

THE ALKALINE HYDROLYSIS OF METHYL-SUBSTITUTED ARYL PHOSPHATES

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Abstract. The rates of $S_N2(P)$ reactions in the alkaline hydrolysis of a series of methylaryl phosphates with varying leaving groups have been measured in water at 39° and a constant ionic strength of 1.0. Logarithmic plot of the rate constants against the pK_a 's of the leaving groups is linear with a slope of -0.70. Kinetic isotope effect and activation parameters are consistent with the bimolecular nucleophilic displacement mechanism.

INTRODUCTION

Continuing our studies of the reactivity of simple phosphate diesters with nucleophiles [1], we have examined in detail the effect of the leaving group on the rates of $S_N2(P)$ reactions in the alkaline hydrolysis of a series of methylaryl phosphate esters. The reactions of phosphoryl compounds with nucleophiles have been studied by numerous authors [2,3]. Any meaningful discussion of the kinetics and mechanism of enzymic or intramolecular catalysis must be based on a sound knowledge of the type of reaction concerned in the absence of catalysis. The rates of simple reactions can often be predicted with some accuracy if a linear free-energy relationship can be found to describe the variation of reactivity with the structure of the reactants. Although many data are available for the hydroxide ion-catalysed hydrolysis of various phosphoric acid derivatives, only in a few cases an attempt has been made to correlate the rates of alkaline hydrolysis of phosphate esters with the basicity of the leaving groups. Hoodonk and Ginjaar [4], and Khan and Kirby [5] have determined such a correlation for separate series of fully esterified phosphoric

acid, and Brown and Usher [6] have reported the effect of the leaving group on the alkaline hydrolysis of phosphate diesters in a series of 2-hydroxypropylaryl phosphates. In the present investigations an attempt has been made to determine a similar linear free-energy relationship to describe the variation of reactivity with structure of the leaving group for the alkaline hydrolysis of simple phosphate diesters and for this purpose kinetically more convenient methyl-substituted aryl phosphate esters have been used.

EXPERIMENTAL

Preparations of methyl-substituted aryl phosphates have been reported elsewhere [1]. Oxalic acid, sodium hydroxide and potassium chloride were of analytical grade and were used without further purification. Distilled water was further distilled in an all-glass apparatus. 1.0M sodium hydroxide was prepared by standardisation against 1.0M oxalic acid, 2.0M potassium chloride was used to maintain the ionic strength of the reaction solutions. All solutions were filtered before use.

All rate constants were determined by measuring the rate of release of the displaced phenolate anion spectrophotometrically using Spektromom 203 vis-uv spectrophotometer at the absorption maximum (Table 1) of the phenolate anion concerned.

As all the reactions were slow, they were carried out in a thermostatted water bath maintained at 39° and were followed by the initial rate of release of the phenolate anion, except the reactions of methyl-2,4-dinitrophenyl phosphate at higher temperatures which being fast, were followed by the whole rate method. In a few cases both techniques were used and consistent results were obtained. All the solutions were separately brought to 39° before

Table I. Spectral Data of Phenolate Anion (ArO^-)

Phenol	Wavelength $\lambda_{max}(nm)$	Extinction coeff ϵ
2,4-Dinitro	360	14700
2-Nitro-4-acetyl	399	4560
2-Nitro-4-chloro	425	4380
2-Nitro	416	4800
4-Nitro	400	18320

mixing. The experimental procedure was as follows.

10.0 ml of stock solution of known concentration of the phosphate diester were added to a flask containing the required quantity of 1.0M sodium hydroxide and sufficient quantities of 2.0M potassium chloride to bring the final ionic strength to 1.0, and distilled water to keep the total volume to 100 ml. The flask was immersed in the thermostatted water bath maintained at the required temperature. Aliquots were taken after regular intervals and put into a tube immersed in iced water to quench the reaction. The optical density was then measured at the wavelength of the absorption maximum of the phenolate anion concerned with the help of the spectrophotometer. First five percent of the reaction was followed in each case. The end-point for each reaction, to determine the initial concentration, was obtained by hydrolysing separately the phosphate ester with 1.0M sodium hydroxide at 100° to constant optical density. The fast reactions of methyl 2,4-dinitrophenyl phosphate at higher temperatures were followed to three half-lives and the final readings taken after at least ten half-lives. These reactions gave excellent pseudo-first-order semilogarithmic plots. At the concentrations used, phosphate esters did not contribute significantly towards the optical densities of the liberated phenolate anions at their absorption maxima.

