Effect of cations in the hydrolysis of phosphate esters

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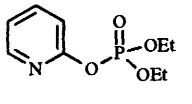
The rates of the acid-catalysed hydrolysis of diethyl 2-pyridyl phosphate and of the base-promoted hydrolysis of *N*-methyl-8-(dimethylphosphoryloxy)quinolinium ion have been determined in the presence of different cations as buffer components. For both substrates the rate depends on the nature of the cations, indicating the participation of a substrate–cation complex in the reaction.

The importance of metal ions in the chemistry and biochemistry of nucleoside phosphates is well established[1] and the metal ion promoted reactions of phosphate derivatives have been thoroughly studied and reviewed.[2] Buncel and co-workers demonstrated that in non-aqueous solutions (*e.g.* in ethanol) the displacement at the phosphoryl centre in simple organophosphorus substrates can be catalysed by the alkali metal ions *via* a mechanism involving complexation of the nucleophile–metal ion pair by the phosphoryl group, followed by the delivery of the nucleophile to the reaction centre.[3] For nucleophilic substitution at carbon, with a phosphate anion as the leaving group, we have shown that the alkali metal ion catalysis is highly effective for the iodide–acetone system,[4] but not for the displacement by thiophenoxide in methanol because of the difference in the ion-pairing behaviour.[5] In our recent study on the fluoride ion catalysis in the hydrolysis of phosphate esters, we found that LiF is much less efficient than other fluoride salts, presumably because of some degree of aggregation even in aqueous solutions.[6] In the latter work, two substrates, diethyl 2-pyridyl phosphate (**1**) and *N*-methyl-8-(dimethylphosphoryloxy)quinolinium trifluoromethanesulfonate (**2**), were studied and their hydrolysis showed very different responses to the F^- catalysis. In this paper we report on the nature of the effect of the cations on the acid-catalysed hydrolysis of **1** and the hydroxide ion promoted hydrolysis of **2**.



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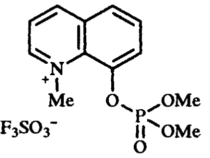

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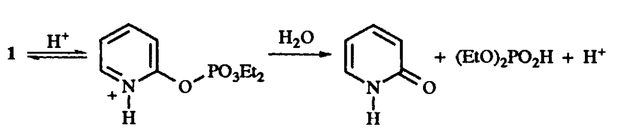
Results and discussion

Because of the susceptibility of **1** to acid catalysis in the hydrolysis reaction, its reaction in pure water is strongly self-catalysed owing to the release of a highly acidic product, diethyl phosphate[6] (Scheme 1).



Scheme 1

In order to determine for the hydrolysis of **1** the specific acid-catalysis rate constant, k_H, the observed rate constants were determined in the pH range 2–4 (citric acid–M^+OH^- buffer, 30 °C). Linear plots of k_{obs} *vs.* $[H^+]$ were obtained, but the slopes of those plots varied with the nature of the cation present as a buffer component. This result suggests that the cations also have an effect on the reaction rate and since the concentration of the cation was not kept constant in the experiment (buffer requirements), the obtained slopes could not be directly related to the k_H values. Consequently, we determined the relationship between k_{obs} and $[H^+]$ for the hydrolysis of **1** at constant concentration of the cations M^+ (0.26 mol dm^{-3}). The required acidity of the medium was obtained by adding variable amounts of MOH to a solution of citric acid and in order to keep $[M^+]$ constant variable amounts of MCl salt were also added. For all salts used ($M^+ = Li^+, Na^+, K^+, NH_4^+, Me_4N^+$) good linearity of the plots was obtained giving the average catalytic rate constant, $k_H = 0.10 \pm 0.02$ dm^3 mol^{-1} s^{-1}. Small differences in the individual values of k_H observed for different cations were interpreted in terms of the difference in the reactivity of the substrates interacting with different cationic species present in the medium. This prompted us to determine the rate of the hydrolysis at constant acidity, but with variable concentrations of M^+ ions. A solution of citric acid–MOH at pH = 2.16 was chosen and variable amounts of MCl were added to that solution. Fig. 1, resulting from that study, gives clear evidence for the electrophilic catalysis operating in the reaction with the individual values of the new catalytic rate constants, k_{M^+},

