chloric acid revealed that the material was a mixture containing approximately 80% of *m*-chlorophenylphosphonic acid (m.p. 136°), which had been described previously,[4] while the remainder was the previously undescribed *m*-fluorophenylphosphonic acid, m.p. 129–130°, which was somewhat more soluble than the chloro analog. In view of the difficulties involved in the separation of mixtures of phosphonic acids with similar solubilities, the actual yield of the fluoro derivatives is uncertain, but appears to have been less than 10% (based on the original diamine). The yield of the above-described mixture of the chloro and fluoro acids was 45%. An authentic specimen of the fluoro derivatives was prepared in the usual manner[5] in 18% yield. This was found to be identical with the specimen obtained from the bis-diazonium salt.

Anal. Calcd. for $C_6H_6O_3PF$: P, 17.59; neut. equiv., 88. Found: P, 17.4, 17.5; neut. equiv., 87.88.

Curiously, the individual halophenylphosphonic acids are not hygroscopic, in contrast to the behavior of their mixture.

The filtrate obtained after the separation of the acid mixture, described above, was evaporated to a small volume, but the residual phosphorous acid prevented any further crystallization. This contaminant was removed as follows. The solution was treated with 30% hydrogen peroxide, added dropwise, until the oxidation was complete. The solution was then dehydrated by means of benzene azeotrope and the dry residue was treated with phosphorus pentachloride until no further reaction was evident. Distillation of the mixture yielded some unreacted phosphorus pentachloride, phosphorus oxychloride (removed under reduced pressure on a steam-bath) and a viscous residue weighing less than 0.5 g. After recrystallization of the latter from dilute hydrochloric acid there was obtained a small amount of a solid which was devoid of phosphorus. Thus, no indication of formation of a diphosphonic acid was obtained.

Reaction of *p*-Phenylene-bis-diazonium Fluoborate.—The preparation of the diazonium salt followed that described previously.[6] The yield of the yellow fluoborate was 78% and the material decomposed at 196°. This salt (19.8 g.) was allowed to react with 17.6 ml. of phosphorus trichloride, precisely as described above. The same treatment of the reaction mixture gave a crop of colorless needles, which showed a neutralization equivalent and a titration curve that were very close to those of *p*-fluorophenylphosphonic acid. However, this material failed to melt at 300° and contained a small amount of a sodium salt. Therefore the material was taken up in water and the solution was passed through a column of Dowex-50 ion-exchange resin on the hydrogen cycle and the solution was evaporated, yielding colorless plates which melted at 177–183°. Several recrystallizations of the material from concentrated hydrochloric acid gave a 10% yield (on fluoborate) of pure *p*-chlorophenylphosphonic acid, m.p. 188°, while the mother liquor gave a very small amount (about 0.1 g.) of *p*-fluorophenylphosphonic acid, m.p. 126–127°; this was reported previously with m.p. 125–127°.[5] The residual solution was treated as described for the *m*-isomer; the result was again negative.

Since the melting points of the *p*- and the *o*-chlorophenylphosphonic acids are rather close to each other, the identification of the above-described specimen of the *p*-isomer was performed both by a mixed melting point with an authentic *p*-chlorophenylphosphonic acid specimen, and by a mixed melting point with a specimen of the *o*-isomer, prepared conventionally from the fluoborate.[1] This specimen melted at 186.5–188° (somewhat above the previously reported 182–184°,[1] and gave a definite depression of melting point on mixing with the *p*-isomer or with the specimen prepared from the bis-diazonium salt.

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[4] G. M. Kosolapoff, THIS JOURNAL, **70**, 3465 (1948).

[5] R. W. Bost, L. D. Quin and A. Roe, *J. Org. Chem.*, **18**, 362 (1953).

[6] P. Ruggli and E. Caspar, *Helv. Chim. Acta*, **18**, 1416 (1935).

AUBURN, ALABAMA

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

The Lanthanum Hydroxide Gel Promoted Hydrolysis of Phosphate Esters

BY W. W. BUTCHER AND F. H. WESTHEIMER

RECEIVED NOVEMBER 22, 1954

Lanthanum hydroxide gel promotes the hydrolysis of methoxyethyl phosphate, of hydroxyethyl phosphate and of aminoethyl phosphate at *p*H 8.5 and 78°. 1-Methoxy-2-propyl phosphate is hydrolyzed at *p*H 4, or by $La(OH)_3$ at *p*H 8.5, with complete retention of stereochemical configuration and with cleavage of the P–O bond. In 1.8 *M* sulfuric acid, the hydrolysis is accompanied by extensive racemization. The mechanisms of these reactions are discussed.

