

Synthesis and Properties of Metal Chelates Based on Natural γ -Pyrone Maltol

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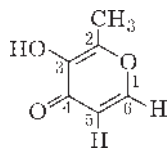
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Abstract

Chelate compounds of maltol, extracted from the needles of Siberian abies, with the ions of such metals as copper (II), cobalt (II), nickel (II), zinc (II), iron (III), aluminium (III), chromium (III) were synthesized. The features of complexation were revealed and the corresponding conditions were optimised. The composition and structure of metal complexes were confirmed with the help of physicochemical and spectral methods (UV, IR, NMR), structural characteristics were obtained with the help of EPR. Stability constants were determined; the complexes were arranged into the stability row under the conditions of physiological pH of the medium. The biological activity of ferric and copper maltolates as potential preparations to cure blood diseases was demonstrated.

INTRODUCTION

3-Hydroxy-2-methyl-4-pyrone (maltol) is a natural compound present in the needles of Siberian abies [1–3], some other plant objects [4–6] and in the products of natural origin (malt, coffee, cocoa, bread, milk, soya *etc.*) [7–9]:



Being a low-toxic compound (LD_{50} 1400 mg/kg) [10] with pleasant odour and antioxidant properties [11–13], maltol finds application in food industry [14–16] (as the additive E 636 allowed in all the countries for taste and odour potentizing) and in cosmetic industry [17].

During the recent years, a number of publications appeared abroad describing the synthesis and investigation of the metal complex

compounds of 3-hydroxy-2-methyl-4-pyrone [18–24]. The development of these investigations is connected with the biological activity of complexes. In particular, the metal transport ligand of maltol is of interest as a potential ionophore that provides the introduction of necessary metal ions into an organism [20–22] and as a detoxifying agent [23, 24].

However, these investigations are rather unsystematic in character. In addition, though physicochemical and spectral characteristics are very important for biologically active substances, not all the synthesized compounds were correspondingly characterized.

While studying the physicochemical properties of maltol [25] and the reactivity of its active centres (hydroxyl and carbonyl groups [26, 27]), we obtained a series of its metal complex compounds possessing unique properties [27, 28]. In the present paper we describe optimisation of the synthesis conditions for a num-

ber of maltol complexes with the ions of metals that are necessary microelements, and report the new data on their spectral, physico-chemical properties and biological activity.

EXPERIMENTAL

Maltol was extracted from the needles of Siberian abies and purified according to the procedure developed previously [3]. The reagents of ch. d. a. grade (pure for analysis) were used. Chlorides and nitrates were used as metal salts.

IR spectra were recorded with Specord 75 IR spectrophotometer within the range 4000–800 cm^{-1} and with Specord M-82 within the range 800–200 cm^{-1} using in the former case the samples prepared as tablets with KBr and in the latter case the powder of complexes suspended in vaselin oil.

Electron spectra were recorded within the range 230–370 nm, for coloured complexes within the range 230–800 nm in methanol using SF-26 spectrophotometer.

The ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on Bruker DPX-400 and AV-400 instruments with internal stabilization on deuterium (frequency for ^1H and ^{13}C was 400.13 and 100.61 MHz, respectively). Chemical shifts in the (δ) scale for ^1H and ^{13}C are given with respect to TMS. The ^{13}C NMR spectra were recorded under the conditions of full uncoupling from protons and also without uncoupling from protons. To assign the ^{13}C NMR signals, were used the procedure of heteronuclear two-dimensional NMR spectroscopy (HMBC – Heteronuclear Multiple Bond Correlation) taking into account the long-range constants. The parameters of the pulse sequence were optimised with the $^3J_{\text{CH}}$ value equal to 10.0 Hz.

The EPR spectra were recorded with SE/X-2542 spectrometer (working frequency: 9.6 GHz) equipped with a magnetometer, at room temperature. The reference was free radical DPPH ($g = 2.0037 \pm 0.0002$).

The acidity (pH) of solutions was measured with the multi-purpose ion meter EV-74.

Total and step stability constants were determined using the procedure developed previously [29, 30]. It is based on isomolar series method. The determined values of constants

were confirmed with the help of apparent deviation from Buger–Lambert–Ber law.

