Thermodynamics of mixed-ligand complex formation of copper(II) ethylenediaminetetraacetate with amino acids in solution

M. A. Bazanova · D. F. Pyreu · E. V. Kozlovskii

Abstract The mixed-ligand complex formation in the systems Cu^{2+}–$Edta^{4-}$–L (L = His, Lys, Orn, Arg, Im) has been calorimetrically, pH-potentiometrically, and spectrophotometrically studied in aqueous solution at 298.15 K and the ionic strength of $I = 0.5$ (KNO₃). The thermodynamic parameters of formation of the CuEdtaL, CuEdtaHL, and (CuEdta)₂L complexes have been determined. The probable coordination mode for the complexone and the ancillary ligand in the mixed-ligand complexes was discussed.

Keywords Thermodynamic parameters · Mixed-ligand complex · Copper (II) ethylenediaminetetraacetate · Amino acid · Denticity

Introduction

EDTA has a widespread clinical application as a so-called chelation therapy agent. Owing to its strong complexing capability, in particular with respect to transition metal ions and radionuclides, it has been used in vivo to remove toxic metal ions or an excess of biometal ions. The formation of relatively stable mixed complexes of the type CuEdtaL at a physiologic pH value should be accounted under chelation therapy and its excretion from the human organism [1]. The account of the interaction of copper (II) complexonate with amino acid and peptide molecules can make the application of chelating agents (complexones) more effective. The sufficiently strong affinity of copper (II) ion to ligands with N donor atoms makes the amino acids containing the so-called additional donor group (His, Lys, Arg, and some others) an interesting object of mixed complexes formation research.

The presence of several donor atoms in amino acids being studied results in various coordination modes. Earlier, the stability of mixed-ligand complexes of Hg(II) ethylenediaminetetraacetate with the above-mentioned amino acids had been studied [2]. It was noted that the chelation number (denticity) of amino acid in mononuclear mixed complexes did not achieve the maximum. The presence of an uncoordinated group of amino acid in HgEdtaL leads to the formation of a binuclear complex in which amino acid has a bridge function. Such effect has been revealed in the systems including histidine, lysine, cysteine, and methionine.

Copper (II)–EDTA–amino acid interaction has been previously studied in [3] by potentiometric titration. The mixed complexes CuEdtaL formation and their possible role in blood plasma models have been investigated. The possible coordination mode of ligands and structure of mixed complexes have not been proposed by the authors. It was interesting to continue the study of systems Cu^{2+}–$Edta^{4-}$–amino acids in aqueous solution in a wide range of pH in order to reveal the coordination mode of ligands in the mixed complex.

Recently, some metal (II) complexonates (Edta, Edda, Nta) have been investigated by different methods [4, 5]. The mixed complex formation of metal (II) nitrilotriacetates with amino acids has also been studied [6]. Transition metal complexes of complexones (Ida, Nta, Edta) were widely used in biotechnology, particularly in the protein purification technique known as Immobilised Metal-ion Affinity Chromatography (IMAC). It should be noted that calorimetry became a powerful instrument of investigation of metal ion complexation by amino acids, peptides, and other biologically active ligands [7].

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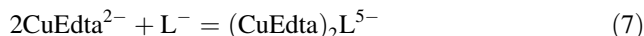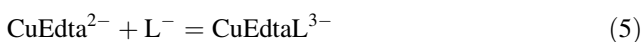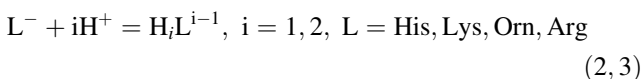e-mail: pyreu@mail.ru

Experimental

Materials

Sodium salt of copper (II) ethylenediaminetetraacetate Na$_2$CuEdta·4H$_2$O used in the work was purified by recrystallization from an aqueous-DMFA solution. A solution of the complexonate was prepared from the exact weight of the reagent. Carbonate-free NaOH solution was prepared according to standard procedure. Analytical grade KNO$_3$ used for adjusting the solution ionic strength was doubly recrystallized from distilled water. L-Histidine HHis·HCl (high-purity grade) (Renal), L-Lysine HLys·HCl (Acros), L-Ornithine HOrn HCl (Acros), and L-Arginine HArg·HCl (Renal) were used without further purification. Imidazole was recrystallized from benzene.

pH-metric measurements

The mathematical simulation of the equilibrium compositions of the solutions containing CuEdta^{2-} and amino acid in a wide pH range at various CuEdta^{2-} to L ratios has been carried out by means of the RRSU computer program [8].

