Acid-Catalyzed and Alkaline Hydrolyses of Phosphinamides. The Lability of Phosphorus–Nitrogen Bonds in Acid and the Mechanisms of Reaction[1]

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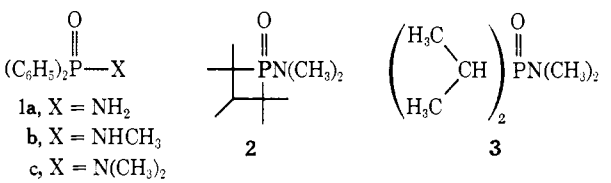
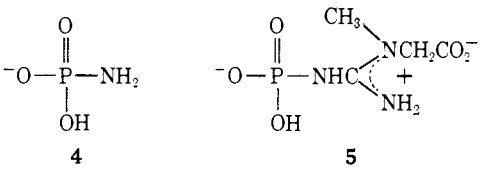
Abstract: The chemical dynamics of the hydrolytic cleavage of the P–N bond in phosphinamides, $R_2P(O)NR_2'$ ($R' = H, CH_3$), have been studied. The results reflect on the fundamental nature of the P–N bond and therefore are relevant to understanding phosphorus amides as solvents, synthetic intermediates, and phosphate transfer agents in biochemistry. Phosphinamides undergo alkaline hydrolysis with first-order dependence on [HO^-]. The rates are comparable to the alkaline hydrolysis of analogous carboxylic amides. Oxygen-18 studies of the basic hydrolysis reveal a small amount of ^{18}O exchange into unhydrolyzed amide: k(hydrolysis)/k(exchange) = 70. This may provide direct evidence for a pentacoordinate intermediate in the mechanism of alkaline hydrolysis. Although phosphinamides are no more reactive toward hydroxide than carboxylic amides, these amides hydrolyze in acidic solutions about 10^5 times more rapidly than carboxylic amides. In order to elucidate the source of this rate enhancement, a study was made of the hydrolysis of N-substituted diphenylphosphinamides (**1**), *N*,*N*-dimethyl-2,2,3,4,4-pentamethyltrimethylenephosphinamide (**2**), and *N*,*N*-dimethyldiisopropylphosphinamide (**3**). In acidic media, specific acid catalysis was observed for **1** in the pH range 1.5–3.5. The low solvent isotope effect, $k_D/k_H = 1.3$, and the highly negative activation entropy, $\Delta S^* = -35$ eu, indicate an A_2 mechanism. Partial hydrolysis in acidic $H_2{}^{18}O$ introduced 1 equiv of solvent oxygen into diphenylphosphinic acid. The variation in rate with nitrogen substituents, $\rho^* = -1.0$, is consistent with a mechanism involving the N-protonated species, and it is the tendency to protonate on nitrogen that appears to be the source of the lability of phosphorus amides. Introduction of angle strain at phosphorus in **2** produced a marked inhibition of hydrolysis: **2** reacts 10^3 times more slowly than its open-chain analog, **3**. This unusual retarding effect of small ring geometry in displacement at phosphorus together with the evidence for N-protonation indicates a process involving direct displacement rather than a pentacoordinate intermediate with significant stability.

Many studies of carboxylic amides have demonstrated the chemical dynamics of hydrolytic reactions.[2] In general, carboxylic amides are resistant to hydrolysis; high temperatures and strongly acidic or basic conditions are required. Both in acid and base, hydrolysis normally proceeds by nucleophilic attack to form a tetrahedral intermediate; after proton shifts resulting in protonation of nitrogen, the tetrahedral intermediate decomposes by loss of amine to form the products. In this paper we describe our studies on the hydrolysis of phosphorus amides **1**, **2**, and **3**; we conclude that the acid-catalyzed hydrolysis of a phosphinamide such as **1** proceeds over 10^5 times more rapidly than the corresponding carboxylic amide and by a fundamentally different mechanism.

There have been several studies of amides of phosphoric acid.[3,4] It has been known for some time that such amides could be highly reactive under mild conditions. These studies have demonstrated that a rate maximum occurs at the pH where the concentration of **4** is maximal; the P–N bond in **4** is cleaved in a unimolecular mechanism in which a metaphosphate ion, PO_3^-, is generated as a transient species.[3] In biochemistry, phosphorocreatine (**5**) is a source for rapid formation of ATP; we have shown that a metaphosphate mechanism is particularly favorable for **5**.[4]





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In our investigations of the fundamentals of the chemical dynamics of the P–N bond, we have chosen to study phosphinamides (for example, **1–3**),[5] because the structure of these amides precludes possible internal catalysis by the O^- and OH groups in **4** and **5**. The combination of knowledge of the hydrolysis of phosphinamides and phosphoramides provides considerable insight into the structure and chemical dynamics of P–N bonds.[3,4,6] We also have gained some insight into important concepts governing displacement at phosphorus in general.

Results

Under acidic conditions, phosphinamides **1a**, **1b**, and **1c** were readily hydrolyzed to phosphinic acid and amine (eq 1). We measured the rate of disappearance of phosphinamide in buffered 10% MeOH–H_2O (v/v) or

(1) Research supported by Grant AM-12743 from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service, and by Grant GP-29498 from the National Science Foundation. Parts of this research were communicated briefly: P. Haake and T. Koizumi, *Tetrahedron Lett.*, 4845 (1970).

(2) See, for example, C. O'Connor, *Quart. Rev., Chem. Soc.*, **24**, 553 (1970).

(3) The literature has been summarized by S. J. Benkovic and E. J. Sampson, *J. Amer. Chem. Soc.*, **93**, 4009 (1971).

(4) G. W. Allen and P. Haake, *ibid.*, **95**, 8080 (1973); P. Haake and G. W. Allen, *Proc. Nat. Acad. Sci., U. S.*, **68**, 2691 (1971).

