Displacement at Phosphorus by a Mechanism with A₁ Character. Acid-Catalyzed Hydrolysis of Phosphinanilides[1,2]

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Abstract: Studies of the acid-catalyzed hydrolysis of phosphinanilides demonstrate that protonation has a profound labilizing effect on P–N bonds. In H_2SO_4, N-(p-nitrophenyl)diphenylphosphinamide exhibits a kinetic dependence on h_0 with rate law, $v = k[\text{amide}]h_0^{0.59}$, and nonlinear dependence of log k on log [acid]. Examination of the dependence of the rate constants on acidity functions indicates an A_1 mechanism: application of the Zucker–Hammett or Bunnett methods requires an acidity function which correctly describes the protonation behavior of the substrate—when log k is plotted $vs.$ H_A, the acidity function for amides, a straight line with slope 1.0 results. This analysis of the dependence of rate on acidity and the large solvent isotope effect, $k_D/k_H = 2.8$, provides strong evidence for an A_1 mechanism. The variation in rate with N-aryl substituents, $\rho = -1.7$, is consistent with a transition state involving the N-protonated species. Although $\Delta S^* = -25$ eu, ΔS^* is a combination of ΔS (protonation) and ΔS (rate-determining step), and an A_1 mechanism is indicated when the entropy of protonation is considered. All of this evidence indicates that, in this case, hydrolysis proceeds by a dissociative mechanism and the transition state must have some of the character of a phosphinylium ion. A mechanism with more associative character is indicated in the acid-catalyzed hydrolysis of N-(phenyl)methylphenylphosphinamide by the smaller deuterium solvent isotope effect, $k_D/k_H = 2.3$. Acid-catalyzed methanolysis of the (−)-S enantiomer gave optically active, inverted product (−)-(S)-methyl methylphenylphosphinate. These data indicate a merging of associative and dissociative mechanisms in the acid-catalyzed hydrolysis of phosphinamides, with the structure of the transition state dependent upon the nucleophilicity of the leaving group. These results indicate enzymatic labilization of P–N bonds by acid catalysis.

There has been considerable interest in the chemistry of compounds with P–N bonds.[4] Phosphoramidates have been used in phosphorylation reactions for the synthesis of phosphate derivatives, and more detailed studies of the chemical dynamics have demonstrated that the P–N bond of $^-HO_3PNHR$ is unstable and either generates the reactive metaphosphate ion, PO_3^-, in a unimolecular, dissociative decomposition or undergoes rapid bimolecular transfer of the PO_3^- moiety to generate a new phosphate derivative.[4–6]

This lability of P–N bonds plays an important role in biochemical systems for phosphorylation of various substrates.[6d] Most notably, phosphorocreatine (**1**) functions as a phosphagen, phosphorylating ADP to generate ATP in a reaction catalyzed by creatine kinase. Our solvolytic studies of **1** indicate that the mechanism is one of the clearest examples yet found of phosphorylation by a dissociative reaction with production of PO_3^- as an intermediate.[7]

The multifunctional nature of phosphates is probably important to their roles in life. For example, in **1** the OH and O⁻ groups have been shown to be essential for rapid cleavage of the P–N bond. Therefore, studies of phosphate derivatives do not necessarily permit one to elucidate the fundamental properties of P–N bonds because of the perturbing effects of the other functional groups at phosphorus.

For these reasons, in our research directed toward understanding the fundamental chemistry of individual functional groups at phosphorus,[3] we have investigated mainly derivatives of phosphinic acids (*e.g.*, **2**) which are monofunctional. This article examines the acid-catalyzed hydrolysis of phosphinanilides (**3**) with particular attention to **4**. The results enable one to better assess the lability of P–N bonds and they provide better understanding of the balance between associative and dissociative displacement at phosphorus.[8b] The results demonstrate that the P–N bond is very labile in acid and that there is a spectrum of mechanisms from a largely dissociative, A_1 mechanism for **4** to a merged A_1 and A_2 mechanism for **5** to an associative, A_2 mechanism for **6**.[9–11]

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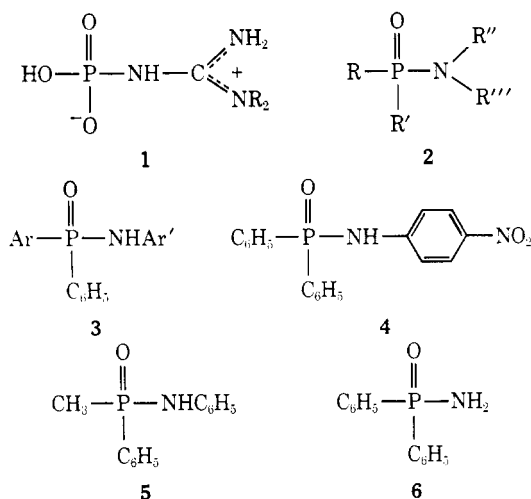
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(8) See the following articles and previous articles which have summarized our research on: (a) esters, C. E. Diebert and P. Haake, *J. Amer. Chem. Soc.*, **93**, 6931 (1971); (b) halides, P. Haake and P. S. Ossip, *ibid.*, **93**, 6924 (1971); (c) basicity, P. Haake, R. D. Cook, and G. Hurst, *ibid.*, **89**, 2650 (1967); P. Haake and T. Koizumi, *Tetrahedron Lett.*, 4849 (1970); (d) linear free energy relations, P. Haake, *et al.*, *ibid.*, 5247 (1968); (e) mass spectrometry, P. Haake, M. Frearson, and D. E. Diebert, *J. Org. Chem.*, **34**, 788 (1969); P. Haake and P. S. Ossip, *Tetrahedron*, **24**, 565 (1968).

(9) For **6** and related compounds, see T. Koizumi and P. Haake, *J. Amer. Chem. Soc.*, **95**, 8073 (1973).

(10) For other research on phosphinanilides, see (a) I. N. Zhmurova and A. V. Kirsanov, *Zh. Obshch. Khim.*, **33**, 1015 (1963); (b) G. Tomaschewski and G. Kuhn, *J. Prakt. Chem.*, **38**, 222 (1968).