E. Bamann[1] discovered that the hydroxides of lanthanum, cerium, thorium, etc., promote the hydrolysis of α-glyceryl phosphate (equation 1) in the region from *p*H 7–10, and suggested that the reaction serves as a model[2] for the metal-ion promoted alkaline phosphatases.[3] The present research was undertaken to elucidate further this metal-ion promoted hydrolysis.

$$\mathrm{HOCH_2CHOHCH_2OPO_3^{=}} + \mathrm{La(OH)_3} \longrightarrow \mathrm{HOCH_2CHOHCH_2OH} + \mathrm{LaPO_4} + 2\mathrm{OH^-} \quad (1)$$

Bailly[4] and Desjobert[5] have shown that (in the absence of heavy metal ions) a monoester of phosphoric acid is stable to alkali, and is moderately stable at a *p*H of 1 or 2, but it is readily hydrolyzed at *p*H 4 or in strong acid solution. (The region around *p*H 4 corresponds to a maximum in the concentration of the monoanion, $ROPO_3H^-$; see Fig. 1.) In view of these findings, the rate of hydrolysis of 1-methoxypropyl-2 phosphate was determined over a wide range of acidity, in the presence and in the absence of lanthanum hydroxide gel. The point of cleavage was determined by stereochemical and by O^{18} tracer experiments. Several other esters were tested with lanthanum hydroxide gel to determine the structural requirements for the metal-ion catalysis. A mechanism for the hydrolysis of phosphate esters, based on the new data is here advanced.

Experimental

Materials. Barium Ethyl Phosphate.—Phosphorous oxychloride (0.2 mole) and water (0.2 mole) were mixed in a

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[1] E. Bamann and M. Meisenheimer, *Ber.*, **71**, 1711 (1938); E. Bamann, *Angew. Chem.*, **52**, 186 (1939); E. Bamann and E. Nowotny, *Ber.*, **81**, 451, 455, 463 (1948); E. Bamann, E. Nowotny and E. Henmüller, *Arch. Pharm.*, **283**, 4 (1950); E. Bamann, F. Fischler and H. Trapmann, *Biochem. Z.*, **325**, 413 (1951).

[2] *Cf.* F. H. Westheimer, Abstracts of Papers, 120th Meeting, Am. Chem. Soc., N. Y., 1951, p. 7P.

[3] See A. Lehninger, *Physiol. Rev.*, **30**, 393 (1950).

[4] M. C. Bailly, *Bull. soc. chim.*, [5] **9**, 421 (1942).

[5] A. Desjobert, *Compt. Rend.*, **224**, 575 (1947); *Bull. soc. chim.*, [5] **14**, 809 (1947).

flask cooled by an ice-bath.[6,7] When the initial reaction was over, the flask was allowed to stand at room temperature for 12 hours. The mixture was again cooled to 0°, and 0.2 mole of ethanol added. After two hours, the hydrogen chloride was pumped from the reaction mixture, which was then diluted with 100 cc. of water and neutralized with hot saturated barium hydroxide. The barium phosphate was removed by centrifugation and the aqueous solution concentrated on the steam-bath until barium ethyl phosphate began to precipitate. The solution was cooled and diluted with an equal volume of ethanol. The product which separated was recrystallized from water-ethanol and dried at 110°.

Most of the phosphate esters used in this work were prepared in a similar manner from the corresponding alcohols. Since these salts have no melting points, they were identified by analysis; the data appear in Table I.

Barium 2-hydroxyethyl phosphate was prepared according to Atherton, Openshaw and Todd,[8] aminoethyl phosphate (m.p. 237°, lit. 238°) and its barium salt according to Outhouse[7] and the barium salt of choline phosphate according to Baer.[9]

TABLE I

ANALYSES OF PHOSPHATE ESTERS

Ester	Barium, % Calcd.	Barium, % Found	Phosphorus % Calcd.	Phosphorus % Found
Ethyl[10]	52.5	52.8	11.9	11.7
2-Propyl[11]	49.5	50.1	11.2	11.2
Hydroxyethyl[8]	49.5	49.9	11.2	11.0
2-Methoxyethyl[12]	47.1	47.3	10.7	10.6
Aminoethyl[7]	49.7	49.9	11.2	11.1
Choline[9]	38.7	39.0	8.7	8.3

Barium 2-methoxypropyl-1-phosphate was prepared according to the procedure outlined for ethyl phosphate. In order to remove barium chloride (which has solubility properties similar to those of the barium salt of this ester), the mixture of salts was triturated with water and silver oxide and filtered. The filtrate was brought to the phenolphthalein end-point with carbon dioxide, filtered again, and the barium salt of the ester precipitated with two volumes of ethanol for each volume of water. The yield was about 20%.

