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AMBIDENT ELECTROPHILICITY OF ALKYL ARYL PHOSPHATES

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Hydrolysis of dimethyl aryl phosphates, $(MeO)_2P(O)OAr$, where the ArO group is derived from *N*-methyl-8-hydroxyquinolinium or 4-hydroxy-(*N*,*N*,*N*-trimethylanilinium) ion, proceeds with the cleavage of the P—OAr and Me—O bonds. The effect of external factors on the relative contributions of those two reaction pathways was studied. The increase in temperature favours, owing to the difference in activation entropies, the reaction at carbon. The addition acetone to the aqueous reaction medium slows down the reaction at carbon more rapidly than the reaction at phosphorus, indicating higher hydration requirements of the dealkylation transition state. In water–trifluoracetic acid mixtures only the P—OAr bond cleavage is acid catalysed; the catalytic effect is superimposed on the general, decelerating medium effect. Specific nucleophilic catalysis was demonstrated for the Me—O bond fission by thiosulphate ion (*ca* 60-fold acceleration), and for the reaction at phosphorus by fluoride ion (*ca* 500-fold acceleration).

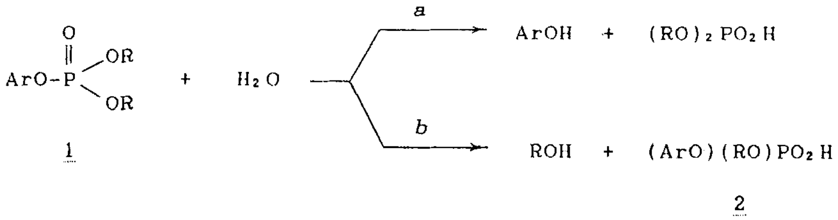
INTRODUCTION

Whereas sulphonic acid esters RSO_2OR' generally give C—O bond cleavage in reactions with nucleophiles[1] and carboxylic esters typically undergo substitution at the carbonyl center,[2] phosphoric esters, $(RO)_3PO$, occupy an intermediate position, offering both the phosphorus and the α-carbon atom as the reactive electrophilic centre. The reaction at phosphorus represents the phosphorylation process,[3] whereas substitution at the α-carbon (*O*-dealkylation) has found wide application in the 'triester' method of oligonucleotide synthesis,[4] and also is responsible for the *in vivo* detoxification mechanism for compounds with anticholinesterase activity.[5] For a suitably selected phosphate ester, both reactions can occur within a single molecular framework and, as indicated in Scheme 1 for the hydrolysis of the mixed ester **1**, give two pairs of reaction products.

In this work, we studied the effect of external factors, such as temperature, medium, weak acids and ions, on the relative contributions of pathways a and b (Scheme 1) in the solvolysis (hydrolysis) of some aryl dimethyl phosphates (**1**, R = Me). We expected this study to shed additional light on the mechanism of the nucleophilic cleavage of the P—O and C—O bonds in organic phosphates.

RESULTS AND DISCUSSION

In order to achieve comparable contributions from both hydrolysis reactions, the ArO function in **1** should



Scheme 1

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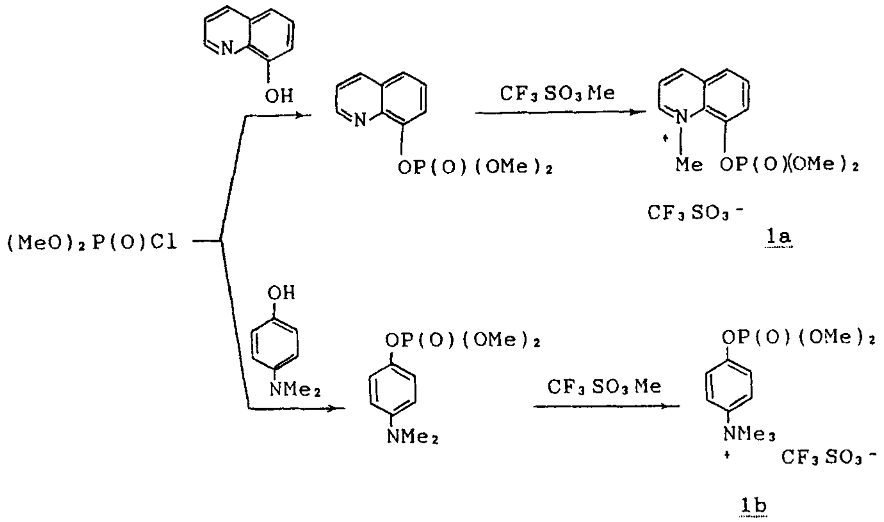