The coordination equilibrium was investigated by potentiometric titrations in aqueous solution ($I = 0.5$ M KNO$_3$ and $T = 298.15 \pm 0.1$ K). The series of pH-potentiometric titrations of solutions containing Na$_2$CuEdta, HL·HCl, and supporting electrolyte KNO$_3$ with a NaOH solution have been performed. The emf of the transfer chain including glass and saturated Ag/AgCl electrodes was measured by the compensation method. The pH glass electrode was calibrated in aqueous solution using standard buffer solutions. The standard potential value was determined using a standard solution of (HCl + KNO$_3$). The constants of complex formation were evaluated from 3 to 4 independent titrations (30–50 data points per titration). The applied ratio of the CuEdta and amino acid was 2:1, 1:1, and 1:2 with the amino acid concentrations varied between 0.01 and 0.02 M. The experimental pH-metric data were processed by means of the PHMETR computer program [8] based on the minimization of the likelihood function $F = \Sigma(p_cH_{exp} - p_cH_{calc})^2$, where $p_cH = -\log[H^+]$ are the experimental values and those calculated by the model, respectively. The possibility of the following reactions has been taken into account:

$$H_2O = H^+ + OH^- \tag{1}$$

$$L^- + iH^+ = H_iL^{i-1}, \ i = 1, 2, \ L = His, Lys, Orn, Arg \tag{2, 3}$$

$$CuEdta^{2-} + OH^- = CuEdtaOH^{3-} \tag{4}$$

$$CuEdta^{2-} + L^- = CuEdtaL^{3-} \tag{5}$$

$$CuEdta^{2-} + HL = CuEdtaHL^{2-} \tag{6}$$

$$2CuEdta^{2-} + L^- = (CuEdta)_2L^{5-} \tag{7}$$

Computer simulation has shown that the substitution processes of the type CuEdta + nL = CuL$_n$ + Edta under a small excess of L have not taken place. The agreement between the theoretic and experimental curves was achieved only when the complexes of the type CuEdtaL^{3-} and CuEdtaHL^{2-} formation were considered (Fig. 1). Unfortunately, the formation constants of binuclear complexes (CuEdta)$_2$L^{5-} have not been potentiometrically determined. The simultaneous treatment of lg$K$ and Δ_rH of reaction (7) has been calorimetrically performed. The lgK_1 value was received by the extrapolation technique at an ionic strength of $I = 0.5$ by means of Davis's equation. The lg$K$ and Δ_rH values of reactions (2, 3) and (2, 3) were taken from critical reviews [9, 10]. The lgK_4 and Δ_rH_4 values have earlier been determined by us [11]. The potentiometrically determined lg$K$ values were taken for the reactions (5) and (6). The weighted average values of received equilibrium constants of the addition of L and HL to the CuEdta^{2-} are given in the Table 1.

Calorimetric measurements

The heats of the reactions were measured on an isothermal-jacket ampoule flow-mixing calorimeter equipped with a thermistor temperature gage and automated recording of temperature–time curves. The calorimeter was verified against the heat of the solution of KCl in water at 298.15 K. The computer simulation permitted us to choose the optimal reagent concentrations. The heats of mixing $\Delta_{mix}H$ of a CuEdta solution with alkaline solutions of amino acids containing the supporting electrolyte (KNO$_3$)
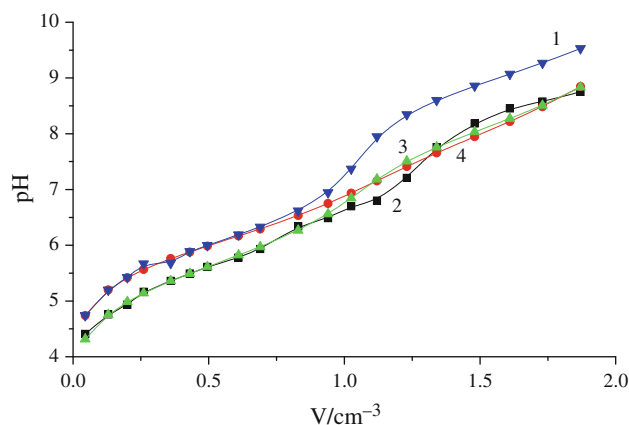
Fig. 1 pH-metric titration *curve* of a solution (20.09 cm^{-3}) containing 0.01021 mol dm^{-3} Na$_2$CuEdta + 0.01034 mol dm^{-3} HHis·HCl + 0.48 mol dm^{-3} KNO$_3$ with a NaOH solution (0.1978 mol dm^{-3})(2) and model curves plotted with an account for the formation of mixed-ligand complexes CuEdtaHis^{3-} (4) ($F_{min} = 7.53$), CuEdtaHHis^{2-} (1) ($F_{min} = 27.84$), and both CuEdtaHis^{3-} and CuEdtaHHis^{2-} (3) ($F_{min} = 1.79$)

