Hydrolysis of Phosphonoformate Esters: Product Distribution and Reactivity Patterns

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Phosphonoformate triesters are hydrolysed to mixtures of hydrogen phosphonate and phosphonoformate esters and free acids; the rates and product distribution are dependent on pH and ester leaving group abilities.

The trisodium salt of phosphonoformate (PFA) **1** is an effective anti-viral agent with potential application in AIDS therapy.[1] The utility of PFA is hampered by the poor membrane permeability of polyanionic phosphates,[2] resulting in attempts to increase permeability by the use of PFA esters as pro-drugs intended to undergo intracellular hydrolysis to PFA itself.[3] Since α-carbonylphosphonates, such as PFA, possess a labile P–C bond, the success of this approach is dependent on knowledge of the lability and reactivity patterns of PFA esters. Hithertofore no study of solvolysis of PFA esters has been made. We have studied the kinetics and products of hydrolysis of various triesters of PFA in acetonitrile–water mixtures at $-1 < pH < 14$.†

In the low pH region the pH–rate profile for hydrolysis of the triesters **2d–i** is characterized by a pH-independent mechanism for $0 < pH < 5$ and an acid-catalysed mechanism for $pH < 0$ (Table 1). Both reactions are accelerated by electron-withdrawing carboxy ester substituents: the acid-catalysed pathway to a lesser degree.‡ Hydrolysis occurs *via* P–C and C–O bond cleavage to give diethyl hydrogenphosphonate as an initial product which undergoes subsequent hydrolysis.

Comparison of the rate data with that for hydrolysis of methyl carbonate,[6] PFA[7] and *p*-methoxybenzoyl dimethyl phosphonate[8] suggests that under our reaction conditions the initial carbonate products of P–C bond cleavage break down too rapidly to be observed and also that the initial C–O cleavage product would be observable only for the *p*-nitrophenyl esters. A reactive intermediate is observed, in hydrolysis of the *p*-nitrophenyl ester, with a ^{1}H NMR spectrum and rate of decomposition compatible with its identification as the diethyl ester **3x**. Our observations therefore confirm hydrolysis of **2i** by initial carbonyl C–O bond cleavage, but the mechanism of hydrolysis of the less reactive triesters **2d–h**,

Table 1 Acid-catalysed and pH-independent rate constants for hydrolysis of PFA triesters $-1 < pH < 5$[a]

Substrate ester	$10^5 k_{H+}$/ dm^3 mol^{-1} s^{-1}	$10^5 k_w$/s^{-1}
2d	1.8	2.3
2e	1.3	1.5
2f	2.7	6.2
2g	1.0	1.0
2h	0.7[b]	0.4[b]
2i	4.5	140

[a] Second-order (k_{H+}) and first-order (k_W) rate constants from fitting of pseudo-first order rate data; esters (0.1 mmol dm^{-3}) in 40% MeCN–H_2O; monitoring of phenol generation by UV analysis (except **2h**, in deuteriated solvents by NMR analysis), at 36 °C. Buffers employed at $pH > 1.5$. Ionic strength was varied, demonstrating the absence of any significant salt effects. [b] Based on small data set.

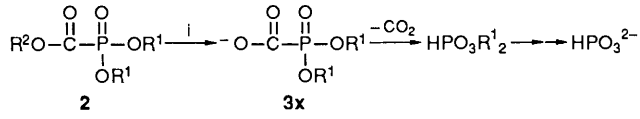
† Alkyl, aryl and mixed triesters of PFA were synthesized by the Arbuzov reaction of phosphite [ROP(OR′)$_2$ R = alkyl] with alkyl and aryl chloroformates. Starting materials not commercially available were synthesized by adaptation of literature procedures from phosphorus trichloride (phosphites)[4] and phosgene (chloroformates).[5] Purity of triesters was assayed by ^{31}P, ^{1}H and ^{13}C NMR prior to kinetic analysis. Kinetics were monitored by UV–VIS or NMR (^{31}P, ^{1}H) spectroscopy. Reaction intermediates and product distribution were observed by NMR spectroscopy and comparison with authentic samples of PFA, hydrogenphosphonates and the PFA mono- and di-esters **3y, z**, synthesized by selective deesterification.