First-order rate constants were calculated from the slopes of the linear plots of optical density converted to concentration units using ϵ value for the liberated phenolate anions at their absorption maxima, against time, by dividing it by the initial concentration of the phosphate ester. Second-order rate constants were obtained from the slopes of the linear plots of the first-order rate constants at different hydroxide ion concentrations, against the concentration of hydroxide ion. Since hydroxide ion, also attacks on the aromatic carbon atom and the attack on phosphorus atom is only 55% [1], the rates were corrected for the attack on carbon atom and are given in Table 2.

DISCUSSION

In the reactions of phosphate esters with nucleophiles, particularly the anionic nucleophiles, the electrostatic repulsion is expected to hinder the reactions. But despite this electrostatic repulsion, nucleophilic attack by anions upon the phosphorus atom in anions of phosphate esters can occur in favourable cases [2]. Hydroxide and alkoxide ions have been reported to react with the dianions of

Table 2. Second-order rate constants for the $S_N2(P)$ reactions of hydroxide ion^a with methyl substituted aryl phosphates at 39° and ionic strength 1.0.

Phosphate diesters	pK_a of the leaving group	k_2 (1 mole ⁻¹ min ⁻¹)	$[S_N2(P)]$
Methyl-2,4-dinitrophenyl	4.07	2.78	$\times 10^{-2}$
The same, at 46°		4.90	$\times 10^{-2}$
The same, at 53°		8.91	$\times 10^{-2}$
The same, at 60°		1.35	$\times 10^{-1}$
The same, in D ₂ O		2.57	$\times 10^{-2}$
Methyl-2-nitro-4-acetylphenyl	5.09	5.25	$\times 10^{-3}$
Methyl-2-nitro-4-chlorophenyl	6.36	7.24	$\times 10^{-4}$
Methyl-4-nitrophenyl	7.15	1.92	$\times 10^{-4}$
Methyl-2-nitrophenyl	7.23	1.70	$\times 10^{-4}$
For methyl 2,4-dinitrophenyl at 39°,			
	$\Delta S^\ddagger = -24.4$	e.u.	
	$\Delta H^\ddagger = 15.4$	kcal mole ⁻¹	
	$k_{H_2O} / k_{D_2O} = 1.08$		

* Concentration range : 0.1 - 0.6; No. of runs: 6 in each case.

2,4- and 2,6- dinitrophenyl phosphates [7,8]. The attack is more favourable in the case of bis (2,4-dinitrophenyl) phosphate monoanion [9] due to less electrostatic repulsion. The bis monoanion ($k_2 \sim 3 \times 10^{-3}$ 1 mole⁻¹ sec⁻¹) is approximately 80 times more reactive towards hydroxide ion than is 2,4-dinitrophenyl phosphate dianion [8] ($k_2 \sim 4 \times 10^{-5}$ 1 mole⁻¹ sec⁻¹) showing that the negative charge effectively inhibits the anionic attack. The electrostatic effect becomes more evident from the fact that the second-order rate constants for attack by acetate, phosphate, carbonate and hydroxide ions are from 2000 to 7200 times greater for the triester [5] than for the diester anion [1], while no reaction at all is observed with the dianion of the monoester [10]. Significantly, the ratio is largest for the two dianion, i.e., carbonate (7200) and phosphate (4000) and close to 2000 for the two monoanions. The ratio is much smaller for the reactions with neutral amine nucleophiles, from 2 to 40 for substituted pyridines. The importance of this electrostatic repulsion is expected to become more significant in the case of phosphate esters with poor leaving groups.

It has been shown previously [1] that the point for the second-order rate constant for the reaction of hydroxide

ion with methyl-2,4-dinitrophenyl phosphate falls on the line drawn for the rate constants as a function of the pK_a 's of the nucleophiles, for reactions of the same phosphate ester with other oxyanions which clearly involve a bimolecular nucleophilic attack on phosphorus. This indicates that hydroxide ion also acts as a nucleophile towards phosphorus atom of methylaryl phosphates. This is consistent with the present observation that there is no significant solvent deuterium isotope effect for the reaction of hydroxide ion with methyl-2,4-dinitrophenyl phosphate ($k_{H_2O}/k_{D_2O} < 1.1$). An Arrhenius plot for the alkaline hydrolysis of methyl-2,4-dinitrophenyl phosphate shown in Fig. 1 gives entropy of activation of -24.4 e.u., a value which is consistent with a bimolecular reaction.

