Fluoride ion in phosphoryl transfer. A catalyst or an inhibitor?

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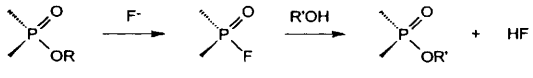
Fluoride ions have been found to affect hydrolysis of aryl phosphates by more than one mechanism. For substrates with a leaving group like the anions of *p*-nitrophenol or the *N*-methyl-8-hydroxyquinolinium ion, F^- accelerated the rate *via* fast formation and decay of the phosphorofluoridate intermediate. For a case when the reaction was autocatalysed (protonation of the leaving group by the acidic product), fluoride ion acted as a net inhibitor due to the elimination of acidic catalysis. The same effect was observed for the hydrolysis of dimethyl phosphorofluoridate. LiF was found to be much less effective in nucleophilic catalysis than other fluoride salts.

The dynamics of the P–F bond have attracted considerable attention since the early work on the organophosphorus nerve gases,[1] followed by the application of the fluoride ion as a catalyst in the transesterification of phosphate esters.[2] Solvolytic stability of the P–F bond in dithymidylyl-3',5'-phosphorofluoridates has been investigated[3] in connection with the reported[4] potential of mono- and di-deoxynucleoside phosphorofluoridates in the preparation of oligonucleotides. The mechanism of the hydrolysis of the P–F bond in Sarin and related substrates was studied in detail more than 30 years ago. Aksnes and Snaprud established that the reaction is strongly acid-catalysed, but did not propose a clear model explaining the activation of the substrate by the acid.[5] Investigation of the metal ion[6] and metal chelate complexes[7] catalysis led to the conclusion that the catalytic activity requires the presence of two oxo groups on the metal (delivery of the nucleophile and promotion of the departure of the F^- ion). For the fluoride-catalysed transesterification of phosphate triesters the initial attack on phosphorus, followed by the rapid reaction of the phosphorofluoridate with an alcohol was postulated (Scheme 1); the intermediate fluoridate was observed for some



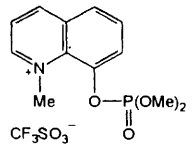
Scheme 1

nucleotide triesters.[2] For the reactions in alcoholic media, however, the same authors considered a mechanism according to which the fluoride ion simply increases the nucleophilicity of the alcohol *via* hydrogen bonding to a degree that a displacement at phosphorus occurs directly.[2]

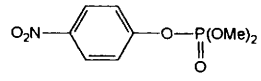
We have recently shown that the hydrolysis of the P–OAr bond in dialkyl aryl phosphates is catalysed by fluoride ion, but the effectiveness of the catalysis can depend on the nature of the fluoride counterion.[8] In this paper we report the results of a more detailed study of the effect of fluoride salts on the hydrolysis of three dialkyl aryl phosphates (**1a**, **1b** and **1c**), and of the dimethyl phosphorofluoridate (**2**), the expected intermediate of the F^--catalysed hydrolysis of **1a** and **1b**.

Results and discussion

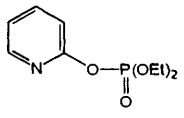
According to our earlier observation,[9] in phosphates **1a** and **1b** the electrophilic reactivity of phosphorus and of the methyl ester carbon are comparable, so in the hydrolysis, the cleavage of both the P–OAr and the Me–O bond was observed. The effect of the fluoride ion on the chemoselectivity of the hydrolysis of **1a** and **1b** could be therefore directly determined.