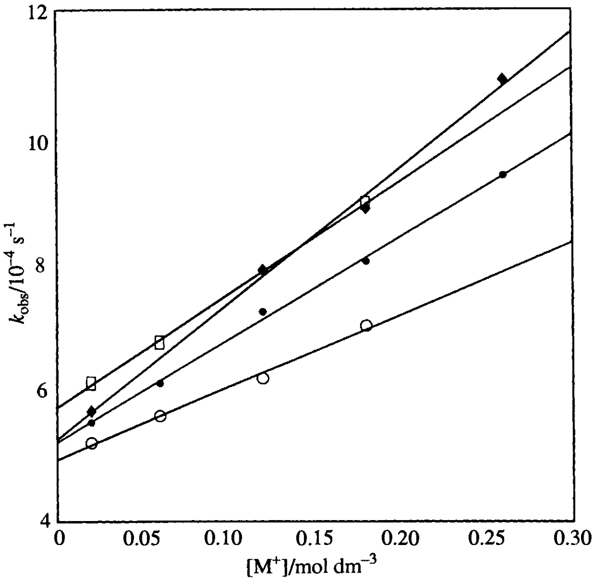


Fig. 1 Observed rate constants for the hydrolysis of **1** at pH = 2.16 as a function of the cation concentration at 30 °C; [**1**] = 0.001 mol dm^{-3}, buffer: citric acid–M^+OH^-–M^+Cl^-. $M^+ = Me_4N^+$ (○); Na^+ (●); NH_4^+ (□); K^+ (◆).

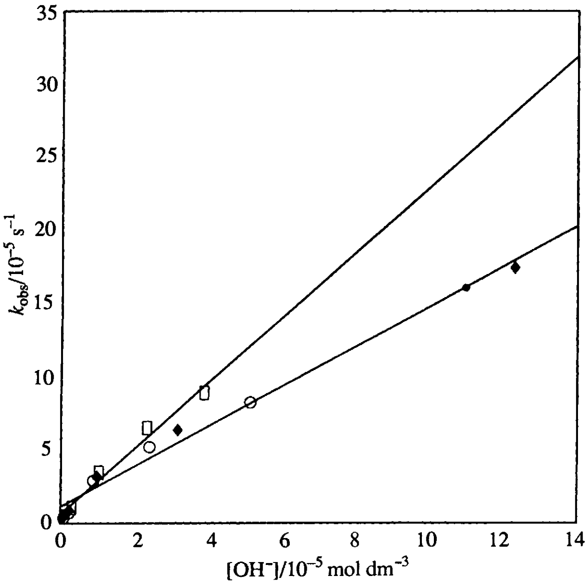


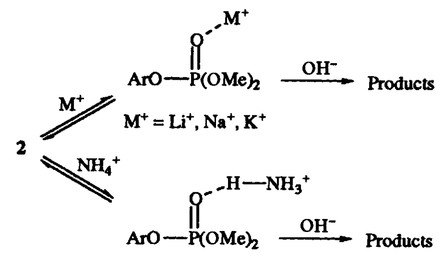
Fig. 2 Observed rate constants for the hydrolysis of **2** as a function of hydroxide ion concentration at constant concentration of a cation (0.096 mol dm^{-3}) at 30 °C; [**2**] = 1.5×10^{-4} mol dm^{-3}, buffer: boric acid–M^+OH^-–M^+Cl^-. M^+ = Li^+ (●), Na^+ (◆), K^+ (○); NH_4^+ (□).

varying in the order: $k_{K^+} = 2.2 \times 10^{-3}$, $k_{NH_4^+} = 1.8 \times 10^{-3}$, $k_{Na^+} = 1.6 \times 10^{-3}$ and $k_{Me_4N^+} = 1.1 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}. The total observed rate constant for the hydrolysis of **1** can therefore be given by eqn. (1). It has to be concluded that the

$$k_{obs} = k_{H_2O} + k_H[H^+] + k_{M^+}[M^+] \qquad (1)$$

Lewis acid–base interactions between a cation and a molecule of **1** (either at nitrogen, or at the phosphoryl oxygen, or in a chelate type structure) offers an additional catalytic pathway for the hydrolysis, *ca.* 100-fold less effective than the catalysis involving protonation of the substrate.

