rato]ytterbium(III) two well-separated signals for the SCH_3 group. The more downfield shifted signal could be assigned to the R_C,S_S enantiomer, the other one to the S_C,S_S compound. The same phenomenon was observed with a racemic mixture of **10**. According to this method, compounds **9** and **10** were found to be optically pure. With the methyl sulfoxides **7** and **8**, no chemical shift difference could be observed in the presence of the shift reagent used or with the Pr or Eu analogues. ^{1}H NMR ($CDCl_3/CD_2Cl_2$): **7** δ 2.64 (s, 3 H, S(O)CH_3), 2.84 (d, 2 H, CH_2S(O)), 3.30-3.71 (m, 3 H, $CHCH_2O$); **8** δ 2.63 (s, 3 H, S(O)CH_3) 2.55-3.02 (m, 2 H, CH_2S(O)), 3.30-3.80 (m, 3 H, $CHCH_2O$); **9** δ 2.33 (s, 3 H, SCH_3), 2.87 and 3.05 (8 lines, AB part of ABX spectrum, 2 H, J_{AB} = 13 Hz, J_{AX} = 5 Hz, J_{BX} = 6 Hz, $CHCH_2$S(O)), 3.33-3.71 (m, 3 H, $CHCH_2O$), 3.72 and 3.86 (AB spectrum, 2 H, J = 13.5 Hz, S(O)CH_2S); **10** δ 2.34 (s, 3H, SCH_3), 2.80-3.00 (AB part of ABX spectrum, 2H, $CHCH_2$S(O)), 3.33-3.71 (m, 3H, $CHCH_2O$), 3.73 and 3.81 (AB spectrum, 2H, J = 13.8 Hz, S(O)CH_2S).

Compounds 7 and 8 from 6 and 5, Respectively. The N-protected alcohol **5** or **6**[15,33] were treated with sodium in liquid ammonia as described for the preparation of the O-protected derivatives of **7-10**. When the reaction was complete and no sodium consumed anymore, slightly more than 1 equiv of ammonium chloride was added, after which the solvent was evaporated. The residue was extracted twice with acetonitrile, and subsequently the solvent was evaporated. The amino alcohols **8** and **7**, both obtained in 80% yield, were identical (TLC, ^{1}H NMR) with those obtained above.

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Supplementary Material Available: Tables of crystal data, scattering factors, bond distances and bond angles, positional and thermal parameters, and calculated and observed structure factor amplitudes (17 pages). Ordering information is given on any current masthead page.

Reactivity and Mechanism of Hydrolysis of Phosphonamides

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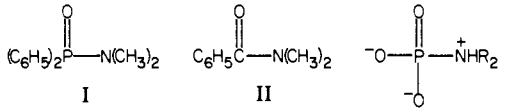
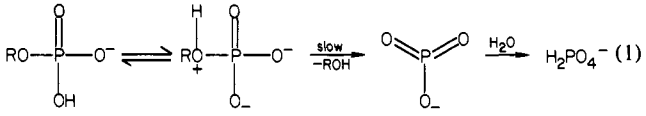
Abstract: The rates of hydrolysis of three phosphonamides, *N,N*-dimethylphenylphosphonamide (XII), *N*-(phenylphosphonyl)pyrrolidine (XIII), and *N*-(phenylphosphonyl)morpholine (XIV), have been investigated. There is first-order dependence on acidity in the pH range 4-7 with a pH independent region at low pHs, consistent with saturation due to complete formation of the neutral amide. The specific rate constant (k_2) and the acidity constant (K_a) were obtained from the dependence of pseudo-first-order rate constants on [H$^+$]: k_2 is 1.27 × 10^{-2} s^{-1} and 1.42 × 10^{-3} s^{-1} and pK_a is 4.8 and 5.3 for XII and XIII, respectively. The small value of the acidity constants is consistent with predominant N-protonation. The activation parameters for XII are $\Delta H^{\ddagger}$ = 11.1 kcal/mol, $\Delta G^{\ddagger}$ = 20.35 kcal/mol, and $\Delta S^{\ddagger}$ = -31 eu. Solvent and salt effects on the rate of hydrolysis of XII are insignificant. The solvent isotope effect, $k_2(H_2O)/k_2(D_2O)$, is 1.2 and $K_a(H_2O)/K_a(D_2O)$ is 3.2. Fluoride ion catalyzed the rate of reaction of XII. The Brönsted β value is about -1, implying rate-determining breakage of the P-N bond. The results appear to be most consistent with an $S_N2(P)$ mechanism. The reactivity of phosphorus amides is discussed in terms of their structure.

Phosphorus amides display interesting reactivity. Diphenylphosphinamide (I) hydrolysis 10^5 times faster than its carbon analogue, benzamide (II), under acidic conditions.[1] Yet their alkaline hydrolysis rates are almost identical, which indicates that they are equally susceptible to nucleophilic reaction. We have suggested[1] that the acid lability of phosphinamides is due to the position of protonation: N-protonation in contrast to O-protonation in carboxylic amides[2] would result in a substantial difference in hydrolytic reactivity.



I II III

The structural similarity between phosphoramidate monoanions (III) and phosphate monoester monoanions ($^-HO_3POR$) (IV) prompted several investigators to look into the amide hydrolytic mechanisms in the hope of clarifying the dynamics of metaphosphate-generating systems.[3-11] A zwitterionic intermediate (V) is throught to be involved in the hydrolysis of monoesters: and there is evidence for a mechanism[12,13] (eq 1) involving the



IV V VI

highly reactive metaphosphate ion (VI) as an intermediate. The

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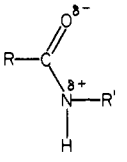
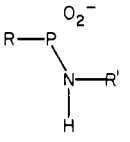
first detailed work on the phosphoramidate system was done by Chanley and Feageson.[3] They proposed a bimolecular mechanism. nucleophilic attack by water, for the hydrolysis of the monoanionic species (V). Their conclusion was based on product partitioning: phosphoramidate demonstrated a greater selectivity toward the more nucleophilic reagent methanol than *p*-nitrophenyl phosphate, a fact that is consistent with bimolecular attack on the former. The research of Jencks and Gilchrist[4,5] with Benkovic and Sampson[8] indicate that the transition state is "loose" with a large extent of bondbreaking and little bondmaking so that one can view the mechanism of hydrolysis of phosphoramide monoanions as partially unimolecular with solvent participation in the transition state. We found a similar picture in the acid-catalyzed hydrolysis of phosphinanilides.[1b] In phosphoroguanidines, we found that reaction appears to proceed by a phosphorus displacement mechanism which appears to be the most completely unimolecular yet found, presumably because of the excellent leaving group—a guanidinium ion.[11]

The special chemistry of phosphorus amides appears related to known and possible functions of P–N compounds in biological chemistry. In particular. a logical molecular mimic for carboxylic amides (including peptides) is the corresponding phosphonamide (VII). But the past research raises the question: would phos-



carboxylic amide



phosphonamide. VII

phonamides be stable? Because of our interest in the P–N bond, we have investigated phosphonamide reactivity and the mechanism of hydrolysis.

Experimental Section

All starting reagents and solvents were purified and/or distilled before use. Water was deionized and preboiled to free it from dissolved gases. D_2O (99.8%) was purchased from Aldrich Chemical Inc. Microanalyses were performed at Baron Consulting Co., Orange. CT. and at Spang Microanalytical Laboratory. Ann Arbor. MI. UV spectra were taken on a Cary 14 scanning spectrophotometer equipped with a thermostated sample compartment through which water circulates from a constant-temperature bath. The absorbance readings were recorded on a Leeds and Northrop Speedomax W recorder. ^1H NMR spectra were taken with use of a Varian A-60 spectrometer. ^{13}C NMR spectra were taken with the use of a Varian XL-200 spectrometer. Chemical shifts are reported with respect to a Me_4Si internal standard. When D_2O was used as solvent. external Me_4Si reference was used. Measurements of pH were performed on a Radiometer TTTlc pH meter equipped with a Radiometer combination electrode. All NMR data appear in Table I.

The starting material for our syntheses was $C_6H_5P(O)Cl_2$. Oxygen gas was bubbled through a solution of freshly distilled phenyldichlorophosphine (17.9 gm or 0.1 mol) in 50 mL of dry benzene. Some refluxing took place as a result of the exothermic oxidation reaction. When the heat subsided. the solvent was evaporated. The product $C_6H_5P(O)Cl_2$ was distilled as a colorless liquid at 95 °C (0.1 mm) (lit.[14] 104 °C (4 mm)).

***N,N*-Dimethylphenylphosphonamidochloridate ($C_6H_5ClP(O)NMe_2$) (VIII).** Liquified dimethylamine (4.5 mg or 0.1 mol) was allowed. upon warming. to bubble through 19.5 g (0.1 mol) of phenylphosphonic dichloride and 11 g of freshly distilled triethylamine in 100 mL of dichloromethane. The reaction mixture was stirred during the reaction with a magnetic stirrer and kept in an ice-water bath. Cloudiness started to appear promptly due to the formation of triethylammonium chloride. When the reaction was over. most of the solvent was evaporated: more precipitate of ammonium salt formed. Dry ether (50 mL) was added to the reaction mixture. All of the ammonium salt precipitated and was removed by filtration. The product. in the ether layer. was distilled at 90 °C (0.01 mm). 50% yield: the NMR spectrum is in Table I.

***N*-(Phenylchlorophosphinyl)pyrrolidine ($C_6H_5ClP(O)N(CH_2)_4$) (IX).** This compound was synthesized in a fashion similar to that of the *N,N*-dimethyl analogue described above. Freshly distilled pyrrolidine was used. The yield of amide was near 75%. although some decomposition took place upon distillation: bp 138 °C (0.002 mm).

***N*-(Phenylchlorophosphinyl)morpholine ($C_6H_5ClP(O)N(CH_2)_4O$) (X).** This compound was synthesized in a fashion similar to that of the *N,N*-dimethyl analogue. However. after the final evaporation of the ether solvent. a white precipitate appeared: mp 89–95 °C. yield 80% (NMR in Table I). The chloride group was confirmed by adding $AgNO_3$ solution.

Methyl *N,N*-(Dimethy)phenylphosphonamidate ($(C_6H_5P(O)OCH_3)N(CH_3)_2$) (XI). A solution of 3.2 g (0.1 mol) of dry methanol and 15 g of freshly distilled triethylamine in 100 mL of anhydrous ether was added dropwise to a stirred solution of 19.5 g (0.1 mol) of phenylphosphonic dichloride in 100 mL of anhydrous ether. The reaction mixture was kept in an ice bath. A white precipitate of triethylammonium chloride appeared instantaneously. When the reaction was over. the precipitate was filtered off. The filtrate. containing $C_6H_5P(O)(Cl)OCH_3$. was used without further treatment because attempts to distill the product resulted in polymerization. A similar observation was described by Hersman and Audrieth.[15]

Dry dimethylamine gas was bubbled through a solution of methyl phosphonochloridate in anhydrous ether at 0 °C. Dimethylammonium chloride precipitated instantaneously. The reaction was judged complete when dimethylamine began to flow out of the exit tube from the reaction flask. The precipitate was filtered off. the solvent evaporated. and the product was distilled in two fractions: (i) bp 97 °C (0.01 mm): (ii) bp 105 °C (0.01 mm). The distillation was hampered by some accompanying decomposition. The yield was about 90%. Both fractions contained some diamide byproduct. Further distillation failed to get rid of the impurity. The product was finally obtained by chromatography on a silica gel column with use of acetone as eluant. A final distillation was used to remove possible impurities formed during the chromatography: bp 88–92 °C (0.2 mm) (NMR in Table I).

