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Research paper

Ternary complex formation in the system Ni(II) with picolinic acid and selected amino acids: Solution studies, isolation and computational calculations

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This contribution is dedicated to Dr. Felipe Brito (1930–2017). A lifetime dedicated to the study of inorganic chemistry and solution equilibria.

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ABSTRACT

The formation of mixed ligand complexes of Ni(II) with picolinic acid (Hpic) in presence of selected amino acids (HL) (serine (Hser), threonine (Hthr), methionine (Hmet) and phenylalanine (Hphe)) has been studied by pH-metric titrations. The pH-titrations of the reaction mixtures are shown to yield the complexes Ni(pic)L, $[Ni(pic)(L)(OH)]^-$ and $[Ni(pic)(L)_2]^-$ in the systems studied with the amino acids ser, met and phe, while in the Ni(II)-Hpic-Hthr system only the complexes Ni(pic)L and $[Ni(pic)(L)_2]^-$ were formed. The equilibrium and formation constants of the resulting ternary complexes have been calculated at I = 1.0 mol.dm^{-3} of NaCl. The stability of the ternary complexes was quantitatively compared with their corresponding binary complexes in terms of the parameters $\Delta \log_{10} K''$. The concentration distributions of various species formed in solution were also evaluated as a function of pH. The synthesis of the ternary species Ni(II)-Hpic-HL, in which HL corresponds to the amino acids ser and phe, was performed, and the solids were characterized using a combination of FT-IR, UV–Vis, elemental analysis, TGA, powder DRX and ^{1}H NMR. The crystallization of the isolated ternary complexes was attempted, yielding only the corresponding binary species $Ni(pic)_2$. Calculations on the stability of the ternary complexes were performed, to account for the impossibility to crystallize them.

1. Introduction

Bioavailability of metal ions depends on their being either in their free form or in a binding or complexed state, with various constituents present in requisite amounts during biological reactions. The changes in various constraints like pH, temperature and ionic strength cause changes in the complexation behavior of metals and their binding state. Hence, complexation can significantly affect the bioavailability of metal ions in various biosystems [1]. In particular, binding studies of metal ions by amino acids, proteins or peptides are fundamental to understand their role in bioinorganic processes [2], and to mimic specific functions of bioinorganic compounds such as metalloproteins, metalloenzymes for catalysis [3] or metallic complexes used in medicine. Chemical speciation studies of essential metal ion complexes are thus of great importance for a more accurate understanding of their distributions, mobility, toxicity, bioavailability, and for setting environmental quality standards. Mixed-ligand complexes are fundamental in biological chemistry, since mixed chelation commonly occurs in biological fluids, as millions of potential ligands usually compete for metal ions *in vivo*. These create specific structures and have been implicated in the storage and transport of active substances through membranes [1].

As a consequence, the binding of metal ions to chelating ligands such as picolinate, has been of great interest in bioinorganic chemistry. For example, the bis(picolinate)oxovanadium(IV), $VO(pic)_2$, has shown a modest glucose-lowering activity [4]. Other metallopicolinate complexes have shown insulinomimetic activity as well [5]. Sakurai et al. [6] studied *in vivo* coordinative structural changes of an insulinomimetic agent, bis(picolinato)oxovanadium(IV), by electron spin-echo envelope modulation spectroscopy, and observed that the original binary complex is transformed into a ternary complex of general composition VO(pic)(X), where X repre-

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sents an amino acid. Substantial variations in insulinomimetic activity were observed upon formation of the ternary species.

The importance of nickel in bioinorganic chemistry has been recognized, among other examples, with the recent discovery of the metalloenzyme NiSOD [7], part of the defense enzymes group called superoxide dismutases (SODs) [8]. Considering the potential applications of metallopicolinato complexes as insulinomimetic agents, our group decided to study the formation of ternary complexes in the Nickel(II)-Hpic-amino acid systems (serine (Hser), threonine (Hthr), methionine (Hmet) and phenylalanine (Hphe)).

Potentiometric studies on the solution chemistry of Ni(II)-peptide systems have been reported [9]. Also, investigations on the mixed-ligand complex formation equilibria for the systems Ni(II)-Hpic and the amino acids glycine, α-alanine, β-alanine and proline have also been carried out in our group [10]. The binary and ternary complexes of Ni(II) with dipicolinic acid and the amino acids of interest in the present study were recently investigated as well [11]. However, to the best of our knowledge, there are no reports on the aqueous-solution speciation of ternary complexes of Ni(II)–Hpic with the amino acids selected for this study, up to date [12,13]. In view of the above facts, it therefore seems to be of considerable interest to conduct investigations of the ternary complexes of nickel(II) with picolinic acid (Hpic) and some selected amino acids (serine (Hser), threonine (Hthr), methionine (Hmet) and phenylalanine (Hphe)) as ligands. In addition, attempts to isolate and crystallize the ternary complexes for the systems in which a major species was identified were performed, to obtain further insights on the behavior of these species in the solid state and compare them with the data in solution.

