IMINOBIS(METHYLENEDIPHOSPHONIC) ACID

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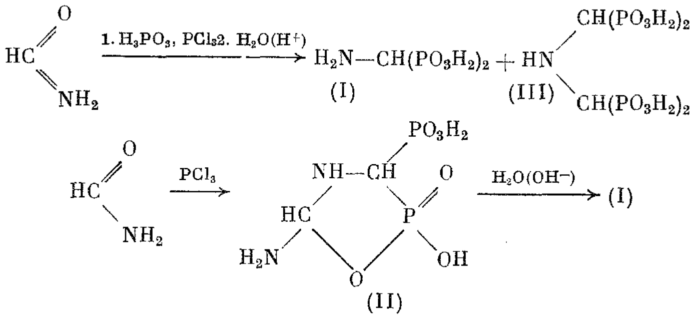
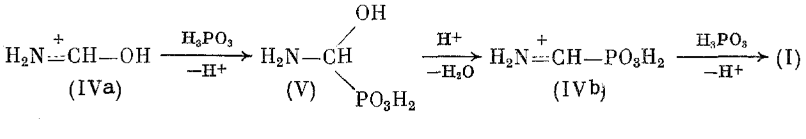
The reaction of formamide with H_3PO_3 and PCl_3 is a method for obtaining aminomethylenediphosphonic acid (I) [1]. Until now no other stable products have been observed in this particular reaction. There is only one reference [2] stating that when excess formamide is treated with PCl_3, 2-oxo-2-hydroxy-5-amino-1,4,2-oxazaphospholidine-3-phosphonic acid (II) is formed, being readily hydrolyzed to (I).

The ^{31}P NMR spectra of the reaction products of $HCONH_2$ with H_3PO_3 and PCl_3 indicate the presence of a wide variety of unidentified compounds which disappear after hydrolysis. In particular, for the case of the reaction mixture obtained as described in [1], at least two of such compounds are formed (δ, 10.5 ppm, d, and 11.1 ppm, d), giving (I) on hydrolysis (δ 9.6 ppm, d, J_{pp} = 16.8 Hz). Hydrolysis with boiling 20% HCl is necessary for the previously known decomposition of different condensation products. The attempted isolation of (I) according to [1] without such hydrolysis gives a mixture containing ~1/3 (I) together with the compounds indicated above. At the same time, after hydrolysis of the reaction mixture of [1], pure (I) is successfully obtained with a yield of more than 30%.



When studying those reaction products of formamide with H_3PO_3 and PCl_3 which were stable to hydrolysis, we detected the formation of iminobis(methylenediphosphonic) acid (III), the presence of which suggests, apart from the conversion of formyl groups to diphosphonates, the breakage and formation of a new C—N bond with separation of a NH_3 molecule.

According to the ideas put forward in [2], conversion of $HCONH_2$ to (I) proceeds by nucleophilic addition of H_3PO_3 to the electrophilic particle (IVa). Such a reaction must inevitably involve a number of stages, such as the formation of the intermediate (V), its dehydration, and addition of another H_3PO_3 molecule



$$\underset{(IVa)}{H_2\overset{+}{N}{=}CH{-}OH} \xrightarrow[-H^+]{H_3PO_3} \underset{(V)}{H_2N{-}CH(OH)(PO_3H_2)} \xrightarrow[-H_2O]{H^+} \underset{(IVb)}{H_2\overset{+}{N}{=}CH{-}PO_3H_2} \xrightarrow[-H^+]{H_3PO_3} (I)$$

On the basis of such a scheme, formation of (III) can be shown as the result of a competing nucleophilic addition of the amino group, of the reaction product (I) or the possible intermediate, hydroxyaminomethylenephosphonic acid (V), to particle (IVa, b). Consistent with this proposal is the fact that introduction of p-toluidine into the reaction completely suppresses the formation of (III), and as a result of this reaction p-tolylaminomethylenediphosphonic acid (VI) is formed.