(5) Derivatives of phosphinic acids are discussed in (a) G. Capozzi and P. Haake, *J. Amer. Chem. Soc.*, **94**, 3249 (1972); (b) P. Haake and C. E. Diebert, *ibid.*, **93**, 6931 (1971).

(6) D. A. Tyssee, L. P. Bausher, and P. Haake, *ibid.*, **95**, 8066 (1973); P. Haake and D. A. Tyssee, *Tetrahedron Lett.*, 3513 (1970).

20% (v/v) dioxane–water over the pH range 1.8–3.1. Most rates constants were obtained using a Cary 16 spectrophotometer with which we could measure the small absorbance differences accurately. Additional measurements made for **1c** by nmr agreed well with the rate constant obtained by following absorbance (Table I). Acidity was maintained by trichloro-, dichloro-, and chloroacetic acid buffers. Sodium chloride was added when necessary to maintain a constant ionic strength of 0.1 *M*. The rate constants were found to depend linearly on acid concentration (Table I). In all cases, log k_{obsd} *vs.* pH yielded a slope of −1.0. Therefore, these reactions obey the following

Table I. Rates of Acid Hydrolysis of Phosphinamides **1–3**

pH	10^4k_{obsd}, sec^{-1} for **1a**[a]	**1b**[a]	**1c**[a]	**2**[c,d]	**3**[c,d]
4 *M* $HClO_4$				0.029	
				0.031	
				0.031	
4 *M* H_2SO_4				0.0184	
				0.0192	
				0.0174	
1.87	12.7				0.30, 0.30
1.98	8.50				
2.18	6.37				
2.38	3.42	11.3	32.2		
2.38	3.73				
2.38	3.23[b]				
2.90	1.12	4.25	10.7		
2.90		3.73	10.0[e]		
2.90			9.95		
3.08	0.770	2.53	6.33		
k_{H^+}, M^{-1} sec^{-1}	0.085	0.32	0.82	7.5×10^{-7}	2.3×10^{-3}

[a] Pseudo-first-order rate constants evaluated spectrophotometrically at 273 nm in 10% MeOH–H_2O (v/v) at 29.2° except as otherwise indicated. Ionic strength was 0.1 *M*. [b] Evaluated at 225 nm. [c] Evaluated by nmr at 29.6° by integration of the N-$(CH_3)_2$ signals. [d] Solvent was 20% dioxane–water by volume.

$$H_2O + R'_2P(O)NR_2 \xrightarrow{H^+} R'_2PO_2H + HNR_2 \quad (1)$$

$$v = k_{obsd}[\text{phosphinamide}] = k_{H^+}[\text{phosphinamide}][H^+] \quad (2)$$

Unlike the other phosphinamides, hydrolysis of **2** was difficult and required highly acidic conditions. Rates measurable by nmr (Table I) were obtained in 4 *N* $HClO_4$ or 4 *M* H_2SO_4 containing 20% dioxane (v/v).

Activation parameters for the acid-catalyzed hydrolysis of **1a** were determined from rates at pH 2.38 over a 27° range in temperature (Table II). A good straight line was obtained for log *k* *vs.* $1/T$. Although there are the usual problems of errors in temperature and rate constants which lead to uncertainty in the ΔS^* value, ΔS^* should be quite accurate due to the large number of rate constants and the wide range of temperature.

Table II. Activation Parameters for the Acid-Catalyzed Hydrolysis of Diphenylphosphinamide (**1a**)

Temp, °K	10^4k_{obsd}, sec^{-1} [a]
298.2	2.97
302.3	3.46[b]
311.2	5.73[b]
321.0	9.55[b]
325.8	11.8
$\Delta H^* = 9.34$ kcal/mol	
$\Delta S^* = -35$ gibbs[c]	
$\Delta G^* = 19.8$ kcal/mol[c]	

[a] Rates were measured at pH 2.38. [b] Average of two values. [c] At 298.2°K, calculated from second-order rate constant.

Linear free energy relationships were found to exist between log k_{obsd} and σ^*[7] and log k_{obsd} and pK_a's of anilinium ions.[8] The ρ^* value is −1.0 and the slope *vs.* pK_a's is 1.9.

The solvent deuterium isotope effect was determined for **1a** in a buffered 10% MeOH–D_2O solution (Table III); $k_D/k_H = 1.3$. The correction[9] which can be made for isotopic dilution due to addition of protonated acid would increase k_D/k_H insignificantly. For **2**, the rate of hydrolysis was measured in 4 *M* D_2SO_4 containing 20% dioxane (v/v) using nmr to quantify the rate of hydrolysis. Two rates yielded $k_{obsd} = 2.30$ and 2.48×10^{-6} sec^{-1}. Therefore, using the average from Table I for 4 *N* H_2SO_4, $k_D/k_H = 1.3$ in the four-membered ring amide as for **1a**.

Table III. Solvent Isotope Effect for the Acid-Catalyzed Hydrolysis of Diphenylphosphinamide (**1a**)

pD (= pH + 0.4)[a]	$10^4k_{obsd}(D_2O)$, sec^{-1}	k_D/k_H[b]
2.16	8.35	1.30
2.35	5.05	1.29
2.56	2.93	1.27

[a] P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960). [b] Rate constants for H_2O were interpolated from Table I; temperature was 29.2°.

Alkaline Hydrolysis. The rates of hydrolysis of **1a**, **1b**, and **1c** in basic 10% CH_3OH–H_2O (v/v) at 90° were measured spectrophotometrically (Table IV).