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Figure 1. Dependence of log $(10^5 k_1)$ for the hydrolysis of N-(p-nitrophenyl)diphenylphosphinamide on $-H_0$ (———) and log $[H_2SO_4]$ (- - - - -) in H_2SO_4 solutions.

Results

Under acidic conditions, phosphinanilides are readily hydrolyzed (eq 1). The kinetics of this reaction can be

$$H_2O + 3 \xrightarrow{H^+} \underset{Ar}{\overset{C_6H_5}{\diagdown}} PO_2H + H_2NAr' \qquad (1)$$
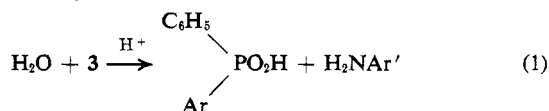
accurately determined by spectrophotometric observation of the decrease in concentration of **3**. The most detailed results were obtained for the p-nitroanilide (**4**) for which pseudo-first-order rate constants were evaluated with catalysis by sulfuric acid (Table I) and per-

Table I. Kinetics for the H_2SO_4 Catalyzed Hydrolysis of N-(p-Nitrophenyl)diphenylphosphinamide at 30.0° [a]

$[H_2SO_4]$	$H_0{}^b$	$H_A{}^c$	$10^5 k_{obsd}$, sec^{-1}
1.14	−0.29		7.73
2.29	−0.91	−0.96	22.5
3.43	−1.43	−1.40	43.3
4.00	−1.73	−1.59	73.7
4.58	−2.02	−1.77	112.2
5.03	−2.25	−1.91	142.8
5.72	−2.63	−2.10	219.7
6.29	−3.03	−2.27	375.0
6.86	−3.37	−2.45	526.7

[a] 10% dioxane–90% water (v/v). [b] H_0 from linear interpolation of H_0 given by Noyce and Jorgenson[14] for 5% dioxane–acid solutions. [c] From linear interpolation of H_A given for aqueous solutions.[15]

chloric acid (Table II). The solvent, 10% dioxane–90% water (v/v), was used because of the insolubility of **4** in a lower concentration of dioxane. The dependence of log k_1 on H_0 (the Hammett acidity function)[12–14] and log $[H_2SO_4]$ is displayed in (Figure 1). Similarly, there is a linear dependence of log k_1 on H_0 for $HClO_4$ (data from Table II, slope = 0.56) and nonlinear dependence of log k_1 on log $[HClO_4]$.[2] The clearly nonlinear dependence on log [acid] is particularly significant.[12] When log k_1 (Table I) is plotted against H_A, the acidity function based on substituted benzamides,[15] the slope is
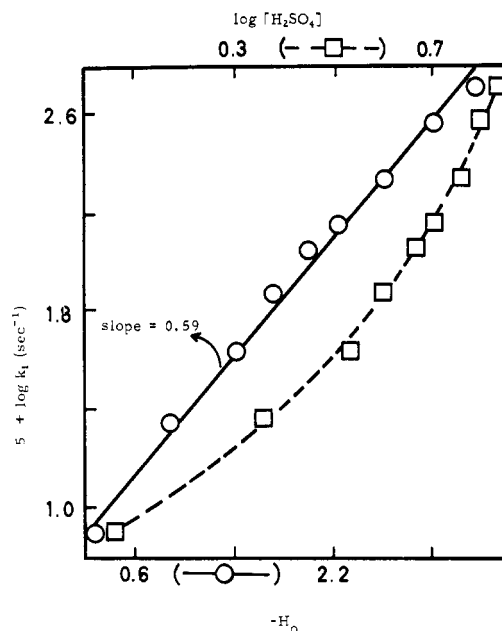
Table II. Kinetics for the $HClO_4$ Catalyzed Hydrolysis of N-(p-Nitrophenyl)diphenylphosphinamide at 25.0° [a]

$[HClO_4]$	$H_0{}^b$	$10^5 k_{obsd}$, sec^{-1}
0.1		0.5
0.44		2.18
0.908	−0.15	5.0
1.73	−0.64	9.4
2.59	−1.05	16.1
3.46	−1.49	27.5
4.38	−1.91	48.2

[a] 10% dioxane–90% water (v/v). [b] From linear interpolation of H_0 given by Paul and Long.[12]

1.0, and this indicates that H_A is an appropriate acidity function for protonation of **4**. The data in Tables I and II have been analyzed[2] by the methods[16,17] suggested for analysis of solvation (eq 2 and 3). It seems particularly significant that the slopes, w and ϕ, are within experimental error of zero when H_A is used as the acidity function.

$$\log k_1 + H_x = w(\log[\text{free } H_2O]) + \text{constant} \qquad (2)$$
$$H_x = H_0 \quad w = 2.4 \text{ in } H_2SO_3, 3.4 \text{ in } HClO_4$$
$$H_x = H_A \quad w = -0.1 \text{ in } H_2SO_4$$

$$\log k_1 + H_x = \phi(\log[\text{acid}] + H_x) + \text{constant} \qquad (3)$$
$$H_x = H_0 \quad \phi = 0.54 \text{ in } H_2SO_4, 0.70 \text{ in } HClO_4$$
$$H_x = H_A \quad \phi = -0.07 \text{ in } H_2SO_4$$

Activation parameters for acid-catalyzed hydrolysis of **3** were determined in 0.49 M $HClO_4$ (Table III). Although there must be considerable uncertainty in ΔS^*, it should be accurate to ±5 cal/(deg mol) possible deviation.[18]

Substituents were varied in both P-aryl and N-aryl

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(16) P. Haake and G. H. Hurst, J. Amer. Chem. Soc., **88**, 2544 (1966).
(17) J. F. Bunnett and F. P. Olson, Can. J. Chem., **44**, 1917 (1966); J. F. Bunnett, J. Amer. Chem. Soc., **83**, 4956 (1961).
(18) S. W. Benson, "Foundations of Chemical Kinetics," McGraw-Hill, New York, N. Y., 1960.

