ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 2, pp. 289–294. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © L.I. Vagapova, D.R. Sharafutdinova, O.B. Bazanova, Yu.K. Voronina, D.B. Krivolapov, A.R. Burilov, I.Kh. Rizvanov, M.A. Pudovik, 2014, published in Zhurnal Obshchei Khimii, 2014, Vol. 84, No. 2, pp. 298–303.

Synthesis and Structure of Phosphorylated Acetals

L. I. Vagapova, D. R. Sharafutdinova, O. B. Bazanova, Yu. K. Voronina,
D. B. Krivolapov, A. R. Burilov, I. Kh. Rizvanov, and M. A. Pudovik

A.E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences,
ul. Akademika Arbuzova 8, Kazan, Tatarstan, 420088 Russia
e-mail: vagapovan@mail.ru

Received March 14, 2013

Abstract—The Kabachnik–Fields reaction in a triple system (aminoacetal–paraform–diethyphosphite) resulted in the formation of the previously unknown aminophosphonates that contained the acetyl group and also their monoesters. Structures of the products were confirmed by ^{1}H NMR, IR spectra and X-ray diffraction analysis. The MALDI mass spectra indicated that the presence of *N*-hydroxyethoxyphosphorylmethylaminomethyl groups underlies the ability of these compounds to self-assembly with the formation of *n*-dimensional H-bonded associations.

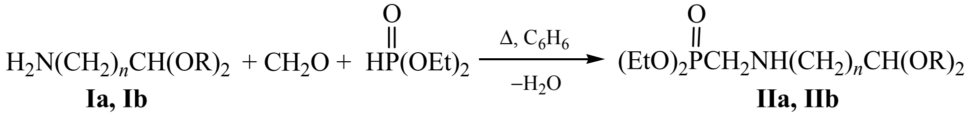
DOI: 10.1134/S1070363214020236

Search for ligands that are capable to form new biologically active complexes with metal ions and organic substrates is an actual trend in bioorganic and supramolecular chemistry [1, 2]. Synthesis of the aminophosphonate group containing receptors that are able to form complex compounds and demonstrate variable biological activity is quite promising [3–7]. It is established that such compounds and their derivatives are applied as amino acids and metal cations carriers as well as promoters of biological accessibility of medical drugs [8–10]. Aminophosphonates complexes with actinides are suggested for application in medical diagnostics [4]. The modification of substituents at N and P atoms can lead to compounds possessing selectivity towards certain kinds of organic and inorganic substrates. In this respect the synthesis of acetals functionalized with the aminophosphonate groups is of pronounced interest.

It is established that aminoacetals and their derivatives are universal structural blocks in synthesis of new heterocycles [11, 12], derivatives of diarylmethane series [13, 14] and calix[4]resorcinarene macrocycles [15]. The presence of phosphonate fragments in aminoacetals allows application of the latter in designing of new phosphorus-containing linear polyphenols, macro(hetero)cyclic structures that are prone to selective recognition of substrates based on principles of multi-points bonding and exhibiting specific complexes formation activity.

In earlier research [16] of reaction of calix[4]resorcinarenes with phosphorylated α-aminoacetal **Ia** and formaldehyde we had obtained in high yields previously unknown macrocyclic receptors that contained [*N*-diethoxyphosphorylmethyl-*N*-(2,2-dimethoxyethyl)amino]methyl fragments on the upper rim of the molecule. It is also known that the necessary condition for effective recognition is the presence of a fragment with a negative charge in the molecule of a receptor [3]. Based on the above the synthesis of calix[4]resorcinarenes containing charged phosphorus-containing fragments on the upper rim of molecules was of certain interest.

In the present study the reaction of diethylacetal of aminobutyraldehyde with diethylphosphite and paraformaldehyde with the ratio of starting compounds 1 : 1 : 1 in the presence of *p*-toluenesulfonic acid (Kabachnik–Fields reaction) resulted in the formation of the new phosphorylated γ-aminoacetal **IIb**.