Anal. Calcd. for $C_4H_9O_5PBa \cdot H_2O$: Ba, 42.5; P, 9.6; C, 14.8; H, 3.4; H_2O, 5.6. Found: Ba, 42.7; P, 9.5; C, 14.8; H, 3.4; H_2O, 5.6.

Barium 1-Methoxypropyl-2-Phosphate.—The sodium salt of 1-methoxypropanol-2 was prepared from 0.2 mole of the alcohol and excess sodium metal in 250 cc. of dry ether. The solution of the sodium alkoxide in ether was separated from excess sodium, and added, drop by drop over a period of three hours, to a stirred mixture of 0.2 mole of $POCl_3$ in 250 cc. of dry ether at 0°. The ether was evaporated; the residue was dissolved in 100 cc. of water and neutralized with barium hydroxide. The salt was separated from barium phosphate and from barium chloride, and then isolated by the method outlined above for the salt of 2-methoxypropyl-1-phosphate; yield about 40%.

Anal. Calcd. for $C_4H_9O_5PBa \cdot H_2O$: Ba, 42.5; P, 9.6; C, 14.8; H, 3.4; H_2O, 5.6. Found: Ba, 42.8; P, 9.4; C, 14.7; H, 3.4; H_2O, 5.9.

Many of the hydrolyses were performed with crude salt which contained barium chloride as impurity.

2-Methoxypropanol-1.—One mole of propylene oxide was slowly added to 1.1 moles of methanol containing 2% by weight of sulfuric acid. The reaction mixture was refluxed for one hour. The acid was then neutralized with sodium hydroxide, and the products *rapidly* distilled. Subsequent fractionation of the distillate through a 36" Podbielniak column gave 0.4 mole of 2-methoxypropanol-1 which boiled at 131-132° and 0.5 mole of 1-methoxypropanol-2, which boiled at 118°.

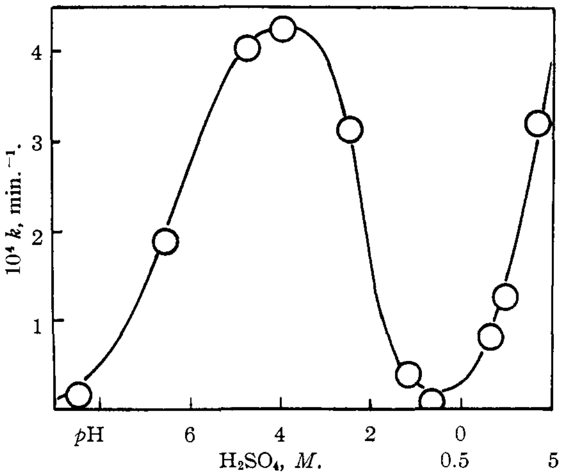

Fig. 1.—pH-rate profile for the hydrolysis of 1-methoxypropyl-2-phosphate.

Anal. Calcd. for $C_4H_{10}O_2$: C, 53.3; H, 11.2. Found: for the primary alcohol: C, 53.5; H, 11.6.

The 3,5-dinitrobenzoate of 2-methoxypropanol-1, prepared from the alcohol and 3,5-dinitrobenzoyl chloride and recrystallized from ligroin, melted at 95°.

Anal. Calcd. for $C_{11}H_{12}O_7N_2$: C, 46.5; H, 4.22; N, 9.9. Found: C, 46.5; H, 4.3; N, 9.9.

1-Methoxypropanol-2 was prepared from propylene oxide, methanol and sodium methoxide[13] in 86% yield; b.p. 118.0–118.5°. The 3,5-dinitrobenzoate, recrystallized from ligroin, melted at 84°.

Anal. Calcd. for $C_{11}H_{12}O_7N_2$: C, 46.5; H, 4.2; N, 9.9. Found: C, 46.5; H, 4.2; N, 9.9.

Resolution of 1-Methoxypropanol-2.—One mole of 1-methoxypropanol-2 and one mole of phthalic anhydride were heated for 48 hours at 105°. The reaction mixture was poured into aqueous sodium carbonate solution. The solution was acidified with hydrochloric acid, yielding a viscous oil, which slowly deposited crystals of phthalic acid. These crystals were removed, but all attempts to crystallize the oil failed. The crude material was therefore used in the resolution without further purification.