Table III. Activation Parameters for the Acid-Catalyzed Hydrolysis of N-(p-Nitrophenyl)diphenylphosphinamide

Temp, °K	k, sec^{-1} [a]
298.2	2.58×10^{-5}
307.8	6.09×10^{-5}
317.3	14.39×10^{-5}

$E_a = 17.0$ kcal/mol	$\Delta G^* = 23.8$ kcal/mol
$\Delta H^* = 16.4$ kcal/mol	$\Delta S^* = -25$ cal/(deg mol)

[a] In 10% dioxane–90% H_2O; [$HClO_4$] = 0.49 M.

rings of **3**. The rate constants for the P-aryl substituted compounds are given in Table IV, and the rate

Table IV. Kinetics for the Acid-Catalyzed Hydrolyses of N-(p-Nitrophenyl)arylphenylphosphinamides at 25.2° [a]

[$HClO_4$], M	10^5k, sec^{-1} for 3 with Ar' = p-$NO_2C_6H_4$, Ar =			
	p-NO_2-C_6H_4	p-Cl-C_6H_4	p-CH_3O-C_6H_4	C_6H_5
0.49	1.10	1.44	1.87	2.58
1.02	2.46	3.11	4.13	5.43
2.01	5.74	6.97	9.90	12.55

[a] Solvent was 10% dioxane–90% water (v/v), [amide] approximately 7.5×10^{-5} M.

constants for the N-aryl substituted compounds are in Table V. In the latter case, the wavelength of observa-

Table V. Kinetics for the Acid-Catalyzed Hydrolyses of N-Aryldiphenylphosphinamides at 25.2° [a]

$HClO_4$[b]	10^5k, sec^{-1} for 3 with Ar = C_6H_5, Ar' =		
	p-NO_2-C_6H_4	C_6H_5	p-CH_3O-C_6H_4
0.49	2.58	56.7	161.0

[a] 10% dioxane–90% water (v/v), [amide] approximately 10^{-4} mol/l. with the exception of Ar = p-$NO_2C_6H_4$ for which [amide] approximately 7.5×10^{-5} M. [b] Concentration expressed in mol/l.

tion was changed in order to observe the decrease in concentration of **3**.

The stereochemistry of the acid-catalyzed *methanolysis* of $(-)$-(S)-N-(phenyl)methylphenylphosphinamide **(5)** was determined by polarimetric methods. A solution of optically pure anilide ($[\alpha]^{22}D$ $-31°$, **[5]** = 0.0074 M, [H_2SO_4] = 0.09 M) reacted rapidly to give nonracemic product with a pseudo-first-order rate constant of 0.002 sec^{-1}. The specific rotation of the product, methyl methylphenylphosphinate, was $-40°$. This $[\alpha]D$ is close to that reported for $(-)$-(S)-ethyl methylphenylphosphinate, $[\alpha]D$ $-45°$,[19] and is evidence that methanolysis of **5** proceeds with predominant inversion.

Solvent deuterium isotope effects were evaluated in dilute $HClO_4$ for **4** and **5** (Table VI). Because the deuterated solution was prepared from reagent 70% $HClO_4$, there was a slight dilution of the deuterium content. However, since the net D content was >95%, the observed values would be corrected by only a small amount;[20] k_D/k_H for **4** would be increased to 2.8. For **5**, the correction includes temperature extrapolation to 25°,[20] and results in k_D/k_H = 2.3.

(19) K. E. DeBruin and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 7393 (1969).

(20) E. L. Purlee, *J. Amer. Chem. Soc.*, **81**, 263 (1959).

Table VI. Solvent Deuterium Isotope Effect for the Hydrolyses of Phosphinamides[a]

Phosphinanilide	[$HClO_4$]	10^5k_{obsd}, sec^{-1}		k_D/k_H
		D_2O	H_2O	
N-(p-Nitrophenyl)diphenyl[b] (4)	0.85	12.6	4.72	2.7
N-(Phenyl)methylphenyl[c] (5)	0.0085	88.0	38.7	2.3

[a] Rate measurements in 10% dioxane–90% water (v/v). [b] Temperature was 25.2°. [c] Temperature was 30.1°.

Discussion

It is clear that phosphinanilides are considerably more reactive in acid than benzanilides. The analog to **4**, benz-p-nitroanilide, has a pseudo-first-order rate constant of 5.3×10^{-5} sec^{-1} at 90° in 1 M acid with 80% ethanol as the solvent;[21] at the same temperature, **3** would hydrolyze over 10^2 more rapidly.

Dependence of Rate on Acidity. Benzanilides hydrolyze with log k linearly dependent on log [acid].[21] This is in contrast to **4**; Figure 1 demonstrates linear dependence of log k_1 on H_0 and nonlinear dependence on log (C_{acid}). This would indicate an A_1 mechanism by the Zucker–Hammett hypothesis if the slope of log k_1 *vs.* H_0 were close to 1.0;[12,13] the slope in this case is 0.59, and a more detailed analysis of the data is advisable.

It is especially noteworthy that our previous studies[16,22] have demonstrated that phosphinyl substrates, $R_2P(O)X$, have protonation behavior which differs from Hammett bases. This differing protonation behavior of phosphinates compared to anilines, on which the H_0 scale is based, has been considered and the difference appears to be due to differences in activity coefficient changes as acidity changes.[22] The slopes of log ([BH^+]/[B]) against $-H_0$ are 0.46 for (C_6H_5)$_2$-PO_2CH_3 and 0.70 for (C_6H_5)$_2P(O)CH_3$. These protonation functions, therefore, show slopes close to the slope of 0.6 found in Figure 1; the similarity suggests that the deviation from 1.0 is due to activity coefficient changes and that the dependence of log k for hydrolysis of **4** on H_0 indicates an A_1 mechanism by the Zucker–Hammett approach.[13]

This conclusion is reinforced by a correlation of log k *vs.* H_A (Table I).[15] The indicators for H_A are benzamides, and previous research on H_A would lead one to expect that H_A function would describe protonation of **4** better than H_0.[23] The plot of log k_1 against H_A is a straight line with slope 1.02 which is fully consistent with an A_1 mechanism.

