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Modeling of Equilibriums of Formation of Polynuclear Chelates of Nickel(II) with Histidine

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Abstract—Electronic absorption spectroscopy has been applied to study of protolytic and complex formation equilibriums in binary and tertiary systems containing nickel(II) salt, ethylenediaminetetraacetic acid and 2-amino-3-(imidazol-2-yl)propionic acid (ionic strength 0.1 mol/L aqueous $NaClO_4$, 20±2°C). Fitting of experimental spectral properties as function of pH and the components concentration requires dissociation constants of the ligands as well as stability constants of homoligand, heteroligand, and polynuclear complexes as parameters. These parameters have been estimated from the best fit model, and possible complexes structures have been suggested.

Keywords: nickel(II), histidine, spectrophotometry, stability constant

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Excess of nickel(II) in the living body causes toxic morphological changes of the cells [1]. Toxicity of nickel is significantly reduced by its complex formation, for instance, with chelates and amino acids. Biological effect of nickel(II) bound in the chelate depends on its concentration, ligands nature, and other factors.

Heteroligand and polynuclear complexes can be formed in the tertiary systems containing nickel salt, ethylenediaminetetraacetic acid EDTA and the second ligand. Formation of polynuclear complexes can be explained as follows: EDTA is a polydentate ligand, but its complexing potential is not fully realized under certain conditions of mononuclear complex formation. Such mononuclear complex bearing EDTA capable of further complex formation then acts as a specific metal-chelate ligand. Finally, the formed complex will contain several metal ions and possibly several bulky ligands. Discussing formation of polynuclear complexes, the ions interference and the ligands compatibility should be accounted for. Formation of such complexes has been confirmed in the Ni(II)–EDTA–X tertiary systems, X being glycine, alanine, serine, ethylenediamine, etc. [2–7].

This study aimed at detailed investigation of complexes formation in the Ni(II)–histidine (His)–EDTA systems containing two chelating ligands, one of them being able to act as a bridging fragment. In particular, we have constructed the complexes formation models and calculated the complexes stability constants basing on the electronic absorption spectroscopy data. To the very best of our knowledge, these issues have not been addressed in the literature so far.

In order to understand the complex formation phenomenon in the tertiary system, we previously determined composition and stability of the complexes formed under similar conditions in the corresponding binary systems, Ni(II)–His [7] and Ni(II)–EDTA [5].

According to the measured spectral properties, in the cases of all the studied binary and tertiary systems the complexes were formed over wide range of pH. We processed the experimental data obtained for tertiary systems taking advantage of models neglecting formation of heteroligand complexes. Comparison of the experimental and the calculated absorbance profiles revealed certain deviations, assigned to formation of heteroligand and polynuclear complexes.

The above-described tertiary systems contained various hydroxo complexes of nickel(II) along with a variety of protonated forms of the polydentate ligands. Due to the system complexity, study of the

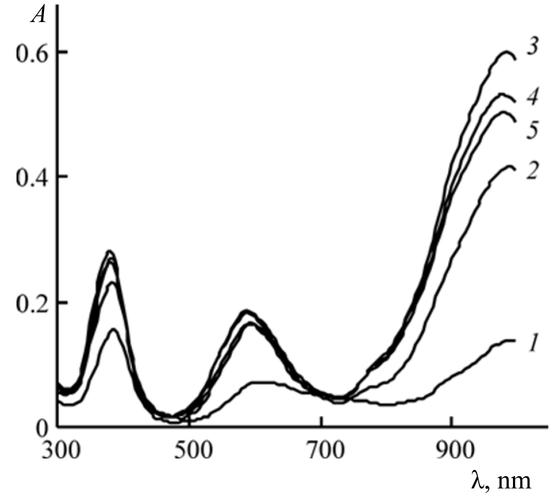


Fig. 1. Absorption spectra of the Ni(II)–His–EDTA (1 : 1 : 1) system at pH 1.4 (*1*), 2.2 (*2*), 4.5 (*3*), 8.3 (*4*), 11.0 (*5*). $c_{\mathrm{Ni}^{2+}} = 2 \times 10^{-2}$ mol/L, l = 1cm.

