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SUBSTITUENT EFFECTS IN THE ACID-CATALYSED HYDROLYSIS OF ALKYLPHENYLPHOSPHINANILIDES

Martin J.P. Harger*, Andrew J. Macpherson, and David Pickering

Department of Chemistry, The University, Leicester LE1 7RH

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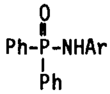
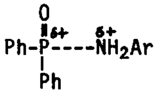
Haake and Tyssee[1] postulated a dissociative (A1 or A1-like) mechanism for the acid-catalysed hydrolysis of diphenylphosphinanilides 1. They considered cleavage of the P-N bond in the protonated anilide to be well advanced in the transition state 2 and nucleophilic participation by water to be small.

Although there is no reason to expect alkylphenylphosphinanilides to react by a fundamentally different mechanism, we observed a marked decline in the rate of hydrolysis of the anilides 3-6 (X=H) as the bulk of the alkyl group attached to phosphorus increased.[2] Such sensitivity to steric hindrance suggested an associative (A2) mechanism with substantial participation of the nucleophile (water) in the transition state.



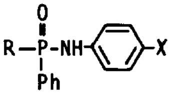
$\mathrm{Ph{-}\underset{Ph}{\overset{O}{\overset{\|}{P}}}{-}NHAr}$

1



$\mathrm{Ph{-}\underset{Ph}{\overset{O}{\overset{\|}{P}}}^{\delta+}{-}{-}{-}{-}\overset{\delta+}{N}H_2Ar}$

2



3 R=Et   4 R=Cyclopropyl

5 R=Pr^i 6 R=1-Methylcyclopropyl

More recently Haake and his colleagues[3] have emphasised that the amount of A1 character in the mechanism of hydrolysis of a phosphinic amide is dependent on the nucleophilicity of the departing amine, being especially pronounced for p-nitroanilides. We therefore thought it important to investigate further the reactions of alkylphenylphosphinanilides, and in particular to vary the nucleophilicity of the aniline leaving group. Accordingly, we have now prepared[4] and examined the substituted anilides 3-6 having X=OMe and X=NO_2.

Pseudo-first-order rate constants (k_ψ) (see Table) were determined by following spectrophotometrically the hydrolyses of the anilides 3-6 (X=OMe,H, and NO_2) as dilute solutions in aqueous methanol containing 2.08 M-hydrochloric acid. For each of the phosphinanilide systems 3-6 the decrease in the value of k_ψ as X changes OMe → H → NO_2 is no doubt primarily a consequence of the decreasing proportion of the substrate which is present in its reactive protonated form.[1,3] Of more immediate concern is the dependence of the rate of hydrolysis on the size of the alkyl group attached to phosphorus. Whether the leaving group is p-methoxyaniline (X=OMe), aniline (X=H), or p-nitroaniline (X=NO_2), the rate decreases as the bulk of the alkyl group increases, and in all cases the relative rates (k_{rel}) for 3, 4, 5, and 6 are similar. Clearly the sensitivity of the rate of hydrolysis to steric hindrance is *not* appreciably dependent on the nucleophilicity of the aniline leaving group.

TABLE. Hydrolysis of alkylphenylphosphinanilides 3-6 (X=OMe,H,and NO$_2$) in 1:1 v/v water-methanol containing 2.08 M-HCl at 31.2°[5]

	Y in anilide = OMe		X in anilide = H		X in anilide = NO$_2$	
Anilide	10^5k_ψ s^{-1}	(k_{rel})	10^5k_ψ s^{-1}	(k_{rel})	10^5k_ψ s^{-1}	(k_{rel})
3	1540	(100)	634	(100)	32.8	(100)
4	675	(43.8)	270	(42.6)	14.0	(42.7)
5	28.2	(1.83)	10.9	(1.72)	0.503	(1.53)
6	9.87	(0.64)	3.97	(0.63)	0.256	(0.78)

Any Al character in the mechanism of hydrolysis of a phosphinanilide will be enhanced by a substituent (e.g. *p*-NO$_2$) which reduces the nucleophilicity of the departing aniline, and will be diminished by one (e.g. *p*-MeO) which increases it. However, our measurements seem to indicate that, with alkylphenylphosphinanilides, the nucleophile (water) participates substantially and more or less equally in the transition state irrespective of the nucleophilicity of the departing aniline. We consider these results to be incompatible with an Al mechanism, and with any mechanism which minimizes the importance of the bonding of the nucleophile to phosphorus in the transition state. Even for *p*-nitroanilides a mechanism with associative (A2) character may be inferred. We further note that the reported[1,3] variation in the rate of hydrolysis of diphenylphosphinanilide with substituents in the aniline leaving group (ratio of k_ψ for *p*-MeO:H:*p*-NO$_2$ = 2.84:1.00:0.046 in aqueous dioxan) is not greatly different from that found here for alkylphenylphosphinanilides (for 3-6, ratio of k_ψ for *p*-MeO: H :*p*-NO$_2$ = 2.43-2.59:1.00:0.046-0.064) and does not of itself suggest a markedly different mechanism. Our suggestion of a hydrolysis mechanism with associative (A2) character may therefore be true for diphenylphosphinanilides as well as for alkylphenylphosphinanilides.

References and Footnotes

1. P. Haake and D.A. Tyssee, Tetrahedron Letters, 1970, 3513.
2. M.J.P. Harger, J.C.S. Chem. Comm., 1973, 774.
3. D. A. Tyssee, L.P. Bausher, and P. Haake, J. Amer. Chem. Soc., 1973, **95**, 8066.
4. The new anilides 3-6 (X=OMe and NO$_2$) were prepared from the appropriate phosphinic acid chlorides and substituted anilines, and gave satisfactory spectra and microanalysis results.
5. The possible error in k_ψ is estimated to be ±5%. The values of k_ψ for 3-6 (X=H) in the Table differ somewhat from those previously obtained (ref. 2). Although the variations are within the possible experimental error, the new values are preferred for the present comparisons since they were obtained under exactly the same conditions as were the values of k_ψ for the other compounds in the Table.