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Preparative Synthesis and Structure of 2,2-Bis(hydroxymethyl)propyl and 2,2-Bis(hydroxymethyl)butyl Phosphites

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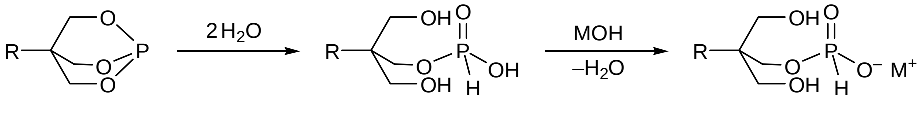
Abstract—Conditions were found for selective hydrolysis of bicyclic phosphites derived from 2,2-bis-(hydroxymethyl)-1-propanol and 2,2-bis(hydroxymethyl)-1-butanol to the corresponding dihydrogen phosphites. The latter were isolated as potassium, sodium, and ammonium salts and were characterized by the ^{1}H, ^{13}C, and ^{31}P NMR spectra. The structure of the ammonium salt was proved by X-ray analysis.

In the last 15 years, alkyl dihydrogen phosphites have been extensively used as intermediate products in the synthesis of glycero- and sphingolipids [1], nucleotides [2, 3], and oligosaccharides [4, 5]. As a rule, intermediate PH-containing compounds were not isolated, and their structure was not proved rigorously.

Alkyl dihydrogen phosphites can be synthesized by partial hydrolysis of trialkyl phosphites [6]. Symmetric bicyclic phosphites of the 1,3,2-dioxaphosphinane series are convenient models for studying stepwise hydrolysis of such compounds. Bicyclic phosphorous esters are more stable to hydrolysis and acidolysis than common phosphites [7]. Verkade and co-workers [8, 9] previously succeeded in effecting the hydrolysis of 4-methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]-octane (**I**), 4-ethyl-2,6,7-trioxa-1-phosphabicyclo-[2.2.2]octane (**II**), and 2,8,9-trioxa-1-phosphabicyclo-[3.3.1.1^{3,7}]decane only to the corresponding monocyclic hydrogen phosphites. For example, treatment of phosphite **I** with an equimolar amount of water in the presence of a catalytic amount of H_2SO_4 gave isomeric 4-methyl-5-hydroxymethyl-1,3,2λ^5-dioxaphosphinane 2-oxides. Heating with a considerable excess of water could result in complete hydrolysis of phosphites **I** and **II** with formation of phosphorous acid and the corresponding triol. We also demonstrated the possibility for effecting partial hydrolysis of bicyclic phosphite **II** [10], but the products were characterized only by ^{31}P NMR spectroscopy without isolation from the reaction mixture. No preparative synthesis of intermediate hydrolysis products, specifically of alkyl dihydrogen phosphites **III** and **IV**, was performed previously.

We now propose a procedure for the synthesis of alkyl dihydrogen phosphites, which can be accomplished in two versions. This procedure makes 2,2-bis-(hydroxymethyl)alkyl phosphites **III** and **IV** accessible for studying their further transformations. According to both versions, the hydrolysis of bicyclic phosphites **I** and **II** is carried out in a two-phase system. In the

Scheme 1.



V, R = Me, M = NH_4; **VI**, R = Me, M = Na; **VII**, R = Me, M = K; **VIII**, R = Et, M = NH_4; **IX**, R = Et, M = Na; **X**, R = Et, M = K.

first case, the system consists of immiscible liquids, e.g., toluene and water or *p*-xylene and water. The preparative synthesis was performed at room temperature by adding ~100-fold excess of water to a solution of phosphite **I** or **II** in xylene or toluene. The progress of the reaction was monitored by TLC and ^{31}P NMR spectroscopy. The hydrolysis was assumed to be complete when the substrate disappeared from the organic phase. The reaction time was 10–12 h, depending on the R group. The products, alkyl dihydrogen phosphites, were isolated from the aqueous phase as the corresponding potassium, sodium, or ammonium salts. Their yields were 68–73%.