***N,N*-Dimethylphenylphosphonamide Tetramethylammonium Salt ($C_6H_5P(NMe_2)O_2^-{}^+NMe_4$) (XII).** Two methods were followed for the synthesis of this compound. (a) In a sealed ampoule. 1 g of methyl *N,N*-dimethylphenylphosphonamidate (XI) was reacted with a large excess of dimethylamine solution which was prepared by bubbling dimethylamine gas into water. The reaction mixture was kept at 95 °C for 1 h. cooled. and then the water removed at reduced pressure. The NMR spectrum of the crude dry product showed the presence of tri- and tetramethylammonium cations. The products were dissolved in an aqueous solution containing an equivalent quantity of tetramethylammonium hydroxide. Evaporation to dryness at reduced pressure without heating yielded the desired product. An NMR spectrum demonstrated that the only cation present was tetramethylammonium ion. The final product was crystallized from acetone–ether. yielding a white. powdery solid: mp 247 °C dec. No mass spectrometric analysis could be obtained because of its extremely low volatility.

(b) To a stirred solution of 50 mL of 1 M tetramethylammonium hydroxide was added slowly 0.025 mol of *N,N*-dimethylphosphonamidochloridate. The pH of the reaction was monitored by a pH meter and kept above pH 8 to avoid hydrolysis of the product. The reaction mixture heated up spontaneously as the reaction proceeded. The addition was stopped when the pH reached 8. The solvent was evaporated with no heating. under reduced pressure. The NMR spectrum of the crude product showed. as expected. the presence of equivalent amounts of tetramethylammonium chloride and the desired product. Purification was accomplished through multiple extractions of the phosphonamide salt with dry acetone. Traces of acidic impurities. which might have catalyzed cleavage of the phosphonamide. were removed by passing the acetone through an activated alumina column. The extracts were collected and the solvent evaporated: the product precipitated on addition of anhydrous ether. The total yield was close to 30%. The NMR spectrum (Table I) indicated the presence of the pure compound. The pyrrolidine amide. *N*-(phenylphosphonyl)pyrrolidine tetramethylammonium salt ($C_6H_5PO_2^-)N(CH_2)_4{}^+N(CH_3)_4$) (XIII). and the morpholine amide. *N*-(phenylphosphonyl)morpholine tetramethylammonium salt XIV were both synthesized by method b.

The structures of these amides are demonstrated partly from the NMR spectra (Table I). which display the characteristic features of the proposed structures. Upon hydrolysis. the multiplicity due to the P–N–C–H coupling disappears. For example. the doublet due to the P–N–CH_3 protons. in the dimethylamide (XII). disappears and a new singlet appears due to the dimethylammonium salt which is produced. The ^{13}C NMR spectra show the appropriate number of peaks in the appropriate regions.[16] The aromatic region shows five peaks presumably because of

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(15) Hersman. M. F.; Audrieth. L. *J. Org. Chem.* **1958**, *23*, 1889.

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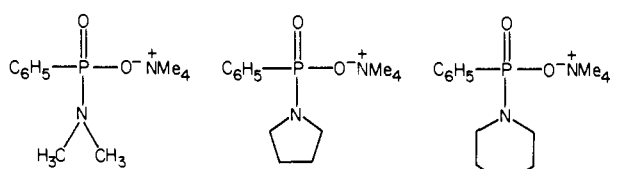
a large one-bond coupling to ^{31}P.[16] The UV spectra of the hydrolysis products of the three compounds are identical with that of phenylphosphonic acid. The kinetic behavior and the relative reactivities of the studied compounds are in accordance with the proposed structures. For example, the presence of an ionizable moiety which appears to be the amine group, as indicated by the relatively high pK_a's (4.8 and 5.3 for the dimethylamine and the pyrrolidine compounds, respectively) agrees with the expected behavior of phosphorus amides.

Finally, the values of the pK_a's (see Results) of the dimethylamide and the pyrrolidine amide indicate the involvement of a P–N linkage in the above compounds. The pK_a values and their trends will be considered more fully in the discussion. Analyses of these compounds were repeatedly low in carbon and nitrogen. We believe this is mostly due to the lability of the phosphorus amide probably caused by the high hygroscopicity and basicity of the amide anion in the solvents in which it was recrystallized. The analyses fit with a small amount of contamination by $(C_6H_5PO_3H)N(CH_3)_4$ and water.

All kinetic measurements in this study were done spectrophotometrically by recording the decrease in absorbance at 240 nm due to the disappearance of the starting material. The identity of the reaction taking place and of the products was determined by NMR. The pH of buffers was checked at the buffer concentration of the reaction. In a typical run, 3 mL of the buffered solution was pipetted into a 1-cm quartz curvette and allowed to thermally equilibrate by keeping it in the sample compartment which was thermostated at the desired temperature. The reaction was initiated by injecting 20–30 μL of the substrate into the reaction solution. The substrate concentration was typically 10^{-3}–10^{-4} M. The observed first-order rate constants (k_{obsd}) were obtained as the negative slope of the plots of ln $(A_t - A_\infty)$ against time. A_t is absorbance at time t and A_∞ is absorbance at infinite time, measured after 10 half-lives. In all cases, linear plots were obtained, to at least 85% reaction with typical correlation coefficients of 0.999. Even the highest rate constants were reproducible within 5%.[17] In the tables, a ±0 values means an insignificant standard deviation.

Results

The rate constants for the hydrolysis of the three phenylphosphonamides XII–XIV in water were determined spectro-



XII XIII XIV

photometrically by following the disappearance of the reactants at 240 nm and 29.5 °C. The logarithmic plots for the dependence of the rate on pH appear in Figure 1. The slopes of the linear portions of the curves for XII–XIV are near 1.0, signifying a first-order dependence on acidity. At pK <5, the rates of compounds XII and XIII no longer are linear in $[H^+]$, but, rather, there is clear indication of a saturation effect which is consistent with rate-determining reaction of the protonated amide, AH (eq 2). At pHs <5, most of the substrate is in the neutral form, AH,

$$A^- + H^+ \underset{K}{\rightleftharpoons} AH \xrightarrow{k_2} \text{products} \qquad (2)$$

so that further increase in the acid concentration cannot cause proportional increases in the rate. At high pH, the neutral species is the minor component and the overall rate is directly proportional to the acid concentration. The observed rate at any pH is given in eq 3 where $A_t = [A^-] + [HA]$ and $K_a = [H^+][A^-]/[HA]$.

$$-dA/dt = k_{obsd}A_t = k_2[HA] = k_2[A_t][H^+]/([H^+] + K_a) \qquad (3)$$

At the higher pHs, $[H^+] \ll K_a$, so eq 3 simplifies to eq 4,

$$k_{obsd} = k_2[H^+]/K_a \qquad (4)$$

consistent with the linear dependence of log k on pH (Figure 1). At low pH, $[H^+]$ is comparable to K_a, so eq 3 in full form must

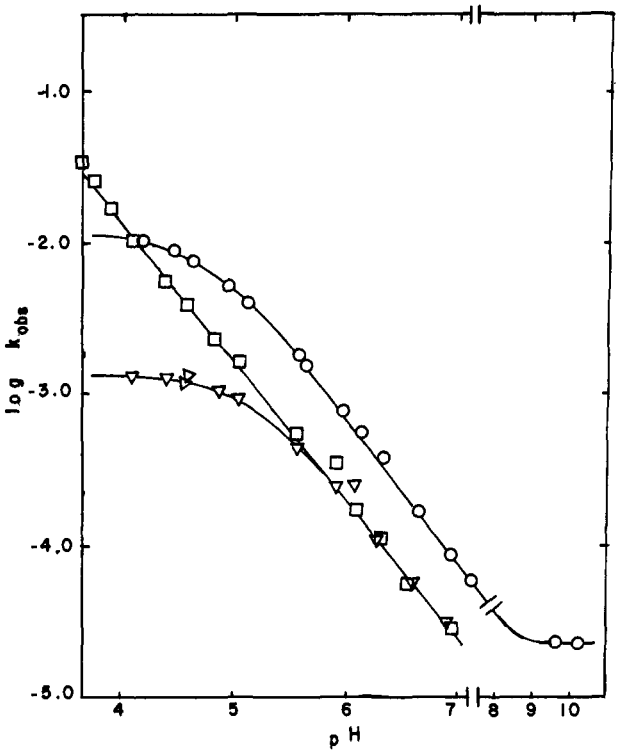


Figure 1. Dependence on pH of the rate of hydrolysis of phenylphosphonamides: *N,N*-dimethyl- (○), pyrrolidine- (△), and morpholine- (□) in 0.4 M acetate buffers at 29.5 °C.

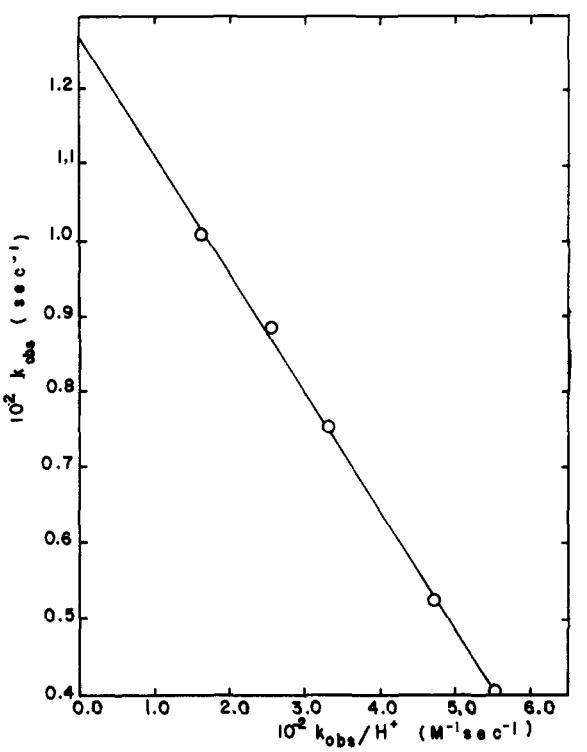


Figure 2. Plot of k_{obsd} vs. k_{obsd}/H^+ for the hydrolysis of *N,N*-dimethylphenylphosphonamide (XII) in 0.4 M acetate buffer at 29.5 °C. The slope is 1.55×10^{-5} M and intercept is 1.27×10^{-2} s^{-1}.

