Propane-1,2,3-triphosphonic Acid and Butane-1,2,3,4-tetraphosphonic Acid

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Abstract: The previously unreported title compounds have been prepared *via* reaction of diethyl hydrogen phosphite, sodium, and 2-propyn-1-ol or 2-butyne-1,4-diol, followed by acid hydrolysis. Titrations of the acids with tetramethylammonium hydroxide have been analyzed in terms of acid dissociation constants which are reported for 1 *M* (tetramethylammonium chloride) ionic strength and 25°. The ^{31}P nmr spectra of the acids and salts are unusual in that at low pH the ^{31}P resonances are degenerate, but with neutralization the resonance gradually divides into two peaks assigned to "middle" and "end" phosphonate groups.

Polyphosphonic acids have in recent years received considerable attention because of their chelating ability for polyvalent metal ions, particularly for alkaline earth metal ions. Many methods of preparing diphosphonates have been reported and most of these are collected in the reviews of Kosolapoff[1] and of Freedman and Doak.[2] However, only a few synthetic methods are available for preparing compounds containing three or more phosphonate groups.

Moedritzer and Irani have reported the synthesis of α-aminomethylphosphonic acids, including (nitrilotrimethylene)triphosphonic acid and ethylenebis(nitrilodimethylene)tetraphosphonic acid, from orthophosphorus acid, formaldehyde, and amines.[3] Schwarzenbach had earlier described a procedure for preparing similar compounds, but his method gave poorer yields and required longer reaction times.[4] Many of the reported methods of synthesis of other tri- and tetraphosphonates[5-9] involve several steps and result in low yields.

This paper reports the direct synthesis of the vicinal polyphosphonates, propane-1,2,3-triphosphonic acid (PTP), and butane-1,2,3,4-tetraphosphonic acid (BTeP) from readily available acetylenic alcohols and diethyl hydrogen phosphites.

Results and Discussion

Hexaethyl propane-1,2,3-triphosphonate (I) can be prepared in 70–75% yield through the reaction of an excess of diethyl hydrogen phosphite with 2-propyn-1-ol in the presence of sodium (eq 1). The reaction can conveniently be carried out in toluene solution at ambient temperatures. Octaethyl butane-1,2,3,4-tetraphosphonate (II) results from the reaction of 2-butyne-1,4-diol and excess diethyl hydrogen phosphite in the presence of sodium (eq 2).

$$HC{\equiv}CCH_2OH + 3HPO_3(C_2H_5)_2 \xrightarrow{Na} \underset{\text{I}}{(C_2H_5)_2O_3PCH_2CH(PO_3(C_2H_5)_2)CH_2PO_3(C_2H_5)_2} + H_2O \quad (1)$$

$$HOCH_2C{\equiv}CCH_2OH + 4HPO_3(C_2H_5)_2 \xrightarrow{Na} \underset{\text{II}}{(C_2H_5)_2O_3PCH_2CH(PO_3(C_2H_5)_2)CH(PO_3(C_2H_5)_2)CH_2PO_3(C_2H_5)_2} + 2H_2O \quad (2)$$

The metal was conveniently introduced by prior reaction with diethyl hydrogen phosphite to form diethyl sodium phosphite. It was found that the best yields were obtained in the reactions when slightly more than 1 equiv of sodium was employed per equivalent of 2-propyn-1-ol or 2 equiv of sodium per equivalent of 2-butyne-1,4-diol. This observation suggests the importance of formation of the acetylenic alkoxide. It is presumed that diethyl hydrogen phosphite is added to this intermediate to the point of saturation, forming a β-hydroxy diphosphonate which is dehydrated under the reaction conditions generating the terminal olefin. The final product is formed by a further addition reaction with diethyl hydrogen phosphite. This proposed mechanism for the preparation of compound I is outlined in Scheme I, a similar mechanism could be written for the preparation of II.

Preis, Myers, and Jensen[10] observed a similar dehydration of a β-hydroxyphosphonate in basic solution. They isolated tetraethyl propane-1,2-diphosphonate from the reaction of propylene oxide and sodium diethyl phosphite and suggested that the β-hydroxypropyl phosphonate intermediate undergoes dehydration followed by addition of a second mole of phosphite to the generated double bond.

Compound I was purified by distillation at reduced pressure. Propane-1,2,3-triphosphonic acid was prepared by refluxing pure I with an excess of concentrated hydrochloric acid for 3 hr. This acid crystallized from concentrated aqueous solution.

Compound II proved to be more difficult to purify as it decomposed at the high temperatures required for distillation (>200°, 0.05 Torr). Conversion to the acid, butane-1,2,3,4-tetraphosphonic acid, and addition

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(1) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley & Sons, Inc., New York, N. Y., 1950, Chapter 7.

