Base-Induced Rearrangement of Ethane-2-chloro-1-hydroxy-1,1-diphosphonic Acid

O. T. QUIMBY, W. A. CILLEY, J. B. PRENTICE, AND D. ALLAN NICHOLSON*

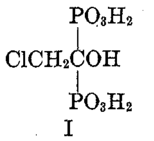
Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

Received November 9, 1972

Ethane-2-chloro-1-hydroxy-1,1-diphosphonic acid is readily dehydrohalogenated on treatment with aqueous base. The rate of chloride loss displays a first-order dependency on the concentration of the parent diphosphonate, and is greatly influenced by the degree of neutralization of the parent acid. The product isolated after all chloride has been removed is $Na_2O_3PCH_2C(O)PO_3Na_2$, wherein one of the geminal phosphonate groups has undergone a 1,2 shift. This structure is deduced from ^{31}P, ^1H, and ^{13}C nmr spectra, and is consistent with ir and uv spectral patterns. Stabilities of various acid and salt forms of this new carbonyl phosphonate are discussed and its conversion to ethane-1-hydroxy-1,1,2-triphosphonic acid *via* addition to the carbonyl group is demonstrated.

Recent publications from these laboratories have described general methods of preparation of alkyl-1-hydroxy-1,1-diphosphonic acids[1,2] and their esters.[3] In exploring methods for converting one such compound, ethane-2-chloro-1-hydroxy-1,1-diphosphonic acid, to another, ethane-1-hydroxy-1,1,2-triphosphonic acid, the complex solution chemistry described in this paper was elucidated.

The preparation of ethane-2-chloro-1-hydroxy-1,1-diphosphonic acid (I) from chloroacetic acid and P_4O_6 has been briefly described.[1] Phosphorus and proton nmr spectra are consistent with the assigned structure. The ^{31}P nmr spectrum (aqueous solution) consists of a triplet centered at δ −15.6 ppm (J_{H-P} = 11 Hz). The CH_2 protons appear as a triplet in the ^1H nmr spectrum centered at τ 5.38 ppm (J = 11.5 Hz).



$$ClCH_2\overset{PO_3H_2}{\underset{PO_3H_2}{C}}OH$$

I

The acid form of I is stable in water to a temperature of ~100°, whereupon slow decomposition begins (oxygen was not excluded from the system). The phosphorus-containing product of this decomposition is H_3PO_4. When I is titrated with aqueous base, dehydrohalogenation occurs. If I remained intact at high pH, the expected titration curve, based on the behavior of analogous diphosphonic acids,[1] would have end points at 2, 3, and 4 equiv of base. Titration curves A and B of Figure 1 indicate a normal first end point (2 equiv). This was substantiated by silver nitrate titration, which showed that no free Cl^- was present in solution at this point.

After 5 equiv of base had been added, the theoretical amount of Cl^- was present regardless of the rate of titration. The large difference in the amount of base required to reach the second end point (3.16 *vs.* 4.00 equiv) demonstrates a dependency of the rate of Cl^- loss on the speed of titration. Curve C is a reverse titration of the solution resulting from either A or B and suggests that a new compound has been formed with different acid–base properties.

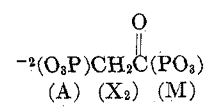
Simple rate studies revealed that the release of free chloride ion was first order with respect to I, independent of the chloride ion concentration but dependent on the ionic charge of I. The first-order rate expression, log [I], plotted *vs.* time was linear for over 80% of the reaction at pH values of 7.0, 9.0, and 10.0. The apparent first-order rate constant, k_{app}, was unaffected by the substitution of 0.1 M NaCl, as an ionic medium, for 0.1 M KNO_3. While k_{app} increased by only a factor of 1.3 as the pH was raised from 7.0 ($k_{app} = 1.5 \times 10^{-3}$ sec^{-1}) to 9.0 ($k_{app} = 2.0 \times 10^{-3}$ sec^{-1}), it increased by a factor of 3.7 (to $k_{app} = 7.4 \times 10^{-3}$ sec^{-1}) as the pH was increased from 9.0 to 10.0. This indicates that the dehydrohalogenation reaction is not simply base catalyzed, but proceeds by parallel pathways at different rates depending on the ionic form of the reactant ion. The apparent rate constant is a combination of the true rate constants for the individual ionic species.

