

cobalt(II), the data seem reasonable since it was shown that cobalt acetate does not react with *t*-butyl hydroperoxide in 50% aqueous acetic acid. In contrast, ferrous ion complexed with EDTA shows no acid dependence in its reaction with cumene hydroperoxide.¹⁸ It was assumed that all the ferrous EDTA-solvent complexes react at the same rate with hydroperoxide.

The reactivity of cobalt(II)-EDTA and the inertness of cobalt acetate with *t*-butyl hydroperoxide in 50% aqueous acetic acid deserve comment. A previous report^{1b} indicates that the decomposition rate of *t*-butyl hydroperoxide with cobalt acetate is reduced by addition of water to acetic acid solvent. Total inactivity of cobalt acetate in 50% aqueous acetic acid is then not unexpected. On the other hand, it is known that strong anionic complexing agents stabilize the higher valence state of transition metal ions relative to the lower valence state.¹⁹ This is no doubt the reason for the observed reactivity of EDTA-complexed cobalt(II) and inert behavior of cobalt acetate and cobalt(III)-EDTA.

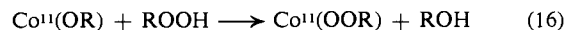
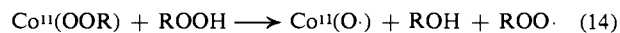
Catalyzed Decomposition. The relationship of the present results to the catalytic decomposition of *t*-butyl hydroperoxide deserves comment. Recently Berger and Bickel²⁰ proposed a mechanism for the catalytic decomposition of *t*-butyl hydroperoxide by cupric phenanthroline diacetate, which incorporated

(18) W. L. Reynolds and I. M. Kolthoff, *J. Phys. Chem.*, **60**, 996 (1956).

(19) F. Basolo and R. G. Pearson, "Mechanism of Inorganic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 61.

(20) H. Berger and A. F. Bickel, *Trans. Faraday Soc.*, **57**, 1325 (1961).

an oxide intermediate. A similar mechanism for cobalt (II) would be



where R is *t*-butyl. Obviously, this mechanism is not operative with EDTA-complexed cobalt(II) since it fits neither the products nor the stoichiometry of the reaction. For similar reasons, the mechanism does not seem likely even for the catalytic decomposition of hydroperoxides with cobalt salts.

Dean and Skirrow¹⁶ have studied the decomposition of *t*-butyl hydroperoxide in acetic acid with cobalt acetate and report orders in cobalt and hydroperoxide to be 1.4 and 1.1. The higher order term in cobalt may be, in part, due to reactions with more than one cobalt species in the activated complex. This would correspond to the third-order term observed in the present study.

Acknowledgments. The author expresses his thanks to Drs. L. L. Ferstandig and T. V. Liston for editing the manuscript and to Dr. S. J. Lapporte for many valuable discussions. In addition, consultation from the Mathematical Services Department at Calresearch and valuable technical assistance from Mr. R. R. Granberg are acknowledged. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Hydrolysis of Phostonates^{1,2}

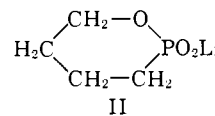
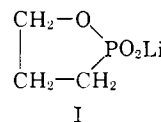
Anatol Eberhard and F. H. Westheimer

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

A five-membered cyclic ester of a phosphonic acid, lithium propylphostonate (I), and a six-membered analog, lithium butylphostonate (II), have been synthesized. The rates of hydrolysis of these compounds, relative to that of sodium ethyl ethylphosphonate (sometimes compared directly, sometimes extrapolated to 75°) in acid are 5×10^4 :3:1, and in alkali are 6×10^5 :24:1. Tracer methods with ¹⁸O show that the phostonates are cleaved at the P-O bond, whereas the hydrolysis of the open-chain phosphonate occurs with about half P-O and half C-O fission. The relative rates of hydrolysis at phosphorus are then slightly more favorable to the phostonates than the figures shown above. The previously established extraordinary reactivity of cyclic five-membered esters of

phosphoric acid is thus paralleled by that of the cyclic phosphonates.

The extraordinarily large rates of hydrolysis of five-membered cyclic esters of phosphoric acid,³ as compared to those of the six-membered cyclic esters,⁴ or of



the corresponding open-chain compounds stimulated an investigation of the properties of the corresponding phosphonates. The dilithium salt of 3-bromopropylphosphonic acid was cyclized to the phostonate, by internal displacement. Similar reaction led to the

(3) J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *J. Am. Chem. Soc.*, **78**, 4858 (1956).

(4) H. G. Khorana, G. M. Tener, R. S. Wright, and J. G. Moffatt, *ibid.*, **79**, 430 (1957).

(1) Presented in part at the 140th National Meeting of the American Chemical Society, Sept. 1961, Abstracts, p. 94Q, and in part in the Abstracts of the 18th National Organic Chemistry Symposium, Columbus, Ohio, 1963, p. 53.

(2) The general name "phostonic acid" was suggested by Conant to describe cyclic phosphonic acids: J. B. Conant and A. D. Macdonald, *J. Am. Chem. Soc.*, **42**, 2337 (1920). The nomenclature here used for phostonates is patterned after the standard nomenclature for phosphonates: see *Chem. Eng. News*, **30**, 4515 (1952).

preparation of the corresponding four-carbon phosphonate II. The rates of acid and alkaline hydrolysis of these phosphonates were then compared to the corresponding rates of hydrolysis of the ethyl ester of ethylphosphonic acid. The net result of the investigation was to show that five-membered cyclic phosphonates, like the five-membered cyclic phosphate esters, are cleaved at the P-O bond very much more rapidly than the corresponding six-ring or open-chain compounds.

