benzene solution of the adduct VII (3.913 g. in 15 ml.) was treated with 0.217 ml. of water (1 mole equiv.). An exothermic reaction occurred within 2 min. The solvent was removed at 40° (15 mm.; last traces at 0.2 mm). The H^1 n.m.r. spectrum (CCl_4) of the *crude* residue showed all the signals of the cyclic triester XIV and in addition two doublets (J = 11.2 c.p.s.) at τ 6.25 separated by 1.5 c.p.s. and a singlet at τ 7.78, which could be due to an open-chain phospho triester (<20%). This material was submitted to short-path distillation (bath 150–155°, 0.1 mm.). The cyclic phosphate XIV had b.p. 109–112° (0.1 mm.), $n^{25}D$ 1.4441, yield 80%.

Anal. Calcd. for $C_{12}H_{23}O_5P$: C, 51.8; H, 8.3; P, 11.5. Found: C, 51.8; H, 8.6; P, 10.8.

The *infrared spectrum* (in CCl_4) had a strong carbonyl band at 5.80, a strong, sharp PO band at 7.68, and a very strong $POCH_3$ band at 5.90 μ. The H^1 *n.m.r. spectrum* (in CCl_4) had a $1H^1$ multiplet at τ 5.8; one $3H^1$ doublet at τ 6.19 and another at 6.21 (Δ = 1.3 c.p.s.), both with J_{HP} = 11.6 c.p.s.; one $3H^1$ singlet at τ 7.70 and another at 7.77 (Δ = 4.2 c.p.s.); there was a singlet at τ 8.46 and another at 8.57 (Δ = 6 c.p.s.), a multiplet at 8.70 and a multiplet at 9.1; these four signals integrated as $16H^1$. There was no trace of the signals due to the open-chain triester.

Hydrolysis of the Cyclic Phosphate XIV to DL-*erthro-3-Methyldecane-3,4-diol-2-one (XVII).* The cyclic phosphate XIV (25 g.) in water (40 ml.) was treated with 3.6 g. of NaOH. This solution, with pH *ca.* 5.1, was kept for 6 hr. at the boiling point, cooled, saturated with NaCl, and extracted with chloroform. Removal of the chloroform left 16 g. (90%) of DL-*erythro*-3-methyldecane-3,4-diol-2-one (XVII), identified by comparison with a sample previously described.[1b]

Acknowledgment. We are grateful to Professor P. C. Lauterbur of this department for instruction and advise in n.m.r. spectroscopy.

Mechanisms in the Hydrolysis of Phosphorodiamidic Chlorides[1]

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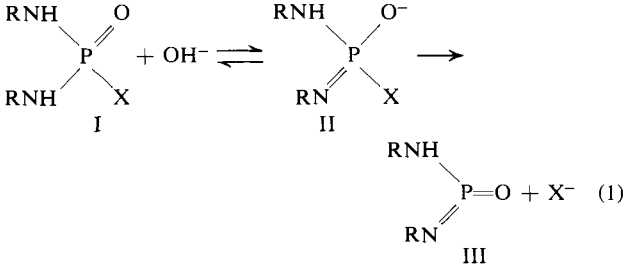
Contribution from the James Bryant Conant Laboratory of Harvard University, Cambridge, Massachusetts. *Received September 29, 1964*

The hydrolyses of N,N,N',N'-tetramethylphosphorodiamidic chloride (TMPC) and of N,N'-dipropylphosphorodiamidic chloride (DPPC) with water under neutral or slightly acidic conditions proceed at comparable rates. Similarly, a number of nucleophiles, such as pyridine, react with the two phosphorodiamidic chlorides at comparable rates in bimolecular reactions. However, in alkaline solution, DPPC is hydrolyzed at least 4 million times faster than TMPC. These results are consistent with a special mechanism for the alkaline hydrolysis of DPPC which involves the formation of an anion of the phosphorodiamidate as an intermediate in the hydrolysis. The possible formation of a monomeric metaphosphate intermediate from the anion is discussed.

In 1956, Heath[2] discovered that the rates of alkaline hydrolysis of phosphorodiamidic fluorides vary enormously with structure, and explained these variations in rate as the result of steric effects to which phosphoramides (and phosphoric esters[3]) are especially sensitive. However, since all of the phosphorodiamidic fluorides and pyrophosphoramides which react rapidly with alkali contain at least one amide hydrogen, one of us suggested[4] that the fast reactions proceed by way of an anion derived from the amidate:

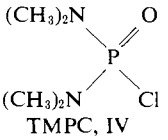


(1)

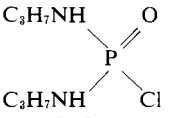
Here X represents a leaving group (*e.g.*, F), and III is an analog of the hypothetical monomeric metaphosphate ion,[5-15] PO_3^-. If III is formed, it would add water rapidly to yield a phosphorodiamidic acid similar to the ones isolated in this study. Considerable support