Scheme 2

represent a good leaving group, that is to be derived from an acidic phenol. In addition, since the reaction was followed by monitoring the ^{1}H NMR spectra of solutions of **1** in D_2O, a high solubility of substrates in water was required. We found that two phosphate esters, each bearing the ionic (ammonium) centre in the Ar group, i.e., those derived from *N*-methyl-8-hydroxyquinolinium ion and from 4-(*N*,*N*,*N*-trimethylammonio)phenol, provided excellent models for our study. The substrates **1a** and **1b** were synthesized as indicated in Scheme 2, and were characterized by NMR spectrometry and elemental analysis.

The hydrolysis of **1a** and **1b** could then be studied under a variety of conditions; in some cases the results were compared with those obtained for dimethyl 4-nitrophenyl phosphate (**1c**), for which the solubility limitations precluded measurement in purely aqueous media. The course of the reaction could be easily determined by ^{1}H NMR spectrometry, as the different hydrolysis products [methanol, dimethyl phosphate (DMP), and the respective methyl aryl phosphates, **2a**, **2b** and **2c**] could be clearly identified and determined according to the characteristic signals of their *O*-methyl groups. All the expected products of solvolysis were prepared independently and were used for comparison with and the analysis of the reaction mixture.

Since under the applied conditions both reactions (a and b, Scheme 1) are of the same kinetic order (pseudo-first order), the proportion of the products resulting from reactions a and b corresponds to the ratio of the respective rate constants:

$$\frac{(\%\text{ of the product of a})}{(\%\text{ of the product of b})} = \frac{2k_P}{k_C} \qquad (1)$$

where k_P and k_C represent the specific rate constants for the nucleophilic reaction of D_2O at the phosphorus atom and the *O*-methyl group in **1**, respectively. Since the disappearance of **1** follows pseudo-first-order kinetics (rate = $k_{obs}[\mathbf{1}]$), the equation

$$k_{obs} = k_P + 2k_C \qquad (2)$$

in combination with equation (1) allowed us to determine the rate constants for the individual reactions (demethylation and phosphorylation) from the experimentally determined values of k_{obs} and the k_P/k_C ratio.

Effect of temperature

The effect of temperature on the hydrolysis of **1a** is given in Table 1. The negative values of the entropies of activation obtained for both reactions are indicative of associative mechanisms operating in both cases. The much less negative value obtained for the *O*-demethylation, however, suggests a relatively 'loose' transition state (TS), in agreement with our earlier observation[6] on the 'early' TS in the de-ethylation of triethyl phosphate. The large negative entropy of activation observed for the reaction occurring at phosphorus, typical of the reactions of water with esters and anhydrides,[7] points to a 'tight' transition state, structurally not far from pentacoordinated intermediate of the addition–elimination process.[8]

Effect of a cosolvent

The addition of acetone-d_6 to the D_2O solutions of **1a** and **1b** had a profound effect on the hydrolysis reaction (Table 2). It is clear that the addition of acetone, which lowers the activity of water, decreases the rate of hydrolysis of both substrates. There are, however, some

Table 1. Rate constants, selectivity and activation parameters for the hydrolysis of **1a** in D_2O