be used: both k_2 and K_a were obtained from the dependence of k_{obsd} on $[H^+]$ by a rearranged form of eq 3 (eq 5). Therefore,

$$k_{obsd} = k_2 - K_a(k_{obsd}/[H^+]) \qquad (5)$$

the equilibrium constant, K_a, can be obtained from the negative slope of the plot of k_{obsd} vs. $k_{obsd}/[H^+]$, and the specific hydrolysis constant, k_2, is the intercept of such a plot. The graph for compound XII appears in Figure 2. The data for XIII yields a similar

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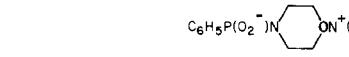
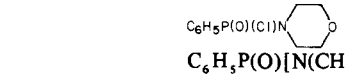
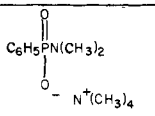
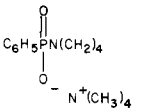
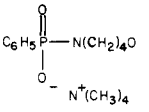
Table I. NMR Chemical Shifts and Coupling Constants

(a) ^{1}H NMR[a]

compd (solvent)	δ (J) C_6H_5	OCH_3	$N(CH_3)_2$	NCH_2	$NCCH_2$	$N(CH_3)_4$
$C_6H_5P(O)(Cl)N(CH_3)_2$ ($CDCl_3$)	7.6 m		2.6 d (15.5)			
$C_6H_5P(O)(Cl)OCH_3$ ($CDCl_3$)	7.6 m	3.8 d (12)				
$C_6H_5P(O)(OCH_3)N(CH_3)_2$ ($CDCl_3$)	7.4 m	3.7 d (11)	2.7 d (9.5)			
$C_6H_5P(O_2^-)N(CH_3)_2(CH_3)_4N^+$ (D_2O)	7.5 m		2.4 d (10)			3.1 s
$C_6H_5P(O_2^-)N(CH_2)_4N^+(CH_3)_4$ (D_2O)	7.4 m			2.9 m	1.6 m	3.1 s
$C_6H_5P(O)(Cl)N(CH_2)_4$ ($CDCl_3$)	7.6 m			3.2 m	1.9 m	
	7.5 m			2.9 m	3.6 m	3.1 s
	7.6 m			3.1 m	3.6 m	
$C_6H_5P(O)[N(CH_3)_2]_2$ (D_2O)	7.4 m		2.5 d (10)			

(b) ^{13}C NMR[b]

compd	δ P-C_6H_5	P-N-C-	P-N-C-C-	$N^+(CH_3)_4$
	128.5 128.9 130.8 131.1 131.5	37.1		55.8
	128.1 128.9 130.9 131.2 131.5	46.9	26.0	55.9
	128.1 128.9 130.7 131.0 131.4	44.9	67.6	55.7

[a] Spectra taken on Varian A-60, δ from Me_4Si: J values are given in Hz. [b] All spectra were taken in D_2O at 50.3 MHz on a Varian XL-200. Values reported are chemical shifts from Me_4Si.

plot. The values for the equilibrium constants (K_a) are 1.55×10^{-6} M ($pK_a = 4.8$) and 4.76×10^{-6} M ($pK_a = 5.3$), and the specific rate constants (k_2) are 1.27×10^{-2} s^{-1} and 0.142×10^{-2} s^{-1} for the *N,N*-dimethylphenylphosphonamide (XII) and the pyrrolidine amide (XIII), respectively (Table II).

The Brønsted β value[18] (eq 6) for the dependence of the rate

$$\log k = -\beta \log K_a + G_B \quad (6)$$

constant on the K_a of the leaving group was determined approximately. For XII and XIII, we can use the k_2 values that were determined and K_a values for dimethylamine and pyrrolidine. There are a number of pK_a's reported in the literature for these amines, but the best values appear to be 10.77 and 11.27, respectively.[19] The ΔpK_a of 0.50 is supported by the pK_a's found for XII and XIII, i.e., 4.8 and 5.3. Using eq 7, we find that β_2

$$\beta_2 = \Delta \log k_2 / \Delta pK_a(\text{amine leaving group}) \quad (7)$$

$\simeq -1.9$. Normally, the minimum value of β should be −1.0. This value may be a result of extensive bond breaking in the transition state combined with an additional effect (see below) and/or experimental error.

The data for the morpholine amide (XIV) give additional information about the value of β. The rate of the morpholine amide did not show saturation behavior within the pH range studied, and the rates were too fast for further investigation at lower pH values. Therefore, we cannot obtain K_a and k_2 for XIV. However, the effect of the leaving group on k_{obsd} is a combination of the effect on protonation and the effect on the rate of P–N bond breaking. The extent of protonation of the amides should increase with increasing basicity of the amine leaving groups in direct proportion. In fact, we find this to be true for XII and XIII because, as mentioned in the paragraph above, ΔpK_a(amides) = ΔpK_a(amines) = 0.50. We can define a β_a (eq 8) for extent of

$$\beta_a = \Delta pK_a(\text{amides}) / \Delta pK_a(\text{amine leaving group}) \quad (8)$$

protonation of the amides: $\beta_a = (5.3 - 4.8)/(11.27 - 10.77) \simeq 1.0$ for XII and XIII.

Examination of Figure 1 demonstrates that k_{obsd} for the morpholine and pyrrolidine amides define the same line in the region for which $k_{obsd} = k_2[H^+]/K_a$. We can therefore define a total dependence on basicity of the leaving group, β_t (eq 9), and

$$\beta_t = \Delta \log k_{obsd} / \Delta pK_a(\text{amine leaving group}) \quad (9)$$

Table II. Selected Rate Constants, K_a, and k_2 Values[a]

compd	pH	$10^3 k_{obsd}$,[b] s^{-1}	$10^2 k_2$, s^{-1}	$10^6 K_a$, M
XII	4.20	10.1	1.27	1.55
	6.34	0.39		
	7.95[c]	0.05		
	9.55[d]	0.02		
	10.17[d]	0.02		
XIII	4.14	1.304	0.142	4.76
	6.29	0.113		
XIV	4.14	8.89		
	6.29	0.111		

[a] See eq 2–5. See Rahil, J., Ph.D. Thesis, Wesleyan University, 1980 for full table of rate constants. [b] Observed rate constant obtained from the plot of $\ln(A_t - A_\infty)$ vs. time. [c] In 0.01 M pyrophosphate buffer at 75.2 °C. [d] In 0.01 M glycine buffer at 75.2 °C.

(18) Hine, J. "Physical Organic Chemistry"; McGraw-Hill: New York, 1962; Chapter 5.

(19) Perrin, D. D. "Dissociation Constants of Organic Bases in Aqueous Soution"; Butterworths: London, 1965.

Table III. Temperature Dependence[a] of the Observed Rate Constant (k_{obsd}), Specific Rate Constant (k_2), and the Acidity Constant (K_a) of Compound XII

T, °C	10^5K_a	10^2k_2, s^{-1}	10^5k_{obsd},[b] s^{-1}
−0.50	2.44	0.168	4.35
11.35	1.64	0.332	8.48
20.55	1.71	0.703	18.3
29.50	1.55	1.270	39.2
E_a, kcal/mol		11.7	12.0
$\Delta H^{\ddagger}$, kcal/mol		11.1	11.4
$\Delta G^{\ddagger}$, kcal/mol		20.4	22.5
$\Delta S^{\ddagger}$, gibbs		−31	−38

[a] Reactions were done in water and acetate buffer. [acetate] = 0.4 M. [b] Values at pH 6.34. [c] Activation parameters, at 29.5 °C, obtained with the use of the following equations: $\log k = -E_a/2.303RT + \log A$; $\Delta H^{\ddagger} = E_a - RT$; $\Delta G^{\ddagger} = 2.303RT \log (k_2T/hk_B)$: $\Delta S^{\ddagger} = (\Delta H^{\ddagger} - \Delta G^{\ddagger})/T$.

this β_t is easily shown to be a sum of β_2 and β_a at any given pH value (ΔpH = 0) by substituting $k_{obsd} = k_2[H^+]/K_a$ into eq 9 ($\beta_2 = \Delta \log k_2/\Delta pK_a$):

$$\beta_t = \frac{\Delta \log k_2 + \Delta \log K_a(\text{amides}) + \Delta \log [H^+]}{\Delta\, pK_a(\text{amine leaving groups})} = \beta_2 + \beta_a \quad (10)$$

Since k_{obsd}(XIII) = k_{obsd}(XIV) at any pH value for which $k_{obsd} = k_2[H^+]/K_a$ (eq 4), $\beta_t = 0$ so $\beta_2 = -\beta_a = -1.0$ for these compounds, indicating that there is extensive P–N bond breaking in the transition state.

Why, then, does the β_2 value (−1.9) based on k_2 for XII and XIII exceed the normal minimum for β? It may be due to steric compression in the ground state and the release of this compression in the transition state. The oxy substituents of a phosphonamide (VII) should be highly solvated in water, and the phenyl group of VII is large. The steric difference between the two methyl groups in XII and the pyrrolidine and morpholine rings of XIII and XIV could then differ sufficiently to account for $\beta_2 \simeq -1.9$. In terms of the display in Figure 1, the steric compression in the ground state of XII would explain the fact that k_{obsd} for XII is greater than k_{obsd} for XIII or XIV over the pH range 5.5–7.

A pH-independent region in the hydrolysis profile of XII occurs at pHs >8 (Table II). The plot of log k_{obsd} against pH has a slope of 0.16 in the pH range 8–10. Kinetic indistinguishability[20] makes it impossible to distinguish between the two possible mechanisms in this region, namely, a water molecule attacking the substrate monoanion, A^-, or a hydroxide ion attacking the neutral form, HA.

The second possibility, hydroxide attacking the neutral form, was investigated to see if the rate constant exceeds the diffusion-controlled limit

$$v = k'[OH^-][AH] = k'K_w[A]/K_a = k_{obsd}[A] \quad (11)$$

where $K_a = [A][H^+]/[HA] = 1.6 \times 10^{-5}$ M and the observed rate constant (k_{obsd}) is 2.4×10^{-5} s^{-1} (Table II). Substituting these values and the value of K_w (10^{-14}) into eq 11 gives $k' = 3.8 \times 10^4$ M^{-1} s^{-1}, which is well below the accepted diffusion-controlled limit.[21]

Activation parameters were determined by studying the temperature dependence of k_2 and K_a values for XII at 29.50, 20.55, 11.35, and −0.50 °C. At each temperature, 9–15 rate constants were obtained (as in Figure 1), and k_2 and K_a were obtained by k_{obsd} vs. $k_{obsd}/[H^+]$ (as in Figure 2). The resulting values for k_2 and K_a are shown in Table III. There is negligible dependence of K_a on temperature. The activation parameters for k_2 were determined in the usual manner[20] and are shown in Table III.

