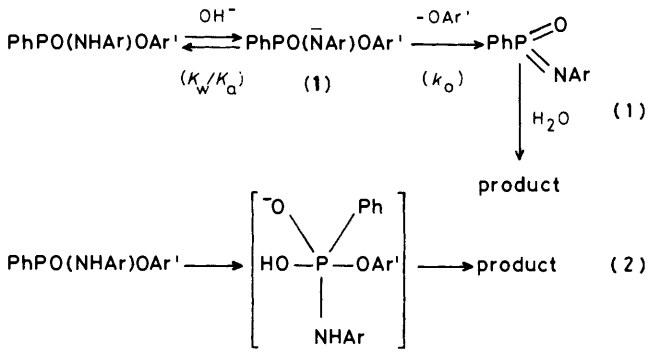
Effect of Basicity on the Decomposition of the Conjugate Base of 4-Nitrophenyl *N*-Aryl-*P*-phenylphosphonamidates

Nicholas Bourne and Andrew Williams*
University Chemical Laboratories, Canterbury, Kent

The hydrolyses at 25 °C in 50% ethanol–water and 1 M ionic strength of the title compounds in alkaline solutions obey the equation $k_{obs.} = k_o/(1 + K_w/K_a[OH^-])$ where k_o is the rate constant for decomposition of the conjugate base and K_a is the ionisation constant. The parameters obey good Hammett relationships $\rho(k_o) = -1.96$ and $\rho(K_w/K_a) = -2.2$ for five substituents varying from 3-chloro to 4-methoxy. The substituent effect monitors the charge development on the nitrogen during the *E*1 reaction and, taken with previous charge data for the leaving oxygen, indicates a transition state with considerable metaphosphorimidate [PhP(O)NAr] character. The substituent effect on nitrogen cannot however differentiate between *E*1cB and $B_{Ac}2$ mechanisms of hydrolysis.

There is strong current interest in phosphoryl ($-PO_3^{2-}$)-transfer reactions which appear to take 'borderline' mechanisms.[1-3] The paths seem to involve neither metaphosphate (PO_3^-) formation nor an intermediate or transition state with strong bonding of phosphorus to leaving or attacking atoms. Analogues of the phosphoryl-transfer system have been studied to investigate the existence of other borderline mechanisms.[4-6] We have provided unequivocal evidence that aryl esters of *N*,*P*-diphenylphosphonamidic acid [equation (1), Ar = Ph] hydrolyse in alkaline solution through an *E*1cB mechanism[4] as opposed to a $B_{Ac}2$-type process [equation (2)] which could involve either concerted or stepwise displacement of the leaving group.



One of the factors responsible for reactivity in formation of the unsaturated intermediate in equation (1) is the 'internal' nucleophilicity of the anion (**1**) driving out the leaving group.[7] A measure of the internal nucleophilicity is the ionisation constant of the neutral molecule which therefore has the potential of controlling the mechanistic path taken. In the previous investigation only the leaving group was altered and it was impossible to study the effect of nitrogen basicity (although this changed throughout the series) because it was swamped by the leaving group effect.

In this study we keep the leaving group constant and measure the effect of the nitrogen substituent on the reactivity of elimination [equation (1)]. The results monitor the change in charge on the nitrogen. Taken with the results for the change in charge on the oxygen[4] we are in a position to discuss the electronic state of both forming (P=N) and cleaving (P–O) bonds in the transition state.

Experimental

Materials.—The *O*-4-nitrophenyl-*N*-aryl-*P*-phenylphosphonamidates were prepared by a variety of methods as no one method was satisfactory for all the esters. The *N*-phenyl ester was prepared by adding a solution of 4-nitrophenol (1.4 g) and pyridine (0.8 ml) in dichloromethane (15 ml) to an ice-cold solution of benzenephosphonyl dichloride (2.0 g) in dichloromethane (20 ml). The mixture was kept overnight at room temperature and was then treated with a solution of aniline (1.9 g) in dichloromethane (10 ml) and kept for a further night. The suspension was then filtered and the filtrate washed with dilute HCl (0.1 M) and water and then dried ($MgSO_4$). Three successive precipitates were formed by addition of light petroleum. The middle fraction was recrystallised from ethanol.

The *N*-(4-methylphenyl) ester was prepared essentially by the above procedure except that a longer period was required for reaction of the intermediate *O*-4-nitrophenyl phenylphosphonochloridate with 4-methylaniline (4 d). The final filtrate was evaporated and the whole residue recrystallised from ethanol.

