

Determination of composition and instability constants of maltol complexes with iron(III) ions

I. A. Antipova, S. A. Mukha, and S. A. Medvedeva*

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences,
1 ul. Favorskogo, 664033 Irkutsk, Russian Federation.
Fax: +7 (395 2) 41 9346. E-mail: msa@irioch.irk.ru

Complexation of maltol (MH) with Fe^{3+} ions in aqueous solutions was studied. The compositions of $[\text{FeMa}]^{2+}$, $[\text{FeMa}_2]^+$, and $[\text{FeMa}_3]$ complexes were determined by the method of isomolar series, and their instability constants were calculated. The values of the latter were confirmed by the method of apparent deviation from the Bouguer–Lambert–Beer law. An increase in the Ma : Fe^{3+} ratio from 1 to 3 decreases the instability constants of the complexes. The $[\text{FeMa}_3]$ complex can be considered as a basis for the antianemic drug with a prolonged effect.

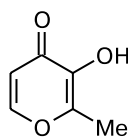
Key words: maltol, iron(III), complexation, instability constants.

Maltol (3-hydroxy-2-methyl-4-pyrone, MaH) is a natural substance found in several plants (leaves of *Passiflora*,¹ Japanese *Cercis*,² *Aralia*,³ and others). Maltol is isolated, as a rule, from needles of Siberian fir (*Abies sibirica* L.), where its content reaches 1–2%.⁴

Since the maltol structure contains the hydroxyl and keto groups in the *ortho*-position, this γ -pyrone is an efficient bidentate chelating ligand and can easily be coordinated with bi- and trivalent metal ions to form bis- and trischelate complexes.^{5–11} These maltol compounds can be considered as ionophores capable of supplying an organism with necessary microelements. Unlike similar chelating keto-alcohols, maltol has great advantages from the biological point of view, because it is a low-toxicity substance (index $\text{LD}_{50} = 1400 \text{ mg kg}^{-1}$),⁸ manifests antioxidant properties¹² (due to which it is used in food and fragrance industries), and possesses fungistatic and antibacterial activity.¹³

The neutral water-soluble tris(3-hydroxy-2-methyl-4-pyronato)iron(III) complex is of interest as a potential medicine for treatment of iron-deficient anemia.^{10,11} A study of complexation and stability of this complex is expected to provide insight into its behavior in the human organism.

The purpose of this work is to study the complexation of maltol with iron(III) chloride, including the determination of



MaH

the compositions and instability constants of the complexes formed at different pH of a medium.

The reaction was studied by the spectrophotometric method using the absorbance of the resulting complexes at 340–600 nm. Maltol does not absorb in this region of wavelengths, and the absorbance of iron(III) chloride is insignificant. This makes it possible to determine directly the absorbance and, correspondingly, the concentration of the colored maltol complexes.

Experimental

Maltol was isolated from needles of Siberian fir (*Abies sibirica* L.) using a procedure proposed by us previously.¹⁴ The following reagents were used: $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, HClO_4 (reagent grade), 25% NH_4OH (analytical grade), glacial AcOH (reagent grade), and bidistilled water.

Electronic spectra were recorded on an SF-26 spectrophotometer. The absorbance of solutions was measured in quartz cells with layer thicknesses of 1 cm and 0.1 cm (in the dilution method) using a buffer with the same pH value as a reference solution. To determine the plots of the absorbance of maltol vs. pH of the medium and $\text{p}K_a$, aqueous solutions of the substance with a concentration of $6.87 \cdot 10^{-5} \text{ mol L}^{-1}$ were used. The pH values of solutions were measured with an EV-74 universal pH-meter.

To control the pH of the medium, 0.2 M solutions of ammonia and perchloric acid were used, because the ClO_4^- anion is much less prone to form complexes with iron compared to anions of other acids. The iron salt ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) is readily hydrolyzed at $\text{pH} > 6$ to form a precipitate of iron hydroxide. Therefore, an acetate–ammonia buffer was used in some experiments, because the acetate anion of this buffer forms an easily dissociating complex with Fe^{III} , whose weak absorption can be neglected compared to that of the iron(III) complexes with maltol.