T (°C)	10^6k_{obs} (s^{-1})	k_C/k_P[a]	$10^6k_{obs}(C)$[b] (s^{-1})	$10^6k_{obs}(P)$[b] (s^{-1})	$\Delta S^\ddagger(C)$ ($J\ mol^{-1}K^{-1}$) $\Delta H^\ddagger(C)$ ($kJ\ mol^{-1}$)	$\Delta S^\ddagger(P)$ ($J\ mol^{-1}K^{-1}$) $\Delta H^\ddagger(P)$ ($kJ\ mol^{-1}$)
40·0	2·4	4·9	1·1	0·22	−55 49·3	−171 54·6
50·0	8·0	7·0	3·7	0·53		
60·0	22·0	10·0	10·5	1·0		

[a] Statistically corrected.

[b] Symbols C and P in this and the following Tables refer to the reactions occurring at the methyl carbon and at the phosphorus atom, respectively.

Table 2. Effect of acetone-d_6 on the hydrolysis of **1a** (40 °C) and **1b** (60 °C)

$(CD_3)_2CO$ (vol %)	D_2O (mole fraction)	k_C/k_P[a]		10^6k_{obs} (s^{-1})		$10^6k_{obs}(C)$ (s^{-1})		$10^6k_{obs}(P)$ (s^{-1})	
		1a	**1b**	**1a**	**1b**	**1a**	**1b**	**1a**	**1b**
0	1·00	7·5	6·0	2·3	4·7	1·1	2·2	0·14	0·36
22	0·94	7·2		1·7		0·8		0·11	
42	0·85	5·0		1·2		0·54		0·11	
54	0·78		3·9		1·4		0·62		0·16
77	0·55	2·0	3·0	0·62	0·56	0·25	0·24	0·12	0·08

[a] Statistically corrected.

obvious differences in the response of the individual substrates and reaction pathways to the changes in the composition of the medium. On moving from pure D_2O to the medium containing a 0·45 mole fraction of acetone, hydrolysis of **1b** is slowed more than twice as much as that of **1a** (8·4 vs. 3·7). For both substrates the reaction at carbon shows greater sensitivity than the reaction at phosphorus towards the decrease in water activity; in fact, over the medium composition studied no significant decrease in the $k_{obs}(P)$ value was observed for **1a**. In terms of the involvement of water in the hydrolysis reaction, the rates of the reactions at both centres can be described by the equations

$$\text{rate(C)} = k_C a_S a^n_{D_2O} \qquad (3)$$

$$\text{rate(P)} = k_P a_S a^m_{D_2O} \qquad (4)$$

where a_S is substrate's activity and n and m represent the minimum number of water molecules necessary to achieve the transition states in the demethylation and phosphorylation, respectively.

Our results indicate that the 'order with respect to water' (n, m) is greater for **1b** than for **1a**, and that for both substrates $n > m$. For both phosphates the charge is being developed in the transition states, hence the rate decrease on the addition of the less polar solvent. The smaller rate retardation observed for **1a** can be explained by the proximity of the positively charged nitrogen atom of the *N*-methylquinolinium group, capable of the direct stabilization of the incipient negative charge developed on the phosphate or the phenolic oxygen atoms. No direct zwitterionic interactions are possible in case of **1b** with the more remote positive centre. The trend $n > m$ suggests that the transition state leading to the *O*-demethylation has greater hydration requirements than that for the reaction at phosphorus. Although it is difficult to predict the exact hydration of a multi-oxygen, negative species, it is known that the free energy of transfer of phosphate diesters (products of the *O*-dealkylation) from chloroform to water is about five orders of magnitude more negative than that for the neutral triesters.[9] Recent calculations showed[10] that three molecules of water coordinate strongly with each anionic oxygen atom in the PO_2^- group. In conclusion, it seems that the departure of the PO_2^- anion (Scheme 1, reaction b) is favoured by a large number of solvating water molecules to a greater extent than is the associative step of the formation of the P^V intermediate.

