198. *A Kinetic Study of the Hydrolysis of Di*iso*propyl Fluorophosphonate.*

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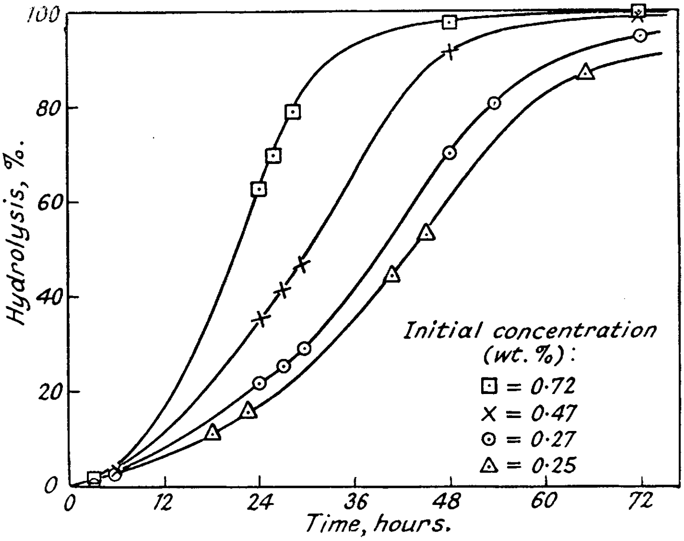
The hydrolysis of di*iso*propyl fluorophosphonate in neutral or acid solution yields hydrogen fluoride and di*iso*propyl phosphate. The reaction is catalysed by hydrogen ions, and therefore differs in mechanism from the hydrolysis of acyl chlorides, R·COCl.

The physiologically active liquid di*iso*propyl fluorophosphonate (McCombie and Saunders, *Nature*, 1946, **157**, 287, 776; Saunders and Stacey, *J.*, 1948, 695) is hydrolysed slowly in water, and rapidly in dilute alkali, to innocuous products. Information concerning these reactions is therefore of some pharmacological interest and the studies which are described below were originally carried out for this reason, though they have a theoretical value which deserves comment. Preliminary investigations showed that the rate-determining process is the separation of fluoride anions (1), though subsequently reaction (2) may occur at a rate which, however, is never more than 5% of (1).

$$(1)\ (C_3H_7{\cdot}O)_2POF + H_2O \longrightarrow (C_3H_7O)_2PO{\cdot}OH + HF$$

$$(2)\ (C_3H_7{\cdot}O)_2PO{\cdot}OH + H_2O \longrightarrow (C_3H_7O)PO(OH)_2 + C_3H_7{\cdot}OH$$

The course of the reaction can be followed quite easily at 25° by withdrawing at intervals aliquot parts of solutions of the fluorophosphonate and titrating each sample (*a*) for free acid, using sodium hydroxide and phenolphthalein, and then (*b*) for fluoride ion, using thorium nitrate (Milton, Liddell, and Chivers, *Analyst*, 1947, **72**, 43; compare *ibid.*, 1944, **69**, 243). Since titration (*b*) is carried out in acid solution the presence of phenolphthalein causes no interference. At first, difficulties due to the reaction of hydrogen fluoride with glass containing vessels were encountered, but they were overcome by the use of copper vessels which had been coated with water-resistant bakelite enamel (Ministry of Supply Specification CD 3). The dissolution of the di*iso*propyl fluorophosphonate could be assisted by the addition of up to 5% of ethyl alcohol without there being any detectable change in the hydrolysis rate. Since the buffering actions of phosphoric acid, and its acid esters, reduce the accuracy of the sodium hydroxide titrations in the later stages of the hydrolysis, the reaction-velocity constants were always computed from the fluoride titres, which were always highly sensitive and reproducible.



*Rate of hydrolysis of di*iso*propyl fluorophosphonate in water at* 25°.

The figure shows that the hydrolysis of di*iso*propyl fluorophosphonate in water at 25° is an autocatalytic process, and that decomposition is substantially complete in 3 days.

The hydrolysis is evidently a process which is catalysed by hydrogen ions, for the initial rate of hydrolysis, *i.e.*, 0·6% per hour, is independent of the initial concentration of the fluorophosphonate. To confirm this, measurements were carried out in the presence of a sufficient concentration of hydrochloric acid to keep the pH of the solution reasonably constant, and also in a solution buffered to pH 3·0 by a chloroacetic acid–sodium chloroacetate mixture. Under these conditions, too, the rate of liberation of fluoride anions was of first order (see Experimental). A check experiment showed that the rate of hydrolysis in 1% sodium chloride solution was the same as in distilled water, so that evidently the catalysis is due to hydrogen ions and not to chloride anions also. Table I lists the results obtained.

TABLE I.

*Rate of hydrolysis of di*iso*propyl fluorophosphonate at* 25° (*time in hours*).

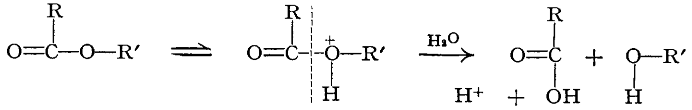
At pH = 7	: k = 0·006	initial rate in water
pH = 3·0	: k = 0·0122	in chloroacetate buffer
pH = 1·7	: k = 0·102	in 0·02N-hydrochloric acid
pH = 1·3	: k = 0·225	in 0·05N-hydrochloric acid

In alkaline solution di*iso*propyl fluorophosphonate hydrolyses very rapidly indeed. With equivalent concentrations corresponding to equation (3) the liberation of fluoride anion is complete in about 15 minutes at 25° (compare Saunders and Stacey *loc. cit.*) :

