Tetrahedron Letters,Vol.23,No.31,pp 3127-3130,1982 0040-4039/82/313127-04$03.00/0
Printed in Great Britain

PHOSPHORUS AMIDES X.[1] RATE ACCELERATION DUE TO SOLVATION EFFECTS IN THE ACID-CATALYZED CLEAVAGE OF PHOSPHINAMIDES. APPLICATION TO ACID-CATALYSIS AT ENZYMIC ACTIVE SITES.

Judith M. Bonicamp and Paul Haake*

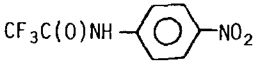
Department of Chemistry, Wesleyan University, Middletown, Connecticut 06457

Summary: Phosphinamides undergo acid-catalyzed reaction with enhanced rates as the amount of water is decreased in acetonitrile from about 20 M to about 1 M. This phenomenon appears to be due to increased activity of acid and increased basicity of substrate as the concentration of water is decreased. The same effects may cause enhanced rates of acid-catalyzed reactions at enzymic active sites.

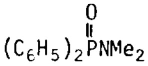
Phosphinamides, $R_2P(O)NHR'$, are a particularly interesting class of phosphorus compounds with respect to mechanism of substitution.[2-8] Carboxylic amides and phosphinamides are comparably reactive in alkali indicating that they have comparable susceptibility to nucleophilic attack;[8] however, in acid phosphinamides are about a million times more reactive than analogous carboxylic amides.[8] It was found that this high reactivity in acid was due to reaction through the N-protonated amides.[1,8,9] N-alkyl amides appear to protonate predominantly on nitrogen in contrast to carboxylic amides;[1,8,9] N-aryl amides must protonate predominantly on oxygen,[4] but the less stable, N-protonated tautomer is the reactive species.[4,9]

The mechanism of reaction of p-nitrophosphinanilides has been a matter of particular interest. We found[4] that the dependence on H_0, the ΔS^*, the deuterium isotope effect, and the effect of N-aryl substituents indicated a mechanism with A-1 character.[4] Harger has investigated this problem and has evidence for nucleophilic participation.[10,11] In the stereochemical work by Harger[11] and by Koizumi,[12] higher acidities gave extensive racemization of p-$O_2NC_6H_4NHP(O)(C_6H_5)_2$. However, recently Harger has found that this may be due to nucleophilic attack by high concentrations of chloride ion.[11] Nucleophilic participation in a predominantly A-1 transition state would not be surprising in view of the demonstrated extreme instability of a phosphinylium ion,[3] the intermediate when p-nitrophosphinanilides react in an A-1 mechanism. The best resolution of our evidence concerning the transition state and Harger's results is a mechanism similar to that found for less stable carbonium ions for which, depending upon medium, nucleophilic participation can be observed.

Recently we have become interested in the rate effects of variable amounts of water in acetonitrile.[13,14] A study of a reactive carboxylic amide (1) gave results which appeared consistent with an associative, tetrahedral, and highly charged transition state.[13] Because of the contrasting mechanistic behavior of phosphorus amides, we decided to apply this method of studying solvation and we have found unusual results which add to our hypothesis that this method may be a new and simple way to gain information about reaction mechanisms and the structures of transition states.

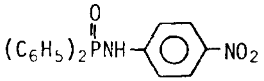


1



$(C_6H_5)_2\overset{O}{\overset{\|}{P}}NMe_2$

2



3

The amides, 2 and 3, were prepared by the methods of Koizumi[8] and Tyssee.[4] Reaction rates were measured spectrophotometrically[4,8] yielding first order rate constants. The spectrophotometric change was the same as observed previously indicating that the reaction involves hydrolysis as expected.[4,8]

The rate constants for H_2SO_4 catalysis are found in Table I. For both amides, the rate reaches a minimum at 20-25 M. water. At lower water concentrations, the rates are considerably faster in contrast to 1 which shows a steady fall off in rate as the concentration of water decreases.