The crude acid phthalate (0.64 mole) and brucine (0.64 mole) were dissolved in 800 cc. of hot acetone. The flask was placed in a Dewar of hot water and allowed to cool slowly. After a day, the precipitate weighed about 400 g. This precipitate dissolved in 1200 cc. of hot acetone; slow cooling produced 113 g. of poorly defined needles; on partial evaporation of the mother liquors, a second crop of 164 g. was obtained. After further digestion and crystallization of these two crops from acetone, the material was recrystallized five times from alcohol-ligroin. After each recrystallization, a small amount of the salt was dissolved in dilute HCl. The solution was extracted with ether, and the optical rotation of the ether solution of the acid phthalate was measured. The specific rotation finally achieved was 20.5° for acid phthalate from a brucine salt which melted at 146°.

Anal. Calcd. for $C_{35}H_{40}O_9N_2$: C, 66.4; H, 6.3; N, 4.4. Found: C, 66.5; H, 6.5; N, 4.4.

Seventy grams of the pure brucine salt was converted to the oily acid phthalate. This material was dissolved in 200 cc. of water containing 2.1 equivalents of NaOH, and the mixture distilled until 150 cc. had been collected. Fractionation of this crude distillate yielded an azeotrope (b.p. 96.5°, $d^{20}{}_4$ 0.986, specific rotation + 19.8°) of water and optically active 1-methoxypropanol-2. Calibration by density showed that this azeotrope contains 52% by weight of the alcohol. The pure alcohol was obtained by saturating the azeotrope with potassium carbonate, drying the alcohol layer with calcium oxide, and distilling; it had a specific rotation of +3.8°, and its 3,5-dinitrobenzoate melted at 90°.

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[6] L. A. Flexser and W. G. Farkas, *Chem. Eng. News*, **29**, 3947 (1951); L. A. Flexser, private communication.

[7] E. L. Outhouse, *Biochem. J.*, **31**, 1459 (1937).

[8] F. R. Atherton, H. T. Openshaw and A. R. Todd, *J. Chem. Soc.*, 382 (1945).

[9] E. Baer, THIS JOURNAL, **69**, 1253 (1947).

[10] J. Pelouz, *Ann. Chim.*, **52**, 37 (1833).

[11] J. Calavier and E. Prost, *Bull. soc. chim.*, [3] **23**, 678 (1900).

[12] O. Bailly and J. Gaumé, *ibid.*, [5] **3**, 1396 (1936).

[13] A. A. Petrov, *J. Gen. Chem.* (*U.S.S.R*), **14**, 1038 (1944).

Anal. Calcd. for $C_{11}H_{12}O_7N_2$: C, 46.5; H, 4.2. Found: C, 46.1; H, 4.2.

The acetone solution, from which the brucine salt of the dextrorotatory acid phthalate had been crystallized, was evaporated and the residue treated with hydrochloric acid. The resulting crude acid phthalate was hydrolyzed, and the 1-methoxypropanol-2 was found to be levorotatory; it was about 55% optically pure. Both dextro and levo alcohols were diluted with inactive 1-methoxypropanol-2 before being converted to the corresponding phosphates.

Hydrolyses. Method.—The hydrolyses were carried out in 1-l. flasks attached to a 36″ Podbielniak column. The azeotrope was removed as it was formed, but no attempt was made to isolate all the liberated alcohol.

(a).—A mixture of 0.25 mole of glycine, 0.2 mole of NaOH, 0.2 mole of lanthanum nitrate hexahydrate and 0.03 mole of optically active barium 1-methoxypropyl-2-phosphate was refluxed for four days; about 2 cc. of the azeotrope was collected. The rotation of the azeotrope from the alcohol used to prepare the phosphate ester was −0.765°/dm.; after hydrolysis, it was −0.740°/dm.

(b).—A similar experiment with 0.03 mole of optically active barium 1-methoxypropyl-2-phosphate, 0.015 mole of potassium acid phthalate, 0.04 mole of sodium sulfate and 500 cc. of water yielded an azeotrope with rotation of −0.760°/dm.

(c).—The barium salt (0.03 mole) was suspended in 500 cc. of 1.8 *M* sulfuric acid. The mixture was filtered to remove barium sulfate and refluxed. The recovered azeotrope showed a rotation of +0.135°/dm.; the azeotrope of the starting alcohol read +0.520°/cm. Control experiments showed that the alcohol could be refluxed with 1.8 *M* sulfuric acid under a Podbielniak column without appreciable racemization, presumably due to the fact that the azeotrope is quickly removed from the acid solution and retained in the distilling column. When a reflux condenser is attached directly to the pot, the alcohol racemized with a half-time at 100° of around 2 hours.

Identification of Products.—The alcohols from the hydrolyses of the barium salts of 2-methoxypropyl-1-phosphate and of 1-methoxypropyl-2-phosphate were identified by means of their 3,5-dinitrobenzoates. Mixtures of these derivatives are easily separated by crystallization from ligroin; they also depress each other's melting points.