(2) L. D. Freedman and G. O. Doak, *Chem. Rev.*, **57**, 479 (1957).

(3) K. Moedritzer and R. R. Irani, *J. Org. Chem.*, **31**, 1603 (1966).

(4) G. Schwarzenbach, H. Ackermann, and P. Ruckstuhl, *Helv. Chim. Acta*, **32**, 1175 (1949).

(5) A. J. Burn, J. I. G. Cadogan, and P. J. Bunyan, *J. Chem. Soc.*, 1527 (1963).

(6) B. C. Saunders and P. Simpson, *ibid.*, 3351 (1963).

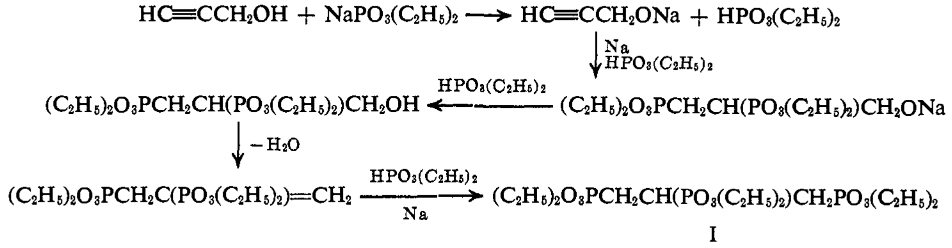
(7) A. N. Pudovik, N. G. Khusainova, and A. B. Ageeva, *Zh. Obshch. Khim.*, **34**, 3938 (1964); *Chem. Abstr.*, **62**, 7792 (1965).

(8) A. N. Pudovik, E. A. Ishmaeva, R. S. Akhmerova, and I. M. Aladzheva, *ibid.*, **36**, 161 (1966); *Chem. Abstr.*, **64**, 14208 (1966).

(9) O. T. Quimby, J. D. Curry, D. A. Nicholson, J. B. Prentice, and C. H. Roy, *J. Organometal. Chem.*, **13**, 199 (1968).

(10) S. Preis, T. C. Myers, and E. V. Jensen, *J. Amer. Chem. Soc.*, **77**, 6225 (1955).

Scheme I



$$\begin{tikzcd}
HC\equiv CCH_2OH + NaPO_3(C_2H_5)_2 \arrow[r] & HC\equiv CCH_2ONa + HPO_3(C_2H_5)_2 \arrow[d, "Na \\ HPO_3(C_2H_5)_2"] \\
(C_2H_5)_2O_3PCH_2CH(PO_3(C_2H_5)_2)CH_2OH \arrow[d, "-H_2O"] & (C_2H_5)_2O_3PCH_2CH(PO_3(C_2H_5)_2)CH_2ONa \arrow[l, "HPO_3(C_2H_5)_2"'] \\
(C_2H_5)_2O_3PCH_2C(PO_3(C_2H_5)_2){=}CH_2 \arrow[r, "HPO_3(C_2H_5)_2", "Na"'] & (C_2H_5)_2O_3PCH_2CH(PO_3(C_2H_5)_2)CH_2PO_3(C_2H_5)_2
\end{tikzcd}$$

I

of either calcium chloride or magnesium chloride at a pH of 7 allowed the isolation of the dicalcium (dimagnesium) salt. After removal of the metal ions by ion exchange the pure acid was crystallized from concentrated aqueous solution. An analytical sample of the octaethyl ester was subsequently prepared *via* esterification of the pure BTeP.

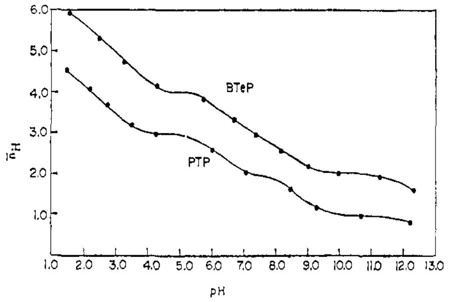


Figure 1. Formation curve, $\bar{n}_H$ *vs.* pH, for PTP and BTeP. Solid lines are calculated on the basis of the dissociation constants (Table I) at 25°, 0.025 *M* PTP and 0.015 *M* BTeP. For clarity only a few of the experimental observations (●) are included.