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On increasing the molar ratio of PCl_3:H_3PO_3, the ratio of (III):(I) decreases, while their overall yield rises, which is consistent with the data of [3] where on obtaining 1-hydroxyethylidenephosphonic acid an increase in the dehydrating capacity of the reaction mixture increased the yield of product. At the same time, the yield of (III) increases when the temperature is raised. A simultaneous increase in temperature and molar ratio of PCl_3:H_3PO_3 is accompanied by the formation of pentavalent phosphorus derivatives and low polymeric phosphorus oxides. Stoichiometric molar ratios of the components were therefore used subsequently according to the reaction equation

$$3HCONH_2 + 5H_3PO_3 + PCl_3 = 3H_2NCH(PO_3H_2)_2 + 3HCl$$

This made it possible to carry out the reaction at 140°C. These conditions proved to be the most favorable for obtaining (III).

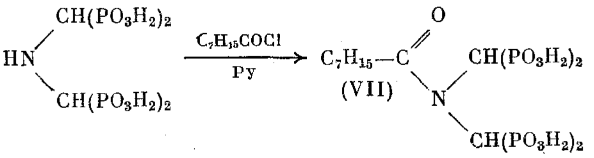
Any deviations from the optimum ratio of reagents cause a decrease in the ratio of (III):(I). At the same time the overall yield of (III) and (I) can be increased without increasing the yield of (III). With an increase in temperature and (or) times of reaction, the ratio of (III):(I) increases but the yield of byproducts, which interfere with the isolation of (III), also rises. A study of the dependence of the composition and yield of products which are stable to hydrolysis on the duration of reaction (120-130°C) showed that (I) is mainly formed during the first half hour while the yield of (III) and impurities rises gradually.

We have studied the effect of addition of aluminum and zinc chlorides on the yields of acids (I) and (III) under conditions where there is a stoichiometric ratio of reagents at 140°C and a reaction time of 4 h. When $ZnCl_2$ is added the yields of (I) decrease, the formation of (III) is suppressed, while the yields and quantity of impurities increases. Introduction of $AlCl_3$ (0.056 moles for 3 moles of $HCONH_2$) lessens the ratio of (III):(I), but increases the overall yield of (III) and (I) and suppresses the formation of impurities; after 6 h of additional heating of the reaction mixture the yield of (III) increases slightly while the yield of (I) remains unchanged. Replacement of PCl_3 by PBr_3 under conditions of the optimum ratio of reagents affects the yields of (I) and (III) in a similar manner to that resulting from the addition of $AlCl_3$. The primary formation of (I) in the first stage of reaction and the gradual increase in quantity of (III) throughout its course is consistent with the proposal that (III) is formed by direct participation of (I) in the reaction with intermediate particle (IVa, b). Compounds (III) and (VI) were isolated and characterized in the form of free acids. Their purity and structure were confirmed by analytical and spectral methods.

In the ^{31}P NMR spectrum of (III) at pH 6 (NH_3), a doublet is observed with J_{PH} = 17.5 Hz, reducing under {^1H} conditions to a singlet at $\delta \approx 13$ ppm, with the chemical shift and spin–spin coupling constant dependent on the change in concentration of solution and especially on the pH of the medium. Thus, at pH 3.5 (NH_3) $\delta = 8.5$ ppm.

The pH curve of the acidimetric titration of (III) has one pronounced and two weakly defined changes of pH corresponding to 3, 4, and 5 equivalents of alkali for 1 mole of (III), and three buffer regions corresponding to detachment of three protons with relatively high acidity ($pK_a \sim 2.5$) and two rather weakly acid protons successively (pK_a ~5 and ~7) with one of them evidently corresponding to the change from an ammonium group to an amino group. Thus, pH titration supports the structure of (III) (compare [2, 4]).

For additional confirmation of the structure of (III), we caused it to react on its imino group. Acylation of (III) with the anhydride or chloride of octanoic acid gave N-(octanoyl)iminobis(methylenediphosphonic) acid (VII), which was isolated and characterized as a dipotassium salt



In the ^{31}P NMR spectrum of (VII) two nonequivalent PH doublets are present (singlets under {^1H} conditions) in the ratio 1:1, which confirms the presence of the amide bond in the mole-

TABLE 1. Conditions and Reaction Results of $3H_2NCHO + 5H_3PO_3 + PX_3 \xrightarrow{catalyst} (I) + (III) + HCl$

Catalyst, moles per 1 mole of PX_3	X	Period of time at 140°C, h	Ratio (III):(I)	Yield (I) + (III), %	Impurities, %
$AlCl_3$, 0,0056	Cl	4	0,72	31	0
		10	0,94	35	0
$ZnCl_2$, 0,014	Cl	4	0,50	17,5	10
$ZnCl_2$, 0,24	Cl	4	0	6	22
–	Cl	4	1,5	26	5,5
–	Br	4	0.58	31.5	2,0

cule of (VII). This is also suggested by the observation in the PMR spectrum of nonequivalent protons of the diphosphonomethyl groups, which appear as two triplets with an intensity ratio of 1:1.