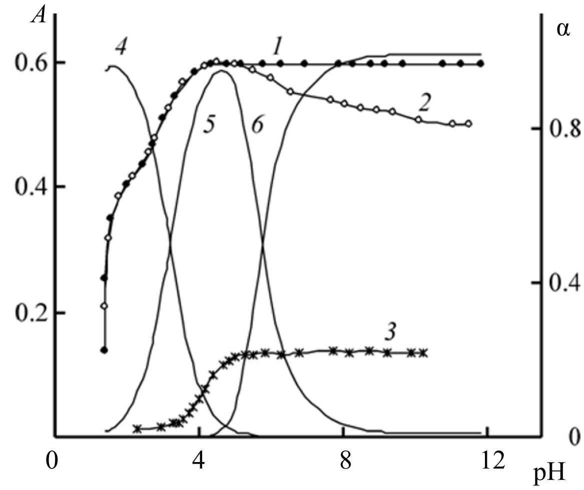


Fig. 2. Absorbance as function of pH: Ni(II)–His–EDTA 1 : 0 : 1 (*1*), Ni(II)–His–EDTA 1 : 1 : 1 (*2*) and Ni(II)–His–EDTA 1 : 1 : 0 (*3*); complexes fractions (α) as function of pH: $[\mathrm{NiHEdta}]^{-}$ (*4*), $[\mathrm{NiEdta}]^{2-}$ (*5*), and $[\mathrm{NiHisEdta}]^{3-}$ (*6*). $c_{\mathrm{Ni}^{2+}} = 2 \times 10^{-2}$ mol/L, λ = 985 nm.

corresponding equilibriums is a nontrivial task. Proper choice of the components forms to be included into consideration was of primary importance, as it dramatically influenced the derived numerical values of the equilibrium constants. The choice of the forms to be included in the model was made basing on the Fisher's test implemented in the software used [8–9]; in particular, the target was to minimize the deviation between experimental and calculated absorbances for each of the components. The software packages allowed reliable determination of the equilibrated system composition and the complexes stoichiometry as well as the related the equilibrium and stability constants. The ion pairs model was used to describe chemical equations.

When analyzing the systems behavior, we used the following input parameters: three hydrolysis constants of nickel(II) [10], four dissociation and two protonation constants of EDTA [11], and dissociation and protonation constants of histidine [12, 13].

Having been given a certain model (set of the particles and the predefined equilibrium constants), we simulated the mixtures electronic absorption spectra $A = f(\lambda)$ and the absorbance profiles as function of pH $A\lambda = f(\mathrm{pH})$. In all the cases we observed that according to the Fisher's test the models not accounting for heteroligand polynuclear complexes were not reliable. In particular, we probed the models including various sets of $[\mathrm{Ni(H}_i\mathrm{Edta)}]^{i-2}$ (i = 0–6), $[\mathrm{Ni(OH)}_j\mathrm{Edta}]^{(j+2)-}$ (j = 0–3), $[\mathrm{NiHis}_n]^{2+}$ (n = 1–2), $[\mathrm{Ni}_m\mathrm{His}_n\mathrm{Edta}]^{2m-n-4}$ (m = 1–3, n = 1–6), $[\mathrm{Ni(OH)}_j]^{2-j}$ (j = 0–3), and $[\mathrm{H}_i\mathrm{Edta}]^{i-4}$ (i = 0–6).

In addition to pH, position of protolytic equilibriums and composition of the formed complexes depended on the components concentrations ratio.

Positions and intensity of spectral bands were significantly different in the cases of solutions of mononuclear and polynuclear complexes. Figure 1 displays the spectra of 1 : 1 : 1 Ni(II)–His–EDTA mixtures recorded at different pH. In that case at pH > 4.0 absorbance was significantly lowered as compared with that in the case of 1 : 1 Ni(II)–EDTA system. Hence, we suggested that at pH > 4.0 some heteroligand nickel(II) chelate was formed. Indeed, the simulation revealed formation of mononuclear complexes of nickel(II) with EDTA along with the $[\mathrm{NiHisEdta}]^{3-}$ heteroligand complex in that system (α = 96% at $\mathrm{pH_{opt}}$ = 4.8) (Fig. 2).