Acid Dissociation Constants. The values obtained for the dissociation constants of the phosphonic acids are given in Table I. The indicated error intervals are for 95% confidence limits. It was impossible to estimate the value of pK_8 for BTeP because, in aqueous solution, the last proton could not be dissociated at any pH that could be reasonably measured with a glass electrode. The computed constants predict the acid formation curve very well, as shown in Figure 1 in which $\bar{n}_H$, the average number of acid protons bound per phosphonate, is plotted as a function of pH. The solid lines are the calculated curves using p*K* values given in Table I, while the points are experimental observations of which, for clarity, only a few were plotted.

Table I. Acid Dissociation Constants[a]

p*K*	BTeP	PTP
7	12.53 ± 0.03	
6	8.25 ± 0.04	12.86 ± 0.03
5	6.38 ± 0.05	8.68 ± 0.02
4	3.49 ± 0.04	6.22 ± 0.01
3	2.39 ± 0.03	2.92 ± 0.02
2		1.64 ± 0.02

[a] Nominal ionic strength = 1.0 *M*, calculated for complete dissociation of phosphonate. Dissociation constants for the strongest acids, pK_1 and pK_2 of BTeP and pK_1 of PTP, were too small to be reliably determined at 0.025 *M*.

^{31}P Nmr. The ^{31}P nmr spectra were recorded for the esters, acids, and several salts of each phosphonate. The chemical shifts, based on an orthophosphoric acid capillary as reference at 0.0 ppm, are given in Table II. For the acids and ethyl esters the ^{31}P resonances are degenerate, but as neutralization proceeds the resonance gradually divides into two peaks assigned to "middle" and "end" phosphonate groups. On the basis of the observed peak areas for Na_4H_2 PTP, as shown in Figure 2, we presume that the upfield resonance is due to "end" groups.

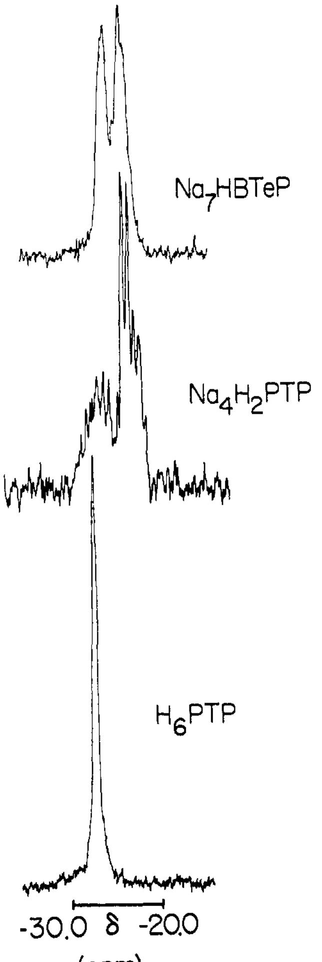


Figure 2. ^{31}P nmr spectra for PTP and BTeP. Chemical shifts are based on an orthophosphoric acid capillary as reference at 0.0 ppm.

That there are no geminal arrangements of two phosphonate groups in these compounds is indicated by the single resonance for the esters at −28.5 (−30.3) ppm. Compounds, such as tetraethyl methylenediphosphonate, containing the geminal diphosphonate unit resonate in the vicinity of −15.0 to −20.0 ppm (ref 9).

Table II. ^{31}P nmr Chemical Shifts

Compd	BTeP, ppm	PTP, ppm
Ethyl ester	−30.3	−28.5
Acid	−27.2	−27.5
Na_3[a]		−25.2
Na_4	−25.6, −24.7	−26.5, −23.2
Na_5	−26.1, −24.3	−26.7, −23.3
Na_6	−26.1, −24.1	−27.0, −23.9
Na_7	−26.1, −24.3	
Na_8	−26.9, −25.0	

[a] This and the following designations indicate the sodium content of the salt before dissolution in water. It is clear from an examination of the titration curves that the widest range of $\bar{n}_H$ values, in the absence of excess base or acid, is about 4.6–0.8 for PTP and 5.9–1.5 for BTeP.

Experimental Section

All melting points reported herein are uncorrected. Elemental analyses were carried out in these laboratories. All manipulations involving oxygen- and moisture-sensitive substances were carried out in an atmosphere of dry oxygen-free nitrogen. Phosphorus nmr spectra were recorded on a Varian Associates HR 60 spectrometer. Chemical shifts are reported in parts per million (ppm) from an external 85% H_3PO_4 reference. Molecular weights were determined on a Model 302 Mechrolab osmometer.

Metallation of Diethyl Hydrogen Phosphite. In a typical experiment sodium (23 g, 1 mol) was combined with 250 ml of toluene in a 1-l. three-necked flask. The sodium was dispersed by stirring at 9000 rpm for 5 min at 110°, then cooled to room temperature. Diethyl hydrogen phosphite (138.1 g, 1 mol) was slowly added to the dispersed sodium with external cooling to maintain a reaction temperature of 25–30°. Stirring was continued until all sodium was consumed (~ 0.5 hr).