TABLE II

IDENTIFICATION OF THE ALCOHOLS OBTAINED ON HYDROLYSES OF THE BARIUM SALTS OF 1-METHOXYPROPYL-2-PHOSPHATE AND 2-METHOXYPROPYL-1-PHOSPHATE

	Experimental conditions		
	*p*H 8.5 + $La(OH)_3$	*p*H 4	1.8 *M* H_2SO_4
B.p. azeotrope from primary phosphate, °C.	98.5	98.5	98.5
B.p. azeotrope from secondary phosphate, °C.	96.5	96.5	96.5
M.p., 3,5-dinitrobenzoate, primary phosphate, °C.	94.0 Needles	94.5 Needles	94.0 Needles
M.p., 3,5-dinitrobenzoate, secondary phosphate, °C.	83.5 Plates	83.5 Plates	83.0 Plates

Isotopic Tracer Studies.—The hydrolysis of 1-methoxypropyl-2-phosphate was carried out under various experimental conditions in water enriched in O^{18}. After hydrolysis of the phosphate ester, the inorganic phosphate was converted to potassium dihydrogen phosphate, and this salt pyrolyzed to form water according to the procedure of Cohn.[14]

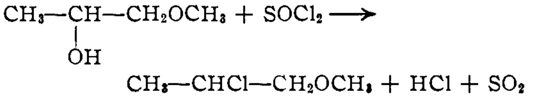
$$nKH_2PO_4 \xrightarrow[\Delta]{} (KPO_3)_n + nH_2O \qquad (2)$$

The water was equilibrated with CO_2, and the O^{18} content of the CO_2 determined with a Consolidated-Nier mass spectrometer.[15] Because the potassium dihydrogen phosphate obtained in the course of this investigation was not pure, the residue from the pyrolysis was analyzed (by the colorimetric procedure described below) for total phosphorus, and the quantity of water formed calculated from equation 2.

(a) **Hydrolysis Promoted** by $La(OH)_3$.—A mixture of 0.83 mole of glycine, 0.041 mole of NaOH, 0.01 mole of $La(NO_3)_3 \cdot 6H_2O$ and 0.02 mole of the barium salt of 1-methoxypropyl-2 phosphate were refluxed at *p*H 8.5 with 100 cc. of water enriched in O^{18}. The precipitate of $LaPO_4$ was dissolved in hydrochloric acid, the lanthanum precipitated (with an aqueous solution of KF) as LaF_3, and the suspension filtered. When ethanol was added to the filtrate, KH_2PO_4 separated. A repetition of this experiment was carried out with 0.035 mole of the barium salt of the phosphate ester.

(b) **Hydrolysis at *p*H 4.**—The barium salt (0.033 mole) was dissolved in 60 cc. of water, enriched in O^{18}, containing 0.05 mole of sodium acetate and 0.26 mole of acetic acid. After seven days refluxing, barium chloride solution was added. The precipitated barium phosphate was treated with sulfuric acid, the solution separated from barium sulfate and neutralized with potassium hydroxide. On addition of alcohol, KH_2PO_4 was isolated as before.

(c) **Analysis of the Alcohol for O^{18}.**—The alcohol obtained from the lanthanum hydroxide-promoted hydrolysis in water enriched in O^{18} was dried, and 1 cc. of it was distilled on a vacuum line into 5 millimoles of thionyl chloride.



$$CH_3-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2OCH_3 + SOCl_2 \longrightarrow CH_3-CHCl-CH_2OCH_3 + HCl + SO_2 \qquad (3)$$

The resulting SO_2 and HCl were freed of other components of the mixture by passing them through a trap at −80°, and they were then distilled onto 10 millimoles of (frozen) water. The tube containing the mixture was sealed and shaken for four days; the water was recovered by distilling the mixture through a −80° trap. This water was then equilibrated with CO_2 for isotopic analysis. (The sulfur dioxide could not be analyzed directly for O^{18} because of the high natural abundance of S^{34}.)

Kinetic Method.—In the kinetic experiments, inorganic phosphate was determined with a Klett–Summerson colorimeter as phosphomolybdovanadate by the method of Murray and Ashley.[16] This method proved superior to the molybdenum blue procedures because it is much less sensitive to interference by silicate. Since the lanthanum hydroxide promoted hydrolysis occurs in heterogeneous mixtures, a separate flask was prepared for each experimental point. In a typical "run," 0.26 g. of barium hydroxyethyl phosphate was dissolved in 100 cc. of water. In each of five 25-cc. glass-stoppered volumetric flasks, the following solutions were introduced: 1 cc. of the ester solution, 1 cc. of 0.01 *M* lanthanum nitrate solution and 2 cc. of a buffer (*p*H 8.5) consisting of 1.48 *M* ammonia and 7.4 *M* ammonium nitrate. The flasks were placed in the thermostat and removed at the stated intervals; the analytical reagents were then added directly to the sample in the volumetric flask. The method was standardized by boiling 1 cc. of the ester solution with concd. nitric acid and hydrogen peroxide, and analyzing by the colorimetric procedure. The results of a typical rate determination are shown in Table III below.