The product of complete dehydrohalogenation is $Na_2O_3PCH_2C(O)PO_3Na_2$ (II). Evidence for this structure comes from elemental analysis, ^{31}P, ^1H, and ^{13}C nmr (Table I), and ir and uv spectroscopy.

TABLE I
NMR SPECTRAL DATA

Counter-ion in M_2O_3P-$CH_2C(O)$-PO_3M_2	^{31}P, δ (50%)	Mult	^1H, τ	Mult	^{13}C, δ	Mult
Na_4	−11.9	4	6.29	2	148.4	4
	−0.3	2			−8.7	4
H_4	−16.3	4	5.92	2		
	+3.8	2				

The splittings found in the nmr spectra of II and its corresponding acid are not what would be expected on the basis of first-order calculations. They are, however, interpretable as follows. Consider $Na_2O_3PCH_2C(O)PO_3Na_2$ as a compound in the AMX_2 system where A is the phosphorus attached to the $-CH_2-$, M is the phosphorus attached to the $>C{=}O$, and X_2 are the two methylene protons. The ^{31}P and ^1H nmr spectra are then consistent with coupling constants of J_{A-X} = 18–21, J_{A-M} = 16–18, J_{M-X} = <1 Hz.



$$\underset{(A)}{^{-2}(O_3P)}\underset{(X_2)}{CH_2}\underset{(M)}{\overset{O}{\overset{\|}{C}}(PO_3)^{-2}}$$

---

[1] J. D. Curry, D. A. Nicholson, and O. T. Quimby, "Topics in Phosphorus Chemistry," Vol. 7, Wiley, New York, N. Y., 1972.

[2] J. B. Prentice, O. T. Quimby, R. J. Grabenstetter, and D. A. Nicholson, *J. Amer. Chem. Soc.*, **94**, 6119 (1972).

[3] D. A. Nicholson and H. Vaughn, *J. Org. Chem.*, **36**, 3843 (1971).

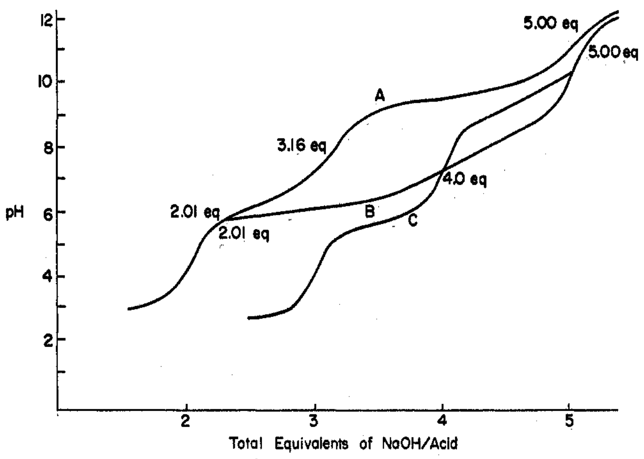
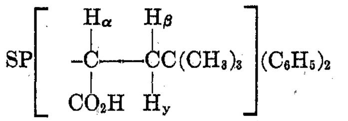


Figure 1.—Titration of $ClCH_2C(OH)(PO_3H_2)_2$ with NaOH: curve A, fast titration, 0.28 equiv/min, total time 10.5 min; curve B, slow titration, 0.037 equiv/min, total time 110 min; curve C, reverse titration of solution resulting from A or B.

Nucleus A appears as a quartet, *i.e.*, a 1–2–1 triplet from the X_2 splitting doubled by the M splitting such that the two 1–2–1 triplets add to form a 1–3–3–1 quartet. Nucleus M appears as a doublet split only by nucleus A. Nuclei X_2 also appear as a doublet split only by nucleus A. The M–X coupling is too weak to be observed in either ^{31}P to ^{1}H nmr.