Chart I. Two-Carbon Phosphonates

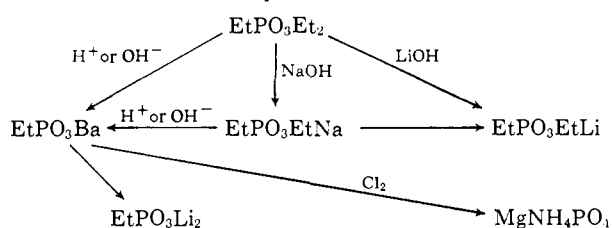


Chart II. Three-Carbon Phosphonates

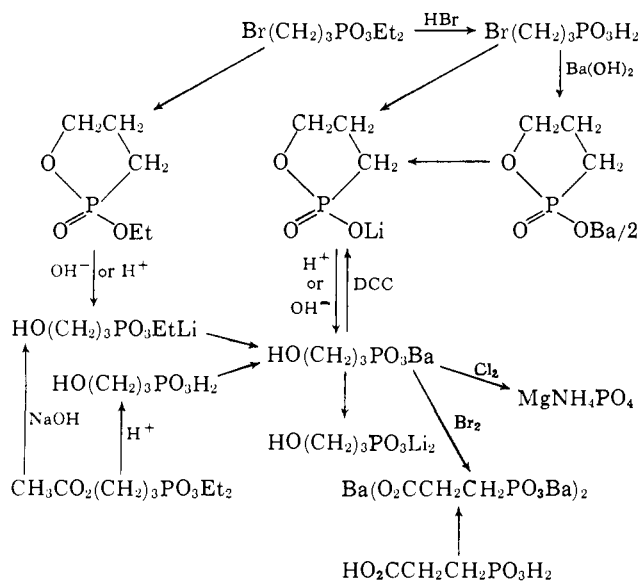
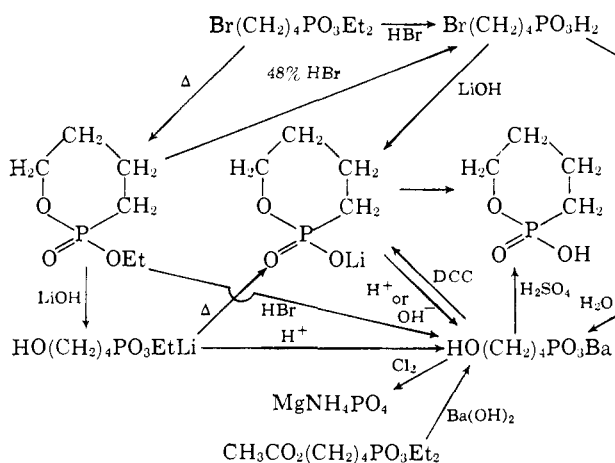
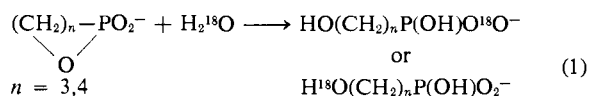


Chart III. Four-Carbon Phosphonates



Most of the reactions which establish the structures and interrelationships of these compounds are summarized in Charts I-III. Supplementary data are

available elsewhere.⁵ The percentages of cleavage at the P-O and C-O bonds were determined for all three compounds by conducting the hydrolyses in water enriched in ¹⁸O and analyzing the products for ¹⁸O. This procedure is straightforward for the phosphonate ester, but the hydrolysis of a phosphonate necessarily results in the incorporation of at least one atom of ¹⁸O into the resulting hydroxyphosphonic acid, regardless of whether the reaction is accompanied by P-O or C-O cleavage. The resulting phosphonate must be de-



graded in such a way as to distinguish between the possibilities shown in eq. 1. This objective was accomplished by two principal methods: (a) reaction of the hydroxyphosphonates with chlorine in aqueous alkali led to the production of inorganic phosphate, with retention of whatever ¹⁸O had been attached to phosphorus, and (b) the phosphonates were allowed to react with dicyclohexylcarbodiimide.^{4,6} This reaction transfers one of the oxygen atoms attached to phosphorus to the reagent to form dicyclohexylurea labeled (to the extent that the phosphonate group was labeled) with ¹⁸O.

Some of the products which are here described have been previously reported but with scanty characterization. These products, as well as those synthesized for the first time, have been identified and characterized by analysis, infrared and n.m.r. spectra, and (for those salts which were not obviously crystalline) by X-ray powder photographs. The actual powder photographs and infrared and n.m.r. spectra are available elsewhere.⁵ The latter, although always consistent with the structures proposed, are generally so complex (because of splitting by ³¹P) that they cannot be analyzed by first-order theory.

Experimental

Materials. Diethyl 3-bromopropylphosphonate,^{7,8} previously described as an "undistillable oil,"⁷ boiled (after two vacuum distillations) at 74° (0.1 mm.). Principal infrared bands were observed at 7.92, 8.10, 9.47, 9.70, and 10.35 μ (neat liquid).

Anal. Calcd. for C₇H₁₆BrO₈P: C, 32.45; H, 6.22; Br, 30.84; P, 11.96. Found: C, 32.67; H, 6.35; Br, 30.74; P, 12.33.

Hydrolysis of 26 g. of this ester under nitrogen in 220 ml. of 48% HBr at 90° for 1.5 hr. yielded, on evaporation, crude 3-bromopropylphosphonic acid.^{7,8} After four recrystallizations from benzene, the acid melted at 112-112.8°. Principal infrared bands were observed at 7.79, 8.02, 9.87, 10.48, 13.02 (m), and 13.65 (m) μ (KBr).

Lithium Propylphosphonate. A solution of 2.03 g. of 3-bromopropylphosphonic acid was brought to pH 10 with 1 M LiOH. After 24 hr. at room temperature, the solution was evaporated to dryness under vacuum.

- (5) A. Eberhard, Thesis, Harvard University, May 1964.
 (6) D. Samuel and B. L. Silver, *J. Am. Chem. Soc.*, **85**, 1197 (1963).
 (7) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 155.
 (8) (a) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947); (b) G. M. Kosolapoff and R. F. Struck, *ibid.*, 3739 (1957); (c) B. Heflerich and U. Curtius, *Ann.*, **655**, 59 (1962).

Lithium bromide was removed by exhaustive extraction with acetone, and the residual lithium propylphosphonate was purified by dissolving in methanol, removing insoluble materials, and evaporating to dryness in vacuum. The yield of bromide-free white powder was 1.23 g. The microcrystalline nature of the salt was demonstrated by an X-ray powder photograph with a Type 12045/3 Philips Electronic instrument; dozens of sharp lines (which were not analyzed) were observed.⁵

Anal. Calcd. for $C_3H_6LiO_3P$: C, 28.15, H, 4.73, Br, 0.00; P, 24.20. Found: C, 28.17; H, 4.85; Br, <0.1; P, 24.55.

Principal infrared bands were observed at 8.44, 8.58, 9.00, 9.57, 9.91 (m), and 12.82 μ (KBr). The exact positions of the infrared bands of this and other salts, determined in KBr disks with a Perkin-Elmer Infracord, proved sensitive to traces of moisture.⁹

The success of the synthesis depends critically on using solutions which are not more than 0.1 *M*; with more concentrated solutions, large amounts of insoluble materials (presumably polymers) are formed.