Following the second version, a suspension of crystalline bicyclic phosphite **I** or **II** (which is insoluble in water) and 50–80 equiv of water was vigorously stirred at room temperature, no other solvent being added. The reaction was complete in 35–40 min. During the process, partial hydrolysis products were transferred into aqueous solution. As in the first procedure, the products were isolated as the corresponding salts which had the same physical constants. Depending on the cation nature, the yield of alkyl dihydrogen phosphites was 82 to 87%. Obviously, the second version is more advantageous from the viewpoint of both reaction time and product yield.

The structure of the products was proved by the ^{1}H and ^{13}C NMR spectra which contained signals from all protons and carbon nuclei with the expected multiplicities (see Experimental). The structure of ammonium 2,2-bis(hydroxymethyl)butyl hydrogen phosphite (**V**) was also examined by the X-ray diffraction method (Fig. 1). It should be noted that no X-ray diffraction data for ammonium salts of phosphorous acid were reported previously. The bond lengths and bond angles in the alkyl fragment are typical of phosphorous esters [11]. The phosphorus atom has a tetrahedral configuration, and the HPO angles are, on the average, 107(1)°. The $P^1–O^1$ and $P^1–O^2$ bonds (Table 1) are appreciably shorter than the corresponding bonds in ammonium dihydrogen phosphate $NH_4^+O_2P(OH)_2^-$ (1.518 and 1.521 Å [12]), indicating increased negative charge density in the PO_2^- fragment. The $P^1–O^3$ bond length falls into the region typical of phosphorus acid esters (1.55–1.59 Å [11]). The principal structural parameters of molecule **V** are listed in Table 1.

Anions of **V** in crystal are linked through strong O–H···O–P and O–H···O intermolecular hydrogen bonds to form double chains along the *101* crystallographic axis (Fig. 2, Table 2). The presence of ammonium cations gives rise to a three-dimensional framework via N–H···O and O–H···O hydrogen bonds (Fig. 3, Table 2). Ammonium cation NH_4^+ forms hydrogen bonds mainly with the O^1 and O^2 atoms which possess an increased negative charge density. The $P^1–H^1$ bond is not involved in intermolecular interactions.

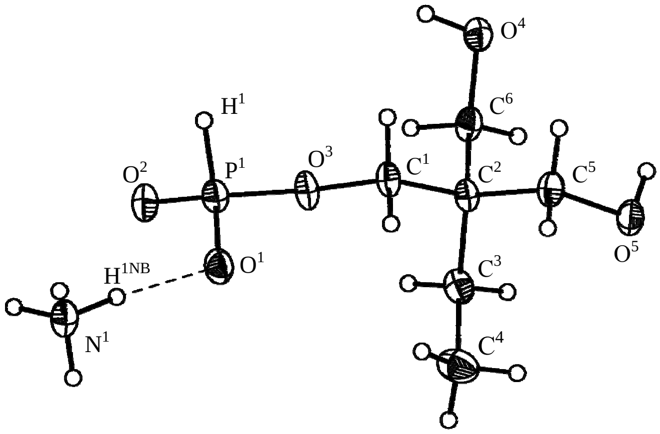


Fig. 1. Structure of molecule **V** according to the X-ray diffraction data. The atoms are shown as 50%-probability thermal ellipsoids.

To conclude, it should be noted that the proposed procedures for partial hydrolysis of symmetric bicyclic phosphites can be applied successfully to the synthesis of difficultly accessible functionally substituted alkyl dihydrogen phosphites which can be stored for a long time in the form of the simplest salts.

