

**739.** *The Effects of Substituents on the Rates of Hydrolysis of Some Organophosphorus Compounds. Part II.\* Rates in Neutral Solution.*

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The approach used in the preceding paper is extended to cover rates of hydrolysis in compounds under conditions such that catalysis by hydroxyl ions can be neglected. Salts catalyse hydrolysis of *NN'*-diisopropyl- and *NN*-dimethyl-*N'*-isopropyl-phosphorodiamidic fluoride.  $k_w$  for the first compound is probably composite, water acting as both an anionoid and a cationoid reagent.

Generally, however, water acts as an anion by an  $S_N2$  mechanism. Substituents have similar effects to those described in Part I, except that in the tetra-alkyl pyrophosphates steric effects are more important than inductive effects, and that P-S-C groups accelerate the rates less in neutral than in alkaline solution.

THE purpose of this paper is to discuss the rate constants in neutral solution along similar lines to those used in Part I\* for alkaline solution.

The overall hydrolysis constant in neutral solution is made up of five terms :

$$k = k_w + k_{H^+}[H^+] + k_{OH^-}[OH]^- + k_A[A] + k_B[B]$$

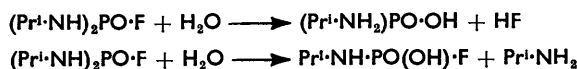
where  $k_B$  and  $k_A$  are the constants for catalysis by general bases and acids respectively. Kilpatrick and Kilpatrick,<sup>1</sup> in their very full study of the hydrolysis of diisopropyl phosphorofluoridate, have shown that  $k_B$  and  $k_A$  are much greater than  $k_w$ . Heath and Casapieri<sup>2</sup> have shown that phosphate ions catalyse the hydrolysis of *NNN'N'*-tetramethyl-phosphorodiamidic fluoride. Phosphate buffers also catalyse the hydrolysis of *NN*-dimethyl-*N'*-isopropylphosphorodiamidic fluoride. To gain some idea of the magnitude of general catalysis on another compound of this type, the rates of hydrolysis at three temperatures

\* Part I, preceding paper.

<sup>1</sup> Kilpatrick and Kilpatrick, *J. Phys. Colloid Chem.*, 1949, **53**, 1371.

<sup>2</sup> Heath and Casapieri, *Trans. Faraday Soc.*, 1951, **47**, 1093.

of *NN'*-diisopropylphosphorodiamidic fluoride have been found in two concentrations of phosphate-citrate buffers at pH 5.70. In the study of the diisopropyl compound it is found that  $k_A + k_B$  (which cannot be separated, as only one buffer system at one pH was used) is much greater than  $k_w$ , and also that a graph of  $\log(k_A + k_B)$  against  $1/T$  gives a straight line corresponding to an activation energy of 16.0 kcal./mole. When  $\log k_w$  is plotted against  $1/T$ , however, the points do not fall on a straight line, and the considerable error in  $k_w$ , which is the relatively small difference between two numbers, cannot account for the disagreement. This indicates that two reactions occur simultaneously, the balance between them differing with the temperature. The two obvious reactions are :



The first is analogous to hydrolysis by hydroxyl ion, the second to hydrolysis by hydrogen ions, as studied by Heath and Casapieri.<sup>2</sup>

Three difficulties may thus be encountered in interpreting the published results.

Where rates were determined in water alone, there is the possibility that products may catalyse the hydrolysis. This is characterised in the graph of  $-\log A$  against  $t$  (where  $A$  is the concentration remaining at time  $t$ ) by an increase in slope with increase in  $t$ . The effect was absent in the results given in the Tables. The present author's results were obtained on very dilute solutions of compounds labelled with <sup>32</sup>P, so that the maximum attainable salt concentration could not influence the rates measurably. Those of Toy<sup>3</sup> on pyrophosphates of the general formula  $(\text{RO})_2\text{PO}\cdot\text{O}\cdot\text{PO}(\text{OR}')_2$ , where R and R' are alkyl groups, probably do not show the effect because the products are strong acids, so that base-catalysis is ruled out. There is no evidence that the hydrolysis of these pyrophosphates is catalysed by acids.

