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Synthesis and Complex-Forming Properties of Thiazolyl-Containing Organophosphorus Complexone

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Abstract—Alkaline hydrolysis of the previously prepared ethyl 2-methyl-2-[diethylamido-*N*-(4'-phenylthiazolyl-2-amido)phosphono]glycidate and 2-phenyl-2-[diethylamido-*N*-(4-phenylthiazolyl-2-amido)-phosphono]glycidate accompanied by decarboxylation in situ of the obtained glycidic acids furnished 2-[diethyl-amido-(4'-phenylthiazolyl-2'-amido)phosphono]propionic and 2-phenyl-2-[diethylamido-(4'-phenylthiazolyl-2'-amido)phosphono]acetic aldehydes. The qualitative and quantitative evaluation of complex-forming ability of the compounds obtained with respect to transition metal ions was carried out. For identification of copper complex the evaluation of the stability constants of copper, cobalt, nickel, and zinc complexes was performed. Thermodynamic parameters of complex formation reactions were calculated. Correlation dependences between the physicochemical properties of metal ions and thermodynamic characteristics of complex formation with the organophosphorus ligands obtained were established.

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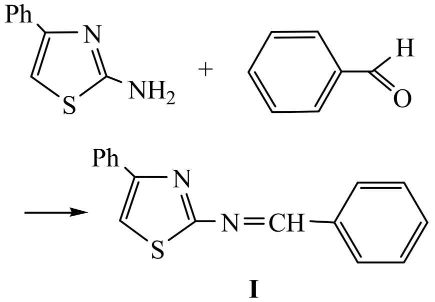
Investigation of complex formation between various organic substances and metal ions has attained a new level. Its determining characteristic is the polyfunctionality or universality of organic substance, in particular, the relationship between the reactivity and biological activity, and between thermodynamic stability and the degree of binding of metal ions provides also for the practical use of these compounds. Hence, for realizing deep processes of biological and ecological character the structural as well as the energy features of various systems must be considered.

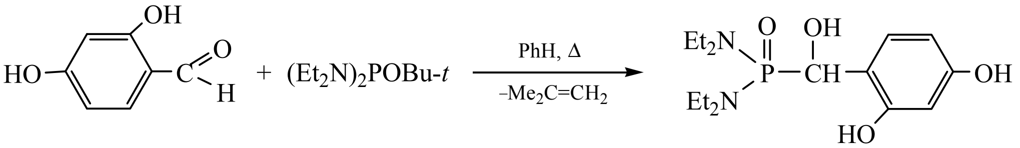
Analysis of the published data [1–5] shows that the presence of phosphorus, nitrogen, and sulfur atoms in the molecules of organic compounds provides them with a high physiological activity and often decreases the toxicity. Such compounds exhibiting the broncholytic, antiviral, antiphlogistic, antitumor, and some other activity are effective drugs. Besides, compounds of thiazole series are widely used in industry and agriculture [6, 7]. In [8, 9] compounds were synthesized inhibiting the growth of *Helminthosporium oryzae*, for example substance **I**, and also some substances possessing the complex-forming properties.



I

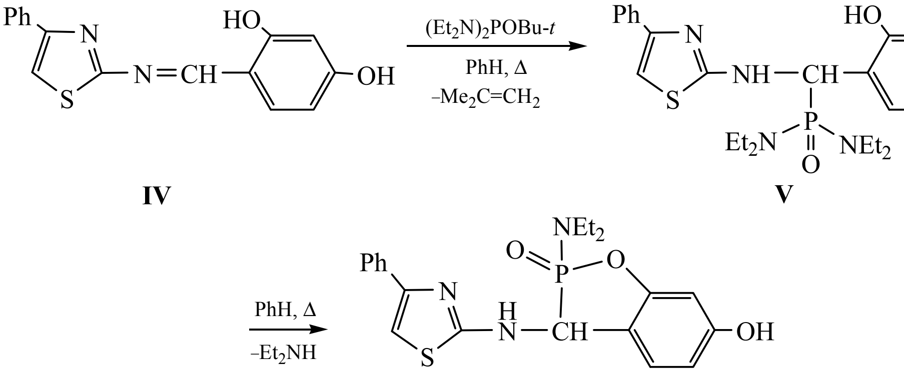
As is known, the complexone chemistry opens practically inexhaustible possibilities of modifying the properties of cations creating wide potential for their use. The necessity of development the broad range of complexones with the wide variety of complex-forming properties at different pH values, in particular, for the medicinal purpose remains the promising field of investigation up to now [10].