(1) Presented in part in the Abstracts of the 18th National Organic Chemistry Symposium of the American Chemical Society, Columbus, Ohio, June 1963, p. 53.
(2) D. F. Heath, *J. Chem. Soc.*, 3796, 3804 (1956).
(3) R. F. Hudson and L. Keay, *ibid.*, 1859 (1960).
(4) F. H. Westheimer, Special Publication No. 8, The Chemical Society, London, 1957, p. 181.
(5) I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 502 (1953).
(6) W. W. Butcher and F. H. Westheimer, *J. Am. Chem. Soc.*, 77, 2420 (1955).
(7) (a) H. K. Hall, Jr., *J. Org. Chem.*, **21**, 248 (1956); (b) H. K. Hall, Jr., and C. H. Lueck, *ibid.*, **28**, 2818 (1963).
(8) A. R. Todd, *Proc. Natl. Acad. Sci. U. S.*, **45**, 1389 (1959).
(9) M. Halmann, A. Lapidot, and D. Samuel, *J. Chem. Soc.*, 4672 (1960); A. Lapidot and M. Halmann, *ibid.*, 1713 (1959); M. Halmann and A. Lapidot, *ibid.*, 419 (1960); M. Halmann, A. Lapidot, and D. Samuel, *ibid.*, 3158 (1961).
(10) J. D. Chanley and E. Feageson, *J. Am. Chem. Soc.*, **80**, 2686 (1958); **85**, 1181 (1963).
(11) D. M. Brown and N. K. Hamer, *J. Chem. Soc.*, 1155 (1960); D. Samuel and B. Silver, *ibid.*, 4321 (1961).
(12) D. M. Brown, J. A. Flint, and N. K. Hamer, *ibid.*, 326 (1964).
(13) G. diSabato and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 4400 (1961).
(14) J. A. Maynard and J. M. Swan, *Proc. Chem. Soc.*, 61 (1963); *Australian J. Chem.*, **16**, 596, (1963).
(15) C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3574 (1958); C. Zioudrou, *Tetrahedron*, **18**, 197 (1962).

for this mechanism has previously been advanced,[16,17] especially in Crunden and Hudson's investigation[17b] of the solvolysis of N,N′-diethylphosphorodiamidic chloride (DEPC). The present independent study of the solvolysis of N,N,N′,N′-tetramethylphosphorodiamidic chloride (TMPC, IV) and of N,N′-dipropylphosphorodiamidic chloride (DPPC, V) is in agreement with most of the findings of Crunden and Hudson with DEPC, but in addition clearly differentiates specific hydroxide ion catalysis, nucleophilic catalysis, and general base catalysis, and so provides additional support for the mechanism of eq. 1. These new findings are presented here.



TMPC, IV



DPPC, V

Experimental

Materials. Dimethoxyethane (DME) from Eastman Distillation Products was refluxed for 10 hr. under nitrogen with lithium aluminum hydride, and then fractionated through a 1.7 × 24 cm. column packed with Podbielniak's Nichrome Heli-Pak 2917. The fraction boiling at 85.0–85.2° (762.2 mm.) was stored under nitrogen. Although when freshly distilled it gave no peroxide test[18] with $Fe(SCN)_2$, a positive test developed after 48 hr. in air. A second sample, which had been refluxed over calcium hydride, showed no peroxide with the starch–iodide test, but gave a positive test with $Fe(SCN)_2$, despite the fact that only a single peak could be detected on a vapor phase chromatogram with an Aerograph gas chromatographic instrument using a column packed with GE/SF/96 silicone on firebrick. Anhydrous dimethoxyethane from Arapahoe Chemicals contained 0.0011% pyrocatechol as inhibitor. Rates of hydrolysis of both DPPC and TMPC in 50% DME–water were independent of the source of the dimethoxyethane used. Furthermore, replacement of 5% of the DME with dioxane rich in peroxides had no detectable effect on the rate of hydrolysis of TMPC.[19] Solutions of sodium hydroxide in the solvent (50% DME–50% water) were prepared from inhibited DME and were quite stable. However, solutions of alkali prepared from purified but uninhibited DME rapidly lost in titer (*e.g.*, half in 24 hr.) on standing in air.

Anhydrous formic acid, dried from Eastman's White Label acid with phthalic anhydride, boiled at 33.0° (62 mm.) through the Helipak column mentioned above. Recrystallized imidazole melted at 89.5–90.0°. Pyridine, picoline, 2,4-lutidine, 3,5-lutidine, and 2,6-lutidine, previously purified in these laboratories,[20] showed in each case a single peak when subjected to v.p.c. with a Ucon-Polar column, No. 0037. Tetraethylammonium nitrate in aqueous solution was prepared from silver nitrate and tetraethylammonium bromide. Phenyl-N,N′-dimethylphosphorodiamidate was obtained from Dr. E. Blair of the Dow Chemical Co.; after recrystallization from toluene it melted[21] at 103–105°. Other chemicals were reagent grade, recrystallized or distilled to effect purification.

N,N,N′,N′-Tetramethylphosphorodiamidic chloride (TMPC) was obtained from the Victor Chemical Works, Division of Stauffer Chemical Co. Distillation through a 9-in., vacuum-jacketed Vigreux column yielded a water-white liquid, boiling at 80–81° (1.2 mm.). Its purity was established from the analysis for chloride after complete hydrolysis.

Anal. Calcd. for $C_4H_{12}ClNOP$: Cl, 20.78. Found: Cl, 20.79.

The compound[22] was stable when stored over phosphorus pentoxide at −10°. N,N′-Dipropylphosphorodiamidic chloride (DPPC) was synthesized as follows. A solution of 18.2 ml. of $POCl_3$ in 300 ml. of dichloromethane was cooled to −80° and stirred while 47.6 ml. of *n*-propylamine in 100 ml. of dichloromethane was added over a period of 2 hr. After several hours at −80°, the solution was allowed to warm to room temperature, then cooled to 0°, and extracted twice with ice–water. More dichloromethane was added as needed to keep the products in solution. The dichloromethane phase was dried over anhydrous sodium sulfate. Addition of ether and cooling to −80° under nitrogen caused crystallization. The crude product was recrystallized under nitrogen from dichloromethane–ether to yield 16.6 g. (48% of theory) of fluffy white needles, m.p. 104.2–104.8°.