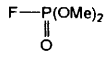
1a



1b



1c



2

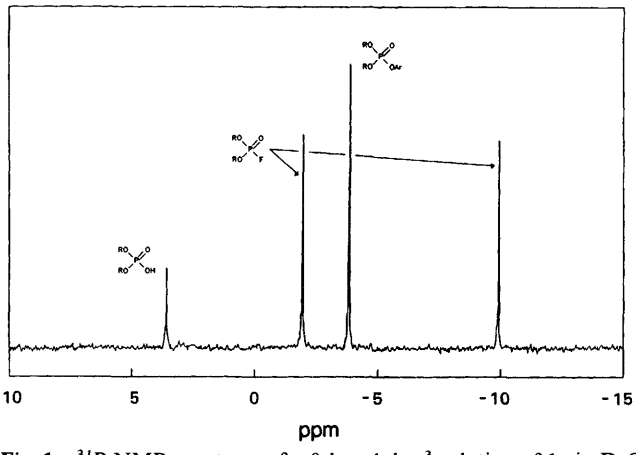


Fig. 1 ^{31}P NMR spectrum of a 0.1 mol dm^{-3} solution of **1a** in D_2O containing one mole equivalent of Me_4NF, recorded after 9 min (30 °C)

Since hydrolysis of **1c** results in the exclusive P–OAr bond cleavage (the dimethyl analogue of **1c** was prepared, but proved too unstable as a substrate for kinetic studies and the ethyl phosphate esters are much less susceptible to nucleophilic dealkylation than methyl esters),[10] in this case the effect of F^- on the reaction rate could only be investigated. When the fluoride salt was added to aqueous (or aqueous acetone) solutions of **1a**–**1c**, the first reaction that occurred was the displacement of the aryloxy group by F^- yielding a common product **2** (or its diethyl analogue for **1c**). Formation of that product was always faster than its subsequent decay, so the course of that two-step reaction could be easily followed by ^1H, ^{31}P or ^{19}F NMR spectroscopy (Fig. 1).

For **1a** and **1b** F^- had a dramatic effect on the chemoselectivity of the hydrolysis. In D_2O the statistically

Table 1 Kinetic data on the hydrolysis of the P–OAr bond in **1a** and **1b**

Substrate	Salt added[a]	$k_F/10^{-2}$ dm^3 mol^{-1} s^{-1}	$k_{hydr}/10^{-6}$ s^{-1}
1a[b]	none		0.047
	LiF	0.040	*c*
	LiF/12C4[d]	0.040	
	NaF	2.4	14.7
	KF	2.6	18.8
	CsF	2.6	12.0
	NMe_4F	2.4	16.8
1a[e]	none		0.028
	LiF	0.001 3	*c*
	LiF/12C4[d]	0.001 4	
1b[f]	none		0.049
	LiF	0.000 29	*c*
	NaF	0.94	26.0
	KF	0.84	27.9
	CsF	0.84	34.5
	NMe_4F	0.80	34.3

[a] One mole equivalent. [b] In D_2O, 30 °C. [c] Not determined as the first step was not completed within the kinetic run. [d] Two mole equivalents of crown ether 12C-4 added. [e] In D_2O–[$^2H_6$]acetone (1 : 1, v/v), 30 °C. [f] In D_2O–[$^2H_6$]acetone (1 : 1, v/v), 60 °C.

corrected ratio of the rates of the reaction at the methyl carbon and at the phosphorus atom, k_c/k_p, is for **1a** (30 °C) and **1b** (60 °C), 4.7 and 2.2, respectively. Addition of one mole equivalent of an MF salt (M = Na, K, Cs, Me_4N) resulted in a complete elimination of the demethylation reaction, with the formation of **2** and its subsequent hydrolysis to dimethyl phosphate (DMP) as the only reaction observed. The behaviour of lithium fluoride was different in a sense that upon the addition of LiF the P-selectivity was still not complete: for **1a** the value of k_c/k_p of 4.7 in D_2O and 3.9 in D_2O–[$^2H_6$]acetone (1 : 1, v/v) was reduced to 0.037 and 0.16, respectively. For **1b** in aqueous acetone the corresponding change of the k_c/k_p ratio was from 2.2 to 0.59. Since we determined independently that the addition of fluoride salts to the aqueous solution of trimethyl phosphate (where only the attack at carbon takes place) has no effect on the rate of hydrolysis, any changes in reactivity observed for **1a** and **1b** reflect solely the effect of F^- on the reaction at phosphorus. Table 1 lists the effect of the fluoride salts, expressed in terms of the rates of the formation of **2** (second-order rate constant, k_{F^-}) and the rates of hydrolysis of **2** (pseudo-first-order rate constant, k_{hydr}), on the hydrolysis of **1a** and **1b**.

