Brief Communications

Reactions of vinylidenediphosphonic acid with nucleophiles
5.* Addition of heterocyclic amines and trimethylamine to vinylidenediphosphonic acid

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It has been shown that heterocyclic amines can be added to the activated double bond of vinylidenediphosphonic acid to form adducts with betaine structures. Of aliphatic amines only trimethylamine reacts with vinylidenediphosphonic acid.

Key words: vinylidenediphosphonic acid, nucleophilic addition, heterocyclic amines, tertiary aliphatic amines.

The reactivity of vinylidenediphosphonic acid (**1**) toward nitrogen-containing heterocycles and tertiary aliphatic amines has been studied in continuation of our previous works[1,2] and to find biologically active substances among substituted ethylidene-1,1-diphosphonic acids.[3,4]

Heterocyclic amines easily react with **1** to form adducts **2a—j** (Scheme 1).

Only derivatives substituted at the endocyclic N atom are obtained in the case of aminopyridines. This is confirmed by pH-metric titration (the ratio of equivalent volumes of alkali is 1 : 2) and ^{1}H NMR spectra, in which signals of protons of the ring are shifted downfield compared to those of the initial aminopyridines. The optimum pH of the reaction medium is in the 2 to 3 range for heterocylic amines, while that for aliphatic amines is in the 7 to 8 range. The reaction was controlled by TLC. Of aliphatic amines only trimethylamine was introduced into the reaction. Adduct **2j** is unstable and decomposed to the initial **1** and Me_3N, especially at increased pH values. Triethylamine does not react.

Compounds **2a—j** are isolated in the form of well crystallized substances with betaine structures.

Experimental

Conditions for recording ^{1}H NMR spectra, performing TLC, and preparing acid **1** and its salts have been described previously.[1] Data on analyses and constants of **2a—j** are presented in Table 1.

[2-(Pyridinio)-1-phosphoryl]ethylphosphonate (2a). A mixture of disodium vinylidenediphosphonate (Na_2-**1**) trihydrate (2.03 g, 7.1 mmol), 2.24 g (28.4 mmol) of pyridine, and 3.4 mL (35.0 mmol) of 32 % HCl was refluxed for 3 h. The mixture was diluted with hot water and passed through a KU-2 cationite (H^+-form). Hot water was used for elution to avoid crystallization of the product in the column. After evaporating

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* For Part 4, see *Izv. Akad. Nauk, Ser. Khim.*, 1992, 2180 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 1709 (Engl. Transl.)].