Propane-1,2,3-triphosphonic Acid. Diethyl sodium phosphite (1.5 mol) and diethyl hydrogen phosphite (2.5 mol) were combined in 500 ml of toluene. 2-Propyn-1-ol (56.1 g, 1 mol) was cautiously added over a 30-min period. The reaction was exothermic and the temperature was kept below 75° by external cooling. After addition was complete the mixture was stirred for several hours at 70–80°. The solvent and excess phosphite were removed at 50° and 0.5 Torr. The residue was then dissolved in water and passed through a Dowex 50W-X8 ion-exchange resin (H^+ form) to remove sodium ions. After the water was removed the remaining material was reesterified with triethyl orthoformate. Distillation of the resulting ester gave a 72% yield (based on 2-propyn-1-ol) of hexaethyl propane-1,2,3-triphosphonate, bp 170° (0.1 Torr).

Anal. Calcd for $C_{15}H_{35}O_9P_3$: C, 39.8; H, 7.8; P, 20.5; mol wt, 452. Found: C, 39.2; H, 8.1; P, 20.6; mol wt, 425.

A portion of the hexaethyl propane-1,2,3-triphosphonate was converted to the acid by refluxing for 4 hr with an excess of concentrated HCl. Removal of the excess HCl left a viscous liquid which was dissolved in water. Addition of an excess of aniline followed by evaporation to dryness left a white solid. This salt was crystallized from a 6:1:3 mixture of isopropyl alcohol–methanol–acetone to give a product melting at 195°. Ion-exchanging this aniline salt and subsequent removal of water gave the pure propane-1,2,3-triphosphonic acid which slowly crystallized.

Anal. Calcd for $C_3H_{11}O_9P_3$: C, 12.7; H, 3.9; P. 32.7. Found: C, 12.5; H, 3.8; P, 33.2.

Butane-1,2,3,4-tetraphosphonic Acid. Crude octaethyl butane-1,2,3,4-tetraphosphonate was prepared from 2-butyne-1,4-diol, sodium diethyl phosphite (2.5 equiv), and diethyl hydrogen phosphite (2.5 equiv) in the manner described above. This crude ester could not conveniently be distilled so it was converted to the acid by refluxing with an excess of concentrated HCl. After removal of excess HCl, a water solution of the crude acid was titrated to pH 7 with NaOH and an excess of $CaCl_2$ was added. A solid (the dicalcium salt) formed and was removed by centrifugation. This solid was ion exchanged to the acid and the precipitation of the dicalcium salt repeated. Again the calcium was removed by ion-exchanging and after removal of water the butane-1,2,3,4-tetraphosphonic acid slowly crystallized.

Anal. Calcd for $C_4H_{14}O_{12}P_4$: C, 12.7; H, 3.7; P, 32.8. Found: C, 12.8; H, 3.9; P, 32.6.

A sample of the butane-1,2,3,4-tetraphosphonic acid was reesterified with triethyl orthoformate. The resulting viscous liquid was molecularly distilled yielding pure octaethyl butane-1,2,3,4-tetraphosphonate.

Anal. Calcd for $C_{20}H_{46}O_{12}P_4$: C, 39.9; H, 7.7; P, 20.6; mol wt, 602.5. Found: C, 39.8; H, 7.6; P, 20.6; mol wt, 580.

Acid Dissociation Constants. All titrations were carried out at 25° under nitrogen, the titrant being added under the surface of a magnetically stirred solution. The pH meter (Radiometer, Model PH 4) was standardized against NBS buffers at pH 4.01 and 9.18. The glass electrode was calibrated as a concentration probe for hydrogen ion according to the method suggested by Irving, *et al.*[11] During a titration both titrant and titrand were of the same concentration in tetramethylammonium phosphonate, 0.025 *M* for PTP, and 0.015 *M* for BTeP, the solutions having been prepared from the solid acid and tetramethylammonium hydroxide. In addition the titrant contained a known concentration of HCl. Tetramethylammonium chloride was added to all solutions to give a nominal ionic strength of 1.0, calculated assuming complete dissociation of the phosphonates. Acid dissociation constants were calculated from appropriate pH–volume measurements, all titrations being done in triplicate. Data reduction was through the use of Letagropvrid[12] and an IBM 360-Model 44 computer.

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(11) H. M. N. H. Irving, M. G. Miles, and L. D. Pettit, *Anal. Chim. Acta*, 38, 475 (1967).

(12) N. Ingri and L. G. Sillén, *Ark. Kemi*, 23, 97 (1964).