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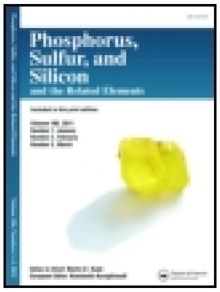

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A STUDY OF THE REACTION OF PHOSPHORUS TRICHLORIDE WITH PARAFORMALDEHYDE IN THE PRESENCE OF CARBOXYLIC ACIDS

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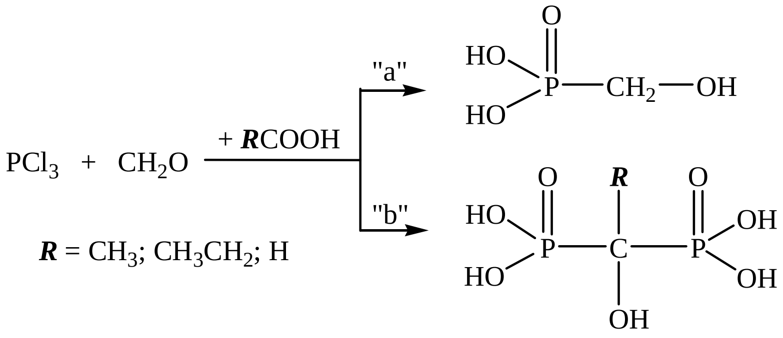

Abstract *We investigated the mechanism of the reaction of paraformaldehyde with phosphorus trichloride in the presence of carboxylic acids (acetic, propanoic and formic). Our results revealed that bisphosphonic acids were obtained without the use of water. The structures of the reaction products were studied by 1D and 2D homonuclear and heteronuclear ^{1}H-, ^{13}C-, ^{31}P-NMR spectroscopy.*

Keywords Hydroxymethylphosphonic acid; bisphosphonic acids; 1-hydroxyalkylidene-1,1-diphosphonic acid; phosphorus trichloride

INTRODUCTION

The reaction between phosphorus trichloride and various aldehydes (acet-, propion-, isobutyr-, isovaler-, hept-, and benzaldehydes) to prepare α-hydroxymethylphosphonic acid derivatives was initially studied by Fossek.[1,2] α-Hydroxymethylphosphonic acid was first synthesized by Page via the reaction of phosphorus trichloride and paraformaldehyde in a 1:1 molar ratio. Subsequent hydrolysis of the reaction product resulted in the formation of hydroxymethylphosphonic acid in 93% yield.[3] The reaction was carried out in the presence of acetic acid. It is well known that phosphorus trichloride reacts with alkanoic acids to form the corresponding chloro anhydrides and dichlorophosphite. Both compounds are very reactive, but in the literature devoted to the reaction of phosphorus trichloride and paraformaldehyde in the presence of acetic acid, the reactivity of these two compounds is not discussed. In our previous work, we described the synthesis of new cycloalkanespiro-5-hydantoin aminophosphonic acids.[4] It was established from the ^{31}P NMR spectrum that the appearance of two signals at 20 to 22 ppm, characteristic of a phosphonic structure, could be explained by the participation of acetic acid, used as a solvent. This was behind our interest in studying the reaction of phosphorus trichloride with paraformaldehyde in the presence of carboxylic acids (formic, acetic and propanoic) by NMR spectroscopy. The main goal of this study was to prove the mechanism and structures of the reaction products.

RESULTS AND DISCUSSION

The reaction of paraformaldehyde with phosphorus trichloride in a molar ratio of 1:1 was realized in the presence of acetic, propanoic and formic acids.