Table IV. Alkaline Hydrolysis of Diphenylphosphinamides at 90.3°

Substituent	[NaOH]	10^5k_{obsd}, sec^{-1}	$10^5k_{obsd}/[OH^-]$
NH_2	0.1	1.55	15.5
NH_2	0.1	1.50	15.0
NH_2	0.2	2.78	13.9
NH_2	0.4	5.92	14.8
NHMe	0.4	2.77	6.93
NMe_2	0.4	0.560	1.40
NMe_2	0.4	0.569	1.42

The values of $k_{obsd}/[OH^-] = k_2$ are consistent with the rate law, $v = k_2[\text{amide}][HO^-]$. There was a fair correlation of log *k* with σ^*; $\rho^* = +1.0$.

^{18}O Studies. Phosphinamide **1a** was hydrolyzed in acid and basic 30% dioxane–70% ^{18}O water (v/v). The reactions were interrupted after partial hydrolysis and both the phosphinic acid, which is the product, and the unhydrolyzed phosphinamide were isolated, purified to remove contamination from solvent, and analyzed for ^{18}O by conversion to CO_2 (Table V).[10] The experiments with 0.20 atom % water establish control values

(7) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.
(8) A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961).
(9) E. L. Purlee, *J. Amer. Chem. Soc.*, **81**, 263 (1959).
(10) P. Haake and F. H. Westheimer, *ibid.*, **83**, 1102 (1961).

Table V. Hydrolysis of $(C_6H_5)_2P(O)NH_2$ in ^{18}O-Enriched Water

Conditions	% Hydrolysis	% Solvent H_2O	Atom % ^{18}O in[a] Product $(C_6H_5)_2PO_2H$	Atom % ^{18}O in[a] Recovered $(C_6H_5)_2P(O)NH_2$
pH 2.4	50	0.201	0.201	0.203
pH 2.4	50	1.770	0.913, Q = 0.91	0.201, Q = 0.00
pH 2.4	50	1.770	0.920, Q = 0.92	0.199, Q = 0.00
0.1 N NaOH	50	0.201	0.200	0.201
0.1 N NaOH	50	1.770	0.958, Q = 0.97	0.210, Q = 0.01
0.1 N NaOH	50	1.770	0.966, Q = 0.98	0.209, Q = 0.01
0.1 N NaOH	75	0.201	0.199	0.199
0.1 N NaOH	75	1.770	0.969, Q = 0.98	0.219, Q = 0.02

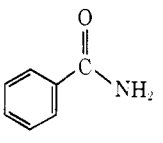
[a] Q values are the number of O atoms incorporated from water in the solvent.

for the Q values which are the number of atoms of oxygen incorporated from water in the solvent and are calculated by $Q = 2(\%\ ^{18}O \text{ in sample} - 0.201)/(\%\ ^{18}O \text{ in solvent} - 0.201)$. The ^{18}O incorporation into product is very close to 1 atom in both acidic and basic hydrolysis.

The validity of the ^{18}O incorporation into unhydrolyzed amide during alkaline hydrolysis might be questioned. Although the amount of incoporation is small (Q = 0.01 after 50% hydrolysis and Q = 0.02 after 75% hydrolysis), it does not appear to be an artifact. The most likely cause of ^{18}O contamination would be $Ph_2P^{18}O_2H$ or $H_2{}^{18}O$, but both these materials should have been removed by the washings with unlabeled water and two recrystallizations during purification. Also, if the enrichment were due to contamination, amide isolated and purified by the same procedures from the acid hydrolyses also should have been contaminated. Since it was not, the amide appears to be exchanging in base. This conclusion is supported by the doubled exchange in the 75% hydrolysis (2 half-lives) compared to the 50% hydrolysis (1 half-life).

Discussion

Alkaline Hydrolysis. In basic solution, phosphinamides undergo slow hydrolysis at rates similar to carboxylic amides; rate constants ($v = k$[amide][HO^-]) for analogous amides at 90° are



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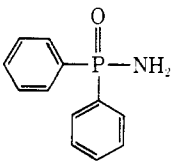


1a

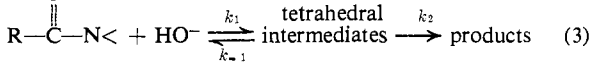
$k^{10a} = 12.5 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$ $k = 14.8 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$

These low rate constants demonstrate that even at 90° both of these amides react slowly with HO^- which is a very strong nucleophile toward acyl carbon and tetracoordinate, pentavalent phosphorus.[11] In comparison, carboxylic esters and phosphinic esters are hydrolyzed much more readily in alkali. Therefore, an important, immediate conclusion is that the unactivated P–N bond is neither inherently labile nor particularly susceptible to nucleophilic attack.

The alkaline hydrolysis of carboxylic amides is a relatively ancient problem in chemical dynamics.[12]

(11) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

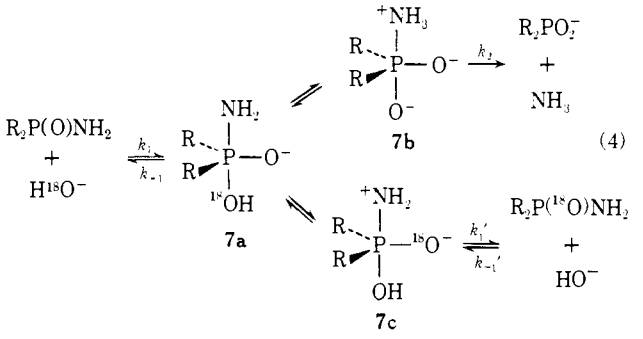
The extensive results are best summarized[2,13] by a mechanism (eq 3) involving tetrahedral intermediates.



$$\text{R—C(=O)—N<} + HO^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{tetrahedral intermediates} \xrightarrow{k_2} \text{products} \quad (3)$$