We have also examined[2] other proposals for analyzing acid-catalyzed reactions. The Bunnett approaches[17,24] to solvation of acid-catalyzed reactions were applied to our data using the concentration of free H_2O as described in an earlier paper.[16] Although our earlier paper[16] described a failure of the Bunnett methods in 40% dioxane, it was subject to criticism because of the large amount of organic solvent which was present. This study,[2] however, also fails to validate these methods using H_0, an acidity function which is

(21) G. Cauzzo, V. Mazzucato, and A. Foffani, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Natur., Rend.*, **29**, 348 (1960); *Chem. Abstr.*, **56**, 12796f (1962).

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

(23) L. M. Sweeting and K. Yates, *Can. J. Chem.*, **44**, 2395 (1966).
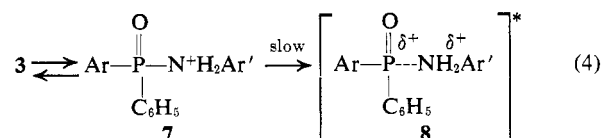
(24) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4968, 4973, 4978 (1961).

based on indicators with different activity coefficient behavior from the substrate.[25] The problem with analysis of solvation changes is that solvation of ions and neutral solutes changes as acidity changes. This is demonstrated by the large changes in activity coefficients as acidity changes.[12] Therefore, the analyses of solvation changes will only give reliable results when the solvation changes are similar for substrate and indicator bases—that is, when substrate and indicator have the same changes in activity coefficients over the range of acidity which is used. When H_A is used as the indicator, both w and ϕ values are consistent with an A_1 mechanism.

An important conclusion seems clear: the crucial requirement for proper treatment, either by the Zucker–Hammett or Bunnett methods, of the kinetics of an acid-catalyzed reaction is an acidity function that properly describes the protonation of the substrate.[26] It is also important to note that the simple Zucker–Hammett hypothesis can frequently be used to distinguish A_1 and A_2 mechanisms on the basis of linear correlations of log k *vs.* H_0 and log [acid]. It is interesting that the method works with slopes deviating widely from 1.0 both here and in other cases.[12]

Solvent Deuterium Isotope Effect. Precedent and the methods developed[27] for analysis of solvent deuterium isotope effects on acid-catalyzed reactions predict that, in an A_1 mechanism, k_D/k_H will be in the range 1.9–2.9, and in an A_2 mechanism, k_D/k_H will be less than 1.9. These predictions are supported by experimental results.[27] Relevant known data for acid-catalyzed reactions include hydrolysis of acetamide (A_2), $k_D/k_H <$ 1.5;[28] hydrolysis of aryl sulfates (A_1), $k_D/k_H =$ 2.4;[29] hydrolysis of S-aryl thiosulfates (A_2), $k_D/k_H =$ 1.4.[29] Comparison of the latter two results is particularly instructive because the similarity in structure should lead to similar degrees of hydrogen bonding in neutral and protonated species. Therefore, there is a clear difference between the k_D/k_H values for A_2 and A_1 hydrolyses.[29] Also, we might expect the results on sulfates to be reasonable guides for analysis of data on phosphinates. The value, $k_D/k_H =$ 2.7, for the hydrolysis of **4** (Table VI), is a clear indication of an A_1 mechanism. It is consistent that $K_a(H)/K_a(D)$ is 2.6–2.7 for dissociation of nitroanilinium ions.[30] That is, almost all the deuterium isotope effect appears to be due to the change in degree of protonation at the nitrogen atom of the phosphinanilide, **4**, as one would expect in the only reasonable A_1 mechanism (eq 4).

Position of Protonation in the Reactive Species. Substitution for the nitro group in **4** has a pronounced effect on the rate of hydrolysis (Table V). Although we have studied only three N-aryl compounds, the inclusion of p-methoxy and p-nitro substituents, which

(25) It is relevant that a study[10] in 60:40 dioxane–water of bis(p-nitrophenyl)phosphinanilide gave results very similar to those in Figure 1; therefore, the amount of dioxane does not appear to affect the validity of the Hammett and H_A methods.

(26) Other authors have previously commented on this problem. See ref 15, 23, and (a) E. M. Arnett and G. W. Mach, *J. Amer. Chem. Soc.*, **88**, 1177 (1966); (b) J. T. Edward and J. K. Liu, *Can. J. Chem.*, **47**, 1117 (1969).

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(29) (a) J. L. Kice and J. M. Anderson, *J. Amer. Chem. Soc.*, **88**, 5242 (1966); (b) J. L. Kice, J. M. Anderson, and N. E. Pawlowski, *ibid.*, **88**, 5245 (1966).

(30) E. Hogfeldt and J. Bigeleisen, *J. Amer. Chem. Soc.*, **82**, 15 (1960).

$$3 \rightleftharpoons \text{Ar}—\overset{\overset{O}{\|}}{\underset{\underset{C_6H_5}{|}}{P}}—N^+H_2\text{Ar}' \xrightarrow{\text{slow}} \left[\text{Ar}—\overset{\overset{O}{\|}\,\delta^+}{\underset{\underset{C_6H_5}{|}}{P}}\overset{\delta^+}{---}NH_2\text{Ar}' \right]^* \quad (4)$$
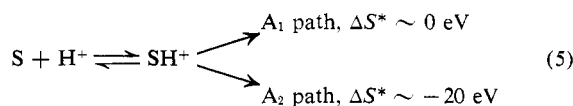
have widely differing substituent effects, makes this a satisfactory set for elucidation of the information desired. The results in Table V are in contrast to results on the rates of acid-catalyzed hydrolysis of benzanilides[21] where $\rho =$ 0.58. The ρ we observe from Table V is -1.73: in the opposite direction and much larger. If hydrolysis of **3** (Ar $=$ C_6H_5) were proceeding by protonation on oxygen followed by bimolecular reaction with water, one would expect a much smaller ρ and probably positive by analogy to benzanilides. Rather, $\rho =$ -1.73 is most satisfactorily explained by a mechanism in which the transition state (**8**) has positive charge on nitrogen thereby leading to a negative ρ of considerable magnitude.