In the presence of acetic acid: In the $^{31}P\{H\}$ NMR spectrum of the reaction product obtained by precipitation in water, there were two signals at 23.20 ppm and at 20.96 ppm. In the ^{31}P NMR spectrum the signal at 23.20 ppm occurred as a triplet with a coupling constant $^{3}J(P,H) = 7.3$ Hz, and that at 20.96 ppm was a quartet with a coupling constant $^{3}J(P,H) = 16.0$ Hz. In the ^{1}H NMR spectrum of the reaction mixture there was a triplet at 1.64 ppm with a coupling constant of 16.0 Hz and a doublet at 3.78 ppm with a coupling constant of 7.3 Hz. Also in the $^{13}C\{H\}$ NMR spectrum there was a triplet at 71.6 ppm with a coupling constant of $^{1}J(P,C) = 152.6$ Hz and a doublet at 58.7 ppm with a coupling constant of $^{1}J(P,C) = 162.4$ Hz. There was also a triplet at 20.7 ppm with a coupling constant of 1.4 Hz. The DEPT spectrum revealed that the signal at 71.6 ppm was a tertiary carbon. The value of the coupling constant revealed that this carbon atom was bonded directly to two phosphorus atoms; the triplet at 20.7 ppm was due to a CH_3 carbon atom in β-position to the phosphorus atoms. The doublet at 58.7 ppm corresponded to a CH_2 carbon, directly bonded to the phosphorus atom. Based on these data it can be assumed that the following compounds are formed: α-hydroxymethylphosphonic acid and 1-hydroxyethylidene-1,1-diphosphonic acid (Figure 1).

Based on the integral intensities of the signals in the $^{31}P\{H\}$ NMR spectrum the mixture consisted of 24% α-hydroxymethylphosphonic acid and 76% 1-hydroxyethylidene-1,1-diphosphonic acid.

In the presence of propanoic acid: In the $^{31}P\{H\}$ NMR spectrum of the reaction mixture, before treating with water, there was a singlet at 20.45 ppm, a doublet ($^{2}J(P,P) = 19.2$ Hz) at 19.22 ppm, singlets at 18.25 ppm, 17.88 ppm and 17.14 ppm, a doublet ($^{2}J(P,P) = 19.3$ Hz) at 16.11 ppm, and singlet at 10.94 ppm, 9.79 ppm, 6.94 ppm and -2.23 ppm. In the ^{31}P NMR spectrum the signal at: 20.45 ppm represents a triplet with a coupling constant ${}^{3}J$(P,H) = 8.2 Hz; 19.22 ppm, a doublet of triplets with a coupling constants ${}^{3}J$(P,P) = 19.2 Hz and ${}^{3}J$(P,H) = 16.1 Hz; 18.25 ppm, a triplet with a coupling constant ${}^{2}J$(P,H) = 14.3 Hz; 17.88 ppm, a triplet with coupling constant ${}^{3}J$(P,H) = 9.1 Hz; 17.14 ppm, a triplet with a coupling constant ${}^{2}J$(P,H) = 14.3 Hz; 16.11 ppm, a doublet of triplets with coupling constants ${}^{2}J$(P,P) = 19.3 Hz and ${}^{3}J$(P,H) = 14.1 Hz; 10.94 ppm, a doublet of quartets with a coupling constants ${}^{3}J$(P,H) = 3.2 and 11.7 Hz; 9.79 ppm, a doublet with a coupling constant ${}^{3}J$(P,H) = 9.8 Hz; 6.96 ppm, a doublet of quartets with a coupling constants of 3.2 and 10.2 Hz. The signal at -2.23 ppm represents a singlet and can be assigned to the phosphorus atom in trichlorophosphate. This compound can be obtained as a result of oxidation of phosphorus trichloride.

In the ^{31}P NMR spectrum of the reaction mixture, obtained after addition of water, there were three signals present: a triplet with a coupling constant of 7.2 Hz at 23.5 ppm, a triplet with a coupling constant of 15.7 Hz at 21.4 ppm and a doublet with a coupling constant ${}^{1}J$(P,H) = 668.8 Hz at 4.85 ppm. The signals at: 19.3, 18.3, 17.9, 17.2, 16.1, 10.9, 9.7, and 6.9 ppm disappeared after adding of water. The new signal at 4.85 ppm represents a doublet with a coupling constant ${}^{1}J$(P,H) = 668.8 Hz assigned to the phosphorus atom in the H-phosphonic acid. The H-phosphonic acid is formed after treating the reaction mixture with H_2O. Obviously, hydrolysis of a four coordinated phosphorus compound resulted in the formation of the H-phosphonic acid because in the ^{31}P{H} NMR spectrum of the reaction mixture before adding water there was no signal in the region 200 - 220 ppm, characteristic of a trivalent phosphorus atom, including the phosphorus atom of phosphorus trichloride, and there was no signal at 4.85 ppm. The only compound, which can be converted via hydrolysis in a H-phosphonic acid, is dichloro H-phosphonate. According to the integral intensity of the phosphorus atoms in the reaction mixture, the content of H-phosphonic acid was 42%.