Substituents on nitrogen[14] have little net effect on the rate due to compensating effects on k_1 and k_2/k_{-1}. Electron donating substituents (*e.g.*, CH_3) decrease the rate of the first step due to the inhibition of hydroxide attack by the increased electron density at the carbonyl carbon atom. Electron-donating substituents at nitrogen increase the rate of the second step by increasing the concentration of the intermediate, $RC(O_2^-)N^+H_2R$, which decomposes to product. These effects are strikingly demonstrated by the nearly identical rates of hydrolysis for benzamide and dimethylbenzamide, yet the former exchanges ^{18}O four times faster than it hydrolyzes while the latter shows virtually no ^{18}O exchange.[15]

Our results on the alkaline hydrolysis of phosphinamides appear best explained by a mechanism (eq 4) involving intermediates which should have trig-



$$R_2P(O)NH_2 + H^{18}O^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\text{7a}}{R_2P(O)(NH_2)(^{18}OH)} \rightleftharpoons \underset{\text{7b}}{R_2P(O)(^+NH_3)(O^-)} \xrightarrow{k_2} R_2PO_2^- + NH_3 \quad (4)$$

$$\underset{\text{7a}}{R_2P(O)(NH_2)(^{18}OH)} \rightleftharpoons \underset{\text{7c}}{R_2P(^{18}O^-)(^+NH_2)(OH)} \underset{k_{-1}'}{\overset{k_1'}{\rightleftharpoons}} R_2P(^{18}O)NH_2 + HO^-$$

onal bipyramidal geometry with apical and basal substituents.[16] The intermediate (**7a**) would be expected to be formed initially due to polarity effects.[17] Hydrolysis requires a proton transfer to generate **7b** which should decompose to form products more readily than **7a** would decompose to form starting materials because NH_3 is a better leaving group than HO^-; that is, $k_2 > k_{-1}$. On the other hand, oxygen-18 exchange into amide requires both proton transfer and pseudorotations for **7a** → **7c**.

Substituents at nitrogen cause rate effects (Table IV) which yield $\rho^* = -1.0$. This demonstrates that the predominant substituent effect is in k_1 in contrast to phosphinic esters which are discussed in a subsequent paper.[16] This also leads to the conclusion that either the proton transfer required for **7a** → **7b** is rate determining, or **7b** is the favored tautomer in **7a** ⇄ **7b**. The latter appears reasonable if one considers the base strengthening effect on nitrogen of the two adjacent O^- substituents in **7b**. The following paper discusses another example of this in phosphoroguanidines.[4]

(12) E. E. Reid, *Amer. Chem. J.*, **21**, 284 (1899).
(13) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969.
(14) (a) M. L. Bender and R. J. Thomas, *J. Amer. Chem. Soc.*, **83**, 4183 (1961); (b) G. Cauzzo, U. Mazzucato, and A. Foffani, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Natur. Rend.*, **29**, 348 (1960).
(15) C. A. Bunton, B. Nayak, and C. O'Connor, *J. Org. Chem.*, **33**, 572 (1968).
(16) R. D. Cook, C. E. Diebert, W. Schwarz, P. C. Turley, and P. Haake, *J. Amer. Chem. Soc.*, **95**, 8088 (1973).
(17) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).

The results on ^{18}O exchange during the alkaline hydrolysis of **1a** (Table V) enable one to calculate the ratio of the rates of hydrolysis and exchange: k_h/k_e is approximately 70. Although this is a small amount of exchange, the result appears significant because the most likely pathway for exchange involves pentacoordinate intermediates (eq 4).[18] The large k_h/k_e ratio is not unexpected because of $k_2 > k_{-1}$ and because of the possible barrier to pseudorotation in pentacoordinate species such as **7a**.[16] In the alkaline hydrolysis of phosphinic esters, we have shown that there is no observable ^{18}O exchange in a solution enriched in ^{18}O by 1.6%, and the most likely barrier to ^{18}O exchange is the barrier to pseudorotation of the initially formed pentacoordinate intermediate.[16,17] The results in Table V indicate that **7a** can isomerize to **7c** but the precise mechanism is not obvious because of the likely barrier to pseudorotation of **7a**. One possibility involves **7a** → **7b** → **7c**.

These initial results on the alkaline hydrolysis of phosphinamides indicate that this may be a fruitful system for understanding the dynamics of pentacoordinate intermediates, and they demonstrate that phosphinamides are not inherently unstable toward nucleophilic attack.

Acid-Catalyzed Hydrolysis. *The second-order rate constant for acid-catalyzed hydrolysis of* **1a** *is 10^5 times greater than k_{H^+} for benzamide* (**6**).[19] This is in sharp contrast to the ratio, $k(\mathbf{1a})/k(\mathbf{6}) = 1.2$, for alkaline hydrolysis. The kinetic characteristics of phosphinamide hydrolyses are typical of an A_2 reaction: the reaction is first order in $[H^+]$ for **1a**, **1b**, and **1c**; the solvent deuterium isotope effect[20] is 1.3 for **1a** and **2**; and the entropy of activation is −35 eu for **1a**.[21] It is clear, therefore, that the rate-determining step is a nucleophilic attack by water on the protonated phosphinamide.[22] However, there are two important questions. Is the reactive species O-protonated or N-protonated? Is the water–phosphinamide complex a pentacoordinate intermediate of sufficient stability to be detected or does this reaction have the characteristics of a direct displacement reaction? The answers to these questions should be consistent with the large rate enhancement compared to carboxylic amides in acid but no rate enhancement in base although both reactions involve nucleophilic attack.