The *N*-(chlorophenyl) and *N*-(4-methoxyphenyl) esters required the use of isolated *O*-4-nitrophenyl phenylphosphonochloridate in their synthesis. This was accomplished by adding a solution of 4-nitrophenol (7.0 g) and pyridine (4.0 g) in toluene (30 ml) dropwise to a solution of benzenephosphonyl dichloride (9.8 g) in toluene (20 ml) and keeping the mixture overnight. The mixture was filtered, the solvent stripped under vacuum, and the oil distilled under reduced pressure. The first fraction containing mostly pyridine hydrochloride was discarded and the *O*-4-nitrophenyl phenylphosphonochloridate collected at 180 °C (0.05 Torr). The *N*-(4-chlorophenyl) ester was prepared by adding a solution of 4-chloroaniline (2.3 g) in dichloromethane (20 ml) to the chloride (1.8 g) in dichloromethane (10 ml) and keeping the mixture for 2 d. The mixture was filtered; the filtrate was washed with dilute HCl (0.1 M), dried ($MgSO_4$), and evaporated. The residue was recrystallised from ethanol.

The *N*-(3-chlorophenyl) ester was prepared in essentially the same way as for the 4-isomer but the reaction mixture was refluxed for 4 h and then kept for 3 days before work-up. The residue was recrystallised from acetonitrile.

The *N*-(4-methoxyphenyl)ester was prepared from 4-anisidine and the acid chloride under reflux. Refluxing was continued for 3 h after mixing and the solution was kept

Table. Base-catalysed hydrolysis of 4-nitrophenyl *N*-aryl-*P*-phenylphosphonamidates at 25 °C, 50% v/v ethanol–water, and 1M ionic strength

Aryl group	M.p. (°C)[a]	$10^2k_o/s^{-1}$ [b,c]	$10^2K_w/K_a/M$ [b,c]	pK_a	$[OH^-]/M$ [d]	N [e]
Ph	130—33	5.9 (0.2)[f]	2.3 (0.5)[g]	12.37	0.02—1.0	10
4-MeC_6H_4	175	11.8 (0.5)	6.3 (0.5)	12.81	0.02—1.0	10
4-ClC_6H_4	155	2.1 (0.1)	0.63 (0.1)	11.81	0.002—1.0	20
3-ClC_6H_4	168	1.0 (0.1)	0.30 (0.08)	11.49	0.002—1.0	15
4-$MeOC_6H_4$	122	18.5 (1.5)	6.3 (1.0)	12.81	0.02—1.0	15

[a] Melting points were determined with a Kofler block apparatus and are corrected. [b] Values in parentheses are the difference between the maximum and minimum values of k_o or K_w/K_a that can be fitted to the data. [c] The Hammett ρ value for k_oK_a/K_w is −0.24. [d] Range of hydroxide ion concentration used. [e] Number of data points not including duplicates. [f] Literature value 8.3×10^{-2} s^{-1} for 27 °C.[4] [g] Literature value 1.7×10^{-2}M for 27 °C.[4]

overnight before being worked up. The product was recrystallised from acetonitrile.

I.r. and ^1H n.m.r. spectra (JEOL 100 MHz instrument) and the CHN elemental analyses (see Supplementary Publication No. SUP 56127 (1 p.),* Carlo Erba CHN analyser) are consistent with the proposed structures of the esters.

Acetonitrile was purified by the method of Lewis and Smyth[8] and then redistilled from calcium hydride. Other reagents were of analytical reagent grade and water used throughout the investigation was doubly distilled from glass.

Methods.—Kinetics were determined at 25 °C using 50% v/v ethanol–water solvent. The ionic strength was maintained at 1M with NaCl. Reactions were initiated by adding an aliquot (0.05 ml) of the substrate solution in ethanol (except for the 3-chloro-substituted ester which was dissolved in acetonitrile) to the reaction mixture (2.5 ml) in a 1 cm path length silica cell on the flattened tip of a glass rod. A pumping motion effected mixing and the change in absorbance was followed at 410 nm using a Perkin-Elmer model 124 spectrophotometer with a thermostatically controlled cell housing. Concentrations of sodium hydroxide were kept well in excess of the substrate concentration and the pseudo-first-order kinetics were analysed from plots of $A_t - A_\infty$ *versus* time on two-cycle semi-logarithmic graph paper.