Table I. Dependence of the Observed First-Order Rate Constants on Water Concentration for the H_2SO_4-Catalyzed Hydrolysis of 2 and 3 in Water-Acetonitrile.[a]

$(C_6H_5)_2P(O)N(CH_3)_2$[b]		$(C_6H_5)_2P(O)NHC_6H_4NO_2$[c]			
$[H_2O]$ (M.)	$10^4k_{obs}(s^{-1})$	$[H_2O]$ (M.)	$10^5k_{obs}(s^{-1})$	$[H_2O]$ (M.)	$10^5k_{obs}(s^{-1})$
50.00	84.9[d]	49.6	42.8	15.6	2.30
23.4	7.53	45.3	19.7	10.57	4.41
17.9	8.65	40.3	6.66	5.58	12.8
12.5	11.2	35.3	4.27	2.58	30.8
8.1	14.0	30.3	2.36	1.57	33.0
4.83	18.6	25.6	1.90		
1.55	95.0	20.6	1.80		

[a] At 30.0±0.1 C. [b] [2] = 6.41×10^{-4} M, $[H_2SO_4]$ = 0.01 M. [c] [3] = 7.5×10^{-5} M, $[H_2SO_4]$ = 1.82 M. [d] Estimated from data in ref. 8, in 10% $MeOH-H_2O$ (v/v).

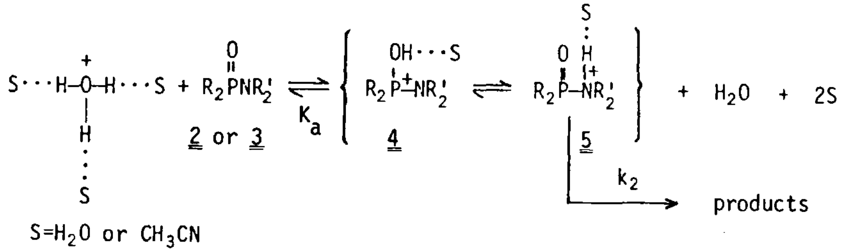
Because sulfate ion and bisulfate ion are known to be fairly effective nucleophiles, we were concerned that this unusual dependence on water concentration might be associated with desolvation of these anions. Therefore, we also studied the same phenomenon with $HClO_4$ catalysis (Table II). Comparison of rates indicates that nucleophilic catalysis by the anions is not important. This is consistent with previous results which indicate that the protonation step is very important.[1a]

Table II. Dependence of the Observed First-Order Rate Constants on Water Concentration for the $HClO_4$-Catalyzed Hydrolysis of 2 and 3 in Acetonitrile.[a]

$(C_6H_5)_2P(O)N(CH_3)_2$[b]				$(C_6H_5)_2P(O)NHC_6H_4NO_2$[c]	
$[H_2O]$	$10^4k_{obs}(s^{-1})$	$[H_2O]$	$10^4k_{obs}(s^{-1})$	$[H_2O]$	$10^5k_{obs}(s^{-1})$
49.1	164.	18.8	10.3	50.7	23.5
35.2	22.6	13.3	18.6	40.0	2.50
29.7	13.7	7.9	24.9	30.0	1.88
24.2	14.6	2.4	73.3	20.0	3.04
				10.0	7.10
				4.0	25.4

[a] At 30.0°C. [b] [2]=6.41×10^{-4}M, $[HClO_4]$=0.02M.
[c] [3]=7.5×10^{-5}M, $[HClO_4]$=1.64M.

The rate enhancement that we have found at 20 M to 1 M water is understandable in the context of the following mechanism which is based on the literature cited in the summary at the beginning of this paper. In our previous studies,[13,14] we found that the rate of reaction in nucleophilic displacements at both carbon and phosphorus decreased as the amount of water in the medium decreased. This mass action effect should also apply to the second step (k_2,eq.1) of the reaction, acid-catalyzed hydrolysis, of 2 and 3. Therefore, the rate increase at low concentrations of water (Tables I and II) must be due to increased concentration of the reactive intermediate (5).[1a] We suggest that this is due to several important factors:



(1)

Decrease in the concentration of water will shift the protonation equilibrium to the right in eq. 1. It seems likely that the identity and activity of the protonating species is changing. Water is several powers of 10 more basic than acetonitrile[16] so that the protons introduced into these media will certainly bond to water molecules forming H_3O^+. The additional solvation which forms $H_9O_4^+$ in pure water presumably will be strongly affected by dipole interactions. Acetonitrile has a dipole moment near 4 D so its dipole interaction towards the H_3O^+ cation will be much stronger than for water molecules. This high dipole moment of CH_3CN also appears to cause highly effective solvation of water by CH_3CN as we have discussed previously.[13] Therefore, we may expect that at $[H_2O]<20M.$, $CH_3CN\cdot\cdot H\overset{+}{O}H_2\cdot\cdot(OH_2)$, $(CH_3CN)_2\cdot\cdot H_2\overset{+}{O}H\cdot\cdot OH_2$, and $(CH_3CN)_3\cdot\cdot H_3\overset{+}{O}$ will be important acidic species.