EXPERIMENTAL

All syntheses with phosphorus(III) derivatives were performed in an inert atmosphere. The ^{31}P NMR spectra were recorded on a Bruker V80SY instrument

Table 1. Principal bond lengths *d* and bond angles ω in molecule **V**

Bond	*d*, Å	Angle	ω, deg
$P^1–O^1$	1.492(2)	$O^1P^1O^2$	118.3(1)
$P^1–O^2$	1.497(2)	$O^1P^1O^3$	111.0(1)
$P^1–O^3$	1.588(2)	$O^2P^1O^3$	105.2(1)
$O^3–C^1$	1.441(3)	$C^1O^3P^1$	119.33(2)
$O^4–C^6$	1.432(3)	$O^3C^1C^2$	108.8(2)
$O^5–C^5$	1.426(3)	$H^1P^1O^1$	110(1)
C–C (av.)	1.530(3)	$H^1P^1O^2$	106(1)
$P^1–H^1$	1.26(2)	$H^1P^1O^3$	106(1)

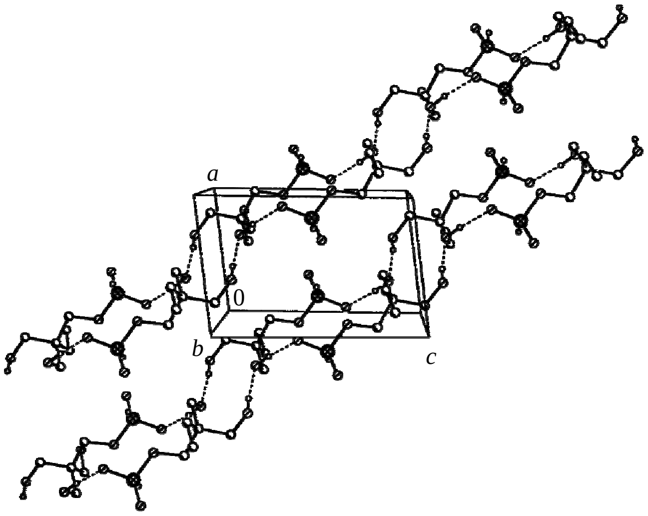


Fig. 2. Chains formed by anions of **V** in crystal via strong O–H···O hydrogen bonds.

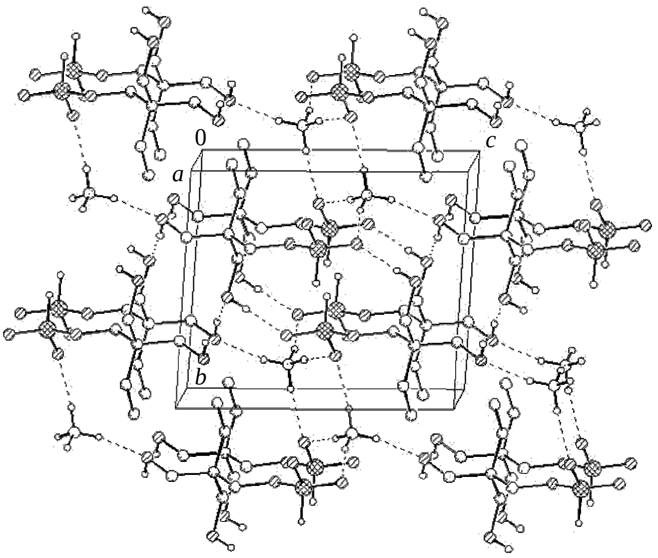


Fig. 3. Three-dimensional framework formed by molecules **V** in crystal via O–H···O and C–H···O hydrogen bonds.

using 85% phosphoric acid as reference. The ^1H and ^{13}C NMR spectra were measured on a Bruker AC-200 spectrometer; the chemical shifts were measured relative to tetramethylsilane as internal reference. The melting points were determined on a Yanaco MP-S3 device. Analytical data were obtained on a Perkin–Elmer 2400 automatic analyzer.