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Scheme 1

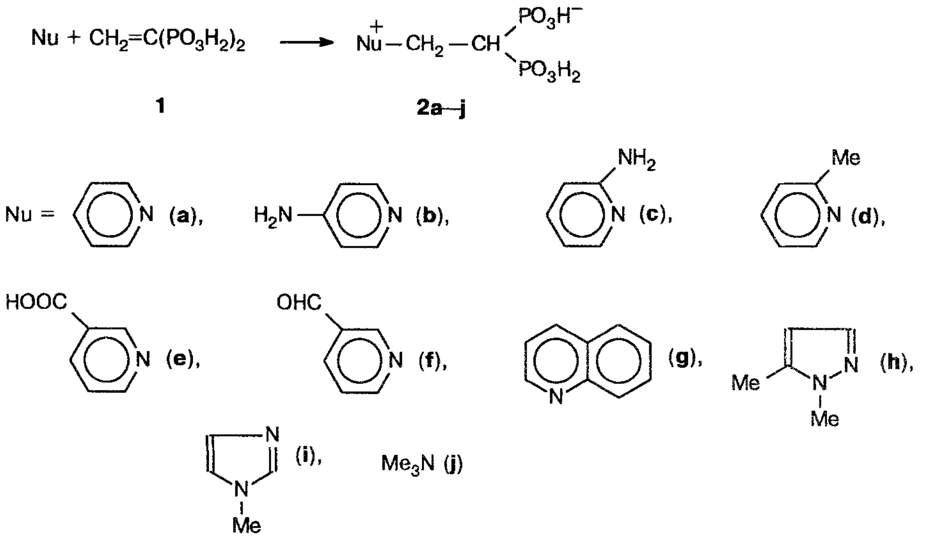

Table 1. Parameters of adducts

Compound	Molecular formula	Alkaline equivalents*, found / calculated		Found / Calculated (%)		^{1}H NMR, δ, *J*/Hz
				C	H	
2a	$C_7H_{11}NO_6P_2$	266.0; 268.0	133.0 134.0	31.51 31.48	4.25 4.15	3.2 (tt, J_{PH} = 20, J_{HH} = 8, 1 H, CH); 5.7 (td, J_{PH} = 14, J_{HH} = 8, 2 H, CH_2); 8.5—9.8 (m, 5 H, Py)
2b	$C_7H_{12}N_2O_6P_2$		141.0 141.0	29.65 29.80	4.35 4.29	2.9 (tt, J_{PH} = 20, J_{HH} = 8, 1 H, CH); 5.1 (td, J_{PH} = 13, J_{HH} = 8, 2 H, CH_2); 7.4 (d, 2 H, Py), 8.8 (d, 2 P, Py)
2c	$C_7H_{12}N_2O_6P_2$	279.0; 282.0	140.5 141.0	29.92 29.80	4.39 4.29	2.4 (tt, J_{PH} = 21, J_{HH} = 5, 1 H, CH); 4.8 (td, J_{PH} = 15, J_{HH} = 5, 2 H, CH_2); 7.0—8.5 (m, 4 H, Py)
2d	$C_8H_{11}NO_6P_2 \cdot$ $\cdot 1/2H_2O$	283.0; 290.0	141.0 145.0	33.02 33.12	4.73 4.86	2.8 (tt, J_{PH} = 20, J_{HH} = 7, 1 H, CH); 3.3 (s, 3 H, Me); 5.3 (td, J_{PH} = 13, J_{HH} = 7, 2 H, CH_2); 8.0—9.3 (m, 4 H, Py)
2e	$C_8H_{11}NO_8P_2 \cdot$ $\cdot H_2O$	165.0; 164.5	111.0 109.7	29.19 29.20	3.98 3.99	3.1 (tt, J_{PH} = 20, J_{HH} = 8, 1 H, CH); 5.7 (td, J_{PH} = 14, J_{HH} = 8, 2 H, CH_2); 8.4—9.9 (m, 4 H, Py)
2f	$C_8H_{11}NO_7P_2 \cdot$ $\cdot CH_3OH$	325.0 327.1		32.83 33.04	4.59 4.62	2.9 (tt, J_{PH} = 20, J_{HH} = 7, 1 H, CH); 3.2 (s, MeOH); 4.9 (td, J_{PH} = 14, J_{HH} = 7, 2 H, CH_2); 6.1 (s, 1 H, 6-H, Py); 8.0 (t, 1 H, 5-H,); 8.5 (d, 1 H, 4-H); 8.8 (d, 1 H, 2-H); 8.95 (s, 1 H, CHO)
2g	$C_{11}H_{13}NO_6P_2$		157.0 158.5	41.58 41.65	4.23 4.13	2.9 (tt, J_{PH} = 20, J_{HH} = 8, 1 H, CH); 5.7 (td, J_{PH} = 14, J_{HH} = 8, 2 H, CH_2); 8.0—9.8 (m, 7 H, quinoline);
2h	$C_7H_{14}N_2O_6P_2$	286.0; 284.1	141.2 142.1	29.34 29.59	5.06 4.97	2.8 (tt, J_{PH} = 20, J_{HH} = 7, 1 H, CH); 2.8 (s, 3 H, 5-Me), 4.4 (s, 3 H, 1-Me); 5.2 (td, J_{PH} = 13, J_{HH} = 7, 2 H, CH_2); 7.0 (d, 1 H, 4-H); 8.6 (d, 1 H, 3-H)
2i	$C_6H_{12}N_2O_6P_2$	268.3; 270.1	134.0 135.1	26.44 26.68	4.62 4.48	2.9 (tt, J_{PH} = 20, J_{HH} = 7, 1 H, CH); 4.3 (s, 3 H, Me); 5.0 (td, J_{PH} = 13, J_{HH} = 7, 2 H, CH_2); 7.9—8.1 (m, 2 H, 4-H, 5-H); 9.2 (m, 1 H, 2-H)
2j	$C_5H_{15}NO_6P_2$	252.3; 247.1	125.4 123.6	24.43 24.30	6.26 6.11	2.7 (tt, J_{PH} = 22, J_{HH} = 4, 1 H, CH); 3.6 (s, 9 H, Me); 4.2 (td, J_{PH} = 15, J_{HH} = 4, 2 H, CH_2)

* Determined by pH-metric titration.

the eluate to 10 mL and diluting it with an equal volume of MeOH, precipitated crystals were filtered off, washed with water, and recrystallized from 3 % HCl. MeOH was evaporated to dryness giving 1.77 g (93 %) of **2a**.