N-Protonated or O-Protonated Phosphinamide. In order to explain the rate differences, we must consider both the protonation step (K) and the step in which products are formed (k_2).

$$B + H^+ \underset{K}{\rightleftharpoons} BH^+ \xrightarrow[H_2O]{k_2} \text{products} \qquad (5)$$

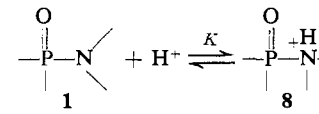
The rate law is $v = k_2[BH^+] = (k_2/K)[B][H^+]$ ignoring any changes in activity coefficients because we have used dilute acid in most of our studies.[5] The acidity constants, $K = [B][H^+]/[BH^+]$, are known for many carboxylic amides.[23] Although most phosphinamides are too labile in acid to allow measurements of pK's, the phosphetane ring in **2** slows the rate sufficiently so that we have been able to measure[24] the pK's of two phosphinamides.

	p$K(BH^+)$		p$K(BH^+)$
$C_6H_5C(O)NHCH_3$	−1.7	P(O)NHCH$_3$	−3.2
$C_6H_5C(O)N(CH_3)_2$	−1.4	**2**	−1.7

The pK of the methyl ester[24] of the four-membered ring phosphinate is close to the p$K(BH^+)$ of $(C_6H_5)_2P(O)OCH_3$[25] so the pK's for the four-membered ring amides are probably close to the pK's of $(C_6H_5)_2P(O)NR_2$. It appears, therefore, that the phosphinamides are similar in basicity to carboxylic amides so the rate difference between **1** and **6** must be due to k_2.

There is also a striking contrast between the rates of acid-catalyzed hydrolysis of **1** and an ester, *p*-nitrophenyl diphenylphosphinate:[26] *the amide* (**1**) *is about 10^4 times faster than the ester* at 30°. The data[25] on basicity of amides and esters indicate that these two compounds have comparable p$K(BH^+)$ values, so again we conclude that the reason for the rate difference must be k_2.

We suggest that the point of protonation of phosphinamides is important because it determines the reactivity of the protonated substrate. We propose that phosphinamides are labile in acid because the N-protonated amide (**8**) is the species which water attacks in the second step (eq 6). This proposal is supported by



1 **8** (6)

the following data and logic.

(1) Reaction through O-protonated phosphinamides is less likely than reactions through the N-protonated species because there is evidence that N-protonation is predominant.[24]

(2) Both carboxylic amides and phosphinate esters (which hydrolyze slowly in acid) appear to hydrolyze *via* an addition intermediate which is generated in the k_2 step (eq 5) by nucleophilic attack of water on the substrate protonated on the oxygen of the C=O or P=O group.[13,26] Since N-protonation converts the amide function into an excellent leaving group, it accounts for the great lability of phosphinamides in acid and accounts for the relative rates mentioned above.

(3) This mechanism is strongly supported by the rate effects of substituents on nitrogen. The order of reactivity in acid, **1c** > **1b** > **1a**, is opposite to carboxylic amides in acid and also opposite to phosphinamides in base (see above). The ρ^* of −1.0 must be explained by

(18) The only reasonable alternative to an exchange mechanism involving a pentacoordinate intermediate is direct displacement; this is exceedingly unlikely because it would require displacement of amide anions, $^-NR_2$, which are too strongly basic to be displaced by ^-OH. Thus, we conclude that it is probable that exchange and hydrolysis proceed through a common intermediate.

(19) I. Meloche and K. J. Laidler, *J. Amer. Chem. Soc.*, **73**, 1712 (1951).

(20) (a) C. A. Bunton and V. J. Shiner, Jr., *ibid.*, **83**, 42, 3207 (1961); (b) O. Reitz, *Z. Phys. Chem., Abt. A*, **183**, 371 (1938).

(21) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

(22) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 935 (1957); see also ref 6 for a comparative analysis of A_1 and A_2.

(23) (a) R. B. Martin, *J. Amer. Chem. Soc.*, **84**, 4130 (1962); (b) K. Yates and J. B. Stevens, *Can. J. Chem.*, **43**, 529 (1965); (c) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 339 (1963).

(24) P. Haake and T. Koizumi, *Tetrahedron Lett.*, 4849 (1970); T. Koizumi, L. P. Bausher, and P. Haake, unpublished results.

(25) P. Haake, R. D. Cook, and G. H. Hurst, *J. Amer. Chem. Soc.*, **89**, 2650 (1967).

(26) P. Haake and G. H. Hurst, *ibid.*, **88**, 2544 (1966).

a mechanism with positive charge on nitrogen in the transition state. This hypothesis is supported by the correlation of log k with pK_a's of anilinium ions—an equilibrium which should resemble **8** $\rightleftarrows$ **1** (eq 6). Since log k = 2.0(pK anilinium ions) + constant, it is clear that protonation on nitrogen is **a** potent labilizing force.

(4) The solvent deuterium isotope effect is consistent with an N-protonated substrate. A_2 reactions in which the reactive species is O-protonated exhibit solvent deuterium isotope effects of 1.3–1.7[20a] (*e.g.*, in acetamide, k_D/k_H = 1.45).[20b] Since N–H and O–H stretching vibrations are almost identical,[27] a similar isotope effect would be expected for eq 6.

(5) Garrison and Boozer[28] have studied the hydrolysis of 2,4-dichlorophenyl methyl *N*-methylphosphoramidate at 65.5°. Interpolating their rate data as a function of pH gives $k = 1.8 \times 10^{-4}$ sec^{-1} at pH 2.4. Extrapolating our data to 65.5° (Table II) gives $k = 24 \times 10^{-4}$ sec^{-1} at pH 2.4. The more than tenfold faster rate for the phosphinamide may be due to predominant O-protonation in the phosphoramidate and evidence for this site of protonation was presented by Garrison and Boozer. It is significant that their data on substituent effects gave $\rho^* = +3$ which is consistent with O-protonation and in the opposite direction to our findings thereby supporting reaction through **8** in phosphinamides.

(6) One would expect that nucleophilic attack of water on O-protonated substrate should generate a pentacoordinate intermediate, but we discuss below the evidence against an intermediate of sufficient stability to be detected.