One of the current directions of investigation of the organophosphorus complexones is the reaction of derivatives of the trivalent phosphorus acids with different electrophilic reagents. Reactions of esteroamidites of P(III) acids with carbonyl compounds are sufficiently thoroughly studied. It is established that their pathway depends on the structure of starting substances [11, 12]. Salkeeva et al. [13,14] showed that phosphonate **III** prepared by the reaction of *tert*-butyl tetraethyldiamidite **II** with 2,4-hydroxybenzaldehyde was capable of complex formation with different metal cations.



II **III**

On the other hand, phosphite **II** reacts with Schiff base **IV** prepared from 2-amino-4-phenylthiazole to give phosphonate **V** which can be further converted into product **VI**.

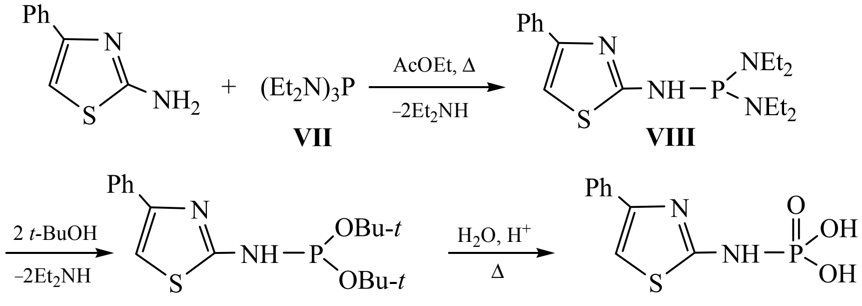


IV **V** **VI**

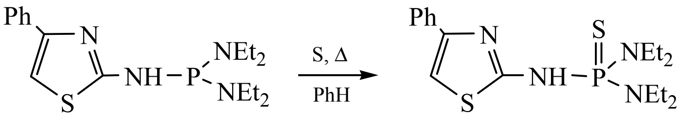
Meanwhile, the reported data show that the number of organophosphorus compounds exhibiting high complex-forming properties with respect to metal ions is not large. That is why the development of organophosphorus complexones on the basis of 2-amino-4-phenylthiazole is topical. The transamidation of phosphorotriamidite **VII** with 2-amino-4-phenylthiazole followed by treating with *tert*-butanol and acid hydrolysis of the reaction products **VIII, IX** yielded the phosphonic acid **X** [14].

Synthetic potential of the amidophosphite **VIII** is determined also by the possibility of its transformation in the pentavalent phosphorus derivatives, as we confirmed by an example of the reaction of compound **VIII** with sulfur in the benzene suspension to form product **XI**.

Structures of the compounds **III, VI, VIII, X** permit to expect the complex-forming properties due to the presence of phosphoryl group, of nitrogen atom, and of hydroxy group.



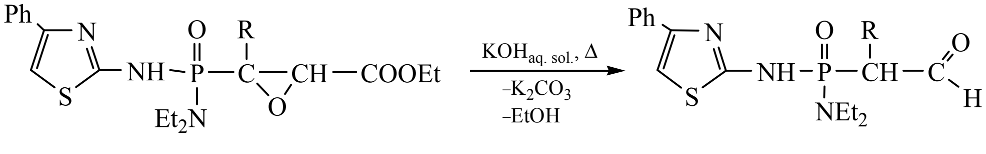
VII **VIII** **IX** **X**



VIII **XI**

β-Dicarbonyl compounds capable of keto-enol tautomerizm are good complex-forming agents. α-Phosphorylated aldehydes can be regarded as their heteroanalogs.