Table 1 The thermodynamic parameters of mixed-ligand complex formation in the systems $CuEdta^{2-}$–L (L = His, Lys, Orn, Arg) at 298.15 K and $I = 0.5$ (KNO_3)

Process	lgK	$-\Delta_r G^0$/kJ mol^{-1}	$\Delta_r H$/kJ mol^{-1}	$\Delta_r S$/J mol^{-1} K^{-1}
$CuEdta^{2-} + NH_3 = CuEdtaNH_3^{2-}$	2.06 ± 0.02	11.76 ± 0.11	-34.9 ± 0.4	-77.6 ± 1.4
$CuEdta^{2-} + Gly^- = CuEdtaGly^{3-}$	1.8 ± 0.1	10.27 ± 0.57	-29.3 ± 1.3	-63.8 ± 4.8
$CuEdta^{2-} + His^- = CuEdtaHis^{3-}$	3.48 ± 0.09	19.86 ± 0.51	-17.47 ± 0.22	8.0 ± 1.9
$CuEdta^{2-} + H + His^- = CuEdtaHHis^{2-}$	11.31 ± 0.10	64.56 ± 0.57	-72.08 ± 0.54	-25.2 ± 2.6
$CuEdta^{2-} + HHis = CuEdtaHHis^{2-}$	2.29 ± 0.10	13.07 ± 0.57	-26.93 ± 0.54	-46.5 ± 2.6
$CuEdta^{2-} + Im = CuEdtaIm^{2-}$	2.65 ± 0.05[a]	15.13 ± 0.29	-43.73 ± 0.42	-95.9 ± 1.7
	2.74 ± 0.05[b]			
$CuEdta^{2-} + Lys^- = CuEdtaLys^{3-}$	3.65 ± 0.07	20.83 ± 0.40	-12.34 ± 0.60	28.5 ± 2.4
$CuEdta^{2-} + H^+ + Lys^- = CuEdtaHLys^{2-}$	12.59 ± 0.24	71.9 ± 1.4	-68.2 ± 1.9	12 ± 8
$CuEdta^{2-} + HLys = CuEdtaHLys^{2-}$	1.88 ± 0.24	10.7 ± 1.4	-14.6 ± 1.9	-13 ± 8
$CuEdta^{2-} + Orn^- = CuEdtaOrn^{3-}$	3.53 ± 0.05	20.15 ± 0.29	-11.02 ± 0.47	30.6 ± 1.9
$CuEdta^{2-} + H^+ + Orn^- = CuEdtaHOrn^{2-}$	12.37 ± 0.16	70.61 ± 0.91	-68.1 ± 1.1	8.4 ± 4.8
$CuEdta^{2-} + HOrn = CuEdtaHOrn^{2-}$	1.85 ± 0.16	10.56 ± 0.91	-16.2 ± 1.1	-18.9 ± 4.8
$CuEdta^{2-} + Arg^- = CuEdtaArg^{3-}$	4.75 ± 0.05	27.11 ± 0.29	-15.11 ± 0.84	40.2 ± 3.0
$CuEdta^{2-} + H^+ + Arg^- = CuEdtaHArg^{2-}$	14.19 ± 0.08	81.00 ± 0.46	-66.4 ± 1.5	49 ± 5
$CuEdta^{2-} + HArg = CuEdtaHArg^{2-}$	2.10 ± 0.08	11.99 ± 0.46	-9.3 ± 1.5	9 ± 5