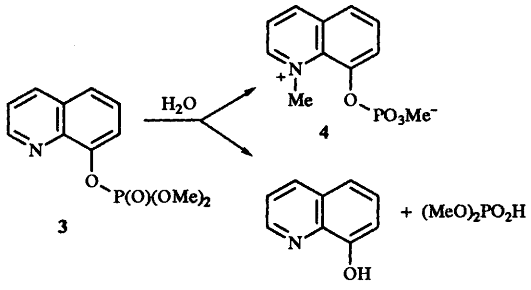
Hydrolysis of ester **2** is not subject to acid catalysis (no basic centre is present at the leaving group). In pure water the decomposition of **2** is very slow and it mostly involves the attack of water at the methyl carbon (formation of methanol).[6,7] The upper limit of the rate constant for the minor pathway of the P–OAr bond cleavage in **2** (D_2O, 30 °C) has been determined using previous results[7] as $k_{D_2O} = 4.7 \times 10^{-8}$ s^{-1}. The hydrolysis can be, however, easily achieved under basic conditions, and, according to the concept of 'hard–hard' interactions,[8] hydrolysis of **2** at pH > 7 involves exclusively the P–OAr bond fission. We have determined the rate of the release of the conjugate base of *N*-methyl-8-hydroxyquinolinium ion from **2** at pH 8–10 (boric acid–M^+OH^- buffer, 30 °C) at a constant concentration of the cation used ([M^+] = 0.096 mol dm^{-3}) (Fig. 2). As for **1**, the pH was varied by addition of MOH to a solution of boric acid and the concentration of M^+ was kept constant by addition of MCl. The first important result is the value of the intercept of the linear plots, corresponding to the reaction rate at zero hydroxide ion concentration. The value (*ca.* 8×10^{-6} s^{-1}) is two orders of magnitude greater than the upper limit of k_{D_2O} determined in pure water. This result indicates the catalytic effect of the species present in the reaction medium (presumably, a cationic component of the buffer). Secondly, the k_{obs} *vs.* [OH^-] relationship generated two linear plots; one common for the alkali metal ions used (M^+ = Li^+, Na^+, K^+) yielding the rate constant value of k_{OH} = 1.38 dm^3 mol^{-1} s^{-1} (r = 0.993) and the other for M^+ = NH_4^+, yielding the value of k_{OH} = 2.24 dm^3 mol^{-1} s^{-1} (r = 0.990). It is clear that the nature of the cation has an effect on the hydroxide ion promoted cleavage of the P–OAr bond, so there is no single value of k_{OH} for that reaction. We propose that the first specific rate constant (k_{MOH}) represents the attack of the hydroxide ion at the phosphoryl centre of a molecule of **2** coordinated to an alkali metal ion, while the latter corresponds to the activation of the substrate *via* the stronger hydrogen bonding between the phosphoryl group and the ammonium ion (Scheme 2). Another possibility is that the reaction is faster in the presence of NH_4^+ ions because it is additionally catalysed by free ammonia existing in a borate buffer.



Scheme 2

The acceleration of the hydrolysis of **2** by the cations relative to the reaction in pure water, k_{rel}, is *ca.* 160. This order of acceleration is in good agreement with the *ca.* 400-fold increase in the rate of the base hydrolysis of trimethyl phosphate (also proceeding with the P–O bond cleavage) upon coordination of the substrate to the iridium(III) ion.[9] As in our case, the reaction was interpreted as the intermolecular attack of hydroxide ion at the phosphorus centre in the coordinated, as well as in the free ligand. Although in systems in which metal ions can promote reactions of phosphate esters *via* an intramolecular delivery of the nucleophile rate acceleration is usually several orders of magnitude bigger,[2] our results show that even in such reaction systems as the OH^- ion promoted substitution in aqueous media, the role of the cationic species present cannot be ignored.