If this conclusion is correct, the ground state → transition state transformation (that is, **3** → **8**) is similar to the protonation of anilines. Therefore, there should be a linear free energy relationship, and in agreement we find that the log k_1 values for N-aryl substitution (Table V) correlate linearly with pK_a's of anilinium ions and the slope is 0.4. This suggests that the transition state does have considerable anilinium ion character and therefore is consistent with reaction through an N-protonated species. The slope of 0.4 also indicates considerable bond-breaking in the transition state. That is, the log k values reflect changes in the ground state (**3**), which is neutral, to the transition state (**8**); a slope of 0.4 indicates only a partial positive charge on the nitrogen atom in **8**.

We have no evidence which would elucidate the predominant position of protonation of **4**. However, the N atom of **4** would be expected to be very weakly basic due to the two electron-withdrawing substituents to which it is bonded. The phosphinyl oxygen, on the other hand, might be expected to be about as basic as in $(C_6H_5)_2PO_2CH_3$ for which a p$K_a =$ -4.8 has been measured.[16] We therefore expect that **4** is predominantly protonated on oxygen, but the less stable, N-protonated tautomer (**7**) is the reactive species.

Entropy of Activation. The use of ΔS^* for distinguishing between A_1 and A_2 mechanisms is based upon the greater ordering necessary in the transition state of an A_2 reaction. The guidelines in eq 5 are

$$\text{S} + \text{H}^+ \rightleftharpoons \text{SH}^+ \begin{cases} \nearrow A_1 \text{ path, } \Delta S^* \sim 0 \text{ eV} \\ \searrow A_2 \text{ path, } \Delta S^* \sim -20 \text{ eV} \end{cases} \quad (5)$$

roughly appropriate for oxy bases.[31] The entropy of activation observed for hydrolysis of **4** (Table III) is -25 eu. The observed ΔS^* for acid-catalyzed reactions actually consists of ΔS (protonation) $+ \Delta S^*$ (reaction of protonated substrate). The guidelines in eq 5 were deduced on the basis of experimental data for substrates for which the point of protonation is a weakly basic *oxygen* atom. The above discussion (especially the substituent effects) strongly supports protonation on the *nitrogen* atom in the acid-catalyzed hydrolysis of **4** (see eq 4). This difference makes it essential to ob-

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

serve Schaleger and Long's warning:[31] "the entropy criterion must be exercised with caution." Entropies of protonation of nitrogen bases appear to vary with the acidity of the ammonium ion, becoming negative in very acidic anilinium ions.[32] The very high acidity of 7 (eq 4) would be expected to cause a high degree of solvation so that ΔS (protonation) of 4 would be quite negative compared to other secondary amines; therefore, it is possible for ΔS (protonation) to be on the order of -20 eu,[33] so that the observed ΔS^* value of -25 eu for 4 may be approximately correct for unimolecular breakdown of 7.

P-Aryl substituents cause small but significant effects (Table IV). With an A_1 mechanism established, these effects add information on the structure of the transition state (8). Since both the p-CH_3O and the p-NO_2 substituents cause slower rates of hydrolysis than in the unsubstituted ring, log k is not linear with σ_p (pK_a's of $ArCO_2H$)[12a] or σ_P (pK_a's of arylphosphonic and -phosphinic acids).[34] However, log k_1 (Table IV) does correlate well with the pK_a's of 4-substituted bicyclo[2.2.2]-octane-1-carboxylic acids in which only inductive effects are involved.[35] This result appears to be experimental evidence for an electronic structure of the developing R_2PO^- ion[8b] involving strong p–p π-bonding in the P–O bond and for the A-frame conformation[36,37] of the two P-aryl rings in the transition state. Both effects will minimize the extent of aryl–phosphorus π interaction in the transition state so that only inductive effects are observed: in the A-frame conformation[36] the p orbitals of the aryl rings are orthogonal to the p–p, P–O π bond in R_2PO^+,[8b] so that only the inductive effects of substituents are effective in the transition state.

Merging of A_1 and A_2 Mechanisms. This discussion of our results has provided considerable evidence for the hypothesis that 4 hydrolyzes by an A_1 reaction *via* a transition state resembling 8. Yet, other data suggest that small perturbations can shift the transition state so that there is A_2 character and the reaction involves merging of A_1 and A_2 mechanisms. The most striking result in support of this is the stereospecific inversion which we observe in the methanolysis of 5. The lower deuterium isotope effect, $k_D/k_H = 2.3$, for 5 indicates that the mechanism of reaction has less A_1 character than in the case of 4. That is, the mechanism of reaction of 5 appears to be a merged A_1–A_2 reaction. This stereochemical result therefore appears to be due to participation of nucleophilic solvent in the transition state leading to reaction of the phosphinylium ion be-

fore solvent can intervene between the R_2PO^+ ion and the departing aniline. The known instability of R_2PO^+ intermediates is consistent with such participation by solvent as the protonated substrate becomes less reactive.[8b]

The solvent deuterium isotope effects, k_D/k_H, are 2.8, 2.3, and 1.3 for acid-catalyzed hydrolysis of 4, 5, and 6; therefore, the respective mechanisms may be characterized as A_1, merged A_1–A_2, and A_2. These results support the concept that as the leaving group in 8 becomes more nucleophilic, the mechanism merges toward A_2 until it is pure A_2 in the case of 6.[9] The position of the transition state on the reaction coordinate appears to shift depending on the nucleophilicity of the leaving group in 8. When 4 is protonated, the leaving group is p-nitroaniline which has low nucleophilicity and departs so readily that little or no solvent assistance is required to reach an A_1 transition state. When 5 is protonated, the leaving group is aniline which has moderate nucleophilicity and some solvent participation is required to reach a merged A_1–A_2 transition state which leads to stereochemical inversion in CH_3OH. When 6 is protonated, the leaving group is NH_3 which has high nucleophilicity and full solvent participation is required to reach an A_2 transition state.