[a] Calorimetrically determined value

[b] Spectrophotometrically determined value

and the heat of dilution $\Delta_{dil}H$ of a CuEdta solution in a solution of the supporting electrolyte were measured according to the first method. A weighed sample of a Cu (II) complexonate solution was placed into a glass ampoule. Neutralized amino acid with supporting electrolyte solution was contained in the reaction vessel of the calorimeter. The relative amount of CuEdtaHHis^{2-} did not exceed 50 % and the relative amount of CuEdtaHis^{3-} achieved ~ 75 % during calorimetric measurements. The series of calorimetric data of mixing of a fully neutralized alkaline solution of L with solutions containing the big excess of Cu (II) complexonate (the second method) demonstrated that the values of $\Delta_{mix}H$ calculated to the amount of amino acid were significantly more than the heats of the reactions (5) and (6). It may be explained only by binuclear complex formation. The simultaneous treatment of lgK and $\Delta_r H$ of reaction (7) taking into account the contributions of processes (1)–(6) permitted us to evaluate their full thermodynamic characteristics. The experimental data are given in the Tables 2, 3. The heats of the reactions are computed by means of the HEAT program [8] based on the minimization of the likelihood function $F = \Sigma(\Delta H_{exp} - \Delta H_{calc})^2$, where the ΔH are the experimental and calculated by model values, respectively, of the heat effects. The calculated thermodynamic parameters are listed in the Table 1. The heats of water ionization ($\Delta_r H = -56.90$ kJ mol^{-1} [12]), ligand stepwise protonation ($\Delta_r H_1 = -45.15$ and $\Delta_r H_{1,2} = -75.65$ [13] for His, $\Delta_r H_1 = -53.55$ and $\Delta_r H_{1,2} = -100.85$ kJ mol^{-1} [10] for Lys, $\Delta_r H_1 = -51.92$

and $\Delta_r H_{1,2} = -99.00$ kJ mol^{-1} [10] for Orn, and $\Delta_r H_1 = -57.07$ and $\Delta_r H_{1,2} = -106.53$ kJ mol^{-1} [9] for Arg), and the formation of hydroxocomplexonate CuEdtaOH^{2-} ($\Delta_r H = -25.5$ kJ mol^{-1}) were accepted according to the published data [11]. The uncertainties of the quantities were calculated as the 95 % confidence intervals according to the Student's test. The diagrams of the fractional distribution in the Cu^{2+}–Edta^{4-}–His system are shown in the Figs. 2, 3.

Electronic absorption measurements

The absorption spectra of solutions have been recorded after calorimetric measurements on CFC-3 spectrophotometer using a cell with 1 cm optical path length at $T = 293$ K. The received visible electronic spectra in the systems CuEdta^{2-}–L are shown in the Fig. 4.

Results and discussion

The content and structure of copper (II) histidine complexes have been studied for a long time and various suggestions have been made for the Cu(II)–His bond modes. The presence of three functional groups in the histidine molecule (–NH$_2$, –COOH, and –N$_{Im}$) makes it a potentially three dentate ligand. Histidine is often coordinated as bidentate ligand resulting in three coordination modes {N$_{am}$,N$_{Im}$}, {N$_{am}$,O}, and {N$_{Im}$,O} due to steric hindrance. Recently,

Table 2 Heats of mixing of a solution of Na$_2$CuEdta (0.4962 mol kg^{-1} of solution) with alkaline solutions of amino acids at 298.15 K and $I = 0.5$ (KNO$_3$)