TABLE III

HYDROLYSIS OF HYDROXYMETHYL PHOSPHATE AT 78°

Time, min.	Phosphate, μmoles	Ester, μmoles	10^3k, min.$^{-1}$
0	0.00	9.34	
110	1.56	7.78	1.6
205	2.42	6.92	1.5
250	3.06	6.28	1.6
300	3.46	5.88	1.5

Results

***p*H-Rate Profile.**—The rate of hydrolysis of 1-methoxypropyl-2-phosphate at 78° as a function of *p*H is shown in Fig. 1. The rate follows the same

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[14] M. Cohn, *J. Biol. Chem.*, **180**, 771 (1948).

[15] The funds for the purchase of the mass spectrometer used in this research were supplied by the Atomic Energy Commission under contract No. At(11-1)-92.

[16] W. M. Murray, Jr., and S. E. Q. Ashley, *Ind. Eng. Chem., Anal. Ed.*, **10**, 1 (1938).

general curve as that which Desjobert[5] found for ethyl and hydroxyethyl phosphate.

Structural Effects.—The rates of hydrolysis of several phosphate esters in the presence of La$(OH)_3$ gel, are shown in the Table IV.

TABLE IV

LANTHANUM HYDROXIDE GEL PROMOTED HYDROLYSIS

*p*H 8.5 and 78°

Ester	10^4k, min.$^{-1}$
2-Hydroxyethyl phosphate	16
2-Aminoethyl phosphate	13
Choline phosphate	2.8
2-Methoxyethyl phosphate	2.3
1-Methoxypropyl-2-phosphate	1.0
Ethyl phosphate	0.2
Propyl-2-phosphate	0.03

The rate constant for the hydrolysis of hydroxyethyl phosphate at *p*H 8.5 in the absence of La$(OH)_3$ is less than 10^{-6} min.$^{-1}$; thus the gel accounts for more than a thousand-fold increase in rate.

Stereochemistry.—The data in the experimental section show that the hydrolysis at *p*H 4, and that at *p*H 8.5 in the presence of lanthanum hydroxide gel proceed with complete stereochemical retention; the hydrolysis in 1.8 *M* sulfuric acid proceeds with retention accompanied by a large amount of racemization.

Isotopic Tracers.—The experimental data for the experiments with water enriched in O^{18} are given in Table V.

TABLE V

HYDROLYSIS OF 1-METHOXYPROPYL-2-PHOSPHATE IN H_2O^{18}

Acidity	Conditions	O^{18} in CO_2, found	Atom % excess CO_2	Atom % excess H_2O	Calcd. for H_2O for cleavage of C–O	Calcd. for H_2O for cleavage of P–O
*p*H 8.5	La$(OH)_3$	0.3714	0.0957	0.1053	0.000	0.1206
*p*H 8.5	La$(OH)_3$	.3785	.1004	.1043	.000	.1107
*p*H 8.5	La$(OH)_3$; anal. of alcohol for O^{18}	.2795	.0	.0	.1107	.0
*p*H 4	No La$(OH)_3$	.3778	.0999	.1090	.000	.1012

A control experiment for the lanthanum hydroxide gel experiments was carried out by hydrolyzing P_2O_5 in water enriched in O^{18}. Calcd. 0.1809% excess O^{18}; found, 0.1962% excess O^{18}. A control experiment for the thionyl chloride method was carried out by letting $SOCl_2$ react with enriched water. Calcd. 0.1107% excess O^{18}; found 0.0964% excess O^{18}. Tracer experiments in strong acid were vitiated by the exchange between phosphoric acid and the solvent; such exchange does not occur in weakly acid, neutral or alkaline solutions.