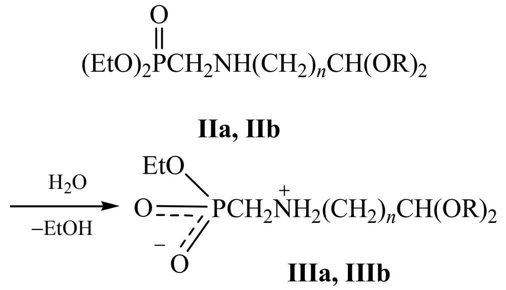
$$H_2N(CH_2)_nCH(OR)_2 + CH_2O + H\overset{O}{\overset{\|}{P}}(OEt)_2 \xrightarrow[-H_2O]{\Delta,\ C_6H_6} (EtO)_2\overset{O}{\overset{\|}{P}}CH_2NH(CH_2)_nCH(OR)_2$$

Ia, Ib **IIa, IIb**

$n = 1$, R = Me (**Ia, IIa**); $n = 3$, R = Et (**Ib, IIb**).

The reaction completed within 3 h followed with the neutralization of the reaction mixture with potassium carbonate, filtering off the precipitate, evaporation of the filtrate in a vacuum of a water-jet pump, and its distillation in a vacuum of an oil-pump.

Aiming at preparation of acetals with charged aminophosphate fragments in the molecules compounds **IIa, IIb** were subjected to hydrolysis. It was shown that under mild conditions (acetone, room temperature) a selective hydrolysis of one alkoxy group at P atom occurred to give monoethyl esters of aminoethylphosphonic acids **IIIa, IIIb**.



$$(EtO)_2\overset{\overset{\displaystyle O}{\|}}{P}CH_2NH(CH_2)_nCH(OR)_2 \xrightarrow[-EtOH]{H_2O} EtO(O^-)(O)PCH_2\overset{+}{N}H_2(CH_2)_nCH(OR)_2$$

IIa, IIb

IIIa, IIIb

n = 1, R = Me (**IIa, IIIa**); *n* = 3, R = Et (**IIb, IIIb**).

The structure of compounds **IIb, IIIa, IIIb** was established by ^{1}H, ^{31}P NMR spectroscopy, XRD analysis of compounds **IIIa, IIIb**, the composition was determined with MALDI mass spectrometry and element analysis.

The ^{1}H NMR spectrum of **IIb** contained a doublet signals of the methylene groups (3.13 ppm) that indicated the formation of the P–CH_2–N bonds. The methyl and methylene groups of the ethoxy radical bonded to the methine carbon were nonequivalent as showed two triplets (1.17, 1.18 ppm) and two multiplets (3.41–3.51, 3.58–3.66 ppm) respectively. In the IR spectrum of **IIb** absorption bands appeared assigned to the following bonds: P–O–C (1041, 1066 cm^{-1}), C–O–C (1135, 1108 cm^{-1}), P=O (1220 cm^{-1}), NH (3440 cm^{-1}).

Products **IIIa, IIIb** were white crystalline compounds soluble in water and ethanol. ^{31}P NMR spectra of **IIIa, IIIb** contained singlet signals at 8.5 and 11.7 ppm respectively that indicated the homogeneity of obtained compounds. The *N*-methylene group signals in ^{1}H NMR spectrum of **IIIa, IIIb** were registered at 3.04–3.08 ppm and the methine proton of the acetal group, as a triplet at (4.60–5.00 ppm), whereas in the spectra of **IIa, IIb** the signals of the corresponding protons were registered at (2.70–2.80 ppm) and (4.49 ppm) respectively. In the IR spectra of **IIIa, IIIb** the absorption bands of the following bonds were observed: P–O–C (1041–1082 cm^{-1}), C–O–C (1108–1135 cm^{-1}), P=O (1220 cm^{-1}), NH_2^+ (1610–1613, 2236–2764, 3440–3424 cm^{-1}). The downfield shift of the methine and methylene protons bonded to the N atom in the NMR spectra and the analysis of IR spectra indicate that the compounds **IIIa, IIIb** were zwitter ionic.