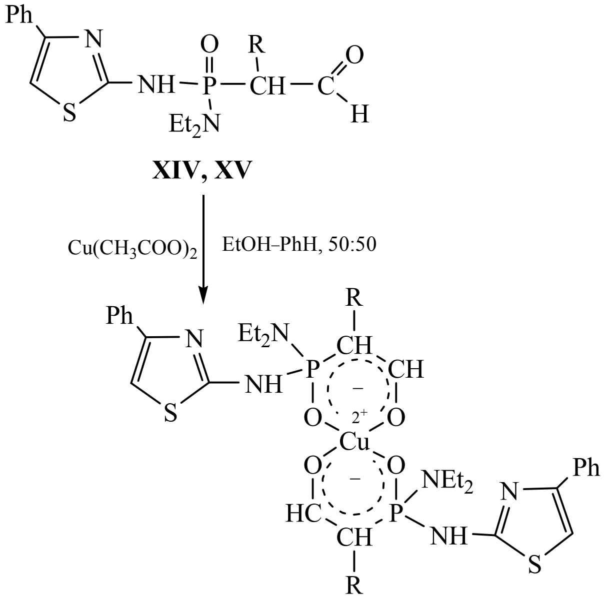
Two representatives of phosphorylated aldehydes **XIV, XV** we synthesized from the glycidyl esters **XII, XIII** [15] by alkaline hydrolysis accompanied by decarboxylation *in situ* of the corresponding phosphorylared glycidic acids. The established experimental conditions require no additional and intermediate stages of isolation and treatment significantly simplifying the procedure. The phosphorylated aldehydes obtained may find wide practical use [16].



XII, XIII **XIV, XV**

R = CH_3 (**XII, XIV**), Ph (**XIII, XV**).

Compounds **XIV, XV** are capable of enolization and may be used as the effective complex-forming agents analogously to β-diketones. It was confirmed by our studies of thermodynamic parameters of complex formation of some compounds synthesized. We believe that the formation of complexes **XVI, XVII** proceeds according to the following scheme.



XVI, XVII

R = CH_3 (**XVI**), Ph (**XVII**).

Note that the compounds synthesized may be used for evaluation of metal ions in different media. In this case the quantitative characteristics of complex formation are important. That is why complex forming ability of phosphorylated aldehyde **XIV** with respect to the transition metal ions was studied. On the basis of potentiometric titration in water–ethanol medium stability constants of *d*-metal ions were evaluated (see the table).

According to the data presented in [17] for the binary solvents in the first solvate shell of the ion the component prevails whose variation in Gibbs energy during the solvation has the more negative value. Therewith the near solvation shell is involved in the complex formation. Comparative analysis of Gibbs energies of hydration for metal ions shows that copper ions are most hydrated, Hence, specific solvation is characteristic of them what leads to low values of the stability constants of complexes. On the other hand, the behavior of ions in solution depends on their geometric characteristics, in particular, on the ion radius, and hence on the value of the hydration entropy ($-\Delta H^0$, J mol^{-1} K^{-1}) [18]. Considering the specific behavior of copper(II) ions in water solution we present here the values for the rest of ions (J mol^{-1} K^{-1}): 277.2 (Ni^{2+}), 244.9 (Zn^{2+}), 257.6 (Co^{2+}). This means that nickel ion exhibits the largest structurizing effect on water molecules, while for zinc ions the smallest action on the molecules of solvent in the nearest hydrate shell is characteristic. Comparative analysis of data on the hydration entropy and the stability constants (see the table) shows that the increase in the absolute value of the hydration entropy leads to decrease in the stability of complexes of *d*-metal ions with the organic component. That means that the degree of structurization of solvent affects significantly the process of complex formation in solution.

Considering the effect of temperature on the reaction of metal ions with the organic ligand it must be noted that at 313 K the stability of complexes decreases in the series $Ni^{2+} > Zn^{2+} > Co^{2+}$, while at 318 K) this dependence is reversed. The above-presented data show that the enthalpy contribution to the Gibbs hydration energy prevails. In the first case the decrease in the hydration enthalpy, and hence in energy of the bond between the metal ion and the molecules of solvent leads to the increase in the hydrate number [19]. For large ions (Zn^{2+}, Cu^{2+}) this effect reveals in the largest degree and is reflected in the stability constants ($\Delta \log K = \log K_{313} - \log K_{318} = -0.13$ and -0.09, respectively) while for Co^{2+} ($\Delta \log K = -0.02$). In the second case the increase in the stability constants for Co^{2+} and their decrease for Zn^{2+} and Ni^{2+} ions is caused by variation in the composition of water–organic solvent, in particular, in the decrease in the ethanol fraction.

