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## Synthesis and Potentiometric Analysis of Organophosphorus Metal Complexes and Complexonates Based on 2-Aminothiazole Derivatives

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**Abstract**—Synthesis conditions of 4-phenyl-2-amidothiazolyl acetate and 2-thiourido-4-diethylphosphothiazole were developed, and the complexation capacity of these compounds in formation of mixed-ligand complexes was studied. The optimal conditions and thermodynamic parameters of the complexation process were determined. The potentiometric method was used to find thermodynamic parameters of the reactions of mixed-ligand complexation with copper(II) and lead(II) ions, the composition of the complexes being formed on the basis of 4-phenyl-2-aminothiazole and its phosphorylated derivatives was determined.

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The synthesis of phosphorylated derivatives of thiazoles is of particular theoretical and practical interest. The complexation capacity of 2-[diethylamido-(4'-phenyl-thiazolyl-2'-amido)phosphono]propionic aldehyde with cations of various metals has been demonstrated previously [1].

The fundamental aspects of the complexation of phosphorylated ligands have been revealed for the example of compounds whose structure fragmentarily includes  $\text{PO}_3\text{H}_2$  and  $\text{PO}_2\text{H}_2$  groups: fully phosphorylated derivatives of amines, i.e., complexones combining two types of complexing groups (i) phosphone and (ii) carboxy, oxyethyl, and mercaptoethyl [2–4].

The presence of multibasic salt-forming groups and a highly basic nitrogen atom in the structure of the phosphorylated complexone provides their successive dissociation in a wide range of pH values for most of cations. It is known that, when interacting with transition metals, phosphorus-containing complexones form strong hydrogen or hydrogen-bonded complexes, which is uncharacteristic of carboxy-containing prototypes.

The potential ability of aminoalkylphosphonic acids to exhibit an enhanced denticity due to the oxygen

of phosphone groups favors complexation with rare-earth elements for which a large coordination number and high oxygen affinity is known to be characteristic. Alkylenepolyaminopolyalkylphosphonic acids form highly stable mononuclear hydrogen or hydrogen-bonded complexes.

Of interest as a complexing agent is a derivative of 2-amino-4-phenylthiazole (**1**), 4-phenyl-2-amiothiazolylacetate (**2**), produced by the reaction of compound (**1**) with acetyl chloride in the presence of triethylamine. The structure of thiazolyl acetate includes an acetyl group capable of enolization, with the +M effect of the amino group making higher the electron density on the oxygen of the carbonyl group, which apparently shifts the equilibrium toward the enolic form. Thus, in our study of 4-phenyl-2-aminothiazolyl acetate (**2**) as a complexing agent, the ability of the object under study to form intramolecular hydrogen bonds in both the ketonic and enolic forms was taken into account (Scheme 1).

The choice of objects for study, containing a phosphorus atom or having the form of various functional derivatives of 2-amino-4-phenylthiazole (**1**) without a phosphorus atom, is governed by the fact that a combi-

nation of phosphorylated and unphosphorylated ligands is possible for obtaining complex compounds with extended range of properties.

Proceeding with studies aimed to synthesize new phosphorylated derivatives of thiazole, we made an attempt to obtain aminothiazole containing a phosphorus component directly at the thiazole ring by using the classical method of closure of the thiazole ring by the known scheme of the Hantzsch reaction (Scheme 2).

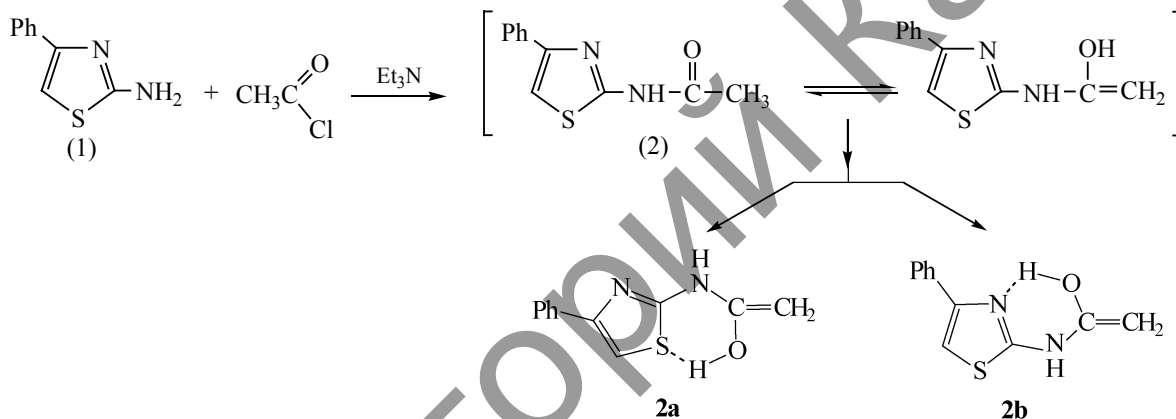
The compound synthesized, 4-(diethylphosphono)-2-aminothiazole (**3**), is a white crystalline substance soluble in water and organic solvents. Its IR spectrum contains characteristic absorption bands at 1040 and

