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Alkaline hydrolysis of arylesters of diphenylphosphorodiamidates—evidence consistent with an elimination—addition mechanism

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Abstract. The alkaline hydrolysis of a series of aryl phosphorodiamidates has been studied in aqueous ethanol and aqueous DMSO mixtures. Although the reactions do not show any saturation kinetics with respect to the hydroxide ion, the low solvent isotope effect, the highly negative Bronsted β value, the large Hammett ρ for the leaving aryloxy group and the decrease in rate with increase in the proportion of DMSO in the solvent mixtures indicate that the hydrolysis proceeds by an elimination–addition pathway. Comparison of rate data with other hydrolytic E1CB reactions show that the title reaction belongs to the $(E1CB)_R$ category.

Keywords. Diphenylphosphorodiamidate esters; alkaline hydrolysis; E1CB mechanism.

1. Introduction

Esters and halides of phosphorodiamidates have two modes of decomposition for alkaline hydrolysis an SN2(P) mechanism and an E1CB mechanism. Evidence for the latter mechanism has accumulated in recent times on the basis of the large difference in the values of the alkaline hydrolysis rate constant of mono- and disubstituted nitrogen esters and halides. The rate enhancement was higher than could be ascribed to the steric hindrance to the approach of the OH^- in an SN2(P) mechanism (Gerrard and Hamer 1967). Structure-reactivity correlations used extensively to establish the operation of this mechanism in the hydrolysis of carbamate (Williams 1972) and arylmethane sulphonates (Williams and Douglas 1974) have been applied to study this hydrolysis and decide in favour of the E1CB mechanism (Williams and Douglas 1972). We have shown earlier that a discriminating effect of a dipolar aprotic solvent such as DMSO can be used to differentiate between an SN2 and an E1CB mechanism in the case of carboxylic esters and arylphenylmethane sulphonates (Krishnan *et al* 1978, 1979 and 1982). We report in this communication an extension of this theory as also a structure-reactivity analysis to the case of phosphorodiamidates to decide the mechanism of alkaline hydrolysis of this system.

2. Experimental

Substituted phenyl N,N-diphenylphosphorodiamidates were prepared according to the method of William and Douglas (1972). The melting points obtained (table 1) agree

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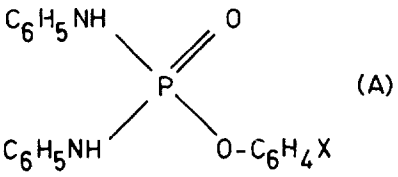
with literature values. Dimethyl sulphoxide (DMSO) was purified under reduced pressure in an all-glass apparatus over calcium hydride (b. pt. 95–96°C; 31 mm) and stored in air-tight bottles. The rates of alkaline hydrolysis of the various esters used were followed using a Carl-Zeiss VSU2-P model spectrophotometer by following the release of the phenoxide ion at appropriate wavelengths. Pseudo first-order rate constants for the hydrolysis were calculated from the slopes of the plots of log $(A_\infty - A_t)$ versus time. The method of least squares was employed and the slopes and correlation coefficients were determined by using a Micro 2200 programmable calculator (Hindustan Computers). The alkaline hydrolysis of *p*-nitrophenyl N,N'-diphenylphosphorodiamidates was also followed in nitrogen atmosphere and aerial oxidation was found to be negligible.

3. Results and discussion

The alkaline hydrolysis of substituted phenyl N,N'-diphenylphosphorodiamidates have been studied in aqueous ethanol and aqueous DMSO. The reaction obeys a good first-order rate expression for the release of phenoxide. The reaction also exhibits a first order dependence on the initial concentrations of sodium hydroxide (table 2). The

Table 1. Melting points of substituted phosphorodiamidates.



(A)

X		M.pt (°C)	λ-O Ar (nm)
p-nitro	(Aa)	169–170	400
m-nitro	(Ab)	171–173	390
p-Cl	(Ac)	169–171	300
p-acetyl	(Ad)	175–177	320
p-H	(Ae)	166–168	300

Table 2. Rate constants for the alkaline hydrolysis of *p*-nitrophenyl N,N-phosphorodiamidates (Aa).