N^o	Weighed sample of Na$_2$CuEdta solution/g	Concentration of Na$_2$CuEdta after mixing/ mol dm^{-3}	$\Delta_{mix}H$/kJ mol^{-1}	$\Delta_{mix}H - \Delta_{dil}H$/ kJ mol^{-1}
$C_{His}^- = 0.01014$ mol dm^{-3}, $C_H^+ = 0.01226$ mol dm^{-3}				
1	0.44560	0.004415	−13.25	−13.71
2	0.45390	0.004497	−13.42	−13.89
$C_{His}^- = 0.005081$ mol dm^{-3}, $C_H^+ = 0.000012$ mol dm^{-3}				
3	0.45900	0.004548	−13.66	−14.12
4	0.45605	0.004519	−13.88	−14.35
5	0.43850	0.004345	−14.13	−14.59
6	0.50430	0.004997	−13.71	−14.17
7	0.48525	0.004808	−13.76	−14.23
$C_{Lys}^- = 0.01010$ mol dm^{-3}, $C_H^+ = 0.01098$ mol dm^{-3}				
8	0.54045	0.005355	−4.87	−5.34
9	0.55410	0.004728	−5.29	−5.76
$C_{Lys}^- = 0.006963$ mol dm^{-3}, $C_H^+ = 0.000076$ mol dm^{-3}				
10	0.47270	0.004682	−11.66	−12.12
11	0.47720	0.004728	−10.96	−11.43
$C_{Orn}^- = 0.01005$ mol dm^{-3}, $C_H^+ = 0.01148$ mol dm^{-3}				
12	0.50765	0.005030	−4.61	−5.07
13	0.57200	0.005668	−4.42	−4.89
$C_{Orn}^- = 0.006405$ mol dm^{-3}, $C_H^+ = -0.00020$ mol dm^{-3}				
14	0.57420	0.005689	−9.80	−10.27
15	0.53790	0.005330	−9.48	−9.95
$C_{Arg}^- = 0.009530$ mol dm^{-3}, $C_H^+ = 0.01043$ mol dm^{-3}				
16	0.47070	0.004664	−4.25	−4.72
17	0.50870	0.005040	−4.36	−4.83
$C_{Arg}^- = 0.008874$ mol dm^{-3}, $C_H^+ = 0.00035$ mol dm^{-3}				
18	0.40395	0.004002	−13.68	−14.14
19	0.40390	0.004002	−14.78	−15.24

the comprehensive studies of the structure of Cu(II)-His complexes in solution have been performed [14, 15]. The formation of various content complexes CuH$_n$His$_2$ and their most probable structure has been determined by different types of spectroscopy. Lysine predominantly binds metal ions through the α-amino and carboxylate groups in the glycine mode to form monoprotonated complexes of the type M(HLys)$_2$ in acidic and neutral solutions. Deprotonated complexes of the types MHLys$_2$ and MLys$_2$ form in alkaline solutions. The ε-amino group is not involved in metal binding in solution practically because chelation through the two amino groups would result in an unstable eight-membered ring. So, Lys does not achieve the chelation number 3 in a majority of cases. Thermodynamic and NMR studies of some copper (II)-diaminomonocarboxylate equilibrium systems in aqueous solution were carried out in [16]. It was concluded that Lysine is coordinated to the copper (II) ion in a "glycine-like" manner. The ω-amino groups were coordinated also in
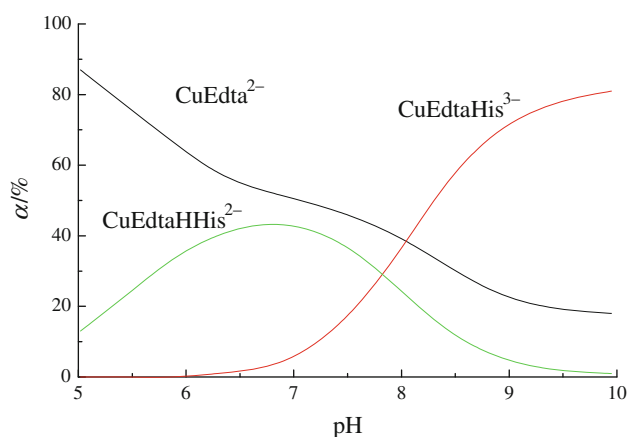
the complexes of other diaminomonocarboxylate ligands (dapa, daba, and ornithine) in a fully deprotonated form.