(7) Although one might propose that there is no intermediate because the O-protonated species transfers a proton from O to N in the rate-determining step, probably involving a solvent molecule as a proton transfer agent, this proposal does not explain the deuterium isotope effect which should be $k_D/k_H < 1$ if proton transfer plays an important role in the transition state, and it probably would not explain the reactivity of phosphinamides.

Although there have been recent suggestions that carboxylic amides protonate predominantly on nitrogen in dilute acid, the known chemistry of amides makes that proposal dubious and it has been refuted recently.[29] There is certainly considerable evidence that the preferred point of protonation of carboxylic amides is the carbonyl oxygen so that a resonance-stabilized cation is generated. This research also contributes to this question because the relative rates of hydrolysis of **1a** and benzamide (**6**) are best explained by the difference in point of protonation. Since the rates of alkaline hydrolysis of **1a** and **6** are similar, there is no difference in susceptibility of >P(O)–N< and –C(O)–N< bonds to nucleophilic cleavage. Therefore, *the very large difference in rates of acid-catalyzed hydrolysis is best explained by the mode of activation by protons;* that is, there is O-protonation in carboxylic amides but N-protonation in phosphinamides.

(27) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958.
(28) A. Garrison and C. E. Boozer, *J. Amer. Chem. Soc.*, 90, 3486 (1968).
(29) (a) M. Liler, *J. Chem. Soc., Chem. Commun.*, 527 (1972); (b) H. Benderly and K. Roshenheck, *ibid.*, 179 (1972); (c) R. B. Martin, *ibid.*, 793 (1972).

Two structural factors appear to contribute to N-protonation of phosphinamides. (1) The structure of **1c** is known,[30] and the nitrogen atom is nonplanar although flattened relative to trimethylamine. The angles at N average 116° in **1c**. Therefore, the lone pair on nitrogen is less involved in π-bonding than in carboxylic amides. (2) In the O-protonated phosphinamide, phosphorus is tetracoordinate and this precludes the strong p–π resonance delocalization which is important in O-protonated carboxylic amide cations. Both factors appear to cause predominant N-protonation and hydrolysis through **8** (eq 6).

The unusually negative ΔS^* for the acid-catalyzed reaction supports our previous suggestion[6] that entropies of activation have to be carefully considered in order to relate them to mechanism. Bimolecular nucleophilic attack on O-protonated substrates generally results in ΔS^* values of approximately −20 gibbs.[21] The ΔS^* = −35 gibbs for hydrolysis of **1a** is probably partly due to the bimolecular reaction of **8** and H_2O and partly due to the entropy change on generation of **8** because of the strong solvation requirements of the $-NH_3^+$ group.

The Question of an Intermediate. In a communication reporting the relative rates of acid-catalyzed hydrolysis of **1**, **2**, and **3**, we suggested[31] that comparison of the rate of reaction of **2** with acyclic cases could provide a criterion of whether the mechanism was a direct displacement or, alternatively, involved an intermediate with sufficient stability and lifetime to be detected.[32] The criterion we suggested for stable pentacoordinate intermediates is the relative rate of strained cyclic, trimethylene phosphinates (such as **2**) and unstrained, acyclic analogs (such as **3**). The availability of a 90° C–P–C angle in a pentacoordinate intermediate and the possibility of pseudorotation[10,17] enables the strained ring in **2** to cause the rate acceleration[17] if an intermediate is involved, but in direct displacement the strained ring should cause rate retardation because of the need to expand the C–P–C ring angle in the transition state. In the alkaline hydrolyses of esters and phosphonium salts there is evidence for intermediates[16,33] and there are a number of examples of strain acceleration[34] following the classic research by Westheimer on ethylene phosphate. We find[31] the reverse, strain retardation, in the rates of solvolysis of phosphinyl chlorides[35] and acid-catalyzed hydrolysis of phosphinamides.

It is probably true that with most leaving groups the tendency of phosphorus to form pentacoordinate intermediates enables a lower energy barrier than would be possible in a concerted process.[31,35] But, with excellent leaving groups, the activation energy for formation of a pentacoordinate species could be higher than the activation energy of the reaction. The metastability of most pentacoordinate phosphorus compounds with respect to tetracoordinate compounds with P=O

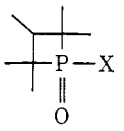
(30) M. Haque and C. N. Caughlan, *Chem. Commun.*, 921 (1966).
(31) P. Haake, R. D. Cook, T. Koizumi, P. S. Ossip, N. Schwarz, and D. A. Tyssee, *J. Amer. Chem. Soc.*, **92**, 3828 (1970).
(32) See particularly the last two paragraphs of ref 31.
(33) M. Zanger, C. A. VanderWerf, and W. E. McEwen, *ibid.*, **81**, 3806 (1959).
(34) P. Haake, R. D. Cook, W. Schwarz, and D. R. McCoy, *Tetrahedron Lett.*, 5251 (1968); W. Hawes and S. Trippett, *Chem. Commun.*, 577 (1968).
(35) P. Haake and P. S. Ossip, *J. Amer. Chem. Soc.*, **93**, 6924 (1971).

bonds supports the concept that pentacoordinate intermediates could have energies too high for participation in reactions with low activation energies.

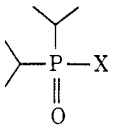
There are a number of experimental facts that bear on this question of mechanism into which we inquired earlier and which we address more fully now because of its fundamental importance in the chemical dynamics of reactions at phosphorus.