The rates of the hydrolytic decay of **2** (last column of Table 1) depend to a certain degree on the nature of the species present in the solution (aryloxide ion, fluoride counterion) and will be discussed separately. The rate of the formation of the phosphorofluoridate **2**, on the other hand, is for each substrate approximately constant for the fluoride counterions, M^+ = Na^+, K^+, Cs^+, Me_4N^+, but not for $M^+ = Li^+$. Although all fluoride salts behave as catalysts, in the case of LiF the catalytic effect is much weaker, both in terms of chemoselectivity and of the rate of formation of **2** from the ester substrate. Since the k_{F^-} values obtained for four other counterions, including the non-complexing Me_4N^+ ion, are for each substrate approximately constant, the first step of the reaction shown in Scheme 1 is not enhanced by the complexation of a cationic part of the nucleophile by the phosphoryl substrate, as was shown to be the case for the delivery of ethoxide to the phosphoryl centre[11] or iodide to the methyl carbon of methyl phosphates.[12] It must be therefore concluded that the 'inhibition' of the F^- ion catalysis by the lithium counterion results from the lower nucleophilicity of LiF in D_2O relative to other fluoride salts and not from any difference in the interactions of the phosphate substrate with the cation. If the delivery of F^- to the phosphorus were assisted by the counterion, a different order of reactivity would be

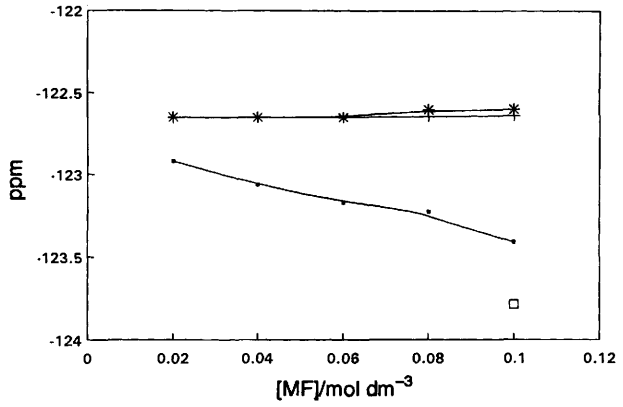
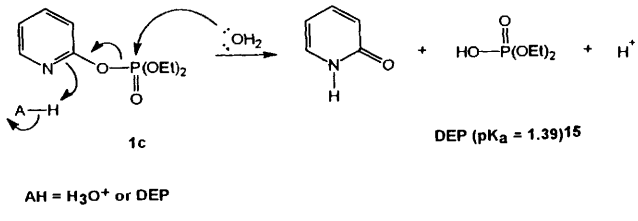


Fig. 2 Effect of concentration on the ^{19}F NMR chemical shift (relative to external CCl_3F) of fluoride ion in D_2O: (+) KF; (*) NMe_4 F; (■) LiF; (□) LiF in the presence of 12C-4