The triplet at 1.16 ppm with coupling a constant of 7.6 Hz in the ^{1}H NMR of the reaction mixture can be assigned based by HSQC to a CH_3 in the fragment -CH_2-CH_3. The DEPT spectrum revealed that the signal was also due to the CH_3 carbon. The doublet at 3.77 ppm with a coupling constant of 7.4 Hz based on the HSQC spectrum was assigned to the $C\underline{H}_2$ protons in the fragment, P-CH_2OH. The DEPT spectrum confirmed this inference. The multiplet at 2.09 ppm (triplet of quartets with a coupling constants ^3J(H,H) = 7.6 and ^3J(P,H) = 15.8 Hz) was assigned to the CH_2 protons in the fragment [P-C- (CH_2-CH_3)-P]; the HSQC spectrum revealed that this signal correlated with the $\underline{C}H_2$ signal at 27.89 ppm in the ^{13}C{H} NMR spectrum and can be assigned to the CH_2 carbon atom in β-position to the phosphorus atom (In the literature a ^2J(P,C) constant close to 0 Hz in phosphonates has been reported[5]). In the ^{13}C{H} NMR spectrum there was a triplet at 74.5 ppm with a coupling constant of 148.3 Hz and a doublet at 58.2 ppm with a coupling constant of 162.8 Hz. There was a triplet at 8.77 ppm with a coupling constant of 6.4 Hz. The DEPT spectrum revealed that the signal at 74.5 ppm was a tertiary carbon atom; that at 58.2 ppm was due to a CH_2 carbon, and the signal at 27.8 ppm was also due to a CH_2 carbon. The triplet at 8.77 ppm is due to the CH_3 carbon atom. The values of the coupling constants for the triplet and doublet revealed that these carbon atoms were directly connected to the phosphorus atom.

NMR data supported the formation of the following two compounds during the reaction between phosphorus trichloride and paraformaldehyde in the presence of propanoic acid: α-hydroxymethylphosphonic acid (Figure 1a) and 1-hydroxypropylidene-1,1-diphosphonic acid (Figure 2).

The content of α-hydroxymethylphosphonic acid was 35% and that of 1-hydroxypropylidene-1,1-diphosphonic acid was 65% based on the integral intensities of the signal for phosphorus atoms in the $^{31}P\{H\}$ NMR spectrum.

In the presence of formic acid: The reaction of phosphorus trichloride with paraformaldehyde in the presence of formic acid resulted in the formation of two phosphorus-containing products. The ^{31}P NMR spectrum of the reaction mixture revealed two types of phosphorus atoms at 23.23 ppm, a triplet with a coupling constant of 7.2 Hz and at 16.78 ppm, a pseudo-triplet with a coupling constant of 9.1 Hz. The contents of the products were 89% and 11%, respectively. The doublet at 3.76 ppm in the ^{1}H NMR spectrum was assigned to the P-C$\underline{H}_2$ protons. The DEPT spectrum confirmed that these protons were bonded to this carbon atom. In the $^{13}C\ \{^{1}H\}$ NMR spectrum there was a doublet at 58.2 ppm with a coupling constant of $^{1}J(P,C)$ = 161.7 Hz, which was characteristic of a carbon atom bonded directly to phosphorus.

NMR data confirmed the formation of α-hydroxymethylphosphonic acid and 1-hydroxymethylene-1,1-diphosphonic acid (Figure 3).