Biological tests

Investigation of the effect of copper maltolate on blood coagulation was carried out with white rats of Wistar line with the initial body mass of 160–170 g. Copper maltolate was introduced intragastrically in the doses of 5, 15 and 25 mg/kg of body mass. To evaluate the state of blood coagulation system, the standardized Burckard autocoagulation test (ACT) modified by L. Z. Barkagan was used [31]. The results of ACT appearing on the autocoagulogram were determined after 30 and 60 min with respect to the following parameters: A is coagulating activity of the hemolysate-calcium mixture (HCM) at the 2nd minute, %; MA is maximal coagulating activity of HCM, %; T_1 , T_2 are time of achievement of $\frac{1}{2}\text{MA}$ and MA, respectively, min; Φ is time of the decrease of thromboplastin and thrombin activity to $\frac{1}{2}\text{MA}$, min; ITI (index of thromboplastin and thrombin inactivation) was calculated using equation $\text{ITI} = \text{MA}/A_{60}$ where A_{60} is coagulating activity at the 60th minute of activation.

Investigation of the effect of ferric maltolate on the indices of red blood was performed with 40 white male rates of Wistar line with the initial body mass of 160–170 g. Lead anemia was induced by intraperitoneal introduction of the 0.5 % solution of lead acetate in the daily dose of 2 mg/kg of body mass, during 3 days. This resulted in the development of anemia at the 5th day (peak of anemia) counting from the start of the experiment [32]. The animals were divided into five groups: intact (the corresponding volume of distilled water was introduced), reference (the solution of lead acetate was introduced in the similar manner), and three experimental groups receiving lead acetate in the doses equal to 5, 15 and 25 mg/kg of body mass starting from the 2nd day of experiment, according to the scheme indicated above. The degree of anemia was estimated after 5 days counting from the start of experiment on the basis of the number of erythrocytes and hemoglobin content measured with the automatic hematological analyser (Abanus Concepts, Inc).

Synthesis of metal complex compounds

Tris-(3-hydroxy-2-methyl-4-pyronato)iron (III). The solution of 2.71 g (0.01 mol) of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in 50 mL of water was added to the solution of 3.78 g (0.03 mol) of maltol in 150 ml of water.

To the resulting dark-red solution (pH 1.8), we added 15 ml of the 2 M NaOH solution (0.03 mol) (pH 7.2). The reaction mixture was stirred for 10 min, and then evaporated in a rotary evaporator. The dry residue was extracted with chloroform to remove the inorganic part, which is insoluble in chloroform. The chloroform extract was evaporated to the dry state. The resulting complex was purified by re-precipitation from methanol to diethyl ether. The precipitated small purple crystals were separated by filtering and dried under reduced pressure. The yield of the pure product was 87.0 %, $T_{\text{melt}} = 320$ °C. Found, %: C 50.01, H 3.92, Fe 12.29. $[\text{Fe}(\text{C}_6\text{H}_5\text{O}_3)_3]$. Calculated, %: C 50.14, H 3.50, Fe 12.95.

Tris-(3-hydroxy-2-methyl-4-pyronato)-aluminium (III). The complexes of maltol with aluminium (III) were obtained according to the above-described procedure but the reaction mixture was heated under permanent mixing for 45–60 min. Small cream-coloured crystals were obtained. The yield of the pure product was 84.7 %, $T_{\text{m}} = 240$ °C. Found, %: C 53.75, H 4.10, Al 6.78. $[\text{Al}(\text{C}_6\text{H}_5\text{O}_3)_3]$. Calculated, %: C 53.73, H 3.73, Al 6.70.

Tris-(3-hydroxy-2-methyl-4-pyronato)-chromium (III). Complexes of maltol with chromium were synthesized according to the above-described procedure but the reaction mixture was boiled in a flask with a backflow condenser for 6 h. Small brown-green crystals were obtained. The yield of the pure product was 55.0 %, $T_{\text{melt}} = 290$ °C. Found, %: C 50.87, H 4.20, Cr 13.20. $[\text{Cr}(\text{C}_6\text{H}_5\text{O}_3)_3]$. Calculated, %: C 50.59, H 3.51, Cr 12.18.