1206  $\text{cm}^{-1}$ , associated with vibrations of P–O–C and P=O bonds, respectively; vibrations of the free amino group appear as two absorption bands at around 3375  $\text{cm}^{-1}$ .

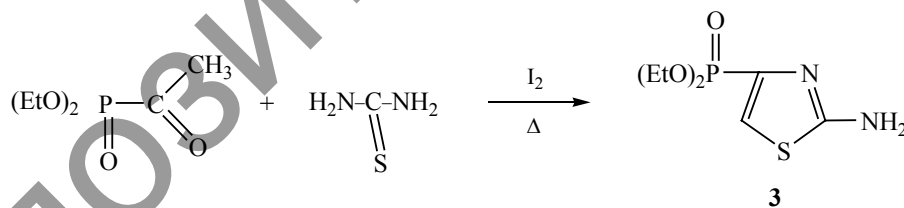
Similarly, we synthesized phosphorylated thiouridothiazole (**4**) having complexing properties from aminothiazole (**3**) (Scheme 3).

The compound obtained, 2-thiourido-4-diethylphosphothiazole (**4**), is a white crystalline substance soluble in water, ethanol, and other polar solvents. The structure of the phosphorylated thiourea derivative we obtained suggests its potential capacity for complexation due to the nitrogen atom of the thiazole ring and to the polar

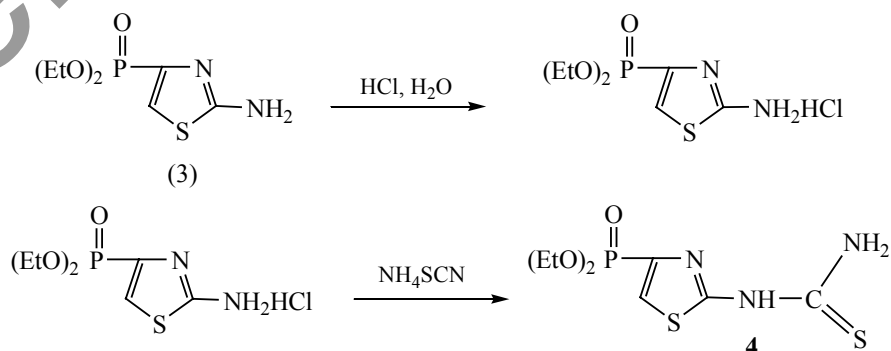
Scheme 1.



Scheme 2.



Scheme 3.



thiocarbonyl group.

The complexing ability of compounds **2** and **4** was studied in the reaction with copper(II) acetate in various aqueous-organic media. As solvents miscible with water served alcohols, acetone, dioxane, and dimethylformamide. On performing these experiments, we found that colored compounds of greenish-light blue color are formed only in an aqueous-alcoholic medium. All further studies were carried out with ethanol. Based on the results obtained in a study of the structure of complexes **5** and **6** we obtained, we suggest the following Scheme 4.

At present, particular attention is given to complexes incorporating two different ligands. Of particular interest are mixed complexes of organophosphorus elements with complexones. Compounds of this kind are more stable as compared with complexes containing two similar ligands. This opens up wide prospects for effective use of polyligand agents in various technological procedures.

