# 209. *Kinetic Studies in the Phosphinyl Chloride and Phosphorochloridate Series. Part V.* Evidence for a One-stage Mechanism in the Hydrolysis of Diethyl Phosphorochloridate.*

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The hydrolysis of $(EtO)_2POCl$ in $H_2{}^{18}O$, and of $(EtO)_2P^{18}OCl$ in ordinary water, proceeds without oxygen exchange between the phosphoryl group and the water. A mechanism of rapid reversible intermediate formation is thus excluded. The probable mechanism is a one-stage bimolecular displacement.

THE kinetic study of solvolytic reactions of dialkyl phosphorochloridates[1] indicated a bimolecular mechanism and definitely excluded a unimolecular mechanism. Two forms of the bimolecular mechanism may be postulated: (1) a one-stage displacement, the approach of the nucleophilic reagent being simultaneous with the ejection of the chloride ion, and (2) rapid reversible formation of an intermediate complex which then slowly decomposes into the products. These forms are often indistinguishable by kinetics. It was considered probable that in the solvolysis of phosphonyl chlorides and phosphorochloridates quasi-phosphosphonium compounds are involved.[2] In the solvolysis of dialkyl phosphorochloridates in absolute ethanol there is kinetic evidence that an intermediate complex mechanism does not contribute appreciably to the reaction. If a phosphorochloridate in solution in ethanol should first be in rapid equilibrium with a complex, which only slowly decomposes to the products:

$$(RO)_2POCl + EtOH \underset{\text{v. fast}}{\overset{\text{fast}}{\rightleftharpoons}} (RO)_2PCl(OH)(OEt) \overset{\text{slow}}{\rightleftharpoons} (RO)_2P(O)OEt + HCl$$

then a sample of, say, dimethyl phosphorochloridate dissolved in a large excess of ethanol should be converted almost completely into diethyl phosphorochloridate since the chances are about equal that in the reverse step not ethanol but methanol will be split off. The

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* Part IV, *J.*, 1953, 516.

[1] Dostrovsky and Halmann, *J.*, 1953, 502, 516.

[2] Kosolapoff," Organo-phosphorus Compounds," Wiley and Sons, New York, 1950, pp. 8, 138, 212.

rate of ethanolysis should then be the same as that of a sample of diethyl phosphorochloridate. In fact, considerable differences are found in the rate of ethanolysis of dimethyl, diethyl, di*iso*propyl, dibenzyl, and diphenyl phosphorochloridates.[1] Also, the products of ethanolysis are in each case different. A reaction sequence passing reversibly through an intermediate complex should produce mainly triethyl phosphate.

The present investigation * was undertaken in order to find out if in the hydrolysis of dialkyl phosphorochloridates the same one-stage mechanism obtains, or if some or all of the reaction passes through an intermediate complex. In a somewhat similar reaction, the hydrolysis of alkyl benzoates in aqueous dioxan, Bender [3] found that a considerable part of the hydrolysis probably involves reversible formation of an intermediate. In the Menschutkin reaction between methyl iodide and trimethylamine, Harman, Stewart, and Ruben [4] ruled out the reversible formation of an intermediate in which all the methyl groups are spatially equivalent. Methyl iodide labelled with tritium was caused to react with excess of inactive trimethylamine in ethanol or in benzene solution. The unchanged amine contained less than 0·1% of the tritium required for random distribution.

Diethyl phosphorochloridate was chosen as most convenient, since it is hydrolysed completely in water at room temperature within 1 min., according to the equation $(EtO)_2POCl + H_2O = (EtO)_2PO{\cdot}OH + HCl$; 2 equiv. of acid are found for each equiv. of chloride ion, and no hydrolysis of the ethyl groups takes place. In 70% aqueous dioxan at 0° the first-order rate constant for hydrolysis is $1{\cdot}4 \times 10^{-5}$ sec.$^{-1}$; the half-time is about 6 min. The diethyl hydrogen phosphate produced is very soluble in water and only very slightly soluble in *n*-hexane; therefore diethyl phosphorochloridate can be separated from the products by extraction with *n*-hexane. After partial hydrolysis of diethyl phosphorochloridate in heavy water (8·1 atom % excess of $^{18}O$) and dioxan, the unchanged diethyl phosphorochloridate was extracted with *n*-hexane and analysed for $^{18}O$. It had not become enriched (cf. p. 1006). Since the method of analysis involved hydrolysis of the extracted diethyl phosphorochloridate in ordinary water and $^{18}O$ determination in the resulting PO·OH group, it was considered possible that, if very fast and reversible exchange of oxygen between enriched water and the phosphorochloridate had occurred in the first stage, then all the $^{18}O$ gained by unhydrolysed phosphorochloridate would be lost in the second stage of hydrolysis in ordinary water. To check this, a number of experiments was made by a different method in which diethyl phosphorochloridate was hydrolysed completely, and the exchange of the phosphoryl oxygen with the water oxygen was determined after completion of the reaction.