After this work was largely completed,[2] Tomaschewski and Kuhn[10] published a related study of the hydrolysis of diarylphosphinanilides in 60:40 dioxane–water. They favored an A_2 mechanism but could not definitely rule out an A_1 mechanism. This problem is clarified by the above discussion; since their leaving group is aniline, they were observing a merged A_1–A_2 mechanism. Consistent with this, they reported a deuterium isotope effect, $k_D/k_H = 1.8$, which we correct to 2.2 considering temperature and dilution.[20] This is in excellent agreement with the above discussion and our results for 5.

Although the net effect of electron-withdrawing groups at nitrogen in P–N bonds is to slow the reaction because these groups greatly increase the difficulty of protonation, once protonated, these same groups labilize the P–N bond because they are less nucleophilic. That is, the p-nitroanilide reacts slowly because at any acidity it is less protonated at N, but when protonated it is so reactive that it decomposes by an A_1 mechanism.

These results on acid-catalyzed cleavage of phosphorus amides are applicable to phosphorocreatine (1) in which proton transfer to the nitrogen of the P–N bond appears essential and is probably the crucial step in the action of creatine kinase.[7] Generally, one can expect that enzymes will use acid catalysis to cleave P–N bonds because of the pronounced labilization obtained by N-protonation.

(32) Although absolute values of ΔS (protonation) vary in two articles [A. I. Gel'bshtein, G. G. Shcheglova, and M. I. Temkin, *Zh. Neorg. Khim.*, 1, 282, 506 (1956); C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, 91, 6654 (1969)], both articles demonstrate this trend with acidity. See also data in R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 65.

(33) A good estimate of ΔS (protonation) for 4 is impossible because so few entropies of protonation are available in the literature, and the basicity at nitrogen of 4 is unknown and is probably impossible to measure because the predominant point of protonation is the oxygen atom. We hope to provide a more detailed analysis of ΔS^* in a future article.

(34) M. I. Kabachnik, T. A. Mastrukova, A. E. Shipov, and T. A. Melentyeva, *Tetrahedron*, 9, 10 (1960).

(35) H. D. Holtz and L. M. Stock, *J. Amer. Chem. Soc.*, 86, 5188 (1964); J. D. Roberts and W. T. Moreland, *ibid.*, 75, 2167 (1953). We prefer to use these data rather than σ_I because this method provides a clearly defined chemical process to measure log k_1 against.

(36) P. Haake, C. E. Diebert, and R. S. Marmor, *Tetrahedron Lett.*, 5247 (1968).

(37) R. S. Marmor, C. R. Diebert, G. Capozzi, R. D. Cook, P. A. Clark, and P. Haake, unpublished results.

Experimental Section

Spectroquality dioxane obtained from Matheson Coleman and Bell was refluxed over the sodium ketyl of benzophenone and distilled under prepurified nitrogen immediately before use.

Unless otherwise stated, "10% dioxane" refers to a water-dioxane solution made up by adding water containing the desired amount of acid to $(0.1V)$ ml of dioxane in a V ml volumetric flask. The molarity of acid for rate measurements in perchloric acid was determined by titration of 10% dioxane solutions.

Stock solutions were prepared by dissolving the appropriate

weight of anilide into freshly distilled dioxane and storing this solution under argon in the dark.

Rate Measurements. The extent of reaction was determined spectrophotometrically using a Hitachi-Perkin-Elmer Model 139 spectrophotometer. The anilides, **3**, had maxima as follows: **4**, 330 mμ; **5**, 232 mμ; **3** (Ar' = C_6H_5), 246 mμ; **3** (Ar' = p-CH$_3$-OC$_6$H$_5$), 250 mμ and a shoulder at 290 mμ. The hydrolysis of the anilides was followed through disappearance of these absorptions. Both the peak and the shoulder for the p-methoxy compound were observed and identical rate constants were obtained. Since p-nitroaniline has a maximum at 380 mμ, the appearance of p-nitroaniline was followed in dilute acid; the rate constant agrees within 2% of that obtained following the disappearance of **4**.

For rates of longer duration, reaction mixtures ($\sim$7.5 $\times$ 10^{-5} M in p-nitroanilide) were suspended in a thermostated bath, aliquots were withdrawn at suitable times, and absorbance (A_t) was measured at 330 or 380 mμ. Other rates were determined by placing the reaction mixture in a cuvette and the absorbance was recorded. The temperature in the cell was checked by a copper–constantan couple. Final absorbances (A_∞) were measured on samples that had been heated on a steam bath and cooled. The ultraviolet spectrum of a 10% dioxane solution made up of p-nitroaniline and diphenylphosphinic acid was consistent with the spectrum of an experimental infinity point in acid of the same molarity. First-order rate constants were obtained by plotting ln ($A_t - A_\infty$) vs. time.

The acid-catalyzed methanolysis of optically active **5** was followed with a Rudolph Model 63 visual polarimeter. Rotational changes were monitored at 589 and 350 mμ.

Reactions in D$_2$O. Acidic deuterium oxide was prepared by diluting 70–72% perchloric acid with 99.7% deuterium oxide in a 25-ml volumetric flask. A portion of this solution was titrated with standard base and the remainder used for rate measurements. Identical procedures were followed for the comparison rate determinations in ordinary water.

Preparations. Diphenylphosphinyl chloride was prepared by bubbling oxygen through a solution of technical grade diphenyl-chlorophosphine (obtained from the Victor Chemical Works) in dry benzene without external heating. The mixture was allowed to reflux during the oxidation. Benzene was removed by distillation and the product vacuum distilled (199–201° (8 mm)) and stored under nitrogen. Melting points are corrected. Analyses were performed by Miss Heather King (UCLA) and by Elek Microanalytical Laboratories.

N-(Phenyl)diphenylphosphinamide. *N*-(Phenyl)diphenylphosphinamide was prepared by adding 5.0 g (0.054 mol) of aniline to 11.83 g (0.05 mol) of diphenylphosphinyl chloride in 35 ml of dry pyridine. The mixture was refluxed overnight and cooled, and a sodium bicarbonate solution was added. The precipitate was filtered and washed two times with a dilute sodium bicarbonate solution and once with water. The anilide was recrystallized from 95% ethanol, mp 239–241.5°. The melting point reported varies from 242 to 248°;[38] yield, 8.9 g (60.5%).