Table IV. Solvent Effects on the Solvolysis of XII at pH 5.93 in 0.4 M Acetate Buffer at 30.2 °C

solvent[a]	10^5k_{obsd}, s^{-1}	k_s/k_{H_2O}
H_2O[b]	89.1	1
25% MeOH[c]	128.8 ± 0.4	1.4
50% MeOH	151.8 ± 0.5	1.7
75% MeOH	156.5 ± 1	1.75
25% dioxan	133.9 ± 6	1.5
50% dioxan	108.3 ± 0.2	1.2
75% dioxan	106.1 ± 0.8	1.2

[a] Percentage by volume. [b] Extrapolated from the experimental value of $k_{obsd} = 80 \times 10^{-5}$ s^{-1} at pH 5.98. [c] Extrapolated from the experimental value of $k_{obsd} = 169.1 \times 10^{-5}$ s^{-1} at pH 5.76.

Table V. Solvent Effects on the Acidity Constant (K_a) and Specific Rate Constant (k_2) of XII at 29.5 °C

solvent	[buffer], M	10^5K_a	10^2k_2, s^{-1}	10^3k_{obsd},[a] s^{-1}
H_2O	0.40	1.55	1.27	1.58
D_2O	0.40	0.49	1.06	4.3
70% MeOH–H_2O	0.40	1.55	1.90	2.57
25% diox–H_2O	0.40	1.15	1.06	1.74
50% *i*-PrOH–H_2O	0.40	1.26	1.27	1.87
D_2O	0.05	0.65	0.95	
0.01 M KF in H_2O		2.6	6.0	

[a] At pH 5.65.

Table VI. pH Dependence of the F^--Catalysed Hydrolysis of *N,N*-Dimethylphenylphosphonamide (XII) in 0.4 M[a] Acetate Buffer and 0.01 M Potassium Fluoride, at 29.5 °C

pH	10^5k_{obsd},[b] s^{-1}	$-\log k_{obsd}$	$10^5k/[H^+]$, M^{-1} s^{-1}
4.49	3302 ± 90	1.48	1.02
4.73	2933 ± 50	1.53	1.58
5.09	1426 ± 9	1.85	1.75
5.22	1175 ± 4	1.93	1.95
5.57	587 ± 1	2.23	2.18
5.82	176 ± 1	2.75	
6.34	105.2 ± 1	2.98	
6.64	46.6 ± 0.3	3.33	
7.13	12.6 ± 0.2	3.90	

[a] Total buffer concentration. [b] Observed rate constant, obtained from the plot of ln $(A_t - A_\infty)$ vs. time. Absorbance was followed at 240 nm.

Solvent Isotope Effects. The hydrolysis of amide XII was studied in buffered solutions of D_2O at 29.5 °C. The average value for $k_{obsd}(D_2O)/k_{obsd}(H_2O) = 3.23$. The isotopic dilution caused by the addition of the protonated acid was insignificant.[22] The acidity constant (K_a) and the specific rate constant (k_2) were obtained with use of eq 5. The data were plotted as in $K_a(H_2O)/K_a(D_2O) = 3.16$ and $k_2(H_2O)/k_2(D_2O) = 1.2$: the pD values were corrected due to change of the potential of the glass electrode when used in D_2O solutions:[23] pD = observed pH + 0.40.

Solvent Effects. Solvolysis of XII in methanol–water and dioxane–water was studied in order to determine the effect of solvent polarity on rate (Table IV). Added organic solvents cause small rate enhancements. pH-dependent studies were carried out in order to determine the solvent effects on K_a and k_2. These studies were done in 70% methanol–H_2O, 25% dioxan-H_2O, and 50% 2-propanol–water. Equation 5 was used to obtain K_a and k_2 (Table V). The solvent effects on K_a and k_2 are so small that they may be within experimental error of the determinations.

Fluoride is a good nucleophile in reactions at the phosphorus atom in phosphorus esters and amides.[24,25] Therefore, the fluoride

(20) Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969.
(21) Eigen, M.; DeMayer, L. *Z. Elektrochem.* **1955**, *59*, 986. Jordan, P. C. "Chemical Kinetics and Transport"; Plenum Press: New York, 1979; p 138.
(22) Purlee, E. L. *J. Am. Chem. Soc.* **1959**, *81*, 263.
(23) Glasoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188.
(24) Halmann, M.; Lapidot, A.; Samuel, D. *J. Chem. Soc.* **1963**, 1299.

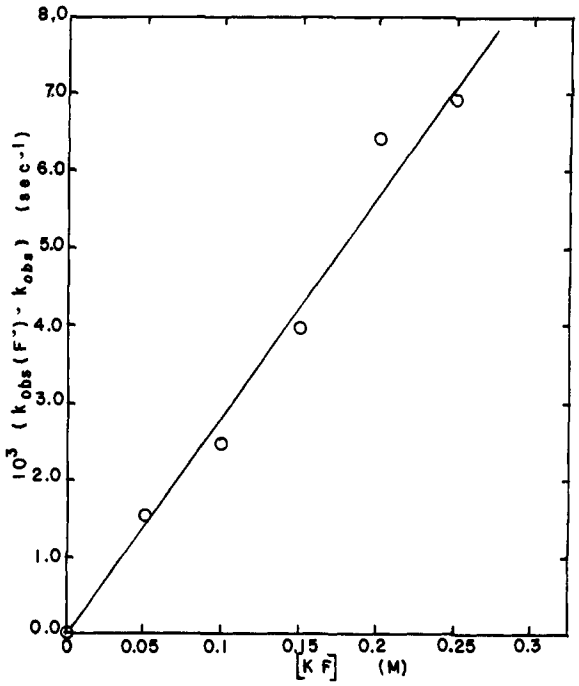


Figure 3. F^--catalyzed hydrolysis of *N,N*-dimethylphenylphosphonamidate (XII) at pH 7.0 and 29.5 °C: slope is 2.8×10^{-2} M^{-1} s^{-1}.

ion effected cleavage of the P–N bond of XII was studied in order to help distinguish between unimolecular and bimolecular reaction mechanism. The data (Table VI) show larger F^- effects on rate at lower pH values. indicating that the major reaction between F^- and amide is with the protonated amide. A plot of k_{obsd} vs. k_{obsd}/H^+ gave $K_a = 2.6 \times 10^{-5}$ M and $k_2' = 6.0 \times 10^{-2}$ s^{-1}, where k_2' is

$$k_2' = k_2 + k_F^\circ[F^-] \quad (12)$$

Substituting the known value of $k_2 = 1.27 \times 10^{-2}$ s^{-1} and $[F^-] = 0.01$ M results in $k_F^\circ = 4.73$ M^{-1} s^{-1}.

The dependence of the rate on F^- concentration was investigated at pH 7 in order to gain additional information about the rate of reaction with F^- and whether F^- reacts with the amide anion. The slope of the plot of $(k_{obsd}(F^-) - k_{obsd})$ vs. [KF] (Figure 3) was 2.8×10^{-2} M^{-1} s^{-1}. where k_{obsd} is from the data in Figure 1 for XII. From eq 13 one can see that this slope is k_F at pH 7. Using

$$k_{obsd}(F^-) = k_{obsd} + k_F[F^-] \quad (13)$$

eq 14 and the acidity constant of the amide. $K_a = 2.6 \times 10^{-5}$ M.

$$k_F = k_F^\circ a + k_F^-(1 - a): a = \frac{[HH]}{[HA] + [A^-]} \quad (14)$$

$$k_F^- = (k_F - k_F^\circ a)/(1 - a) \simeq 0.01 \text{ } M^{-1} \text{ } s^{-1} \quad (15)$$

we calculate that it appears that k_F is approximately 0.01 M^{-1} s^{-1} whereas $k_F^\circ \simeq 5$ M^{-1} s^{-1}, so F^- reacts with the neutral amide about 500 times faster than with the amide anion in agreement with nucleophilic attack by F^- and the expected electrostatic repulsion between F^- and the amide anion.

There is a slight negative salt effect on adding sodium chloride. This probably is due to the effect on the protonation equilibrium. slightly favoring dissociation of the HA. the protonated amide (XII) (vide infra).

We found a small increase in rate due to increase in the concentration of acetate buffers at pH 4.5. 5.0. and 5.5 and phosphate buffers at pH 6.3. The slopes of the plots of k_{obsd} vs. buffer are 1.4×10^{-3} and 3.8×10^{-3} M^{-1} s^{-1} for phosphate and acetate. respectively. The acetate slope is not pH dependent within experimental error. Kinetic equivalence does not allow for distinguishability between general-acid catalysis on reaction of the amide anion and general-base catalysis or nucleophilic reaction.

(25) Jencks. W. P. *Brookhaven Symp. Biol.* **1962**. *No. 15*. 134.

$$v = k_{obsd}[A]_t = k_2^\circ[HA] + k_B[B][HA] \quad (16)$$

$$v = k_2^\circ[HA] + k_A[BH][A^-] \quad (17)$$

where B = buffer base, BH = buffer acid, and HA and A^- represent amide XII and the amide anion. Then

$$k_A[BH][A^-] = (k_A K_a^{BH}/K_a^{HA})[B][HA] \quad (18)$$

so k_B could be $(k_a K_a^{BH}/K_a^{AH})$, and it is impossible to tell whether there is buffer catalysis by base or acid.

Combining eq 3 with eq 16, we obtain

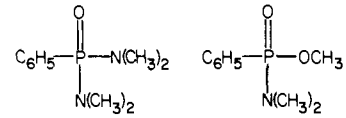
$$k_2 = k_2^\circ + k_B[B] \quad (19)$$

so it is important to evaluate the contribution of $k_B[B]$ to the total values of k_2 (Table VIII). Since the K_a and k_2 values in Table VIII have all been determined from k_{obsd} at pH values from about 4 to 5.2, at these pHs, the buffer component of k_{obsd} is a minor part of the total k_{obsd}.

Because we were concerned about the effect of buffer on the solvent deuterium isotope effect, we determined K_a and k_2 at low buffer concentration (Table V). As the above discussion would predict, the values changed little. The conclusion that k_H/k_D is only slightly greater than 1.0 is not perturbed by the buffer contribution to k_{obsd}.