Based on the data from NMR studies we propose the following mechanism for the reaction of phosphorus trichloride with paraformaldehyde in the presence of carboxylic acids (Scheme 1). The reaction proceeds in two directions: pathway “a” and pathway “b”. In pathway “a” phosphorus trichloride reacts with formaldehyde to form chloromethyl dichlorophosphite (**2**) which undergoes an Arbuzov rearrangement to give chloromethyl dichorophosphonate (**3**). Hydrolysis of **3** resulted in α-hydroxymethylphosphonic acid **4**. At the same time phosphorus trichloride reacts with the carboxylic acid to furnish the corresponding acid chloride **5** and dichlorophosphite (**6**). Dichorophosphite tautomerizes in to dichloro H-phosphonate (**7**) which reacts with acid chloride **5** to give dichloro acylphosphonate **8**.

The addition of dichloro H-phosphonate **7** to **8** furnished the tetrachloride of 1-hydroxyalkylidene-1,1-diphosphonic acid **9**. Hydrolysis of **9** resulted in the formation of 1-hydroxyalkilidene-1,1-diphosphonic acid **10**. This reaction scheme explains the observed signals in the ^{31}P NMR spectrum of the reaction mixture before adding water. The singlets at 20.45 ppm, 18.22 ppm, 17.88 ppm and 17.14 ppm can be assigned to dichlorochloromethyl phosphonic acid (**3**), partially hydrolyzed **3**, dichloro acylphosphonate **8** and partially hydrolyzed **8**. It is well known that 1-hydroxyalkylidene-1,1-diphosphonic acid can be obtained by reaction of acylating agents with H-phosphonic acid or a carboxylic acid with phosphorus trichloride and a calculated amount of water.[6-11] When phosphorus trichloride is used water is added in order to obtain the H-phosphonic acid, which further reacts with acid anhydride. Our experimental results revealed that the reaction of phosphorus trichloride with paraformaldehyde in the presence of carboxylic acids in the absence of water resulted in the formation of 1-hydroxyalkylidene-1,1-diphosphonic acids.

Interaction of phosphorus trichloride with glacial acetic acid

We also carried out the reaction of phosphorus trichloride with glacial acetic acid. In the ^{31}P{H} NMR spectrum of the reaction mixture there were four signals at 20.43, 16.54, 15.97 and 5.66 ppm. The signal at 20.43 ppm in the ^{31}P NMR spectrum represents a quartet with coupling constant ^{3}J(P,H) = 16.1 Hz, that at 16.54 ppm is a quartet with a coupling constant ^{3}J(P,H) = 15.4 Hz and that at 15.97 ppm is a quartet with a coupling constant ^{3}J(P,H) = 15.5 Hz. The signal at 5.66 represents a doublet with a coupling constant ^{1}J(P,H) = 680.9 Hz which is characteristic for ^{1}J(P,H) hence this doublet can be assigned to the H-phosphonic acid. According to the integral intensity of the signals at 20.43, 16.54, 15.97 and 5.66 ppm the content of the product mixture was 18%, 7%, 7% and 68% respectively. In the ^{1}H NMR spectrum of the reaction mixture there was a triplet at 1.12 ppm with a coupling constant ^{3}J(P,H) = 16.3 Hz which was assigned to the CH_3 protons, split by two phosphorus atoms. There were also two doublets at 1.57 (^{3}J(P,H) = 16 Hz) ppm and 6.39 (^{1}J(P,H) = 680.8 Hz) ppm. This coupling constant is characteristic for a P-H proton. In the ^{13}C{H} NMR spectrum there were a triplets at 69.4 (^{1}J(P,C) = 152.6 Hz) ppm and at 78.1 ppm with a coupling constant ^{1}J(P,C) = 147.1 Hz of extremely low intensity. The DEPT spectrum revealed that these signals were due to tertiary carbon atoms. The values of the coupling constants revealed that these carbon atoms were bonded directly to two phosphorus atoms and the triplet at 69.4 ppm could be assigned to the tertiary carbon atom of 1-hydroxyethylidene-1,1-diphosphonic acid (**11**).

Additional signals in ^{13}C and in ^{31}P NMR spectra can be explained by the formation of a conformer of **11** with intramolecular hydrogen bonding. The triplet at 78.1 ppm ^{13}C{H} NMR spectrum with a coupling constant J(P,C) = 147.1 Hz is shielded to lower field. The quartets at 16.54 and 15.97 ppm (for two non-equivalent phosphorus of the H-bonded **11**) in ^{31}P{H} NMR spectrum are supporting this suggestion too.