It is now generally assumed that the attack of hydroxide ion at the central phosphorus atom of a phosphate ester can be described in a way analogous to bimolecular nucleophilic displacements in carbon chemistry [11]. Thus alkaline hydrolysis of phosphate esters can be represented by an $S_N2(P)$ mechanism and the steric arrangements of the initial and the transition states are thought to be tetrahedral and bipyramidal respectively. The hydroxide ion also attacks at the aromatic carbon atom to a considerable extent and the attack on phosphorus atom is to the extent of 55% [1]. This extent was determined for the reaction of hydroxide ion with methyl 2,4-dinitrophenyl phosphate and the contribution towards the overall rate due to the attack on carbon atom may become greater in the case of phosphate esters with poor leaving groups where the importance of electrostatic repulsion for the attack on phosphorus atom becomes more significant as mentioned earlier.

It is commonly assumed that the electron-attracting substituents in the leaving group increase the rate of hydrolysis; the reverse is the case with electron-repelling substituents. It is thus reasonable to expect that the leaving tendency of the substituted phenoxide ion will be directly related to its affinity for a proton. It follows from a plot of logarithms of second-order rate constants against the pK_a values of the parent phenol in the alkaline hydrolysis of a series of methylaryl phosphates that such a trend is indeed observed. The slope of this linear free energy relationship, shown in Fig. 2, is -0.70. The equation of the straight line of this figure being

$$\log k_2 = 1.29 - 0.70 pK_a$$

In fact, the slope may be slightly greater than this if the

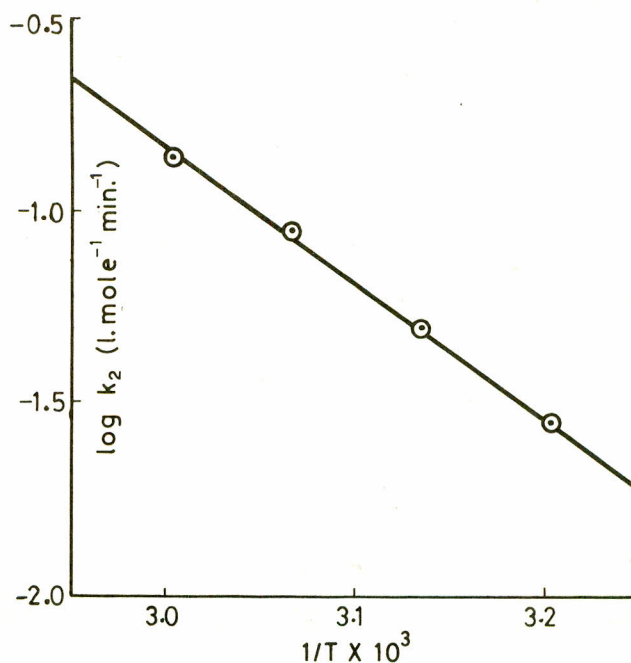


Fig. 1. Arrhenius plot for the second-order rate constants for the $S_N2(P)$ reactions of hydroxide ion with methyl-substituted aryl phosphates at ionic strength 1.0.

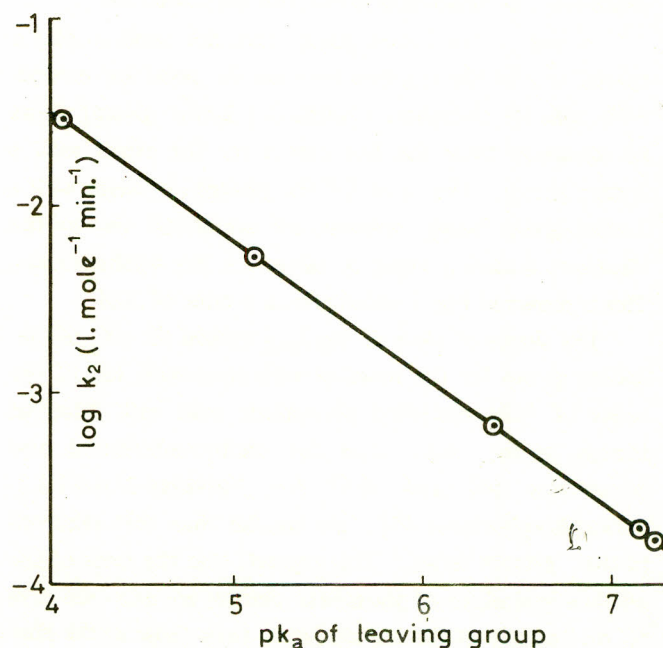


Fig. 2. Linear free energy relationship between the second-order rate constants for the $S_N2(P)$ reactions of hydroxide ion with methyl-substituted aryl phosphates at 39° and ionic strength 1.0, and the pK_a of the conjugate acids of the leaving groups.