The 4-nitrophenyl substrate **1c** is too weakly soluble in D_2O to be studied in that solvent, and its hydrolysis in acetone–water mixtures was very slow [in 1 : 1 (v/v) D_2O–acetone-d_6 at 60 °C, $t_{1/2} \approx 77$ h], so no reliable kinetic data could be obtained. In the mixtures containing 33 or 71% of acetone-d_6 the $k_{obs}(C)/k_{obs}(P)$ ratio for **1c** was approximately constant (*ca* 3), indicating similar responses of both reactions to the water content in the reaction medium.

Table 3. Effect of TFA-*d* on the hydrolysis of **1a** (40 °C) and **1b** (60 °C)

TFA-*d* (vol %)	D_2O (mole fraction)	k_C/k_P[a]		10^6k_{obs} (s^{-1})		$10^6k_{obs}(C)$ (s^{-1})		$10^6k_{obs}(P)$ (s^{-1})	
		1a	**1b**	**1a**	**1b**	**1a**	**1b**	**1a**	**1b**
0	1·00	7·5	6·0	2·3	4·7	1·1	2·2	0·14	0·36
0·8	>0·99	4·6		2·6		1·2		0·25	
1·9	0·99	2·7		2·8		1·2		0·44	
3·8	<0·99	1·6		3·0		1·1		0·71	
7·5	0·98		0·90		6·4		2·1		2·3
10·0	0·97	0·68		3·4		0·94		1·38	
20·0	0·94	0·42		2·5		0·56		1·34	
30·0	0·91	0·33	0·80	1·5	1·9	0·30	0·58	0·90	0·73
50·0	0·81	0·36		0·65		0·14			0·38
75·0	0·59	[b]		[b]		[b]		[b]	

[a] Statistically corrected.

[b] Reaction very slow. Some formation of DMP (*ca* 4%) after 8 days. No MeOD detected in the ^1H NMR spectrum.

The effect of a protic acid (deuteriated trifluoroacetic acid, TFA-*d*) also showed some interesting features, and the results are shown in Table 3. For both substrates the reaction at carbon showed systematic rate retardation on the addition of TFA-*d*, similar in magnitude to that observed for D_2O–acetone-d_6 mixtures. We conclude, therefore, that the *O*-demethylation is not subject to acid catalysis, and that the observed rate decrease results from the 'general' solvent effect involving only the decrease in the water activity term. The effect of TFA-*d* on the hydrolysis of the P—OAr bond is more complex, however. Up to *ca* 10 vol% of TFA-*d* about a tenfold rate acceleration was observed, followed by the 'normal' rate retardation effect at the higher content of the cosolvent. It is clear that the reaction is subject to the acid catalysis by TFA-*d*, and that this effect is superimposed on the general solvent effect, dominant at higher contents of TFA-*d*. Since the pK_a values for substrates **1** should be more negative than that estimated[11] for trimethyl phosphate (p$K_a \approx -4$), they are not fully protonated even in concentrated solutions of TFA-*d*, hence the observed rate maxima for the reaction at phosphorus are not the consequence of the complete protonation of the substrates.

For the acid catalysis observed in the hydrolysis of aryl phosphates, Bunton[12] proposed two mechanisms involving rate-determining proton transfer to the phenolic oxygen atom either directly in the substrate or in the pentacoordinated intermediate formed by the addition of water to the substrate's conjugate acid. Our results are not inconsistent with those mechanisms, and again indicate significant differences in the susceptibility of the P—O and C—O bond fission to the proton-donating properties of the reaction medium. In a related study on the acid-catalysed hydrolysis of benzimidate esters where the nucleophilic attack can occur at either the carbonyl or the alkyl carbon atoms, McClelland[13] demonstrated different response of those two reactions to the addition of sulphuric acid.