Bis-(3-hydroxy-2-methyl-4-pyronato)-copper (II). The solution of 2.5 g (0.01 mol) of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in 50 mL of water was added to the solution of 3.15 g (0.025 mol) of maltol in 150 mL of water. After adding a 2 M NaOH solution dropwise under permanent mixing to reach pH 7.5, green flaky precipitate started to form. The mixture was stirred for 10–15 min. The formed precipitate was separated by fil-

tering, washed several times with cold water, alcohol and dried under reduced pressure. Green flaky crystals were obtained. The yield of the pure product was 77.6 %, $T_{\text{melt}} = 210$ °C. Found, %: C 46.18, H 3.00, Cu 20.06. $[\text{Cu}(\text{C}_6\text{H}_5\text{O}_3)_2]$. Calculated, %: C 45.93, H 3.19, Cu 20.25.

Complexes of cobalt (II), nickel (II), zinc (III) were synthesized according to the similar procedure.

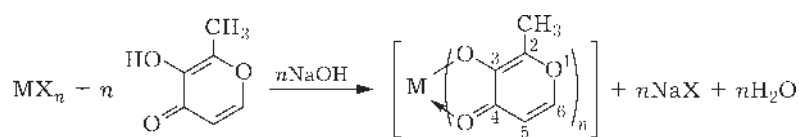
Dihydrate of bis-(3-hydroxy-2-methyl-4-pyronato)-cobalt (II). The acidity of the reaction medium was brought to pH 8.75. The time of precipitate formation was 20–30 min. Yellow flaky crystals were obtained. The yield of the pure product was 77.0 %, $T_{\text{melt}} = 260$ °C. Found, %: C 41.88, H 3.90, Co 16.92. $[\text{Co}(\text{C}_6\text{H}_5\text{O}_3)_2] \cdot 2\text{H}_2\text{O}$. Calculated, %: C 41.75, H 4.06, Co 17.07.

Dihydrate of bis-(3-hydroxy-2-methyl-4-pyronato)nickel (II). The acidity of the reaction medium was brought to pH 8.4. The time of precipitate formation was 12–15 h. Light-green flaky crystals were obtained. The yield of the pure product was 85.0 %, $T_{\text{melt}} = 210$ °C. Found, %: C 41.62, H 4.30, Ni 17.33. $[\text{Ni}(\text{C}_6\text{H}_5\text{O}_3)_2] \cdot 2\text{H}_2\text{O}$. Calculated, %: C 41.74, H 4.06, Ni 17.10.

Dihydrate of bis-(3-hydroxy-2-methyl-4-pyronato)-zinc (II). The acidity of the reaction medium was brought to pH 8.6. The time of precipitate formation was 15–18 h. Small white crystals were obtained. The yield of the pure product was 73.4 %, $T_{\text{melt}} = 230$ °C. Found, %: C 40.61, H 3.78, Zn 18.41. $[\text{Zn}(\text{C}_6\text{H}_5\text{O}_3)_2] \cdot 2\text{H}_2\text{O}$. Calculated, %: C 40.98, H 3.98, Zn 18.60.

RESULTS AND DISCUSSION

The interaction of maltol (HL) with a metal ion is due to the presence of two functional groupings (C=O group in position 4 and OH group in position 3) able to get coordinated with a metal ion in the γ -pyrone ring of maltol. It is evident that the coordination should be promoted by deprotonation at the O–H bond with the formation of the singly charged maltolate anion $\text{C}_6\text{H}_5\text{O}_3^-$ (L). Because of this, the reaction was conducted in the presence of alkali (2 M NaOH), which also promotes the shift of reaction to the formation of the target



Scheme 1.