A value of pK_w was obtained for the solvent system used by measuring the pH of a 1M-KOH solution. The pH meter was previously calibrated against known concentrations of HCl in the same solvent with ionic strength maintained at 1M with NaCl. KCl does not dissolve at 1M in the present solutions. We found a relationship of pH = measured pH − 0.13, if the instrument (Radiometer PHM 26) was standardised against EIL buffer standards (accurate to ±0.01 pH unit). Unfortunately we are unable to check any influence of the specific effect of potassium as opposed to sodium ions on the measured pH at the high pH employed in measuring pK_w.

Results

The reaction rates of all the substrates obeyed perfect pseudo-first-order kinetics up to 90% of the total reaction under all conditions quoted here. The pseudo-first-order rate constants ($k_{obs.}$) depended on the hydroxide ion concentration according to equation (3). Data for k_o and K_w/K_a are recorded in the Table

$$k_{obs.} = k_o/(1 + K_w/K_a[OH^-]) \quad (3)$$

and K_a is also recorded. The value of K_w ($10^{-14.01}$) may be slightly inaccurate due to the salt effect problem. The absolute value of K_a will therefore be correspondingly uncertain but it is not essential for the arguments used in this paper.

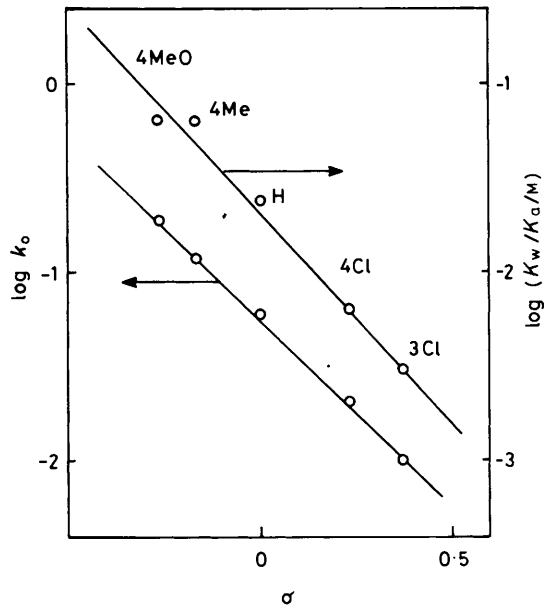


Figure 1. Hammett correlations for the rate and equilibrium parameters for the alkaline hydrolysis of 4-nitrophenyl *N*-aryl-*P*-phenylphosphonamidates at 25 °C, 50% v/v ethanol–water, and 1M ionic strength. Data are from the Table and the lines are calculated from equations given in the text

Both k_o and K_w/K_a obey good Hammett relationships [equations (4) and (5)] and these are illustrated in Figure 1.

$$\log k_o = -1.96 \pm 0.04\sigma - 1.25 \pm 0.01 \; (r = 0.999) \quad (4)$$

$$\log K_w/K_a = -2.20 \pm 0.03\sigma - 1.68 \pm 0.04 \; (r = 0.991) \quad (5)$$

Data obeying a similar rate law were obtained by Mollin *et al.*[9] for the alkaline hydrolysis of diphenyl *N*-arylphosphoramidates [$(PhO)_2PONHAr$]. These workers found that the ionisation of the NH group had a value for the Hammett selectivity (ρ = −2.94) which is close to that found here for the slightly different species.

Discussion

The linear Hammett correlation (Figure 1) for the parameter k_o indicates a constant mechanism for all the members of the series. Since the parent ester (Ar = Ph) has been shown to hydrolyse *via* the *E*1cB pathway[4] we can safely assume that this mechanism holds for the esters studied here. The kinetically determined parameters k_o and K_a therefore represent respec-

* For details of the Supplementary Publications Scheme see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, 1985, Issue 1, section 4.0.