Anal. Calcd. for $C_6H_{16}ClN_2OP$: C, 36.28; H, 8.12; Cl, 17.85; N, 14.10; P, 15.59. Found: C, 36.13; H, 8.08; Cl, 17.73; N, 13.40; P, 14.9.

The melting point was unchanged after storing for 1 year over phosphorus pentoxide at −10°. The compound had previously been prepared by Michaelis[23] by a similar method, but his melting point was 16° lower than that reported here. The n.m.r. spectrum (Varian A-60) shows an uneven triplet centered at τ 8.98 with J = 6.6 c.p.s., a sextuplet centered at τ 8.35 with J = 7.0 c.p.s., a pentuplet centered at τ 6.99 with J = 6.0 c.p.s., and a singlet at τ 5.80. The areas of these peaks have the ratios 3:2:2:1. This spectrum is entirely consistent with the structure assigned, provided that the hydrogen atoms on nitrogen are exchanging rapidly.

Products. Sodium N,N,N′,N′-tetramethylphosphorodiamidate was isolated as the product of hydrolysis of TMPC by the following procedure. TMPC (1.706 g.) was dissolved in 20 ml. of 1 *N* aqueous sodium hydroxide and allowed to stand at room temperature for 24 hr. Water was removed by rotary evaporation, and the organic product was extracted from residual sodium chloride with warm absolute ethanol. The ethanol in turn was removed by evaporation, giving an almost quantitative yield of product, which was then recrystallized from a large volume of isopropyl alcohol to give fine, fluffy white needles of the extremely hygroscopic sodium salt.

Anal. Calcd. for $C_4H_{12}N_2NaO_2P$: C, 27.59; H, 6.95; N, 16.09; P, 17.79. Found: C, 27.65; H, 6.72; N, 16.11; P, 17.50.

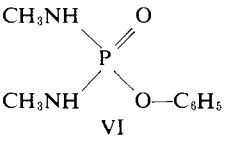
(16) D. Samuel and F. H. Westheimer, *Chem. Ind.* (London), 51 (1959).
(17) (a) E. W. Crunden and R. F. Hudson, *ibid.*, 1478 (1958); (b) E. W. Crunden and R. F. Hudson, *J. Chem. Soc.*, 3591 (1962).
(18) F. Feigl, "Spot Tests in Organic Analysis," Elsevier Publishing Co., Amsterdam, 1956, p. 474.
(19) An effect of peroxide on an hydrolysis rate has been observed in at least one case: see M. L. Bender and B. Turnquest, *J. Am. Chem. Soc.*, 79, 1655 (1957).
(20) F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1773 (1963).
(21) L. F. Audrieth, *ibid.*, **64**, 1337 (1942).
(22) H. Tolksmith, *ibid.*, **75**, 5270 (1953).
(23) A. Michaelis, *Ann.*, **326**, 175 (1903).

N,N′-Dipropylphosphorodiamidic acid was isolated as the product in the hydrolysis of DPPC under several experimental conditions. In one experiment, a 50% DME–water solution containing 0.001 mole of DPPC and 0.001 mole of lithium hydroxide was allowed to stand at room temperature for approximately 4.5 hr. The solvent was removed by rotary evaporation, and the white crystalline residue was recrystallized from acetone in the form of plates melting at 135.0–135.5°.

Anal. Calcd. for $C_6H_{17}N_2O_2P$: C, 39.99; H, 9.51; N, 15.55; P, 17.19. Found: C, 39.75; H, 9.23; N, 15.40; P, 16.9.

Methods. pH was measured with a Radiometer Model TTT-1 automatic titrator equipped with a Type PHA630Ta scale expander. For measurements in 50% DME–water, the meter was standardized against carefully prepared 0.001 *N* hydrochloric acid in 50% DME–water, which was defined as having a "pH" of 3.00. The hydrolyses of TMPC and DPPC were followed by three different methods. (a) Conductivity: An Industrial Instruments Inc. Model RC 16B1 conductivity bridge was used with a cell of cell-constant approximately unity. About 40 points were used for each rate constant. (b) pH-stat: The "pH" of reacting solutions in 50% DME–water was kept constant to 0.01 pH unit by addition from the automatic titrator of standard sodium hydroxide in 50% DME–water. The total volume added was less than 3% of that of the reacting solution. Since the rate of hydrolysis of DPPC is extremely sensitive to hydroxide ion, the method of mixing was found to be critical. First-order kinetics were obtained when the solution was vigorously agitated with a Vibro Mixer. When the pH was above 7, the titrations were conducted under nitrogen. A typical rate experiment consisted of about 40 points to 80–85% reaction. (c) Titration for chloride ion: Seven to 14 samples were withdrawn from a reaction mixture during each experiment, and the samples were quenched by delivery into cold (−10°) DME containing enough nitric acid to acidify the sample. Crushed Dry Ice was added directly to the sample to freeze the water out of the solution, and more Dry Ice was added if needed to maintain this state until the sample could be titrated. The titrations were conducted at 0° to a potentiometric end point using a Beckman Model G pH meter and, as electrodes, a bare silver wire and a saturated calomel reference half-cell. End points, determined analytically,[24] were stable. After 10–12 half-lives, the chloride ion concentration so determined agreed with that expected from the initial weight of sample usually to within 1%.