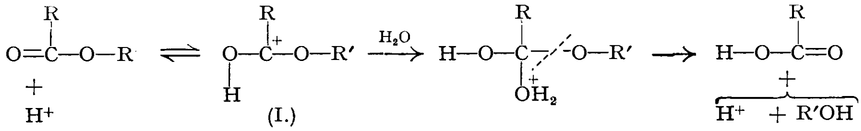
$$(3)\quad (C_3H_7{\cdot}O)_2POF + 2NaOH = (C_3H_7O)_2PO{\cdot}ONa + NaF + H_2O$$

Discussion.—Since the hydrolysis of di*iso*propyl fluorophosphonate is an acid-catalysed process, the rate-determining stage cannot be the direct heterolysis of the P–F link. Thus although it resembles an acyl halide it behaves in a very different manner from the acyl chlorides which undergo simple unimolecular (S_N1) hydrolysis (compare Berger and Olivier, *Rec. Trav. chim.*, 1927, **46**, 861). Acid-catalysed hydrolysis, however, occurs in esters, R·CO$_2$R′, and in ortho-esters, R·C(OR′)$_3$. It is usually ascribed to a proton attack on the alkyloxy-group which brings about a weakening of the C–O link sufficient for the rapid solvolysis of the molecule-ion complex (Mechanism *A* ; compare Lowry, *J.*, 1925, **127**, 1380; Waters, *J.*, 1936, **1014**; Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686) rather than attack at the C=O group (mechanism *B* ; compare Watson, " Modern Theories of Organic Chemistry," 1937, p. 130) since this cannot occur with the ortho-esters.

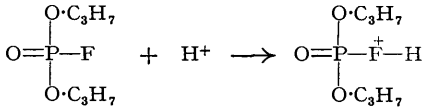
(*A*)



(*B*)

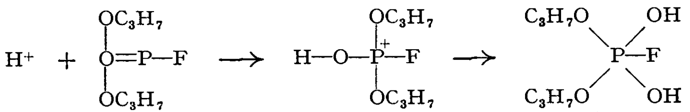


With di*iso*propyl fluorophosphonate, the process which is equivalent to (*A*) would involve the fluorine atom rather than the oxygen atoms of the *iso*propoxy-groups, *i.e.* :



(II.)

The breakdown of (II) would have to be a solvolysis by water acting as a nucleophilic reagent, and attacking the phosphorus atom of the *weakly* polar P=O group and not the positively charged fluorine atom. A justification of the bicovalency of fluorine in (II) would be extremely difficult. The alternative mechanism of proton attack on the oxygen atom of the double bond is, in this case, much more probable : it would lead to the formation of a phosphonium kation



(III.) (IV.)

(III) in which the positively charged phosphorus atom might well be able to abstract a hydroxyl anion from a water molecule so as to yield a quinquecovalent complex (IV), structurally analogous to phosphorus pentafluoride. Thereupon the loss of hydrogen fluoride regenerates anew the P═O double bond in di*iso*propyl phosphate.

Although a firm decision in favour of this second mechanism for the hydrolysis of the fluorophosphonate is impossible upon the scant evidence now available, yet it is clear that the mechanisms of reactions of compounds of phosphorus, and of fluorine, cannot safely be inferred from consideration of similar compounds of carbon and chlorine. The essential differences may be due to (i) the different electronic structures of C═O and P═O linkages, in the latter of which *d* electrons are concerned, and (ii) a marked difference in the partial ionic characters of P–F and C–Cl covalencies. In this latter connection, a kinetic study of the hydrolysis of acyl fluorides would be of great interest.

EXPERIMENTAL.

The di*iso*propyl fluorophosphonate was purified by repeated distillation under reduced pressure (b. p. 68°/9 mm.) and had 100% purity as determined by fluorine content. After storage for 5 weeks in a dry glass bottle the purity had fallen to 97%. Samples were weighed into graduated flasks, dissolved in a few ml. of ethyl alcohol, and then diluted with distilled water and, after thorough mixing, transferred to bakelite-enamel-coated copper vessels immersed in a thermostat at 25°. Since the solubility of di*iso*propyl fluorophosphonate is 1·54% at 25° (Ministry of Supply Report), concentrations of up to 0·8% could be handled without difficulty. Table II shows typical results of titration (i) with sodium hydrc[illegible] using phenolphthalein, and (ii) with thorium nitrate using Solochrome-blue. Table III indica[illegible] that the hydrolysis is pseudo-unimolecular in the presence of an acid catalyst: $k = (1/t)\log_e a/(a - x)$, with t in hours.

TABLE II.

Hydrolysis of a 0·37% solution in water at 25° (enamelled vessel).

Time (hours)	3	5	24	28	47	49	53	71
Hydrolysis, % (method i)	1·34	2·19	17·5	22·0	52·4	54·9	61·4	77·7
,, (method ii)	1·43	2·00	15·6	20·2	50·1	51·8	58·0	71·7

TABLE III.

*Hydrolysis of di*iso*propyl fluorophosphonate in 0·02N-hydrochloric acid (in glass) at 25°: Initial concentration = 0·0309M.*

Time	Hydrolysis, %.			Time	Hydrolysis, %.		
(hours).	By NaOH.	By $Th(NO_3)_4$.	*k*.*	(hours).	By NaOH.	By $Th(NO_3)_4$.	*k*.*
0·5	4·9	4·8	0·119	4·5	40·6	37·0	0·104
1·0	9·4	10·2	0·108	5·0	41·4	38·8	0·099
2·3	20·8	20·5	0·099	5·0	45·5	45·0	0·109
3·0	26·0	24·9	0·095	6·0	47·9	46·0	
3·5	31·2	30·0	0·101				Mean 0·102

* From thorium nitrate titres.

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