Finally, the hydrolysis of another phosphate ester, dimethyl 8-quinolyl phosphate (**3**) was studied, since **3** is stucturally closely related to both previous substrates, **1** and **2**. The hydrolytic reactivity of **3** in pure water could not be determined, because, as we have established before,[10] under those conditions the P–OAr bond cleavage represents only a minor pathway, the main reaction being the bimolecular disproportionation to the zwitterionic isomeric product **4** (Scheme 3). Formation of **4** can be, however, eliminated by carrying out the reaction under alkaline conditions, when the the displacement of the ArO^- anion by a strong nucleophile (OH^-) from the phosphoryl centre is much faster than the displacement of the ester methyl group by the quinolyl nitrogen of another molecule of the substrate (Scheme 3, the pathway leading to **4**). Alkaline



Scheme 3

hydrolysis of **3** yielded the specific rate constant, k_{OH} = 1.7×10^{-2} dm^3 mol^{-1} s^{-1}, *ca.* 100 times smaller than the rate constant for the alkaline hydrolysis of its *N*-methylated derivative, **2**, as expected for a substrate with a less electronegative aromatic substituent in the leaving group ArO. Within experimental error, the determined value of k_{OH} for **3** was identical for the Li^+, Na^+, K^+ and Me_4N^+ ions used as hydroxide counterions. Unfortunately, this value could not be compared, as for **2**, with the rate constant for $NH_4{}^+$ as a counterion, since in aqueous solutions of ammonia, as in pure water, the reaction at the methyl carbon (*O*-demethylation) competed successfully with the substitution at phosphorus.

Experimental

Preparation of substrates **1** and **2**,[6] as well as substrate **3** and the product **4** (required for identification purposes and for the determination of the δ_P value),[10] has been described before. The buffer solutions were prepared according to the literature.[11]

Rate measurement

For **1** and **2** kinetic measurements were made spectrophotometrically by recording the changes in absorbance at 220–340 nm using a Varian Cary 2390 spectrophotometer fitted with a thermostatted cell holder. Solutions were prepared by dissolving the required amount of substrate in a prepared buffer solution and incubated in a water bath at 30 ± 0.2 °C. At selected time intervals samples were withdrawn and the UV spectra were recorded. For faster runs the quartz cell containing the reaction solution was placed directly in the sample holder thermostatted at 30 °C, and the instrument was programmed to record absorbance at the substrate's and product's λ_{max} at selected time intervals. For **1**: buffer, citric acid–MOH; $[\mathbf{1}] = 1.0 \times 10^{-3}$ mol dm^{-3}; substrate λ_{max} 258 nm ($\varepsilon_{max} = 2840$); product (2-hydroxypyridine) $\lambda_{max} = 292$ nm ($\varepsilon_{max} = 5500$). For **2**: buffer, boric acid–MOH–MCl; $[\mathbf{2}] = 1.5 \times 10^{-4}$ mol dm^{-3}; substrate $\lambda_{max} = 241$ nm ($\varepsilon_{max} = 46\,200$); product (conjugate base of *N*-methyl-8-hydroxyquinolinium ion) $\lambda_{max} = 272$ nm ($\varepsilon_{max} = 31\,800$). Kinetic runs were carried out to at least 80% conversion and good linearity of the second-order kinetic plots was obtained ($r = 0.9950$–0.9999). The identity of the reaction taking place and the identity of the products were determined by recording the UV spectra of the corresponding compounds.

The kinetics of the hydrolysis of **3** were measured in D_2O containing two mole equivalents of MOH (M = Li, Na, K, Me_4N) using ^{31}P NMR spectroscopy (Bruker AC 300 spectrometer; probe temperature 30 °C; chemical shift values relative to 85% H_3PO_4 as external standard). The conversion was determined from the signal intensity of the substrate ($\delta_P = -2.0$) relative to the signal of the hydrolysis product, the dimethyl phosphate ion ($\delta_P = 3.6$). At lower hydroxide ion concentrations (*e.g.* one mole equivalent of MOH) the kinetics were complicated by the simultaneous formation of the isomerization product **4** ($\delta_P = -2.5$). The formation of **4** is a function of hydroxide ion concentration and becomes an exclusive reaction in pure D_2O. The runs were carried out to *ca.* 60% conversion and the second-order rate constants were determined in the usual way. The obtained value of $k_{OH} = 1.7 \times 10^{-2}$ dm^3 mol^{-1} s^{-1} was within ± 7% the same for all four cations introduced as hydroxide salts.

Acknowledgements

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