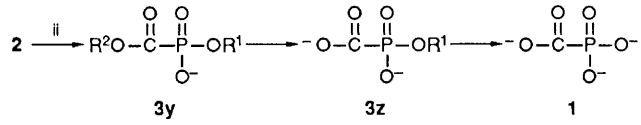
‡ Plots of log k_W and log k_{H+} *vs.* σ give $\rho = 1.8$ and 0.6 for the pH-independent and acid-catalysed pathways, respectively.

Table 2 Product distribution for triester hydrolysis in dilute and concentrated base solution by NMR analysis[a]

Substrate		Conditions[c]	Pathway ii		
ester	δ (^{31}P)[b]		product	δ (^{31}P)[d]	yield (%)[e]
2a	−11.6	0.45 mol dm^{-3} NaOH	**3z**, **1**	−1.2, 1.78	>95
		pH 9.5	**3y**	−8.1	95
2b	−3.6	0.45 mol dm^{-3} NaOH	**3z**	2.08	>95
		pH 9.5	**3y**	−4.4	50
2d	−4.6	0.45 mol dm^{-3} NaOH	**3z**	2.15	>95
		pH 9.5	**3y**	1.3	<10

[a] Reactions were carried out at 25 °C in 40% MeCN–H_2O; [ester] <0.04 mol dm^{-3}. [b] In MeCN. [c] pH 9.5 solution is 0.1 mol dm^{-3} carbonate buffer; [ester] <0.01 mol dm^{-3}. [d] At 162 MHz; assignments confirmed by ^{1}H NMR (400 MHz) in deuteriated carbonate buffer and in NaOD solution. [e] Pathway ii products as percentage of whole.





a, R^2 = Et, R^1 = Ph; **b**, R^2 = R^1 = Et; **c**, R^2 = Bn, R^1 = Et; **d**, R^2 = Ph, R^1 = Et; **e**, R^2 = *p*-MeOPh, R^1 = Et; **f**, R^2 = *p*-ClPh, R^1 = Et; **g**, R^2 = *p*-BnOPh, R^1 = Et; **h**, R^2 = Cl_3CCH_2, R^1 = Et; **i**, R^2 = *p*-NO_2Ph, R^1 = Et

Scheme 1

initial P–C *versus* initial C–O bond cleavage, cannot be unambiguously assigned.

In the high pH region two hydrolysis pathways are observed (Scheme 1), such that initial nucleophilic attack at carbon yields hydrogenphosphonate products (pathway i), whereas initial attack at phosphorus generates PFA and its anionic esters (pathway ii). P–C bond cleavage in pathway ii can be ruled out, since the ionized phosphite leaving group has a pK_a of *ca.* 30 (as compared to 13 for diethyl phosphite).[9]

Hydrolysis in dilute base is rapid and in 0.45 mol dm^{-3} OH^- is complete on admixing of base and substrate. In concentrated alkali (0.45 mol dm^{-3}), hydrolysis yields little (<5%) of pathway i products (Table 2). However, PFA itself is generated at an observable rate only for the *P*-phenyl ester **2a**.

Use of dilute alkali solution [0.1 mol dm^{-3} NaOH(D)] leads to self-quenching of the reaction by the products when substrate and hydroxide concentrations are equivalent. Under these conditions it is clear that the increasing electron-withdrawing nature of the *C*-ester group increases the flux of pathway i. The proportion of pathway i products for the esters **2b**, **c**, **e**, **d**, **f**, **i** is 50–60, 70, 75, 90, 95, >95%, respectively.

In carbonate buffer at pH 9.5 the observed products are PFA diesters **3y** and hydrogenphosphonates. The presence of a good leaving group on phosphorus gives almost exclusive hydrolysis by pathway ii (Table 2).

The complex reaction pathways for hydrolysis of PFA esters result from competititon between initial nucleophilic substitution at phosphorus and at carbonyl carbon. Hydrolysis *via* P–C bond cleavage accounts for a significant fraction of products. In the design of PFA pro-drugs, abortive hydrogenphosphonate generation may be avoided only if the leaving group on phosphorus is better than that on carbon. However a good leaving group on carbon is required for PFA generation and anti-viral activity.[3a]

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