*Ethyl Propylphosphonate.*¹⁰ About 20 g. of diethyl 3-bromopropylphosphonate was heated under nitrogen for 2 hr. between 180 and 200°. Ethyl bromide (identified by infrared) was evolved during the first hour. Two vacuum distillations gave 4.4 g. of liquid boiling at 74° (0.55 mm.). Principal infrared bands were observed at 7.85, 9.52, 9.78, and 9.99 μ (CCl_4).

Anal. Calcd. for $C_6H_{11}O_3P$: C, 40.00; H, 7.39; P, 20.63. Found: C, 40.07; H, 7.36; P, 20.77.

*Diethyl 3-Acetoxypropylphosphonate.*¹¹ A mixture of 6.8 g. of crude 3-acetoxypropyl bromide¹² and 10 g. of triethyl phosphite was heated for 5 hr. at 160°. On vacuum fractionation, the major fraction (4.5 g.) distilled at 96° (0.1 mm.). Principal infrared bands were observed at 5.71, 8.02 (shoulder), 8.12, 9.45, 9.71, and 10.40 μ (CS_2).

Anal. Calcd. for $C_9H_{19}O_5P$: C, 45.38; H, 8.04; P, 13.00. Found: C, 45.12; H, 8.00; P, 13.31.

Dilithium 3-Hydroxypropylphosphonate. Diethyl 3-acetoxypropylphosphonate was hydrolyzed in sulfuric acid presumably to 3-hydroxypropylphosphonic acid.¹³ Addition of barium hydroxide gave the barium salt which was purified by precipitation from aqueous solution with ethanol. This material could not be obtained as a definite hydrate (see below) and gave correspondingly poor analyses. It was, however, easily recognized by its infrared spectrum which showed a complex multiplet: 9.11, 9.45, 9.71, 9.82, 10.04, and 10.19 μ (KBr). The dilithium salt was prepared from the barium salt by ion exchange with Dowex-50- Li^+ and was purified by inverse crystallization from ethanol-water (*i.e.*, the solid is more soluble cold than hot).

(9) Similar observations are recorded by F. Covitz and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 1773 (1963), and references cited therein.

(10) A. Y. Garner, U. S. Patent 2,953,591 (Sept. 20, 1961); *Chem. Abstr.*, **55**, 5346 (1961).

(11) The compound was previously prepared from allyl acetate, diethyl hydrogenphosphonate, and dibenzoyl peroxide, but not characterized; British Patent 694,772 (July 29, 1953); *Chem. Abstr.*, **49**, 4705 (1955).

(12) S. Oae, *J. Am. Chem. Soc.*, **78**, 4030 (1956).

(13) A. R. Stiles, F. F. Rust, and W. E. Vaughan [*ibid.*, **74**, 3282 (1952)] prepared the acid as a liquid; a preparation is also reported in British Patent 673,451 (June 4, 1952); *Chem. Abstr.*, **47**, 5426 (1953). No properties are given.

The latter salt shows infrared bands at 9.10, 9.49, and 9.93 μ (KBr). An X-ray powder photograph showed that the salt¹⁴ is crystalline.

Anal. Calcd. for $C_3H_7Li_2O_4P$: C, 23.72; H, 4.64; P, 20.39. Found: C, 23.65; H, 4.61; P, 20.22.

Lithium ethyl 3-hydroxypropylphosphonate was prepared in 84% yield by hydrolysis of ethyl propylphosphonate and crystallized (X-ray powder photograph) from ethanol-acetone. The infrared spectrum showed principal bands at 8.39, 9.23, 9.52, 10.45, 12.20, and 12.35 μ (KBr).

Anal. Calcd. for $C_5H_{12}LiO_4P$: C, 34.47; H, 6.90; P, 17.81. Found: C, 34.69; H, 7.09; P, 17.71.

Lithium ethyl 4-hydroxybutylphosphonate was prepared similarly in 31% yield from ethyl butylphosphonate (see below), but was of questionable crystallinity. It showed principal infrared bands at 8.29, 9.50, 10.46, and 12.15 μ (KBr).

Anal. Calcd. for $C_6H_{14}LiO_4P$: C, 38.31; H, 7.50; P, 16.47. Found: C, 38.07; H, 7.37; P, 16.49.

2-Carboxyethylphosphonic acid,¹⁵ recrystallized from acetic acid, melted at 159–160°.

Diethyl ethylphosphonate,¹⁶ boiling at 64–66° (5 mm.) through a 24-cm. Helipak column, showed no impurities on v.p.c. analysis with a Wilkins Aerograph. The very hygroscopic sodium ethyl ethylphosphonate was prepared by the hydrolysis of the diethyl ester in alkali¹⁷ and identified by analysis.⁵ Principal infrared bands were observed at 8.30, 9.05, 9.18, 9.45, 10.55, and 12.80 μ (KBr). The corresponding nonhygroscopic lithium salt was prepared in 70% yield by hydrolysis of the diester in lithium hydroxide. Principal infrared bands were observed at 8.33, 9.28, 9.51, and 10.47 (m) μ (KBr).

Anal. Calcd. for $C_4H_{10}LiO_3P$: C, 33.35; H, 7.00; P, 21.50. Found: C, 33.04; H, 7.01; P, 21.75.

An X-ray powder photograph showed that the salt is crystalline.

Dilithium Ethylphosphonate. The barium salt¹⁸ of ethyl phosphonic acid¹⁹ is known but is hard to free from ethanol of crystallization (identified⁵ by n.m.r. as well as analysis) or to prepare in anhydrous form. An aqueous solution of the barium salt was passed through a column of Dowex-50- Li^+ . Evaporation of the effluent gave the white, crystalline (X-ray powder photograph) anhydrous lithium salt with infrared bands at 9.13, 9.49, 9.89, and 13.60 μ (KBr).

Anal. Calcd. for $C_2H_5Li_2O_3P$: C, 19.70; H, 4.13; P, 25.41. Found: C, 19.70; H, 4.49; P, 25.02.

4-Bromobutylphosphonic Acid. Crude diethyl 4-bromobutylphosphonate was prepared from 500 g. of 1,4-dibromobutane and 96.5 g. of triethylphosphite by heating for 1 hr. under nitrogen at 150°. Excess starting materials were removed at temperatures below 102° at 0.2 mm. About 55 g. of the crude remaining

(14) The preparation of the corresponding lead salt was reported by V. K. Kuskov, G. F. Bebikh, and A. D. Yaroshenko, *Dokl. Akad. Nauk SSSR*, **120**, 786 (1958); *Chem. Abstr.*, **52**, 19913 (1958).