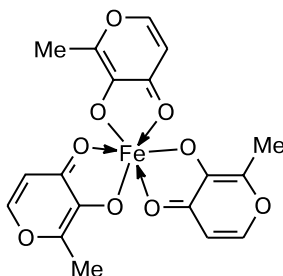


Table 1. Degrees of dissociation and instability constants of the iron(III) maltolate complexes determined by the method of isomolar series

Complex	pH	α	$K_{\text{instab}}/\text{mol L}^{-1}$
[FeMa] ²⁺	1	0.35	$1.48 \cdot 10^{-4}$
[FeMa ₂] ⁺	3	0.16	$2.44 \cdot 10^{-5}$
[FeMa ₃]	6	0.10	$8.70 \cdot 10^{-6}$

The compositions of the complexes were determined by the method of isomolar series.^{15–17} Three isomolar series with pH 1, 3, and 5.5 were prepared. For this purpose, the starting aqueous solutions of FeCl₃·6H₂O and maltol with equal concentrations ($7.9 \cdot 10^{-4}$ mol L⁻¹) were mixed in different ratios, so that the sum of moles of the substances in solutions of the series remained unchanged. The absorbances of solutions were detected at $\lambda = 500, 460,$ and 412 nm, respectively. The compositions of the complexes formed and their instability constants were determined by the extrapolation of the initial regions of each "ratio of components—absorbance" diagram to the intersection point.

The accuracy of measurements (Tables 1 and 2) was expressed by standard deviations (s).¹⁸

Results and Discussion

Maltol, whose single-charged anion is a ligand in the complexes with Fe^{III}, is a weak acid, and its p*K*_a in water is 8.68.¹⁰ The concentration of the ionized form of a weak acid is known to increase considerably with an increase in the pH of solution. Therefore, the dependence of the absorbance of maltol itself in the 220–360 nm region on the pH of medium was studied first.

In an interval of pH = 1–6, the UV spectra (Fig. 1) exhibit one absorption maximum with $\lambda_{\text{max}} = 275$ nm ($\log \epsilon = 4.242$), which is characteristic of the non-dissociated maltol molecule. With an increase in the pH from 7 to 9, the intensity of this absorption maximum decreases ($\log \epsilon = 4.159$ at pH 8) and a new maximum appears at $\lambda_{\text{max}} = 320$ nm ($\log \epsilon = 3.044$). This maximum is charac-

Table 2. Degrees of dissociation and instability constants of the iron(III) maltolate complexes determined by the method of apparent deviation from the Bouguer—Lambert—Beer law

Complex	λ/nm	D_1	D_{10}	Δ	Δ_{av}	s	α	$K_{\text{instab}}/\text{mol L}^{-1}$
[FeMa] ²⁺	400	0.37	0.27	0.27	0.30	± 0.025	0.14	$1.5 \cdot 10^{-4}$
	410	0.37	0.26	0.31				
	420	0.36	0.25	0.32				
	430	0.35	0.23	0.33				
	440	0.34	0.22	0.34				
	450	0.36	0.23	0.36				
	460	0.39	0.25	0.36				
	470	0.42	0.28	0.33				
	480	0.46	0.30	0.35				
	490	0.48	0.32	0.33				
[FeMa ₂] ⁺	400	0.46	0.40	0.13	0.11	± 0.012	0.05	$2.0 \cdot 10^{-5}$
	410	0.46	0.405	0.12				
	420	0.46	0.40	0.13				
	430	0.45	0.39	0.13				
	440	0.44	0.39	0.11				
	450	0.45	0.40	0.12				
	460	0.46	0.41	0.11				
	470	0.48	0.43	0.10				
	480	0.49	0.44	0.11				
	490	0.50	0.45	0.10				
[FeMa ₃]	400	0.60	0.56	0.006	0.07	± 0.002	0.03	$8.4 \cdot 10^{-6}$
	410	0.60	0.56	0.006				
	420	0.60	0.56	0.006				
	430	0.58	0.54	0.069				
	440	0.57	0.53	0.070				
	450	0.57	0.53	0.071				
	460	0.56	0.52	0.072				
	470	0.55	0.51	0.075				
	480	0.53	0.50					
	490	0.50	0.46					
500	0.45	0.42						