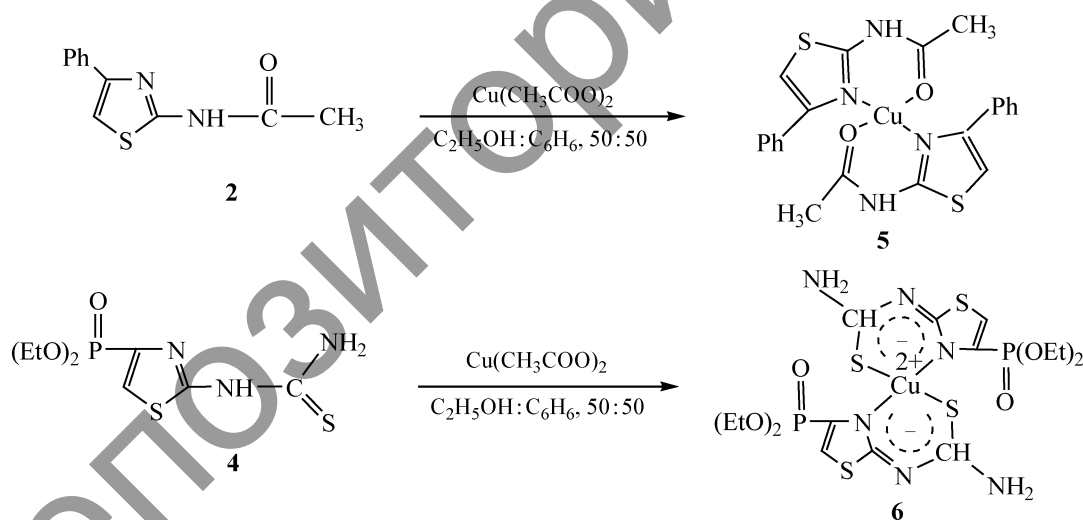
To evaluate the complexing ability of 2-thiourido-

4-diethylphosphothiazole (**4**) and 4-phenyl-2-amidothiazolyl acetate (**2**), we made an attempt to synthesize copper and lead complexones on the basis of these compounds. The reaction was performed by heating of equimolar amounts of compounds **2** and **4** and copper and lead acetates in a benzene-ethanol medium. In the heterophase system, blue green crystals were formed for complexes with copper ions and white crystals for complexes with lead ions. When studying the structure of the complexes being formed, we took into account the ability of the ligands under study to form intramolecular hydrogen bonds (Scheme 5).

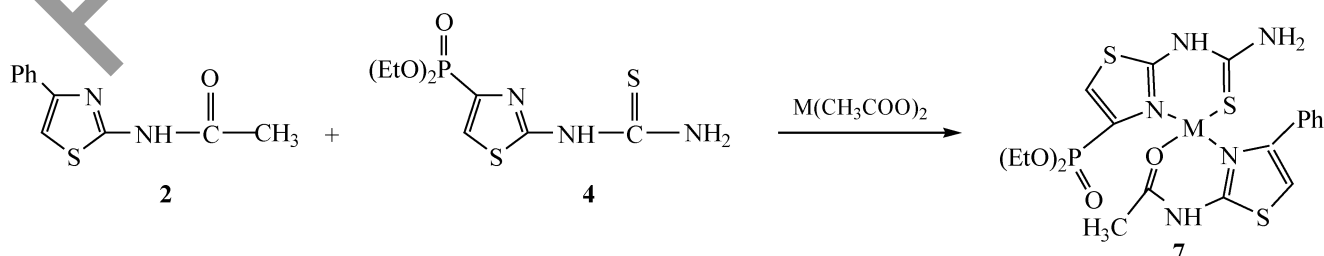
At present, the key characteristic in studies of the complexation of various organic compounds with metal ions is the polyfunctionality or versatility of an organic substance.

We believe that the synthesized mixed-ligand complexes of compounds **2** and **4** with heavy metal ions are more stable than their single-ligand analogs because of being stabilized not only by covalent bonds and electrostatic forces, but also by the hydrophobic

Scheme 4.



Scheme 5.



interaction. A study of the interaction of phosphorylated complexones with cations from various groups of the Periodic table revealed a number of specific features in the behavior of these ligands. Particular attention should be given to the ability of the compounds under study to form strong complexes with copper and lead.