(15) Ref. 7, p. 161.

(16) A. H. Ford-Moore and B. J. Perry, *Org. Syn.*, **31**, 33 (1951); see also ref. 7, p. 149.

(17) D. F. Peppard, J. R. Ferraro, and G. W. Mason, *J. Inorg. Nucl. Chem.*, **12**, 60 (1959); R. Rabinowitz, *J. Am. Chem. Soc.*, **82**, 4564 (1960).

(18) N. Anand and A. R. Todd, *J. Chem. Soc.*, 1867 (1951).

(19) A. E. Canavan, B. F. Dowden, and C. Eaborn, *ibid.*, 331 (1962), and ref. 7, p. 149.

ester was hydrolyzed to the corresponding acid with 48% hydrobromic acid. After five crystallizations, 18.3 g. of product^{8c,20} melted at 126.5–127.8°. Principal infrared bands were observed at 7.88, 9.78, 10.04, and 10.51 μ (KBr).

Anal. Calcd. for $C_4H_{10}BrO_3P$: C, 22.14; H, 4.64; Br, 36.82; P, 14.27; mol. wt., 217. Found: C, 22.33; H, 4.50; Br, 37.03; P, 14.58; mol. wt. (by titration), 214.

Ethyl butylphostonate^{10,21} was prepared by distillation from crude diethyl 4-bromobutylphosphonate at 105–110° (0.7 mm.), followed by three vacuum fractionations giving a final boiling point of 56° (0.08 mm.). Principal infrared bands were observed at 7.67, 7.88, 7.98, 9.48, 9.71, 10.52, 10.66, 12.24, and 12.75 μ (CS_2).

Lithium butylphostonate was prepared from pure 4-bromobutylphosphonic acid by a procedure paralleling the synthesis of the corresponding propylphostonate. Principal infrared bands were observed at 8.31, 8.69, 9.10, 9.37, 9.73, 10.75, 12.30, and 13.13 μ (KBr). An X-ray powder photograph showed that the salt is crystalline.

Anal. Calcd. for $C_4H_8LiO_3P$: C, 33.83; H, 5.68; P, 21.81. Found: C, 34.03; H, 5.76; P, 22.02.

Barium 4-Hydroxybutylphosphonate. A solution of 0.135 g. of diethyl 4-acetoxybutylphosphonate²¹ and 5 ml. of saturated barium hydroxide was heated for 6 days in a nichrome tube at 200°. The resulting mixture was diluted with 40 ml. of water, clarified by centrifugation, and treated with an equal volume of ethanol. The barium salt crystallized and was collected by centrifugation after 30 min. Repetition of the purification procedure gave 0.129 g. of crystalline (X-ray powder photograph) barium 4-hydroxybutylphosphonate,¹⁴ with infrared bands at 9.29, 9.85, 9.97, and 10.24 μ (KBr).

Anal. Calcd. for $C_4H_8BaO_4P$: C, 16.60; H, 3.13; Ba, 47.61; P, 10.70; mol. wt., 289.5. Found: C, 16.49; H, 3.17; Ba, 48.3; P, 10.67; mol. wt. (by titration), 293.

Butylphostonic Acid. A solution of 0.050 g. of lithium butylphostonate in 0.5 ml. of water was passed through 2 ml. of Dowex-50- H^+ , and the effluent was evaporated. The resulting solid was dissolved in 0.25 ml. of methanol, 20 ml. of ether was added, and the mixture was refrigerated at about 5° for 5 days. The resulting crystals (0.033 g.) melted at 104.5–106°. Infrared bands were observed at 7.68 (m), 8.23, 9.46, 9.80, 10.18, 10.48, 11.85, 12.3, 12.8, and 14.2 μ (KBr).

Anal. Calcd. for $C_4H_9O_3P$: C, 35.30; H, 6.67; P, 22.76. Found: C, 35.50; H, 6.70; P, 22.50.

Reaction Products. In each case, the product of hydrolysis of a phosphonate or phostonate was isolated and identified by comparison of its infrared spectrum with that of an authentic sample.

Methods. ¹⁸O from Hydroxyphosphonates. (a) *Reaction with Chlorine in Alkali.* A solution of 0.20 g. of barium 3-hydroxypropylphosphonate in 2 ml. of saturated barium hydroxide solution plus 0.5 ml. of 50% NaOH was heated to near boiling, and chlorine was slowly introduced for 15 min. About 0.5 ml. more 50% alkali was added, and the solution was centrifuged to collect the solid containing the barium phosphate which

(20) J. M. Nys and M. J. Libeer, Belgian Patent 568,840 (Oct. 16, 1958); *Chem. Abstr.*, **54**, 24051 (1960).

(21) B. A. Arbuzov and D. Kh. Yarmukhametova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1767 (1960); *Chem. Abstr.*, **55**, 15507 (1961).

had been formed. The white pellet was washed several times with water, dissolved in a minimum amount of hydrochloric acid, and the solution was passed through a column of Dowex-50- H^+ . Magnesium ammonium phosphate was precipitated from the solution.²² The salt, obtained in 50% yield, was pyrolyzed to magnesium pyrophosphate prior to analysis for ¹⁸O. The yields of phosphoric acid from other phosphonates were as follows: $HO_2CCH_2CH_2PO_3H_2$, 6–11%; $HO(CH_2)_4PO_3Ba$, 80%; $C_2H_5PO_3Ba$, 44%; and CH_3PO_3Ba , less than 0.5%. The mechanisms of the reactions liberating inorganic phosphate have not yet been investigated. Most phosphonic acids do not give precipitates with magnesia solution in the cold²³; in any event, the identity of the magnesium ammonium phosphate was established by infrared spectrum.

(b) *Reaction with Dicyclohexylcarbodiimide (DCC).* Barium 3-hydroxypropylphosphonate and barium 4-hydroxybutylphosphonate were converted to the corresponding pyridinium salts by ion exchange. Dicyclohexylurea was isolated from the reactions of these pyridinium salts with DCC in dry pyridine.^{4,6} The respective phosphonates were isolated from the reaction mixtures as the lithium salts.