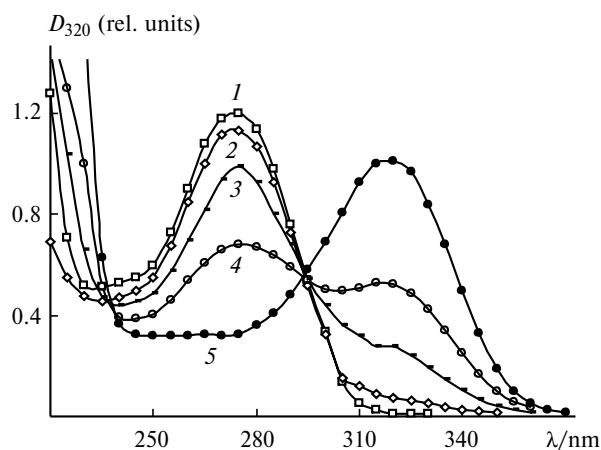


Fig. 1. Electronic spectra of aqueous solutions of maltol ($6.87 \cdot 10^{-5} \text{ mol L}^{-1}$) at pH 1–5 (1), 7 (2), 8 (3), 9 (4), and 10 (5) in the medium.

teristic of the Ma^- anion, and its intensity increases with an increase in the pH ($\log \epsilon = 4.167$ for pH 8). For pH 10–10.5, the maximum at $\lambda = 275 \text{ nm}$ disappears, and the single maximum at $\lambda = 320 \text{ nm}$ is observed in the spectrum.

The plot of the absorption intensity of maltol at $\lambda = 320 \text{ nm}$ vs. pH of the medium (Fig. 2) allows one to find the pH value corresponding to the 50% dissociation of the substance, when $K_{\text{HR}} = [\text{H}^+]$.¹⁶ This point corresponds to the half-sum of the absorbances of the acid and salt forms of the substance for the equal concentrations

$$D_{\text{m}} = 0.5(D_{\text{HR}} + D_{\text{R}^-}).$$

For maltol $D_{\text{m}} = 0.5(0.05 + 1.05) = 0.55$. The abscissa of this point corresponding to pH 8.6 shows a correlation with the $\text{p}K_{\text{a}}$ value, because in this point $\text{pH} = \text{p}K_{\text{a}}$.

To study the reaction of maltol with iron(III) chloride, we recorded electronic spectra of solutions of the complexes formed at a constant concentration of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$

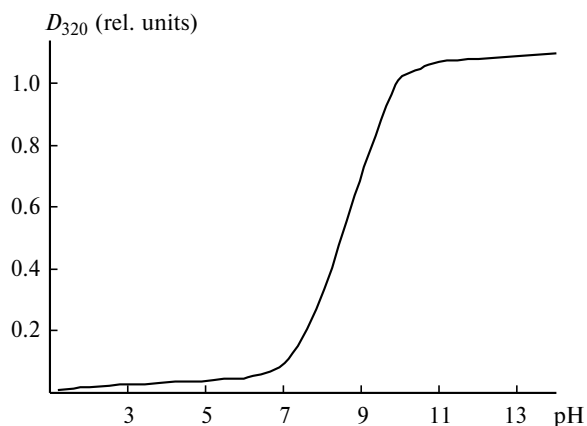


Fig. 2. Absorbance of an aqueous solution of maltol ($6.87 \cdot 10^{-5} \text{ mol L}^{-1}$) vs. pH of the medium at $\lambda = 320 \text{ nm}$.

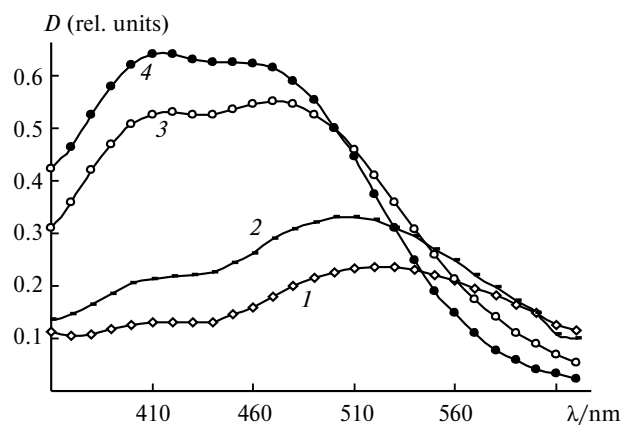


Fig. 3. Electronic spectra of a mixture of aqueous solutions of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and maltol (molar ratio 1 : 5) at pH 1 (1), 2 (2), 3 (3), and 5–9 (4) of the medium.