Where rates were determined in buffer solutions there are generally no data by means of which one can allow for the contribution made by acid-base catalysis. Consequently, while such results are consistent *inter se*, they cannot be compared with results obtained on other compounds in water alone.

Finally, it must be decided whether water is acting as an anionoid or a cationoid reagent, or as both simultaneously. The effect of substituents on acid-catalysed rates is different, and not well understood. In so far as water acts as a cationoid reagent it is analogous in action to hydrogen ions, and the most basic substituent is thus likely to be displaced first. This may however be followed by a rapid breakdown of the rest of the molecule, as in the acid hydrolysis of octamethylpyrophosphoramidate.<sup>2</sup> Consequently, unless it is shown that basic groups are not displaced (as Toy<sup>3</sup> did) it cannot be assumed that water is acting solely as an anionoid reagent. Therefore, we must be cautious in interpreting the attack on compounds by water as anionoid when their hydrolyses are catalysed by hydrogen ions. The R-O-P bonding is, however, very stable to acids, so that it is reasonable to suppose that the attack on molecules of the  $(\text{RO})_2\text{PO}\cdot\text{X}$  type is anionoid, even when this has not been proved.

#### EXPERIMENTAL

*Hydrolysis of NN'-Diisopropylphosphorodiamidic Fluoride.*—The rates were followed by the method (ai) of the previous paper, with tracer quantities of the compound only. McIlvaine's phosphate-citrate buffer of pH 5.70 was prepared according to the instructions in "Handbook of Chemistry and Physics" (Chemical Rubber Publishing Co., Cleveland), at total molar concentrations of 0.1274 and 0.01274. The pH was checked before and after each run with a Doran pH-meter and a glass electrode against a saturated calomel electrode, and, with one exception, agreed to within 0.01 pH unit of 5.70. The value at the end of the run at 72.9° in the lower concentration was 5.75. By using the set-up as a millivoltmeter the pH at 72.9° was found to be 5.70. The pH is thus independent of temperature.

$k_H$  was found to be 0.656[H<sup>+</sup>] in 0.005N-hydrochloric acid at 25° [method (ai) of Part I]. A similar constant is found for the tetramethyl analogue,<sup>3</sup> for which  $E = 14$  kcal./mole. This

<sup>3</sup> Toy, *J. Amer. Chem. Soc.*, 1948, **70**, 3882; 1950, **72**, 2065.

value of  $E$  was used to find  $k_H$  for the  $NN'$ -diisopropyl compound at different temperatures. ( $k_A + k_B$ ) and  $k_w$  are not very sensitive to  $E$ .  $k_{OH}$  was found from the results in Part I.

$k_H$  in Table I was calculated by assuming that the secondary salt effect raises the constant 25% at the lower concentration and 100% at the higher. These estimates are based on the

TABLE I. Constants for the hydrolysis of  $NN'$ -diisopropylphosphorodiamidic fluoride in phosphate-citrate buffer at pH 5.70.

| Molarity of buffer |           | 25.0°<br>10 <sup>5</sup> $k$ (min. <sup>-1</sup> ) | 50.0°<br>10 <sup>4</sup> $k$ (min. <sup>-1</sup> ) | 72.9°<br>10 <sup>3</sup> $k$ (min. <sup>-1</sup> ) | $E$<br>(kcal./mole) |
|--------------------|-----------|--|--|--|---------------------|
| 0.1274             | $k$       | 8.12 ± 0.10  | 6.816 ± 0.048                                      | 3.687 ± 0.026                                      | —                   |
|                    | $k_H$     | 0.27   | 0.145  | 0.072  | 14                  |
|                    | $k_{OH}$  | 0.02   | 0.010  | 0.006  | 11.2                |
| 0.01274            | $k$       | 1.181 ± 0.015                                      | 1.040 ± 0.012                                      | 0.803 ± 0.014                                      | —                   |
|                    | $k_H$     | 0.169  | 0.091  | 0.045  | 14                  |
|                    | $k_{OH}$  | 0.024  | 0.010  | 0.006  | 11.2                |
| 0 (calc.)          |           | 0.421  | 0.404  | 0.486  | —                   |
| 1.0                | $k_A + B$ | 59.7   | 49.9   | 24.9   | 16.0 ± 0.2          |
|                    | $k_w$     | 0.228 ± 0.03                                       | 0.303 ± 0.03                                       | 0.435 ± 0.03                                       | —                   |

activity coefficients of salts given by Robinson and Harned.<sup>4</sup> They must be considerably in error to introduce errors as great as those in the original runs.