The practical use of complexones and their effect on biochemical processes require a comprehensive study of thermodynamic parameters of the reactions of complexation of these compounds in solutions. It is noteworthy that the compounds synthesized can act as reagents for metal ions in analyses of various media, in which the quantitative aspect is important. This is confirmed by our study of the thermodynamic parameters of the complexation process of some of the compounds synthesized.

### EXPERIMENTAL

IR spectra of the compounds synthesized were recorded on a Nicolet Avatar-360 spectrometer in pellets with KBr (measurement error  $0.2 \text{ cm}^{-1}$ ), and  $^1\text{H}$  NMR spectra, on a Bruker DRX500 spectrometer with a working frequency of 500 MHz in  $\text{DMSO-}d_6$  solutions relative to TMS as internal standard (error  $\pm 0.1\text{--}0.2 \text{ ppm}$ ). The melting point was determined with a Boetius instrument (measurement error  $\pm 0.1^\circ$ ). The course of all the reactions and the individual nature of the compounds was monitored by thin-layer chromatography on standard Silufol UV-254 plates in a 6 : 1 benzene–ethanol system. The chromatograms were developed with an iodine vapor.

The potentiometric method was used to determine on an ion-meter the thermodynamic parameters of the reactions of complexation with copper(II) and lead(II) aqueous-alcoholic solution at 298.15–318.15 K and ionic force  $I$  of 0.1, 0.5, 1.0 ( $\text{KNO}_3$ ). An I-500c pH-meter with a rated measurement error of  $\pm 2.5 \text{ mV}$  and silver chloride and glass electrodes served for measurements under thermostated conditions. The EVL-1 M silver chloride reference electrode was always separated from the working solution by an electrolytic bridge filled with a 0.1 M KCl solution. The potential of the reference electrode was refined relative a quinhydrone electrode. The solutions were agitated with a magnetic rable. Titration was performed in stages; roughly and precisely by the dropping method, with the final titration point found from integral and differential curves. The working solution of a complexonate was prepared from

a precisely weighed portion of the reagent.  $\text{KNO}_3$  of analytically pure grade, used to create the ionic strength, was purified by double recrystallization from 6 water. The concentration of the solutions under study was 0.01 M in all experiments. The M : L ratio was varied from 1 : 1 to 1 : 3.

The experimental data were processed using PHMETR software intended for calculation of stability constants in systems with an arbitrary number of reactions from the equilibrium concentration of one of the species. A processing of the potentiometric data by PHMETR software revealed all the possible species formed in the system. It was possible to determine a number of mixed-ligand ions and to calculate estimated values of thermodynamic parameters of the complexation reactions. Based on the results of a potentiometric titration in an aqueous-alcoholic medium, we determined logarithms  $\log \beta$  of the stability constants of the complexes of metal ions.

It follows from the temperature dependence of the logarithms  $\log \beta$  of the stability constants of mixed-ligand complexes of thiazole derivatives with copper ions (Fig. 1) that an increase in temperature impairs the stability of these compounds. This is primarily due to a change in the hydrate environment of a metal ion in the complexing agent. However, the data related to logarithms of stability constants are insufficiently informative. Therefore, we calculated the main thermodynamic parameters of the processes under study (Table 1).

The thermodynamic stability constants of the complexes were calculated by extrapolation of the concentration constants to zero ionic strength. An important issue for understanding the nature of the stability of the complexes is an analysis of how the

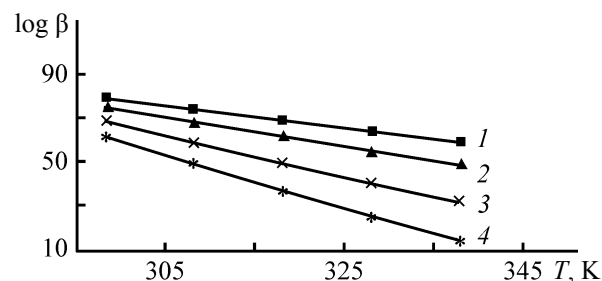


Fig. 1. Logarithms  $\log \beta$  of the stability constants of complexes of 4-phenyl-2-amidothiazolyl acetate (2) and 2-thiourido-4-diethylphosphothiazole (4) with  $\text{Cu}(\text{CH}_3\text{COO})_2$  vs. temperature  $T$ . Ionic strength ( $\text{g ion l}^{-1}$ ): (1) 0, (2) 0.1, (3) 0.5, and (4) 1.0.