NMR data confirmed that the reaction of phosphorus trichloride with glacial acetic acid resulted in formation of 1-hydroxyethylidene-1,1-diphosphonic acid **11.**

The transformation of dichlorophosphite (**6**) into dichloro H-phosphonate (**7**) was confirmed by NMR study of the reaction mixture, PCl_3 and H_2O (large excess of PCl_3). The ^{31}P{H} NMR spectrum of the reaction mixture showed a signal at 220.29 ppm (intensity 100.0), 10.81 ppm (intensity 4.51) and at -2.19 ppm (intensity 16.49). In the ^{31}P NMR spectrum the signal at 220.29 ppm was a singlet and was assigned to phosphorus atom in PCl_3; that at 10.81 ppm was a doublet with a coupling constant of 737.4 Hz and was assigned to the phosphorus atom in chlorohydroxy H-phosphonate. In ACD Labs software[12] $^{1}J(P,H)$ constant for chlorohydroxy H-phosphonate is 748.5 Hz. The signal at –2.19 ppm is a doublet with a coupling constant of 777.5 Hz and can be assigned to phosphorus atom in dichloro H-phosphonate (**7**). In the database of ACD Labs software[12] it was found that the $^{1}J(P,H)$ constant for dichloro H-phosphonate was 772.0 Hz. In the ^{1}H NMR spectrum of the same mixture, there were two doublets at 7.23 ppm with $^{1}J(P,H)$ = 781.4 Hz assigned to the P-H proton in dichloro H-phosphonate (**7**) and at 7.07 ppm with $^{1}J(P,H)$ =735.9 Hz assigned to the P-H proton of chlorohydroxyl-H-phosphonate. There was a broad signal at 11.9-13.1 ppm assigned to the proton of the P-OH group. These data confirmed that under the reaction conditions, dichlorophosphite (**6**) tautomerized into dichloro H-phosphonate. The equilibrium was shifted to dichloro H-phosphonate (**7**). There was no other signal due to a trivalent phosphorus atom except for the phosphorus atom of PCl_3 at 220.29 ppm.

CONCLUSION

In conclusion, it was shown that the carboxylic acid used in the reaction of PCl_3 with parafomaldehyde plays the dual role of solvent and reagent. The carboxylic acid cannot be used as the solvent in the reaction of PCl_3 with parafomaldehyde for the preparation of α-hydroxymethylphosphonic acid because it reacts with PCl_3. Our results have revealed that bisphosphonic acids can be obtained from carboxylic acids and PCl_3 without the addition of water. The dichlorophosphite obtained from the reaction of the carboxylic acid and PCl_3

generates dichloro H-phosphonate, the reagent which reacts with the acid chloride to give an acylphosphonate, and it addition to acylphosphonate furnished the resulting tetrachloride of 1-hydroxyalkylidene-1,1-diphosphonic acid.

EXPERIMENTAL

Instruments and Reagents

All reagents were used as purchased from commercial suppliers without further purification. Solvents were dried and purified by conventional methods prior to use. We used glacial acetic acid ≥99.99%; propionic acid ≥99.5%; formic acid ≥96.0 % from Sigma-Aldrich. ^{1}H, ^{13}C and ^{31}P spectra were recorded on Bruker DRX 250 spectrometer using QNP probehead and on Bruker Avance II+ 600 spectrometer using BBO probehead. The ^{1}H and ^{13}C NMR chemical shifts are given relative to TMS, while the ^{31}P NMR chemical shifts are given relative to 85% H_3PO_4. Chemical shifts are expressed in ppm and coupling constants in Hz. The precise assignment of the ^{1}H and ^{13}C NMR spectra was accomplished by measurement of 2D homonuclear correlation (COSY), DEPT-135 and 2D inverse detected heteronuclear (C–H) correlations (HMQC and HMBC). Sample ^{1}H, ^{13}C and ^{31}P NMR spectra from reactions are found in the Supplemental Materials (Figures S 1 – S 12)

General Procedure of the Reaction of Phosphorus Trichloride with Paraformaldehyde in the Presence of Carboxylic Acids.