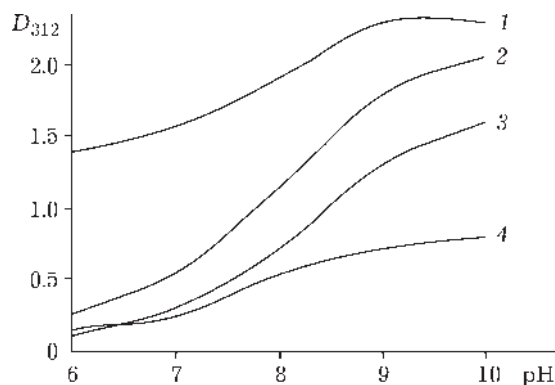


Fig. 1. Dependence of the changes of optical density of the reaction mixture (metal salt and maltol taken at the molar ratio of 1 : 5) on pH: 1 - CuCl_2 ($C_M = 1.25 \cdot 10^{-4}$ M), 2 - $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ ($C_M = 1.52 \cdot 10^{-4}$ M), 3 - $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ ($C_M = 1.00 \cdot 10^{-3}$ M), 4 - ZnCl_2 ($C_M = 1.00 \cdot 10^{-4}$ M).

product due to neutralization of the released acid (for maltol in water, $\text{p}K_a = 8.6$) (Scheme 1).

The synthesis was carried out according to the procedures described in literature [33–35]. It was established in the investigations that, in spite of the common principle of obtaining, the synthesis of the complexes of each metal has its own specific features. To avoid the formation of the hydroxide of a metal to be coordinated (in the case of formation of low-soluble complexes precipitating from the reaction medium), alkali was added gradually drop by

drop, and the reaction was conducted under a small excess of the ligand. The yield of some complexes is to a higher extent affected by pH of the medium, while the yield of others is to a higher extent affected by temperature mode or reaction time.

One can see in Fig. 1 that, unlike for copper (II), complex formation with the ions of cobalt (II), nickel (II) and zinc (II) proceeds in more alkaline medium (pH 8.3–8.9). Though the yield continues increasing with the further pH rise, this increase is insignificant while the risk of hydroxide formation increases. Because of this, the indicated pH range was chosen as the optimal one.

Rather high yield of the complexes of aluminium (III) and chromium (III) can be achieved only by heating the reaction mixture to a definite temperature (Fig. 2). Temperature equal to 70 °C was chosen as optimal for aluminium and 100 °C for chromium (solvent boiling temperature).

The duration of reaction is important for the complexes of nickel and zinc (Fig. 3). Unlike for the complexes of copper and cobalt that form precipitates within 10–20 min, 12–18 h is required for the complexes of nickel and zinc.

As a result, we succeeded in optimising pH of the medium, temperature and duration of reaction for each synthesis, which allowed us

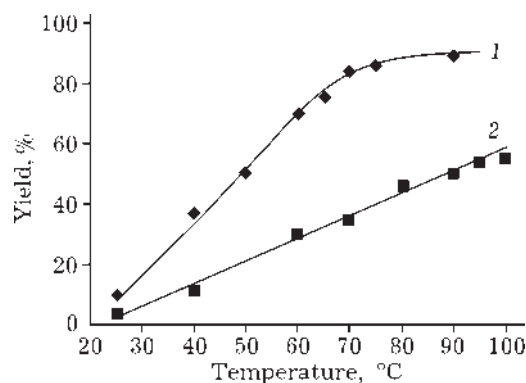


Fig. 2. Dependence of the yield of maltol complexes on the temperature of reaction medium: 1, 2 - with aluminium (III) and chromium (III) ions, respectively.

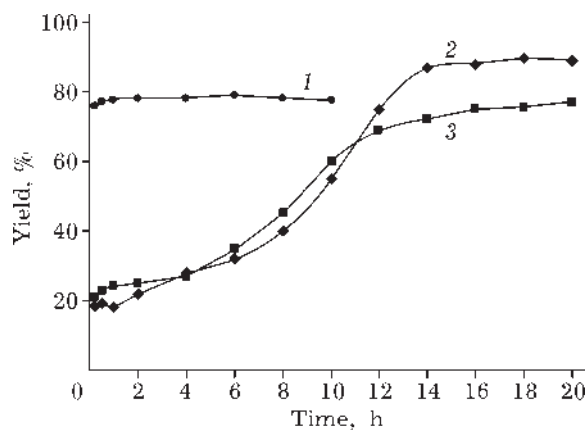


Fig. 3. Dependence of the yield of maltol complexes on reaction time: 1–3 - with copper (II), nickel (II) and zinc (II) ions, respectively.