XRD study of monoesters of aminophosphonates **IIIa, IIIb** was aimed at the determination of their spatial structure.

The geometry of compounds **IIIa, IIIb** is presented in the corresponding Figs. 1 and 2. According to the

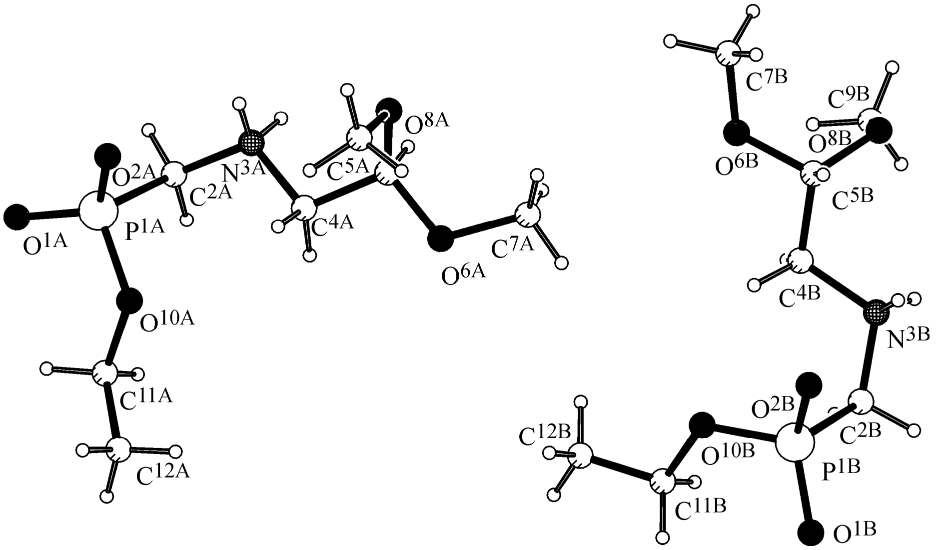


Fig. 1. General view of a molecule of compound **IIIa** in a crystal.

data in the asymmetrical part of the unit cell of the compound **IIIa** two independent molecules are present and in the unit cell of **IIIb** there is one molecule. Geometrical characteristics of the molecules of crystalline compounds **IIIa** and **IIIb**, i.e. bonds length and bonds angles, are within the range typical of each type of bonds. The presence of H-bond centers in the molecules leads to formation of infinitely long parallel zig-zag chains in both compounds. In compound **IIIa** the parallel chains were directed along the diagonal b0c and formed by the H-bonds NH···O between the molecules A and B separately (Fig. 3). Similar chains in the crystalline compound **IIIb** were directed along the 0a axis and bonded by CH···O interactions weaker than NH···O bonds, forming layers in the *a*0*b* plain (Fig. 4, Table 1).

MALDI mass spectra of compounds **IIIa, IIIb** that contained the hydroxy group revealed the trend in these compounds to self-assembly with the formation of dimeric, trimeric, and tetrameric H-bonded associations of the following composition $[M_n]H^+$ (n = 2–4). Figure 5 demonstrates as an example the mass spectrum of compound **IIIa**.

A number of signals of ions in mass spectrum of **IIIa** makes it possible to suggest that the molecules are involved in intermolecular interactions leading to the formation both of ions $[nM + H]^+$ and the salts with Na^+ and K^+. The mass spectrum contains a protonated molecular ion $[M + H]^+$ (m/z 228) and the corresponding cationated forms m/z 250 and 266 (Fig. 5). The composition of the claster ions is presented in Table 2. The similar pattern was observed in the mass spectrum of compound **IIIb**. The results were supported by measuring the exact masses and composition of the most informative molecular and fragment ions in the spectra of compounds **IIIa, IIIb**.