The pH curve of the acidimetric titration of the free acid (VII), obtained from the dispotassium salt by ion exchange, has two pronounced changes and two buffer regions corresponding to detachment of four acidic protons ($pK_a \sim 3.0$) and one weakly acidic ($pK_a \sim 8.0$). The remaining protons [as in the case of (III)] are so firmly held by the pentaanion that they are not titratable in an aqueous medium.

EXPERIMENTAL

PMR spectra were recorded on a pulsed Varian XL-200 spectrometer (200.06 MHz) in D_2O (stabilization on deuterium) relative to TMS. In order to increase the solubility, anhydrous Na_2CO_3 was added where necessary. ^{31}P NMR spectra were recorded on the same spectrometer (80.98 MHz) in a mixture of H_2O and D_2O at pH ~ 6 (NH_3) relative to 85% H_3PO_4 unless other conditions indicated. TLC was carried out as in [5].

Iminobis(methylenediphosphonic) Acid (III). To 75.92 g (0.93 mole) of dry H_3PO_3 and 22.5 ml (0.57 mole) of formamide at 20-50°C was added dropwise with agitation 21 ml (0.24 mole) of PCl_3. The mixture was then agitated for 4 h at 130-135°C, supplemented with 120 ml of 20% HCl, and hydrolyzed by boiling for 6 h. The solution obtained was evaporated until dry and dissolved in NH_4OH. ^{31}P NMR spectrum (δ, ppm): 0.9 (H_3PO_4, 3%), 2.4 d (J_{PH} = 596 Hz, H_3PO_3, 55%), 9.1 d (J_{PH} = 16.5 Hz, (I), 16%), 12.3 d (J_{PH}) = 17.1 Hz (III), 16%), other compounds 10%. The diluted solution was passed through a KU-2 cation-exchange resin in H^+ form and eluted with water until neutral reaction. The eluate was concentrated under vacuum, supplemented with ~0.5 liters of acetone, and boiled for 4 h. The precipitate was filtered off and thoroughly washed with acetone; 33.5 g in weight, content of (I) and (III) more than 87% (according to ^{31}P NMR). Yield of diphosphonic acids 30.5% based on formamide. The mixture obtained was boiled for 5 h with 100 ml of water, 100 ml of methanol was rapidly added, and the main portion of (I) was filtered off and washed with 100 ml of 60% MeOH and anhydrous MeOH. The precipitate was dissolved in a mixture of 53 ml of water and 18 ml of Et_3N, and (I) was precipitated by adding a mixture of 53 ml of water and 18 ml of concentrated HCl. 16 g (15%) of (I) was obtained.

The filtrate was evaporated under vacuum. (III) obtained was cleared of traces of (I) by precipitation of the trianiline salt of (III) (the ratio of (III):$PhNH_2$ in the aniline salt determined from PMR spectrum). In order to do this, 2.2 g of purified acid was dissolved in 8 ml of hot water, and 5.5 ml of MeOH and 5 ml of aniline were added. The precipitated crystals were filtered off, washed firstly with 85% aqueous MeOH then with anhydrous MeOH. To convert it to the free acid the trianiline salt was dissolved in dilute aqueous ammonia, the aniline was extracted with ether, and cations were removed by passing through KU-2 in H^+ form. Where necessary the operation for purification as the trianiline salt was repeated. For final purification (III) was recrystallized from 25% HCl, the precipitate was filtered off and washed with 25% HCl and acetone. (III) was obtained in the form of a monohydrate (yield 4%), decomp. temp. 260°C. PMR spectrum: δ 4.2 ppm, t, J_{HP} = 19 Hz. Found, %: eq_3 127, eq_4 95, eq_5 77; C 6.30; H 2.96. $C_2H_{13}O_{13}P_4$. Calculated, %: eq_3 128, eq_4 96, eq_5 77; C 6.27; H 3.42.

Reaction of Formamide with Stoichiometric Quantities of H_3PO_3 and PCl_3 or PBr_3. The reagents were mixed as described above. The conditions and results of the reactions and also the quantity of the catalyst when it was added are given in Table 1. The reaction mixtures were hydrolyzed, treated as described above, and analyzed according to their ^{31}P NMR spectra.