Experiments with Water Enriched in ¹⁸O. *Analyses for ¹⁸O.* Phosphonate and phosphate salts and dicyclohexylurea were analyzed for ¹⁸O by the method of Anbar and Guttman.^{24,25} The samples were dried on a vacuum line at 10⁻⁶ mm., and the combustions with mercuric chloride and mercuric cyanide were carried out at 400–450° for about 3 hr. The results, although reasonably consistent, gave values of ¹⁸O which were somewhat more scattered and somewhat lower than anticipated.²⁶ The carbon dioxide was purified from HCl with quinoline²⁷ and from cyanogen by distillation on the vacuum line²⁵ and then analyzed with a Consolidated Engineering Corp. Model 21-103C mass spectrometer. The spectrum from mass number 16 to about 65 was rapidly scanned to establish the purity of the sample, and then the mass 44–46 region was scanned four times for the determination of the ratio of $CO^{18}O$ to CO_2 .

The ¹⁸O content of water was determined by equilibrating it^{25,28} with CO_2 .

Tracer Method to Determine Water Content of Salts. The major source of potential error in the determinations of ¹⁸O in salts arises from the possibility of water of crystallization, or more precisely, uncertain amounts of water of crystallization in the salts. In order to determine the water content of the various salts here used, each was crystallized, precipitated, or evaporated

(22) S. Greenfield, "Comprehensive Analytical Chemistry," Vol. Ic, C. L. Wilson and D. W. Wilson, Ed., Elsevier Publishing Co., Amsterdam, 1962, pp. 220–236.

(23) L. D. Freedman and G. O. Doak, *J. Am. Chem. Soc.*, **77**, 6221 (1955).

(24) M. Anbar and S. Guttman, *Intern. J. Appl. Radiation Isotopes*, **5**, 233 (1959).

(25) P. C. Haake and F. H. Westheimer, *J. Am. Chem. Soc.*, **83**, 1102 (1961); P. C. Haake, Thesis, Harvard University, 1960.

(26) Similar difficulties were inferred from the work of F. R. Williams and L. P. Hager, *Science*, **128**, 1434 (1958). M. Anbar (private communication) suggests that the use of twice-sublimed mercuric chloride and baking of the combustion tubes at 500° prior to use leads to more satisfactory results in analysis for ¹⁸O.

(27) D. Rittenberg and L. Ponticorvo, *Intern. J. Appl. Radiation Isotopes*, **1**, 208 (1956).

(28) M. Cohn, "Methods in Enzymology," Vol. IV, S. P. Colowick and N. O. Kaplan, Ed., Academic Press, Inc., New York, N. Y., 1957, p. 905.

Table I. Rate Constants for the Alkaline Hydrolysis of Phosphonates and Phostonates at an Ionic Strength of 1.0

Phosphonate or phostonate	Temp., °C.	Concn., M	Concn. OH ⁻ , M	10 ³ k, M ⁻¹ min. ⁻¹
Lithium propylphostonate	30	0.020	0.100	2.3
		0.040	0.100	2.3
		0.020	0.500	2.3
	50	0.040	1.00	2.5
		0.020	0.100 ^a	12.0
		0.020	1.0	11.7
		0.020	0.10	11.8
Sodium ethyl ethylphosphonate	124.7	0.020	1.0	0.0097
		0.040	0.5	0.0087
		0.030	1.0 ^b	0.010
	149.2	0.020	1.0	0.055
		0.020	1.0	0.060
		0.040	1.0	0.057
		0.020	0.5	0.054
Lithium butylphostonate	124.7	0.040	1.0	0.237
		0.040	1.0	0.234
		0.020	0.5	0.223

^a Ionic strength of 1.0 maintained with NaNO₃. In all other experiments, NaClO₄ was used. ^b Teflon tube. In all other experiments at 124.7 and 149.2° nichrome tubes were used, while Pyrex containers were used for experiments at 30 and 50°.

from a homogeneous solution in water enriched to the extent of 1.73% in ¹⁸O. The salts were then subjected to the usual drying procedure, and analyzed for ¹⁸O. Lithium propylphostonate, lithium butylphostonate, dilithium 3-hydroxypropylphosphonate, dilithium ethylphosphonate, barium 4-hydroxybutylphosphonate, dilithium 4-hydroxybutylphosphonate, and magnesium pyrophosphate were completely or almost completely dry after 10–30 hr. on the vacuum line at room temperature. On the other hand, even more strenuous drying conditions failed to remove the heavy isotope from (*i.e.*, failed to dry) barium 3-hydroxypropylphosphonate, barium ethylphosphonate, and magnesium ammonium phosphate. Only salts which had been proved to be dry by this isotope tracer technique were used for analysis for ¹⁸O.

Kinetic Methods. The kinetics of the hydrolysis of sodium ethyl ethylphosphonate, of lithium propylphostonate, and of lithium butylphostonate was followed by measuring the acid generated. The starting materials are salts of acids with p*K* values in the neighborhood of 2, whereas the hydrolysis in each case produces a second acidic proton with a p*K* in the neighborhood of 7 (eq. 1). A titration curve of the products therefore shows equivalence points somewhat below pH 5 and somewhat above pH 9. The extent of hydrolysis can be determined by careful titration of an aliquot, and plotting of the titration curve. These titrations were carried out with a Radiometer TTT1b titrator with scale expander, using a GK 2021B combined electrode. To avoid precipitation of KClO₄ in the asbestos plug, the KCl in the reference electrode was replaced by a saturated solution of NaCl. The titrations were accomplished under nitrogen by means of an Aminco titrator with Fisher 1 M NaOH; standardization of Lot No. 723201 against potassium acid phthalate gave a concentration of 1.000 ± 0.001 M, and less than 2 parts per thousand of carbonate.

Hydrolysis in acid solution was carried out in Pyrex or Corning 79820 tubes. The very slow alkaline hy-

drolysis of lithium butylphostonate and of sodium ethyl ethylphosphonate made the proper choice of container difficult. Brass-enclosed Teflon containers²⁹ worked fairly well at temperatures below 115°, but leaked at higher temperatures. Satisfactory containers were prepared by drilling out 5/8-in. rods of nichrome IV (80% Ni, 20% Cr) purchased from the Driver-Harris Co. in Harrison, N. J. The caps to these tubes were threaded for 7/16 in., and closed with a Teflon O-ring held in place with a ring of brass sheeting and a sturdy hose clamp. The tubes were 3/8 in. in inner diameter and 5 in. long, and contained about 5.5 ml. of solution. They showed no leakage or reaction with sodium hydroxide solution for a week at 200°.

Results

The results of the kinetic experiments are presented in Tables I–IV, and in the paragraph discussing the hydrolysis of ethyl propylphostonate. The results of the experiments conducted with ¹⁸O are presented in Table V, followed by the results from ³¹P n.m.r. spectra.