10^3 NaOH M	$10^3 k_1\ s^{-1}$	k_2 lit $mol^{-1}\ s^{-1}$
5·0[a]	1·54	0·303
6·0[a]	1·87	0·312
11·0[a]	3·39	0·308
15·0[a]	4·71	0·314
5·0[b]	0·290	0·058
10·0[b]	0·574	0·0574
15·0[b]	0·870	0·058

Temperature – 30°C; [ester] = 5×10^{-5} M; [a] solvent 50% EtOH – 50% H_2O; [b] solvent 50% DMSO – 50% H_2O.

second-order rate constants for the various esters in both these solvent media and for different compositions are presented in table 3.

A solvent deuterium isotope effect kH_2O/kD_2O nearly equal to one has been observed for the *p*-nitrophenyl ester (Aa) in both 50% EtOH and 50% DMSO systems (table 4). The effect of substituents in the leaving phenoxy group has been brought out by a Hammett treatment of the data in table 5 (figure 1). The bimolecular rate constants obey a good Hammett correlation—but only when σ constants rather than σ^- constants are used for *p*-nitro and *p*-acetyl substituents. The Hammett reaction

Table 3. Substituent and solvent effects in the alkaline hydrolysis of aryl phosphorodiamidates.

Compound	% Organic solvent-% H_2O	EtOH-H_2O	DMSO-H_2O	HMPT-H_2O
		($10\,k_2$ lit mol^{-1} s^{-1})		
Aa	50–50	3·08	0·574	—
	60–40	2·12	0·424	3·82
	70–30	1·68	0·322	2·68
	80–20	1·40	0·255	1·62
Ab	50–50	1·47	0·457	
	60–40	1·20	0·400	
	70–30	0·881	0·266	
	80–20	0·631	0·122	
		$10^4\,k_2$ lit mol^{-1} s^{-1}		
Ac	50–50	44·7	33·1	
	60–40	17·8	14·1	
	70–30	10·0	5·62	
	80–20	3·98	0·316	
Ad	50–50	168	72·4	
	60–40	70·8	32·4	
	70–30	44·7	17·8	
	80–20	20·2	2·24	
		$10^5\,k_2$ lit mol^{-1} s^{-1}		
Ae	50–50	73·5	105	
	60–40	25·1	20·9	
	70–30	11·2	3·87	
	80–20	3·98	0·174	

Temperature—30°C; [ester] = 5×10^{-5} M.

Table 4. Solvent isotope effect in the hydrolysis of *p*-nitrophenyl phosphorodiamidate (Aa

Sovent composition	$10\,k_2$ lit mol^{-1} s^{-1}	kH_2O/kD_2O
50% EtOH - 50% H_2O	3·08	0·96
50% EtOH - 50% D_2O	3·21	
50% DMSO–50% H_2O	0·574	0·98
50% DMSO–50% D_2O	0·585	
Aa = 5×10^{-5} M	NaOD = 1×10^{-2} M	

Temperature—30°C; [ester] = 5×10^{-5} M

Table 5. Dependence of Hammett ρ on solvent composition.

% Organic Solvent – % H_2O	$\rho 30^{\circ}_{EtOH}$	$\rho 30^{\circ}_{DMSO}$
50–50	3·6	2·3
60–40	3·7	2·8
70–30	4·0	3·6
80–20	4·5	5·6