In this connection the consideration of the above-presented effects from the thermodynamic point of view seemed interesting. Therefore on the basis of temperature dependence of the stability constants of complexes we have calculated variations in the enthalpy contribution in the Gibbs energy (see the figure).

It was established that for nickel(II) and zinc(II) the increase in temperature favors the increase in heat evolution of the process meaning that the formation of more stable complex is accompanied by variation in the solvate surrounding, in particular, by elimination of water molecules from the first and the second hydrate shell of complex-forming metal. But at high temperatures together with the above-mentioned variations in heat evolution the decrease in the stability of complexes is observed. On the one hand, it is connected with the destruction of the solvate shell of metal ion and binding of the greater amount of water molecules, and on the other hand, with substitution of water molecules in the freshly formed solvate shell of metal by the molecules of ligand. For copper ions no significant variations in enthalpy value take place caused by the composition stability of the complex. In contrast, the formation of cobalt(II) complexes is accompanied by an increase in the heat absorption due to the formation of associates between the molecules of water and ethanol. Thus a stabilization of complex with solvent takes place. This fact is connected with weaker electrostatic field created by Co^{2+} ion providing the delocalization of electronic density.

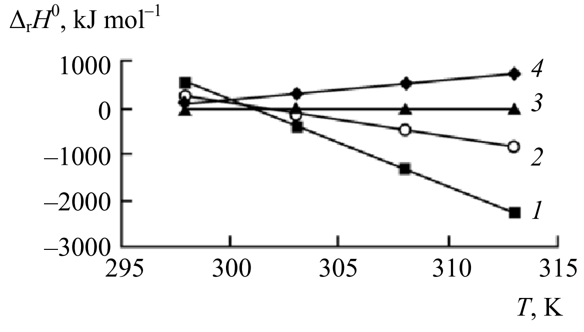
Stability constants of metal ion complexes with 2-[diethylamido-(4-phenylthiazolyl-2'-amido)phosphono]propionic aldehyde in water–ethanol media

M^{2+}	298 K	303 K	308 K	313 K
	log β			
Co	9.02	9.39	9.32	11.00
Ni	8.19	9.01	9.71	6.79
Cu	0.56	0.46	0.37	0.28
Zn	9.33	9.79	9.66	9.17

Hence, the investigation of complex formation between *d*-metal ions and the organic component in water–ethanol media showed that linear dependences between the stability constants of complexes and the hydration enthalpy and entropy takes place. From the thermodynamic data on complex formation it follows that the structurization degree of solvent affects significantly the process of complex formation in solution. At high temperatures it leads to increase in the hydrate number. From the other point of view the above-mentioned effects are caused also by the specific features of electronic structure of the complex-forming metal ion which are revealed in variation of intensity of the electrostatic field of ion and reflected in the overall dipole moment of the forming complex.

EXPERIMENTAL

IR spectra of the compounds synthesized were recorded on a Nicolet Avatar-360 spectrometer in KBr pellets (measurement error 0.2 cm^{-1}). ^1H NMR spectra were taken on a Bruker DRX-500 spectrometer (500 MHz) in DMSO-d_6 against internal TMS



Dependence of enthalpy of complex formation of *d*-metal ions with 2-[diethylamido-(4-phenylthiazolyl-2-amido)-phosphono]propionic aldehyde on temperature. (*1*) Ni^{2+}, (*2*) Zn^{2+}, (*3*) Cu^{2+}, and (*4*) Co^{2+}.

(measurement accuracy ±0.1–0.2 ppm). Melting points were evaluated on a Boetius apparatus (experimental error ±0.1°C).

The reaction progress and individuality of compounds were controlled by TLC on the standard Silufol UV-254 plates, elution with 6:1 benzene–ethanol. Chromatograms were developed by iodine vapor.