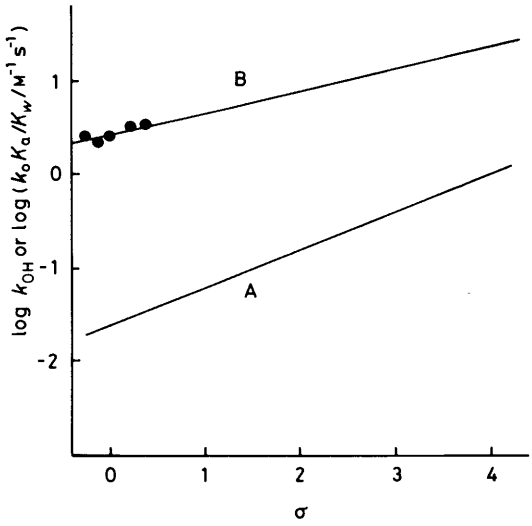


Figure 2. Hammett diagram indicating the point of changeover from *E*1cB to $B_{Ac}2$ mechanisms. Line A for k_{OH} ($B_{Ac}2$) is computed from the value for the $B_{Ac}2$ reactivity of PhNHPO(Ph)$OC_6H_4NO_2$-4[4] and the ρ value estimated in the text. Line B for k_oK_a/K_w is calculated from equations (2) and (3) in the text

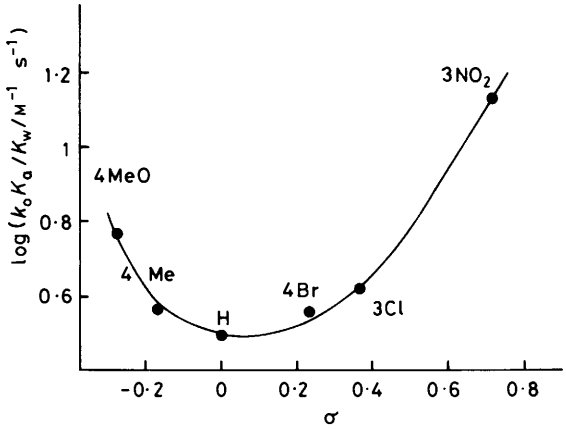
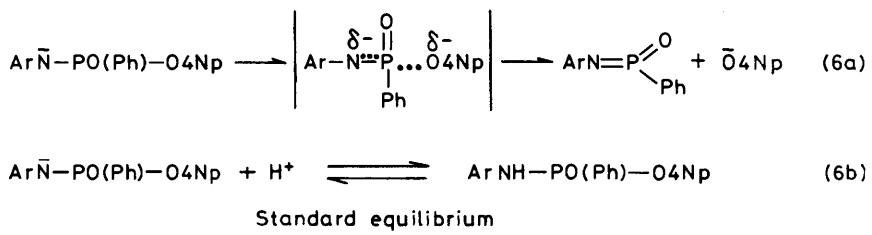


Figure 3. Hammett correlation for the parameter k_oK_a/K_w for the alkaline hydrolysis of diphenyl *N*-arylphosphoramidates. Data are taken from Mollin *et al.*[9] and are for 46 °C, ethanol–water at 50% w/w

tively the '*E*1' rate constant for decomposition of the anion (**1**) and the ionisation constant for the conjugate acid.

The similarity between the effect of substituents on k_o (ρ = −1.96) and the effect on the ionisation constant K_w/K_a (−2.20) is consistent with substantial neutralisation of charge on nitrogen in the transition state. In order to obtain a more accurate charge description we require to know the effect of substituents on the over-all equilibrium [equation (6a), –O4Np = $-OC_6H_4NO_2$-4). It is possible that this effect will be close to that in the standard equilibrium employed [equation (6b)]

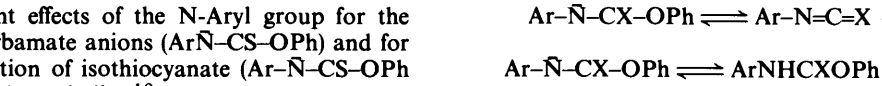


because the substituent effects of the N-Aryl group for the protonation of thiocarbamate anions (ArN̄–CS–OPh) and for the equilibrium formation of isothiocyanate (Ar–N̄–CS–OPh ⇌ ArN=C=S + ŌPh) are similar.[10]

A previous study of the effect of substituents on the leaving phenol group indicates a $\rho_{l.g.}$ for k_o closely similar to the value of 2.23 for the ionisation of phenols.[4] Measurements of the effective charge on oxygen in neutral and charged phosphate esters[11] indicate that the effect of the leaving group substituent on the equilibrium formation of the metaphosphorimidate may not be very different from that on the ionisation of phenols. Taken together the charge data for nitrogen and leaving group oxygen indicate that the transition state of the elimination reaction has an electronic structure close to that of the intermediate products. The ρ values themselves are substantial and we can therefore be sure that the conclusions are qualitatively correct. The large observed $\rho_{l.g.}$[4] for the formation of the metaphosphorimidate is consistent with a small ρ_{nuc} for the reverse direction as might be expected for a very reactive intermediate.