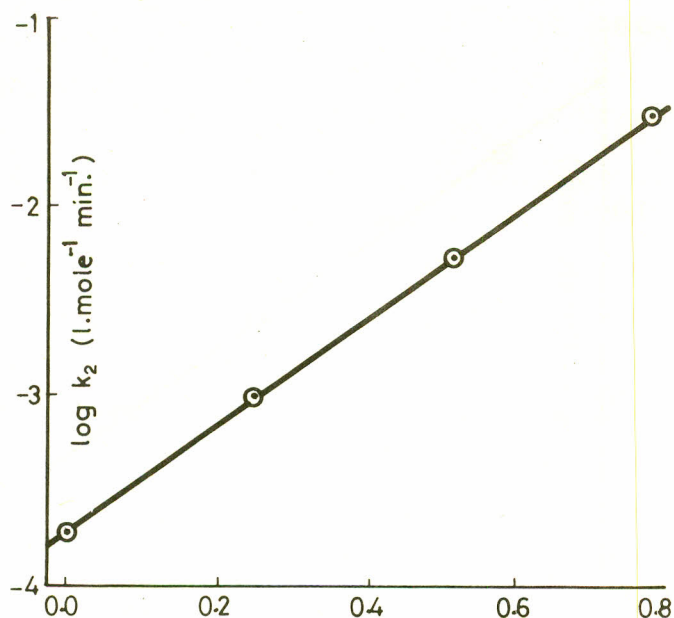


Fig. 3. Hammett plot for the second-order rate constants for the $S_N2(P)$ reactions of hydroxide ion with methyl-substituted aryl phosphates at 39° and ionic strength 1.0; using σ values for the 4-substituents.

contribution due to the attack on carbon atom towards the overall rate, is determined in the case of each phosphate ester, as mentioned above, and accounted for.

In this series 2-nitro group does not seem to play a special role in the reaction because the point for methyl-4-nitrophenyl phosphate (without a 2-nitro group) shows no deviation from the line drawn for the esters with a 2-nitro group. The rates for the phosphate esters with a 2-nitro group being common, are correlated also by the Hammett equation using σ values for the 4-substituents. This is shown in Fig. 3 which gives a ρ value of 2.84.

The slopes of plots of $\log k_{OH}$ against the pK_a of the leaving group for the reaction with hydroxide ion of the series of fully esterified phosphoric acid with different leaving groups, e.g., -0.56 for diethyl-substituted aryl phosphates [4] and -0.41 for 2-aryloxy-2-oxo-1,3,2-dioxaphosphorinans [5], are smaller than that observed in the present series. This suggests that the rates of the alkaline hydrolysis of phosphate diesters are more sensitive to the basicity of the leaving group than those of the phosphate triesters. This difference in sensitivities to the basicity of the leaving group could be attributed to the

fact that phosphorus atom is more electrophilic in a triester than in a diester.

Brown and Usher [6] have reported -0.56 as a slope of the plot of $\log k_2$ against the pK_a 's of the leaving groups for the alkaline hydrolysis of a series of 2-hydroxypropylaryl phosphate esters which shows a lower sensitivity of the reactivity to the basicity of the leaving group. In this case the reaction is catalysed by the 2-hydroxy group and the bond breaking is less advanced in the transition state and therefore is less sensitive to the changes in the leaving group. Furthermore, the rates at 80°C, in this case have been plotted and since the differences in rates of hydrolysis between members of the series are largely due to differences in the activation energy, the gradient would have been steeper if the rates at 39° have been plotted.

Greater sensitivity of the rates of alkaline hydrolysis in the series of methylaryl phosphates to the basicity of the leaving group indicates that the bond breaking is more advanced in the transition state in this case than in the case of the other series discussed above.

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