Ethyl 2-methyl-2-[diethylamido-*N*-(4'-phenylthiazolyl-2'-amido)phosphono]glycidylate (XII). A solution of sodium ethylate was prepared from 0.3 mol of sodium and 300 ml of anhydrous ethanol in a three-neck flask equipped with a reflux condenser, a dropping funnel, and a stirrer. After the complete dissolution of sodium a mixture of 3.67 g of ethyl chloroacetate and 6.74 g of diethylamido-*N*-(4'phenylthiazolyl-2-amido)acetylphosphonate **III** was added dropwise with stirring and cooling with the ice water. After the reaction was complete (TLC control) the mixture obtained was left overnight at room temperature, neutralized with the equimolar amount of acetic acid, and poured in 100 ml of the ice water. Water layer was several times extracted with ether, ether extracts were several times washed with water and dried over sodium sulfate. The solvent was distilled off, and the residue was crystallized from ethanol. Yield of compound **XII** 6.34 g (75%), mp 202–203°C. IR spectrum, ν, cm^{-1}: 1749 (COO), 1483 (C=N), 1205 (P=O), 1442, 1461, 1547, 1549 (C=C), 3345 (NH). ^{1}H NMR spectrum, δ, ppm: 7.25–7.40 m (C_6H_5, CH), 1.15 t (CH_3–CH_2, 6H), 2.56 m (CH_3–CH_2, 4H), 7.8 s (NH, 1H). Found, %: C 53.76, H 6.67, N 9.45, P 7.18, S 7.84. *M* 423. $C_{19}H_{26}N_3O_4PS$. Calculated, %: C 53.90; H 6.14; N 9.93, P 7.33, S 7.56.

2-[Diethylamido-(4'-phenylthiazolyl-2'-amido)-phosphono]propionic aldehyde (XIV). A mixture of 4.24 g of glycidyl ester **XII**, 1.96 g of potassium hydroxide, 25 ml of water, and 50 ml of ethanol was refluxed with stirring for 4 h. After the reaction was complete the main part of ethanol was distilled off, the residue was dissolved in small amount of water, and acidified with hydrochloric acid to pH 1 under cooling with ice. The reaction mixture was 4–5 times extracted with ether, and the combined extracts were dried over sodium sulfate. Ether was distilled off, and the residue was crystallized from ethanol. Yield of compound **XIV** 2.31 g (65%), mp 182°C. IR spectrum, ν, cm^{-1}: 1475 (C=N), 1194 (P=O), 1476, 1502, 1564, 1576 (C=C), 1685 (CH=O), 3372 (NH). ^{1}H NMR spectrum, δ, ppm: 7.45–7.55 m (C_6H_5, CH), 1.20 t (CH_3–CH_2, 6H), 2.62 m (CH_3–CH_2, 4H), 7.82 s (NH, 1H), 7.15 s (thiazole, C^{5}H), 8.57 s (CH=O). Found, %: C 54.56, H 6.67, N 11.45, P 8.94, S 9.42. *M* 351. $C_{16}H_{22}N_3PS$. Calculated, %: C 54.70, H 6.27, N 11.97, P 8.83, S 9.12.

Potentiometric studies of complex-forming properties of aldehyde XIV. Cobalt(II), nickel(II), zinc (II) chlorides, and copper(II) sulfate of "chemically pure" grade were used. All the substances were dissolved in 1:1 water–ethanol mixture. Reaction of aldehyde **XIV** with *d*-metal cations was studied potentiometrically at 298–313 K with 5 K step by means of Cu_2S and FeS_2 electrodes. Their selectivity with respect to the transition metal ions was evaluated in [20]. Silver chloride reference electrode was used, and the electromotive force measurements were performed on an I-500 pH-meter–millivoltmeter. Potentiometric titration of 0.001 M solutions of *d*-metal salts with 0.001 M solution of 2-[diethylamido-(4'-phenylthiazolyl-2'-amido)phosphono]propionic aldehyde was carried out according to the procedure [20]. The temperature of the titrated mixture was maintained by means of the UTU-2/77 thermostate with the accuracy ±0.1 K.

