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HYDROLYSIS OF PHOSPHINAMIDES AND THE NATURE OF THE P-N BOND[1]

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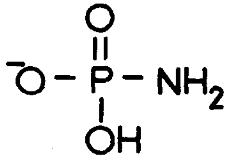
Carboxylic amides are quite stable towards chemical hydrolysis; elevated temperatures and high concentrations of acid or base are required for appreciable rates of hydrolysis. Yet, amides of phosphoric acid appear to be highly reactive. Phosphoramidate (1) is a reactive phosphorylating agent[2] and creatine phosphate (2) is a source for rapid generation of ATP. Part of the reactivity of these amides could be due to the polyfunctional nature of phosphates: both O^- and OH could facilitate cleavage of the P-N bond. We have studied monofunctional phosphinamides (3) in order to understand the fundamental chemistry of the P-N bond in the absence of the perturbing effects present in phosphoramides (e.g., 1). The results demonstrate that the P-N bond in phosphorus amides is unusually labile under acid-catalyzed conditions.



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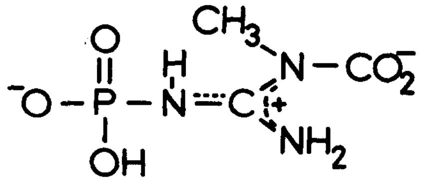

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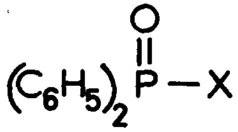


3: X = NH_2
4: X = $NHCH_3$
5: X = $N(CH_3)_2$

In basic solution, phosphinamides undergo slow hydrolysis. The second-order rate constant (v = k $[HO^-][\text{Amide}]$) for hydrolysis of 3 is approximately the same as for benzamide.[3] The comparison with benzamide is valuable because it demonstrates that the P-N bond is quite resistant to nucleophilic attack.

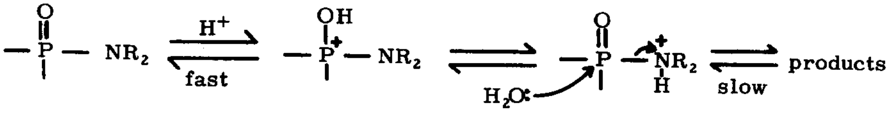
In contrast, phosphinamides are labile in dilute acid whereas fairly concentrated acid is required to achieve a relatively slow rate of hydrolysis of carboxylic amides. Pseudo-first-order rate constants for the hydrolysis of 3, 4, and 5 were obtained by spectrophotometric measurements in buffered 10% CH_3OH-H_2O 90% (v/v) over the pH range 1.8 to 3.1 (Table 1). First order dependence on $[H^+]$ was observed. There was no indication of general acid-catalysis with the buffers we employed. The activation parameters for the hydrolysis of 3 (pH 2.4, T = 25-53°C) are: $\Delta H^{\ddagger} = 9.3$ kcal/mol, $\Delta S^{\ddagger} = -35$ eu and $\Delta F^{\ddagger} = 19.2$ kcal/mol. The highly negative entropy of activation is consistent with an A-2 mechanism[4] even if the entropy of protonation is taken into account.[5] The deuterium solvent isotope effect, k_{D_2O}/k_{H_2O}, is 1.3(pH 2.4, 29.2°C) for the hydrolysis of 3. This also suggests an A-2 mechanism[6] with rapid protonation preceding rate-determining nucleophilic attack by H_2O. The rates observed and the activation parameters for 3 indicate that this phosphinamide undergoes acid-catalyzed hydrolysis 5 x 10^5 times faster than benzamide.[7] The contrast with the results of alkaline hydrolysis (see above) suggests that the P-N bond is labilized in acid.