Addition of histidine to the nickel–EDTA complex followed the equation below.

$$[\mathrm{NiEdta}]^{2-} + \mathrm{His}^{-} \overset{K_1}{\rightleftarrows} [\mathrm{NiHisEdta}]^{3-}. \qquad (1)$$

Formation of the (1 : 1 : 1) heteroligand complex could occur via one or two iminodiacetate groups of the chelating agent. However, in the both cases the $[\mathrm{NiHisEdta}]^{3-}$ complex housed two free $\mathrm{CH_2COOH}$ groups, as in the first case histidine acted as bidentate ligand, being tridentate ligand in the second case.

Figure 3 shows absorbance (at 985 nm) and molar fractions of several particles included in the model in the case of 2 : 4 : 1 Ni(II)–His–EDTA system as function of pH. The calculated absorbances perfectly coincided with the experimental ones thus confirming the model validity. From data shown in Fig. 3 it follows that mononuclear nickel(II) complexes prevailed in acidic, neutral, and weakly alkaline media: $[\mathrm{NiHEdta}]^-$ ($\alpha_{\max}$ = 50% at pH = 1.0), $[\mathrm{NiEdta}]^{2-}$ ($\alpha_{\max}$ = 50% at pH = 5.0), $[\mathrm{NiHis}]^+$($\alpha_{\max}$ = 42% at pH = 4.5), and $[\mathrm{NiHis}_2]$ ($\alpha_{\max}$ = 47% at pH = 6.0). At pH > 5.5 the $[(\mathrm{NiHis}_2)_2\mathrm{Edta}]^{4-}$ binuclear complex was formed, being practically the only form existing in the solution at 8.5 < pH < 10.7.

In that binuclear complex, coordination octahedrons of nickel(II) were connected via the diaminoethane bridge of EDTA, the two $\mathrm{CH_2COOH}$ at different nitrogen atom not forming the coordination sphere. As monodentate histidine coordination at carboxylic oxygen occurred exclusively in strongly acidic medium, histidine likely acted as bidentate ligand (via donor nitrogen atoms of amine and imidazole groups) upon the binuclear complex formation. Suggested structure of the above-discussed binuclear complex is shown in Scheme 1.

Such complex is formed following Eq. (2).

$$[\mathrm{NiHisEdta}]^{3-} + [\mathrm{NiHis}_2] + \mathrm{His}^- \overset{K_2}{\rightleftarrows} [(\mathrm{NiHis}_2)_2\mathrm{Edta}]^{4-}. \quad (2)$$

At pH of 10.7 the binuclear complexes was hydrolyzed [Eq. (3)]:

$$[(\mathrm{NiHis}_2)_2\mathrm{Edta}]^{4-} + 4\mathrm{OH}^- \overset{K_3}{\rightleftarrows} \{[\mathrm{NiHis(OH)}_2]_2\mathrm{Edta}\}^{6-} + 2\mathrm{His}^-. \quad (3)$$

The hydroxo complex was formed due to substitution of two histidine molecules with four hydroxyl groups.

