Fluoride Ion Catalysis in the Hydrolysis of Aryl Phosphates. Deactivating Effect of Lithium Counter Ion

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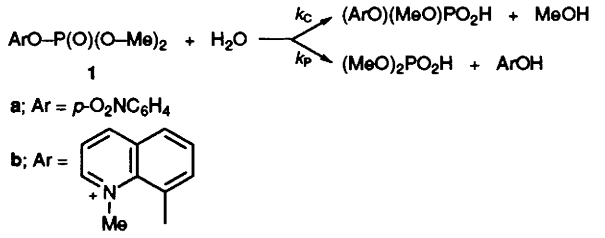
Hydrolysis of the P–OAr bond in dimethyl aryl phosphates is catalysed by fluoride ion due to the fast formation of intermediate phosphorofluoridate; LiF shows a much weaker catalytic effect than other alkali metal and tetramethylammonium fluoride salts.

Fluoride ion has been employed as a nucleophilic catalyst in a transesterification method for the synthesis of mixed trialkyl phosphates.[1] Although phosphorofluoridates were postulated as intermediates, only in a single case of the transesterification of nucleotide phosphotriesters was a corresponding fluoridate observed and characterized chromatographically.[2] Stereochemical studies have indicated the participation of pentacoordinated difluorophosphoranes as a transient species.[3]

We have recently shown that neutral hydrolysis of some dimethyl aryl phosphates can involve the cleavage of both, the P–OAr, and the O–Me bonds proceeding with comparable rates (Scheme 1).[4] We have now discovered that the rate and selectivity of the hydrolysis of esters **1** are dramatically increased when the reaction is carried out in the presence of a fluoride salt. Reaction products and the rates of their formation were easily determined by NMR spectroscopy, since all species down in Scheme 1 can be identified by the characteristic ^{31}P NMR signals, and/or the signals of methyl groups and aromatic hydrogens in the ^{1}H NMR spectra. The effect of the fluoride salts on the hydrolysis is given in Table 1; the results obtained for the hydrolysis of trimethyl phosphate (TMP) (a substrate for which only the attack at methyl carbon takes place) are included for comparison. As expected, the F^- ion has no effect on the rate of demethylation of TMP, but it has a profound effect on the hydrolysis of mixed esters **1**. With one exception (the effect of LiF on the hydrolysis of **1a**), the reaction in the presence of F^- is fully regiospecific and involves exclusively the P–OAr bond fission. The rate increase is very large: hydrolysis of **1a** is accelerated by M^+F^- ($M^+ = K^+, Cs^+, Me_4N^+$) by a factor of *ca.* 8 × 10^3; for **1b** the effect of M^+F^- ($M^+ = Na^+, K^+, Cs^+, Me_4N^+$) is even greater (2.2 × 10^4). The rate increase results from the fast displacement of the leaving group by F^- ion yielding dimethyl phosphorofluoridate (DPF), which then undergoes further hydrolysis (Scheme 2). In all cases the first step of the nucleophilic catalysis is faster than the second, and the formation and decay of DPF could be easily observed (^{31}P NMR spectra: **1a**, δ_P −3.2; **1b**, δ_P −3.8; DFP, δ_P −5.3, J_{PF} 970 Hz; lit.[5]: δ_P −5.2, J_{PF} 943 Hz; dimethyl phosphate, δ_P 3.6). *E.g.*, ^{31}P NMR spectrum of the reaction mixture of **1a** in the presence of KF reveals after 10 min 70% of the unchanged substrate, 30% of DPF, and still negligible amounts of dimethyl phosphate. Similarly, hydrolysis of **1b** in the presence of NaF yields after 10 min 41% of **1b**, 46% of DPF and only 13% of dimethyl phosphate.



Scheme 1

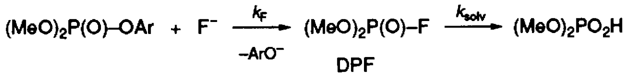
The most remarkable result is the poor catalytic effect demonstrated by lithium fluoride. For **1a**, that salt affects the selectivity and the rate only to a very modest degree, and for **1b**, although the selectivity is shifted completely towards the reaction at phosphorus, the rate acceleration is still *ca.* forty times lower than that observed for other fluoride salts. The inhibition of F^- catalysis is also observed, albeit to a much lower degree, for the sodium counter ion in the hydrolysis of **1a**, where the rate acceleration is about 40% of that observed for other salts. The effect of the counter ion on the

Table 1 Hydrolysis of trimethyl phosphate (TMP), dimethyl(4-nitrophenyl) phosphate **1a** and *N*-methyl-8-(dimethylphosphoryloxy)quinolinium trifluoromethylsulfonate **1b** at 60 °C

Ester	Fluoride salt[a]	*t*/min	Conversion (%)[b]	Reaction at P (%)	Reaction at C (%)	k_P (rel)[c]
TMP[d]	None	44640	24		24	
	LiF	44640	21		21	
	CsF	44640	22		22	
1a[d]	None	44640	91	17	74	1.0
	LiF	44640	94	43	51	2.5
	NaF	67	79	79		3100
	KF	10	30	30		7900
	CsF	9	30	30		8700
	NMe_4F	11	34	34		8100
1b[e]	None	21677	62	6	56	1.0
	LiF	270	40	40		530
	LiF–CE[f]	168	38	38		820
	NaF	10	59	59		21300
	KF	9	57	57		22900
	CsF	10	60	60		21700
	NMe_4F	9	56	56		22500

[a] 1 mol equiv. [b] Kinetics of the reaction was measured and the results will be discussed in a full paper. For the purpose of this communication, selected times, required for a similar degree of conversion, are given. [c] Effect of the M^+F^-, relative to the hydrolysis of the P–OAr bond with no salt added. [d] In D_2O–[$^2H_6$]acetone, 1 : 1 (v/v). [e] In D_2O. [f] 1 mol equiv. of crown ether 12-C-4.

effectiveness of the fluoride ion catalysis suggests that the catalytic effect depends on the exact state of the fluoride salt in solution. The solubility of LiF in water is only *ca.* 0.25 and 0.13% of that for KF and CsF, respectively, indicating strong aggregation tendency of the former salt. In order to find experimental evidence for the difference in the behaviour of various fluoride salts in the reaction medium, we measured the ^{19}F NMR chemical shift of some M^+F^- salts in D_2O as a function of the concentraton. Over the $[M^+F^-]$ range of 0.02 -0.1 mol dm^{-3} the δ_F value for $M^+ = K^+$ and Me_4N^+ remains absolutely constant (-122.65), while for $M^+ = Li^+$ the upfield shift from δ_F -122.90 to δ_F -123.40 is observed. The addition of crown ether to the reaction mixture had only weak activating effect, suggesting similar reactivity of the LiF and LiF·CE species. The deactivating effect of the fluoride counter ions should be more pronounced in aqueous acetone (hydrolysis of **1a**) than in pure water (hydrolysis of **1b**); this is exactly what we observe for the hydrolysis of two phosphate esters, where in the formed medium even NaF shows some 'deactivation' relative to the fluoride salts containing larger cations. We believe therefore, that in the fluoride ion catalysis of phosphoryl transfer reactions, the effect of the counter ion cannot be ignored.



$$(MeO)_2P(O){-}OAr + F^- \xrightarrow[-ArO^-]{k_F} \underset{\text{DPF}}{(MeO)_2P(O){-}F} \xrightarrow{k_{solv}} (MeO)_2PO_2H$$

Scheme 2

Financial support from the University of Pretoria and the Foundation for Research Development is gratefully acknowledged.

Received, 18th April 1994; Com. 4/02284J

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