TABLE 1

Absorption maxima (λ_{max}) in the electron spectra of maltol and its metal complexes, nm

HL	FeL ₃	AlL ₃	CrL ₃	CuL ₂	CoL ₂ · 2H ₂ O	NiL ₂ · 2H ₂ O	ZnL ₂ · 2H ₂ O
215	225	220	220	235	217	225	225
275	305	305	335	315	303	330	315
	412		430	690	490	700	
			590				

to isolate the target reaction products in the crystal state with a good yield (55–87 %) and high degree of purity. On the basis of the obtained physicochemical and spectral characteristics of the target products, their structure and arrangement were established. Some constant and spectral characteristics were obtained for the first time.

According to the data of elemental analysis, the stoichiometric ratio of metal to ligand for the complexes of iron (III), aluminium (III) and chromium (III) is 1 : 3, while for the complexes of copper (II), cobalt (II), nickel (II) and zinc it is equal to 1 : 2.

The bathochromic shift of the $\pi \rightarrow \pi^*$ transition band in the electron spectra of all the synthesized compounds (305–335 nm) in comparison with the spectrum of maltol (275 nm) and the appearance of the long-wavelength absorption band of $d \rightarrow d^*$ transition in coloured compounds (Table 1) provide evidence of the formation of metal derivatives of maltol.

The fact that maltol coordinates a metal ion through the oxygen atom of carbonyl group is confirmed by a decrease in the frequency of its stretching vibrations $\nu(\text{C}=\text{O})$ in the IR spectra of complexes in comparison with the spectrum of the free ligand by 40–50 cm^{-1} (Ta-

TABLE 2

Characteristic frequencies (ν) in the IR spectra of maltol and its metal complexes, cm^{-1}

Compound	Assignment				
	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{C})$	$\nu(\text{M}-\text{O})$	$\nu(\text{O}-\text{H})$	$\nu(\text{H}_2\text{O})$
HL	1660	1625		3240	
		1565			
FeL ₃	1600	1576	469		
		1500	277		
AlL ₃	1620	1580	465		
		1508	445		
			410		
CrL ₃	1602	1568	480		
		1500	275		
CuL ₂	1610	1570	391		
		1502	232		
CoL ₂ · 2H ₂ O	1600	1574	465		3463
		1500	270		
NiL ₂ · 2H ₂ O	1594	1570	468		3471
		1500	278		
ZnL ₂ · 2H ₂ O	1600	1562	456		3400
		1500	244		

TABLE 3
Data on chemical shifts (δ , ppm) in ^1H and ^{13}C NMR spectra and on the constants of spin-spin interaction (J , Hz) for maltol and its metal complexes

Compound	^1H NMR		^{13}C NMR							
	H(5)	H(6)	CH_3	OH	C(2)	C(3)	C(4)	C(5)	C(6)	CH_3
HL	6.4	7.70	2.36	7.31	149.51	143.44	173.25	113.35	154.22	14.37
	$^3J_{5,6} = 5.2$	$^3J_{5,6} = 5.2$			$^2J_{\text{CH}} = 7.4$	$^2J_{\text{CH}} = 2.8$	$^2J_{\text{CH}} = 7.4$	$J_{\text{CH}} = 167.9$	$^1J_{\text{CH}} = 199.7$	$^1J_{\text{CH}} = 129.6$
AL ₃	6.60	7.81	2.39		152.25	151.31	177.41	109.29	153.82	14.98
	$^3J_{5,6} = 4.9$	$^3J_{5,6} = 4.9$						$^1J_{\text{CH}} = 168.5$	$^1J_{\text{CH}} = 197.7$	$^1J_{\text{CH}} = 129.1$
ZnL ₂ ·2H ₂ O	6.50	7.68	2.43		153.57	150.10	177.98	110.98	152.67	15.38
	$^3J_{5,6} = 5.2$	$^3J_{5,6} = 5.2$					$^2J_{\text{CH}} = 7.2$	$^1J_{\text{CH}} = 168.4$	$^1J_{\text{CH}} = 197.1$	$^1J_{\text{CH}} = 129.4$
							$^3J_{\text{C-H}} = 2.4$	$^2J_{\text{CH}} = 9.1$	$^2J_{\text{CH}} = 6.4$	