H Exchange. The n.m.r. spectrum of phenyl N,N′-dimethylphosphorodiamidate (VI) in dimethyl-d_6 sulfoxide shows (in addition to a peak for phenyl protons) a quartet centered at τ 7.53 and a broad multiplet centered at 5.37. The first of these peaks can be assigned to the hydrogens of the methyl groups, split both by ^{31}P and by the hydrogen atom on the amide nitrogen atom; the second peak may be assigned to the amide hydrogen itself. When 0.1 ml. of D_2O was added to 0.3 ml. of this solution, the methyl group appears as a doublet centered at τ 7.43, and a new sharp



VI

singlet appears at 5.70; the broad multiplet, assigned to the N–H protons, completely disappears. Therefore, the amide hydrogens exchange rapidly, even in neutral solution, with those in water. The exchange was complete by the time (30 sec.) the first measurement could be obtained.

Unsuccessful Attempts to Trap the Postulated Monomeric Metaphosphate. The postulated metaphosphate derivative, III, could in principle react with nucleophiles such as F^-, N_3^-, or imidazole. However, in alkaline solution, the fluoride was shown to be too unstable to be found. Experiments designed to detect the reaction of III with imidazole were unsuccessful.

Results

The rates of hydrolysis of TMPC in water, of TMPC in 50% DME–water, and of DPPC in 50% DME–water, in the presence of various salts and nucleophiles, are shown in Tables I, II, and III. The rates of hydrolysis of DPPC in alkaline solutions are presented in Table IV.

Table I. Rates of Hydrolysis of Tetramethylphosphorodiamidic Chloride in Water at 10°

Method	TMPC, *M*	Added reagent	Concn., *M*	$k \times 10^4$, sec.$^{-1}$
Cond.	0.01			18.2
Cond.	0.0025			18.1
Chloride	0.0157			18.0 ± 0.6
Chloride	0.0157	$NaClO_4$	0.500	19.2
Chloride	0.0157	$NaNO_3$	0.500	19.3
Chloride	0.0157	Et_4NNO_3	0.40	18.0
Chloride	0.0157	Na_2SO_4	0.167	21.4
Chloride	0.0157	Na_2SO_4	0.500	25.7
Chloride	0.0157	Li_2SO_4	0.167	20.8
Chloride	0.0157	Li_2SO_4	0.500	24.1
Chloride	0.00704	NaN_3	0.050	19.4[a]
Chloride	0.00704	NaN_3	0.100	20.8[a]
Chloride	0.0157	NaN_3	0.150	21.8[a]
Chloride	0.0157	NaN_3	0.200	22.7[a]
Chloride	0.0157	NaF	0.100	20.5[a]
Chloride	0.0157	NaF	0.200	22.4[a]
Chloride	0.0157	NaF	0.300	24.5[a]
Chloride	0.0157	NaF	0.400	27.0[a]
Chloride	0.0157	NaF	0.500	29.4
Chloride	0.0157	NaOH	0.100	21.0[a]
Chloride	0.0157	NaOH	0.200	23.4[a]
Chloride	0.0157	NaOH	0.300	26.5[a]
Chloride	0.0157	NaOH	0.400	29.3[a]
Chloride	0.0157	NaOH	0.500	32.3
Chloride	0.0157	Pyridine	0.500	32.6
Chloride	0.0157	Imidazole	0.300	21.9
		Imidazole·$HClO_4$	0.500	
Chloride	0.0157	2,6-Lutidine	0.500	12.2
Chloride	0.0157	DME	0.546	15.1
Cond.	0.01	D_2O as solvent		13.6[b]
Chloride	0.0157	D_2O as solvent		13.4[b]

[a] Ionic strength maintained at 0.500 by addition of $NaClO_4$. [b] Average value of $k_{H_2O}/k_{D_2O} = 1.34$.

Salt Effects. The data in Tables I, II, and III show that the salt effects for the first-order hydrolysis of both TMPC and DPPC are small. Neither perchlorates

(24) J. J. Lingane, "Electroanalytical Chemistry," 2nd Ed., Interscience Publishers, Inc., New York, N. Y. 1958, pp. 93, 94.

Table II. Hydrolysis of Tetramethylphosphorodiamidic Chloride in 50% DME–Water at 30°