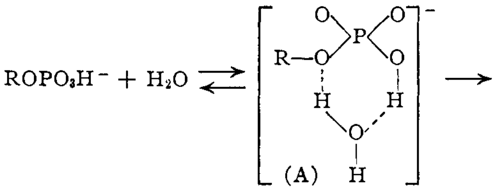
Discussion

The oxygen exchange experiments show that, at *p*H 4 and at *p*H 8.5 in the presence of lanthanum hydroxide, the cleavage of the phosphate ester takes place at the phosphorus–oxygen and not at the carbon–oxygen bond.

$$R—O—PO_3H^- + H_2O^{18} \longrightarrow ROH + H_2PO^{18}O_3^- \quad (4)$$

The results of the stereochemical experiments, which show essentially complete retention of configuration confirm this result and place an upper limit on the extent to which any competing mechanism which involves C–O cleavage can intrude upon the dominant one. Furthermore, no rearrangement occurs during the hydrolysis of 1-methoxypropyl-2-phosphate or of 2-methoxypropyl-1-phosphate, in sharp contrast to the rearrangements which accompany the acid hydrolysis of glyceryl phosphate, and the alkaline hydrolysis of methylglyceryl phosphate.[17] These facts also support the assumption of simple cleavage of the P–O bond in the hydrolyses here considered. The point of cleavage is thus the same as that found for the hydrolysis of β-glyceryl phosphate catalyzed by alkaline phosphatase.[18] In strong acid solution, however, the hydrolysis of 1-methoxypropyl-2-phosphate is accompanied by considerable racemization (plus retention of configuration); these facts suggest that at least one mechanism for strong acid hydrolysis involves the cleavage of the C–O bond.

The relatively fast hydrolysis of monoesters of phosphoric acid at *p*H 4 (as contrasted with the slower rates at *p*H 1 and *p*H 8) shows that the monoanion, $ROPO_3H^-$ (or its kinetic equivalent) undergoes hydrolysis more rapidly than the dianion, $ROPO_3^=$, or the uncharged acid, $ROPO_3H_2$. The stability of the dianion to attack by hydroxide ion is readily understood on purely electrostatic grounds.[19] The special instability of the monoanion to attack by water can be interpreted as indicating that hydrolysis proceeds by way of the intermediate, A.



$$ROH + H_2O + PO_3^- \quad (5)$$

$$H_2O + PO_3^- \xrightarrow{\text{fast}} H_2PO_4^- \quad (6)$$

In equation 5, the alcohol, ROH, and the monomeric metaphosphate ion, PO_3^-, are postulated as primary products of the hydrolysis. Monomeric metaphosphates have been postulated as intermediates in phosphorylations[20]; if the ion PO_3^- is formed in reaction (5), the shape of the *p*H-rate profile (Fig. 1) can be explained (see below). The decomposition of the intermediate, A, can occur readily because the alcohol, ROH, is formed rather than the high energy anion, RO^-. The dianion $ROPO_3^=$ does not react readily with hydroxide ion because of the electrostatic repulsion of the mutual negative charges on the ions; and $ROPO_3^=$ can enter reaction with water by way of an ion analogous to A only by involving the endothermic ionization of water to produce OH^-. These considerations explain why the rate is greater at *p*H 4 than in alkaline solutions. Furthermore, in acid solution, where

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[17] M. C. Bailly, *Bull. soc. chim.*, [5] **9**, 314 (1942). O. Bailly and J. Guamé, *ibid.*, [5] **2**, 354 (1935). See also S. Winstein and L. L. Ingraham, THIS JOURNAL, **74**, 1160 (1952).

[18] S. S. Stein and D. E. Koshland, Jr., *Archives Biochem. Biophys.*, **39**, 229 (1952).

[19] C. K. Ingold, *J. Chem. Soc.*, 1375 (1930); 2170 (1931); C. K. Ingold and H. Mohrhenn, *ibid.*, 1482 (1935); F. H. Westheimer and M. W. Shookhoff, THIS JOURNAL, **62**, 269 (1940).

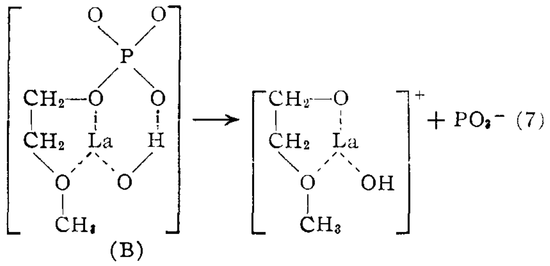
[20] A. R. Todd, in the Arthur D. Little lectures, Massachusetts Institute of Technology, 1954.

$ROPO_3H_2$ is present in high concentration, hydrolysis by way of an intermediate analogous to A would lead to the alcohol, ROH, and monomeric metaphosphoric acid, HPO_3. But presumably such an intermediate will not lose ROH, with the bonding electron pair accompanying oxygen, as readily as will the negatively charged intermediate, A. In strong acid, one or more additional mechanisms, which require C–O cleavage, dominate the hydrolysis. Thus the distinctive *p*H–rate profile for the phosphate hydrolysis may be explained provided that (at moderate acidities) proton transfer to the alcoholic oxygen atom is an obligatory part of the process.