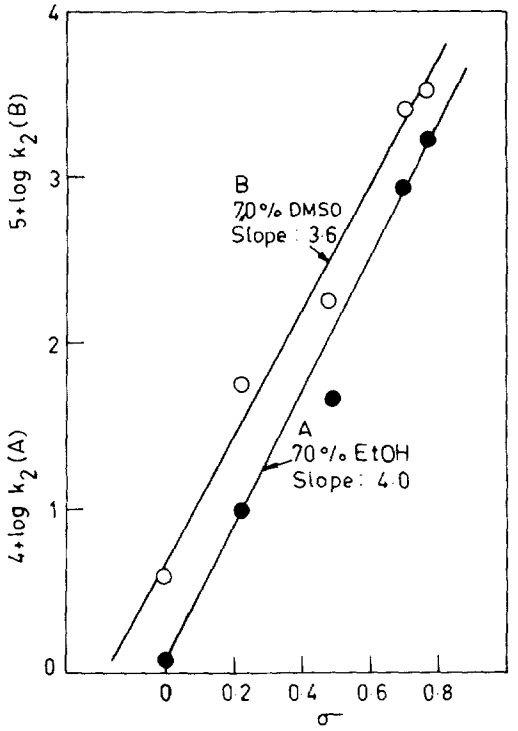
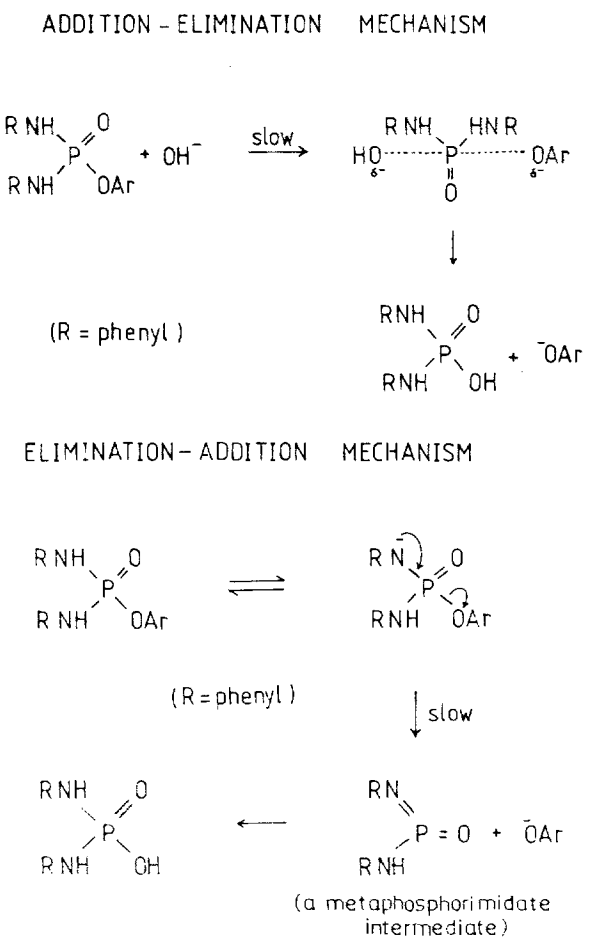


Figure 1. Hammett plot for the alkaline hydrolysis of arylphosphorodiamidates 1. p-NO_2 2. m-nitro 3. p-$COCH_3$ 4. p-Cl 5. -H.

constants are large for these hydrolytic reactions. The magnitude of these values also depends on the nature of the solvent to a large extent. The rate data also fit a Bronsted relationship when the pK_a of the leaving phenols are plotted against log k_2 yielding a value of $\beta = -1{\cdot}2$ and $-1{\cdot}1$ for the reaction in 70% EtOH and 70% DMSO respectively (figure 2).

The foregoing kinetic data for the hydrolysis of the aryl phosphorodiamidates showing a rate dependence on both the substrate and the hydroxide ion concentration are *a priori* in accord with both the addition-elimination and the elimination-addition pathway (schemes 1 and 2).



The experimental observation that the Hammett ρ values for the leaving group are between 2·0 and 5·0 for the hydrolysis indicates, as in the case of phenylmethanesulphonates (Krishnan *et al* 1979) considerable rate-determining cleavage of the P–O bond in the transition state. The transition state for an SN2(P) reaction involves little cleavage of the P-OAr bond and one could expect that the rate of hydrolysis will not be subject to any appreciable change on varying the leaving group. The rate-determining step for a E1CB reaction on the other hand is the unimolecular expulsion of the aryloxy groups with the concomitant formation of the N=P double bond. The transition state of such a process would have extensive P-OAr bond cleavage and hence substituents in the leaving group can effectively interact with the reaction centre. It is interesting to draw an analogy with the corresponding sulphonate esters where arylbenzenesulphonates have a ρ value of 1·5 (Davy *et al* 1977) for alkaline hydrolysis whereas the arylphenylmethanesulphonates exhibit a ρ value of 4·0 for substitution in the leaving aryloxy group. It may also be pointed out that the high negative β value ($-1{\cdot}25$) is characteristic of an elimination-addition pathway and as has been explained in the case of carbamates, would arise out of the twin processes of bond formation (N=P) and bond cleavage (P-OAr). A β value greater than unity may be considered as indicative of