($3.95 \cdot 10^{-4} \text{ mol L}^{-1}$) and a fivefold excess of maltol ($1.97 \cdot 10^{-3} \text{ mol L}^{-1}$) for different pH values (Fig. 3). For detection of the complexes, $\lambda = 412 \text{ nm}$ was chosen. The plot of the absorbance (D_{412}) vs. pH of the solution is presented in Fig. 4. The shape of the curve indicates the stepwise formation of three complexes with different optical properties. The observed jumps of the absorbance and comparison of the plots presented in Figs. 3 and 4 suggest the following. In a region of pH 1–2 a complex of maltol with Fe^{3+} ions (1) is formed, and its spectrum is characterized by the absorption maximum with $\lambda_{\text{max}} = 500 \text{ nm}$. Complex 2 with $\lambda_{\text{max}} = 460 \text{ nm}$ is formed in a region of pH 3–4, and complex 3 with $\lambda_{\text{max}} = 412 \text{ nm}$ is formed at pH 5–6. The formation of various complexes is confirmed by the color of solutions changing from violet (1) to red (2) and then to yellow (3). The decrease in the absorbance at pH 8–10 indicates that hydrolysis of the starting salt $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ occurs predominantly in this medium.

The compositions of the complexes were determined by the method of isomolar series.¹⁵ Three isomolar series

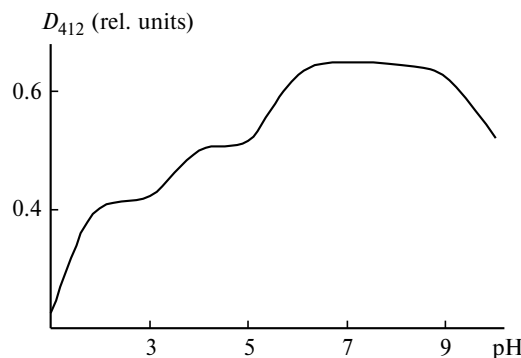


Fig. 4. Absorbance of a mixture of aqueous solutions of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and maltol (molar ratio 1 : 5) vs. pH of the medium at $\lambda = 412 \text{ nm}$.

differed by the pH value: the first series had pH 1, the second series had pH 3, and the third series was characterized by pH 5.5. These pH values were chosen, because a noticeable amount of the Fe^{3+} ions, which are not bound in the corresponding $[\text{FeMa}_n]^{(3-n)+}$ complex, remains under these conditions. This corresponds graphically (see Fig. 4) to a rise of the region of the absorbance curve attributed to this complex. The absorbance was measured at $\lambda = 500, 460,$ and 412 nm corresponding to the absorption maxima of the complexes. As can be seen from the data in Fig. 5, the maximum absorbance is observed for

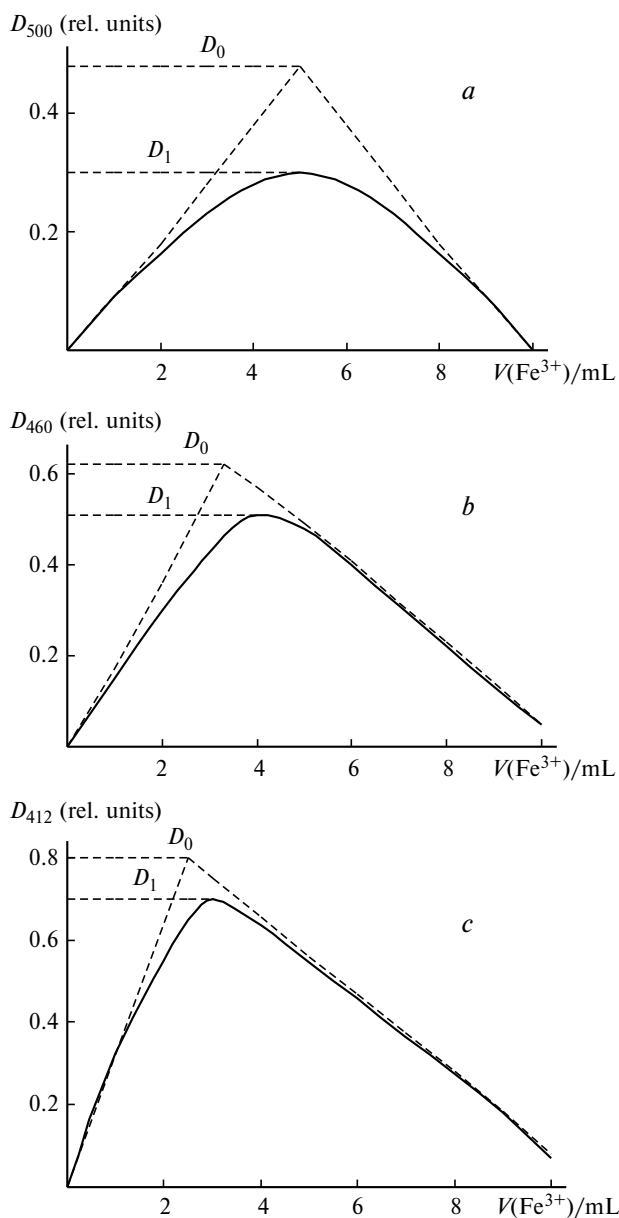
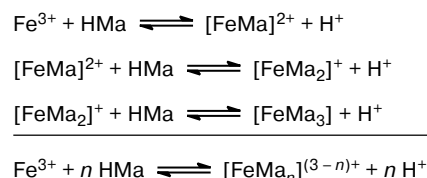


