_0 \simeq 1$.

as the monoionic species. Extrapolation of the straight line portion of the curve gives as intercept 0.23 hr.$^{-1}$ for the specific rate constant, k_0, for the hydrolysis of the neutral species, while the slope of the line gives k_H = 0.88 l./mole hr. The observed rate of hydrolysis at pH *ca.* 5 at 0° (μ = 2.0 M) was found to be 0.034 hr.$^{-1}$. At this pH the compound exists 100% in the monoionic form and consequently the observed rate is identical with the specific rate constant (k_1). The results are summarized in Table II.

A reasonable approximation of the second ionization constant, K_2, may now be evaluated. The observed rate (0°) in 0.125 M HCl was found to be 0.263 hr.$^{-1}$. Substitution into equation 1 then gives

$$0.263 = 0.88(0.125)M_0 + (0.23)M_0 + (0.03)M_1$$

the last term in the above equation may be neglected, as it is insignificant compared to the sum of the first two terms; M_0 then becomes 0.83 and pK_2 = *ca.* 1.6. Employing this value for pK_2, M_0 and M_1 were evaluated[13] at pH 2.41 and the theoretical rate of hydrolysis deduced by substitution into equation 1 was 0.056 hr.$^{-1}$. The found value (k_{obsd}) was 0.054 hr.$^{-1}$. This excellent agreement indicates that the derived value for the second ionization constant, as well as k_0 and k_H, are reasonable.

The difference in the shapes of pH *vs.* hydrolysis rate curves for the water (no minimum) and water–dioxane mixture (minimum) results from the fact that in the latter solvent the specific rate constant (k_0) associated with the neutral species [M_0] is smaller than that (k_1) associated with the singly charged species [M_1], while the reverse is true in water. (The slight shift in the observed pH's is a consequence of the change in solvent and has no relevance in these considerations.) This dioxane effect may conceivably be accounted for by postulating that since the charge and presumably the mechanism of hydrolysis of the two species differ, the relative diminution in rates of hydrolysis of these species would so differ in passing from water to the water–dioxane mixture as to make $k_1 > k_0$. However, the authors believe it not to be fortuitous that the pH *vs.* hydrolysis rate curve of the closely related aromatic phosphates[13] in water, is completely analogous to the amidophosphate II in the dioxane–water mixture. While the aforementioned factors (charge, mechanism) may contribute to the dioxane effect, it appears more likely and consistent to presuppose that both the dioxane effect and the difference observed in the hydrolysis in water of amidophosphates ($k_0 > k_1$) and phosphate esters ($k_1 > k_0$) resides primarily in the composition of the neutral species. The neutral form of amidophosphates may exist in two modifications: (a) the dipole (zwitterion) and (b) the non-dipole (non-zwitterion). Such is not the case for aromatic phosphate esters. The preponderance of the nonpolar form over that of the dipolar form in water is indicated by the low pK_2 (*ca.* 1.6)[16]; pK_2 is, however, significantly larger than that of phenyl phosphate (pK_1 1).[13] It may be inferred that a small but significant amount of dipolar ion exists in water. The faster rate of hydrolysis ($k_0 > k_1$) of the neutral species in water may then be attributed to the extremely rapid hydrolysis of the zwitterion. In the dioxane–water solvent the formation of the zwitterion is repressed.[16] The hydrolysis of the non-zwitterion form is even slower than that of the monoionic species [M_1]. The relative concentrations of the charged and uncharged form of the neutral species could not be ascertained, and consequently the particular specific rate constants associated with each of these forms could not be evaluated (see Table III).

TABLE III

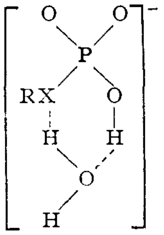
SPECIFIC RATE CONSTANTS

Compound	Solvent	t, °C.	k_1, hr.$^{-1}$	k_0, hr.$^{-1}$	k_H, l./mole hr
I	H_2O	20	0.350	>0.350	..
II	H_2O	20	.377	> .377	..
III	H_2O	20	.370	> .370	..
II[a]	H_2O	0	.034	.23	0.88
II	50% dioxane	20	.22	< .055	..