Such a small coupling constant for PCCH is unusual but not without precedent. Although PCCH coupling constants are normally in the range of 15–19 Hz,[4] compounds are known wherein much smaller values have been observed. A noteworthy example has been described by Peterson.[5] In the phosphine sulfide



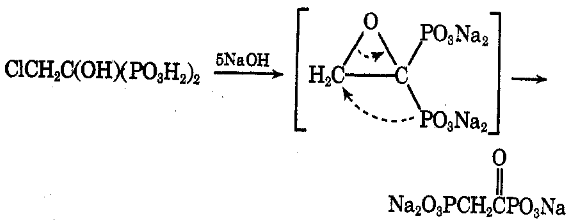
$$SP\left[-\underset{CO_2H}{\overset{H_\alpha}{C}}-\underset{H_\gamma}{\overset{H_\beta}{C}}C(CH_3)_3\right](C_6H_5)_2$$

$J_{PCCH_\gamma} = 19$ Hz, while $J_{PCCH_\beta} = 2.5$ Hz.

The ^{13}C nmr spectrum further substantiates this interpretation. The resonance at −8.7 ppm with respect to CS_2 corresponds to that of a carbonyl carbon. It appears with a major splitting into a doublet caused by phosphorus M, and very minor further splitting by coupling with phosphorus A. This secondary splitting further shows small perturbations owing to phosphorus–phosphorus coupling. The methylene carbon appears at 148.4 ppm as a doubled doublet, the major splitting being due to phosphorus A and further splitting caused by phosphorus M. There is no observable ^{13}C–^{13}C coupling since the experiment was performed with natural abundance ^{13}C, requiring the averaging of 8000 scans to obtain the spectrum.

An infrared spectrum of II in D_2O showed methylene vibrations at 2860, 2920, and 2960 cm^{-1}, and strong absorption at 980 and 1635 cm^{-1}, assigned to a P–O stretch and the phosphonate-coupled carbonyl, respectively. An ultraviolet spectrum of II in aqueous solution exhibited an absorption band at 344 nm ($\epsilon \sim 90$), which we ascribe to the carbonyl n → π^* transition.

Equation I describes a possible route to II. Rearrangements of α,β-epoxyalkylphosphonate esters have



(1)

been extensively studied by Churi[6] and his observations are consistent with the above 1,2 migration of phosphorus. Phosphorus nmr experiments were designed in an attempt to detect the epoxide intermediate suggested in eq 1. Sufficient NaOH was added to an nmr tube containing aqueous I to bring the pH to 7.0. Immediate scanning of these solutions failed to provide any evidence for the intermediate; all resonances detected were assignable to either I or II (Na_2 salts). Our conclusion is that whatever intermediate is involved in this rearrangement is short-lived with respect to the nmr time scale or is not formed in sufficient concentration to be detected by ^{31}P nmr.

When the neutralization in eq 1 was carried out with ammonium hydroxide, the solid tetraammonium salt precipitated from aqueous solution as well-formed, hydrated crystals. Ion exchange or titration to a pH of 1–2 allowed the isolation of the corresponding acid. The free acid was slow to crystallize but was obtained as either the monohydrate[7] from concentrated aqueous solutions or as the anhydrous acid from acetic acid solution.

The free acid, $H_2O_3PCH_2C(O)PO_3H_2$, is much more stable toward hydrolysis than would be expected based on the known instability of 1-ketophosphonates.[8] The rate of decomposition has not been thoroughly studied, but this acid was found to be stable in aqueous solution for 2–3 hr at 70°. It was completely decomposed when refluxed in aqueous solution for 48 hr. The fully neutralized salt, II, is stable for long periods of time to hot aqueous base. In this respect it is reminiscent of tetrasodium carbonyldiphosphonate.[9]

Using the general conditions outlined for the reaction of acylating agents and P(III) sources,[1,2] it was found that PCl_3 reacted with $H_2O_3PCH_2C(O)PO_3H_2 \cdot H_2O$ in di-*n*-propyl sulfone solvent to form, after hydrolysis, ethane-1-hydroxy-1,1,2-triphosphonic acid in nearly quantitative yields. Authentic $H_2O_3PCH_2C(OH)(PO_3H_2)_2$ was prepared from phosphonoacetic acid[1] and shown to be identical with the product (after hydrolysis) of $H_2O_3PCH_2C(O)PO_3H_2 + PCl_3$.