expected, as the complexation ability of alkali metal ions toward phosphate donors decreases in the order: $Li^+ \gg Na^+ > K^+ \approx Cs$.[13] Because of the smallest mismatch in size between the ions in LiF relative to other salts, the former should show higher propensity to aggregate,[14] hence the effective nucleophilicity of the fluoride should be diminished. We have tested the behaviour of three fluoride salts in D_2O by monitoring the values of the ^{19}F NMR chemical shift as a function of concentration (Fig. 2). While for potassium and tetramethylammonium fluorides the δ_F values were identical and concentration independent, for the lithium salt an upfield shift was observed with an increase in concentration. The behaviour of LiF indicates that the detailed form of the salt in solution is different from that of other fluorides, hence the difference in the nucleophilic reactivity of the F^- ion. The addition of crown ether to the concentrated solution of LiF did not result in the reversal of δ_F to a 'normal' value; the opposite (more shielding) effect was observed. The additional shielding results probably from the change in the direct environment of the fluoride ion which, together with the Li^+ counterion, is transferred to the cavity of the ether. The effect is in full agreement with the rate studies (Table 1), where the addition of crown ether had negligible effect on the rate of the reaction of **1a** with LiF. In conclusion, in the hydrolysis of the phosphate esters of the type **1a** and **1b**, fluoride ion behaves as a powerful nucleophilic catalyst, but its activity is seriously diminished when Li^+ is used as a counterion.

Hydrolysis of diethyl 2-pyridylphosphate, **1c**, and the effect of the fluoride salts on that reaction followed an essentially different pattern. For a 0.1 mol dm^{-3} solution of **1c** in D_2O at 30 °C, after a 40 min induction period, the reaction was very fast (total conversion after *ca.* 90 min) and the decay of **1c** did not follow first-order kinetics, but showed a distinct upward curvature, typical for a product-catalysed process. Since one of the reaction products (DEP) is a strong acid (pK_a[15] = 1.39) and since the leaving group contains (as opposed to **1a** and **1b**) a basic centre, the mechanism of the autocatalysis can be easily explained (Scheme 2). In this respect, hydrolysis of **1c** resembles that of dimethyl phosphorofluoridate, **2**, for which the same



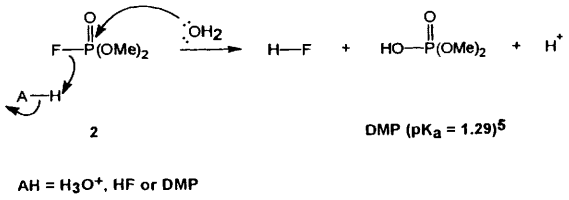
Scheme 2

Table 2 Effect of fluoride salts on the hydrolysis of the P–OAr bond of **1c** in D_2O at 30 °C

Salt added[a]	$k_F/10^{-4}$ dm^3 mol^{-1} s^{-1}	$k_{hydr}/10^{-6}$ s^{-1}
LiF	0.37	*b*
NaF	2.3	2.5
NaF (2 mole equiv.)	2.6	4.4
KF	2.4	2.4
CsF	2.9	2.5
NMe_4F	2.3	2.2

[a] Unless otherwise stated, one mole equivalent. [b] Not determined as the first step was not completed within the kinetic run.

kinetic behaviour was reported.[5] We have repeated the hydrolysis of **2** and obtained a plot analogous to that obtained for **1c**, indicating the same type of the autocatalytic mechanism (Scheme 3). Since in purely aqueous solutions HF is a weak



Scheme 3

acid,[16] the departure of its conjugate base as a leaving group is subject to acidic (general or specific) catalysis.