**Table 1.** Thermodynamic characteristics of complexation processes in the 4-phenyl-2-amidothiazolyl acetate (**2**) + 2-thiourido-4-diethylphosphothiazole (**4**) system with  $\text{Cu}(\text{CH}_3\text{COO})_2$

<i>I</i>	$-\Delta_r H_{298}^\circ$	$-\Delta_r H_{308}^\circ$	$-\Delta_r H_{318}^\circ$
	kJ mol <sup>-1</sup>		
0.1	259.019	258.131	257.244
0.5	-270.02	-269.10	-268.17
1.0	-591.59	-589.56	-587.53
<i>I</i>	$-\Delta_r G_{298}^\circ$	$-\Delta_r G_{308}^\circ$	$-\Delta_r G_{318}^\circ$
	kJ mol <sup>-1</sup>		
0.1	162.43	159.25	156.06
0.5	119.76	132.78	145.80
1.0	113.55	137.08	160.61
<i>I</i>	$-\Delta_r S_{298}^\circ$	$-\Delta_r S_{308}^\circ$	$-\Delta_r S_{318}^\circ$
	J mol <sup>-1</sup> K <sup>-1</sup>		
0.1	324.12	321.06	318.18
0.5	-1308.01	-1304.81	-1301.82
1.0	-2366.22	-2359.21	-2352.65

entropy changes. The change in the entropy of systems in complexation is due to several factors: disintegration of hydration shells of ligand groups, displacement of water molecules from the first coordination sphere of the metal ion, and formation of chelate structures. The positive contribution of the first two factors to disordering of the systems probably cannot surpass the decrease in entropy because of the loss of the configuration entropy due to an increase in the chain rigidity upon incorporation of functional groups into the first coordination sphere of copper and lead ions to give rather stable polychelate structures. Table 1 lists thermodynamic parameters of the complexation process.

The observed changes in the free Gibbs energy depend on the enthalpy and entropy factors. The relative contribution of each of these factors depends on the nature of the ligand and the central metal ion, on the type of the indifferent salt ( $\text{KNO}_3$ ) creating the ionic strength of the solution, and on the value of this strength. In other words, addition of each metal ion is regarded as cross-linking of the molecule. For the processes under study, the Gibbs energy only slightly changes with increasing temperature.

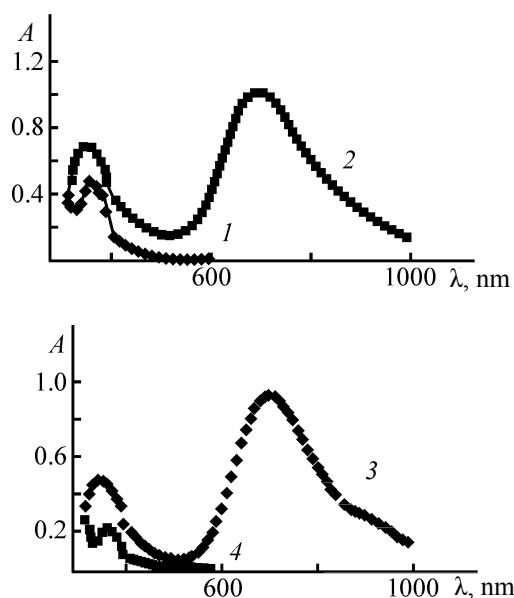
Spectrophotometric determination of metals as complex compounds with organic reagents by extraction methods is widely used in practice. However, the extraction technique is labor consuming and requires toxic solvents. Of particular interest in this context is development of new no-extraction methods for determination of metals.

The absorption spectra of complexes **5** and **6** contain two peaks: in the UV ( $\lambda = 350$  and  $340$  nm) and visible ( $\lambda = 705$  and  $700$  nm) spectral ranges, respectively. The absorption spectrum of aqueous-alcoholic solutions of thiazoles **2** and **4** has a single absorption peak in the UV spectral range at  $\lambda = 360$  and  $355$  nm, respectively. The graphical dependence of the optical density of the synthesized compounds **2**, **5** and **4**, **6** on the wavelength is shown in Fig. 2.