As can be shown from the Table 1, the addition of amino acids to CuEdta^{2-} is accompanied by negative enthalpy changes and slightly positive or negative entropy changes, which are characteristic of mixed-ligand complex formation involving the coordinately saturated copper (II), nickel (II), zinc (II), and cadmium (II) complexonates and occurring with a decrease in the EDTA denticity due to the opening of one or two glycinate chelate rings. The factors that cause such thermodynamic characteristics are comprehensively described in [11].
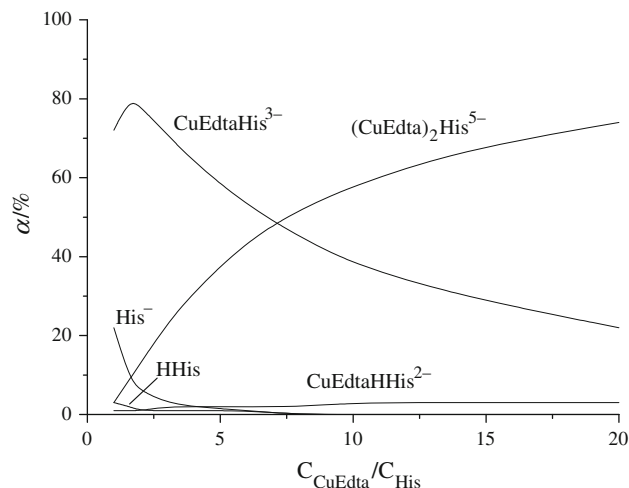
The addition of HHis to CuEdta is more an exothermic effect than the addition of anion His$^-$. Previously performed research [2] has revealed that mercury (II) ethylenediaminetetraacetate with histidine and lysine formed the binuclear complexes in which the amino acid acted, most likely, as a bridge linking the coordination spheres

Table 3 Heats of mixing of alkaline solutions of amino acids with solutions of $Na_2CuEdta$ at 298.15 K and $I = 0.5$ (KNO_3)

Weighed sample of L solution/g	Concentration after mixing/mol dm^{-3}		$\Delta_{mix}H/$ kJ mol^{-1}	$\Delta_{mix}H - \Delta_{dil}H/$ kJ mol^{-1}
	$CuEdta^{2-}$	L		
L = His				
0.54265	0.02014	0.004667	−31.09	−29.91
0.58155	0.02014	0.005001	−30.18	−28.99
0.47060	0.04997	0.004125	−41.19	−40.00
0.52510	0.04997	0.004603	−40.27	−39.08
0.51120	0.1002	0.004396	−47.03	−45.84
0.48805	0.1002	0.004197	−47.42	−46.24
L = Lys				
0.51930	0.02008	0.004651	−26.32	−24.46
0.54220	0.02008	0.004856	−−25.69	−23.82
0.50425	0.05037	0.004516	−36.71	−34.84
0.48000	0.05037	0.004299	−37.63	−35.76
0.49835	0.1011	0.004647	−44.99	−43.12
0.49015	0.1011	0.002334	−44.88	−43.01

Fig. 3 Diagram of the fractional distribution of histidine containing species in the $CuEdta^{2-}$–His^- system ($C_{His} = 0.005$ mol dm^{-3})

Fig. 2 Diagram of the fractional distribution of the species in the $CuEdta^{2-}$–His^- system at a 1:1 molar ratio ($C_{His} = 0.01$ mol dm^{-3})
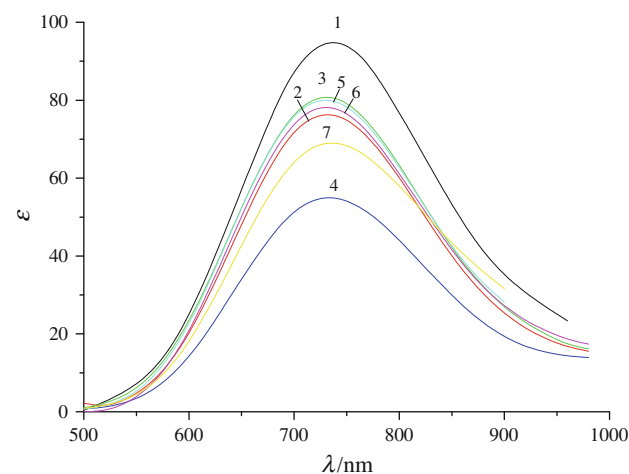
Fig. 4 Absorption spectra of solutions: *1* 0.005 mol dm^{-3} $Na_2CuEdta$; *2* 0.005 mol dm^{-3} $Na_2CuEdta$ + 0.01 mol dm^{-3} HHis; *3* 0.005 mol dm^{-3} $Na_2CuEdta$ + 0.0051 mol dm^{-3} His^-; *4* 0.005 mol dm^{-3} $Na_2CuEdta$ + 0.02 mol dm^{-3} Im; *5* 0.005 mol dm^{-3} $Na_2CuEdta$ + 0.0070 mol dm^{-3} Lys^-; *6* 0.005 mol dm^{-3} $Na_2CuEdta$ + 0.0065 mol dm^{-3} Orn^-; *7* 0.005 mol dm^{-3} $Na_2CuEdta$ + 0.0088 mol dm^{-3} Arg^-