ble 2). In turn, the disappearance of the absorption band belonging to the hydroxyl group of the free ligand $\nu(\text{O-H})$ at 3240 cm^{-1} is the evidence of the fact that maltol binds metal ion through the oxygen atom of the deprotonated hydroxyl group. So, it may be stated that the formed complexes have the chelate structure. Redistribution of the electron density in chelates leads also to a decrease in the frequencies of stretching vibrations of the conjugated double bonds $\nu(\text{C=C})$ of γ -pyrrone. The appearance of bands in the long-wavelength part of the IR spectrum (in the regions $400\text{--}460$ and $230\text{--}270\text{ cm}^{-1}$) can serve as a confirmation of the presence of metal-oxygen bond. The presence of hydrated water molecules in the complexes of Co(II), Ni(II) Zn(II) ensures a broad absorption band within the region $3400\text{--}3470\text{ cm}^{-1}$ of their IR spectra (see Table 2). The obtained IR characteristics are in good agreement with literature data for some known complexes of maltol [33–35].

The ^1H NMR spectroscopic data (Table 3) confirm the participation of the OH group of maltol in complexation: a broad resonance signal at 7.31 ppm which is due to the proton of hydroxyl is absent from the spectra of chelates. The resonance signals of all the protons of metal derivatives are shifted to the weak field with respect to the positions of these signals in maltol (except for the H(6) proton of the complex with zinc), which is the evidence of redistribution of the electron density in the new formed molecule. Chemical shifts of H(5) and H(6) are represented by doublets (the constant of spin-spin interaction is $^3J_{\text{HH}} = 4.9\text{--}5.5\text{ Hz}$), CH_2 group is represented by the singlet.

The formation of chelate complexes also agrees with the results of ^{13}C NMR spectroscopy (see Table 2). The resonance signals of C(4), C(3) and C(2) atoms of metal complexes are shifted to the weak field. Descreening is connected with the immediate proximity of these carbon atoms to the coordination centre and with their participation in conjugation with this centre. Quite contrary, the shift of the signals from C(5) and C(6) to the strong field may be explained by a decrease in conjugation in the pseudo-aromatic system of γ -pyrrone ring. To assign the carbon signals, ^{13}C NMR spectra without uncoupling over protons and two-dimensional (2D) HMBC spectra were recorded.

It was established that the constant of spin-spin interaction $^1J_{\text{CH}}$ for C(6) atom is larger than that for C(5), which is due to the neighbourhood of C(6) with the oxygen atom.

For two paramagnetic complexes of maltol (with Fe^{3+} and Cu^{2+}), the structural characteristics were obtained for the first time with the help of EPR.

The EPR spectrum of the polycrystalline complex of maltol with Fe^{3+} consists of an intense line ($g_{\text{eff}} = 4.1$) and a weak one ($g_{\text{eff}} = 2.3$) (Fig. 4, a), which is characteristic of high-spin ($S = 3/2$) octahedral complexes of Fe(III) having strong trigonal distortion [36].

Similarly to the known compound tris-(acetylacetonato)iron (III) the EPR spectrum of which consists of two lines (with g_{eff} equal to 4.5 and 2.7), tris-(3-hydroxy-2-methyl-4-pyronato)iron (III) was characterized as a chelate complex in which the oxygen atoms of three bidentate maltol ligands form the coordination sphere shaped as a trigonally distorted octahedron. This is in good agreement with the X-ray structural data [38].

The formation of such a complex occurs due to bonding the oxygen atoms of hydroxyl and carbonyl groups with Fe^{3+} . As a result, the central iron ion encloses the five-membered O,O-chelate cycle. As the coordination number characteristic of Fe^{3+} is 6, three single-charged

maltol anions get arranged as the ligands around the coordinating ion.

The EPR spectrum of the polycrystalline complex $\text{Cu}(\text{C}_6\text{H}_5\text{O}_3)_2$ is composed of one exchange-narrowed line ($g_{\text{eff}} = 2.16$) (see Fig. 4, b).