Anal. Calcd for $C_{18}H_{16}NOP$: C, 73.71; H, 5.51. Found: C, 73.83; H, 5.66.

N-(*p*-Nitrophenyl)diphenylphosphinamide (4) was prepared by adding 17.1 g (0.124 mol) of p-nitroaniline in 40 ml of dry pyridine to a stirred solution of 29.35 g (0.124 mol) of diphenylphosphinyl chloride in 30 ml of dry pyridine at room temperature. A precipitate formed immediately. Approximately 60 ml of benzene was added, and the mixture was refluxed for 1 hour and then cooled. After removal of the solvent by rotary evaporation, a saturated solution of sodium bicarbonate was added to partially dissolve the remaining solid. The undissolved portion was filtered off and recrystallized from acetone to give a light yellow solid, mp 231.5–233.5°; yield, 14.8 g (33%).

Anal. Calcd for $C_{18}H_{15}N_2O_3P$: C, 63.9; H, 4.48; N, 8.28. Found: C, 63.8; H, 4.73; N, 8.21.

The melting point of the anilide prepared in this way is not in agreement with a previously reported melting point for the same compound. Zhmurova and Kirsanov[10] reported that the anilide had mp 255–257°. Repeating their published procedure gave a product identical in all respects with the *N*-(*p*-nitrophenyl)diphenylphosphinamide we prepared from p-nitroaniline and diphenylphosphinyl chloride. Spectra (Table VII) are consistent with the structure.

N-(*p*-Methoxyphenyl)diphenylphosphinamide. *N*-(*p*-Methoxy-

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Table VII. Nmr[a] and Infrared[b] Spectra of Phosphinamides

Ar	
	(C$_6$H$_5$)$_2$P(O)NHAr
C$_6$H$_5$	
ir	3100, 1598, 1490, 1432, 1412, 1270, 1232, 1180, 1170, 1120, 1100, 930
nmr (CDCl$_3$)	1.7–2.7 (mult)
p-NO$_2$C$_6$H$_4$	
ir	3150, 1590, 1490, 1437, 1340, 1297, 1247, 1193, 1125, 1103, 918
nmr (CH$_3$)$_2$SO	1.5–2.8 (mult)
p-CH$_3$O-C$_6$H$_4$	
ir	3050, 1500, 1432, 1275, 1230, 1190, 1175, 1110, 1100, 1028, 930
nmr (CDCl$_3$)	1.7–2.8 (mult, 10 H), 3.1 (AB q, 4 H), 4.3 (d, J = 10 Hz, 1 H), 6.2 (s, 3 H)
	(C$_6$H$_5$)ArP(O)NHC$_6$H$_4$-p-NO$_2$
p-CH$_3$OC$_6$H$_4$	
ir	3100, 1590, 1510, 1495, 1335, 1292, 1250, 1180, 1120, 1100, 1020, 915
nmr (CH$_3$)$_2$SO	1.6–2.8 (mult, 13 H); 6.15 (s, 3 H)
p-ClC$_6$H$_4$	
ir	3100, 1585, 1510, 1490, 1472, 1433, 1383, 1325, 1285, 1242, 1180, 1115, 1100, 1080, 1008, 910
nmr (CD$_3$)$_2$SO	1.6–2.7 (mult)
p-NO$_2$C$_6$H$_4$	
ir	3100, 1587, 1510, 1480, 1333, 1287, 1240, 1175, 1113, 1097, 917
nmr (CD$_3$)$_2$SO	1.6–2.7 (mult)

[a] τ scale used for chemical shifts. [b] KBr disks.

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phenyl)diphenylphosphinamide was prepared by adding a solution of 21.0 g (0.171 mol) of p-anisidine in 100 ml of dry pyridine dropwise to a stirred solution of 40.3 g (0.17 mol) of diphenylphosphinyl chloride in 100 ml of dry pyridine. More pyridine (100 ml) was added and the resulting mixture was refluxed for 15 hr, cooled, and filtered. The solid obtained by filtration was slurried in 0.1 N sodium hydroxide, filtered, and recrystallized from benzene–absolute ethanol, mp 198–199°.

Anal. Calcd $C_{19}H_{18}NO_2P$: C, 70.58; H, 5.62. Found: C, 70.83; H, 5.71.

N-(*p*-Nitrophenyl)-*p*-methoxydiphenylphosphinamide (3: Ar = p-CH$_3$OC$_6$H$_4$, Ar' = p-O$_2$NC$_6$H$_4$). p-Methoxyphenylphenylphosphinic acid was prepared as described previously.[39] The solid acid was recrystallized from ethanol, mp 183–184° (lit.[39] mp 184°). The acid chloride was then prepared. p-Methoxyphenylphenyl-phosphinic acid (12.7 g or 0.051 mol) was added to an excess (44 g) of thionyl chloride and the mixture heated at approximately 79° for 14 hr. The excess thionyl chloride was removed by distillation and the product distilled through a spinning band column (203° (2.1 mm)); yield, 9.96 g (73%). To verify that the product was actually the acid chloride of p-methoxyphenylphenylphosphinic acid, a portion of the product was hydrolyzed with water to give a solid with mp 183°; the melting point of the acid is 183–184°.[39] The acid chloride (2.28 g or 8.55 $\times$ 10^{-3} mol) was refluxed with 2 g of p-nitroaniline in 50 ml of pyridine for 48 hr. All but 15 ml of the pyridine was removed under vacuum and 100 ml of water added. A dark brown, oily layer was formed in the bottom of the flask. Chloroform extraction was carried out several times and the chloroform evaporated by an air stream. The remaining solid was recrystallized several times from 95% ethanol to give about 0.1 g of very light yellow solid, mp 214.5–215.5°.

Anal. Calcd for $C_{19}H_{17}N_2O_4P$: C, 61.96; H, 4.66. Found: C, 61.86; H, 4.78.