The mechanism for the hydrolysis of simple phosphate esters also can be formulated without the additional water molecule postulated in A so that the hydrolysis goes by way of a four-membered, rather than a six-membered, ring. However, the intermediate A bears somewhat the same relationship to the zwitterion, $R-\overset{+}{\underset{H}{O}}-PO_3^{=}$, as the cyclic, hydrogen-bonded intermediate in the decarboxylation of beta ketoacids[21] bears to its corresponding zwitterion; the six-membered ring appears *a priori* more probable than the other possibilities. Alternatively, the hypothetical ion, PO_3^-, might be hydrated to $H_2\overset{+}{O}-PO_3^{=}$ simultaneously with the decomposition of A. These formulations can also explain the *p*H–rate profile.

A mechanism somewhat analogous to that shown in equations 5 and 6 can explain the hydrolysis promoted by lanthanum hydroxide gel. Since the rate is considerably increased (see Table IV) by a substituent in the β-position in the ester, the oxygen or nitrogen atom of this substituent is probably coördinated with lanthanum ion; since the methoxy group causes an increase in rate, the ionization of the substituent is certainly not a necessary part of the process. (Choline phosphate is a special case; perhaps here the positive charge of the nitrogen atom has a favorable electrostatic effect upon the rate of hydrolysis.) A plausible mechanism for the hydrolysis of methoxyethyl phosphate is shown in equation 7.

$$ROPO_3^{=} + La(OH)^{++} + H_2O \rightleftarrows$$



(B)

(7)

$$PO_3^- + H_2O \longrightarrow H_2PO_4^- \qquad (6)$$

Alternatively, the postulated intermediate, B, may hydrolyze directly to $H_2PO_4^-$ or may rearrange directly to a lanthanum phosphate complex. In eq. 7 the positive lanthanum ion replaces, as to essential function, the proton of the monoanion, $ROPO_3H^-$, in the hydrolysis shown in eq. 5.

Bamann pointed out that the effect of lanthanum ion in promoting the hydrolysis of α-glyceryl phosphate can be observed only in alkaline solution where the gel, $La(OH)_3$, is present as a separate phase. The exact statement of mechanism for a heterogeneous reaction is extraordinarily difficult at the present time; a more accurate formulation must, in all probability, await a determination of the kinetics of metal-ion promoted hydrolysis of a phosphate ester in homogeneous solution.

Cambridge, Mass.

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[21] F. H. Westheimer and W. A. Jones, This Journal, **63**, 3283 (1941).

[Contribution from the Entomology Research Branch, Agricultural Research Service, U. S. Department of Agriculture]

Insecticidal Phosphates Obtained by a New Rearrangement Reaction[1a]

By W. F. Barthel, B. H. Alexander, P. A. Giang and S. A. Hall

Received December 10, 1954[1b]

Dehydrochlorination of O,O-dialkyl 2,2,2-trichloro-1-hydroxyethylphosphonates causes rearrangement to dialkyl 2,2-dichlorovinyl phosphates. The products of dehydrochlorination were compared with compounds of known structure obtained by another synthesis and found to be identical. Other isomeric structures were considered and ruled out by chemical and physical data. New compounds are reported, several of which possess high insecticidal activity. O,O-Diethyl 2,2-dichloro-1-hydroxyethylphosphonate was converted to the systemic insecticide diethyl 2-chlorovinylphosphate.

In a previous paper[2] we described a series of O,O-dialkyl-2,2,2-trichloro-1-hydroxyethylphosphonates (I), which are readily prepared by condensing chloral with a dialkyl hydrogen phosphite. The lower members of this series possess insecticidal activity, and the methyl ester (I, R = CH_3), as "Bayer L $^{13}/_{59}$," has been widely tested. Recently Mattson, Spillane and Pearce[3a] have reported on their original discovery that "L $^{13}/_{59}$" undergoes dehydrochlorination in the presence of alkali, to yield a volatile, more highly insecticidal ester, to which they assigned the enol structure, II. They subsequently[3b] assigned the keto structure, III, to the dehydrochlorination product on the basis of infrared absorption data and formation of an

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[1] (a) This work was conducted in part under funds allotted by the Department of the Army to the Department of Agriculture. (b) Original manuscript received November 11, 1954.

[2] W. F. Barthel, P. A. Giang and S. A. Hall, This Journal, **76**, 4186 (1954).

[3] (a) A. M. Mattson, J. T. Spillane and G. W. Pearce. Abstract of paper for presentation at the 126th Meeting of the American Chemical Society at New York, N. Y., September 12–17, 1954; (b) *ibid.*, paper as actually presented.