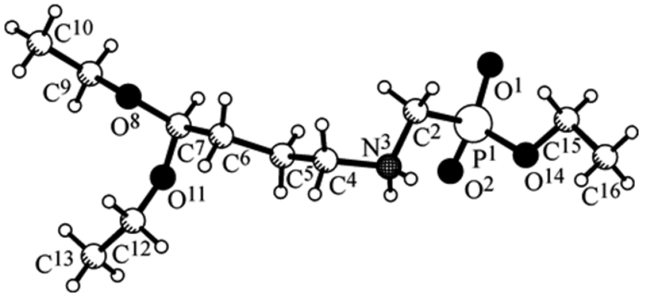


Fig. 2. Geometry of a molecule of compound **IIIb** in a crystal.

On the contrary the mentioned above associates were not formed by compounds **IIa, IIb**. Their mass spectra contained only entirely protonated $[M + H]^+$ and cationated $[M + Na]^+$ and $[M + K]^+$ ions. Presumably these compounds were not able to form intermolecular hydrogen bonds of the type $CH_2NH···O=P$ that could have led to associates. Thus the formation of dimeric and trimeric structures could result from the existence intermolecular hydrogen bonds of the type P–OH···O=P [3]. This conclusion is supported indirectly by the fact that addition of salts of univalent cations Li^+, Na^+, K^+, Cs^+ to species **IIIa, IIIb** led to disintegration of the associates. In the corresponding mass spectra there were registered only cationated ions salts of metals.

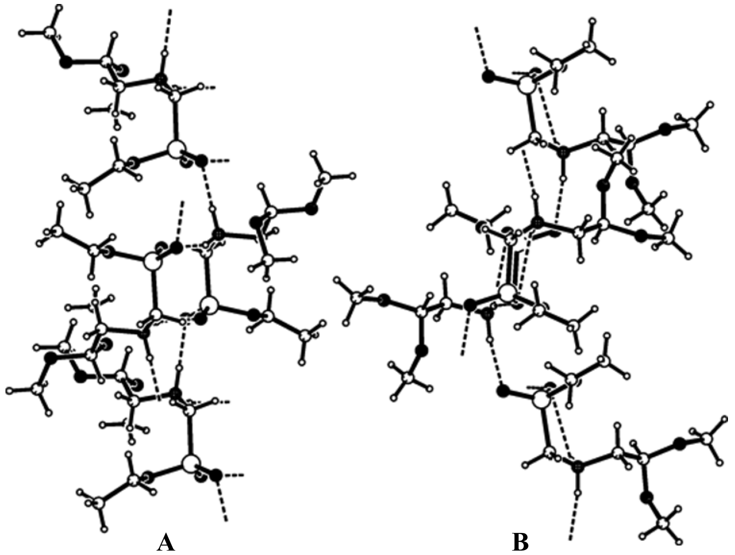


Fig. 3. Hydrogen bonds system in a crystal of compound **IIIa**.

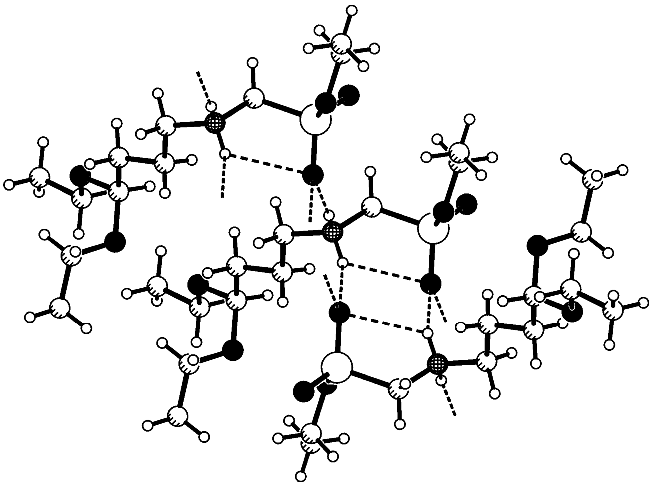


Fig. 4. Hydrogen bonds system in a crystal of compound **IIIb**.

The established properties of the synthesized compounds and also the presence of acetal and secondary amino groups in their molecules provide a possibility of their application as precursors in targeted design of new linear and macrocyclic ligands prone to self-association and selective recognition of substrates.