Calculations. Each experiment followed first-order or second-order kinetics, depending upon the initial conditions chosen. In acid solution, the hydrolysis of the butylphostonate led to an equilibrium mixture containing about 12% of phostonate; this was, of course, taken into account in the calculations. (The equilibrium was approached from both sides, and the phostonate in the equilibrium mixture identified by infrared spectra.)

Although the rate constants for individual experiments were easily calculated, the specific constants for acid-catalyzed reactions were more difficult to obtain. The rate could be expressed, for the phostonates, by the equation

$$v = (\text{phostonic acid})(k_w + k_H(\text{H}^+)) = k_{\text{obsd}}(\text{stoichiometric concentration of phostonate}) \quad (2)$$

In order to obtain *k_w* and *k_H*, not only must the rate be obtained as a function of H⁺, but the ionization constant of the phostonic acid must be known. The direct determinations of the ionization constants of the phostonates and phosphonate at ionic strength of 1.0 and the temperatures used for the hydrolyses proved experimentally difficult. But eq. 2 can be transformed into 3

$$k_{\text{obsd}}(1 + K/(\text{H}^+)) = k_H(\text{H}^+) + k_w \quad (3)$$

where *K* is the acid ionization constant of the phostonic acid. Therefore, provided that *K* has been correctly chosen, a plot of *k_{obsd}*(1 + *K*/(H⁺)) against (H⁺) should yield a straight line with intercept *k_w* and slope of *k_H*. The kinetic data were plotted according to eq. 3 for several choices of *K*. For the hydrolysis of lithium butylphostonate and of sodium ethyl ethylphosphonate, a unique value of *K* could be chosen so as to make eq. 3 linear. For lithium propylphostonate all reasonable values of *K* led to linear plots, and only *k_H* could be obtained.⁵ In these calculations, the concentration of hydrogen ion was calculated for each point from the stoichiometric composition of the solutions and the value of *K* which had been assumed.

Errors. An assumption inherent in eq. 2 and 3 is that the first ionization constants of the products of

(29) J. R. Cox, Jr., Thesis, Harvard University, 1958.

Table II. Rate Constants for the Acid Hydrolysis of Phosphonates and Phostonates

Phosphonate or phostonate	Temp., °C.	Concn.			Phosphonate or phostonate	Temp., °C.	Concn.		
		Concn., M	H ⁺ , M ^{a,b}	10 ³ k, min. ⁻¹			Concn., M	H ⁺ , M ^{a,b}	10 ³ k, min. ⁻¹
Lithium propylphostonate	30.0	0.020	0.0095	0.13	Sodium ethyl ethylphosphonate	124.7	0.020	0.120	1.50
		0.020	0.0150	0.24			0.020	0.220	1.70
		0.020	0.0233	0.38			0.020	0.320	1.90
		0.020	0.0567	1.13			0.020	0.420	2.05
		0.020	0.110	2.33			0.020	0.520	2.25
		0.020	0.213	4.88			0.020	0.620	2.37
		0.020	0.315	7.6			0.020	0.720	2.59
		0.020	0.416	10.4			0.020	0.820	2.64
		0.020	0.520	13.2			0.020	0.920	2.80
		0.020	0.617	15.8			Lithium butylphostonate	99.4	0.020
	0.020	0.717	18.9	0.020	0.067	0.353			
	0.020	0.820	22.8	0.020	0.118	0.400			
	50.0	0.020	0.0150	1.6	0.020	0.219			0.448
		0.020	0.0286	3.0	0.020	0.319			0.490
		0.020	0.0413	4.4	0.020	0.420			0.522
		0.020	0.0534	5.7	0.020	0.520			0.590
		0.020	0.0650	7.1	0.020	0.620			0.619
		0.020	0.0764	8.2	0.020	0.720			0.700
		0.020	0.0875	9.5	0.020	0.820			0.715
		0.020	0.0985	10.7	0.020	0.920	0.770		
0.020		0.1093	12.0	0.020	1.02	0.840			
Sodium ethyl ethylphosphonate		99.1	0.020	0.010	0.059	124.7	0.020	0.010	0.80
	0.030		0.070	0.148	0.020		0.010	0.75	
	0.020		0.080	0.153	0.020		0.020	1.47	
	0.020		0.220	0.177	0.020		0.033	1.93	
	0.030		0.328	0.193	0.020		0.050	2.10	
	0.030		0.429	0.204	0.020		0.080	2.44	
	0.030		0.529	0.218	0.020		0.120	2.56	
	0.030		0.629	0.237	0.020		0.220	2.86	
	0.020		0.620	0.227	0.020		0.320	3.28	
	0.030		0.729	0.245	0.020		0.420	3.95	
	0.030	0.829	0.257	0.020	0.520	4.03			
	0.030	0.929	0.274	0.020	0.620	4.37			
	0.030 ^c	0.020	0.088	0.020	0.720	4.75			
	0.030 ^c	0.124	0.178	0.020	0.805	4.87			
	0.030 ^c	0.829	0.297	0.020	0.820	5.04			
	124.7	0.020	0.010	0.58	0.020	0.820	4.96		
		0.020	0.020	1.02	0.020	0.920	5.21		
		0.020	0.050	1.34	0.020	1.02	5.88		
		0.020	0.080	1.42	0.020	1.02	5.34		

^a Concentration of perchloric acid added; the actual concentration of hydrogen ions in the experiment must be computed as explained in the text. ^b Ionic strength of unity, maintained with NaClO₄, except as noted. ^c Ionic strength of unity maintained with NaNO₃.