TABLE 1. *Hydrolysis of diethyl phosphorochloridate* ($f$ = atom % excess of $^{18}O$).

| | Reactants | | | | $f$ in excess $H_2O$ : | | |
|---|---|---|---|---|---|---|---|
| Run | $(EtO)_2POCl$ | | $H_2O$ | | | Calc. for | |
| No. | mmoles | $f$ | mmoles | $f$ | Found | No exchange | Complete exchange |
| 154 | 1·6 | 1·60 | 5·7 | 0·00 | 0·01 | 0·00 | 0·30 |
| 156 | 3·1 | 1·60 | 5·1 | 0·00 | 0·01 | 0·00 | 0·60 |
| 168 | 8·0 | 1·60 | 18·5 | 0·01 | 0·01 | 0·01 | 0·48 |
| 159 | 8·2 | 0·00 | 16·3 | 0·00 | 0·00 | — | — |
| | | | | | $f$ in PO·OH : | | |
| 188 | 0·38 | 1·60 | 55·9 | 0·00 | 0·82 | 0·80 | 0·01 |
| 201 | 1·15 | 0·00 | 37·1 | 3·86 | 1·80 | 1·93 | 3·74 |
| 214 | 1·37 | 0·00 | 18·5 | 5·52 | 2·72 | 2·76 | 5·14 |
| 219 | 1·65 | 0·00 | 15·9 | 5·64 | 2·88 | 2·82 | 5·10 |

In some experiments a small excess of ordinary water reacted with labelled phosphorochloridate (Table 1, Nos. 154, 156, 168); after completion of hydrolysis the excess of water was recovered by distillation: it had not become enriched appreciably in $^{18}O$ (Table 1, col. 6). If oxygen exchange had taken place during the reaction, the recovered

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* A preliminary communication of part of this work was presented at the XIV International Congress of Pure and Applied Chemistry, Zürich, July 1955.

[3] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1628.

[4] Harman, Stewart, and Ruben, *ibid.*, 1942, **64**, 2294.

water should have become enriched in $^{18}O$. For complete exchange, the required atom % excess of heavy oxygen is given in the last column of Table 1. The accuracy of these experiments is sufficient to decide that no more than 2% of the total reaction could have involved oxygen exchange. Incidentally, these results also prove that the product, diethyl hydrogen phosphate, does not exchange oxygen in aqueous solution at room temperature during several days.

No isotope effect on the rate of hydrolysis was observed (see Run 159). After reaction of ordinary diethyl phosphorochloridate with ordinary water, the excess of water was found to have remained unchanged in $^{18}O$ content. Thus diethyl phosphorochloridate does not differentiate between $H_2{}^{16}O$ and $H_2{}^{18}O$ within the experimental error.

In other experiments a large excess of water was used (Runs No. 175—219). In these cases it was evidently impossible to detect a considerable change in the $^{18}O$ content of the recovered excess of water because the change would be too small. Here, however, analysis of the $^{18}O$ enrichment in the PO·OH group of the resulting diethyl hydrogen phosphate can be used to detect oxygen exchange. A simple substitution of chlorine of the phosphorochloridate by hydroxyl must yield a PO·OH group in which the $^{18}O$ content per oxygen atom becomes the average of the $^{18}O$ contents of the original phosphoryl group and the water. It is assumed that in dilute aqueous solution the diethyl hydrogen phosphate is completely ionsied and the two oxygen atoms become equivalent. A mechanism in which the oxygen atoms of the phosphoryl group and of the water exchange completely should yield a PO·OH group in which the $^{18}O$ content becomes close to that of the water, which was in large excess. The calculated values for the excess of heavy oxygen in the PO·OH group are given in cols. 7 and 8 of Table 1 for the two extreme cases of reaction with no exchange and with complete exchange. As can be seen from col. 6, the experimental results are close to those required for hydrolysis without exchange.