Effect of ionic species

Small amounts (up to 0·20 M for 0·05 M substrates) of salts such as sodium perchlorate or tetrabutylammonium hydrogensulphate had negligible effects on both the rate and the regioselectivity of the hydrolysis of **1a** and **1b**. Similarly, when the counter ion in **1b** was changed from the triflate to the nitrate anion (substrate **1b**′), no change in the course of the hydrolysis was observed. The addition of large amounts of sodium triflate had, however, a significant effect on the reaction (Table 4). Although the total rate of hydrolysis (k_{obs}) was decreased about threefold, the selectivity (k_C/k_P) remained approximately constant over the wide range of concentrations. This result suggests some general effect of the added salt, expressed most likely in the stabilization ('salting-in') of the ground state of the substrate. We have independent evidence[14] for strong ion-pairing effects between phosphoryl substrates and alkali metal salts, which should stabilize the phosphate and reduce its electrophilic reactivity.

Marked effects of the ionic content of the medium were observed, however, when the initial concentration of phosphate substrates was varied (Table 5). The effect is highly selective; on a tenfold increase in the initial substrate concentration the k_C/k_P ratio decreased by a factor of *ca* three. That change in the selectivity resulted from the effect on the reaction at phosphorus: while the values of $k_{obs}(C)$ did not change significantly, a *ca* threefold decrease in $k_{obs}(P)$ was observed for both substrates. We have found that the results shown in Table 5 are the consequences of the autocatalysis by the phosphoric acid diesters (Scheme 1, DMP or com-

Table 4. Effect of sodium trifluoromethanesulphonate on the hydrolysis of **1a** (0·05 M) in D_2O (40 °C)

Total salt[a] (M)	k_C/k_P[b]	10^6k_{obs} (s^{-1})	10^6k_{obs}(C) (s^{-1})	10^6k_{obs}(P) (s^{-1})
0·05	12	2·4	1·15	0·096
0·14	10	2·3	1·1	0·11
0·20	10	2·1	1·0	0·10
0·40	13	1·9	0·91	0·070
1·4	12	1·3	0·62	0·052
2·7	10	0·8	0·38	0·038

[a] C_{tot} = [**1a**] + [CF_3SO_3Na].
[b] Statistically corrected.

Table 5. Effect of the initial concentration of **1a** (40 °C) and **1b** (60 °C) on their hydrolysis in D_2O

[**1**]$_0$ (M)	k_C/k_P[a]		10^6k_{obs} (s^{-1})		10^6k_{obs}(C) (s^{-1})		10^6k_{obs}(P) (s^{-1})	
	1a	**1b**	**1a**	**1b**	**1a**	**1b**	**1a**	**1b**
0·040		21		5·4		2·6		0·12
0·049	9·0		2·4		1·14		0·13	
0·082	8·1		2·4		1·13		0·14	
0·10		12		4·9		2·3		0·20
0·21	5·5		2·3		1·05		0·19	
0·30		6		4·7		2·2		0·36
0·40	3·1		2·3		0·99		0·32	

[a] Statistically corrected.

pounds **2**) produced in both hydrolytic pathways. Since the reaction products are strongly acidic (for DMP, $pK_a = 1{\cdot}29$;[15] diesters **2** should be even more acidic), hydrolysis involving the P—OAr bond cleavage becomes increasingly subject to the acid catalysis, in agreement with earlier results obtained for the D_2O–TFA-*d* mixtures. This conclusion was confirmed by the addition of DMP to the reaction mixture. While sodium dimethylphosphate had a negligible effect on the reaction, addition of free dimethylphosphoric acid (0·30 M) to the D_2O solution of **1a** resulted in the decrease in the k_C/k_P ratio by a factor of 2·4. Because of this autocatalytic effect, all the reported k_C/k_P values have to be considered as approximate, and they should be a function of the concentration of the acidic products, i.e of the percentage of the conversion. Indeed, when the k_C/k_P ratio was measured for the hydrolysis of **1a** in D_2O (40 °C) at 18, 33, 63 and 75% conversion, k_C/k_P values of 5·8, 5·7, 4·7 and 4·1, respectively, were obtained.