EXPERIMENTAL

^{1}H and ^{31}P NMR spectra were registered on a spectrometer by Bruker AVANCE-400 at operating frequency 400 and 100.62 MHz respectively. IR spectra were recorded on a spectrophotometer UR-20 in the range 400–3600 cm^{-1} from mulls in mineral oil, MALDI mass spectra were measured on an instrument ULTRAFLEX III. Measurements were made using plastic and metal plates. 2,5-dihydroxybenzoic acid was used as a matrix. On the plates were applied in succession 0.50 μL of matrix solution (0.1% in ethanol), 0.5 μL solution of specimens under study (0.010 and 0.002% solutions in ethanol), and in case of additional ionization of samples with metal cations 0.5 μL of the salt solution (0.01% in ethanol) on top of the sample.

X-Ray experiment was carried out on a diffractometer Bruker SMART Apex II (graphite monochromator, λMoK_α 0.71073 A). No correction for extinction was introduced because of its low level. The structure was solved by the direct method and refined by isotropic followed by anisotropic approximation with the program SHELX [19]. Hydrogen atoms were placed in calculated positions. All calculations were made with the programs WinGX [20] and APEX2 [21]. Figures are drawn with the program PLATON [22].

The X-ray data were deposited in Cambridge Crystallographic Data Center [CCDC 923751 (**IIIa**), CCDC 828931 (**IIIb**)].

Crystals of the compound **IIIa** are monoclinic, at 20°C: *a* 22.62(2), *b* 10.888(10), *c* 9.666(9) Å, β 99.95(1)°, *V* 2345(4) Å^3, *Z* 8 (two independent molecules), d_{calc} 1.287 g/cm^3, space group $P2_1/c$, μMo 2.33 cm^{-1}. There were measured 4579 intensities of independent reflections, 2842 of those with $I \geq 2\sigma$. Resulting deviation factors *R* 0.1447, R_W 0.4085.

Crystals of compound **IIIb**, $C_{11}H_{26}NO_5P$, are triclinic, at 20°C: *a* 5.009(2), *b* 8.644(3), *c* 18.356(7) Å, α 91.757(5)°, β 95.154(5)°, γ 96.382(5)°, *V* 786.0(5) Å^3, *Z* 2, d_{calc} 1.197 g/cm^3, space group *P*-1, μMo 0.187 cm^{-1}. There were measured 3031 intensities of independent reflections, 2061 of those have $I \geq 2\sigma$. Resulting deviation factors *R* 0.0517, R_W 0.1485.

Diethyl-(4,4-diethoxybutylamino)methyl phosphonate (IIb). The mixture of 3 g of aminobutyraldehyde diethylacetal, 2.57 g of diethylphosphite, and 0.53 g of paraformaldehyde in 15 mL of benzene was refluxed in a flask with Dean-Stark trap for 3–4 h. The

Table 1. Hydrogen bonds data for crystals of compounds **IIIa, IIIb**

Interaction	Operation of symmetry	D–H, Å	H···A, Å	D···A, Å	D–H···A, deg
		IIIa			
$N^{3A}–H^{31A}···O^{2A}$	$-x, 1-y, -z$	0.90	1.90	2.72(1)	152
$N^{3A}–H^{32A}···O^{1A}$	$-x, -1/2+y, 1/2-z$	0.90	1.74	2.63(1)	170
$N^{3B}–H^{31B}···O^{1B}$	$1-x, 1/2+y, 3/2-z$	0.90	1.86	2.75(1)	170
$N^{3B}–H^{32B}···O^{2B}$		0.90	2.58	2.93(1)	104
$N^{3B}–H^{32B}···O^{2B}$	$1-x, 1-y, 1-z$	0.90	1.79	2.66(1)	162
		IIIb			
$N^3–H^{31}···O^2$	intra	0.90	2.52	3.030(3)	117
$N^3–H^{31}···O^2$	$1-x, 1-y, -z$	0.90	2.02	2.769(3)	140
$N^3–H^{32}···O^2$	$1+x, y, z$	0.90	1.79	2.671(3)	168