Solvation differences between ground state and transition state can strongly affect the ΔG^* for the reaction. Many solvation effects are possible, but desolvation of the ground state may be particularly important in the rate enhancement observed at low concentrations of water. The P = O oxygen and P-N nitrogen may normally be strongly hydrogen bonded to water. Because acetonitrile has a high dipole moment, as $[H_2O]$ is decreased and $[CH_3CN]$ is increased in the medium, acetonitrile molecules will compete with the amides (2 and 3) as hydrogen bond acceptors therefore causing desolvation of the amide (fewer water molecules solvating the amide). The phosphinamide thereby will be more basic causing increased concentration of protonated substrate in the low aqueous media. Since the rate of reaction is dependent on the concentration of 5, this effect will increase the rate of reaction.

A rate increase also could result from increased concentration of 5 due to a perturbation of the equilibrium between the two tautomeric forms of the protonated substrate (eq. 1). Because N-protonation appears to be predominant for 2,[9] this factor must be less important than the other two mentioned above.

We had speculated in earlier papers that the low aqueous medium of enzymic active sites might lead to catalytic effects in enzymic catalysis.[13,14,18] The results in this paper indicate that such enzymic active sites might have catalytic consequences because any acidic functional group on the enzyme could have stronger acidity and desolvation of the substrate should cause it to be more basic. These are the two factors that seem most likely to explain the rate enhancement reported here: higher activity of acid and increased basicity of substrate causing a higher concentration of 5 as $[H_2O]$ is decreased.

Acknowledgment. This research was supported by grant AM-12743 from NIH and by Wesleyan University.

REFERENCES AND FOOTNOTES

1. Previous papers with references to earlier publication: a. J.Rahil and P.Haake, J. Am. Chem. Soc., 103, 1723 (1981); b. G.W.Allen and P.Haake, Bioorganic Chem., 9, 325 (1980)
2. There is a detailed discussion in reference 1a, pp. 1731-4.
3. P.Haake and P.S.Ossip, J.Am.Chem.Soc., 93, 6924 (1971).
4. D.A.Tyssee, L.P.Bausher and P.Haake, ibid., 95, 8066 (1973); G.Tomaschewski and G.Kühn, J.Prakt. Chem., 38, 222 (1968).
5. G.W.Allen and P.Haake, J.Am.Chem.Soc., 98, 4990 (1976).
6. R.D.Cook, C.E.Diebert, W.Schwarz, P.C.Turley and P.Haake, J.Am.Chem.Soc., 95, 8088 (1973).
7. P.Haake, R.D.Cook, T.Kozumi, P.S.Ossip, W.Schwarz and D.A.Tyssee, J.Am.Chem.Soc., 92, 3828 (1970).
8. T.Koizumi and P.Haake, J.Am.Chem.Soc., 95, 8073 (1973).
9. P.Haake and T.Koizumi, Tetrahedron Lett., 4849 (1970); K.E.Debruin, A.G.Padilla and D.M. Johnson, Tetrahedron Lett., 4279 (1971). Although T.A.Modro et al, J.Org.Chem., 46, 1923 (1981), have disagreed with the conclusion[1,8] that N-protonation is predominant in 2, they have no experimental data which refutes the experimental evidence,[1,8] which has been summarized in reference 1a. The N-aryl amides are discussed in reference 4, p. 8069.
10. M.J.P.Harger, J.Chem.Soc., Perkin II, 154 (1980) and references therein.
11. M.J.P.Harger, J.Chem.Soc., Perkin I, 2057 (1977); ibid., 1294 (1979).
12. T.Koizumi, Y.Kobayashi, and E.Yoshii, J.Chem.Soc.Chem.Comm., 678 (1974).
13. J.W.Henderson and P.Haake, J.Org.Chem., 42, 3989 (1977).
14. G.Wallerberg and P.Haake, J.Org.Chem., 46, 43 (1981).
15. It is relevant that bases are more highly protonated at any acidity in CH_3CN; J.F.Coetzee, Prog.Phys.Org.Chem., 4, 45 (1967).
16. E.M.Arnett, ibid., 1, 278-9 (1963).
17. B.Springs and P.Haake, Bioorganic Chem., 6, 181 (1977).
18. G.Wallerberg, J.Boger and P.Haake, J.Am.Chem.Soc., 93, 4938 (1971).

(Received in USA 9 March 1982)