$k_{OH}$  is corrected both for the secondary salt effect and the increasing dissociation of water with increase in temperature.

Primary salt effects may lead to systematic errors in  $k_{A+B}$ , which may affect  $E$  for salt-catalysis, and also  $k_w$ . The influence on the latter is again likely to be unimportant compared with the errors in  $k$ .

*Hydrolysis Rates in Water* (see Tables).—The published and the present results are tabulated; numbering of the compounds continues from Part I.

TABLE 2. Constants for the hydrolysis in water, at 25°, of some pyrophosphates, (RO)<sub>2</sub>PO-O-PO(OR')<sub>2</sub>.

| Compound |    |    | Compound |    |                 | Compound |    |                 | Compound |                 |                 |
|----------|----|----|----------|----|-----------------|----------|----|-----------------|----------|-----------------|-----------------|
| No.      | R  | R' | No.      | R  | R'              | No.      | R  | R'              | No.      | R               | R'              |
| 37       | Me | Me | 40       | Et | Et              | 43       | Et | Bu <sup>n</sup> | 46       | Pr              | Pr <sup>i</sup> |
| 38       | Me | Et | 41       | Me | Pr <sup>i</sup> | 44       | Pr | Pr              | 47       | Bu <sup>n</sup> | Pr <sup>i</sup> |
| 39       | Me | Pr | 42       | Et | Pr              | 45       | Et | Pr <sup>i</sup> | 48       | Pr <sup>i</sup> | Pr <sup>i</sup> |
|          |    |    |          |    |                 |          |    |                 |          |                 |                 |
|          |    |    |          |    |                 |          |    |                 |          |                 |                 |

The constant for tetraethyl pyrophosphate is taken from Ketelaar and Bloksma's results.<sup>5</sup> The remainder are taken from the figures given by Toy.<sup>4</sup> Of Toy's results, those for compounds which do not contain diisopropylphosphato-groups follow first-order kinetics until hydrolysis is nearly complete. The graph of  $\ln A$  against  $t$  for those which do contain this group is initially a straight line, but curves to a line of lower gradient after 50—90% hydrolysis; this is most readily explained if they contain impurities more stable in water. These rate constants have therefore been calculated from the first straight portion of the curves, with allowance for such impurities. Results obtained in such a way are necessarily of low accuracy. The interpretation of the graph for tetraisopropyl pyrophosphate is particularly difficult: 0.09 is the greatest possible value of the constant.

TABLE 3. Constants for the hydrolysis of some compounds at 37° in 0.067M-phosphate buffer at pH 7.4.

| No. | Compound  | $k$ (min. <sup>-1</sup> ) | % hydrolysed | No. | Compound  | $k$ (min. <sup>-1</sup> ) | % hydrolysed |
|-----|---|---------------------------|--------------|-----|---|---------------------------|--------------|
| 49  | (EtO)(EtS)PO·O·C <sub>6</sub> H <sub>4</sub> ·NO <sub>2</sub> - <i>p</i>          | 8 × 10 <sup>-4</sup>      | —            | 54  | (EtO) <sub>2</sub> PO·O·C <sub>6</sub> H <sub>4</sub> Cl- <i>o</i>                | 2.3 × 10 <sup>-5</sup>    | 7.9          |
| 50  | (EtO) <sub>2</sub> PO·S·C <sub>6</sub> H <sub>4</sub> ·NO <sub>2</sub> - <i>p</i> | 4.7 × 10 <sup>-4</sup>    | —            | 55  | (EtO) <sub>2</sub> PO·O·C <sub>6</sub> H <sub>4</sub> Cl- <i>p</i>                | 7.2 × 10 <sup>-7</sup>    | 4.2          |
| 51  | (EtO) <sub>2</sub> PO·O·C <sub>6</sub> H <sub>4</sub> ·NO <sub>2</sub> - <i>o</i> | 5.6 × 10 <sup>-5</sup>    | 78           | 56  | (EtO) <sub>2</sub> PO·O·Ph  | 1.6 × 10 <sup>-7</sup>    | 2.6          |
| 52  | (EtO) <sub>2</sub> PO·O·C <sub>6</sub> H <sub>4</sub> ·NO <sub>2</sub> - <i>p</i> | 3.9 × 10 <sup>-5</sup>    | 65           | 57  | (EtO) <sub>2</sub> PS·O·C <sub>6</sub> H <sub>4</sub> ·NO <sub>2</sub> - <i>p</i> | 7.0 × 10 <sup>-7</sup>    | —            |
| 53  | (EtO) <sub>2</sub> PO·O·C <sub>6</sub> H <sub>4</sub> ·NO <sub>2</sub> - <i>m</i> | 1.4 × 10 <sup>-5</sup>    | 45           |     |   |                           |              |