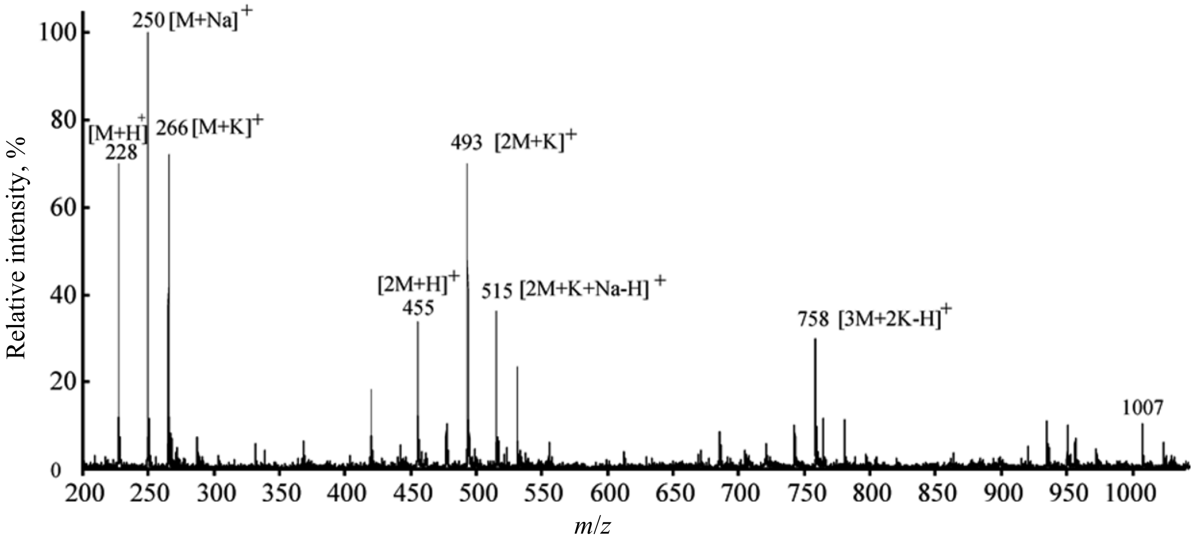


Fig. 5. MALDI mass spectrum of compound **IIIa** (0.01% solution in ethanol on a plate).

reaction was monitored by ^{31}P NMR spectra. It was followed by 0.5 h refluxing with 160 mg of K_2CO_3, the precipitate was filtered off, the residue was evaporated in a vacuum. Yield 5.4 g (93%). IR spectrum, ν, cm^{-1}: 1041, 1066 (POC); 1135, 1108 (COC), 1220 (P=O), 2256–2470 (NH$^+$), 3440 (NH). NMR ^{1}H ($CDCl_3$, 20°C), δ, ppm (*J*, Hz): 1.17 t (3H, $OCH_2C\underline{H}_3$, $^3J_{HH}$ 7.05), 1.18 t (3H, $OCH_2C\underline{H}_3$, $^3J_{HH}$ 7.05), 1.31–1.36 m (6H, $POCH_2C\underline{H}_3$,), 1.52–1.63 m [4H, $(C\underline{H}_2)_2CH$], 2.84–2.86 m (2H, NCH_2), 3.13 d (2H, PCH_2, $^2J_{PH}$ 12.54), 3.43–3.51 m (2H, OCH_2), 3.58– 3.66 m (2H, OCH_2), 4.11–4.15 m (4H, $POCH_2$), 4.49 t (1H, CH, $^3J_{HH}$ 5.31). ^{31}P NMR spectrum, δ_P, ppm: 26.52. Found, %: C 49.50; H 9.69, N 4.42; P 9.90; $C_{13}H_{30}NO_5P$. Calculated, %: C 50.15; H 9.71; N 4.50; P 9.95.