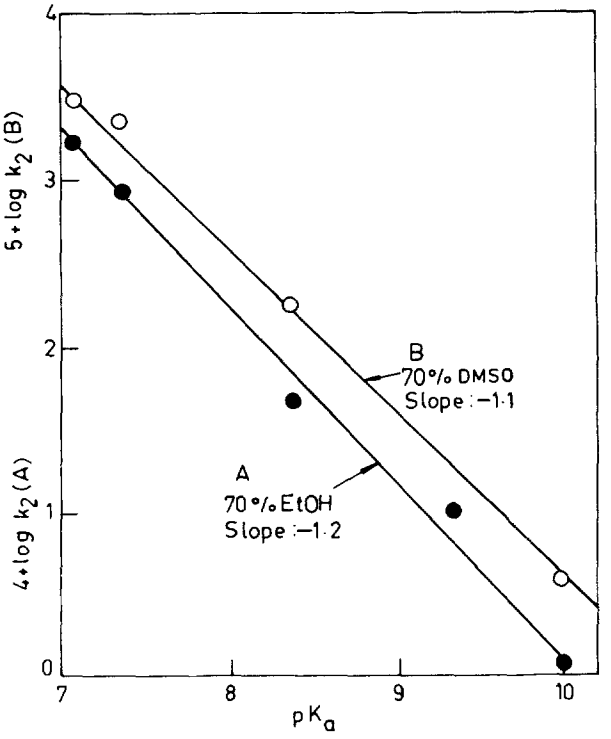


Figure 2. Bronsted plot for the alkaline hydrolysis of arylphosphorodiamidates (Numbers as in figure 1).

greater charge accumulation on the phenolate oxygen in the transition state of the hydrolysis reaction as compared to the ionisation of phenols. The solvent isotope effect of ~ 1 is also indicative of an elimination addition pathway rather than SN2(P). Although this criterion has not been well established for a reaction at a phosphorous centre, it is known in the case of carboxylic esters that reactions proceeding by $B_{AC}2$ process have kH_2O/kD_2O values exceeding 1·5 while those that react by a E1CB pathway have values near unity. The observed pronounced reduction in rate on transfer to solvent systems consisting of larger proportions of DMSO (or HMPT) also convincingly establishes that the reaction proceeds via the formation of an ionised substrate, for it has already been establsihed that reactions that proceed by a $B_{AC}2$ mechanism exhibit considerable rate acceleration when transferred to dipolar aprotic solvents but hydrolysis by E1CB which generates an anion in the pre-equilibrium step exhibits the opposite effect. Indeed pronounced rate retardations have been noticed in the alkaline hydrolysis of benzoyl acetates (Krishnan *et al* 1979b) pyridyl acetates and indole-2-carboxylates (Rao *et al* 1978) aryl acetates (Chandrashekar and Venkatasubramanian *loc cit*) aryl 4-nitro-phenylmethanesulphonates (Krishnan *et al loc cit*)—situations where an ion is very easily formed in a pre-equilibrium step. The observed retardations in DMSO may be traced directly to the effective solvation of the reactant anion, which is charge-extended and polarisable, by DMSO and this being the ground state of the reactant molecule results in rate retardations.

The larger question still remains whether the title reaction is indeed a E1CB reaction or an E2 one. An E2 reaction involving the N–H bond of the parent molecule is difficult to demonstrate by isotope effect studies but the pronounced acidity of this hydrogen atom along with the low solvent isotope effect would rule out the operation of such a pathway. Also the large ρ value for the leaving aryloxy group goes against the mechanism. The hydrolysis reactions exhibit high ρ values of 2·3 to 5·6 in DMSO-H_2O mixtures. Such a high sensitivity to the variation in the leaving group is typical of $(E1CB)_R$ reactions (Williams and Douglas 1975).

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