N-(*p*-Nitrophenyl)-*p*-chlorodiphenylphosphinamide (3: Ar = p-ClC$_6$H$_4$, Ar' = p-O$_2$NC$_6$H$_4$). A slurry of 31.7 g (0.183 mol) of PCl$_5$ in 30 ml of dry benzene was added with stirring at room temperature to a mixture of 14.5 ml (0.168 mol) of PCl$_3$, 18 ml of benzene, and 11.2 g (0.045 mol) of p-methoxydiphenylphosphinic acid. After stirring for 30 min at room temperature, the mixture was refluxed for 90 min. Volatile materials were removed at reduced pressure, excess PCl$_5$ was removed by sublimation, and an acid chloride was isolated by vacuum distillation, bp 166–168° (0.3 mm);

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(38) (a) N. Kreutzkamp and H. Schindler, *Arch. Pharm.*, **293**, 296 (1960); (b) B. B. Hunt and B. S. Saunders, *J. Chem. Soc.*, 2413 (1957).

(39) (a) R. C. Hinton, F. G. Mann, and D. Todd, *ibid.*, 5454 (1961); (b) F. G. Mann, B. P. Tong, and V. P. Wystrach, *ibid.*, 1155 (1963).

yield, 9.9 g (83%). Although this procedure was expected to give the acid chloride of *p*-methoxydiphenylphosphinic acid, subsequent reactions and mass spectra demonstrated that it was the acid chloride of *p*-chlorodiphenylphosphinic acid. That is, PCl₃ converted the *p*-CH₃O group to a *p*-Cl group. The *p*-nitroanilide was prepared by adding a solution of 1.38 g (0.01 mol) of *p*-nitroaniline in 5 ml of pyridine to 2.67 g of the acid chloride. Triethylamine (1 ml) was added and the mixture kept at 50° for 15 hr. After removing the solvent under vacuum, the residue was taken up in acetone and a saturated solution of sodium bicarbonate added. This solution was then extracted with chloroform, and the chloroform layer was dried and evaporated. The remaining solid was recrystallized several times from acetone, mp 190–191.5°; yield, 0.3 g (8%).

Anal. Calcd for C₁₈H₁₄ClN₂O₃P: C, 57.99; H, 3.76; N, 7.52. Found: C, 57.56; H, 3.96; N, 7.41.

In order to ascertain that this was the amide of *p*-chlorodiphenylphosphinic acid, a sample was hydrolyzed in aqueous acid and washed several times with aqueous acid, and the remaining white solid was isolated, mp 151–153°; the melting point reported for *p*-chlorodiphenylphosphinic acid is 150–152°.[40] Mass spectra and nmr spectra of the anilide also support the conclusion that it is the *p*-chloro compound.

N-(*p*-Nitrophenyl)-*p*-nitrodiphenylphosphinamide (3: Ar = Ar′ = *p*-O₂NC₆H₄). *p*-Nitrodiphenylphosphinic acid was prepared by the same method used to prepare *p*-methoxydiphenylphosphinic acid and crystallized from ethanol–water, mp 152–153° (lit.[41] mp 153–154°); yield based on diazonium salt, 43%. The acid chloride was then prepared; an excess of thionyl chloride (200 ml), approximately seven drops of dimethylformamide, and 53.2 g (0.2 mol) of the *p*-nitro acid were refluxed for 5 days. Thionyl chloride was distilled and repeated addition and distillation of benzene carried out several times to ensure that all excess thionyl chloride was removed. The residue remaining after the last benzene distillation was used to prepare the amide.

The amide was prepared from the acid chloride by refluxing 27.6 g (0.2 mol) of *p*-nitroaniline in 200 ml of dry pyridine with the acid chloride for 18 hr. Removal of the pyridine resulted in a dark brown tar which was taken up in a minimum amount of acetone, aqueous sodium bicarbonate was added, and the resulting mixture was heated to evaporate the acetone. Filtration gave the crude amide which was washed several times with dilute aqueous sodium bicarbonate solution and finally with water. The most efficient method of purification consisted of Soxhlet extraction of the crude amide with acetone to give the purified amide as a light tan solid, mp 228–229°; yield, 31.2% based on initial amount of acid.

Anal. Calcd for C₁₈H₁₄N₃O₅P: C, 56.4; H, 3.66; N, 10.95. Found: C, 56.28; H, 3.84; N, 10.81.

(−)-(*S*)-*N*-(Phenyl)methylphenylphosphinamide (5). (−)-(*S*)-Methyl methylphenylphosphinate[42] and a tenfold excess of lithium anilide were refluxed in benzene for 6 hr. The solution was cooled, washed with a dilute sodium bicarbonate solution, dried over magnesium sulfate, and evaporated. The anilide was purified by silica gel chromatography (eluent, acetone–ether (1:1)) followed by recrystallization from acetone–hexane: yield, 50%; mp 163.5–165.5°; α^{22}D −28° (*c* 0.171, methanol) (lit.[43] yield, 38%; mp 161–163°; α^{25}D −26.2° (*c* 1.33, methanol)).

Spectral Measurements and Analyses. Nuclear magnetic resonance spectra (nmr) were recorded on a Varian A-60 spectrophotometer. Infrared spectra were recorded on either a Perkin-Elmer Infra-cord or Beckman IR-4. Mass spectral data were obtained using an Associated Electrical Industries, Ltd., Model MS-9 spectrometer. The nmr and infrared spectral data were consistent with the above structural assignments and are reported in Table VII. Appropriate parent peaks in the mass spectra were observed for all the above compounds, and fragmentation patterns[8e] were consistent with the structural assignments.

(40) P. Haake and D. McCoy, unpublished results, reported in brief in *Tetrahedron Lett.*, 5243 (1968).

(41) L. D. Freedman and G. O. Doak, *J. Amer. Chem. Soc.*, **74**, 2884 (1952).

(42) O. Korpiun, R. A. Lewis, J. Chickos, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4842 (1968).

(43) A. Nudelman and D. J. Cram, *ibid.*, **90**, 3869 (1968).