Ethyl-(2,2-dimethoxyethylamino)methylphosphonate phosphonate IIIa. 0.50 g of compound **IIa** was kept in aqueous acetone for 7 days. There was formed 0.25 g (55%) of the compound **IIIa**, mp 147–149°C (decomp). IR spectrum, ν, cm^{-1}: 1043, 1082 (POC), 1107, 1134 (COC), 1219 (P=O), 2236–2883 (NH$^+$), 3424 (NH). ^{1}H NMR spectrum (D_2O, 20°C), δ, ppm (*J*, Hz): 1.26 t (3H, $OCH_2C\underline{H}_3$, $^3J_{HH}$ 6.98), 3.044 s (2H, NCH_2), 3.054 d (2H, PCH_2, $^2J_{PH}$ 17.44), 3.39 s (6H, OCH_3), 3.95–4.02 (2H, OCH_2, $^3J_{HH}$ 6.98), 5.00 m (1H, CH, $^3J_{HH}$ 5.39). ^{31}P NMR spectrum: δ_P 8.52 ppm. Found, %: C 37.14; H 7.98; N 6.02; P 13.50; $C_7H_{18}NO_5P$. Calculated, %: C 37.01; H 7.99; N 6.17; P 13.63.

Ethyl-(4,4-diethoxybutylamino)methyl phosphonate IIIb. The procedure was similar to that of **IIIa**. 0.5 g of **IIb** gave 0.20 g (44%) of the compound **IIIb**, mp 145–146°C. IR spectrum, ν, cm^{-1}: 1041, 1066 (POC), 1108 1134 (COC), 1220 (P=O), 1613, 2236–2604 (NH$^+$), 3440 (NH). ^{1}H NMR spectrum, (D_2O, 20°C), δ, ppm (*J*, Hz): 1.13 т (6H, $OCH_2C\underline{H}_3$, $^3J_{HH}$ 7.06), 1.21 t (3H, $POCH_2C\underline{H}_3$, $^3J_{HH}$ 7.06), 1.64–1.71 m (4H, $(C\underline{H}_2)_2CH$], 3.08–3.13 m (4H, NCH_2, PCH_2,), 3.51–3.59 m (2H, OCH_2), 3.64–3.71 m (2H, OCH_2), 3.87–3.95 m (2H,

Table 2. Composition and point masses of ionic peeks for the specimens **IIIa, IIIb**

Sample	*m*/*z*	M_{exp}	Composition	M_{calc}
IIIa	266	266.0523	$C_7H_{18}NO_5PK$	266.0560
	455	455.1902	$C_{14}H_{37}N_2O_{10}P$	455.1923
	493	493.1412	$C_{14}H_{36}N_2O_{10}PK$	493.1482
	515	515.1285	$C_{14}H_{35}N_2O_{10}P_2NaK$	515.1301
	758	758.1879	$C_{21}H_{53}N_3O_{15}P_3K_2$	758.1963
IIIb	306	306.1484	$C_{11}H_{26}NO_5PNa$	306.1440
	322	322.1186	$C_{11}H_{26}NO_5PK$	322.1180
	475	475.2336	$C_{18}H_{41}N_2O_8P_2$	475.2333
	513	513.1748	$C_{18}H_{40}N_2O_8P_2K$	513.1896
	567	567.3104	$C_{22}H_{53}N_2O_{10}P_2$	567.3169
	605	605.2702	$C_{22}H_{53}N_2O_{10}P_2K$	605.2734
	888	888.4238	$C_{33}H_{79}N_3O_{15}P_3K$	888.4282
	956	956.3702	$C_{33}H_{77}N_3O_{14}P_3K_2Na_2$	956.3688

$POCH_2$), 4.60 t (1H, CH, $^3J_{HH}$ 5.32). ^{31}P NMR spectrum, (D_2O): δ_P 11.66 ppm. Found, %: C 46.36; H 9.15; N 4.42; P 9.90; $C_{11}H_{26}NO_5P$. Calculated, %: C 46.63; H 9.25; N 4.94; P 10.93.

ACKNOWLEDGMENTS

The research was supported by the Russian Foundation for Basic Research (grant no. 12-03-31138_mol_a).