X-Ray diffraction study of ammonium salt V. Colorless crystals of **V** were obtained by recrystallization from hexane–HMPA (10:1). $C_6H_{18}NO_5P$. Unit cell parameters: $a = 6.227(1)$, $b = 8.599(2)$, $c = 9.855(2)$ Å; $\alpha = 92.43(4)°$, $\beta = 97.794(5)°$, $\gamma = 93.927(4)°$; $V = 520.9(2)$ Å^3; space group $P\bar{1}$; $Z = 2$, $d_{\text{calc}} = 1.372$ g/cm^3; M 215.18. The unit cell parameters and intensities of 4195 reflections were measured at 110 K on a Smart 1000K CCD automatic diffractometer (graphite monochromator, MoK_α radiation, $\lambda = 0.71072$ Å, ω-scanning with a step of 0.4°, $2.7 \geq 2\theta \leq 30°$). In the subsequent calculations, 2838 independent reflections were used. The structure was solved by the direct method. The positions of non-hydrogen atoms were refined with respect to F^2 in the full-matrix anisotropic approximation. The positions of hydrogen atoms were determined from the difference Fourier syntheses of electron density and were refined in isotropic approximation. The final divergence factors were $R_1 = 0.0595$ (from 1756 reflections with $I > 2\sigma$) and $wR_2 = 0.1328$ (from all reflections), GOF 0.997. All calculations were performed using SHELXTL PLUS version 5.10 software package [13].

4-Methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]-octane (**I**) [14] and 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane (**II**) [15] were synthesized by known methods.

Partial hydrolysis of bicyclic phosphites I and II. *a.* Phosphite **I**, 5.0 g, was dissolved in 120 ml of *p*-xylene or toluene, 120 ml of distilled water was added, and the mixture was vigorously stirred for 12 h under nitrogen. The aqueous layer was separated and concentrated by half under reduced pressure at 60°C, a 15% excess of aqueous KOH, NaOH, or ammonia was added, and water was removed under reduced pressure until a glassy syrup was obtained. The residue was dissolved in hot ethanol, the solution was cooled, the precipitate of inorganic salt (K_2HPO_3 or Na_2HPO_3) was filtered off, and the filtrate was concentrated until a syrupy material was obtained. This material was washed with acetone (3×25 ml) to remove 2,2-bis-(hydroxymethyl)-1-propanol and dried under reduced pressure, and the solid residue was recrystallized from methanol– acetone (1:2).

Ammonium 2,2-bis(hydroxymethyl)propyl hydrogen phosphite (V). Yield 4.71 g (68%). Syrupy liquid. ^{31}P NMR spectrum (32.4 MHz, CD_3OD): δ_P 6.3 ppm, $J_{PH} = 623.7$ Hz. ^1H NMR spectrum (200 MHz, D_2O), δ, ppm: 0.89 m (3H, CH_3C), 3.51 m (4H, $C\mathbf{H}_2OH$), 3.56 br.s (2H, $CH_2O\mathbf{H}$), 3.79 d (2H, CH_2OP, $^2J_{HH} = 7.15$ Hz), 6.71 d (1H, PH, $J_{PH} = 635.1$ Hz), 8.11 br.s (4H, NH_4). ^{13}C NMR spectrum [50.32 MHz, $(CD_3)_2SO$], δ_C, ppm: 17.8 (CH_3), 43.4 ($CH_3\mathbf{C}$, $J_{CP} = 2.5$ Hz), 65.4 (CH_2OP, $J_{CP} = 4.8$ Hz), 66.5 (CH_2OH). Found, %: C 29.76; H 8.03; P 15.39. $C_5H_{16}NO_5P$. Calculated, %: C 29.85; H 7.96; P 15.42.

Sodium 2,2-bis(hydroxymethyl)propyl hydrogen phosphite (VI). Yield 5.11 g (72%). Syrupy liquid. ^{31}P NMR spectrum (32.4 MHz, CD_3OD): δ_P: 5.4 ppm, J_{PH} = 626.3 Hz. ^{1}H NMR spectrum (200 MHz, D_2O), δ, ppm: 0.88 m (3H, CH_3C), 3.47 m (4H, C**H**$_2$OH), 3.52 br.s (2H, CH_2O**H**) 3.74 d (2H, CH_2OP, $^2J_{HH}$ = 7.15 Hz), 6.69 d (1H, PH, J_{PH} = 635.1 Hz). ^{13}C NMR spectrum [50.32 MHz, $(CD_3)_2SO$], δ_C, ppm: 18.3 (CH_3), 43.6 (CH_3**C**, J_{CP} = 2.3 Hz), 65.5 (CH_2OP, J_{CP} = 4.8 Hz), 66.2 (CH_2OH). Found, %: C 29.08; H 4.89; P 15.00. $C_5H_{12}NaO_5P$. Calculated, %: C 29.13; H 5.82; P 15.05.