Fig. 5. Absorbances of aqueous solutions of mixtures of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and maltol (overall volume 10 mL) for the molar ratios of the components of the isomolar series at pH = 1 (a), 3 (b), and 5.5 (c).

ratios of volumes of the starting solutions of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and maltol of 5 : 5 (see Fig. 5, a), 3.3 : 6.6 (see Fig. 5, b), and 2.5 : 7.5 (see Fig. 5, c). This corresponds to the following compositions of the Fe^{3+} —Ma complexes: 1 : 1 (1), 1 : 2 (2), and 1 : 3 (3). The complexes can be presented by the common formula $[\text{FeMa}_n]^{(3-n)+}$. The stepwise formation of the complexes occurs *via* Scheme 1.

Scheme 1



HMa is the maltol molecule, and Ma is the single-charged maltol anion

The instability constants of the $[\text{FeMa}_n]^{(3-n)+}$ complexes were determined by the equation⁸

$$K_{\text{instab}} = \alpha^2 C / (1 - \alpha),$$

where C is the concentration of the solution/ mol L^{-1} , α is the degree of dissociation of the complex determined by the formula

$$\alpha = D_0 - D_1 / D_0,$$

where D_0 is the absorbance corresponding to the complex when dissociation is completely absent and D_1 is the absorbance corresponding to the maximum in the curve for an isomolar series.

The instability constants of the $[\text{FeMa}_n]^{(3-n)+}$ complexes are presented in Table 1.

Since the method of isomolar series gives reliable results only when one and the simplest complex (1 : 1) is formed, the method of apparent deviation from the Bouguer—Lambert—Beer law was additionally used to confirm the K_{instab} values obtained.^{15–17}

Three mixtures of solutions of the reacting components were prepared. Solutions had an equal starting concentration of $7.9 \cdot 10^{-3} \text{ mol L}^{-1}$ with Fe^{3+} : Ma ratios of 1 : 1 (pH = 1), 1 : 2 (pH = 3), and 1 : 3 (pH = 6), which corresponded to the $[\text{FeMa}]^{2+}$, $[\text{FeMa}_2]^+$, and $[\text{FeMa}_3]$ complexes. The spectra of the resulting solutions were recorded in a region of 400–600 nm to obtain the D_1 value in a cell with a layer thickness of 0.1 cm. The solutions were tenfold diluted ($n = 10$), and the absorbance (D_{10}) was determined in a cell with a layer thickness of 1 cm. The relative change in absorbance (Δ) was calculated for each chosen wavelength by the formula

$$\Delta = D_1 - D_{10} / D_1.$$

The degrees of dissociation of the complexes were found by the formula¹⁵

$$\alpha = \Delta_{av}/10^{0.5} - 1,$$

where α is the degree of dissociation of the non-diluted complex and 10 is the number of dilution times of the starting solution. We calculated the instability constants of the complex using the dilution law based on α and the initial concentration of the complex (C):

$$K_{instab} = \alpha^2 C.$$

The K_{instab} values obtained by the methods of apparent deviation (see Table 2) and isomolar series (see Table 1) agree well.

