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# Hydroxide Ion Catlysed Hydrolysis of Diaryl Phosphates

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Summary: Hydroxide ion catalysed hydrolysis of a series of diaryl phosphates with varying leaving groups, has been studied in water at $39^\circ C$ and an ionic strength of 1.0. Mechanism involves a bimolocular nucleophilic attack of the hydroxide ion concerted with the departure of the leaving group. A linear free energy relationship has been determined with a slope of -0.68 for a logarithmic plot of the second-order rate cosntants for the hydrolysis, against the $pK_a$ of the leaving groups.

## Introduction

Containuing our studies of the alkaline hydrolysis of simple phosphate esters[1], we have now examined the hydroxide ion catalysed hydrolysis of another series of phosphate diesters. In fact, the study of catalysis of the hydrolysis of phosphate esters was stimulated by the observation that the phosphate esters with neighbouring functional groups such as hydroxyl[2] and carboxyl3 are hydrolysed at greatly increased rates as compared with the phosphate esters without a neighbouring function.

The catalysis of the reactions of phosphate esters has been extensively studied by various authors[2,4,5] and it has been reported that the hydrolysis of phosphate esters is catalysed by a wide range of acidic, basic, nucleophilic and enzymic catalysts. The study has recently been extended to metal ion catalysed hydrolysis of phosphate esters[6].

The kinetics and mechanism of catalysis can only be fully understood when compared with the corresponding reactions without catalysis. a linear free energy relationship describing variation of reactivity with the structure of the reactants, helps in predicting the rates of simple reactions with some accuracy. Inspite of the fact that the alkaline hydrolysis of various phosphate esters has been studied extensively, not in many cases the rates have been correlated with basicity of the leaving groups. Such a correlation has been reported for phosphate triesters[7,8] and 2-hydroxypropyl aryl phosphates[9], We have already reported the effect of leaving group on the rates of the alkaline hydrolysis of methyl aryl phosphates[1]. In the present investigation we have determined a similar linear free energy relationship to describe the variation of reactivity with structure of the leaving group

for the hydroxide ion catalysed hydrolysis of a series of diaryl phosphates.

## Experimental

Inorganic salts were of analytical grade and were used without further purification. Distilled water was further distilled in an all-glass apparatus. Sodium hydroxide solution was standardised against oxalic acid. Di2,4-initrophenyl phosphate was prepared as the 2,6-lutidinium salt. Phosphate diesters of 2-nitro-4-acetylphenol 2-nitro-4-chlorophenol and 4-nitrophenol were prepared as the trethyl (methyl) ammonium salts whereas those of 2-nitrophenol and 3-nitrophenol were free acids. the preparations of these compunds have already been reported[10]

Reactions were followed by measuring the rate of release of the phenolate anion at its absorption maximum[1] spectrophotometrically using Spektromom 203 vis-uv spectrophotometer. All the reactions were carried out in a thermostatted water bath maintained at $39^\circ C$ and were followed by the initial-rate method. In some cases the reactions were also followed by the whole-rate method and consistent results were obtained. The ionic strength was maintained at 1.0 with KCI. Fresh solutions were preapared each time and all solutions were filtered before use and incubated at $39^\circ C$ before mixing.

In an actual experiment, a stock solution of known concentration of phosphate diester (10.0 ml) was added to the required quantity of 1.0M sodium hydroxide, sufficient quantity of 2.0M potassium chloride to bring

the final ionic strength to 1.0 and water to make the total volume to 100 ml in a flask which was then immersed in the thermostatted water bath. Aliquots were taken after regular intervals and put into a tube immersed in the in iced water to stop the reaction. the optical density was then measured at the wave length of the absorption maximum of the phenolate anion concerned with the help of the spectrophotojeter. First five percent of the reaction was followed in each case. In the case of whole-rate method, the reaction was followed to three half-lives. End-points, to determine the initial concentration, were obtained by hydrolysis of aliquots of the phosphate solution in 2.5M hydrochloric acid solution at 100°C to a constant optical dinisty which was measured after making the solution alkaline with sodium hydroxide solution to a known volume. The phosphate esters at these concentrations did not absorb significantly at the absorption maximum of the phenolate anion. The alkaline hydrolysis of phosphate diesters, under the given experimental conditions, is so much faster than that of the corresponding monoester that it can be assumed that only one molecule of the phenol is released for each molocule of the phosphate.