of two mercury (II) ethylenediaminetetraacetate complexes. Received data permitted us to assume that the coordination of histidine molecule in complex $HgEdtaHis^{3-}$ was carried out via glycine fragment, but in protonated species $HgEdtaHHis^{2-}$ through imidazole fragment. The similarity of thermodynamic parameters of the secondary ligands $HHis^{\pm}$ and imidazole addition to HgEdta proved this suggestion. The more basic glycinate fragment was protonated in this case. The formation of CuEdtaIm served as a model process. The addition of Im to CuEdta is accompanied by a well-pronounced exothermic effect. The sufficiently close $\lg K$ and $\Delta_r H$ values of the addition of HHis and Im to copper (II) complexonate demonstrate that histidine residue is coordinated via a nitrogen donor atom of imidazole fragment.

At the same time, the reaction (5) for histidine is sufficiently less exothermic in comparison with the reaction (6), but $\Delta_r S_6$ value is more negative than $\Delta_r S_5$ value. Received thermodynamic data do not exclude the possible existence of the complexes $CuEdtaHis^{3-}$ with ambidentate character of histidine due to (N_{am},N_{im}) or (N_{am},O) coordination modes. Apparently, the equilibrium between two forms of mixed complex $CuEdtaHis^{3-}$, where histidine is coordinated in a glycine-like or histamine-like manner, takes place. The heat effects of reaction (5) in the case of His and Lys are sufficiently close. So, this equilibrium is shifted to the complex with (N_{am},O) coordination mode of histidine. In the case of amino acids with a long aliphatic chain (Lys,

Fig. 5 The addition of histidine to the copper (II) ethylenediaminetetraacetate
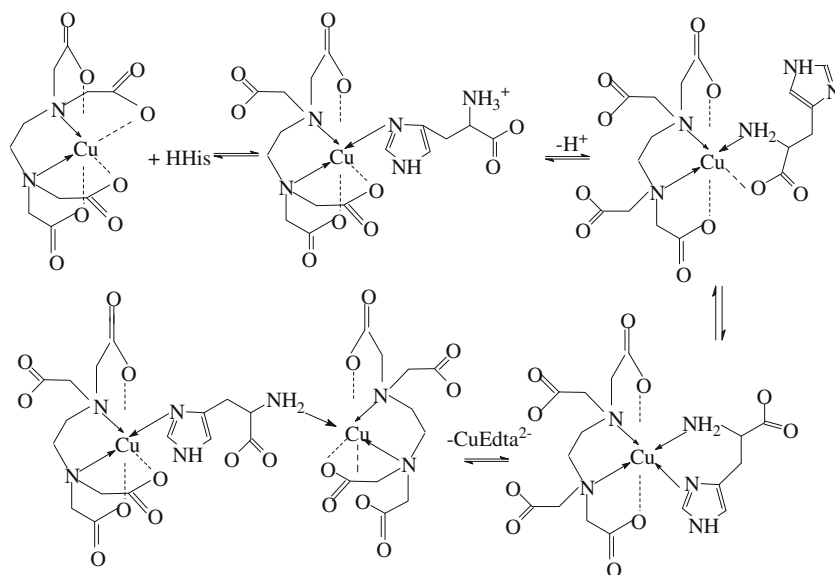

Table 4 The thermodynamic parameters of binuclear mixed-ligand complex formation in the systems $CuEdta^{2-}$–L (L = $(CH_2)_6(NH_2)_2$, His, Lys) at 298.15 K and $I = 0.5$ (KNO_3)

