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Thermodynamics of mixed-ligand complex formation of zinc nitrilotriacetate with amino acids and dipeptides in solution

Dmitrii Pyreu [a,*], Matvey Gruzdev [b], Roman Kumeev [b], Sergei Gridchin [c]

[a] Department of Inorganic and Analytic Chemistry, Ivanovo State UniversityErmak 39, Ivanovo 153025, Russia
[b] G.A. Krestov Institute of Solution Chemistry of the Russian Academy of Sciences, Ivanovo, Russia
[c] Ivanovo State University of Chemistry and Technology, Ivanovo, Russia

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ABSTRACT

The isothermal calorimetry, pH-potentiometric titration and ^{1}H and ^{13}C NMR methods has been used to study the mixed-ligand complex formation in the systems Zn^{2+}–Nta^{3-}–L^- (L = His, Orn, Lys, GlyGly, AlaAla) in aqueous solution at 298.15 K and the ionic strength of I = 0.5 (KNO_3). The thermodynamic parameters of formation of the mixed complexes have been determined. The relationship between the probable coordination modes of the complexone and amino acid or dipeptide molecules in the mixed-ligand complex and the thermodynamic parameters has been discussed.

1. Introduction

Zinc(II) ions play important role in cell mainly in zinc containing enzymes. The disturbance of zinc homeostasis in human organism and diseases caused by it has been intensively investigated [1]. To remove the toxic excess of metal ions and radionuclides from human organism the complexones (Nta, Edta, Dtpa) and its derivatives are actively used *in vivo* under chelation therapy. Formation of relatively stable mixed complexes of metal complexonates with amino acids and peptides at physiological pH value has been detected earlier [2,3]. This effect should be accounted in order to make the application of chelating agents (complexones) more effective. The computer simulation of zinc distribution model taking into account the mixed ligand complex formation becomes more correct. The protein purification technique known as immobilized metal-ion affinity chromatography (IMAC) is based on interaction of immobilized transition metal complexonates (Ida, Nta) with peptide molecules forming the mixed ligand complexes. So, the mixed complex formation of metal complexonates with amino acids, peptides and other biologically active molecules should be comprehensively investigated. The Zn(II) mixed complexes with complexones and amino acids and dipeptides can serve as simple models for investigation of zinc(II) complexation by some biologically important molecules.

Previously Zn(II)–Nta–amino acid system has been studied in some papers [4–12] by means of potentiometric titration. The formation of mixed complexes ZnNtaL has been determined. As rule only stability constants of mixed-ligand complexes have been determined by authors [4–12] but full thermodynamic parameters of reactions have not been received. Unfortunately, the critical choice of valid complexation model and types of complexes has not been provided in these researches. In some cases the determination of types of mixed ligand complexes was not absolutely correct. So, it was interesting to improve the study of systems Zn(II)–NTA–amino acids, dipeptides in aqueous solution in wide range of pH in order to reveal the coordination mode of ligands in the mixed complexes. This aim can be effectively achieved using thermodynamic approach.

2. Experimental

2.1. Materials

The crystalline sodium salt of zinc(II) nitrilotriacetate NaZnNta·H_2O has been synthesized. It was identified by means of

* Corresponding author. Tel.: +7 909 2486987.
E-mail address: pyreu@mail.ru (D. Pyreu).

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elemental analysis and thermogravimetry. L-histidine HHis·HCl (high-purity grade, Reanal), L-lysine HLys·HCl (Acros), L-ornithine HOrn·HCl (Acros), Glycylglycine HGlyGly (HGG) (high purity grade) and DL-α-alanyl-DL-α-alanine HαAlaαAla (HαAαA) (pure for analysis, Reanal) were used without further purification. Imidazole was recrystallized from benzene. Carbonate-free NaOH solution was prepared according standard procedure. Analytical grade KNO_3 used for adjusting the solution ionic strength was doubly recrystallized from distilled water. Deuterated water D_2O (99 atom % D) was purchased from Sigma–Aldrich.

2.2. Potentiometric titration

For determination of the stability constants of ternary complexes aqueous solutions containing NaZnNta HL·HCl and supporting electrolyte KNO_3 (at ZnNta: L ratios of 1:1 and 2:1) were potentiometrically titrated with 0.2 M NaOH solution at 25 ± 0.02 °C. The emf of the transfer chain equipped with glass and Ag/AgCl electrodes was measured by the compensation method. The initial total amino acid concentration was 0.01 M. The conditions of potentiometric measurements and computer treatment of potentiometric data using the PHMETR program [13] are described in [14]. The following complexation model has been taken into account:

$$3H_2O = H^+ + OH^- \quad (1)$$

$$Zn^{2+} + H_2O = ZnOH^+ + H^+ \quad (2)$$

$$Nta^{3-} + iH^+ = H_iNta^{i-3},\ i = 1-3 \quad (3,5)$$

$$L^- + iH^+ = H_iL^{i-1},\ i = 1, 2\ (L = His^-, Orn^-, Lys^-) \quad (6,7)$$

$$Zn^{2+} + iNta^{3-} = Zn(Nta)_i^{2-3i},\ i = 1, 2\ (8,9) \quad (8,9)$$

$$Zn^{2+} + 2HL = Zn(HL)_2^{2+} \quad (10)$$

$$Zn^{2+} + HL + L^- = ZnHL_2^+ \quad (11)$$

$$Zn^{2+} + 2L^- = ZnL_2 \quad (12)$$

$$ZnNta^- + H^+ = ZnHNta \quad (13)$$

$$ZnNta^- + OH^- = ZnNtaOH^{2-} \quad (14)$$

$$ZnNta^- + L^- = ZnNtaL^{2-} \quad (15)$$

It was shown that complexation model which took into account only formation of the complex of the type $ZnNtaL^{2-}$ had no agreement with experiment (Fig. 1). The agreement between the theoretical and experimental curves was achieved when the complexes of the type $ZnNtaL^{2-}$ and $ZnNtaHL^-$ formation has been considered. The protonated mixed complexes formed under reaction:

$$ZnNta^- + L^- + H^+ = ZnNtaHL^- \quad (16)$$

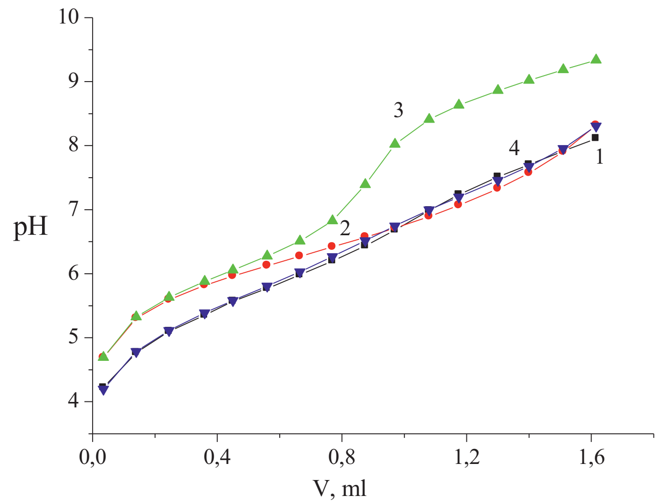

Fig. 1. pH-metric titration curve of a solution (20.09 ml) containing 0.01016 mol dm^{-3} NaZnNta 0.01013 mol dm^{-3} HHis·HCl and 0.48 mol dm^{-3} KNO_3 with a NaOH solution (0.2282 mol dm^{-3}) (1) and model curves plotted with account of formation of mixed-ligand complex $ZnNtaHis^{2-}$ (2) (F_{min} = 5.24), $ZnNtaHHis^-$ (3) (F_{min} = 57.4) and both $ZnNtaHis^{2-}$ + $ZnNtaHHis^-$ (4) (F_{min} = 0.21).

In contrast to copper(II) complexes [14] the treatment of potentiometric data at ZnNta: L ratio of 2:1 has not revealed the binuclear complex formation of the type $(ZnNta)_2L^{3-}$. In the case of dipeptides the agreement between the theoretical and experimental titration curves was achieved when the complexes of the type $ZnNtaL^{2-}$ and $ZnNtaLH^{3-}_{-1}$ formation has been taken into account. The last species forms during acidic dissociation of peptide group according equation

$$ZnNta^- + L^- = ZnNtaLH_{-1}^{3-} + H^+ \quad (17)$$

The log K values of dissociation processes of Nta were received by critical review [15]. The log K values of protolytic processes (6) and (7) for His (9.02 and 15.07 accordingly), Lys (10.66 and 19.86) and Orn (10.52 and 19.35) also have been taken by critical reviews [16] and [17]. Stability constant of hydroxy complexonate ZnNtaOH have been specified during supplementary pH-titration. All determined stability constants of mixed complexes are given in the Table 1. The diagram of the fractional distribution of the $ZnNta^-$–His^-–H^+ system is given in the Fig. 2. It demonstrates that both $ZnNtaHis^{2-}$ and $ZnNtaHHis^-$ mixed complexes exist in solution at physiological pH value. Moreover the contribution of homoligand *bis*-complexes formation into observed pH and heat of mixing values under given conditions is practically negligible. The mathematical simulation of the equilibria in solutions containing $ZnNta^-$and amino acid in a wide pH range at ZnNta to L ratio of 1:1 has been carried out using the RRSU computer program [13].

3.1. Isothermal calorimetry

All calorimetric measurements have been carried out using an isothermal-jacket ampoule flow-mixing calorimeter equipped with a thermistor temperature gage. The calorimeter was verified by measurement of the heat effects of 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 fully or partly neutralized alkaline solution of amino acid or dipeptide with solutions containing NaZnNta and supporting electrolyte (KNO_3) were measured. Further they were corrected taking into account the heat of dilution $\Delta_{dil}H$ of an alkaline amino acid or dipeptide solution in a solution of supporting electrolyte. Weighed samples of an alkaline amino acid solution were placed