(1) The strained ring in **2** enhances the rate of alkaline hydrolysis of esters but inhibits the rates of solvolysis of $R_2P(O)Cl$ and $R_2P(O)N^+H_3$ (Table VI).[31,35]

Table VI. Effect of Angle Strain on Rates of Reaction at Phosphorus



2



3

Reaction	Nucleophile	X	Relative rates for 2	Relative rates for 3	Ref
a	HO^-	$-OCH_3$	100	1	16, 34
b	H_2O	-Cl	1	1500	35
c	H_2O	$-N^+H(CH_3)_2$	1	3000	Table I

It was subsequently suggested[36] that the rate retardations were due to electronegativity effects in trigonal-bipyramidal intermediates. This argument states that pentacoordinate intermediates are involved in all the reactions in Table VI, and that the rate retardations due to the four-membered ring are caused by strong apical preferences by the X group and by the entering group. This argument is doubtful because it rests on the basis that the chloro substituent in reaction b will have a much greater apical preference than the alkoxy substituent in reaction a. In order for this to be true, chloro substituents would have to be considerably more electronegative than alkoxy groups.[37] The reverse is true.[38]

Although Corfield, De'Ath, and Trippett[36] disagreed with our choice of **3** as a standard of comparison with **2**, this is a matter of little consequence since the important features of Table VI and our communication[31] are the *relative* comparisons, not the absolute comparisons. However, it does seem reasonable that the four α-CH_3 groups, which in **2** are held away from the reaction center by the 90° angles and are fixed in position, might approximate the steric effect caused by the rotating isopropyl substituents in **3**; therefore, the comparison of **2** with **3** enables an *approximate* determination of the strain effect with the steric effect removed.

Consistent with the lability of phosphinyl chlorides and the P–N bond of protonated phosphinamides, the data (Table VI) demonstrating strain retardation indicate that the normal geometry of the activated complex has entering and leaving groups colinear with the phosphorus atom. That is, the excellent leaving groups appear to enable product formation without the intervention of a pentacoordinate intermediate which could pseudorotate.[16] Therefore, this mechanism resembles SN2 displacements at carbon, and it seems likely that the colinear geometry is a consequence of the reactivity of the leaving group and the energy advantage of attack at the face of the tetrahedron opposite the breaking bond in order to maximize bond strengths along the reaction coordinate. This is an argument that has been used in SN2 reactions at carbon and has survived experimental and theoretical tests.

(2) Both the reactions involving strain inhibition have close analogies where the P–X bond breaks in a unimolecular decomposition: the solvolysis of di-*tert*-butylphosphinyl chloride is an SN1(P) reaction,[35] and the acid-catalyzed hydrolysis of *p*-nitrophosphinanilides is an $A_1(P)$ reaction.[6]

These data fit into a picture of a continuous spectrum of mechanisms for displacement at phosphorus ranging from reactions proceeding through a stable intermediate produced by association of nucleophile with the substrate[16] to unimolecular dissociation of the leaving group.[6,35] The former extreme involves cases where one has a poor leaving group and the intermediacy of pentacoordinate species is advantageous to the pathway of lowest energy between reactant and products; the latter extreme involves species so reactive that the leaving group dissociates in a unimolecular reaction. Solvolysis of phosphinyl chlorides and acid-catalyzed hydrolysis of phosphinamides involve leaving groups sufficiently labile so that it is reasonable that there should be a mechanism intermediate between these two extremes.

(3) Consistent with the hypothesis of direct displacement, there is no ^{18}O exchange during the acid-catalyzed hydrolysis of amides. However, although ^{18}O data have yielded definitive information on reactions at acyl carbon, the problem of apical and basal substituents[16] in pentacoordinate intermediates can cause ambiguity in interpreting ^{18}O results for hydrolysis of phosphinates as we have shown for reactions of phosphinate esters.[16]

(4) Part of the driving force for reactions b and c in Table VI undoubtedly comes from the much larger bond energy for P–O bonds than for P–N or P–Cl bonds.[39] As a $P-N^+$ or P–Cl bond breaks, a stronger P–O bond forms, and reaction by direct displacement allows the P=O bond to maintain its very large bond energy. In contrast, reaction through a pentacoordinate species would require that the P=O bond lose considerable bond energy. This factor is undoubtedly important in tipping the balance toward an SN2-like mechanism.

Although it is possible that **2** reacts by a nonlinear mechanism because of the strain barrier to the colinear pathway, the *normal* mechanism for these reactions appears to be an "SN2-like colinear direct displacement."[31] It may be significant that the relative rate ratio for **2** and **3** in Table VI (1:3000) is even larger than that for SN2 reactions of cyclobutyl bromide and isopropyl bromide (1:130).[40] There may be some increase in bond order, some pentacoordinate stabiliza-

(36) J. R. Corfield, N. J. De'Ath, and S. Trippett, *Chem. Commun.*, 1503 (1970).

(37) E. L. Muetterties and R. A. Schunn, *Quart. Rev., Chem. Soc.*, **20**, 245 (1966).

(38) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 3rd ed, Interscience, New York, N. Y., 1972, p 115; D. H. McDaniel and A. Yingst, *J. Amer. Chem. Soc.*, **86**, 1334 (1964).

(39) S. B. Hartley, W. S. Holmes, J. K. Jacques, M. R. Mole, and J. C. McCoubrey, *Quart. Rev., Chem. Soc.*, 17, 204 (1963).

(40) A. Streitwieser, *Chem. Rev.*, **56**, 571 (1956).

tion, during the acid-catalyzed hydrolysis of **1**, but it is clear from the above evidence that the dominant character of the reaction is an SN2-like direct displacement.

If **2** is an exception and does react by a nonlinear pathway, it should show up in stereochemical studies, and more data of the kind provided by Trippett and his colleagues[36] may answer this question.