The complexation in the systems we revealed was studied in the visible region, because the starting reagents have a considerable absorption in the UV spectral range.

To determine the optimal conditions of interaction between copper(II) ions and solutions of thiazoles **2** and **4** we synthesized, the influence exerted on the complexation process by various factors: percentage content of the organic solvent, reagent concentration, and solution acidity, was studied.

It was found that the dependence of the optical density on the ethanol content at the wavelengths at



**Fig. 2.** Electronic absorption spectra of compounds (1) **2**, (2) **5**, (3) **4**, and (4) **6**. (A) Optical density and ( $\lambda$ ) wavelength.

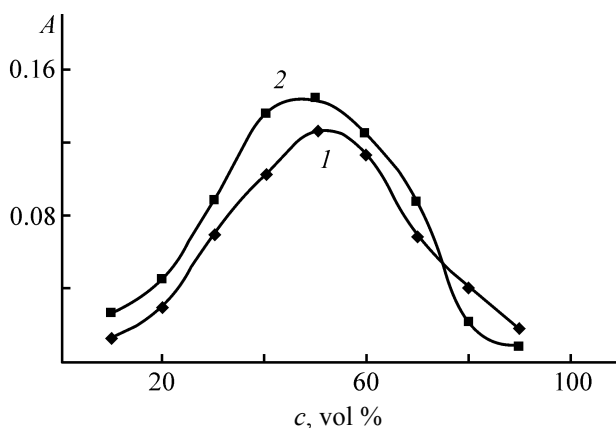


Fig. 3. Optical density  $A$  at the wavelength at which lie absorption peaks of (1) starting reagents **2** and **4** and (2) complexes **5** and **6** obtained vs. the ethanol content  $c$  in the mixed solvent.

which lie the absorption peaks of the starting reagents **2** and **4** and of the resulting complexes **5** and **6** is described by a curve with a peak (Fig. 3). It can be seen that the highest value of the optical density is observed at an ethanol content of 50 vol % in both cases.

Figure 4 shows the effect of the acidity of the medium on the strength of complexes **5** and **6** being formed, expressed in terms of how the optical density of solutions varies with the pH of the medium. It follows from the results obtained that the degree of complexation is the largest at pH 8–8.5.

The results obtained in determining the concentration of reagents **2** and **4** necessary for full binding of the ion being analyzed into a colored compound are presented in Fig. 5. It can be seen that the reagent concentration is 1.25 M for compound **2** and 1.5 M for **4**.

We found the composition of complexes **5** and **6** by the Garvey–Manning slope ratio method employed to study various reactions yielding a strong complex,  $M_mR_n : mM + nR \leftrightarrow M_mR_n$ .

We carried out two series of experiments. In the first of these, the initial concentration of reagents **2** ( $c_R$ ) and **4** ( $c_{R1}$ ) was maintained constant at a value substantially exceeding the varied concentration of the central ion M ( $Cu^{2+}$ ),  $c_R > c_M$ .

Because of the large excess of reagents R **2** and **4**, it can be assumed that ion M will fully pass into complex  $M_mR_n$  whose concentration will be  $1/mc_M$ . The optical density  $A_1 = k_1c_M/m$ , where  $k_1$  is a proportionality factor, whence the slope ratio  $\tan \alpha_1 = k_1/m$  of this straight line can be found.

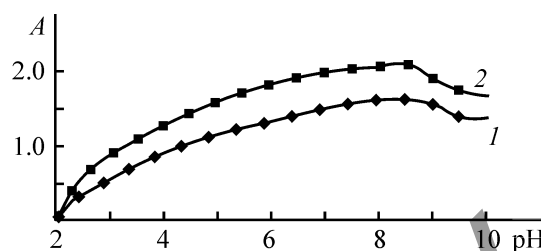


Fig. 4. Optical density  $A$  of solutions vs. the pH of the medium. Compound: (1) **5** and (2) **6**.