The results (51)—(56) are given by Aldridge and Davison.<sup>6</sup> It is obvious that some of the results are very inaccurate. The remainder are taken from Aldridge and Davison's work,<sup>7</sup> and are corrected for the contribution made by hydroxyl-ion catalysis. This correction lowers the constant by 32% for compounds (49) and (57), and by 11% for no. (50). The correction to no. (52) would be about 3%.

<sup>4</sup> Robinson and Harned, *Chem. Rev.*, 1941, **28**, 419.

<sup>5</sup> Ketelaar and Bloksma, *Rec. Trav. chim.*, 1948, **67**, 665.

<sup>6</sup> Aldridge and Davison, *Biochem. J.*, 1952, **51**, 62.

<sup>7</sup> *Idem, ibid.*, 1952, **52**, 663.

TABLE 4. Hydrolysis constants for some fluoro-compounds.

| No. | Compound  | Temp. | $k$ (min. <sup>-1</sup> ) | Ref. |
|-----|---|-------|---------------------------|------|
| 60  | (Pr <sup>i</sup> O) <sub>2</sub> PO·F                               | 25°   | 1.2 × 10 <sup>-4</sup>    | 1    |
| 61  | (Pr <sup>i</sup> ·NH) <sub>2</sub> PO·F                             | 25    | 2.3 × 10 <sup>-6</sup>    |      |
| 62  | (Me <sub>2</sub> N)(Pr <sup>i</sup> ·NH)PO·F                        | 100   | 1.5 × 10 <sup>-3</sup>    |      |
| 63  | (O < [CH <sub>2</sub> ·CH <sub>2</sub> ] <sub>2</sub> > N)(EtO)PO·F | 25    | 4 × 10 <sup>-7</sup>      |      |

Compounds (61)–(63) were measured in very dilute solution by method (ai) of Part I, or are corrected for salt effects. The constants are thus  $k_w$  only.

*Triethyl (58) and Trimethyl (59) Phosphate.*—Cavalier<sup>8</sup> gives  $k_w$  for triethyl phosphate as 1.15 × 10<sup>-4</sup> hr.<sup>-1</sup> at 44°, and 1.14 × 10<sup>-2</sup> hr.<sup>-1</sup> at 88°, whence at 25°  $k = 1.7 \times 10^{-7}$  min.<sup>-1</sup>,  $E = 23.8$  kcal./mole. For trimethyl phosphate, Cavalier gives  $k = 6.32 \times 10^{-2}$  hr.<sup>-1</sup> = 1.05 × 10<sup>-3</sup> min.<sup>-1</sup> at 88°.

*Hydrolysis Constants for Some Chloro-compounds.*—Dostrovsky and Halman<sup>9</sup> determined the rates of hydrolysis of five chloro-compounds in aqueous alcohol, and showed that the inductive effects of the substituents are in fair quantitative agreement with the inductive effects of the same substituents in chloroformic esters.

## DISCUSSION

It is convenient to divide the compounds into three groups: the pyrophosphates of Table 2, in which the differences in rate must be due solely to the inductive and steric effects of the different alkyl substituents; those of Table 3, together with triethyl and trimethyl phosphate, where the differences are predominantly due to differences in the acidic groups; and those of Table 4, of compounds containing more complex alterations in the basic substituents.