Reaction of Formamide with H_3PO_3 and PCl_3 in the Presence of p-Toluidine. PCl_3 was added dropwise with agitation to a mixture of dry H_3PO_3, p-$CH_3C_6H_4NH_2$, and $HCONH_2$ at 20-60°C (molar ratio of reagents was 1:5:0.9:3, respectively). Then the mixture was agitated for 4 h at 135-145°C, supplemented with azeotropic HCl, and boiled for 6 h. The solution obtained was evaporated to dryness, dissolved in NH_4OH, and extracted with ether, after which the aqueous layer was concentrated and treated with KU-2 as indicated above. ^{31}P NMR spectrum (δ, ppm): 1.4 (H_3PO_4, 6%), 3.1 d (J_{PH} = 594 Hz, H_3PO_3, 80%), 9.4 d [(I), 3%], and 16.1 d [J_{PH} = 19.6 Hz, (VI), 11%)]. The dry mixture of the free acids was boiled for 4 h with acetone and the precipitate was filtered off and washed with acetone. It was then dissolved in a small quantity of hot water and separated from (I) by filtration. (VI) obtained was crystallized twice from water; decomp. temp. >245°C. PMR spectrum (δ, ppm): 2.46 (3H, CH_3), 4.07 t (J_{HP} = 19 Hz, 1H, CH), 7.30 d, 7.40 d (J_{HH} = 8 Hz, 4H, H_{arom}). Found, %: C 33.81; H 4.57. $C_8H_{13}NO_6P_2$. Calculated, %: C 34.18; H 4.66.

N-(Octanoyl)iminobis(methylenediphosphonic) Acid (VII). To a homogenized solution of 5.42 g (14.5 mmole) of (III) in a mixture of 21 ml of water, 29 ml (360 mmole) of pyridine, and 5 ml of dioxane with vigorous agitation at 0-1°C was added after 5 h 26 ml (153 mmole) of octanoyl chloride; the mixture was then agitated for a further 2 h and left overnight at 0°C. The mixture was gradually warmed to 20°C and left for a further 24 h, then diluted with 100 ml of Et_2O; the lower layer was separated, dissolved in water, and acidified with HCl until pH 2.5 was reached. The caprylic acid that separated out was extracted with ether and the aqueous layer evaporated under vacuum. The residue obtained (47 g) after standing for several days was recrystallized. The crystals were washed with small quantities of water and then Me_2CO. After drying under vacuum the product was close in composition to the dihydrate of the dipyridinium salt of (VII); 5.34 g (54%) was isolated. For final purification the product was converted to the dipotassium salt, for which 5.14 g of dipyridinium salt was passed through KU-2 in H^+ form. Water was used for elution, and half of the eluate was neutralized with KOH until pH 6 was reached, the second half of the eluate was added, the solution was concentrated to a syrupy liquid, and the salt was precipitated by MeOH. It was filtered off, washed with MeOH, and dried under vacuum at 50°C. 4.43 g of the dipotassium salt monohydrate of (VII) was obtained. Found, %: eq_2 292, eq_3 196; C 20.66; 4.36. $C_{10}H_{25}NO_{14}P_4K_2$. Calculated, %: eq_2 293, eq_3 195; C 20.52; H 4.30. PMR spectrum (δ, ppm): 1.05 t (CH_3, J_{HH} = 6 Hz), 1.4-1.8 m (5 CH_2), 2.84 t (CH_2CO, J_{HH} = 7 Hz), 4.48 t (CH, J_{HP} = 23 Hz), 4.92 t (CH, J_{HP} = 22 Hz). ^{31}P NMR spectrum (D_2O + K_2CO_3): two doublets of equal intensity at 11.3 ppm (J_{PH} = 23 Hz) and 15.3 ppm (J_{PH} = 22 Hz).

The dipyridine salt of (VII) was obtained in lower yield by acylation of (III) with caprylic anhydride in an aqueous dioxane solution in the presence of Et_3N at 15-60°C with subsequent ion exchange on KU-2 and addition of pyridine.

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CONCLUSIONS

When formamide was reacted with phosphorous acid and phosphorus trichloride, the formation of iminobis(methylenediphosphonic) acid was detected.

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