Discussion

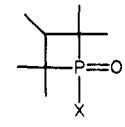
We compare rates of reaction of phosphorus amides in Table VII. In each case, we are interested in the rate for the species in which a proton is available so that the leaving group is the neutral amine. This table includes data for the diamide XV and



XV XVI

the amide–ester XVI.[26] The neutral rate for both these compounds is negligible but they undergo acid-catalyzed reaction at a measurable rate. leading to the rate constants in Table VII. There appears to be many orders of magnitude difference in the rates of hydrolysis of protonated XII and the analogues XV and XVI. Both XV and XVI react in acid with P–N bond cleavage.[26]

Phosphonamides exhibit strikingly greater reactivity in acid-catalyzed hydrolysis than the phosphoramide analogues (Table VII). In order to compare rates with those of phosphinamides, a specific rate constant (Table VII) for the acid-catalyzed hydrolysis of *N,N*-dimethyldiphenylphosphinamide (I) was calculated from the data in ref 1a. At the moderate acidities used in the above study, the concentration of the protonated amide is negligible and the equation $k_2 = K_a k_H^+$ applies, where k_H^+ is the bimolecular rate constant for the acid-catalyzed hydrolysis of (I) and K_a is the acidity constant of its conjugate acid, which is assumed to be the same as that of the phosphetane (XVIIa) for which the acidity constant has been measured. $pK_a = -2$. The rationale behind this assumption is the demonstrated similarity of the $pK_a(BH^+)$ of the methyl ester of the four membered ring phosphinate (XVIIc) to that of the acyclic analogue $(C_6H_5)_2P(O)OCH_3$.[1,27,28]

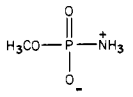
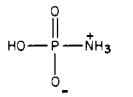
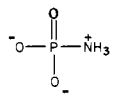
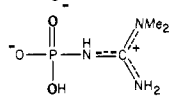
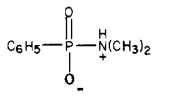
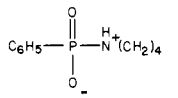
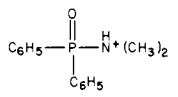
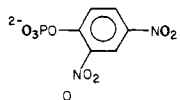
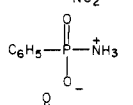
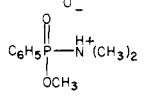
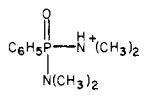


XVIIa, X = NMe_2
XVIIb. X = NHMe
XVIIc. X = OMe

The data in Table VII show a factor of nearly 10^3 rate enhancement for hydrolysis of the monoprotonated species upon

(26) Haake. P.; Rahil. J. manuscript in preparation. Rahil. J.. Ph.D. Thesis. Wesleyan University. 1980.
(27) Haake. P.; Koizumi. T. *Tetrahedron Lett.* **1970**. 4849. Haake. P.. unpublished results substantiate the conclusion in this paper.
(28) Haake. P.; Cook. R. D.; Hurst. G. H. *J. Am. Chem. Soc.* **1967**. *89*. 2650.

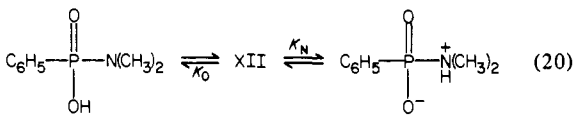
Table VII. Specific Rate Constants for the Solvolysis of a Number of Phosphorus Amides and Esters[a,b]

compd	$10^5 k_2$, s^{-1} in solvents: H_2O	50% MeOH	50% dioxan	T, °C	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$ eu	ref
	16.10	8.22	8.90	36.8			6
	11.66	14.4		25	18.1	−18.1	3
	6.94	14.4	8.75	25	23.6	−1.6	3
	62.3	16.6		30.5	22.9	+0.4	11
 XII	1270	1900[c]	1057[d]	29.5	11.07	−30.7	this work
 XIII	142			29.5			this work
	10^7[e]			29.2	9.3	−35	1
	0.647	3.22	9.91	39			*f*
	10^4						this work
	3.23[h]						26
	0.14[h]						26

[a] Rate constants for the solvolysis of the protonated species. [b] Percentage of solvent mixture in (v/v). [c] Reaction done in 70% MeOH-H_2O (v/v). [d] Reaction done in 25% dioxan-H_2O (v/v). [e] Calculated from $k_2 = K_a k_{H^+}$ by assuming a pK_a of about −2.[1a] k_{H^+} is the bimolecular rate constant for the acid-catalyzed hydrolysis. [f] Kirby, A. J.; Varvoglis, A. G. *J. Chem. Soc. B* 1968, 135. [g] Extrapolated rate from the acidity constant of N^+H_4, the β value = 1.0, and the k_2 value for XIII. [h] Acid-catalyzed rate constant, k_H (M^{-1} s^{-1}), for reaction of neutral XV and XVI.

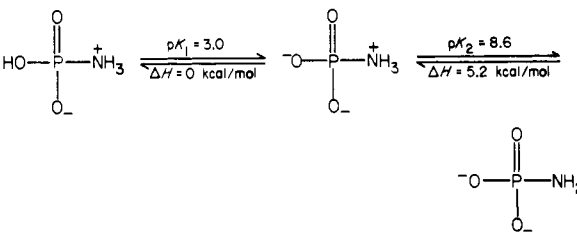
going from phosphoramides to phosphonamides and another 10^3 or 10^4 in going from phosphonamides to phosphinamides.

N-Protonation of Phosphonamide Anions. The high lability of phosphonamides in acidic media prevented direct spectroscopic determination of the site of protonation of the anion, the two possible sites being the amide nitrogen (XIX) or the phosphonyl oxygen (XVIII). Previous research on other phosphorus amides



XVIII XIX (20)

is useful regarding the question of whether XVIII or XIX is predominant. Phosphoramidate monoanion exists predominantly in the zwitterionic form (III) in the solid phase and in aqueous solution. Supporting evidence comes from X-ray crystallographic work[29] as well as thermodynamic measurement of the heats of ionization in aqueous solutions: Wilson and Levine[30] found the second ionization enthalpies of phosphoramidate (ΔH = 5.2 kcal/mol) to be characteristic of an ionization from an ammonium functionality rather than hydroxyl (where $\Delta H \approx 0$ kcal/mol), (eq 21).



(21)

While investigating phosphinamides, we found that we could observe protonation of the relatively stable phosphinamide pentamethyltrimethylenephosphinamide (XVIa,b).[27] The experimental evidence favors predominant N-protonation. First, the large effect of the nitrogen substituents on the $pK_a(BH)^+$ of

(29) (a) Hobbs, E.; Corbridge, D. E. C.; Raistrick, B. *Acta Crystallogr.* **1953**, *6*, 621. (b) Corbridge, D. E. C.; Lowe, E. J. *J. Chem. Soc.* **1954**, 493.

(30) Levine, D.; Wilson, E. B. *Inorg. Chem.* **1968**, *7*, 818.

the above compounds (pK_a(XVIa) = −1.7 and pK_a(XVIb) = −3.2) would not be expected if protonation were on the phosphinyl oxygen. The acidity constants of amines (N-protonation) demonstrate large substituent effects, but in analogous work on carboxylic amides (O-protonation), N-substituents have small effects. Second, the coupling constant J(P–N–C–H) decreases upon protonation of phosphinamides XVIa and XVIb from 10.2 to 7.9 Hz. This is in contrast to the observed increase in the coupling constant J(P–O–C–H) when phosphine oxides and phosphinate esters such as XVIc are protonated on the phosphinyl oxygen (P=O).[28] It is expected that protonation on the P=O oxygen should increase the coupling constant by increasing the amount of positive charge on phosphorus, but N-protonation in phosphinamides decreases the corresponding coupling by changing the hybridization at nitrogen (less s character in the N–P and N–C bonds). DeBruin[31] studied O-alkylated phosphorus amides and esters in which O-alkylation simulates protonation of the phosphinyl oxygen: the coupling constants for alkylated esters resemble the couplings in protonated esters, but alkylated amides have considerably larger couplings than protonated amides. These results all are consistent with O-protonation in esters but N-protonation in the amides.

In agreement with the properties of other phosphorus amides, phosphonamides seem to exist preferentially in the N-protonated, zwitterionic form. We find that the pK_a's of *N,N*-dimethyl- and pyrrolidinephosphonamides are 4.8 and 5.3, respectively. These values are much higher than the expected pK_a's of the OH group in such amides: in phenylphosphonic acid, the pK_a is 1.83 (Table VIII).[32] Therefore, the pK_a's we have determined are inconsistent with O-protonation. Similarly, large pK_a values have been reported in the literature for suspected zwitterions. For example, the pKa of phosphoramide ($^{2-}O_3P^+NH_3$) is 8.2[4] and the pK_a of the diamide $Me_2NP(O_2^-)N^+HMe_2$ is 6.7.[33,34] Other examples appear in Table VIII. The pK_a of $EtOP(O_2^-)N^+HEt_2$ is 7.2,[34] which seems higher than expected from the electron-withdrawing substitutents effect of the $EtOPO_2^-$ group, especially when compared to $MeOPO_2^-N^+H_3$ (pK_a = 2.5)[6] and $MeOPO_2^-N^+H_2C_6H_{11}$ (pK_a = 3.1).[35]

Consistent with N-protonation, a large effect on the pK_a of the protonated amides is produced by nitrogen substituents[9,36,37] as is true for the effect of N-alkyl substituents on the solution basicity of ammonium ions. In going from the dimethylphosphonamide XII to the pyrrolidine phosphonamide XIII, the pK_a changes from 4.8 to 5.3. Such a pronounced change would not be expected if protonation were on the oxygen because of the distance between the substituent and the point of protonation. Carboxylic amides undergo O-protonation and show smaller effects of N-substituents: the pK_a of benzamide is −2.16, the pK_a of *N,N*-dimethylbenzamide is −1.62, and the pK_a of *N*-methylbenzamide is −2.13.[38]

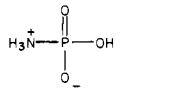
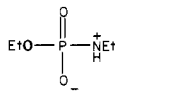
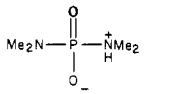
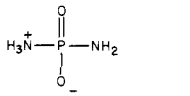
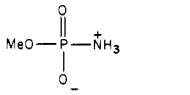
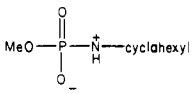
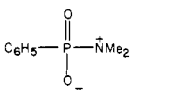
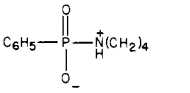
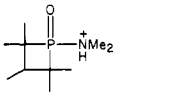
The insensitivity of the acidity constants to solvent effects (Table V) also is evidence for predominance of the zwitterionic species. The acidity constant of the O-protonated species XVIII would be expected to be very solvent dependent; but the equilibrium for formation of the N-protonated zwitterion XIX involves no change of total charge, so one expects little change of K_a as change of solvent dielectric.[39]

We can estimate K_z (eq 22) because $K_z = K_a^O/K_a^N$. We have

$$K_z = [XIX]/[XVIII] = [\text{N-protonation}]/[\text{O-protonation}] \quad (22)$$

measured $K_a^N = 10^{-4.8}$ (Table V) and we can estimate K_a^O from substituent effects:[40,41] the σ(P)'s are −1.22 for $N(CH_3)_2$ and −0.48 for C_6H_5, and the ρ value for ionization, ρ = 1.07, then enables us to calculate $pK_a^O = 0.87 - 1.07(-1.70) = 2.69$ or $K_a^O = 10^{-2.7}$. Therefore, we calculate that $K_z \simeq 10^{2.1}$ so that there should be about 100 times more zwitterionic (XIX) than O-protonated (XVIII) amide.