Finally, the hydrolysis reaction of the mixed phosphate triesters was tested for a specific nucleophilic catalysis. Fluoride ion is known to attack the 'hard' phosphorus of phosphate esters;[16] this property has been used in fluoride ion-catalysed transesterification of phosphoric esters.[17] In contrast, the 'soft' thiosulphate ion [Swain–Scott parameter in H_2O, $n = 6{\cdot}35$ (Ref. 18)] was expected to attack selectively the methyl carbon atoms in **1**. The effects of addition of the sodium salts of these ions on the hydrolysis of **1a** are shown in Table 6. As expected, NaF and $Na_2S_2O_3$ had a dramatic effect on the rate and selectivity of the hydrolysis, giving evidence for the susceptibility of both

Table 6. Effect of sodium fluoride and sodium thiosulphate on the hydrolysis of **1a** (0·14 M) in D_2O (50 °C)

Salt added (0·14 M)	10^6k_{obs} (s^{-1})	k_C/k_P[a]
None	8.0	7.0
NaF	4000[b]	0.05
$Na_2S_2O_3$	500[b]	$\geqslant 20$[c]

[a] Statistically corrected.
[b] Approximate values owing to fast decay of **1a**.
[c] Lower limit; no products resulting from the attack at phosphorus were detected in the ^1H NMR spectra.

reactions (P—O and C—O cleavage) to specific nucleophilic catalysis.

In conclusion, we believe that we have demonstrated that phosphate triesters of the type **1** can undergo parallel substitutions at phosphorus and at the α-carbon atom yielding products of phosphorylation and dealkylation reactions. The relative contributions from these two pathways can be modified, however, for a given substrate by external factors: the alkylating ability of the substrates is enhanced by increasing the reaction temperature or via specific nucleophilic catalysis; the cleavage of the P—OAr bond can be facilitated by acidic (or specific nucleophilic) catalysis or by the addition of an aprotic solvent.

EXPERIMENTAL

Solvents and commercially available reagents were purified by standard methods before use. Solvents were evaporated on a Buchi rotary evaporator. Bulb-to-bulb distillations were carried out using a Buchi GKR-50 glass tube oven. ^{1}H NMR spectra were recorded on a superconducting Bruker AC300 Fourier transform NMR spectrometer. Elemental analyses (C, H, N) were performed at the Department of Chemistry, University of Cape Town. A Gallenkamp digital melting point apparatus was used to determine melting points, which are uncorrected. The following deuteriated solvents were used: Merck Uvasol chloroform-*d*, min. 99·8% D; Merck Uvasol deuterium oxide, min. 99·75% D; Aldrich acetone-d_6, min. 99·5% D; and Aldrich trifluoroacetic acid-*d*, min. 99% D.

Materials. Dimethyl phosphorochloridate was prepared according to the literature procedure.[19]

N,*N*-Dimethyl-4-aminophenol was prepared from *N*,*N*-dimethyl-4-aminoanisole[20] by heating its solution in hydrobromic acid (47%) under reflux for 6 h. After neutralization, extraction (benzene) and removal of the solvent the crude product was purified by crystallization from benzene; 72% yield, m.p. 77·5–78·0 °C. ^{1}H NMR (D_2O): δ 2·66 (6H, s, NMe_2), 6·73–6·85 (2H, m, 3,5-H), 6·88–7·01 (2H, m, 2,6-H).

Sodium salts of the phosphate diesters were prepared in the following manner. Sodium iodide (dried at 150 °C) (*ca* $2·7 \times 10^{-3}$ mol) was dissolved in dry acetone (3 ml). The aryl dimethyl phosphate (**1a**, **b**, **c**) or trimethyl phosphate (*ca* $2·7 \times 10^{-3}$ mol) was added and the mixture was heated under reflux for 6 h. Some of the solvent was removed under reduced pressure and the crystalline product was washed with dry diethyl ether and dried.

Sodium dimethyl phosphate (DMP-Na), 82% yield. ^{1}H NMR (D_2O): δ 3·52 (d, J_{HP} = 10·5 Hz, 2 × OME).