Method	TMPC, M	Added reagent	Concn., M	Added salt, etc.	Concn., M	$k \times 10^4$ sec.$^{-1}$
Cond.	0.008					10.3
Cond.	0.016					10.7
Cond.	0.01					10.2 ± 0.2
Cond.	0.01	Peroxides[a]				9.87
pH-stat	0.001					9.60
Chloride	0.0157					10.3
Chloride	0.0451					9.75
Chloride	0.0157			$NaClO_4$	0.200	10.9
Chloride	0.0451			$NaClO_4$	0.200	9.74
Chloride	0.00704			$NaClO_4$	0.250	9.78 ± 0.08
Chloride	0.00704			Na_2SO_4	0.047	9.64
Chloride	0.0157			Li_2SO_4	0.167	9.38
Chloride	0.0157			$NaNO_3$	0.500	11.0
Chloride	0.00704			Et_4NNO_3	0.20	9.26
Chloride	0.0157	KF	0.250			24.3
Chloride	0.0157	KF	0.500	HNO_3	0.250	17.1
Chloride	0.0157	KF	0.500	HNO_3	0.149	24.6
Chloride	0.0157	NaN_3	0.200	$NaClO_4$	0.300	16.8
Chloride	0.00704	NaOH	0.050	$NaClO_4$	0.200	13.6
Chloride	0.00704	NaOH	0.100	$NaClO_4$	0.150	17.2
Chloride	0.00704	NaOH	0.150	$NaClO_4$	0.100	20.7
Chloride	0.00704	NaOH	0.200	$NaClO_4$	0.050	25.0
Chloride	0.00704	NaOH	0.250			28.7
Chloride	0.0157			Pyridine·$HClO_4$	0.500	9.07
Chloride	0.0157	Pyridine	0.500	Pyridine·$HClO_4$	0.500	28.0
Chloride	0.0157	2,4-Lutidine	0.500	2,4-Lutidine·$HClO_4$	0.500	9.40
Chloride	0.0157	2,6-Lutidine	0.500			7.66
Chloride	0.0157	2,6-Lutidine	0.500	2,6-Lutidine·$HClO_4$	0.500	7.16
Chloride	0.0157	50% DME–50% D_2O as solvent				7.50[b]
Cond.	0.01	50% DME–50% D_2O as solvent				8.08[b]

[a] Solvent was 45% DME–5% dioxane (containing peroxides)–50% water. [b] Average value of $k_{H_2O}/k_{D_2O} = 1.30$.

Table III. Rates of Hydrolysis of Dipropylphosphorodiamidic Chloride in 50% DME–Water at 30°

Method	DPPC, M	Added reagent	Concn., M	Added salt, etc.	Concn., M	$k \times 10^4$, sec.$^{-1}$
pH-stat[a]	0.0008					3.51
pH-stat[b]	0.006					3.45
Chloride	0.00446					3.45
Chloride	0.020					3.36
Chloride	0.03					3.26
Chloride	0.0508					3.40
Chloride	0.0200			$NaClO_4$	0.100	3.45
Chloride	0.0200			$NaClO_4$	0.500	3.56
Chloride	0.0200	NaN_3	0.100			4.26
Chloride	0.0200	NaN_3	0.150	$NaClO_4$	0.050	4.14
Chloride	0.0150	KF	0.500	HNO_3	0.149	68.7
Chloride	0.020			Pyridine·$HClO_4$	0.500	3.05
Chloride	0.00995	Pyridine	0.100	Pyridine·$HClO_4$	0.500	6.80
Chloride	0.0200	Pyridine	0.200	Pyridine·$HClO_4$	0.500	14.9
Chloride	0.0200	Pyridine	0.300	Pyridine·$HClO_4$	0.500	18.4
Chloride	0.0200	Pyridine	0.400	Pyridine·$HClO_4$	0.500	21.6
Chloride	0.0200	Pyridine	0.500	Pyridine·$HClO_4$	0.500	22.6
Chloride	0.0200	4-Picoline	0.300	4-Picoline·$HClO_4$	0.500	18.1
Chloride	0.0200	4-Picoline	0.500	4-Picoline·$HClO_4$	0.500	27.4
Chloride	0.00994	Imidazole	0.250	Imidazole·$HClO_4$	0.500	14.1
Chloride	0.0200	3,5-Lutidine	0.300	3,5-Lutidine·$HClO_4$	0.500	13.6
Chloride	0.0200	3,5-Lutidine	0.400	3,5-Lutidine·$HClO_4$	0.500	16.9
Chloride	0.0200	3,5-Lutidine	0.500	3,5-Lutidine·$HClO_4$	0.500	20.8
Chloride	0.0200	2,4-Lutidine	0.500	2,4-Lutidine·$HClO_4$	0.500	3.15
Chloride	0.0200	2,6-Lutidine	0.050	2,6-Lutidine·$HClO_4$	0.500	3.01
Chloride	0.0200	2,6-Lutidine	0.500	2,6-Lutidine·$HClO_4$	0.500	2.62
Chloride	0.0200	50% DME–50% D_2O as solvent				2.39[c]
Cond.	0.0050	50% DME–50% D_2O as solvent				2.54[c]

[a] "pH" held constant at 3.80 ± 0.02. [b] "pH" held constant at 4.10 ± 0.01. [c] Average value of $k_{H_2O}/k_{D_2O} = 1.38$.

Table IV. Hydrolysis of Dipropylphosphorodiamidic Chloride in Alkaline Solutions of 50% DME[a]–Water at 30°[b]

DPPC, M	"pH"	$(OH^-) \times 10^9$, M[c]	$k \times 10^4$, sec.$^{-1}$
0.00040	7.05	5.13	4.87
0.00031	7.15	6.45	5.46
0.00049	7.45	12.9	7.11
0.00029	7.60	18.2	8.59
0.00029	7.65	20.4	9.41
0.00029	7.80	28.8	11.9

[a] Inhibited DME. [b] Rates followed by automatic titration with sodium hydroxide. [c] Based on $pK_w = 15.34$.

nor nitrates affect the rates very much; sodium sulfate somewhat increases the rate of hydrolysis of TMPC in water, but not in the mixed solvent.

Solvent Effects. The rate of solvolysis of TMPC is sharply diminished by the addition of dimethoxyethane to water. The rate falls by a factor of more than two powers of ten as the concentration of DME is increased from 0 to 80%. Our detailed quantitative data,[25] obtained at several temperatures, are more or less paralleled by the four points published for DEPC by Crunden and Hudson,[17] and our data show that the logarithm of the rate constant is not linear in the Grunwald–Winstein[26] "Y" value.