The method of $^{18}O$ determination in the PO·OH of diethyl hydrogen phosphate was based on its reaction with di-*p*-tolylcarbodi-imide :[5]

$$2(EtO)_2PO{\cdot}OH + (p\text{-}MeC_6H_4{\cdot}N{:})_2C = (EtO)_2PO{\cdot}O{\cdot}PO(OEt)_2 + (p\text{-}MeC_6H_4{\cdot}NH)_2CO$$

The resulting di-*p*-tolylurea was isolated and decomposed at 320° in the presence of a catalyst to carbon dioxide, which was analysed by mass spectrometry for its $^{18}O$ content.

Run 188, between labelled diethyl phosphorochloridate and ordinary water, is of particular interest since it shows complete retention of the enriched oxygen of the phosphoryl group in spite of the large excess of ordinary water. In runs 201, 214, and 219, ordinary diethyl phosphorochloridate was caused to react with different proportions and concentrations of $^{18}O$ enriched water. In each case the PO·OH group of the resulting hydrogen phosphate contained half the excess of heavy oxygen of the original water.

The above results exclude a mechanism of rapid reversible formation of an intermediate in the hydrolysis of diethyl phosphorochloridate, and favour a simple one-stage displacement of the chlorine atom by water. An alternative to the one-stage displacement, indistinguishable experimentally, is slow formation of an intermediate, which breaks up immediately into the products.

## EXPERIMENTAL

*Materials.*—Heavy oxygen-enriched water was obtained from the fractionating column of this laboratory.

$(Et^{18}O)_2P^{18}OCl$ was prepared by McCombie, Saunders, and Stacey's method :[6] To $^{18}O$-labelled ethanol (6·2 g.)[7] and carbon tetrachloride (7 ml.) phosphorus trichloride (4 ml., freshly distilled) was added dropwise with stirring. Atmospheric moisture was excluded. The solution was refluxed for ½ hr. and dry nitrogen was then bubbled through for an hour. On distillation, 4·6 g. of diethyl hydrogen phosphite were obtained, b. p. 83—90°/20 mm. The product was dissolved in carbon tetrachloride, cooled in brine, and dry chlorine was passed through until a green colour developed. Dry nitrogen was then bubbled through the solution. On distillation,

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[5] Khorana and Todd, *J.*, 1953, 2259; Khorana, *Chem. Rev.*, 1953, **53**, 145.

[6] McCombie, Saunders, and Stacey, *J.*, 1945, 380.

[7] Halmann and Samuel, *Bull. Res. Counc. Israel*, to be published.

4·6 g. of diethylphosphorochloridate were obtained, b. p. 78—81°/7 mm.; it was stored in a glass-stoppered flask in a desiccator.

*Procedure.*—(a) *Partial hydrolysis.* To a solution of $^{18}O$-enriched water (8·10 atom % excess; 1·519 g.) in dioxan (3·5 ml.) in a thermostat at 0°, diethyl phosphorochloridate (1·5 ml.) was added. After 8 min. the mixture was extracted with *n*-hexane (6 ml.), a syringe being used as separatory funnel. The hexane layer was washed with distilled water (2 × 2 ml.) and the solvent was removed by evaporation under reduced pressure. The residual oil was dissolved in distilled water (1 ml.), and after 5 min. was dried at 0·05 mm. The $^{18}O$ content of the resulting diethyl hydrogen phosphate was determined by the carbodi-imide method.[8] and was found to be equal to that of natural water within $\pm 2\%$. The extent of exchange during hydrolysis must therefore be less than 0·1% of that calculated for complete equilibration.

(b) *Complete hydrolysis.* Reactions were carried out in 10-ml. flasks with TS 10/30 inner joints fitted with similar outer stoppers. The phosphorochloridate and the water were weighed into the flask and mixed. When hydrolysis was complete, the excess of water was distilled at room temperature in a vacuum still. The apparatus consisted of a three-way stopcock, one limb of which was connected to a vacuum line (20 microns). The other limbs were fitted with TS 10/30 outer joints. To one of these the reaction flask was connected, and to the other a similar empty flask. The reaction flask was cooled in liquid nitrogen and both flasks were evacuated. The stopcock was then turned to connect only the two flasks, and Dewar flask containing liquid nitrogen was transferred to the empty flask. After most of the water had distilled over, the reaction flask was connected to the vacuum line in order to remove residual water from the diethyl hydrogen phosphate, which was then analysed for $^{18}O$ by the carbodi-imide method. A sample of the distillate was equilibrated with a small amount of ordinary carbon dioxide in a sealed bulb and was assayed by mass spectrometer for its $^{18}O$ enrichment; at the same time a sample of the water initially used in the reaction was analysed.

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[8] Halmann, *J.*, to be published.