Sodium methyl 4-nitrophenyl phosphate (**2c**-Na), 67% yield. ^{1}H NMR (D_2O): δ 3·67 (3H, d, J_{HP} = 11·2 Hz, OMe), 7·23–7·27 (2H, m, 2,6-H), 8·16–8·19 (2H, m, 3,5-H).

Sodium *N*-methyl-8-(methylphosphoryloxy) quinolinium trifluoromethanesulphonate (**2a**-Na), 70% yield. ^{1}H NMR (D_2O): δ 3·73 (3H, d, J_{HP} = 11·3 Hz, OMe), 4·48 (3H, s, NMe^+), 7·85–8·00 and 8·99–9·02 (4H and 2H, m, aromatic H).

Sodium *N*,*N*,*N*-trimethyl-4-(methylphosphoryloxy) anilinium trifluoromethanesulphonate (**1b**-Na), 50% yield. ^{1}H NMR (D_2O): δ 3·58 (9H, s, NMe_3^+), 3·64 (3H, d, J_{HP} = 11·1 Hz, OMe), 7·31–7·35 (2H, m, 2,6-H), 7·74–7·78 (2H, m, 3,5-H).

Dimethyl aryl phosphates (intermediates in the preparation of **1a** and **1b**; see Scheme 2) were prepared as follows. Sodium hydride (*ca* 0·04 mol) was placed in a flask protected from moisture and washed several times with dry toluene. The required phenol (0·02 mol) dissolved in toluene (20 ml) was added dropwise with stirring to the suspension of NaH in toluene. The mixture was then stirred at room temperature until the evolution of hydrogen has ceased (*ca* 3 h). The solution was transferred to a dropping funnel and added dropwise with stirring and exclusion of moisture to a cooled (*ca* 5 °C) solution of dimethyl phosphorochloridate (0·02 mol) in dry diethyl ether (50 ml). After the addition the mixture was stirred at room temperature for 2 h and left overnight in refrigerator. The precipitate (NaCl) was filtered off and the solvent was removed under reduced pressure, yielding the crude triester, which was purified by successive washing with dry light petroleum.

Dimethyl quinolin-8-yl phosphate, 60% yield, m.p. 59·5–62·5 °C. ^{1}H NMR (D_2O): δ 3·67 (6H, d. J_{HP} = 11·4 Hz, 2 × OMe), 6·87–7·17 (4H, m, 3,5,6,7-H), 7·55 (1H, dd, J_{HH} = 8·1, 0·9 Hz, 4-H), 8·38 (1H, dd, J_{HH} = 4·1, 1·2 Hz, 2-H).

Dimethyl 4-(*N*,*N*-dimethylamino)phenyl phosphate, 33% yield, m.p. 32–36 °C. ^{1}H NMR /$CDCl_3$): δ 2·88 (6H, s, NMe_2), 3·81 (6H, d, J_{HP} = 11·6 Hz, 2 × OMe), 6·61–6·66 (2H, m, 3,5-H), 7·03–7·07 (2H, m, 2,6-H).

Preparation of 1a and 1b. A solution of freshly distilled methyl trifluormethanesulphonate (0·040 mol) in dichloromethane (40 ml) was added dropwise with stirring and cooling (*ca* 0 °C) to a solution of the required dimethyl aryl phosphate (0·026 mol) in dichloromethane (40 ml). The reaction mixture was stirred at 0 °C for 2 h and then overnight at room temperature. Volatile materials were removed under reduced pressure. Crude **1a** and **1b** were obtained as oils and were purified as described below.

N-Methyl-8-(dimethylphosphoryloxy)quinolinium trifluoromethansulphonate (**1a**): the crude product was dissolved in dry dichloromethane (50 ml), poured slowly into vigorously stirred dry diethyl ether (700 ml) and the mixture was left overnight. After decanting the solvent, the residual oil was kept under reduced pressure until it solidified to a yellow, crystalline material; 74% yield, m.p. 68·5–70·0 °C (hygroscopic). Analysis: calculated for $C_{13}H_{15}F_3NO_7PS$, C 37·4, H 3·6, N 3·4; found, C 36·9, H 3·4, N 3·3%. ^1H NMR (D_2O): δ 3·96 (6H, d, J_{HP} = 11·7 Hz, 2 × OMe), 4·28 (3H, s, NMe^+), 7·88–8·18 (4H, m, 3,5,6,7-H), 9·07–9·13 (2H, m, 2,4-H).