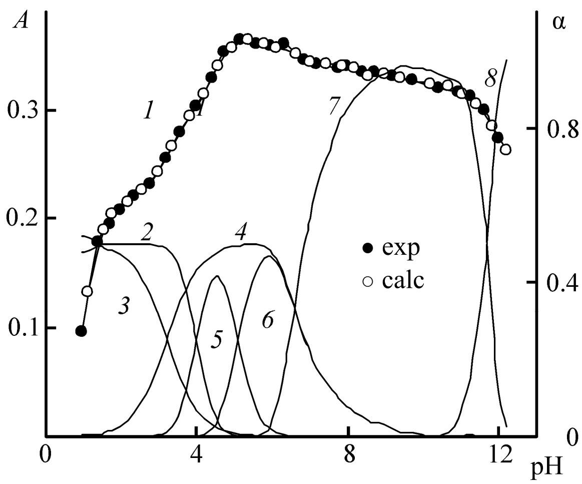


Fig. 3. Absorbance of the Ni(II)–His–EDTA 2:4:1 solution as function of pH (*1*); complexes fractions (α) as function of pH: Ni^{2+} (*2*), $[\mathrm{NiHEdta}]^-$ (*3*), $[\mathrm{NiEdta}]^{2-}$ (*4*), $[\mathrm{NiHis}]^+$ (*5*), $[\mathrm{NiHis}_2]$ (*6*), $[(\mathrm{NiHis}_2)_2\mathrm{Edta}]^{4-}$ (*7*), and $\{[\mathrm{NiHis(OH)}_2]_2\mathrm{Edta}\}^{6-}$ (*8*). $c^{2+}_{\mathrm{Ni}} = 2 \times 10^{-2}$ mol/L, λ = 985 nm.

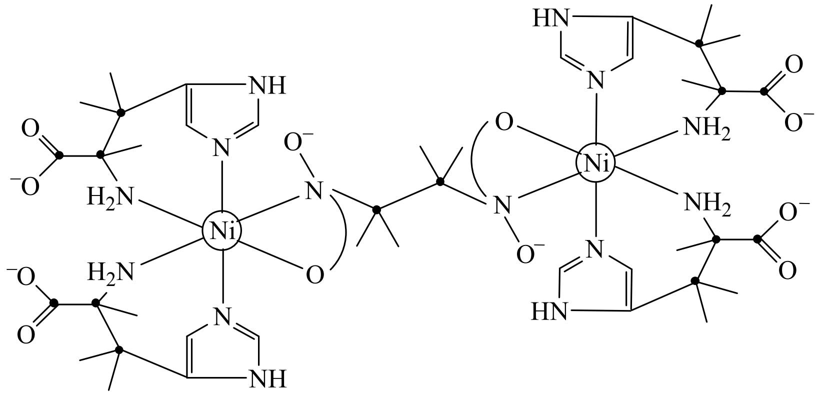
Absorption spectra of the 3 : 6 : 1 Ni(II)–His–EDTA system revealed blue shift of the *d*–*d*-band. The results of simulation of the equilibriums in that system are shown in Fig. 4. Again, the calculated points perfectly matched the experimental profile.

Analysis of the presented results revealed that mononuclear complexes were formed predominantly in that system over wide pH range. At pH > 6.0, the $[(\mathrm{NiHis}_2)_3\mathrm{Edta}]^{4-}$ complex was formed, its maximal fraction being of 88% at pH 10.5.

That trinuclear complex was formed following Eq. (4).

$$[(\mathrm{NiHis}_2)_2\mathrm{Edta}]^{4-} + [\mathrm{NiHis}_2] \overset{K_4}{\rightleftarrows} [(\mathrm{NiHis}_2)_3\mathrm{Edta}]^{4-}. \quad (4)$$

Scheme 1.



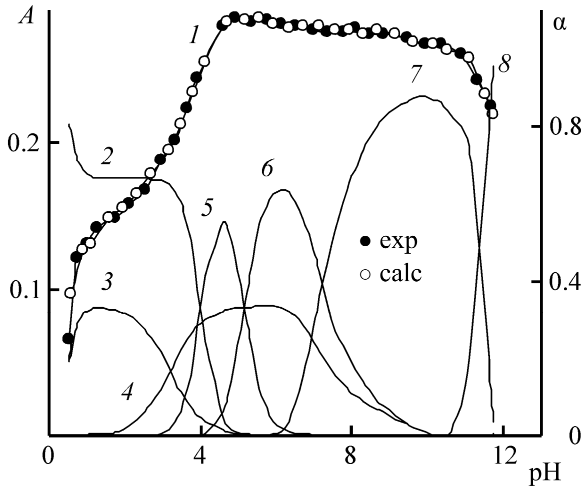


Fig. 4. Absorbance of the Ni(II)–His–EDTA 3:6:1 solution as function of pH (*1*); complexes fractions (α) as function of pH: Ni^{2+} (*2*), $[NiHEdta]^-$ (*3*), $[NiEdta]^{2-}$ (*4*), $[NiHis]^+$ (*5*), $[NiHis_2]$ (*6*), $[(NiHis_2)_3Edta]^{4-}$ (*7*), $\{[NiHis(OH)_2]_3Edta\}^{7-}$ (*8*); $c_{Ni}^{2+} = 2 \times 10^{-2}$ mol/L, λ = 985 nm.