Table III. Computed Rate Constants for Acid and Alkaline Hydrolyses

Phosphonate or phostonate	Temp., °C.	Assumed value of K	10 ³ k _w , min. ⁻¹	10 ³ k _H , M ⁻¹ min. ⁻¹	10 ³ k _{OH} , M ⁻¹ min. ⁻¹
Lithium propylphostonate	30.0	0.01		26.8	2.4
		0.05		27.5	
	50.0	0.01		112.	12.
		0.05		117.	
Sodium ethyl ethylphosphonate	99.1	0.001	0.145	0.144	
		0.0025	0.151	0.136	
	124.7	0.001	1.33	1.70	0.0095
		0.0025	1.41	1.61	
Lithium butyl phostonate	99.4	0.0025	0.34	0.49	0.056
		0.01	0.39	0.44	
	124.7	0.0025	2.2	3.5	0.23
		0.01	2.6	3.0	

hydrolysis are the same as those of the starting materials; otherwise the acidity changes as the reaction proceeds. This potential source of error is probably a minor one. The only large uncertainties arise because eq. 2 really contains three parameters: *k_w*, *k_H*, and (implicitly) the ionization constant, *K*. Although the calculation

Table IV. Rate Constants for the Hydrolyses of Phostonates Relative to Those for Sodium Ethyl Ethylphosphonate

Temp., °C.	Lithium butylphostonate <i>k_w</i>	Lithium butylphostonate <i>k_H</i>	Lithium butylphostonate <i>k_{OH}</i>	Lithium propylphostonate ^a <i>k_H</i>	Lithium propylphostonate ^a <i>k_{OH}</i>
125	1.7	2.0	24		
99	2.5	3.3			
75				5 × 10 ⁴	6 × 10 ⁵

^a Constants extrapolated to 75°.

of all three parameters from the data is open to the possibility of considerable error, the data determine *k_H* with precision. In the presence of moderately high concentrations of perchloric acid, and with any reasonable choice of the ionization constant, *K*, the phosphonic and phosphonic acids are present almost exclusively as unionized molecules. Under these experimental conditions, the concentration of hydrogen ion is known, and the effect of acidity on the rate is experimentally unambiguous. These qualitative statements are borne out by the data of Table III. Ionic strength effects in acid solution were found to be small, and can be neglected. The rate of hydrolysis of lithium propylphostonate in 0.1 M sodium hydroxide solution was

Table V. Summary of Results Obtained with ^{18}O

Compd. hydrolyzed	Approximate P-O cleavage, %		
	Acidic	Neutral	Basic
Lithium propylphosphonate	90-100	85-100	90-100
Lithium butylphosphonate	90-100		90-100
Sodium ethyl ethylphosphonate	60-70		45-70
	70-90 ^a		85-100 ^b
Diethyl ethylphosphonate			90-100

^a Low acid concentration, HCl. ^b In the presence of Ba^{2+} .

found to be about one-half of that in 0.1 M sodium hydroxide plus 0.9 M sodium perchlorate; this is the expected salt effect for the attack of hydroxide ion on a negatively charged species.

Alkaline Hydrolysis of Ethyl Propylphosphonate and Diethyl Ethylphosphonate. Ethyl propylphosphonate in water was allowed to react with water at pH 8 and 10 with the pH controlled by a Radiometer TTT1b automatic titrator. The rate constants, at 25°, were 0.0016 and 0.13 min.⁻¹, respectively, so $k_{\text{OH}} = 1.3 \times 10^3 \text{ M}^{-1} \text{ min.}^{-1}$. Isolation of product as the lithium salt gave only $\text{HO}(\text{CH}_2)_3\text{PO}_3\text{EtLi}$. A 0.05 M solution of diethyl ethylphosphonate was allowed to react with 0.1 M sodium hydroxide at 25°, and aliquots were withdrawn for titration. The second-order rate constant was found to be $1.6 \times 10^{-3} \text{ M}^{-1} \text{ min.}^{-1}$. A corresponding experiment with 0.2 M ester and 1 M sodium hydroxide gave $k_{\text{OH}} = 1.9 \times 10^3 \text{ M}^{-1} \text{ min.}^{-1}$.

Phosphorus-31 N.m.r. Spectra. The phosphorus n.m.r. spectra of a series of phosphonates and phosphates were measured with a Varian high resolution n.m.r. spectrometer, Model V4300B, operating at 15.1 Mc. and 8000 gauss. The data were compared⁵ with those obtained previously by others³⁰⁻³⁶ for various phosphates and phosphonates. Relative to 85% phosphoric acid, the ^{31}P signal was found at the following positions (p.p.m.): ethyl butylphosphonate, -23; lithium butylphosphonate, -23 (in water); ethyl propylphosphonate, -49; lithium propylphosphonate, -47 (in water). The ^{31}P signal for the other phosphonate esters and ester salts measured by us and by others³⁰⁻³⁶ falls in the range from -20 to -33 p.p.m. Thus the five-membered phosphonates show an n.m.r. signal at a position about 20 p.p.m. more negative than that of corresponding acyclic or six-membered ring analogs. A similar phenomenon had previously been noted^{34,36} for the corresponding phosphate esters.

Discussion

The kinetic data are summarized in Table IV. The summary of experiments with ^{18}O , directed to a determination of the point of cleavage in the hydrolysis of the phosphonates and phosphonates, is presented in Table V. Details are available elsewhere.⁵

The data of Table V have been corrected for the exchange of the oxygen atoms of the hydrolysis products

(30) J. R. Van Wazer, C. F. Callis, J. N. Shoolery, and R. C. Jones, *J. Am. Chem. Soc.*, **78**, 5715 (1956).

(31) N. Muller, P. C. Lauterbur, and J. Goldenson, *ibid.*, **78**, 3557 (1956).

(32) K. Moedritzer and R. R. Irani, *J. Inorg. Nucl. Chem.*, **22**, 297 (1961).

(33) H. Finegold, *Ann. N. Y. Acad. Sci.*, **70**, 875 (1958).

(34) R. A. Y. Jones and A. R. Katritzky, *J. Chem. Soc.*, 4376 (1960).

(35) R. A. Y. Jones and A. R. Katritzky, *J. Inorg. Nucl. Chem.*, **15**, 193 (1960).

(36) F. Ramirez, private communication.

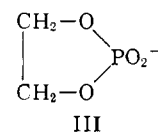
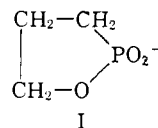
with those of the solvent during hydrolysis by measuring the amount of ^{18}O incorporated into the products when subjected to conditions similar to those used for the hydrolyses. These corrections were relatively small for the reactions carried out in acid solutions and zero for those in alkali. Reisolated starting materials after partial hydrolysis in ^{16}O -enriched media showed no detectable enrichment in the label.

These data clearly show that the five-membered cyclic phosphonate, lithium propylphosphonate, is hydrolyzed in both acid and alkali very much more rapidly than its acyclic analog, sodium ethyl ethylphosphonate. The six-membered cyclic phosphonate is only slightly more reactive toward hydrolysis than the corresponding open-chain phosphonate. Thus the cyclic phosphonates behave in a manner qualitatively similar to that of the cyclic phosphates^{3,4} where only the five-membered esters are extraordinarily sensitive to hydrolysis.