Thus, the stability of the complexes increases in the series $[\text{FeMa}]^{2+}$, $[\text{FeMa}_2]^+$, and $[\text{FeMa}_3]$. The tris-maltolate complex formed in an interval of pH 5.5–8 is most stable and can be considered as a basis for an anti-anemic medicine with a prolonged effect.

References

1. A. Nobuo, K. Ryochi, and M. Toshiro, *Chem. Farm. Bull.*, 1974, **22**, 1008.
2. K. Takaishi, *Phytochemistry*, 1971, **10**, 3302.
3. Y. Masaiti, K. Norihisa, and I. Kaichiro, *Yakugaku Zasshi*, 1968, **88**, 390.
4. S. A. Mukha, I. A. Antipova, and S. A. Medvedeva, *Tez. dokl. V Vseros. nauch.-prakt. konf. "Bezopasnost'-2000" [Proc. V All-Russia Scientific Practical Conf. "Safety-2000"] (Irkutsk, 2000)*, Irkutsk, 2000, 245 (in Russian).
5. H. Morita, S. Shimomura, and S. Kawaguchi, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 3213.
6. C. Gerard, *Bull. Soc. Chim. Fr.*, 1979, **1**, 451.
7. M. Finnegan, T. G. Lutz, W. O. Nelson, A. Smith, and C. Orvig, *Inorg. Chem.*, 1987, **26**, 2171.
8. S. A. Mukha, I. A. Antipova, and S. A. Medvedeva, *Tez. dokl. Mezhdunar. nauch.-prakt. konf. "Chelovek. Sreda. Vseleennaya" [Proc. Intern. Scientific Practical Conf. "Human Being. Environment. Universe"] (Irkutsk, 2001)*, Irkutsk, 2001, 115 (in Russian).
9. M. T. Achmet, C. S. Frampton, and J. Silver, *J. Chem. Soc., Dalton Trans.*, 1988, 1159.
10. A. Stefanovic, J. Havel, and L. Sommer, *Coll. Czech. Chem. Commun.*, 1968, **33**, 4198.
11. S. A. Mukha, *Tez. dokl. XIII Zimnei mezhdunar. molodezhn. nauch. shkoly "Perspektivnye napravleniya fiziko-khimicheskoi biologii i biotekhnologii" [Proc. XIII Winter Intern. Youth Scientific School "Promising Directions of Physicochemical Biology and Biotechnology"] (Moscow, 2001)*, Moscow, 2001, 81 (in Russian).
12. I. V. Babenkova, Yu. O. Teselkin, S. A. Medvedeva, N. A. Tyukavkina, Yu. A. Kolesnik, L. B. Rebrov, V. A. Bykov, S. A. Mukha, and I. A. Antipova, *Voprosy biologicheskoi meditsinskoi i farmatsevticheskoi khimii [Problems of Biological Medical and Pharmaceutical Chemistry]*, 2001, **4**, 22 (in Russian).
13. S. A. Medvedeva, Ph. D. (Chem.) Thesis, Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, Irkutsk, 1973, 138 pp. (in Russian).
14. RF Pat. 2171805, 2001; *RZhKhim. [Abstract J. Chem.]*, 2002, 02.02—190.203P (in Russian).
15. A. K. Babko, *Fiziko-khimicheskii analiz kompleksnykh soedinenii v rastvorakh [Physicochemical Analysis of Complexes in Solutions]*, Izd. Akad. Nauk UkrSSR, Kiev, 1955, 104 (in Russian).
16. M. I. Bulatov and I. P. Kalinkin, *Prakticheskoe rukovodstvo po fotometricheskim metodam analiza [Practical Guide on Photometric Methods of Analysis]*, Khimiya, Leningrad, 1986, 280 (in Russian).
17. V. A. Chernyshev and M. E. Shishniashvili, in *Khelaty metallov prirodnykh soedinenii i ikh primenenie [Metal Chelates of Natural Compounds and Their Application]*, Metsniereba, Tbilisi, 1974, 34 (in Russian).
18. A. J. Gordon and R. A. Ford, *The Chemist's Companion, a Handbook of Practical Data, Techniques and Referens*, J. Wiley and Sons, New York—London, 1972.

Received June 3, 2003;
in revised form November 24, 2003