In that complex, coordination spheres of two of Ni(II) ions were connected via the diaminoethane bridge of the chelating agent. The third metal ion was added via the two free carboxymethyl groups of EDTA. Octahedral surrounding of the metal ions contained two histidine molecules each (Scheme 2).

Suggested 3D structure of the trinuclear heteroligand complex is shown in Fig. 5; some of the ligands atoms are omitted for clarity.

The molecular model was constructed via the structure optimization approach based on molecular mechanics algorithm accounting for bonds stretching and deformation, internal rotation, and van der Waals interactions [14]. The molecular mechanics algorithm was based on CHARMM parameterization; the modifications included slight simplification of the potential functions as well as additional heuristic routine introduced to avoid poor starting conformations [14]. At pH > 10.0 the trinuclear complex was hydrolyzed; the process was manifested by significant decrease of the absorbance (Fig. 4). The simulation revealed formation of trinuclear complex containing six hydroxyl groups, as represented by Eq. (5).

$$[(NiHis_2)_3Edta]^{4-} + 6OH^- \overset{K_5}{\rightleftarrows} [(NiHis(OH)_2)_3Edta]^{7-} + 3His^- . \quad (5)$$

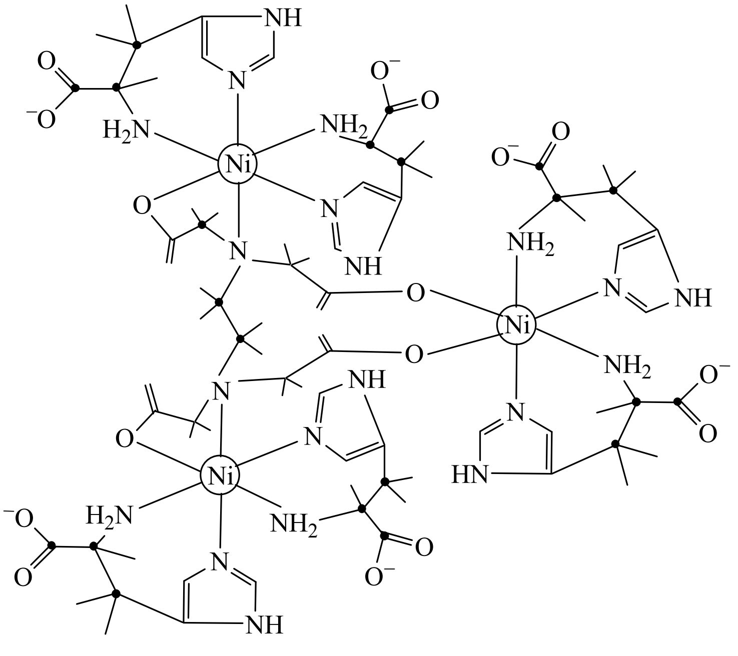
Suggested structure of the trinuclear heteroligand hydroxo complex is shown in Fig. 6.

Equilibrium constants of the discussed reactions and stability constants of the detected complexes are collected in the table.

EXPERIMENTAL

Formation of Ni(II) complexes with EDTA and His was studied by spectrophotometric titration; the elec-

Scheme 2.