---

(4) V. Mark, C. H. Dungan, M. M. Crutchfield, and J. R. Van Wazer, "Topics in Phosphorus Chemistry," Vol. 5, Wiley, New York, N. Y., 1967, pp 227–457.

(5) D. J. Peterson, *J. Org. Chem.*, **31**, 950 (1966).

(6) R. H. Churi, Thesis, University of Pittsburgh, 1966.

(7) A referee has suggested that the water of hydration might actually be present as the carbonyl hydrate, $H_2O_3PCH_2C(OH)_2PO_3H_2$. The ^{31}P nmr spectrum would seem to rule this out, since such hydration would shift the contiguous phosphonate resonance some 15 ppm downfield.[9] Such a shift is not observed.

(8) G. M. Kosolapoff, "Organophosphorus Compounds," Wiley, New York, N. Y., 1950, p 139.

(9) O. T. Quimby, J. B. Prentice, and D. A. Nicholson, *J. Org. Chem.*, **32**, 4111 (1967).

Experimental Section

Elemental analyses were carried out by the Analytical Section of these laboratories. Temperatures reported herein are uncorrected.

The phosphorus nmr spectra were measured using spinning 9-mm glass tubes with a Varian HR-60 spectrometer operating at 24.3 MHz. Chemical shifts are accurate to ±0.5 ppm. Sideband calibration was used. A Varian HR-60 spectrometer was used to obtain the proton spectra. A Bruker HX-90 pulsed Fourier transform nmr spectrometer with a Nicolet 1084 computer system was used to obtain the ^{13}C nmr spectra. Chemical shifts are reported as parts per million from an external CS_2 reference. Since the nmr spectra are adequately discussed in the text, they will not be repeated here. Infrared spectra of D_2O solutions were recorded on a Perkin-Elmer Model 421 recording spectrophotometer. Ultraviolet spectra were recorded on a Cary Model 11 spectrometer.

Phosphonoacetic acid, chloroacetic acid, and di-*n*-propylsulfone were purchased from various chemical supply houses.

$ClCH_2C(OH)(PO_3H_2)(PO_3HNH_4)$ from $ClCH_2COOH$.—Chloroacetic acid (219 g, 1.2 mol) was heated to 62° to form a mixed liquid and crystalline slush. Phosphorus trioxide (22.1 g, 0.1 mol) was added with rapid stirring. The temperature dropped to 55° and the reaction mixture became clear. This solution was then heated to 65° and maintained there for 18 hr. The resulting condensates were hydrolyzed by adding 14.4 g of water, whereupon the solution was stirred at 65° for an additional 21 hr. The NH_4H_3 salt was precipitated from the clear solution by adding 14.1 g of ammonium acetate to the reaction solution at 60°. After 2-hr digestion the solids were removed by filtration, washed with ethyl ether, and air dried (yield 33.9 g, 66%). The solid had mp 159–160° and assayed as 100% $ClCH_2C(OH)(PO_3H_2)(PO_3HNH_4)$ by acid–base titration.

Anal. Calcd for $C_2H_{10}O_7P_2NCl$: C, 9.3; H, 3.5; P, 24.1; N, 5.4; Cl, 13.8. Found: C, 9.5; H, 3.9; P, 24.6; N, 5.5; Cl, 13.8.

Preparation of $Na_2O_3PCH_2C(O)PO_3Na_2$.—A crude sample of $ClCH_2C(OH)(PO_3H_2)_2$ (containing ~35 g of the acid) was dissolved in 450 ml of water and NaOH was added to a final pH of 10. A solid precipitated on cooling the warm solution to room temperature. The slurry was diluted with 125 ml of acetone and stirred for a short time at 25°, and the solid was removed and air dried. This solid was recrystallized from a 1:1 water–acetone mixture, yielding 49 g of hydrated $Na_2O_3PCH_2C(O)PO_3Na_2$.