The effect of fluoride salts on the hydrolysis of **1c** was very specific: as for **1a** and **1b**, the only reaction observed was the formation of the corresponding phosphorofluoridate as the intermediate product, followed by its hydrolysis to DEP, but the autocatalytic effect of DEP was completely eliminated and the total rate of the hydrolysis of **1c** to DEP and 2-hydroxypyridine was *much slower* than in the absence of the fluoride salt. In other words, fluoride ion, although reactive toward the substrate, behaved as a net inhibitor, not a catalyst of the hydrolysis. The rates of the two-step hydrolysis of **1c** in the presence of fluorides are shown in Table 2; the substrate was found to be about 100 times less reactive toward F^- than **1a**, and, as before, LiF was found to be a much less effective nucleophile than other fluoride salts. With respect to **1c**, fluoride ion therefore plays a dual role: as a good nucleophile toward the phosphoryl centre, it still effectively substitutes the leaving group in the first step of the reaction. On the other hand, by modifying the acidity of the medium, the same ion limits the protonation of the leaving group (pyridyl nitrogen), thus removing to a large extent the autocatalytic effect of DEP responsible for the fast (and non-linear) hydrolysis of **1c** in pure water. When a 0.1 mol dm^{-3} solution of **1c** in water was incubated at 30 °C, the pH of the solution dropped within 90 min from the initial value of *ca.* 9.0 (expected for a solution of a substrate with the pK_a of *ca.* 5) to the final value of pH = 1.4, corresponding to the complete conversion to DEP. In the presence of one mole equivalent of KF, the increase in the acidity of the medium was much slower, reaching the value of pH = 5.4 after 20 h, 3.6 after 45 h, 2.4 after 72 h and finally stabilizing at pH = 2.0 after 190 h of incubation. The observed dual effect (nucleophilic catalysis and the retarding 'buffering' effect) of F^- on the hydrolysis of **1c** prompted us to investigate the effect of that ion on the hydrolysis of **2**, a substrate also subject to the autocatalytic effect of the dialkyl phosphate formed. The results of that study were most revealing and are summarized in Fig. 3. Addition of 0.25 mole equivalent of NaF slows down significantly the rate of the hydrolysis, but

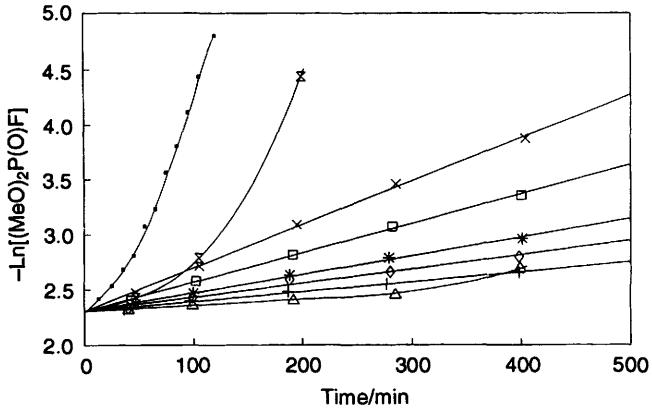


Fig. 3 Hydrolysis of a 0.1 mol dm^{-3} solution of **2** in D_2O (30 °C): (■) pure D_2O; (⧖) 0.25 mole equiv. NaF; (△) 0.5 mole equiv. NaF; (+) 1.0 mole equiv. NaF; (◇) 1.0 mole equiv. 2,6-dimethylpyridine, (*) 2.0 mole equiv. NaF; (□) 3.0 mole equiv. NaF; (×) 4.0 mole equiv. NaF

the disappearance of **2** still follows a curve typical for an autocatalytic reaction. With 0.5 mole equivalent of NaF, the autocatalytic effect is almost absent and a slow, almost linear decay of **2** is observed. For the equimolar ratio of the substrate and NaF, an excellent first-order plot is obtained, but the hydrolysis of **2** is rather slow (k_{hydr} = 1.48 × 10^{-5} s^{-1}). It has to be concluded that under those conditions the fluoride ions present have a full 'buffering' effect on the acidic products of the reaction and eliminate the acidic catalysis in the hydrolysis of the substrate. The same effect was achieved when one mole equivalent of 2,6-dimethylpyridine was added instead of NaF; the autocatalytic effect has been removed and the hydrolysis followed 'slow', first-order kinetics. Under those conditions the observed rate constant is k_{hydr} = 2.14 × 10^{-5} s^{-1} and we believe that this value represents the reactivity of **2** towards water, with no acidic catalysis or other effects taking place. Perhaps the most surprising results were obtained upon further addition of the fluoride salt to the reaction solutions. In the presence of two, three and four mole equivalents of NaF, hydrolysis of **2** followed first-order kinetics (as expected for an excess of a 'buffer'), but the reaction was increasingly *faster*, giving evidence for yet additional, this time accelerating effect of the fluoride salt. It can only be concluded that the NaF salt affects the reaction through *both* ions: the F^- ion by 'mopping up' the acidic species produced in the course of the reaction and the Na^+ ion by complexing to the phosphoryl group, thus increasing the electrophilic reactivity of the phosphoryl centre.[11,12] From a kinetic point of view, the reaction can therefore be divided into two distinct sections. For the molar ratio [**2**]/[NaF] > 1, the rate of hydrolysis can be described by eqn. (1)[5] and a positive deviation from linearity is observed.