Paraformaldehyde (1.50 g, 0.05 mol) and glacial acetic acid (24 mL) were added to a four-necked round–bottom flask equipped with a magnetic stirbar, reflux condenser, thermometer, dropping funnel and argon inlet. A white suspension formed. The mixture was refluxed (approximately 115 °C) for 2 h, after which it became a clear solution. The temperature was lowered to 20 ^{o}C and PCl$_3$ (4.20 mL, 0.05 mol) was added dropwise. For the whole duration of the reflux (6 h) during and after the addition of PCl$_3$, hydrogen chloride was evolved. After 6 h refluxed, the reaction was stopped, and the mixture was analyzed by NMR spectroscopy. After that to this reaction mixture was added distilled water (28 mL) and refluxed again for 2.5 h. After 2.5 h refluxing the solvent was removed *in vacuo* to give a yellow tarry residue. This residue was dissolved in and filtered over activated carbon is used in methanol purification resulting a colorless solution. Then the solution was concentrated under reduced pressure to give a residue, which was purified by precipitation from water and collected by filtration.

Analytical data:

In the presence of:

a) ***Acetic acid:*** ^{1}H NMR (600 MHz, CD$_3$OD) δ (ppm): 1.64 (t, ^{3}J(P,H) = 16.0 Hz, P - C(CH$_3$)-P); 3.78 (d, ^{2}J(P,H) = 7.3 Hz, P-CH$_2$-OH); ^{13}C {^{1}H} NMR (150 MHz, CD$_3$OD) δ (ppm): 71.66 (t, ^{1}J(P,C) = 152.6 Hz, (P-C-P); 58.73 (d, ^{1}J(P,C) = 162.4 Hz, P-CH$_2$-), 20.77 (t, ^{3}J(P,H) = 1.4 Hz, P-C(CH$_3$)-P); ^{31}P NMR (243 MHz, CD$_3$OD) δ (ppm): 20.96 (q, ^{3}J(P,H) = 16.0 Hz); 23.20 (t, ^{2}J(P,H) = 7.3 Hz).

b) ***Propanoic acid:*** ^{1}H NMR (600 MHz, CD$_3$OD) δ (ppm): 1.16 (t, ^{3}J(H,H) = 7.6 Hz, -CH$_2$-C*H*$_3$); 3.76 (d, ^{2}J(P,H) = 7.25 Hz, P-CH$_2$-OH), 2.09 (tq, ^{3}J(P,H) = 15.2 Hz, ^{3}J(H,H) = 7.6 Hz, P-C- (C*H*$_2$-CH$_3$)-P); ^{13}C {^{1}H} NMR (150 MHz, CD$_3$OD) δ (ppm): 74.55 (t, ^{1}J(P,C) = 153.9 Hz, P-C-P); 58.25 (d, ^{1}J(P,C) = 162.0 Hz, P-CH$_2$-); 27.89 [P-C- (*C*H$_2$-CH$_3$)-P]; 8.77 (t, ^{3}J(P,C) = 6.0 Hz [P-C- (CH$_2$-*C*H$_3$)-P]; ^{31}P NMR (243 MHz, CD$_3$OD) δ (ppm): 21.43 (t, ^{3}J(P,H) = 15.7 Hz); 23.56 (t, ^{2}J(P,H) = 7.2 Hz).

*c) **Formic acid:*** ^{1}H NMR (600 MHz, CD_3OD) δ (ppm): 3.76 (d, ^{2}J(P,H) = 7.25 Hz, P-CH_2-); ^{13}C {^{1}H} NMR (150 MHz, CD_3OD) δ (ppm): 58.20 (d, ^{1}J(P,C) = 162.9 Hz, P-CH_2-); ^{31}P NMR (243 MHz, CD_3OD) δ (ppm): 23.23 (t, ^{2}J(P,H) = 7.1 Hz); 16.78 (t, ^{2}J(P,H) = 9.1 Hz).