The ratios of rate constants presented in Table IV need to be adjusted to represent rates of attack at phosphorus. However, the phosphonates are cleaved exclusively or almost exclusively at phosphorus, and sodium ethyl ethylphosphonate is cleaved about half at phosphorus. The correction for attack at carbon is then considerably less than that required for the corresponding phosphates.²⁵

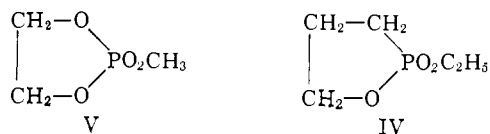
The precise ratios of rates, however, are difficult to assign. The difference in reactivity between the five-membered phosphonate and the acyclic phosphonate is so great that the reactions were necessarily studied at quite different temperatures, and a comparison must be made with extrapolated rates. Not only will the ratio of rates be a function of temperature, but the long extrapolations required will, in all probability, introduce errors into the comparison. Furthermore, since the rates for sodium ethyl ethylphosphonate were measured at quite high temperatures, the opportunities for error are correspondingly great, and the values of the heats of activation, which are inherently difficult to obtain with precision, are here especially uncertain. To minimize errors, the rate for lithium propylphosphonate was extrapolated from measurements at 30 and 50° up to 75°, and that for sodium ethyl ethylphosphonate extrapolated from measurements at 150 and 125° in alkali and 125 and 100° in acid down to 75°. Although the ratios of rates are somewhat uncertain, the numbers are so large (5×10^4 in acid, and 6×10^5 in alkali) as to leave no doubt as to the qualitative and semiquantitative result.

The enhanced rate of reaction of the five-membered phosphonate salt I must be compared with the enhanced rate for the five-membered cyclic diester of phosphoric acid, III, in each case relative to its acyclic analog.



Whereas the acceleration for hydrolysis at phosphorus for the former is about 10^5 - 10^6 , that for the latter is more than 10^8 . Although both five-membered cyclic esters react rapidly relative to their open-chain analogs, the rate enhancement is much greater for the diesters. However, a consideration of the corresponding rate

ratios for the fully esterified phosphonate IV and phosphate V shows that each reacts about 10^6 times as fast with alkali as its acyclic analog.³⁷



The large rates of hydrolysis for the cyclic five-membered phosphates have been shown to be related in large part (but not completely) to thermochemical strain in the ring.^{38,39} The cause of this thermochemical strain has not been established. In all probability, a part of it is simple angle strain.⁴⁰ The idea that part of the strain may arise from distortion of a natural dihedral angle between C-O-P bonds in phosphates³⁹ has also been discussed, but seems relatively unlikely. If such were the fact, then the rate enhancements in the

(37) F. Covitz, unpublished.

(38) J. R. Cox, Jr., R. E. Wall, and F. H. Westheimer, *Chem. Ind. (London)*, 929 (1959).

(39) M. Panar, E. T. Kaiser, and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 602 (1963).

(40) F. H. Westheimer, Special Publication No. 8, The Chemical Society, London, 1957, p. 1.

esters of phosphoric acid would probably greatly exceed that for the phosphonates, since the bonding for C-C-P and C-O-P are quite different.

The negative shift for the phosphorus n.m.r. signal for the highly reactive as opposed to the normal phosphates and phosphonates suggests that the phosphorus atom is less shielded in the cyclic, five-membered esters.³⁶ This interpretation (which must be accepted with considerable caution) is consistent both with the more rapid rate of hydrolysis and the strain for the five-ring; quite possibly the $p\pi-d\pi$ overlap between phosphorus and oxygen is diminished in the cyclic compound because of geometrical considerations. X-Ray investigations of the detailed structure of some of these compounds have been begun in the laboratories of Professor W. N. Lipscomb.

Acknowledgment. The authors gratefully acknowledge the support of the National Science Foundation, through grants G-15819 and GP-2098. One of us (AE) wishes also to thank the Woodrow Wilson Foundation and the National Institutes of Health for Predoctoral Fellowships (GF-12,657). We are also indebted to Mr. Frank Covitz for assistance with the ³¹P n.m.r. spectra.

Secondary Valence Force Catalysis. I. Kinetics of Schiff Base Hydrolysis in the Presence of Micelle-Forming Detergents¹

M. T. A. Behme and E. H. Cordes

Contribution No. 1256 from the Department of Chemistry, Indiana University, Bloomington, Indiana. Received July 2, 1964

The kinetics of the hydrolysis of *p*-chlorobenzylidene-1,1-dimethylethylamine in aqueous solution at 25° and ionic strength 0.05 were investigated in the pH range 1-13 in (a) the absence of detergent, (b) the presence of sodium lauryl sulfate, (c) the presence of cetyltrimethylammonium bromide, and, in part, (d) the presence of a nonionic detergent. From this and related data, rate constants for the individual steps of the hydrolysis reaction were approximately evaluated for the aqueous, anionic micellar, cationic micellar, and nonionic micellar phases. The second-order rate constant for the attack of hydroxide ion on the protonated Schiff base is substantially the same for the aqueous and cationic micellar phases but is markedly reduced in the anionic micellar phase. The observed rate constant for the attack of water on the protonated substrate is largely independent of the nature of the phase in which the reaction occurs. In the region of rate-determining carbinolamine decomposition, the reaction rate is strongly inhibited in the anionic micellar phase compared to that in the aqueous, cationic micellar, or nonionic micellar phases. Several of these results were substantiated in a similar study of the kinetics of hydrolysis of benzhydrylidenedimethyl-

ammonium ion in the presence and absence of micelle-forming detergents. Values of pK_a for protonated *p*-chlorobenzylidene-1,1-dimethylethylamine were determined as 6.55 in aqueous solution, 7.02 in the anionic micelle, 4.96 in the cationic micelle, and less than 5 in the nonionic micelle.

Introduction

Ideally, model reactions for enzymatic processes should include an association, through weak binding forces, of substrate and catalyst or other reactant leading to a facilitation of bond-changing reactions and conferring specificity on the reaction. Reactions occurring in or on micelles, in inclusion compounds, and in ice may exhibit these characteristics in a modest degree. For example, Duynstee and Grunwald have reported 4- to 50-fold increases in the rate of attack of hydroxide ion on certain cationic dyes upon their incorporation into a cationic micelle formed from cetyltrimethylammonium bromide.² Cramer and co-workers have demonstrated cyclodextrin-catalyzed decomposition, involving phosphorylation of the cyclo-

(1) Supported by Grant GB-431 from the National Science Foundation.

(2) E. F. J. Duynstee and E. Grunwald, *J. Am. Chem. Soc.*, **81**, 4540, 4542 (1959).