REFERENCES

1. Oae, S., *Khimiya organicheskikh soedinenii sery* (Chemistry of the Organosulfur Compounds), Moscow: Khimiya, 1975.
2. Dianov, V.M., Zarudiy ,F.S., and Strokin, Yu.V., *Khim.-Farm. Zh.*, 1998, vol. 32, no. 3, p. 27
3. Ivanov, E.I., Grishchuk, L.V., Vysotskaya, V.V., and Stepanov, D.E., *Khim.-Farm. Zh.*, 1993, vol. 27, no. 7, p. 37.
4. Chumakov, V.A., Demchenko, A.M., Krasovskii, A.N., Bukhtiarova, T.A., Mel'nichenko, O.A., Grinus, F.P., and Lozinskii, M.O., *Khim.-Farm. Zh.*, 1999, no. 8, p. 20.
5. Martirosyan, A.O., Gasparyan, S.P., and Oganesyan, V.E., *Khim.-Farm. Zh.*, 2006, no. 2, p. 13.
6. Georgiev, T.R., Davarski, K., and Shirev, F., *God. Vestn. Khim.-Tekhnol. Instituta Burgas*, 1983, vol. 18, no. 2, p. 55.
7. Mishra, V.K. and Bahel, S.C., *J. Indian Chem. Soc. Pharmacol.*, 1984, vol. 61, no. 10, p. 916.
8. Singh, M.W. and Dash, B.C., *Pesticides*, 1988, vol. 22, no. 11, p. 33.
9. Sadigova, S.E., Magerramov, A.M., and Allakhverdiev, M.A., *Zh. Obshch. Khim.*, 2003, vol. 73, no. 12, p. 2043.
10. Kumok, V.N., *Zakonomernosti v ustoichivosti koordinatsionnykh soedinenii v rastvorakh* (Stability Rules for

the Coordinational Compounds in Solutions), Tomsk: Tomsk. Gos. Univ., 1988, p. 227.

11. Karmazina, L.D., *Issledovaniya v ryadu kompleksonatov perekhodnykh metallov s fosfororganicheskimi ligandami* (Investigations in the Series of the Transition Metal Complexonates with the Organophosphorus Ligands), Moscow: IREA, 1977.
12. Kostromina, N.A., Chernichenko, T.F., and Mikhailichenko, N.I., *Ukr. Khim. Zh*., 1963, vol. 49, no. 10, p. 1015.
13. Sal'keeva, L.K., Nurmaganbetova, M.T., and Minaeva, E.V., *Vest. Kar. Gos. Univ., Ser. Khim*., 2005, vol. 37, no. 1, p. 46.
14. Sal'keeva, L.K., Nurmaganbetova, M.T., and Minaeva, E.V., Abstracts of Papers, *1st Int. Forum: "Actual Problems of Modern Science,"* Samara, 2005, p. 81.
15. Sal'keeva, L.K., Nurmaganbetova, M.T., Minaeva, E.V., and Kusainov, A.S., Abstracts of Papers, *IX Junior Scientific School-Conf*., Moscow, 2006, p. 249.
16. Sal'keeva, L.K., Nurmaganbetova, M.T., Minaeva, E.V., and Mantel', A.I., Abstracts of Papers, *Int. Scientific Conference "Chemistry, Chemical Technology, and Biotechnology on the Border of Milleniums,"* Tomsk, 2006, p. 308.
17. *Kompleksoobrazovanie v nevodnykh rastvorakh* (Complex Formation in Non-aqueous Solvents), Krestov, G.A., Afanas'ev, V.N., and Agafonov, A.V., Eds., Moscow: Nauka, 1989.
18. Vasil'ev, V.P., *Termodinamicheskie svoistva rastvorov elektrolitov* (Thermodynamic Properties of the Electrolyte Solutions), Moscow: Vysshaya Shkola, 1982.
19. Bakeev, M.I., *Gidratatsiya i fiziko-khimicheskie svoistva rastvorov elektrolitov* (Hydration and Physicochemical Properties of the Electrolyte Solutions), Alma-Ata: Nauka, 1978.
20. Amerkhanova, Sh.K., *Khal'kogenidy metallov v potentsiometrii. Teoriya, metodika, praktika* (Metal Chalcogenides in Potentiometry. Theory, Procedures, and Practice), Karaganda: Profobrazovaniye, 2002.