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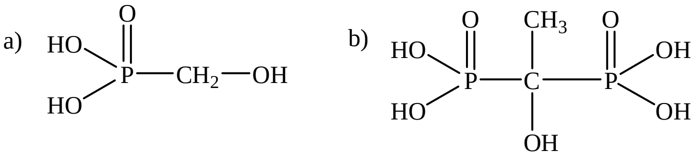


Figure 1. a) α-Hydroxymethylphosphonic acid and b) 1-hydroxyethylidene-1,1-diphosphonic acid

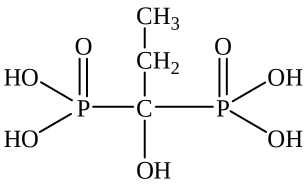


Figure 2. Structure of 1-hydroxypropylidene-1,1-diphosphonic acid

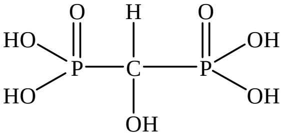
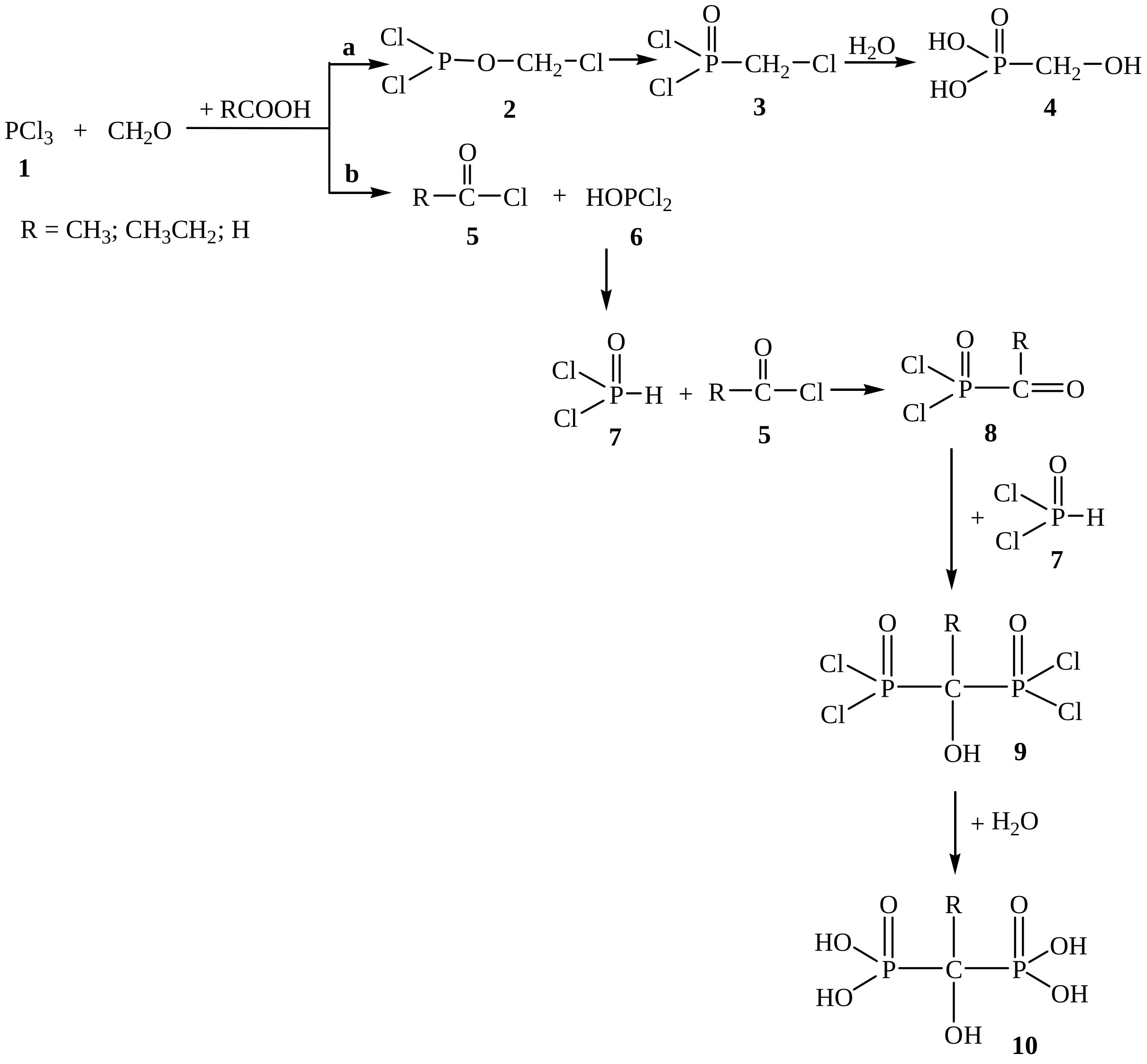
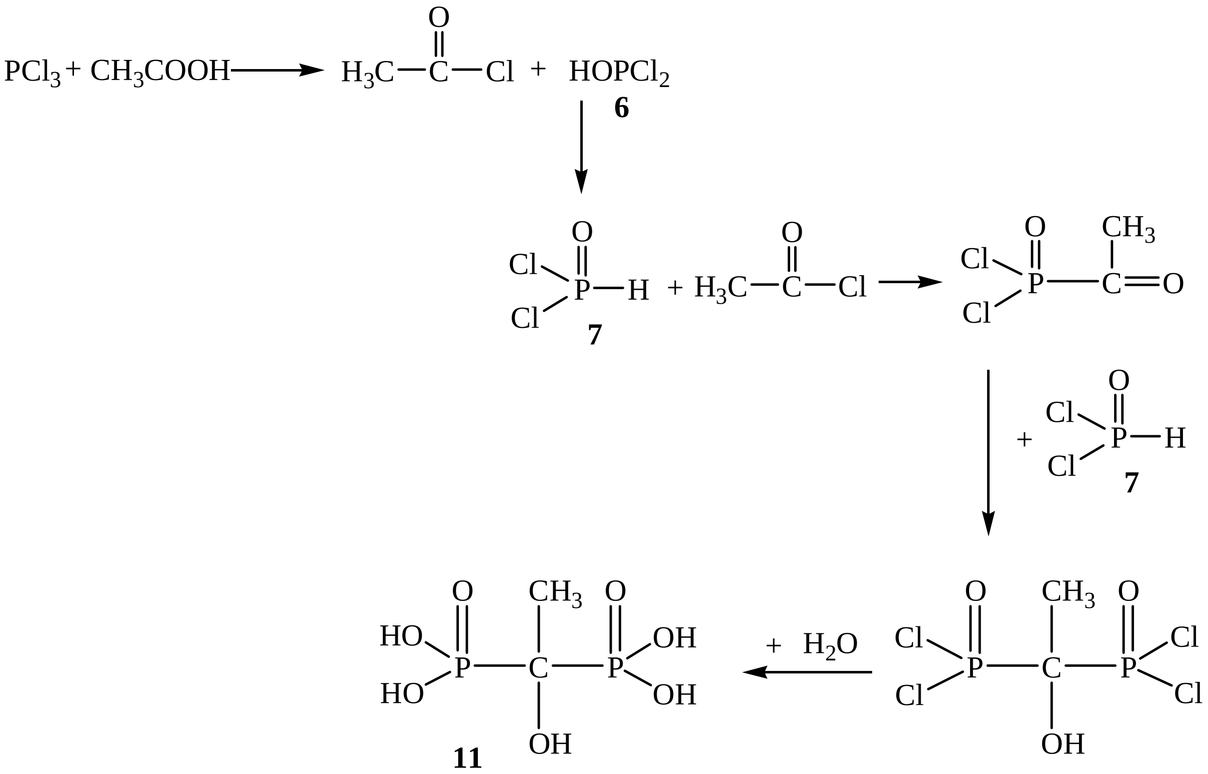


Figure 3. Structure of 1-hydroxymethylene-1,1-diphosphonic acid



Scheme 1. Reaction of phosphorus trichloride with paraformaldehyde in the presence of carboxylic acids.



Scheme 2. Reaction of phosphorus trichloride with glacial acetic acid.