[a] For runs at 0° ionic strength μ = 2.0 M; all others at μ = 0.1 M.

The acid catalysis observed at high acidity is common to both aromatic amido-phosphates and aliphatic phosphoric acid esters.[12] Although acid catalysis has not been demonstrated for aromatic phosphoric acid esters[12] in water up to 7 M in perchloric acid, in a medium of intrinsically higher acidity (HCl–dioxane) the hydrolysis of aromatic phosphates is in fact acid catalyzed.[17] The acid catalysis encountered with aromatic amidophosphates is obviously connected with the protonation of the nitrogen. The relatively greater ease for this to occur with nitrogen as compared to oxygen, adequately accounts for the experimental findings.

The mechanism of hydrolysis of the monionic form of phosphoric acid esters has received a great deal of attention.[11–13] It would be reasonable to presuppose that both the latter and the corresponding form of amidophosphoric acid are hydrolyzed by the same mechanism. It has been shown that the hydrolysis of trialkyl phosphates is catalyzed by hydroxyl ion, while triamidophosphates are stable in alkali up to 130°.[18] If the hydrolysis of the monoionic form in both phosphoric acid esters and monoamidophosphates proceeds by way of attack of the water molecule on the phosphorus, then one might expect that phenyl phosphate would hydrolyze faster than N-(phenyl)-amido-



X = NH or O
R = C_6H_5, p-ClC_6H_5, or p-$CH_3OC_6H_5$

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[16] E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides as Ions and Dipolar Ions," Am. Chem. Soc. Monograph Series, Reinhold Publishing Corp., New York, N. Y., 1943, pp. 96–115.

[17] J. D. Chanley, unpublished observations.

[18] D. F. Heath and P. Casapieri, *Trans. Faraday Soc.*, **47**, 1093 (1950); D. F. Heath, *J. Chem. Soc.*, 3796 (1956); 3804 (1956); *cf.* H. K. Hall, *J. Org. Chem.*, **21**, 248 (1956).

phosphoric acid; actually the latter, at 20°, hydrolyzes *ca.* 10^3 as fast as phenyl phosphate.[13] The cyclic mechanism of Westheimer,[11] which postulates a cyclic intermediate of the following nature is particularly attractive as it better accommodates the facts in both the hydrolysis of phosphoric acid esters and amidophosphoric acid. The much faster rates of hydrolysis observed for the monoionic species of amidophosphates as compared to the comparable ionic species of phosphate esters is probably associated with the basicity of nitrogen. The view that the hydrolysis of the monoionic species proceeds primarily by way of an internal hydrogen transfer does not appear as probable as the cyclic intermediate mechanism. If an internal proton transfer were the principal pathway of hydrolysis, then the reactive intermediate would be in fact the zwitterionic form of the monoionic species. It might be anticipated that the reduction in rate of hydrolysis in the dioxane-water mixture would be as pronounced as that observed at the lower *p*H's Actually the rate is lowered but two-fold. The invariance of the rate of hydrolysis of the phosphonamides with substitution (Cl or OCH_3) is at least consistent with the cyclic mechanism.

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Derivatives of the Hydrogen Cyanide Tetramer: Structure and Chemistry[1]

BY P. S. ROBERTSON[2] AND J. VAUGHAN

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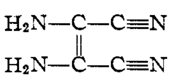
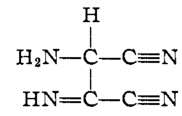
Further physical and some chemical evidence is adduced for the diaminomaleonitrile structure for the hydrogen cyanide tetramer and its acetyl, benzoyl and azomethine derivatives. With the last-named derivatives, it appears that the displacement of one aldehyde by another is related to electron deficiency at the carbonyl carbon atom of the aldehydes concerned.