The depressing effect of nonpolar compounds is also shown in the tables. In particular, the rates of hydrolysis of both TMPC and of DPPC are diminished by about 25% by 2,6-lutidine in the presence of 2,6-lutidinium ion. The relationship of these results to those of Crunden and Hudson is examined in the Discussion.

Nucleophiles. The rate data in the tables show that nucleophiles react with both TMPC and DPPC. The data for the attack of pyridine bases on DPPC are shown in Figure 1. The solvent effect of such bases depresses the rate (as is shown by the effects of the sterically hindered bases) while the salt effects are negligible; the acceleration must then be due to catalysis by the basic molecules themselves. Such catalysis could arise either by nucleophilic attack of the base on the phosphorus atom of the phosphorodiamidic chloride or, alternatively, by general base catalysis in which the base attacks a water molecule in the rate-limiting step to produce an incipient hydroxide ion which in turn attacks at phosphorus. Examples have been established for both types of catalysis in the solvolysis of phosphates.[1,20,27,28] Although steric effects are the rule in general base catalyzed reactions[1,20] as well as in nucleophilic catalysis, the effects which have so far been noted for general base catalysis are considerably smaller than those here reported. In particular, 2,4-lutidine would be expected[20] to be a good general basic catalyst. Since it shows no catalytic effect with DPPC, the successful reactions of pyridine bases with TMPC and DPPC are presumably nucleophilic in character. These results accord with the generalization offered by Kirsch and Jencks[29] to the

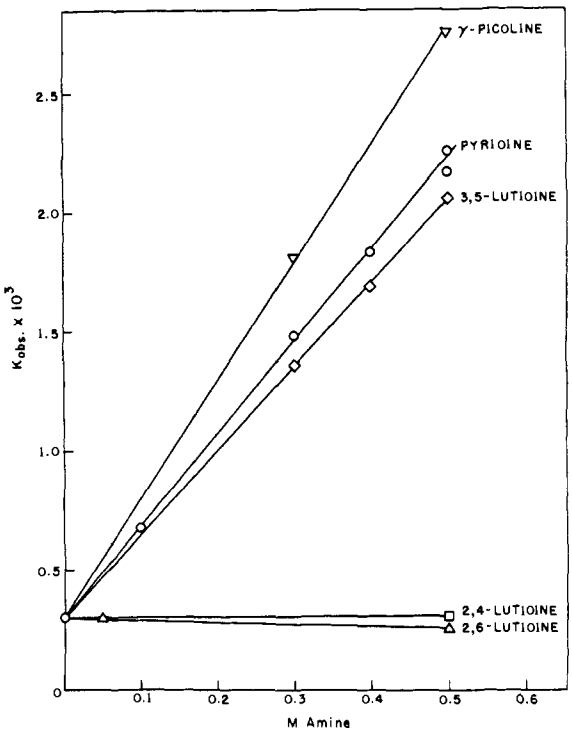


Figure 1. Rate constants for the hydrolysis of N,N′-dipropylphosphorodiamidic chloride in 50% DME–water as a function of the concentrations of tertiary amines.

effect that nucleophilic catalysis predominates with relatively good leaving groups (here the chloride ion), whereas general base catalysis predominates with relatively poor leaving groups (as in the case of the catalyzed solvolysis of methyl ethylenephosphate).[20]

A further demonstration of nucleophilic catalysis has been obtained from the reaction of TMPC with 0.5 M NaF or with 0.2 M NaN_3. In both cases, the reactions were allowed to proceed for 10 half-lives (rates determined by titration for the chloride ion produced), and then titrated for hydrogen ion. If only hydrolysis had occurred, 2 moles of acid would have been produced for each mole of TMPC consumed or chloride ion formed. However, nucleophilic reaction would lead to a neutral product, and (provided that the product did not itself hydrolyze rapidly) would produce no acid. The deficit for acid produced by the attack of F^- was 40%, that by N_3^- was 27%. These represent minimum values for nucleophilic attack, since of course the products will undergo partial solvolysis. These data reinforce those of Samuel and Westheimer.[16]

The effect of fluoride ion as a nucleophile is complicated by the formation of the HF_2^- ion. The equilibrium constant for the formation of HF_2^- in 50% DME–water was estimated from kinetics in the presence of HNO_3, and the true rate constant for nucleophilic attack by F^- calculated.[25]

Hydroxide Ion. The effect of hydroxide ion in accelerating the hydrolysis of TMPC in water is small,[30] and could perhaps be attributed to a specific salt effect. However, in 50% DME–water, the increase in rate is considerable. Since the nonnucleophilic salts

(25) P. S. Traylor, Thesis, Harvard University, 1963.
(26) E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, **70**, 846 (1948); A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2770 (1956).
(27) G. O. Dudek and F. H. Westheimer, *ibid.*, **81**, 2641 (1959).
(28) R. Blakeley, Thesis, Harvard University, 1964.
(29) J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, **86**, 837 (1964).

(30) H. K. Hall, Jr.,[7a] detected no effect of hydroxide ion on this hydrolysis in dilute aqueous solutions of alkali.