Therefore, although the A_1 mechanism for *p*-nitroanilides[6] has become an A_2 mechanism for reaction of **1**, the P–N bond is highly labile and only a small energy contribution from nucleophilic attack appears to be needed for reaction. The data in the previous article[6] and this article demonstrate a blending of mechanisms for displacement at phosphorus, and this blending reaches the opposite extreme in the alkaline hydrolysis of phosphinate esters where we have found experimental evidence for pentacoordinate intermediates as discussed in a following paper.[16]

Application to Phosphates and Enzymic Catalysis. In the introduction we raised the question of the reasons for the reactivity of phosphoramidates such as **4** and **5**. Although the O^- and OH functional groups undoubtedly play a role, the above discussion demonstrates that the P–N bond is inherently susceptible to cleavage when a proton can be donated to the N atom. Even in **5**, which has a very weakly basic N atom bonded to phosphorus, we have recently shown[4] that N-protonation is likely to be the crucial event in cleavage of the P–N bond. For this reason, it is likely that the important characteristic of enzymes which catalyze the cleavage of P–N bonds, such as creatine kinase,[4] will be acid catalysis rather than nucleophilic catalysis as in many other enzymes.

Experimental Section

The solvent, 10% MeOH–H_2O (v/v), was prepared from Baker's spectroquality methanol and distilled water. The solutions were buffered with reagent grade trichloro-, dichloro-, and chloroacetic acids and sodium hydroxide. The ionic strength was maintained by the addition of reagent grade NaCl. The pH of the solutions was determined potentiometrically. Stock solutions of phosphinamide were prepared by dissolving phosphinamide ($6–9 \times 10^{-3}$ *M*) in 50% aqueous CH_3OH.

The phosphinamides were synthesized by reacting the appropriate phosphinyl chloride and amine in anhydrous pyridine.[41] The melting points of **1a** and **1c** are in excellent agreement with literature values. The formulas were verified by elemental analyses and the nmr and infrared spectra were consistent with structural assignments (Table VII).

D_2O Experiments. Reaction solutions were prepared as above, but D_2O (99.7%, Columbia Organic Chemicals) was substituted for H_2O. The pD was calculated by adding 0.4 to the pH reading.[42]

^{18}O Experiments. The buffer for acidic hydrolysis was prepared by dissolving chloroacetic acid (0.010 mol) and sodium hydroxide (0.005 mol) in ^{18}O-enriched water (35 ml). Diphenylphosphinamide (0.0024 mol) was dissolved in dioxane (15 ml) and mixed with buffer solution. The sealed mixture was maintained at a temperature of 30° for 15 hr. Sodium hydroxide (0.015 mol) was added and the solvent evaporated *in vacuo*. In the basic hydrolyses, we quenched by cooling and then evaporated the solvent. The residue was taken up in water (50 ml) and extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate, and evaporated yielding unreacted phosphinamide (after two recrystallizations from acetone–cyclohexane, mp 163–164°). Acidification of the aqueous layer induced phosphinic acid to precipitate (after recrystallization from CH_3OH–H_2O, mp 193.5–194.5°).

Unhydrolyzed amide and acid product were also isolated from blank runs in unenriched water. Control experiments eliminated the possibility of oxygen exchange into the product phosphinic acid under the hydrolysis conditions and subsequent work-up.

The amide and acid were analyzed for ^{18}O by conversion to CO_2 with a 1:1 mixture of mercuric chloride and mercuric cyanide and the data treated as previously described.[10] Mass spectral analyses were made on an MS 10.

Table VII. Analytical Data

	Diphenylphosphinamide (**1a**)
Yield	66%, mp 160–162° (lit.[41] 165–167°)
Anal.	Calcd for $C_{12}H_{12}NOP$: C, 66.41; H, 5.57; N, 6.46. Found: C, 66.33; H, 5.50; N, 6.43.
Nmr	τ 1.8–2.8 (phenyl), 6.7 (N–H)
Uv	225 nm (16,500), 260 (720), 266 (1300), 272.5 (1000)
	N-Methyldiphenylphosphinamide (**1b**)
Yield	31%, mp 112–114°
Anal.	Calcd for $C_{13}H_{14}NOP$: C, 67.53; H, 6.06. Found: C, 67.69; H, 6.03.
Nmr	τ 1.8–2.8 (phenyl), 6.8 (N–H), 7.35 (N–CH_3), J = 12.3 Hz
Uv	225 nm (15,800), 260 (1200), 266 (1500), 272.5 (1700)
	N,*N*-Dimethyldiphenylphosphinamide (**1c**)
Yield	70%, mp 105–106.5° (lit.[41] 103–105°)
Anal.	Calcd for $C_{14}H_{16}NOP$: C, 68.63; H, 6.58. Found: C, 68.72; H, 6.72.
Nmr	τ 1.8–2.8 (phenyl), 7.34 τ (N–CH_3), J = 11.0 Hz
Uv	225 nm (17,100), 261 (1480), 266.5 (1720), 274 (1330)
	N,*N*-Dimethyl-2,2,3,4,4-pentamethyltrimethylenephosphinamide (**2**)
Yield	~25%, mp 93–95°
Anal.	Calcd for $C_{10}H_{22}NOP$: C, 59.12; H, 10.83. Found: C, 59.31, H. 10.96.
Nmr	τ 7.27 (6 H, doublet, J = 10.6 Hz), 8.72 (6 H, doublet, J = 17.2 Hz), 8.75 (6 H, d, J = 17.3 Hz), 9.05 and 9.17 (3 H, 2 doublets, J = 1.5 Hz)
	N,*N*-Dimethyldiisopropylphosphinamide (**3**)
Yield	~40%, bp 100° (3 mm)
Anal.	Calcd for $C_8H_{20}NOP$: C, 54.24; H, 11.30. Found: C, 54.11; H, 11.18.
Nmr ($CDCl_3$)	τ 7.35 (6 H, doublet, J = 7.5 Hz), 7.95 (2 H, multiplet) 8.7–9.2 (12 H, 2 quartets, J = 15.2 and 4.2 Hz)

Acknowledgment. We thank Patricia C. Turley for valuable discussions.

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