REFERENCES

1. Skopenko, V.V., Tsivadze, A.Yu., Saranovskii, L.I., and Garnovskii, A.D., *Koordinatsionnaya khimiya* (Coordination Chemistry), Moscow: IKC “Akademkniga,” 2007, p. 487.
2. Fegtle, F. and Weber, E., *Chemistry of “Guest–Host” Complexes. Synthesis, Structure and Applications*, Moscow: Mir, 1988, p. 513.
3. Finnocchiaro, P., Failla, S., and Consiglio, G., *Russ. Chem. Bull*., 2005, no. 6, p. 1355.
4. Cherkasov, R.A. and Galkin, V.I., *Russ. Chem. Rev.,* 1998, vol. 67, no. 10, p. 857.
5. Kafarski, P. and Lejczak, B., *Phosphorus, Sulfur, Silicon and Relat. Elem*., 1991, vol. 63, p. 193.
6. Kukhar, V.P. and Hudson, H.R., *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, Chichester: Wiley and Sons, 2000.
7. Cherkasov, R.A., Garifzyanov, S.V., Zakharov, A.I., Vinokurova, A.I., and Galkin, V.I., *Russ. J. Gen. Chem*., 2006, vol. 76, no. 3, p. 417.
8. Garifzyanov, A.R., Zakharov, S.V., Krukov, S.V., Galkin, V.I., and Cherkasov, V.A., *Russ. J. Gen. Chem*., 2005, vol. 75, no. 8, p. 1208.
9. Pinkassik, E. AND Danila, D.S., USA Patent WO2009114538, 2009.
10. Danila, D.S., Wang, X., Hubble, H., Antipin, I.S., and Pinkassik, E., *Bioorg. Med. Chem. Lett*., 2008, vol. 18, p. 2320.
11. Antipin, I.S., Stoikov, I.I., Pinkassik, E.M., Fitseva, N.A., and Konovalov, A.I., *Tetrahedron Lett*., 1997, vol. 38, no. 33, p. 5865.
12. Burilov, A.R., Gazizov, A.S., Khakimov, M.S., Kharitonova, N.I., Pudovik, M.A., Konovalov, A.I., *Russ. J. Gen. Chem*., 2008, vol. 78, no. 12, p. 2411.
13. Khakimov, M.S., Gazizov, A.S., Burilov, A.R., Pudovik, M.A., and Konovalov, A.I., *Russ. J. Gen. Chem*., 2009, vol. 79, no. 6, p. 1163.
14. Gazizov, A.S., Burilov, A.R., Khakimov, M.S., Kharitonova, N.I., Pudovik, M.A., and Konovalov, A.I., *Russ. J. Gen. Chem*., 2009, vol. 79, no. 9, p. 1929.
15. Vagapova, L.I., Burilov, A.R., Pudovik, M.A., Habicher, W.D., Syakaev, V.V., and Konovalov, A.I., *Mendeleev Commun*., 2011, vol. 21, p. 44.
16. Burilov, A.R., Gazizov, A.S., Pudovik, M.A., and Konovalov, A.I., *Russ. J. Gen. Chem*., 2007, vol. 77, no. 1, p. 98.
17. Vagapova, L.I., Fahertdinova, A.F., Burilov, A.R., and Pudovik, M.A., *Mendeleev Commun*., 2012, vol. 22, no. 6, p. 325.
18. Markovsky, L.N., Kalchenko, V.I., Solovyov, A.V., Finnocchiaro, S., Failla, S., Atamas, L.I., Consiglio, G., and Tsymbal, I.F., *Anales de Quimica*, 1998, vol. 94, p. 164.
19. Sheldrick, G.M., *Acta Cryst. (A)*, 2008, vol. 64, p. 112.
20. Farrugia, L.J., *J. Appl. Cryst*., 1999, vol. 32, p. 837.
21. *APEX2 (Version 2.1), SAINTPlus. Data Reduction and Correction Program*, Version 7.31 A, Bruker Advanced X-Ray Solutions, BrukerAXS Inc., Madison, Wisconsin, USA, 2006.
22. Spek, A.L., *Acta Cryst. (A)*, 1990, vol. 46, p. 34.