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STERIC INHIBITION OF THE ACID-CATALYSED HYDROLYSIS OF DIPHENYLPHOSPHINIC AMIDES

Anne C. Clements, Martin J.P. Harger,* Alan Leonard, and Michael D. Reed

Department of Chemistry, The University, Leicester LE1 7RH

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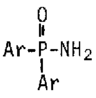
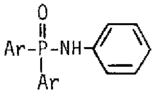
A range of mechanisms has been proposed for the acid-catalysed hydrolysis of diphenylphosphinic amides, depending on the nucleophilicity of the departing amine.[1-3] In particular, it has been argued that hydrolysis is associative (A2) for the amide (1a)[1] but dissociative (A1) for the *p*-nitroanilide (3a),[2] with the anilide (2a) following an intermediate 'merged A1-A2' pathway.[2] In order to gain a better understanding of this mechanistic spectrum, we have investigated the steric effects of methyl substituents in the P-phenyl groups of the amides (1)-(3).



$$Ar-\overset{\overset{O}{\|}}{\underset{\underset{Ar}{|}}{P}}-NH_2$$

1



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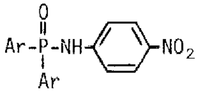

3

a; Ar = Phenyl
b; Ar = *p*-Tolyl
c; Ar = *o*-Tolyl
d; Ar = Mesityl

The required compounds (1-3, a-d) were prepared from the appropriate phosphinic acid chlorides.[4] The highly hindered dimesitylphosphinic chloride is rather resistant to attack by nucleophiles,[5] and reaction with ammonia to give the amide (1d) proceeded slowly at room temperature. The anilide (2d) was obtained by heating dimesitylphosphinic chloride with aniline in pyridine at 170° (sealed tube) for 65 h, and the *p*-nitroanilide (3d) by addition of the phosphinic chloride to a mixture of *p*-nitroaniline and sodium hydride in THF (room temp., 20 h).

The rates of hydrolysis of the phosphinic amides (1-3, a-d) were examined spectrophotometrically using dilute solutions (10^{-3}-10^{-5}M) in aqueous $HClO_4$ containing 10% dioxan.[6] In each case a linear first-order plot was obtained, and from this the pseudo-first-order rate constant (k_ψ) was deduced (see Table). No evidence was found for hydrolysis products other than the expected amines and phosphinic acids;[7] in this respect the behaviour of the hindered phosphinic amides (1-3, c and d) seems to differ from that of comparable sulphonic amides.[8]

Irrespective of the nature of the departing amine, the rate of hydrolysis of a P-*p*-tolyl amide (1-3, b) is similar to that of the corresponding P-phenyl compound (1-3, a), showing that the electronic effect of *para*-methyl substituents in the P-phenyl groups is small. In marked contrast, *ortho*-methyl substituents cause a substantial decrease in rate, as evidenced by the values of k_ψ for the P-*o*-tolyl (1-3, c) and P-mesityl (1-3, d) compounds.

TABLE. Hydrolysis of phosphinic amides in 9:1 v/v water-dioxan containing $HClO_4$ [6]

Ar	$Ar_2P(O)NH_2$		$Ar_2P(O)NHC_6H_5$		$Ar_2P(O)NHC_6H_4NO_2$	
	Amide	10^6k_ψ s^{-1}	Amide	10^6k_ψ s^{-1}	Amide	10^6k_ψ s^{-1}
Phenyl	1a	3630	2a	5440	3a	724
p-Tolyl	1b	2340	2b	4470	3b	702
o-Tolyl	1c	81.0	2c	54.9	3c	6.57
Mesityl	1d	3.27	2d	0.88	3d	0.098

In the case of the N-unsubstituted amides (1, a-d), high sensitivity of the hydrolysis to steric hindrance is not unexpected. In an associative (A2) mechanism, rate-determining cleavage of the P-N bond in the protonated substrate will require nucleophilic assistance from water, and will therefore be subject to inhibition by substituents which sterically shield the phosphorus from attack by a nucleophile. For the anilides (2, a-d), where a mechanism with appreciable A1 character has been proposed,[2] it might be expected that steric inhibition of attack of water on phosphorus would be of less consequence. In fact, however, the variation in the value of k_ψ for (2, a-d) is at least as great as for (1, a-d). The results for the p-nitroanilides (3, a-d) are still more remarkable. In spite of the earlier indications of an A1 mechanism for the hydrolysis of (3a),[2] we find that this reaction is no less sensitive to steric hindrance than is the A2 hydrolysis of the N-unsubstituted amide (1a)

While hydrolysis by an A1 mechanism could be sterically retarded by hindrance both to formation of the N-protonated substrate and to solvation of the dissociative transition state $[Ar_2\overset{\delta+}{P}(O)\text{---}\overset{\delta+}{N}H_2R]$, these factors seem inadequate to account for the observed variations in rate Thus our results, while not bearing directly on the question of the extent of P-N bond breaking in the transition state, do suggest that P-O bond making is far from negligible, whatever the departing amine, and that both the phosphinic anilides (2) and the p-nitroanilides (3) hydrolyse by associative (A2) mechanisms similar to those of the amides (1).

References and Footnotes

1. P. Haake and T. Koizumi, Tetrahedron Letters, 1970, 4845; J. Amer. Chem. Soc., 1973, 95, 8073.
2. P. Haake and D.A. Tyssee, Tetrahedron Letters, 1970, 3513; D.A. Tyssee, L.P. Bausher, and P. Haake, J. Amer. Chem. Soc., 1973, 95, 8066.
3. G. Tomaschewski and G. Kühn, J. prakt. Chem., 1968, 38, 222.
4. The new amides (1-3, c and d) gave satisfactory spectra and elemental analyses.
5. B.I. Stepanov, A.I. Bokanov, E.N. Karpova, and N.V. Danilova, J. Gen. Chem. (U.S.S.R.), 1970, 40, 2204.
6. For (1, a-d), $[HClO_4]$ = 0.0662M, T = 30.2°; for (2, a-d), $[HClO_4]$ = 1.36M, T = 39.9°; for (3, a-d), $[HClO_4]$ = 2.58M, T = 39.9°. The maximum possible error in k_ψ is estimated to be ±5% generally and ±15% for (2d) and (3d).
7. In the hydrolyses of (2d) and (3d) there were indications that dimesitylphosphinic acid, once formed, could suffer some further reaction.
8. S. Searles and S. Nukina, Chem. Rev., 1959, 59, 1077.