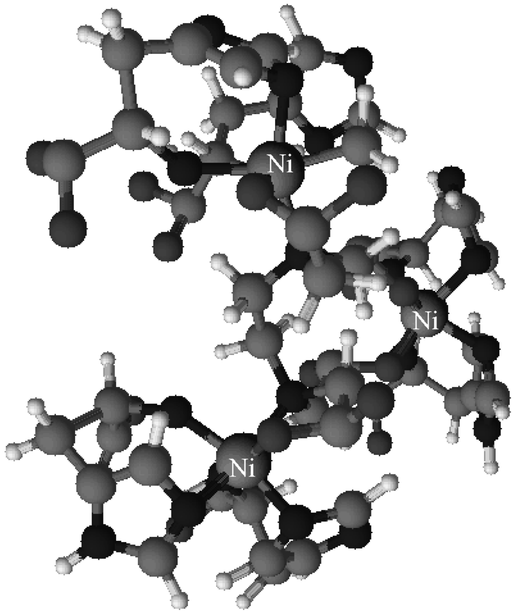


Fig. 5. Suggested structure of the $[(NiHis_2)_3Edta]^{4-}$ complex.

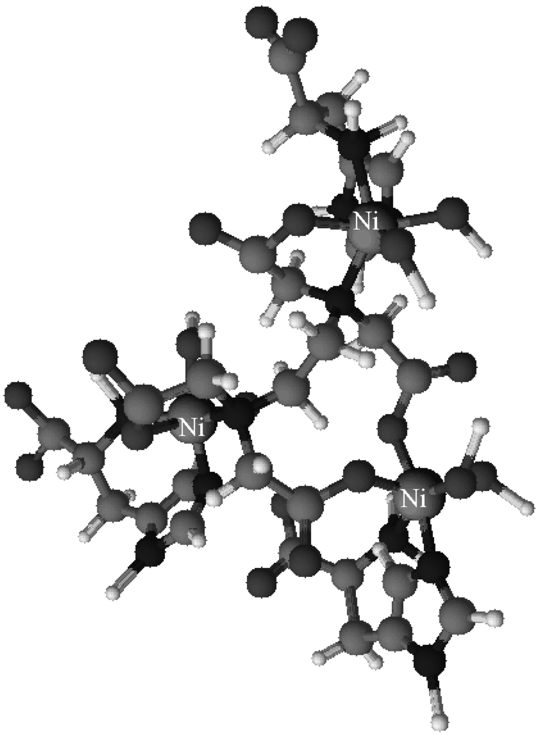


Fig. 6. Suggested structure of the $[(NiHis(OH)_2)_3Edta]^{7-}$ complex.

tronic absorbance spectra were recorded using the SF-2000 spectrophotometer with bidistilled water as reference. The experiments were performed taking advantage of the special device equipped with the titration unit enabling for simultaneous measurement of absorbance, pH, and temperature.

Activity of protons was measured with the I-160 ionometer using the ES-10601/7 working electrode and the ESR-10101 reference electrode. The instrument was calibrated with buffer solutions prepared from the standard solutions, and verified with the UPKP-1 test bench. pH of the tested solutions was adjusted with NaOH and $HClO_4$ (both of "analytical pure" grade) solutions. The experiments were run at constant ionic strength of I = 0.1 mol/L ($NaClO_4$, "analytical pure" grade) and at 20±2°C. The studied solution of nickel(II) perchlorate was prepared by dissolving a weighed specimen of metal nickel ("chemical pure"grade) in perchloric acid. EDTA solution was prepared from standard solution; L-histidine hydrochloride (Reanal) was used as received. Titration results were processed with CPESSP [8] and HypSpec [9] software; molecular models were visualized and optimized using ACD/Labs [14] software package.

Equilibrium constants and stability constants of nickel(II) complexes with histidine and EDTA

Complex	Reaction number	log K_i	log β
$[NiHisEdta]^{3-}$	1	5.55	24.45±0.12
$[(NiHis_2)_2Edta]^{4-}$	2	5.17	44.89±0.05
$[(NiHis(OH)_2)_2Edta]^{6-}$	3	5.32	50.21±0.05
$[(NiHis_2)_3Edta]^{4-}$	4	1.09	61.25±0.11
$[(NiHis(OH)_2)_3Edta]^{7-}$	5	9.76	71.01±0.12

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