Table 1. Rate Constants for Hydrolysis of Phosphinamides in 10% CH_3OH - H_2O

Substrate	pH	T(°C)	$10^4 k_{obs}$ $(sec^{-1})^a$
3	1.9	29.2	12.7
3	2.4	29.2	3.42
3	2.4	25.0	2.97
3	2.4	38.0	5.77
3	2.4	47.8	9.85
3	2.4	52.6	11.3
3	3.1	29.2	0.77
4	2.4	29.2	11.3
4	3.1	29.2	2.53
5	2.4	29.2	35.5
5	3.1	29.2	6.33

[a] Pseudo-first-order rate constants evaluated spectrophoto metrically

Substituent effects are useful in understanding the mechanism. The substituent effect on nitrogen (3 > 4 > 5, $\rho^* = -1.0$) (Table 1) is different from that for acid-catalyzed hydrolysis of carboxylic amides for which the ρ^* value is close to 0 or slightly positive.[8,9] The ρ^* we observe for phosphinamides is in the expected order if the N-protonated species were reactive. A good correlation of log k_{obs} with pK_a of N-alkylanilinium ions also suggests reaction through the N-protonated species.[10] Partial hydrolysis of 3 in acidic ^{18}O–H_2O results in one equivalent of solvent-oxygen introduced into $(C_6H_5)_2PO_2H$ and no exchange into 3. These data strongly support a mechanism (eq. 1) involving nucleophilic attack by water on 7.[11]



(1)

6 7

Although both protonated species (6 and 7) may be present, the reactive tautomer appears to be 7. It is relevant that, unlike carboxylic amides, the nitrogen atom in $\phi_2P(O)N(CH_3)_2$ is pyramidal although flattened somewhat from the geometry of trimethylamine.[12] In the accompanying communication[10] we report pK_a's for protonated phosphinamides and some evidence on the predominant position of protonation.

The labilizing action of N-protonation is also seen in the case of anilides of diphenylphosphinic acid[5] where N-protonation apparently causes dissociative displacement at phosphorus to be a lower energy pathway than eq. 1 which involves nucleophilic attack by water.

These results demonstrate that in the enzymic cleavage of P-N bonds, acid-catalysis should be very important. In contrast to many hydrolytic enzymes, the enzymes catalyzing hydrolysis of phosphorus amides may have greater function for electrophilic catalysis.

REFERENCES

(1) Research supported by grant AM-12743 from the U. S. Public Health Service and grant GP-13453 from the National Science Foundation.

(2) (a) R. F. Hudson, "Structure and Mechanism in Organo-phosphorus Chemistry," Academic Press, New York, 1965, Chap. 8;

(b) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, Amsterdam, 1967;

(c) S. J. Benkovic and P. A. Benkovic, *J. Am. Chem. Soc.*, **89**, 4714 (1967);

(d) I. Oney and M. Caplow, *ibid.*, **89**, 6972 (1967);

(e) N. K. Hamer, *J. Chem. Soc.*, (C), 404 (1966).

(3) For the HO^- catalyzed hydrolysis of **3**, $k_2 = 15.5 \times 10^{-5} M^{-1} sec^{-1}$ was obtained at 90°C; k_2 for benzamide was reported as $12.5 \times 10^{-5} M^{-1} sec^{-1}$ at 90°C.[7]

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

(5) P. Haake and D. A. Tyssee, *Tetrahedron Letters*, 3513 (1970).

(6) C. A. Bunton and V. J. Shiner, *J. Am. Chem. Soc.*, **83**, 42, 3207 (1961).

(7) The relative rate of the acid-catalyzed hydrolysis of **3** and benzamide is obtained using Meloche and Laidler's data (*J. Am. Chem. Soc.*, **73**, 1712 (1951)) for benzamide.

(8) G. Cauzzo, U. Mazzucato and A. Fiffani, *Atti Accad. Nazl. Lincei*, *Rend.*, *Classe Sci. Fis.*, *Mat. Nat.*, **29**, 348 (1960); *C. A.*, **56**, 12796f (1962).

(9) P. D. Bolton and T. Henshall, *J. Chem. Soc.*, 1226 (1962). U. Mazzucato *et al*, *Ann. Chim. (Rome)* **50**, 521 (1960), *C. A.*, **54**, 23643h (1960).

(10) We conclude that the ρ^* value supports reaction through N-protonation after consideration of the effect of substituents on both protonation and nucleophilic attack; see also T. Koizumi and P. Haake, *Tetrahedron Letters*, 4841(1970)

(11) P. Haake, R. D. Cook, T. Koizumi, P. S. Ossip, W. Schwarz and D. A. Tyssee, *J. Am. Chem. Soc.*, **92**, 3828 (1970).

(12) M. Haque and C. N. Caughlan, *Chem. Comm.*, 921 (1966).