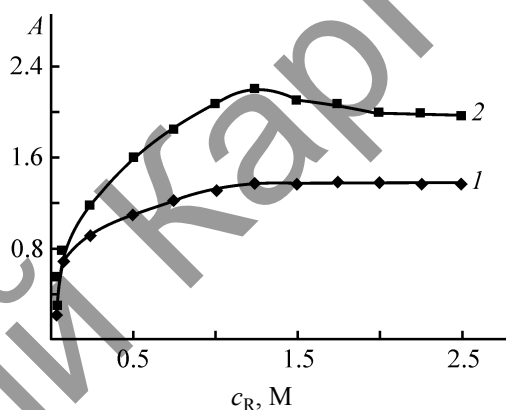


Fig. 5. Optical density  $A$  of the  $2 \leftrightarrow 5$  and  $4 \leftrightarrow 6$  systems at wavelengths of the absorption peaks of the complexes vs. the concentration  $c_R$  of reagents (1) **2** and (2) **4**.

In the second series of experiments, maintaining constant the concentration of component M,  $c_M$ , and varying the concentration of reagent R, we obtained under similar conditions a graphical dependence of the optical density  $A_2$  on the concentration R:  $A_2 = k_2c_R/n$ , whence the slope ratio  $\tan \alpha_2 = k_2/n$  of the straight line was determined.

Applying the basic law of light absorption to expressions for the optical density  $A_1$  and  $A_2$ , we obtain the equations  $A_1 = k_1c_M/m = \tan \alpha_1c_M = c_M\varepsilon \times 1/m$  and  $A_2 = k_2c_R/n = \tan \alpha_2c_R = c_R\varepsilon \times 1/n$ . Hence  $\tan \alpha_1 = \varepsilon \times 1/m$ ,  $\tan \alpha_2 = \varepsilon \times 1/n$ .

Dividing one equality by the other, we obtain the ratio of slope ratios, equal to the ratio of the stoichiometric coefficients in the formula of the complex,  $M_mR_n$ , in accordance with the expression

$$\tan \alpha_1 / \tan \alpha_2 = n/m. \quad (1)$$

Using the data obtained in the spectrophotometric study (Tables 2 and 3), we calculated by the least-squares

**Table 2.** Concentrations of reagent **2** and optical densities of the **2** ⇌ **5** system

$c_M,^a \text{ M}$	$A_1$	$c_R,^b \text{ M}$	$A_2$
$2.2 \times 10^{-6}$	0.103	$0.43 \times 10^{-5}$	0.091
$4.3 \times 10^{-6}$	0.215	$0.86 \times 10^{-5}$	0.196
$6.5 \times 10^{-6}$	0.316	$1.30 \times 10^{-5}$	0.296
$8.6 \times 10^{-6}$	0.407	$1.71 \times 10^{-5}$	0.388

<sup>a</sup> At  $c_R = \text{const.}$ <sup>b</sup> At  $c_M = \text{const.}$ **Table 3.** Concentrations of reagent **4** and optical densities of the **4** ⇌ **6** system

$c_M,^a \text{ M}$	$A_1$	$c_{R1},^b \text{ M}$	$A_2$
$2.2 \times 10^{-6}$	0.110	$0.43 \times 10^{-5}$	0.101
$4.3 \times 10^{-6}$	0.220	$0.86 \times 10^{-5}$	0.208
$6.5 \times 10^{-6}$	0.358	$1.30 \times 10^{-5}$	0.300
$8.6 \times 10^{-6}$	0.424	$1.71 \times 10^{-5}$	0.396

<sup>a</sup> At  $c_{R1} = \text{const.}$ <sup>b</sup> At  $c_M = \text{const.}$ 

method the slope ratios characterizing the dependences of  $A_1$  on  $c_M$  and  $A_2$  on  $c_R$  in accordance with the formulas

$$\tan \alpha = \frac{n \sum c_i A_i - c_i \sum A_i}{n \sum c_i^2 - (\sum c_i)^2}, \quad (2)$$

$$\tan \alpha_1 = \frac{4 \cdot 0.67 \times 10^{-5} - 2.16 \times 10^{-5} \times 1.04}{4 \times 1.39 \times 10^{-10} - 4.66 \times 10^{-10}} = 4.78 \times 10^4, \quad (3)$$

$$\tan \alpha_2 = \frac{4 \times 1.257 \times 10^{-5} - 4.30 \times 10^{-5} \times 0.971}{4 \times 1.39 \times 10^{-10} - 4.66 \times 10^{-10}} = 2.34 \times 10^4, \quad (4)$$

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