A portion of this salt was passed through Dowex 50W-X8 cation exchange resin in the acid form. The aqueous eluent was concentrated on a rotary evaporator. The resulting viscous liquid crystallized on standing. This solid was washed with acetic acid and air dried. It assayed as 91.85% active $H_2O_3PCH_2C(O)PO_3H_2$, corresponding to the monohydrate. A titration curve for this acid, when plotted on the scale used in Figure 1, was essentially superimposable on curve C.

Anal. Calcd for $C_2H_6O_7P_2 \cdot H_2O$: C, 10.8; H, 3.6; P, 27.9; H_2O, 8.1; Cl, 0. Found: C, 10.8; H, 3.6; P, 28.2; H_2O, 8.1; Cl, <0.1.

Preparation of $H_2O_3PCH_2C(OH)(PO_3H_2)_2$ from $H_2O_3PCH_2C(O)PO_3H_2$.—The free acid prepared as above (4.46 g, 0.02 mol) was slurried in 18 ml of di-*n*-propyl sulfone, and PCl_3 (1.9 ml, 0.022 mol) was added at 29°. The slurry quickly resolved to two liquid phases and the temperature rose to 35°. The reaction mixture was heated to 90° over a 1.5-hr period. White solids formed during this heating period. The slurry was digested for 3 hr at 90° and then filtered. After this solid had been washed thoroughly with ethyl ether and air dried (yield 6.8 g) it was dissolved in 50 ml of water and the solution was refluxed for 2 hr. A ^{31}P nmr spectrum of this solution was superimposable on the spectrum of an aqueous solution of authentic ethane-1-hydroxy-1,1,2-triphosphonic acid (see below).

$Na_2O_3PCH_2C(OH)(PO_3HNa)(PO_3Na_2) \cdot 4H_2O$ from Phosphonoacetic Acid.—The literature method[1] for the preparation of this compound was employed with the following alteration. Purification was accomplished by titrating the aqueous solution, obtained from hydrolysis of the $H_2O_3PCH_2COOH + PCl_3$ reaction mixture, to a pH of 10.2. To this solution was added, with rapid stirring, an equal volume of acetone. The solid which separated was removed by filtration and washed with additional acetone. It was dried for 4 hr in an oven at 120°. Acid–base titration showed the resulting material to be the pentasodium salt of ethane-1-hydroxy-1,1,2-triphosphonic acid, solvated with 4 equiv of water. Proton and phosphorus nmr spectra were identical with those reported in the literature.[1]

Anal. Calcd for $C_2H_{12}O_{14}P_3Na_5$: C, 5.1; H, 2.6; P, 19.9; Na, 24.6. Found: C, 5.3; H, 2.9; P, 20.0; Na, 24.4.

Ion exchange employing Dowex 50W-X8 in the acid form produced the water solution of ethane-1-hydroxy-1,1,2-triphosphonic acid used for comparison with the product prepared above.

Kinetics of Dehydrohalogenation.—The rate of chloride release from I was followed at 25° by means of an Orion Model 94-17 solid state chloride electrode. The pH was maintained through the addition of a standard NaOH solution by a Radiometer recording pH-Stat. Reaction mixtures were made 0.1 *M* in KNO_3 to maintain the ionic strength, except during one experiment, at pH 9.0, in which the solution was made 0.1 *M* in NaCl to observe the possible effect of chloride ion on the reaction rate. For this experiment the rate was followed by the rate of consumption of standard base normalized to that of the pH 9.0 reaction run in KNO_3.

Registry No.—I, 34550-07-7; II, 36939-22-7; $ClCH_2C(OH)(PO_3H_2)(PO_3HNH_4)$, 36939-23-8; $ClCH_2COOH$, 79-11-8; $H_2O_3PCH_2C(O)PO_3H_2$, 6874-58-4; $H_2O_3PCH_2C(OH)(PO_3H_2)_2$, 21396-22-5; $Na_2O_3PCH_2C(OH)(PO_3HNa)(PO_3Na_2)$, 21396-24-7; $H_2O_3PCH_2COOH$, 4408-78-0.

Acknowledgments.—The authors wish to thank Dr. T. J. Flautt for help in interpretation of the nmr spectra.