To determine the anisotropic EPR parameters, we performed recrystallization of the complex of maltol with copper under the hundred-fold excess of maltol, which ensures the magnetic dilution of the complex in a solid diamagnetic matrix. In this case, the EPR spectrum at room temperature has rather good resolution allowing one to determine the EPR parameters with high accuracy: $g_{\parallel} = 2.295$; $g_{\perp} = 2.089$; $A(^{63}\text{Cu})_{\parallel} = 187.4 \cdot 10^{-4} \text{cm}^{-1}$; $A(^{63}\text{Cu})_{\perp} = 26.4 \cdot 10^{-4} \text{cm}^{-1}$.

The recorded EPR parameters are typical for the tetragonal complexes of Cu^{2+} with the first coordination sphere composed of oxygen atoms [34]. The axial symmetry of Cu complex points to the equivalence of all the oxygen atoms of the chelate unit. On this ground, the compound of maltol with Cu^{2+} was characterized as a flat-square tetragonal complex with the chelate unit composed of oxygen atoms.

An important characteristic of metal complexes, especially in view of possible use in medical practice, is their stability in solutions, in particular under the physiological pH values. However, some literature sources report only the equilibrium constants of the formation of some complexes [39, 40], which does not allow one to carry out their comparative analysis because these physical values are strongly dependent on experimental conditions. We determined both total and step stability constants of a number of maltol metal chelates (Table 4).

It was established that, depending on pH of the medium, metal-ligand complexes with the ratios equal to 1 : 1, 1 : 2, and 1 : 3 (for trivalent metals) are formed. Therefore, the stage dissociation of complexes with gradual release of metal ion should proceed in an aqueous solution with a decrease in pH. One can see in Table 4 that the strongest complexes are electrically neutral ones; we isolated them in the individual crystal states. The neutral complexes may be arranged in the following stability row according to the determined values of total constants: $\text{FeL}_3 > \text{AlL}_3 > \text{CuL}_2 > \text{NiL}_2 > \text{CoL}_2$.

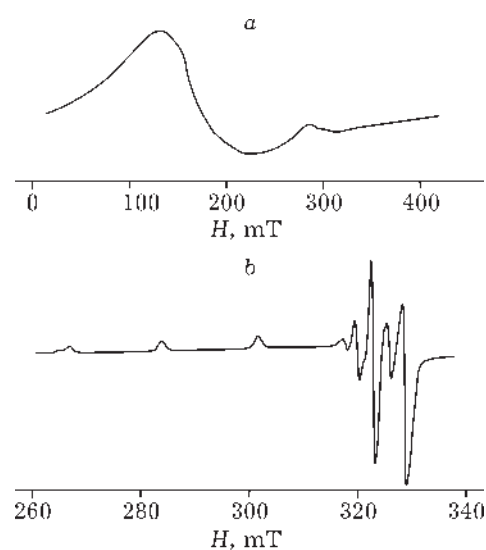


Fig. 4. EPR spectrum of tris-(3-hydroxy-2-methyl-4-pyronato)iron (III) (a) and bis-(3-hydroxy-2-methyl-4-pyronato)copper (II) (b).

TABLE 4
Total and step stability constants of maltol metal complexes

Composition of complex in solution	pH	Constant	
		step	total
[FeL] ²⁺	1-2.5	1.15 · 10 ⁵	3.19 · 10 ¹³
[FeL ₂] ⁺	3-4.5	4.10 · 10 ⁴	
[FeL ₃]	5.5-9	6.76 · 10 ³	
[AlL] ²⁺	2-3	3.76 · 10 ³	4.57 · 10 ¹²
[AlL ₂] ⁺	3-5	1.40 · 10 ⁴	
[AlL ₃]	5-8	9.43 · 10 ⁴	
[CuL] ⁺	2-3	4.57 · 10 ³	8.77 · 10 ⁷
[CuL ₂]	3-8	1.92 · 10 ⁴	
[NiL] ⁺	4-6	4.10 · 10 ³	5.68 · 10 ⁷
[NiL ₂]	6-9	1.32 · 10 ⁴	
[CoL] ⁺	5-7	4.10 · 10 ³	5.40 · 10 ⁷
[CoL ₂]	7-9	0.94 · 10 ⁴	

Among the investigated metal chelates, the complexes of iron and copper are of the largest biological importance. It is known that the ions of these metals are functional parts of blood proteins and play an important part in hematoses and enzymatic oxidation. We investigated the effect of copper maltolate on blood coagulation in white rats. It was shown that the introduction of this compound in the doses of 5, 15 and 25 mg/kg of body mass (Table 5) causes a substantial decrease in the intensity of thromboplastin and thrombin formation, the time of decay of their own activity shortens, which results in the liberation of fibrinopeptides and in inhibition of fibrin polymerisation (which is confirmed by a decrease in the index of thromboplastin-thrombin activation down to zero).