To our knowledge, isocyanate and isothiocyanate formation from the corresponding carbamate anion [equation (7a), X = O or S] represent the only *E*1cB reactions where the charge on the internal nucleophile has been monitored by substituents. The thioncarbamate reaction involves a ρ value approximately half that of the over-all equilibrium [equation (7a), X = S].[10]

The ρ value for the rate of degradation of carbamate [equation (7a), X = O] cannot be compared with that of the equilibrium as the latter is unknown; it is, however, slightly more than half that for the standard equilibrium [equation (7b), X = O].[12] Both of these results indicate transition states with structures by no means close to those of the products. Neither of



the heterocumulenes, which are well known stable species, are as reactive as metaphosphorimidate is likely to be.

The pathway for phosphonamidate ester hydrolysis will change from *E*1cB when the apparent second-order rate constant k_oK_a/K_w becomes equal to the rate constant for the $B_{Ac}2$ process. This changeover point could occur at high or low σ values depending on the relative slopes of the Hammett relationships for the two rate constants. The substituent effect on the $B_{Ac}2$ reaction of hydroxide ion with 4-nitrophenyl *N*-aryl-*P*-phenylphosphonamidate is unknown; we may estimate it from that for attack of hydroxide ion on phenyl *P*,*P*-arylphenylphosphinates [ArPO(Ph)–OPh][13] using an attenuation value for the –NH– group. The latter value is unknown

but it should not be less than that for oxygen (–O–), which we deduce to be 0.6 from the ionisation of aryloxyacetic acids.[14] The reactivity of phenyl *N*-aryl-*P*-phenylphosphonamidates to hydroxide ion in the $B_{Ac}2$ pathway will thus be 0.7[13] multiplied by 0.6. We can assume that the Hammett selectivity will be the same for the 4-nitrophenyl ester.[15] The rate constant for the $B_{Ac}2$ process is about 100-fold smaller than the apparent second-order rate constant (k_oK_a/K_w) for the *E*1cB process.[4] Figure 2 illustrates that the range of available σ values will not be sufficient to cause a change in mechanism which should only occur at very high pK_a values. The low values of the Hammett ρ selectivities (0.24 for the *E*1cB and 0.42 for the $B_{Ac}2$ mechanisms) mean that any differences are close to the error limits to these values. For this reason the Hammett selectivities for variation on the nitrogen substituent are not diagnostic between the two pathways.

The data of Mollin *et al.*[9] for the hydrolysis of diphenyl *N*-arylphosphoramidates [ArNHPO(OPh)$_2$] in alkali indicates that k_oK_a/K_w (the *k'* term in the ref. 9) obeys a markedly U-shaped dependence on Hammett's σ for the variation of the nitrogen substituent (Figure 3). These results cannot indicate a single mechanism and in the low σ region the negative Hammett slope cannot be consistent with simple hydroxide ion attack on the neutral ester. The data are consistent with a changeover in mechanism from *E*1cB (for substrates of high pK_a and low σ) to $B_{Ac}2$ for the substituents of high σ. Such behaviour would appear to explain the observation of a low entropy of activation for the *N*-phenyl (−8.6 cal K^{-1} mol^{-1}) and high negative entropy for the *N*-(3-nitrophenyl) species (−33.7 cal K^{-1} mol^{-1}). The Hammett relationship for the ionisation of these phosphoramidates will be linear because this process is not related to the mechanism taken by the reaction. This system, studied by the Czech workers, may well be the first example of a changeover in mechanism from *E*1cB to $B_{Ac}2$ in a single phosphoramidate substrate type caused by remote substituent effects.

No changeover in mechanism was observed in the alkaline hydrolysis of aryl methyl phosphoramidates [MeOPO(NH$_2$)-OAr] and the corresponding thion esters.[5] These reactions were shown by Hamer and Tack to possess the $B_{Ac}2$ mechanism.

We are not in a position to predict exactly the mechanism followed in phosphonamidate hydrolyses catalysed by alkali but the results up to now indicate that the presence of nitrogen and aromatic carbon adjacent to the phosphorus favours the *E*1cB path. Adjacent oxygen appears to favour the $B_{Ac}2$ mechanism.

Acknowledgements

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