2. Experimental

2.1. Reagents

$NiCl_26H_2O$, $Ni(OOCCH_3)_24H_2O$ and the amino acids serine (Hser), threonine (Hthr), methionine (Hmet) and phenylalanine (Hphe) were obtained from commercial sources (Merck p.a.) and used without further purification. $Na_2EDTA{\cdot}2H_2O$ and bromopyrogallol Red (Merck p.a.) as indicator were used to standardize the nickel(II) stock solution. The HCl and NaOH solutions were prepared using 100.0 mmol.dm^{-3} Titrisol Merck ampoules. The NaOH solution was standardized against potassium hydrogen phthalate (Merck p.a., recrystallized and dried at 120 °C) using phenolphthalein as indicator. The HCl solution was standardized with NaOH solution of known concentration [14]. The solutions were prepared using triply glass-distilled water, which was boiled before preparation of the solutions to remove dissolved CO_2. 100 mmol.dm^{-3} HCl was added to the $NiCl_2$ stock solution to prevent its hydrolysis. $NiCl_2$ is hygroscopic and must be weighed on a very short timescale. In light of this observation, it becomes necessary to standardize the $NiCl_2$ stock solution using a $Na_2EDTA{\cdot}2H_2O$ solution (0.01 mol.dm^{-3}) in a buffer media (pH = 10) using bromopyrogallol red as indicator [14]. The acidity of the $NiCl_2$ stock solution was determined by the Gran method [15]. Potentiometric measurements were carried out in aqueous solution using 1.0 mol.dm^{-3} NaCl as ionic medium. Nitrogen free of O_2 and CO_2 was used.

2.2. Equipments

The potentiometric measurements were performed using the following instruments: Thermo Orion model 520A pH meter, Metrohm EA 876–20 titration vessel, Lauda Brikmann RM6 thermostat bath. The sealed 100 mL thermostated double-walled glass titration vessel was fitted with a combined Orion Ross 8102BN pH electrode with a titrant inlet, magnetic stirrer, and an inert nitrogen atmosphere inlet with outlet tubes. The temperature was kept at (25.0 ± 0.1) °C by constant circulation of water from the thermostat bath.

UV–Vis absorption spectra were recorded on an Agilent 8453 spectrophotometer in water or dimethyl sulfoxide (DMSO) solution. FT-IR spectra were recorded on a Nicolet I.S10 spectrometer in KBr discs. The absorption bands are described as follows: strong (*s*), very strong (*vs*), middle (*m*), weak (*w*), or broad (*br*). ^{1}H NMR spectra were recorded on a Bruker Avance 300 spectrometer. The chemical shifts (δ) were measured according to IUPAC [16] and expressed in parts per million (ppm) relative to TMS for ^{1}H. Deuterated solvents (D_2O and DMSO d_6) were purchased from Armar Chemicals. The abbreviation br. is given for broadened signals. X-ray powder diffraction (XRD) analysis was carried out at ambient temperature using a Siemens D-5005 diffractometer. The instrument is equipped with a copper anode generating Ni-filtered CuK_ radiation (λ = 1.54056A°, 40 kV, 30 mA). Diffractograms were recorded in the 2θ range between 5.0° and 89.96° with a step size (2θ) of 0.020° and a step time of 0.42 s. Thermogravimetric analysis (TG) of the complexes were carried out in a dynamic nitrogen atmosphere (20 ml/min) with a heating rate of 10 °C/min using a Mettler Toledo TGA/DSC STAR^e System analyzer. Temperature range: 25–500 °C.

2.3. Methods

The emf (H) measurements were carried out by means of the REF//S/GE cell, where REF = Ag/AgCl/3.0 mol.dm^{-3} KCl; S = equilibrium solution and GE = glass electrode. At 25 °C the emf (mV) of this cell follows the Nernst equation, $E = E^0 + jh + 59.16\ \log\ h$, where h represents the free hydrogen ion concentration, E^0 is the standard potential and j is a constant which takes into account the liquid junction potential [17]. The experiments were carried out as follows: a fixed volume of 0.100 mol.dm^{-3} HCl was titrated with successive additions of 0.100 mol.dm^{-3} NaOH until near neutrality in order to get the parameters E^0 and j. Then, aliquots of the HPic and the amino acid under study were added and finally an aliquot of the Nickel(II) stock solution was added sequentially. The titration was continued with 0.100 mol.dm^{-3} NaOH. The measurements were done using a total metal concentration, M_T = 2–3 mmol.dm^{-3} and Nickel(II):HPic:amino acid molar ratios R = 1:1:1, 1:1:2 and 1:2:1.

The systems Ni^{2+}- pic$^-$ - Amino Acids (B$^-$) were studied according to the reaction scheme:

$$pH^+ + qNi^{2+} + rpic^- + sB^- \rightleftharpoons [Ni_q(H)_p(pic)_r(B)_s],\ \beta_{p,q,r,s}$$

where B$^-$ represents the amino acids: ser$^-$, thr$^-$, met$^-$ and phe$^-$ and [Niq(H)p(Pic)r(B)s] is the ternary (p, q, r, s) complex (the charges were omitted) and β_{pqrs} is the respective stability constant.

The potentiometric data was analyzed using the program LETAGROP [18,19], in order to minimize the function $Z_C = (H - h)/[\text{ligand}]$ and $Z_B = (H - h)/M_T$, where Z_C and Z_B are the average number of mole of H^+ associates per mole of ligand and metal respectively. H is the total (analytical) concentration of H^+, h represents the concentration in equilibrium of H^+, and M_T represents the total (analytical) concentration of Nickel (II).The pK_w of water was calculated at the ionic strength of 1.0 mol·dm^{-3} NaCl to be 13.69 (±0.01). Equilibria corresponding to the formation of the hydroxo complexes of Nickel (II) were considered in the calculation of the stability constants of the ternary complexes. The following species were assumed: $[Ni(OH)]^+$, log $\beta_{1,-1}$ = −9.4(1); $Ni(OH)_2$, log $\beta_{1,-2}$ = −16.94(4); and $[Ni_4(OH)_4]^{4+}$, log $\beta_{4,-4}$ = −27.73(3) [20]. The binary Nickel (II)-Hpic [20] and the Nickel (II)-H_2dipic-Amino Acid systems (amino acid = ser, met, thr, phe) [11,21] were previously studied in our group. The stability constants of the Nickel (II)