*Pyrophosphates.*—Both phosphate groups in each molecule are open to attack. Each constant in Table 2 is thus the sum of two constants. If it is assumed that the hydrolysis is an S<sub>2</sub> replacement in which the rate is controlled by the rate of attachment of a water molecule to a phosphorus atom, the rates will decrease as the  $-I$  effects increase, in the order Me < Et < Bu<sup>n</sup> < Pr<sup>i</sup>. It was shown in Part I, by comparing the pairs (16) and (17), and (14) and (10), that the transmission of effects along the pyrophosphate bonds is slight. Thus the inductive effect of groups on one phosphorus atom has little effect on the reactivity of the other. Therefore, if  $k_1$  is the constant for the reaction with one phosphorus, and  $k_2$  the constant for the reaction with the other, the total constant ( $k$ ) given in the Table equals  $k_1 + k_2$ . In some instances  $k_1$  and  $k_2$  can be found from the rates for the symmetrical compounds. The constant for (Bu<sup>n</sup>O)<sub>2</sub>P cannot be found in this way, but as  $n$ -butyl has slightly more  $-I$  effect than  $n$ -propyl, it is reasonable to assume that  $k_{\text{Bu}} = 0.9k_{\text{Pr}}$ . Comparison of the observed and the calculated constants (Table 5)

TABLE 5. Observed and calculated constants for some pyrophosphates, (RO)<sub>2</sub>PO·O·PO(OR')<sub>2</sub>.

| No. | Compound |                 | 10 <sup>3</sup> $k$ (min. <sup>-1</sup> ) |       | No. | Compound        |                 | 10 <sup>3</sup> $k$ (min. <sup>-1</sup> ) |       |
|-----|----------|-----------------|---|-------|-----|-----------------|-----------------|---|-------|
|     | R        | R'              | obs.                                      | calc. |     | R               | R'              | obs.                                      | calc. |
| 37  | Me       | Me              | 25  | 25    | 43  | Et              | Bu <sup>n</sup> | 0.95                                      | 1.1   |
| 38  | Me       | Et              | 7.0                                       | 13.3  | 44  | Pr              | Pr              | 0.65                                      | 0.65  |
| 39  | Me       | Pr              | 5.6                                       | 12.8  | 45  | Et              | Pr <sup>i</sup> | 0.28                                      | 0.85  |
| 40  | Et       | Et              | 1.6                                       | 1.6   | 46  | Pr              | Pr <sup>i</sup> | 0.20                                      | 0.37  |
| 41  | Me       | Pr <sup>i</sup> | 1.1                                       | 12.5  | 47  | Bu <sup>n</sup> | Pr <sup>i</sup> | 0.20                                      | 0.34  |
| 42  | Et       | Pr              | 1.0                                       | 1.1   | 48  | Pr <sup>i</sup> | Pr <sup>i</sup> | 0.09                                      | 0.09  |

Italicized constants were used to determine  $k_1$  and  $k_2$ .

shows satisfactory agreement for compounds (42) and (43) containing neither methyl nor isopropyl groups. The discrepancies are most readily explained by steric effects;  $n$ -alkyl groups other than methyl groups exert a constant steric effect somewhat greater than that of methyl groups, and isopropyl groups a very much greater steric effect than any other group, as suggested by Toy.<sup>3</sup> The substitution of two methyl groups for two ethyl groups increased the constant by a factor of only about 3–4 in the compounds discussed in Part I,

<sup>8</sup> Cavalier, *Ann. Chim. Phys.*, 1899, **18**, 449.

<sup>9</sup> Dostrovsky and Halmann, *J.*, 1953, 503.

whereas the equivalent substitution here (absence of P–O–P interaction being assumed) of four methyl for four ethyl groups increases the rate by a factor of 16, a difference most readily explained by steric hindrance by ethyl groups. Steric hindrance by *isopropyl* groups is the simplest explanation of the slow hydrolysis of *diisopropyl* fluorophosphate (2), discussed in Part I. Of course, the assumption of no P–O–P interaction is not justifiable. Doubtless such interaction contributes to the results, but if this alone is to explain them then the unlikely assumption must be made that groups on one phosphorus atom exert as great an inductive effect on the other phosphorus atom as on that to which they are attached.