Potassium 2,2-bis(hydroxymethyl)propyl hydrogen phosphite (VII). Yield 5.2 g (70%). mp 131–132°C. ^{31}P NMR spectrum (32.4 MHz, CD_3OD): δ_P 7.8 ppm, J_{PH} = 634.3 Hz. ^{1}H NMR spectrum (200 MHz, D_2O), δ, ppm: 0.86 m (3H, CH_3C), 3.49 m (4H, C**H**$_2$OH), 3.58 br.s (2H, CH_2O**H**) 3.79 d (2H, CH_2OP, $^2J_{HH}$ = 7.15 Hz), 6.71 d (1H, PH, J_{PH} = 635.1 Hz). ^{13}C NMR spectrum [50.32 MHz, $(CD_3)_2SO$], δ_C, ppm: 17.7 (CH_3), 43.2 (CH_3**C**, J_{CP} = 2.5 Hz), 65.4 (CH_2OP, J_{CP} = 4.8 Hz), 66.6 (CH_2OH). Found, %: C 26.98; H 5.49; P 13.90. $C_5H_{12}KO_5P$. Calculated, %: C 27.03; H 5.41; P 13.96.

Likewise, compounds **VIII**–**X** were obtained from 3.73 g of phosphite **II** in 80 ml of toluene and 75 ml of water.

Ammonium 2,2-bis(hydroxymethyl)butyl hydrogen phosphite (VIII). Yield 3.27 g (66%). mp 81–82°C. ^{31}P NMR spectrum (32.4 MHz, CD_3OD): δ_P 6.3 ppm, J_{PH} = 623.4 Hz. ^{1}H NMR spectrum (200 MHz, D_2O), δ, ppm (*J*, Hz): 0.69 t (3H, CH_3C), 1.21 q (2H, CH_3C**H**$_2$), 3.33 m (4H, C**H**$_2$OH), 3.51 br.s (2H, CH_2O**H**), 3.52 d (2H, CH_2OP, J_{HH} = 6.8), 6.31 s (4H, NH_4), 6.70 d (1H, PH, J_{PH} = 637.7). ^{13}C NMR spectrum [50.32 MHz, $(CD_3)_2SO$], δ_C, ppm (*J*, Hz): 8.7 (CH_3), 22.7 (CH_3CH_2C), 45.7 [$(CH_2)_4$**C**, J_{CP} = 2.1), 62.6 (CH_2OH), 63.4 (CH_2OP, J_{CP} = 5.7). Found, %: C 36.22; H 8.43; P 14.37. $C_6H_{18}NO_5P$. Calculated, %: C 36.28; H 8.37; P 14.42.

Sodium 2,2-bis(hydroxymethyl)butyl hydrogen phosphite (IX). Yield 3.49 g (67%). Syrupy liquid. ^{31}P NMR spectrum (32.4 MHz, CD_3OD): δ_P 5.3 ppm, J_{PH} = 627.1 Hz. ^{1}H NMR spectrum (200 MHz, D_2O), δ, ppm: 0.69 t (3H, CH_3C), 1.17 q (2H, CH_3C**H**$_2$), 3.49 m (4H, C**H**$_2$OH), 3.79 d (2H, CH_2OP, $^2J_{HH}$ = 7.15 Hz), 6.69 d (1H, PH, J_{PH} = 635.1 Hz). ^{13}C NMR spectrum [50.32 MHz, $(CD_3)_2SO$], δ_C, ppm: 8.7 (CH_3), 22.7 (CH_3**C**H_2C), 45.7 [$(CH_2)_4$**C**, J_{CP} = 2.1 Hz], 62.6 (CH_2OH), 63.4 (CH_2OP, J_{CP} = 5.7 Hz). Found, %: C 34.48; H 6.25; P 13.68. $C_6H_{14}NaO_5P$. Calculated, %: C 34.51; H 6.19; P 13.72.