So, copper maltolate in the indicated doses decreases the activity of the inner mechanism

TABLE 5
Effect of copper maltolate on the indices of blood coagulation in white rats

Indices of ACT	Reference (intact)	Dose, mg/kg					
		5		15		25	
		Time, min					
		30	60	30	60	30	60
A, %	59.0±2.1	8.0±0.65*	0	7.9±0.56*	38.0±1.14*	22.5±0.76*	4.2±0.12*
MA, %	81.3±3.84	45.7±3.46*	24.5±0.73*	26.5±2.02*	86.5±3.38	47.3±3.78*	49.0±2.15*
T ₁ , min	1.2±0.08	2.4±0.12*	2.8±0.12*	4.8±0.23*	2.0±0.11	1.6±0.08	2.8±0.18*
T ₂ , min	8.0±0.15	4.0±0.28*	4.0±0.26*	10.0±0.56*	10.0±0.72*	6.0±0.31*	4.0±0.22*
Φ, min	56.0±4.48	26.0±1.56*	6.8±0.21*	32.0±1.92*	20.8±1.16*	24.0±1.24*	7.2±0.36*
ITI, rel. units	4.3±0.25	2.0±0.22*	0	0	0	0	0

* Difference is reliable with respect to the reference for $p \leq 0.05$.

TABLE 6
Effect of ferric maltolate on blood characteristics under experimental anemia in white rats

Animal groups	Blood values	
	Erythrocytes, 10 ¹² /L	Hemoglobin, g/L
Intact (distilled water)	7.8±0.18	142.6±3.53
Reference (lead acetate)	6.1±0.24*	119.4±4.76*
Experimental (ferric maltolate)		
doses, mg/kg:		
5	6.3±0.32*	128.0±5.12*
15	7.2±0.28	168.0±6.72
25	7.6±0.38	154.0±4.62

* Difference is reliable with respect to the reference for $p \leq 0.05$.

of prothrombinase formation and exhibits anticoagulant properties.

With the model of anaemia arising during poisoning with lead, the effect of ferric maltolate on the characteristics of red blood in white rats was studied.

It was established that the introduction of iron maltolate in the doses of 15 and 25 mg/kg (Table 6) decreases the toxic effect of lead, essentially prevents or decreases the pathologic shifts of red blood characteristics and thus prevents the development of anaemia.

CONCLUSION

Thus, the optimal conditions of the reactions of maltol complexation with the ions of di- and trivalent metals of medical and pharmaceutical importance were developed.

The synthesized metal chelates were characterized using a broad range of physicochemical and spectral (UV, IR, NMR, EPR) data; some of them were obtained for the first time. It was established that maltol forms tris-(3-hydroxy-2-methyl-4-pyronato)-derivatives with the cations of trivalent metals and bis-(3-hydroxy-2-methyl-4-pyronato)-derivatives with the cations of divalent metals. Depending on the coordinating ability of metal ions, maltol complexes have different spatial structure. By means of EPR spectroscopy, we proved the octahedral structure of the iron-containing maltol complex having a strong tetragonal distortion and the tetragonal structure of the copper-containing maltol complex with the chelate unit composed of oxygen atoms.

It was demonstrated that the complexes of different compositions are formed in aqueous solutions within the physiological pH range (1–9). The step and total constants of stability of maltol complexes with the ions of iron, aluminium, copper, nickel and cobalt were calculated; the row of stability of metal chelates was composed on this basis.

The anticoagulant activity of copper maltolate and antianaemic activity of ferric maltolate were established, which opens the new outlooks for the use of maltol as a natural synton for obtaining preparations to treat blood diseases.

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