$$\text{Rate} = k_{AH}[AH][\mathbf{2}] \quad (1)$$

Under the conditions when [**2**]/[NaF] ⩽ 1, the acidic catalysis is absent and the rate can be expressed by eqn. (2), where k_{hydr}

$$\text{Rate} = k_{hydr}[\mathbf{2}\cdot Na^+] \quad (2)$$

represents the specific rate constant for the reaction of water with the phosphorofluoridate complexed to the Na^+ ion. The value of the k_{hydr} could be determined from the first-order plots obtained under the conditions of [**2**]/[NaF] = 1, 0.5, 0.33 and 0.25 (Fig. 3); k_{hydr} = (1.50 ± 0.10) × 10^{-4} s^{-1}. When compared with the k_{hydr} value obtained in the presence of 2,6-dimethylpyridine (*vide supra*), the difference reflects the effect of the Na^+ ion on the hydrolytic reactivity of substrate **2**.

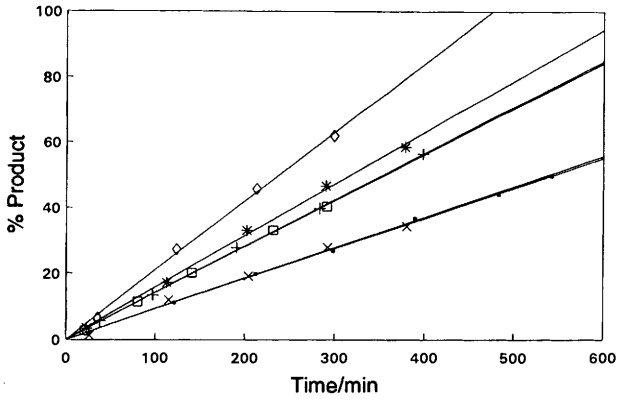


Fig. 4 Hydrolysis of 2-pyridyl acetate (0.1 mol dm^{-3}, 30 °C) in D_2O and in the presence of one mole equivalent of a salt: (■) pure D_2O; (×) KF; (□) NaF; (+) NaCl; (*) LiF; (◇) Me_4NF

In summary, we believe that the fluoride salts can affect hydrolysis (or other phosphoryl transfer reactions) of phosphate esters according to three mechanisms. First, as a powerful nucleophile, F^- can catalyse the reaction by reacting quickly with the substrate yielding the reactive phosphorofluoridate intermediate. Secondly, for substrates in which the departure of the leaving group can be acid-catalysed, fluoride ion acts as an inhibitor by diminishing the acidity of the medium resulting from the acidic products. Finally, the metallic ion introduced as a fluoride salt can enhance the electrophilicity of the phosphorus atom *via* complexation to the phosphoryl group. The behaviour of phosphate esters contrasts sharply with that of the carboxylic analogues, as illustrated by the hydrolysis of 2-pyridyl acetate (Fig. 4). No nucleophilic catalysis by F^- would be expected for that substrate and since a much weaker acid (acetic) is produced in the reaction, no significant product catalysis effect should be observed. The results shown in Fig. 4 indicate, however, some accelerating effect of the added alkali metal salts. The identical effect observed for NaF and NaCl gives evidence for the irrelevance of the nature of the anion and the effect increases in the order K^+ (no effect) < Na^+ < Li^+, in agreement with the usual order of the complexing ability of alkali metal ions toward oxygen centres. The only unexpected result was perhaps an unusually strong effect of tetramethylammonium fluoride, indicating some specific interactions between this salt and the carboxylate substrate.