Process	lgK	$-\Delta_r G^0$/kJ mol^{-1}	$\Delta_r H$/kJ mol^{-1}	$\Delta_r S$/J mol^{-1} K^{-1}
$2CuEdta^{2-} + En = (CuEdta)_2En^{4-}$	6.02 ± 0.05	34.36 ± 0.29	-56.75 ± 0.26	-75.1 ± 1.3
$CuEdtaEn^{2-} + CuEdta^{2-} = (CuEdta)_2En^{4-}$	1.70 ± 0.11	9.70 ± 0.64	-21.98 ± 0.38	-41.2 ± 2.5
$2CuEdta^{2-} + L = (CuEdta)_2L^{4-}$	4.13 ± 0.05	23.57 ± 0.29	-66.85 ± 1.67	-145.2 ± 5.7
$CuEdtaL^{2-} + CuEdta^{2-} = (CuEdta)_2L^{4-}$	1.57 ± 0.06	8.96 ± 0.34	-33.24 ± 1.69	-81.4 ± 5.8
$2CuEdta^{2-} + His^- = (CuEdta)_2His^{5-}$	5.04 ± 0.05	28.77 ± 0.29	-54.8 ± 1.1	-87.3 ± 3.8
$CuEdtaHis^{3-} + CuEdta^{2-} = (CuEdta)_2His^{5-}$	1.56 ± 0.10	8.90 ± 0.57	-37.3 ± 1.1	-95.3 ± 4.2
$2CuEdta^{2-} + Lys^- = (CuEdta)_2Lys^{5-}$	4.93 ± 0.05	28.14 ± 0.29	-59.71 ± 0.64	-105.9 ± 2.4
$CuEdtaLys^{3-} + CuEdta^{2-} = (CuEdta)_2Lys^{5-}$	1.28 ± 0.09	7.31 ± 0.51	-47.37 ± 0.88	-134.4 ± 3.4

Orn, Arg), the close values of $\Delta_r H_5$ and $\Delta_r H_6$ prove the glycine-like coordination mode of these amino acids in mixed complexes of the types CuEdtaHL and CuEdtaL. Evidently, the ε-amino group is not coordinated by a central ion in mononuclear complexes (Fig. 5).

Earlier [17], it was shown that the noncoordinated amino group in the complexes CuEdtaL (L = $(CH_2)_n(NH_2)_2$, $n = 2,6$) bound with the second CuEdta residue, resulting in binuclear complex formation with bridging function of diamine. Thermochemical data proved it by means of the second method. Thermodynamic data given in the Table 4 well demonstrate that increasing of the aliphatic chain length of the diamines and diaminocarboxylic acids brings in more negative entropy change value under the binuclear complex formation. The big negative entropy change in reaction (7) is caused not only by translational term, but also by loss of configurational entropy of amino acid residue with the long aliphatic chain. It has been noted in [2] that binuclear complex formation was a result that dentate number of these amino acids did not achieve the maximum value in the mononuclear complexes.

The Fig. 4 shows that the changes in the electronic spectra of copper (II) complexonate in a solution containing amino acid provide evidence of mixed complex formation. The spectrophotometrically received value of the equilibrium constant of reaction (5) for imidazole has a sufficiently good agreement with the same value calorimetrically obtained (Table 1). The visible spectra collected for the systems CuEdta-amino acid indicate a decrease of d–d transition intensity and a small blue shift under the addition of amino acid residue. The same trend has been observed in the systems CuEdta–$(CH_2)_n(NH_2)_2$ ($n = 2,6$). So, it proves the coordination of amino acid via N donor atom. The close ε values of CuEdtaHHis and CuEdtaIm complexes also provide evidence of coordination of HHis$^\pm$ in mixed complex via imidazole fragment.

Conclusions

So, the basic amino acids can be monodentate in the mononuclear mixed complexes or bidentate with the bridging function in the binuclear complexes. Moreover,

the formation of relatively stable mixed complexes of the type CuEdtaL at a physiologic pH value should be accounted under chelation therapy. The account of the interaction of copper (II) complexonates with His and Lys containing peptide molecules can make the application of chelating agents (complexones) more effective.

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