Why methyl and ethyl groups should exert different steric effects in these molecules and not in those studied in Part I is not clear. Perhaps the P–O–P system is considerably more rigid, owing to its partially double-bonded character, than most of the P–X bonds previously considered. This may make it more difficult for the molecule to accommodate itself in the transition state. Whatever the reason, it appears that steric effects are more important than inductive effects in this series of compounds, but that inductive effects also operate.

*Compounds of Table 3.*—The constants are comparable *inter se*, but, being determined in buffer solutions, cannot be compared with those in the other Tables. The effects of substituents in the aromatic ring are as would be expected from the structure of the molecules. The hydrolysis is a side-chain reaction with respect to the benzene ring, so that electromeric effects will be less important than inductive effects. Thus a nitro-group will exert a greater +*I* effect than a chlorine atom, and a chlorine atom a greater one than a hydrogen atom. As however the P–O–C ester system is to some extent conjugated, as can be deduced from the electromeric effects described in Part I, electromeric effects will somewhat modify the inductive effects, causing *o*-nitro- and *p*-nitro- to be more positive than *m*-nitro-groups. *ortho*-Groups produce greater effects than *para*-groups in the absence of steric hindrance or specific interaction between neighbouring groups. These considerations lead to the observed order, in which the rates increase as the — (*I* + *E*) effects decreases, *viz.*, H, *p*-Cl, *o*-Cl, *m*-NO<sub>2</sub>, *p*-NO<sub>2</sub>, *o*-NO<sub>2</sub>.

It is interesting that diethyl phenyl phosphate (56) is hydrolysed at a very similar rate to triethyl phosphate (58), although the phenyl group usually exhibits a weak +*I* effect.

The substitution of P=S for P=O inhibits hydrolysis by water [cf. nos. (57) and (52)] rather more than by hydroxyl ions [nos. (20) and (26)], but qualitatively the effect is the same.

It is notable that, while the order of the constants for *OS*-diethyl *O-p*-nitrophenyl phosphorothiolate (49), *OO*-diethyl *S-p*-nitrophenyl phosphorothiolate (50), and diethyl *p*-nitrophenyl phosphate (52) is the same for hydrolysis by both water and hydroxyl ions, the differences are much less in water. That the ethylthio-group should be more activating than the phenylthio-group still appears to require some such explanation as that proposed in Part I. In accordance with that hypothesis the constants for all three compounds are closer for reactions with the less polar reagent.

*Compounds of Table 4.*—There are too few in this group for general conclusions to be drawn. Kilpatrick and Kilpatrick<sup>1</sup> assumed that in the hydrolysis of *diisopropyl* phosphorofluoridate (60) water acted as an acid, not as a base. There are reasons for believing this may be true in the hydrolysis of *NN'*-*diisopropyl*phosphorodiamidic fluoride (61). It is interesting that the first compound is hydrolysed in water about 50 times as rapidly as the second, whereas in alkaline solution the rates are about equal [nos. (2) and (3)]. It is also certain that at the same temperature *NN*-dimethyl-*N'*-*isopropyl*-phosphorodiamidic fluoride (62) would be hydrolysed more rapidly than ethyl morpholino-phosphorofluoridate (63), although a dimethylamino-group exerts a greater —*I* effect than a morpholino-group (see Part I) and *isopropylamino*- a greater —*I* effect than an ethoxy-group. Such differences may indicate that these compounds are not hydrolysed by the same mechanism in water and in alkaline solution.

*General Conclusions.*—While a combination of steric, inductive, and electromeric effects accounts for the observed rates of hydrolysis in water of most of the compounds studied, and the effects in these instances are consistent with water's acting as an anionoid reagent

which replaces the most acidic radical by an  $S_2$  mechanism, there are instances, possibly confined to phosphoramidic compounds, in which water probably acts as a cationoid reagent, and the general rules then do not hold.

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