N, *N*, *N*-Trimethyl-4-(dimethylphosphoryloxy)anilinium trifluoromethanesulphonate (**1b**): the oily product was washed several times with dry diethyl ether until it solidified. The solid product was dissolved in a minimum volume of dichloromethane and the solution was added dropwise to cold diethyl ether. The white precipitate was filtered off and dried under reduced pressure; 88% yield, m.p. 78–80 °C. Analysis: calculated for $C_{12}H_{19}F_3NO_7PS$, C 35·2, H 4·7, N 3·4; found, C 35·1, H 4·7, N 3·9%. ^1H NMR (D_2O): δ 3·60 (9H, s, NMe^+), 3·89 (6H, d, J_{HP} = 11·4 Hz, 2 × OMe), 7·41–7·44 (2H, m, 2,6-H), 7·83–7·87 (2H, m, 3,5-H).

N, *N*, *N*-Trimethyl-4-(dimethylphosphoryloxy)anilinium nitrate (**1b**′): dimethyl 4-(*N*,*N*-dimethylamino)-phenyl phosphate ($4·4 \times 10^{-4}$ mol) was dissolved in acetonitrile (10 ml, freshly distilled from P_4O_{10}). Silver nitrate ($7·1 \times 10^{-4}$ mol) was added and the mixture was stirred at 0 °C for a few minutes. Excess of iodomethane (*ca* 0·0027 mol) was added at once to the solution and the mixture was stirred at room temperature overnight. After filtration through a layer of Celite and anhydrous $MgSO_4$, the solvent was removed under reduced pressure, yielding **1b**′ as pale brown crystals; 86% yield, m.p. 190–191 °C. The ^1H NMR spectrum (D_2O) was identical with that of **1b**.

Dimethyl 4-nitrophenyl phosphate (**1c**) was obtained according to the literature procedure[21] and purified by bulb-to-bulb distillation (oven temperature 190–200 °C/0·07 mmHg); 69% yield. Analysis: calculated for $C_8H_{10}NO_6P$, C 38·9, H 4·1, N 5·7; found, C 39·4, H 3·7, N 5·9%. ^1H NMR (acetone-d_6): δ 3·89 (6H, d, J_{HP} = 11·3 Hz, 2 × OMe), 7·49–7·52 (2H, m, 2,6-H), 8·27–8·31 (2H, m, 3,5-H).

Kinetics. Solutions of substrates in the required deuteriated solvents (or solvent mixtures) were transferred to an NMR tube and incubated in a thermostated water-bath capable of maintaining a constant temperature within ±0·2 °C. Tubes were withdrawn at selected time intervals and the ^1H NMR spectra of the reaction mixtures were recorded immediately. The k_C/k_P ratio was determined directly from the $[P_C]/2[P_P]$ ratio, where P_C and P_P represent products of the reaction at carbon and phosphorus, respectively:

$$\frac{k_C}{k_P} = \frac{[P_C]}{2[P_P]} = \frac{\text{integral for the signal of } P_C}{\text{integral for the signal of } P_P} \tag{5}$$

where the integrals on the right-hand side are corrected for the number of protons.

The k_C/k_P ratios showed an average scatter of ±12% within individual kinetic runs. For all species the concentration changes followed strictly first-order kinetics. Kinetic runs were carried out for at least three half-lives. The observed (pseudo-first-order) rate constants, k_{obs}, were derived in the usual way by plotting the values of $\ln[100/(100 - \%\ \text{conversion})]$ vs time. Good linear plots were obtained with values of $r^2 = 0·9945–0·9999$.

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