Table VIII. Acidity Constants of Some Relevant Phosphorus and Nitrogen Compounds in Aqueous Solution

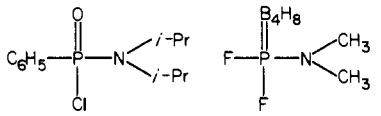
compd	T, °C	pK_a	ref
H_3PO_4	25	2.16, 7.21, 12.33	12b
$C_6H_5PO_3H_2$		1.83, 7.07	32
$(C_6H_5)_2PO_2H$			
	25	3.0, 8.2	19
		7.2	34
		6.7	33
	25	4.9	12b
	36.8	2.5	6
		5.3	35
	29.5	4.8	this work
	29.5	5.3	this work
	29.2	−1.7	1
$^+NH_4$		9.2	19
$^+NH_2Me_2$		10.8	19

Therefore, the high reactivity of phosphorus amides in dilute acidic media clearly appears to be correlated with protonation on the nitrogen atom.[1] Carboxylic amides are much less reactive and protonate on the carbonyl oxygen to give a delocalized cation.[2] The basicity of the nitrogen atom in phosphorus amides presumably reflects the degree of involvement of the nitrogen lone electron pair in π bonding with the phosphorus atom.

Bond lengths are useful in understanding the extent of delocalization of the nitrogen long pair in amides. In carboxylic amides, the nitrogen lone electron pair is involved in efficient p–p π overlap with the carbonyl carbon: Pauling[42] concluded from structural data that the polar resonance contributor $-C(O^-)N^+<$ contributes 40% to the structure of carboxylic amides. Hence, the oxygen atom is the most basic point in carboxylic amides.[2] It appears that the P–N bond length can be used as a measure of the bond order between nitrogen and phosphorus.[43] A number of amides have been studied crystallographically and their P–N

(31) DeBruin, K. E.; Padilla, A. G.; Johnson, D. M. *Tetrahedron Lett.* **1971**, 4279.
(32) Jaffe, H. H.; Freedman, L. D.; Doak, G. O. *J. Am. Chem. Soc.* **1953**, *75*, 2209.
(33) Heath, D. F.; Casapieri, P. *Trans. Faraday Soc.* **1951**, *47*, 1903.
(34) Crunden, E. W.; Hudson, R. F. *J. Chem. Soc.* **1962**, 3591.
(35) Hamer, N. K. *J. Chem. Soc.* **1965**, 46.
(36) Selim, M.; Tanh, T. N. *C. R. Hebd. Seances Acad. Sci.* **1960**, *250*, 2377.
(37) Garrison, A.; Boozer, C. E. *J. Am. Chem. Soc.* **1968**, *90*, 2486.
(38) Edwards, J. T.; Chang, H. S.; Yates, K.; Stewart, R. *Can. J. Chem.* **1960**, *38*, 1518.
(39) Edsall, J. T.; Blanchard, M. H. *J. Am. Chem. Soc.* **1933**, *55*, 2337.
(40) Mastryukova, T. A.; Kabachnik, M. I. *J. Org. Chem.* **1971**, *36*, 1201.
(41) Hansch, C.; Leo, A. J. In "Substituent Contants for Correlation Analysis in Chemistry and Biology"; Wiley: New York, 1979.
(42) Pauling, L. *Symp. Protein Struct.*, [Proc.] **1958**; "The Nature of the Chemical Bond", 3rd ed.; Cornell University Press: Ithaca, New York, 1960.
(43) Kwart, H.; Wing, K. G. in "d-Orbitals in the Chemistry of Silicon, Phosphorus and Sulfur"; Springer-Verlag: Berlin, Heidelberg, Germany, 1977.

bond lengths measured. In *N,N*-dimethyldiphenylphosphinamide (I),[44] the P–N bond length is 1.681 Å. In *N,N*-diisopropylphenylphosphonamidic chloride (XX), it is 1.614 Å.[45] Both values



XX XXI

are considerably shorter than the accepted P–N single bond distance of 1.769 Å for phosphoramidic acid (III).[46] Apparently, higher electronegativity of the substituents at phosphorus leads to a shorter P–N bond:[45] for example, the P–N bond length in (dimethylamino)difluorophosphine tetraborane (XXI) is 1.593 Å.[47]

The geometry of the bonds around nitrogen and the plararity of the nitrogen atom also reflect the P–N bond order. The sum of angles around nitrogen is about 325° in pyramidal compounds such as trimethylamine and 360° in trigonal compounds such as carboxylic amides which are planar at N (sp^2 hybridized).[42] This range covers the two extremes of bonding at nitrogen: the complete absence of π interaction and full π bonding, respectively. The nitrogen in XXI is very nearly planar with the sum of angles being 359.8°.[47] In compound XX the sum of angles is 358.8°.[45] But in I the nitrogen is midway between planar and pyramidal, with the sum of angles being 348.9°.[44] in agreement with a longer P–N bond than in XX or XXI. That is, the geometries of the bonds around nitrogen parallel the P–N bond distances: high π bonding causing a planar N and a short P–N distance.

In contradiction to the experimental evidence summarized above, in a recent report molecular orbital calculations on phosphinamide ($H_2P(O)NH_2$) have been claimed to support preferential O-protonation.[48] According to Modro et al., rate accelerations in the hydrolysis could be due to the increased electrophilicity of the phosphorus center. In addition to the notorious difficulties in achieving proper theoretical treatment of bonding at phosphorus, it can be noted that theoretical calculations are more descriptive of the gaseous molecule since these calculations do not take into account solvation effects. While studying the basicity of phosphinyl compounds, we noted that the

group is very heavily solvated by water. In work concerning phosphine oxides ($R_3P{=}O$), a salting-in effect on these oxygen bases was noted in acidic media.[28] We attributed this behavior to the large extent of solvation of the P=O oxygen through hydrogen bonding with the solvent. If the oxygen is protonated, these H bonds would lose much of their energy. Therefore, neglect of the strong solvation of the phosphinyl oxygen may be the source of the conflict between the theoretical paper[48] and the experimental data[27,31] on the basicity of oxygen vs. nitrogen atoms in phosphinamides.

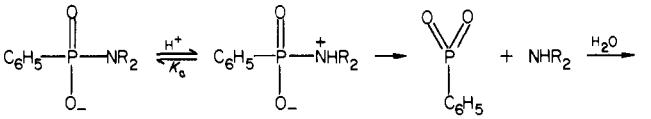
The Reactive Species. Although predominant N-protonation of phosphonamides seems clear, it would still be possible for the cleavage reaction to proceed through the O-protonated species. However, we have evidence for the reactivity of the N-protonated species. Our finding[26] that the hydrolysis of the OCH_3 ester, methyl *N,N*-dimethylphenylphosphonamidate (XVI), is 400 times slower (Table VII) than the corresponding acid indicates that hydrolysis does not proceed through the O-protonated adduct (XVIII). Substituent effects also support reaction through the N-protonated species, the zwitterion (XIX). Reaction through the O-protonated species would lead to dependence of the observed k_2 on Z_Z and k_2^{OH} (the k_2 for reaction of XVIII)

$$k_2 = k_2^{OH}K_Z/(K_Z + 1) \quad (23)$$

where K_Z = [O-protonated amide]/[N-protonated amide]. Since the concentration of the zwitterion XIX is predominant, K_Z is much less than 1. Therefore, $k_2 \simeq k_2^{OH}K_Z$. Then, the dependence of the rate on substituents should be close to 0 because of the existence of two cancelling effects as it is in the acid-catalyzed hydrolysis of carboxylic amides. But the observed β value on k_2 for phosphonamides is, in fact, large, eliminating reaction through the O-protonated species. The substituent effect is only consistent with reaction of the zwitterion and a high degree of P–N bond breaking in the transition state.

Possible Mechanisms of Hydrolysis of Phosphonamides. On the basis of a large amount of research on other phosphorus compounds and other amides,[12,49] there are three mechanisms that appear possible.

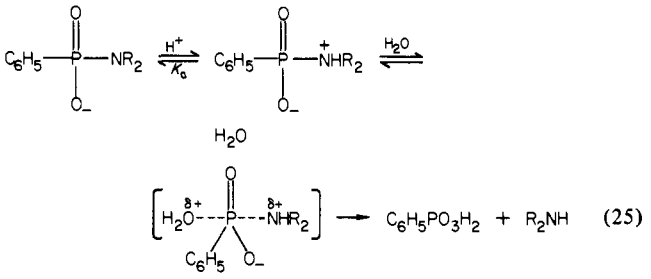
(a) The $S_N1(P)$ mechanism (elimination–addition) has been proposed for the hydrolysis of phosphate monoester monoanions.[12,49,50] It involves a moelcular decomposition passing through a transient metaphosphate-type intermediate (XXII) (eq 24).



XXII

$C_6H_5PO_3H_2$ (24)

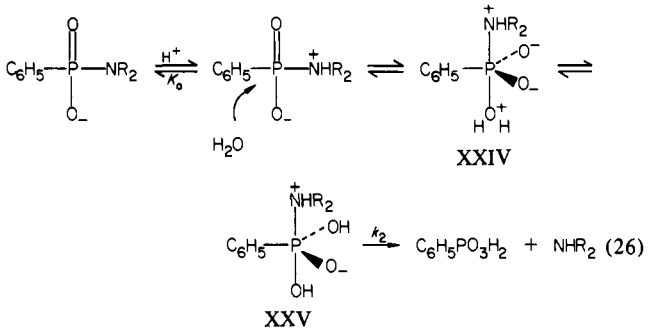
(b) The $S_N2(P)$ mechanism, which is directly analogous to nucleophilic displacement at saturated carbon, has been proposed to explain acid-catalyzed hydrolysis of phosphinamides[1] (eq 25).



XXIII

(25)

(c) The $S_N2I(P)$ mechanism[51] (addition–elimination) involves a pentacoordinate intermediate. It has previously been invoked[12,52] to explain many substitution reactions at phosphorus. The pathway shown in eq 26 includes the assumption of rapid proton-transfer in the pentacoordinate intermediate.