Experimental

Compounds **1a** and **1b** were prepared as described before.[9] Compound **1c** was prepared from 2-hydroxypyridine and diethyl phosphite in CCl_4 according to a literature procedure.[17] Oil (96%), purified by column chromatography [silica gel 60, Merck, chloroform–ethanol, 7:3 (v/v)]. δ_H(300 MHz, $CDCl_3$, Me_4Si) 1.34 (6 H, dt, J_{HH} 7.2, J_{HP} 0.9, 2 Me), 4.28 (4 H, quint, $J_{HH} = J_{HP}$ 7.2, 2 OCH_2), 6.99 (1 H, d, J_{HH} 8.2, 3-H), 7.09 (1 H, dd, J_{HH} 7.0, 4.8, 5-H), 7.68 (1 H, dd, J_{HH} 8.2, 7.0, 4-H) and 8.25 (1 H, dd, J_{HH} 4.8, 1.8, 6-H); δ_P(85% H_3PO_4) −6.72.

Dimethyl phosphorofluoridate **2** was prepared from dimethyl phosphorochloridate and NaF in benzene.[18] Oil (18%), bp 38–40 °C/180–200 mbar (lit.,[18] 149 °C). δ_H(300 MHz, $CDCl_3$, Me_4Si) 3.88 (d, J_{HP} 11.6, 2 OMe); δ_P(85% H_3PO_4) −6.33 (d, J_{PF} 980.0).

2-Pyridyl acetate was prepared from 2-hydroxypyridine and acetyl chloride in ether in the presence of triethylamine and purified by column chromatography (as for **1c**). Oil (40%); δ_H(300 MHz, $CDCl_3$, Me_4Si) 2.32 (3 H, s, COMe), 7.06 (1 H, d, J_{HH} 7.9, 3-H), 7.20 (1 H, dd, J_{HH} 7.4, 4.9, 5-H), 7.77 (1 H, dt, J_{HH} 7.5, 2.0, 4-H) and 8.39 (1 H, dd, J_{HH} 4.9, 2.0, 6-H), which is identical to the spectrum reported in the literature.[19] *m/z* 137 (M^+, 0.3%), 95 (100, M − CH_2CO).

NMR spectra were recorded on a Bruker AC300 spectrometer. Merck Uvasol deuterium oxide, min 99.75% D and Aldrich [$^2H_6$]acetone, min 99.5% D were used as solvents for kinetic measurements. Salts were dried at 150 °C in an oven and stored over P_4O_{10}.

Kinetic experiments were performed by preparing solutions of substrates in the required deuteriated media, transferring to an NMR tube and incubating the tube in a thermostatted water bath capable of maintaining a constant temperature within ±0.2 °C. Tubes were withdrawn at selected time intervals and the NMR spectra of the reaction mixtures were recorded immediately. For faster runs, the tube was placed in the spectrometer's probe operating at 30 °C. Kinetic runs were carried out for at least three half-lives and the conversion was determined directly from the integrated areas of selected NMR signals. The following signals were used. **1a**, 1st step: OMe of **1a**; 2nd step: OMe of **2**. **1b**, 1st step: aromatic Hs of **1b**; 2nd step: ^{31}P NMR signal of **2**. **1c**, 1st step: pyridyl Hs of **1c**; 2nd step: OCH_2 of **2**. **2**, ^{31}P signal of **2**. 2-Pyridyl acetate, Me of COMe of the substrate. The observed pseudo-first-order or second-order rate constants were derived in the usual way by plotting the corresponding functions of the conversion *vs.* time. Good linear plots were obtained with values of r^2 = 0.9945–0.9999.

Acknowledgements

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