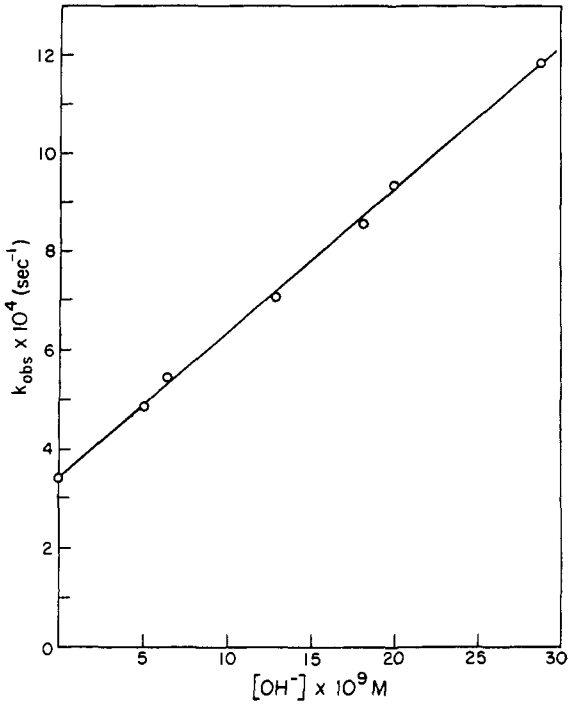


Figure 2. Rate constants for the hydrolysis of N,N'-dipropylphosphorodiamidic chloride in 50% DME–water as a function of the concentration of hydroxide ion.

tested—sodium perchlorate, lithium sulfate, sodium nitrate, and tetraethylammonium nitrate—were essentially without effect upon the rate in the mixed solvent, the most reasonable inference from the data is that hydroxide ion attacks TMPC as a nucleophile.

The effect of hydroxide ion on DPPC is of an entirely different order. The rates with high concentration of alkali are too fast to measure by conventional techniques, so the data were obtained with solutions maintained at slight alkalinity by the automatic titrator. The second-order rate constant computed from the data in Table IV and from the slope of Figure 2 depends critically on the value chosen for K_w, the ion product of water in 50% DME–water. In order to determine the hydroxide ion concentration which corresponds to a given reading of the glass electrode, the "pH" of carefully prepared solutions of 0.00100 *M* NaOH and of 0.00100 *M* KOH were measured. Deionized boiled water and degassed inhibited DME were used for the measurements at −30°. The "pH" rose gradually to a maximum, and then fell over a period of 12 hr., the latter effect presumably because of absorption of CO_2. The maximum value of the "pH" recorded for both bases was 12.34 ± 0.01. From the observations "pK_w" is 15.34, and K_w is 4.6×10^{-16}. This value is larger than that of 2.594×10^{-16} obtained by Harned and Fallon[31] for the ion product of 45% dioxane–water at 30°. Without doubt the largest uncertainty in the determination of the rate constant for the reaction promoted by hydroxide ion arises because of the uncertainty in the value of K_w. If in fact the value here determined is somewhat too large (as suggested by the data of Harned and Fallon[31]), then the concentrations of hydroxide ion present in the solutions are less than those calculated, and the true second-order rate constant for the reaction of OH^- with DPPC is even greater than that here reported. The ratio of the rate constant of DPPC to that of TMPC then has a minimum value of 4 million.

(31) H. S. Harned and L. D. Fallon, *J. Am. Chem. Soc.*, 61, 2374 (1939).

Discussion

The most important feature of the data here presented is the large effect of hydroxide ion in promoting the hydrolysis of dipropylphosphorodiamidic chloride, as contrasted to its relatively small effect on the hydrolysis of tetramethylphosphorodiamidic chloride. The data are summarized in Table V; as pointed out above, the rate factor is at least 4 million.

The extraordinary reactivity of DPPC cannot be caused merely by smaller steric effects for the attack of hydroxide ion on this compound as compared to TMPC, since the rates of attack by F^-, by N_3^-, by pyridine, and by imidazole are comparable for the two compounds and both compounds are sensitive to the steric effect of a methyl substituent in the α-position of the pyridine ring. The large difference in rate for TMPC and DPPC must then be produced by a difference in mechanism.

The special mechanism for DPPC is presumably that of eq. 1. The hydrogen atoms attached to nitrogen in the amidates are quite labile, as demonstrated by the n.m.r. experiments on the rapid exchange between the protons of phenyl-N,N'-dimethylphosphorodiamidate and D_2O in DMSO as solvent. Therefore, the formation of the anion in rapid equilibrium with DPPC and hydroxide ion is entirely reasonable.

Application of the usual concepts of physical organic chemistry suggests that the negative charge on the anion, II, will greatly accelerate its first-order decomposition to a derivative of monomeric metaphosphate, as shown in eq. 1. By contrast, a nucleophile—even an uncharged nucleophile such as water—will presumably attack the anion II less rapidly than it would attack the electrically neutral species DPPC. On this basis, the data here presented support eq. 1. However, attempts to trap the monomeric metaphosphate failed, and success with trapping in other cases[11,13] can be explained away, although some of the explanations are a bit elaborate. (The lack of success in trapping can of course be explained by the extraordinary reactivity of monomeric metaphosphates toward water; after all, they are isoelectronic with SO_3.) The argument[4] in favor of eq. 1 is not uniformly accepted. For example, in an analogous case Maynard and Swan[14] prefer to describe the decompositions[32] of the dianion of halophosphonates as an attack of water on the phosphonate dianion, rather than as a

$$RCHX{-}CH_2{-}PO_3^{2-} + H_2O \longrightarrow RCH{=}CH_2 + X^- + H_2PO_4^-$$

fragmentation of the di-ion to form monomeric metaphosphate. But at least this rule can be formulated: Those decompositions of phosphates, phosphonates, etc., will occur wherever a reasonable reaction can be predicted on the basis of the hypothesis that monomeric metaphosphates can function as intermediates.