XXIV

(26)

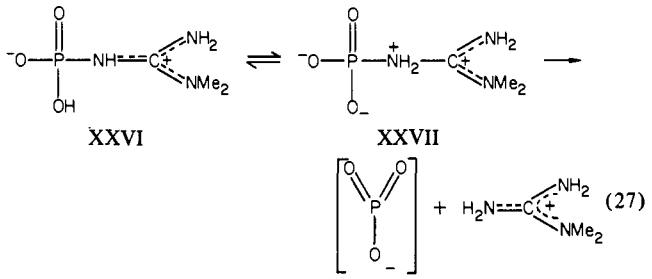
XXV

Chanley and Feageson,[3] in their study of phosphoramidate (III) hydrolysis, found an entropy of activation ($\Delta S^* \approx 0$) which favored an S_N1 mechanism with production of H_3N and the reactive

(44) Ul-Haque, M.; Caughlan, C. N. *J. Chem. Soc., Chem. Commun.* **1966**, 921; *J. Chem. Soc., Perkin Trans. 2* **1976**, 1101.
(45) Paxton, K.; Hamor, T. A. *J. Chem. Soc., Dalton Trans. 2* **1978**, 647.
(46) Cruickshank, D. W. J. *Acta Crystallogr.* **1964**, *17*, 671.
(47) La Prade, M. D.; Nordman, D. E. *Inorg. Chem.* **1969**, *8*, 1669.
(48) Modro, T. A.; Liauw, W. G.; Peterson, M. R.; Csizmadia, I. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1432.
(49) Cox, J. R. Jr.; Ramsay, O. B. *Chem. Rev.* **1964**, *64*, 317.
(50) (a) Bunton, C. A.; Llewellyn, D. R.; Oldham, K. G.; Vernon, C. A. *J. Chem. Soc.* **1958**, 3574. (b) Butcher, W. W.; Westheimer, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 2420.
(51) The symbol $S_N2I(P)$ has been introduced to signify an associative, bimolecular substitution mechanism at phosphorus centers through a pentacoordinate intermediate of kinetically significant lifetime.
(52) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70.

intermediate metaphosphate ion (PO_3^-) which is known to react very rapidly with OH groups. However, their observations of nonrandom product distributions in mixed alcohol–water solvents led them to propose a mechanism of hydrolysis involving nucleophilic participation; a mechanism between $S_N1(P)$ and $S_N2(P)$: a mechanism which has unimolecular character but some nucleophilic participation. It might be best described as a merged S_N1–S_N2 mechanism.[1b]

This mechanistic picture appears to shade toward S_N1 and a free metaphosphate intermediate in hydrolysis of phosphoroguanidines.[11] Upon solvolysis of dimethylphosphoroguanidine in alcohol–water (XXVI), product partitioning followed exactly the molar rations of the alcohol to water content of the solvent.[11c] This behavior was found in methanol and ethanol but there was slightly less phosphate ester from the more sterically hindered 2-propanol. On the basis of these results, entropy of activation ($\Delta S^* = 0$), and solvent isotope effect, a dissociative mechanism of hydrolysis was proposed involving the formation of a "free" metaphosphate intermediate (eq 27). The high reactivity of this compound was



XXVI XXVII (27)

explained by transient formation of the highly labile double zwitterion (XXVII) which readily forms metaphosphate ion.

In the acid-catalyzed hydrolysis of phosphinamides (eq 1), the entropy of activation ($\Delta S^* \approx -30$), the deuterium isotope effect, and rate inhibition caused by small rings all favored an S_N2 reaction but not generation of a pentacoordinate intermediate.[1]

The reactivity of phosphonamides as a function of the pK_a of the leaving group may be utilized as an approximate index of the fraction of bond breaking in the transition state.[53,54] The β parameter, as discussed in the results section, for the dependence of rate on the basicity of the leaving group for phosphonamides indicates a large extent of bond breaking in the transition state; this β value (~ -1) is consistent with all three mechanisms considered above: $S_N1(P)$ involves rate-determining departure of the amine; the $S_N2(P)$ mechanism cna feature a large extent of bond breaking in the transition state: the $S_N2I(P)$ mechanism can involve rate-determining breakdown of the intermediate.

In general, reactions that take place via a unimolecular mechanism are characterized by small (~ 0) and positive entropies of activation (ΔS^*). Biomolecular reactions tend to have large and negative ΔS^*.[55] The entropy of activation associated with bimolecular reactions is large and negative (about −20 Gibbs) due to orientation requirements and loss of translational entropy as the two reacting molecules form an activated complex.

We find that ΔS^* for the hydrolysis of phosphonamides is −31 gibbs (Table III). This value is undoubtedly perturbed to a small extent by the buffer component in k_2 (eq 19). However, as we have discussed at the end of the Results, $k_B[B]$ is a minor part of k_2. Nevertheless, we would expect that the buffer term would have a higher negative entropy ($\Delta S^* \approx -40$) than the k_2^O term, so the ΔS^* for k_2^O appears to be between −20 and −30 gibbs which is characteristic of a bimolecular reaction. This value can be compared to the ΔS^* values which were found in hydrolysis of phosphinamides ($\Delta S^* = -35$ gibbs), Table VII, and the alkaline hydrolysis of phosphinate esters, where the ΔS^* found for phosphonamides is inconsistent with a unimolecular mechanism.[56]

Another very strong argument against an S_N1 mechanism is the large increase in rate caused by adding fluoride ion which is an excellent nucleophile for displacement at phosphorus.[24,25] The only way for F^- to have such a strong effect on the rate is for it to be the nucleophile in an S_N2 or $S_N2(I)$ mechanism. It seems unlikely that phosphonamides (III) would react with F^- and H_2O by two different mechanisms. The simplest hypothesis is that both nucleophiles react by an associative mechanism.

Another strong argument against the occurrence of an $S_N1(P)$ mechanism in phosphonamides is the fact that they react much faster than phosphoramides (Table VII). Phosphoramides have greater tendency for unimolecular, $S_N1(P)$, displacements because of their potential to form a metaphosphate anion intermediate, PO_3^-, which is known to be an unstable intermediate in some cases.[11,12] Therefore, phosphoramides would be expected to hydrolyse faster than phosphonamides if the latter reacted by a unimolecular, $S_N1(P)$, mechanism. It is well-known that the driving force in metaphosphate reactions is the electron density on the phosphoryl group and the relative stability of the metaphosphate intermediate due to resonance stabilization.[7,8,12,13] Phosphonamides lack these features: in an S_N1 displacement, they would have to form a $C_6H_5P(=O)_2$ intermediate, which should be highly energetic relative to PO_3^- because the involvement of the phenyl ring in phosphorus resonance stabilization is minimal on the basis of X-ray structural data which show similar bond lengths for P–C(aromatic) 1.805 Å and P–C(aliphatic) 1.75–1.80 Å.[57] This indicates the absence of interaction between the π cloud of the phenyl ring and the phosphoryl group. Furthermore, neutral metaphosphate species appear to be highly unstable; such intermediates as $(O{=})_2POR$ or $(O{=})_2POH$ have not been found in solution although one appears to have been generated in a high-temperature pyrolysis reaction.[12,58]

The effect of solvent polarity on the specific rate constant (k_2) for the hydrolysis of *N,N*-dimethylphosphonamide is small (Table V); the rate constants in 70% (v/v) methanol–water show a rate enhancement of 1.5 relative to water. Methanol is a stronger nucleophile toward phosphorus centers,[59] but the effect (Table V) could be due to solvent polarity. The methanol and dioxane results in Table V indicate a transition state that has very similar polarity to the zwitterionic ground state. In terms of the possible mechanisms of phosphonamide hydrolysis, the $S_N1(P)$ mechanism again seems unlikely since it involves charge dispersal in the transition state, and the rate should increase significantly in less polar solvents. An example of this type of behavior is the hydrolysis of 2,4-dinitrophenyl phosphate dianion (Table VII). In the solvolysis of *N,N*-dimethylphosphoroguanidine, more charge is created in the transition state (eq 27) than is present in the ground state;[11] as expected, the reaction rates are slower in less polar media (Table VII). Finally, there is no solvent effect on the ionization constant (K_a) (Table V) within experimental error in agreement with the zwitterionic structure of the phosphonamide. A neutral phosphonamide would show a large decrease in K_a; for example, pK_a of benzoic acid increases from 4.20 in H_2O to 9.41 in methanol.[60]

In a similar fashion to the solvent effects, the salt effects on the hydrolysis of phosphonamides indicate that the polarity of the transition state is high, resembling the ground state.[18]

Deuterium Solvent Isotope Effect. The solvent isotope effect on the acidity constant of *N,N*-dimethylphenylphosphonamide $K_a(H_2O)/K_a(D_2O) = 3.1$ (Table V). This behavior is expected[60] since acids are weaker in D_2O because of the unfavorable for-

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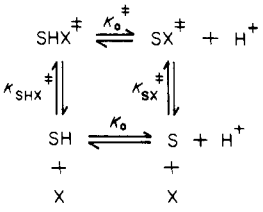
mation of D_2O^+ which weakens the O–D bonds. The observed value of the acidity constant, $pK_a(D_2O) = 5.3$, fits well with the empirical equation $pK_a(D_2O) = 1.02pK_a(H_2O) + 0.41$[61] for changes in acidity constants upon going from H_2O to D_2O.

The solvent isotope effect on the specific rate constant is $k_2(H_2O)/k_2(D_2O) = 1.2$ (Table V). Therefore, on the basis of such a small effect, the operating mechanism should feature little net change in bonding to exchangeable hydrogens in going from ground to transition state.[62] The $S_N1(P)$ mechanism appears excluded on the basis of the entropy of activation, the fluoride effect, the expected instability of $C_6H_5PO_2$, the solvent effects, and the salt effect as discussed above. Instead, the observed solvent isotope effect on k_2 reflects the structure of the transition state in an S_N2 or $S_N2(I)$ mechanism. Since $k_2(H_2O)/k_2(D_2O)$ is near 1.0, the total change in vibrational frequencies of the bonds to exchangeable hydrogens must be near 0. Since we have found that there is extensive P–N bond breaking in the transition state, the N–H bond will move to higher frequency. Regardless of whether the mechanism is S_N2 or $S_N2(I)$, this must be balanced by decreases in OH frequencies in the transition state compared to the ground-state water molecule which is the nucleophile.

Calculation of the Acidity Constant of the Transition State ($pK_a^{\ddagger}$). In order to gain more information about the structure of the transition state, we applied Kurz's method[63] for calculation of $pK_a^{\ddagger}$ using the thermodynamic cycle



(28)

Then

$$K_a^{\ddagger} = K_{SH}^{\ddagger}K_a/K_{SHX^{\ddagger}} \quad (29)$$

and by the Eyring equation $k_{SH} = Kk_BTK_{SX}^{\ddagger}/h$ and $k_{SHX} = Kk_BTK_{SHX}^{\ddagger}/h$ so we can determine the acidity constant of the transition state from

$$pK_a^{\ddagger} = pK_a + \log (k_{SHX}/k_{SH}) \quad (30)$$

We have measured k_{SX} (k_{obsd} at about pH 10 in Figure 1 and Table II), k_{SHX} (same as k_2, Table V), and K_a (Table V). Since water is the nucleophile, we can use first-order rate constants $k_{SHX} = k_2$ from Table III extrapolated to 75 °C and k_{SX} = the plateau k at about pH 10 from Table II and Figure 1. Then $pK_a^{\ddagger} = 4.8 + \log (0.16/2.4 \times 10^{-5}) = 8.6$. Because of kinetic indistinguishability, k_{SX} in eq 30 could refer to the hydrolysis of the neutral amide by OH^- as well as the kinetically equivalent reaction, the hydrolysis of the amide anion by H_2O. But since we use the thermodynamic cycle of eq 28, it does not matter: the composition of the transition state is all that matters so the above analysis is valid.