The structure of the hydrogen cyanide tetramer had been in doubt until the recent work of Webb, *et al.*,[3] and Bredereck, *et al.*,[4] strongly suggested that the tetramer exists as diaminomaleonitrile (I). Such a structure was originally proposed by Grischkevitsch-Trochimovski[5] to account for the relative ease with which derivatives such as 2,3-dicyanopyrazine and 4,5-dicyano-1,2,3-triazole were formed by condensation with glyoxal and nitrous acid, respectively. These cyclic derivatives were analogous with those formed by *o*-phenylenediamine.



$$\begin{array}{l} H_2N-C-C\equiv N \\ \qquad\ \| \\ H_2N-C-C\equiv N \end{array}$$

I



$$\begin{array}{l} \qquad\quad H \\ \qquad\quad | \\ H_2N-C-C\equiv N \\ \qquad\quad | \\ HN=C-C\equiv N \end{array}$$

II

Hinkel, *et al.*,[6] proposed structure II, aminoiminosuccinonitrile, after reconsideration of the chemistry of the tetramer. The existence of an asymmetric carbon atom in a salt of the tetramer was subsequently established by Hinkel and Watkins.[7] By a process of partial solution they isolated a strongly levorotatory diastereoisomeride, using *d*-camphorsulfonic acid.

Webb[3] demonstrated the absence of a C–H bond in the crystalline tetramer by comparison of its infrared absorption spectrum with that of succinonitrile. From an examination of the ultraviolet absorption spectra they concluded that the tetramer also exists in solution as diaminomaleonitrile (I) and measurement of the dipole moment supported a *cis* configuration for the compound.

Bredereck[4,8] further investigated the chemistry of the tetramer and examined the infrared absorption of the tetramer, and of its mono-, di- and triacetyl derivatives. They confirmed structure I for the solid tetramer and showed that acetyl derivatives also have structures based on the diamino formulation. The infrared absorption due to the C=C bond of the tetramer corresponded to a *cis* formulation.

Thus, the combination of Hinkel's resolution experiments and the later work of the above investigators might be taken to indicate that in solution the tetramer displays tautomerism, with the equilibrium greatly favoring structure I.

In the studies reported here, further details of the chemical behavior of the tetramer are presented and, by measurement of the ultraviolet absorption of a number of derivatives, evidence has been obtained supporting the existence of these compounds in solution as derivatives of structure I.

Results and Discussion

The Tetramer.—As in the work of Webb, *et al.*,[3] the ultraviolet absorption evidence was considered in the light of the spectra to be expected from structures I and II. The wave lengths of maximum absorption (λ_{max}) of conjugated diene systems are usually significantly lower than those of conjugated trienes, which usually display a λ_{max} in the region of 2600 Å. The observed λ_{max} of the tetramer is 2980 Å. (in methanol; see Fig. 1); the presence of two bathochromic amino groups has extended the resonance of the conjugated system and has thus further increased λ_{max}.

Acetyl and Benzoyl Derivatives.—Bredereck,

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[1] From thesis of P. S. Robertson, University of New Zealand, 1953.

[2] The Dairy Research Institute (N.Z.), Massey College P. O., Palmerston North, New Zealand.

[3] R. L. Webb, S. Frank and W. C. Schneider, THIS JOURNAL, **77**, 3491 (1955).

[4] H. Bredereck, G. Schmötzer and H. J. Becher, *Ann.*, **600**, 87 (1956).

[5] E. Grischkevitsch-Trochimovski, *Roczniki Chem.*, **8**, 165 (1928).

[6] L. E. Hinkel, G. O. Richards and O. Thomas, *J. Chem. Soc.*, 1432 (1937).

[7] L. E. Hinkel and T. I. Watkins, *ibid.*, 1206 (1940).

[8] H. Bredereck and G. Schmötzer, *Ann.*, **600**, 95 (1956).