The slopes of the linear plots of optical density converted to concentration units using extinction coefficients for the liberated phenolate anions at their absorption maxima, against time, divided by the initial concentration, gave first-order rate constants. 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. the results are given in the Table. The second-order rate constants for the hydroxide ion catalysed hydrolysis of diphenyl phosphate was obtained by plotting the rate constants at 100°C and 75°C and extrapolating to 39°C.

## Discussion

The negative charge on anions of phosphate esters effectively inhibits the attack by an anionic nucleophile on phosphorus atom. This electrostatic repulsion becomes evident from the fact that the second-order rate constants for attack by acetate, phosphate, carbonate and hydroxide ions are much greater for the triestor[8] than for the diester anions[12], while no reaction is observed for the dianion of the monoesters[13], the difference being significantly larger for the two dianions than the two monoanions. The ratio is still smaller for the reactions with neutral amine nucleophiles. The importance of the electrostatic repulsion is expected to become more significant in the case of phosphate esters with poor leaving groups.

Despite the electrostatic repulsion, nucleophilic attack by aniouns upon the phosphorus atom in anions of phosphate esters can occur in favourable cases[4] in

Table : Second-order rate constants for the hydroxide ion catalysed hydrolysis
of diaryl phosphates at 39°C and ionic strength 1.0

| Diaryl phosphates | pK of the Leaving group | $k_{2-1}$ (1. mole min. -1) | Conc. range (Molar) | No. of runs |
|---|---|---|---|---|
| 2,4-Dinitrophenyl | 4.07 | $3.98 \times 10^{-1}$ | 0.1 - 0.2 | 3 |
| 2-Nitro-4-acetylphenyl | 5.09 | $6.00 \times 10^{-2}$ | 0.1 - 0.3 | 5 |
| 2-Nitro-4-chlorophenyl | 6.36 | $9.12 \times 10^{-3}$ | 0.1 - 0.3 | 5 |
| 4-Nitrophenyl | 7.15 | $2.73 \times 10^{-3}$ | 0.1 - 0.6 | 6 |
| 2-Nitrophenyl | 7.23 | $2.46 \times 10^{-3}$ | 0.1 - 0.4 | 4 |
| 3-Nitrophenyl | 8.35 | $4.56 \times 10^{-4}$ | 0.1 - 0.2 | 3 |
| Phenyl | 9.99 | $3.30 \times 10^{-5}$ | Extrapolated[a] | |

[a]Reference 11.

addition to the attack on carbon atom. Hydroxide and alkoxide ions react with the dianions of 2,4- and 2,6-dinitrophenyl phosphates[14]. Similarly, hydroxide ion readily reacts with di-2,4-dinitrophenyl phosphate monoanion[15]. The monoanion of the phosphate diester is approximately fifty times more reactive towards hydroxide ion than is 2,4-dinitrophenyl phosphate dianion[16]. However, powerful electron-attracting groups can minimise the improtance of these electrostatic repulsions.

The spontaneous hydrolysis of phosphate diesters is so slow that monanions of open-chain dialkyl and diaryl phosphates are generally unreactive compared with those of monosubstituted phosphates[4,17] but at higher pH (>13) diaryl phosphates are hydrolysed faster than the monesters so that the hydrolysis could be stopped after first step. The rates of alkaline hydrolysis of phosphate diesters are very sensitive to the $pK_a$ of the leaving group and the difference in reactivity of mono- and diesters towards alkaline hydrolysis decreases rapidly as the basicity of the leaving group decreases. For example, the ratio of the second-order rate constants for the alkaline hydrolysis of di- and monoesters decreases from 5000 for phosphate esters of 4-nitrophenol to 50 for those of 2,4-dinitrophenol and the linear free energy relationship predicts that with a sufficiently good leaving group (e.g., $pK_a$ less than 1.5) the diester could be less reactive than the monoester under those conditions.

It is now generally accepted that hydroxide ion acts as a nucleophile towards phosphorus atom of phosphate diesters[1,15] in a manner analogous to bimolecular nucleophilic displacement in carbon chemistry[18] with the steric arrangements of the initial and the transition states as tetrahedral and bipyramidal respectively. The electron-attracting substituents in the leaving group are commonly assumed to increase the rates of the nucleophilic displacement reactions wheras the electron-repelling groups have the opposite effect. This is also true for phosphate esters acting as substrates towards anionic nucleophiles[12] as well as hydroxide ion[1] Such a trend has in fact been observed in the present series of phosphate diesters.