The value of 8.6 for the acidity of the transition state can be considered together with the isotope effect in terms of whether the S_N2 or $S_N2(I)$ mechanism is involved in the hydrolysis of phosphonamides: In an S_N2 transition state, these results and the β value for the leaving group suggest nearly complete P–N bond cleavage and a bond about half formed to a nucleophilic H_2O to give this pK_a for $H_2O^{\delta+}$----P(XXIII).[28] This would also balance the changes in O–H and N–H force constants. In an S_N2I mechanism, the transition state would have to occur in breakdown of the pentacoordinate intermediate because of the β value. The $pK_a^{\ddagger}$ value (8.6) and the low $k_2(H)/k_2(D)$ would have to fit with a transition state structure resulting from the breakdown of the

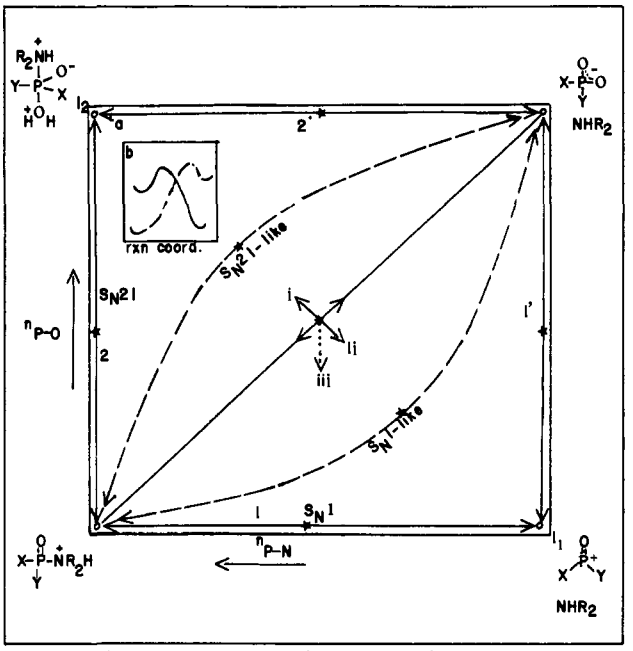
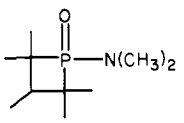


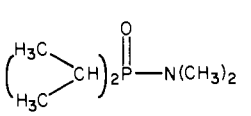
Figure 4. (a) Potential energy surface diagram for concerted, $S_N2(P)$, and stepwise $S_N1(P)$ and $S_N2I(P)$ mechanisms; n is the bond order going from 0 to 1. Energy maxima are indicated by an asterisk and minima by a small open circle. (b) Plot of the potential energy vs. distance along the reaction coordinate.

pentacoordinate intermediate XXV, eq 26. The pK_a value would then be related to the pK_a values of phosphoranes which have been estimated to be 8.5 for $(HO)_5P$ and experimentally determined to be 10–11 in a monohydroxyphosphorane.[64] Since the leaving group effect is large, there must be extensive bond breaking in the transition state. If the bond were fully broken, the $pK_a^{\ddagger}$ would be expected to be similar to $pK_a = 1.8$ for phenylphosphonic acid. Within the $S_N2I(P)$ mechanistic model, the $pK_a^{\ddagger}$ value of 8.6 appears too high because it would reflect too little bond breaking in the transition state. The k_H/k_D value might be consistent with an $S_N2I(P)$ mechanism because it could represent a balance of decreased O–H bond energies and increased N–H bond energy as reflected by the increased acidity of OH groups (in the $pK_a^{\ddagger}$) and decreased acidity of the NH group relative to the ground state.

Structure and Reactivity in Phosphorus Amides. The reactivity of phosphorus amides decreases by a factor of 10^3 in the order: phosphinamides > phosphonamides > phosphoramides (Table V). Similar structure–reactivity relationships have been observed in phosphorus esters and halides.[12] When a pentacoordinate intermediate is formed, experimental data on bond lengths and bond energies indicate a weakening of P–O bonds in the transition state vs. the ground state.[65–68] Changes in P–O bond energies can be expected to be determining in the distinction among possible mechanisms. Experimental evidence favors the $S_N2(P)$ mechanism for acid-catalyzed phosphinamide hydrolysis.[1,69] This finding, which is mainly based on the face that the four-membered cyclic phosphinamide (XXVIII) hydrolyses 10^3 times slower than its



XXVIII



XXIX

acyclic analogue (XIX), is unusual in the chemistry of substitution

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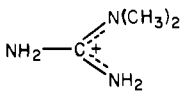
at tetrahedral phosphorus.[12] The corresponding esters show opposite behavior in that the cyclic compound hydrolyses 10^3 time faster than the acyclic diisopropylphosphinate ester.[70,71]

The range of mechanism possible in displacement at phosphorus can be usefully visualized by using a three-dimensional potential energy surface (Figure 4). These "PES" diagrams were used by More O'Ferrall in understanding the relationship between E1 and E1cb mechanisms.[72] They have also been used by Jencks in analyzing the types of catalysis involved in complex reactions in water.[73] Figure 4 represents a model for substitution reactions at phosphorus amides on a potential surface that embraces the possibilities of reaction through concerted $S_N2(P)$ mechanism and step-wise $S_N1(P)$ and $S_N2I(P)$ mechanisms. The axes in the plane of the paper (energy contours are not shown) represent the bond order (n) of P–N (where N is the leaving group) and P–O (where O is the incoming nucleophile which is assumed to be H_2O). The arrows next to the n's point in the direction of increasing bond order, from 0 to 1. The reactants appear at the bottom left of the diagram and the products at top right. The two intermediates are located at bottom right (tricoordinate from an $S_N1(P)$ mechanism) and top left (pentacoordinate from an $S_N2I(P)$ mechanism). Breaking the P–N bond corresponds to a movement to the right, whereas vertical movement corresponds to P–O bond formation. An $S_N1(P)$ mechanism combines paths 1 and 1′ and an $S_N2I(P)$ mechanism combines paths 2 and 2′. A simultaneous P–N bond breaking and P–O bond making represents an $S_N2(P)$ mechanism and corresponds to a movement along the diagonal line.

Structural changes introduced into the molecule by substituents will affect the relative energy of reactants and products. Consequently, the position of the transition state will be shifted along the reaction coordinate in accordance with the Hammond postulate.[74] Since these structural changes move the transition state (TS) along the reaction coordinate, they are usually referred to as "parallel effects".[75] On the other hand, changes in the relative energy of the incipient intermediates (I_1 and I_2) will be conveyed to the TS in a direction "perpendicular" to the reaction coordinate as shown in Figure 4. They will result in changes in the degrees of freedom of the transition state other than those involved in the reaction coordinate, i.e., which correspond to vibrations not involved in bond making and breaking.

To apply the PES diagram described above to the study of phosphorus amides, we start with phosphinamides (i.e., the case where X and Y in $XYP(O)N^+HR_2$ are alkyl or aryl groups) which follow an $S_N2(P)$ mechanism of hydrolysis—the reaction coordinate represented by the diagonal (solid) line. In phosphoramides, the X and Y groups are O^- substituents with strong multiple bonding to phosphorus. This bonding effect stabilizes the unimolecular intermediate, metaphosphate ion, PO_3^-, so the reaction pathway shifts toward the lower right and becomes S_N1-like as discussed above. A fullfledged step-wise $S_N1(P)$ mechanism would require a better leaving group than the amine–N^+HR_2. Such a requirement is satisfied in phosphoroguanidines where the leaving group is the stable cation



In fact, phosphoroguanidines have been found to hydrolyze via a mechanism which appears to be very close to unimolecular.[10]

Phosphonamides, in comparison with the phosphinamide pathway, would be expected to have more electrostatic stabilization in the transition state (XXIII). Because of the charge difference in the transition state, phosphonamides have a negative center of reaction and the entering and leaving groups are partially positive, but phosphinamides have only the partially positive entering and leaving groups. In addition, the additional O^- substituent in phosphonamides will cause a perpendicular shift toward the S_N1 pathway because $C_6H_5PO_2$ should be much more stable than $(C_6H_5)_2PO^+$. Of course, as we have mentioned, one does not expect a highly S_N1-like TS from a $C_6H_5PO_2$ reaction center. Rather, both the electrostatic effect and this perpendicular effect should give a reaction trajectory which would be expected to be S_N2-like with a TS which has less total-bond order to entering and leaving groups than in the TS formed from the corresponding phosphinamide. This fits well with the deuterium isotope effects: $k_2(H)/k_2(D)$ is 1.2 for phosphonamide hydrolysis but 2.3 for phosphinamide hydrolysis in agreement with this PES analysis predicting higher bond order to water in the phosphinamide TS.

We noted above that the negligible solvent (Table V) and salt effects indicate a transition state similar to polarity to the ground state which is a zwitterion. If the $S_N2I(P)$ mechanism (eq 26) were involved in this reaction, the β value demands that the bond to leaving group be extensively broken in the transition state which, therefore, would resemble the products and be nearly neutral (eq 26). This is very strong evidence that the $S_N2I(P)$ mechanism cannot be applicable to acid-catalyzed hydrolysis of phosphonamide anions. The S_N2 mechanism (eq 25) would have net charge and polarity in the TS which would be similar to gound state and, therefore, fits the experimental data in agreement with the above analysis based on the PES in Figure 4.

Comments on the acid-catalyzed hydrolysis of carboxylic amides are also relevant: in this case, there is no ^{18}O exchange[76] so that there appears to be rate-determining formation of intermediate and, therefore, little breaking of the C–N bond in the transition state. In contrast, in phosphonamides P–N bond breaking is nearly complete in the transition state. This suggests that there is not an intermediate and, as our other thinking indicates, the mechanism is $S_N2(P)$ such as in the case of phosphinamides but with a weaker bond to the nucleophile which accounts for the low isotope effect that we have found.

Therefore, in the acid-catalyzed hydrolysis of phosphonamide anions, it appears to us that the $S_N2(I)$ pathway is very unlikely from the PES analysis and from the comparison with carboxylic amides. In addition, the experimental evidence, β, solvent and salt effects, k_H/k_D, and pK_a*, are strongly against an $S_N2(I)$ transition state and are in agreement with TS XXIII in an $S_N2(P)$ mechanism with the bond to leaving amine group extensively broken and the bond to the entering water nucleophile about half-formed.

This mechanism enables us to understand why phosphonamide anions and phosphinamides are so much more reactive in acid-catalyzed hydrolysis than carboxylic amides. Carboxylic amides protonate on oxygen giving a delocalized cation with high resonance stabilization. Hydrolysis requires addition of water as a nucleophile which destroys that resonance; therefore, there is a high activation barrier to reaction. N-protonation in these phosphorus amides provides a sufficiently good leaving group so that the energetically preferred pathway for reaction does not require formation of a pentacoordinate intermediate with loss of PO bond energy; therefore, the S_N2 pathway for phosphorus amides has a much lower energy barrier than the $S_N2(I)$ pathway for carboxylic amides. The demonstration of a linear transition state for phosphoramide monoesters[58] would appear to be due to the preference for the $S_N2(P)$ mechanism.

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