Table 2. Parameters of O–H···O and N–H···O hydrogen bonds in the crystalline structure of compound **V**

D–H···A	D–H, Å	H···A, Å	D···A, Å	DHA, deg
O^4–H^4···O^2 [–*x*, –*y*+1, –*z*+1]	0.87	1.82	2.679(3)	173.5
O^5–H^5···O^4 [–*x*–1, –*y*+1, –*z*]	0.89	1.83	2.709(3)	166.5
N^1–H^{1NA}···O^5 [*x*+1, *y*, *z*+1]	0.90	1.95	2.838(4)	167.8
N^1–H^{1NB}···O^1	0.98	1.86	2.833(4)	175.2
N^1–H^{1NC}···O^2 [*x*+1, *y*, *z*]	0.92	1.90	2.805(3)	168.1
N^1–H^{1ND}···O^1 [–*x*+1, –*y*, –*z*+1]	0.90	1.96	2.852(4)	172.4

Potassium 2,2-bis(hydroxymethyl)butyl hydrogen phosphite (X). Yield 4.07 g (73%). mp 154–155°C. ^{31}P NMR spectrum (32.4 MHz, CD_3OD): δ_P 7.8 ppm, J_{PH} = 634.3 Hz. ^{1}H NMR spectrum (200 MHz, D_2O), δ, ppm: 0.67 m (3H, CH_3C), 1.13 q (2H, CH_3C**H**$_2$), 3.30 m (4H, C**H**$_2$OH), 3.70 d (2H, CH_2OP, J_{HH} = 6.8 Hz), 6.71 d (1H, PH, J_{PH} = 634.2 Hz). ^{13}C NMR spectrum [50.32 MHz, $(CD_3)_2SO$], δ_C, ppm: 8.5 (CH_3), 22.5 (CH_3**C**H_2C), 45.3 [$(CH_2)_4$**C**, J_{CP} = 1.8 Hz], 62.1 (CH_2OH), 63.5 (CH_2OP, J_{CP} = 5.2 Hz). Found, %: C 32.19; H 5.84; P 12.78. $C_6H_{14}KO_5P$. Calculated, %: C 32.23; H 5.79; P 12.81.

b. Distilled water, 50 ml, was added to 2.0 g of bicyclic phosphite **I**, and the mixture was vigorously stirred in an inert atmosphere (N_2). When the initial phosphite dissolved completely (35 min), 15% excess of aqueous KOH, NaOH (Na_2CO_3), or ammonia was added, and the solution was concentrated under reduced pressure, and was then treated as described above in *a*.

Ammonium 2,2-bis(hydroxymethyl)propyl hydrogen phosphite (V). Yield 2.23 g (82%).

Sodium 2,2-bis(hydroxymethyl)propyl hydrogen phosphite (VI). Yield 2.34 g (84%).

Potassium 2,2-bis(hydroxymethyl)propyl hydrogen phosphite (VII). Yield 2.55 g (85%).

Likewise, compounds **VIII**–**X** were obtained from 2.44 g of phosphite **II** and 60 ml of water.

Ammonium 2,2-bis(hydroxymethyl)butyl hydrogen phosphite (VIII). Yield 2.75 g (85%).

Sodium 2,2-bis(hydroxymethyl)butyl hydrogen phosphite (IX). Yield 2.76 g (87%).

Potassium 2,2-bis(hydroxymethyl)butyl hydrogen phosphite (X). Yield 3.09 g (87%).

The physical constants, analytical data, and spectral parameters of compounds **V**–**X** prepared as described in *a* and *b* coincided.

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