The sensitivity of reactivity to the leaving group is conveniently measured by the slope of a plot of the logarithms of the rate constants for hydrolysis against the $pK_a$ of the conjugate acids of the leaving groups. A logarithmic plot of second-order rate constants agains the $pK_a$ of the parent phenol in the alkaline hydrolysis of

diaryl phosphates shown in the Figure, gives a slope of -0.68. The equation of the straight line is

$$\log k = 2.3 - 0.68\, pK_a$$

The dependance of the reactivity on the $pK_a$ of the leaving group also varies linearly with the basicity of the nucleophile. The slopes obtained from the linear logarithmic plots of the second-order rate constants for the $pK_a$ 's of the leaving groups, are -1.06 for pyridine, -1.04 for 4-methylpyridine and -0.96 for 4-aminopyridine. A linear free energy relationship suggests that a slope a close to -0.80 is expected for a nucleophile with $pK_a$ eoual to that of hydroxide ion. A lower slope (0.68) in the case of hydroxide ion can be attributed to the differnce in the steric cnvironments of the nucleophilic atom.

Almost same sensitivity of hydroxide ion catalysed hydrolysis to the basicity of the leaving group was observed in the case of methyl aryl phosphates. This shows that the general behaviour of diaryl phosphates towards alkaline hydrolysis is not different from that of methyl aryl phosphates which proceeds by a mechanism involving a bimolecular nucleophilic attack of hydroxide ion on the phosphorus atom of phosphate diesters. Higher sensitivity of the alkaline hydrolysis to the basicity of the leaving group of phosphate diesters as compared with that of triestors [8] can be ascribed to the fact that
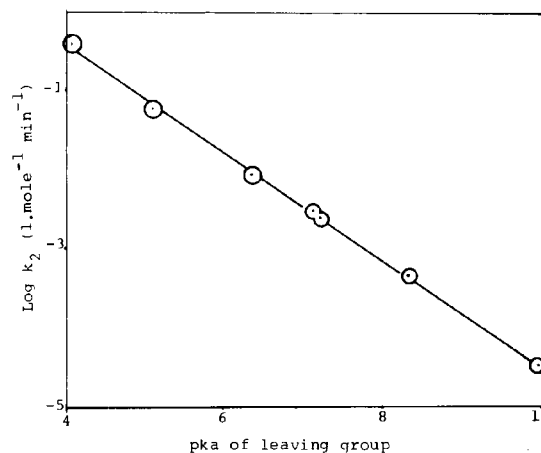


Fig. Linear free energy relationship between the second-order rate constants for the hydroxide ion catalysed hydrolysis of diaryl phosphates at $39^{\circ}C$ and ionic strength 1.0, and the $pK_a$ of the conjugate acids of the leaving group.

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

The sensitivity of reactivity to the basicity of the leaving group also tells about the extent of bond breaking in the transition state. The lope of the logarithmic plot of the rates of hydrolysis of the monoanions of phosphate monoesters against the $pK_a$ of the leaving groups is -0.27 which has been interpretted to occur by a mechanism with rapid pre-equilibrium forma‸ on of a zwitterion followed by phosphorus-oxygen b d fission in the rate determining step[14]

In the case of hydrolysis of dianions of phospl te monoesters where the slope of the plot of log $K_{hyd.}$ verses $pK_a$ of the leaving group is -1.23[14], a mechanism proceeding by an initial dissociation to an anion of monomeric metaphosphate has been suggested. In this case two full negative charges provide the driving froce for the elimination reaction. A similar study of the hydrolysis of phosphate diester anions where the single negative charge must be a less effective driving force so that the elimination in this case would depend more strongly on the leaving group, reveals that the sensitivity of the hydrolysis rate to the basicity of the leaving group is actually lower for diester anion[10] (slope = -0.97) than it is for monoester dianion, and has been interpretted to-gether with other kinetic parameters to involve a bimolecular mechanism with bond breaking slightly more advanced. In the case of the alkaline hydrolysis of a series of 2-hydroxypropyl aryl phosphates which shows a lower sensitivity of the reactivity to the basicity of the leaving group with a slope of -0.56[9], the reaction is catalysed by the 2-hydroxy group and the bond breaking is less advanced in the transition state.

An intermediate sensitivity of the alkaline hydrolysis of the present series of diaryl phosphates to the basicity of the leaving group as shown by the slope of -0.68 suggest that the alkaline hydrolysis of diaryl phosphates involves a bimolecular displacement of the leaving group in a concerted process.

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