[2-(4-Pyridylammonio)-1-phosphoryl]ethylphosphonate (2b). A mixture of 2.32 g (8.1 mmol) of Na_2-**1** trihydrate, 2.60 g (27.6 mmol) of 4-aminopyridine, and 3.57 mL (42 mmol) of 36 % HCl was refluxed for 2 h and diluted with MeOH, and the crystals that precipitated were filtered off. The residue was dissolved in water and treated with a cationite (H^+-form). The eluate was evaporated and crystallized by adding EtOH to give 1.22 g (84 %) of **2b**. The compound obtained was recrystallized from 3 % HCl.

[2-(2-Pyridylammonio)-1-phosphoryl]ethylphosphonate (2c) was obtained similarly to **2b**. Yield 1.59 g (69 %). The compound was recrystallized from water.

[2-(2-Methylpyridinio)-1-phosphoryl]ethylphosphonate semihydrate (2d). A mixture of 2.06 g of **1** monohydrate (10 mmol), 3.92 mL (40 mmol) of α-picoline, 2.6 mL (30 mmol) of 35 % HCl, and 0.9 mL of water was refluxed for 3 h, and after cooling 0.9 mL of 35 % HCl and 30 mL of EtOH were added to the mixture. The crystals that precipitated were filtered off, washed with EtOH, and dried to give 2.36 g (84 %) of **2d**. The compound obtained was recrystallized from water.

[2-(3-Carboxypyridinio)-1-phosphoryl]ethylphosphonate monohydrate (2e). A mixture of 1.03 g (5 mmol) of **1** monohydrate, 2.8 g (23 mmol) of nicotinic acid, and 1.63 mL (19 mmol) of 36 % HCl was refluxed for 2 h and diluted with EtOH. After recrystallization from 7 % HCl 1.1 g (60 %) of **2e** was obtained.

[2-(3-Formylpyridinio)-1-phosphoryl]ethylphosphonate crystallosolvate with MeOH (2f). A mixture of 13.3 g (64.6 mmol) of **1** monohydrate, 6.9 g (64.6 mmol) of nicotinic aldehyde, and 9 mL of water was refluxed for 3 h. An equal volume of MeOH was added to the partially crystallized mass. The crystals that precipitated were filtered off, reprecipitated from water with MeOH, washed with MeOH, and dried *in vacuo* at ~20 °C to give 18.5 g (88 %) of **2f**.

[2-(Quinolinio)-1-phosphoryl]ethylphosphonate (2g) was prepared similarly to **2d**. Yield 2.9 g (92 %). The compound was recrystallized from 11 % HCl.

[2-(1,5-Dimethyl-2-pyrazolio)-1-phosphoryl]ethylphosphonate (2h). A mixture of 3.40 g (16.5 mmol) of **1** monohydrate, 0.89 g (9.3 mmol) of 1,5-dimethylpyrazole, and 2 mL of water was refluxed for 7 h and then diluted with 2 mL of MeOH. Crystals were separated and washed with aqueous MeOH (1 : 1) and MeOH to give 2.56 g (97 %) of **2h**. The compound was recrystallized from 0.1 *M* HCl.

[2-(1-Methyl-3-imidazolio)-1-phosphoryl]ethylphosphonate (2i). A mixture of 2.80 g (13.5 mmol) of **1** monohydrate, 1.45 g (17.7 mmol) of 1-methylimidazole, 0.5 mL of water, and 2 mL of AcOH was refluxed for 3 h. MeOH (2.5 mL) and 1 mL of 36 % HCl were added to the crystallized mass, and the mixture was rapidly heated to boiling. A precipitate that formed after cooling was separated and washed with aqueous MeOH (1 : 1) and then with anhydrous MeOH to give 3.45 g (90 %) of **2i**. The compound was recrystallized from 0.1 *M* HCl.

[2-(Trimethylammonio)-1-phosphoryl]ethylphosphonate (2j). A mixture of 2.72 g (9.5 mmol) of Na_2-**1** trihydrate, 2.9 g (30 mmol) of Me_3N hydrochloride, 2 mL of water, and 3.6 mL (9 mmol) of 2.5 *N* aqueous NaOH was heated at 120 °C in a sealed tube for 12 h with occasional shaking. The contents was treated with a cationite (H^+-form), and the eluate was evaporated at 40 °C *in vacuo* to dryness. The residue was crystallized by adding MeOH to give 0.83 g (32 %) of **2j**, which was reprecipitated from water with MeOH.

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