Prior results, although generally consistent with those here reported, provide some discrepancies which must be mentioned. Crunden and Hudson[17] report

(32) J. B. Conant and B. B. Coyne, *ibid.*, 44, 2530 (1922).

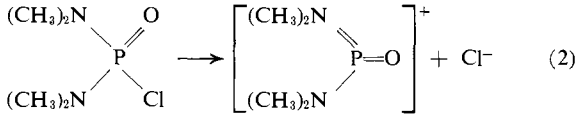
Table V. Second-Order Rate Constants for the Reactions of Tetramethylphosphorodiamidic Chloride and of Dipropylphosphorodiamidic Chloride

Reagent	$k_2 \times 10^3$, M^{-1} sec.$^{-1}$ — TMPC in 50% H_2O[a]	TMPC in 50% DME[b]	DPPC in 50% DME[b]	Ratio in 50% DME
NaOH	2.8	7.6	$\geq 3 \times 10^7$	$\geq 4 \times 10^6$
NaF	2.3	5.7[c]	26[c]	4.5
NaN_3	2.6	3.3	0.87	0.26
Pyridine	4.1	4.2	3.9	.93
3,5-Lutidine			3.6	
4-Picoline			5.0	
Imidazole	4.8		4.6	
p-Toluidine			0.25	
2,4-Lutidine		0.00	0.00	
2,6-Lutidine		0.00	0.00	

[a] 10°. [b] 30°. [c] KF was used in 50% DME–water since NaF is too insoluble.

that 2,6-lutidine increases the rate of hydrolysis of N,N′-diethylphosphorodiamidic chloride. They favor the mechanism advanced here and earlier,[4] and state that this mechanism "explains the catalytic effect of lutidine, or of hydroxide ions in equilibrium with it." The results shown here for DPPC, where 2,6-lutidine in the presence of 2,6-lutidinium ion shows no catalytic effect, suggest that the hydroxide ions must have been responsible for the accelerations they observed. However, one would not then anticipate simple kinetics, since the lutidinium ion formed as a product of the solvolysis should have buffered the solution and caused marked curvature in the plots used for the determination of rate constants. The rate with alkali reported by Samuel and Westheimer for the dimethyl analog of DPPC in water, although large, is much smaller than that found here.

Water. The first-order hydrolysis of TMPC and of DPPC might occur by nucleophilic attack of water molecules on the phosphoroamidate, or with the formation of a pentacovalent intermediate, followed by subsequent decomposition, or by way of a reaction of the SN1 type (eq. 2), followed by rapid hydrolysis of the postulated monomeric metaphosphate[7] cation.



(2)

Crunden and Hudson argued in favor of nucleophilic attack by water molecules since the solvolyses of DEPC and similar compounds are much slower in anhydrous formic acid than in mixed solvents of the same "*Y*" value.[33] Although the slower rate in anhydrous formic acid (TMPC solvolyzes only $^1/_{150}$ as fast in formic acid as in 40% DME–water)[25] might have been caused by protonation of the amide,[34] our experiments show that the initial conductivity of anhydrous formic acid is not increased by TMPC by an amount anywhere near enough to support this explanation. The lack of a positive neutral salt effect also suggests that the reactions with water are displacements.

Hall has argued that the reaction of TMPC with water is an ionization. His extensive and interesting data[7] show that nucleophiles can attack TMPC even in water, but that the range of nucleophilic reactivity toward the phosphorodiamidic chloride is extraordinarily compressed. This can be interpreted by saying that a great deal of bond loosening has occurred in the transition state. Similar mechanistic ambiguity[35] has plagued the interpretation of the solvolysis of alkyl halides. The present evidence and that of Crunden and Hudson[17] suggest that water behaves like other nucleophiles in the attack on TMPC in water as solvent, where in all cases the P–Cl bond is nearly broken in the transition state.[36]

The reaction of DPPC and its analogs with hydroxide ion must proceed by a special mechanism which may involve a derivative of monomeric metaphosphate.

Acknowledgment. The work herein was sponsored by the National Science Foundation under Grant G15819. One of us (P. S. T.) gratefully acknowledges the receipt of predoctoral fellowships for the years 1959–1962 from the National Institutes of Health.

(33) Crunden and Hudson's experiment refers to "65% aqueous $COMe_2$". Presumably this means 35% acetone and 65% water, which has an interpolated "*Y*" value of 2.28, not far from the value of 2.054 for formic acid. They did not measure the rates of hydrolysis of TMPC or DEPC in this solvent, but "extrapolated by using the Grunwald–Winstein equation."

(34) We are indebted to Professor S. Winstein for suggesting this possibility.

(35) E. R. Thornton, "Solvolysis Mechanisms," The Ronald Press, New York, N. Y., 1964, p. 95 ff.

(36) Our earlier conclusion[16] that TMPC reacts by a displacement mechanism with water was based on an analogy with the displacement reaction of TMPC with azide ion. Such analogies are always questionable, and one of us admitted to Hall[7] that we had "overreached our evidence". Now the data comparing rates of solvolysis of TMPC in formic acid and DME–water mixtures should go far to making the situation plain, although a simple name appropriate to the type of transition state is perhaps still lacking.