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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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Speciation
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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.

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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)

hydroxo complexes, the acidity constants of the ligands and the stability constants of the binary complexes were kept fix during the analysis. The aim was to find a complex or complexes giving the lowest sum of the errors squared, $U = \sum (Z_C^{exp} - Z_C^{calc})^2$ and $U = \sum (Z_B^{exp} - Z_B^{calc})^2$,the fittings were done by testing different (p, q) and (p, q, r, s) combinations.

The species distribution diagram were done with the computer program HYSS [22], yielding the β_{pq} and β_{pqrs} values, which are summarized in Tables 1 and 2.

2.4. Isolation of the ternary complexes from the systems Ni (II)-Hpic-L (L = ser, phe)

2.4.1. System Ni(II)-Hpic-Ser

Nickel acetate tetrahydrate (252.1 mg; 1.01 mmol) and serine (106.1 mg; 1.01 mmol) were dissolved in water (5 mL) and the mixture was magnetically stirred for 30 min. Picolinic acid (124.3 mg; 1.01 mmol) was added to the previous solution, upon which the green solution turned light blue. A solution of NaOH (5%) was added dropwise, to adjust the pH of the Ni(II)-Hpic-ser system to approximately 5.7, thus observing the precipitation of a light blue solid. The mixture was stirred for 30 min. The solid was filtered off, washed with cold water (3 portions of 2 mL each), acetone (5 mL) and diethyl ether (5 mL), and dried on air. Characterization was performed on this solid. The mother liquor was reserved on a Petri dish, to allow for the slow crystallization of the compound. After a few days, dark blue rectangular crystals were obtained. Yield of the solid: 122.5 mg, 43%. Anal. Calc. for $C_9H_{10}N_2NiO_5{\cdot}C_2H_4O_2{\cdot}2H_2O$: C, 34.68; H, 4.76; N, 7.35. Found: C, 33.68; H, 4.62; N, 7.46. ^{1}H NMR (300.2 MHz, D_2O, 25 °C): δ [ppm] = 54.48 (br), 46.01 (br), 41.98 (br), 34.35 (br), 20.33 (br), 15.99 (br), 2.53 (br, acetic acid solvate). IR (KBr disk, ν in cm^{-1}): 3166 *br*, 1701 *m*, 1636 *s*, 1597 *s*, 1570 *s*, 1481 *m*, 1447 *m*, 1378 *s*, 1300 *m*, 1247 *m*, 1052 *m*, 1026 *m*, 862 *w*, 767 *s*, 705 *s*, 647 *m*, 451 *m*. UV–Vis (DMSO, λ_{max} in nm): 619, ε = 5.95 L mol^{-1} cm^{-1}.

2.4.2. System Ni(II)-Hpic-phe

Nickel chloride (237.4 mg; 1.00 mmol) and phenylalanine (165.0 mg; 1.00 mmol) were added to water (5 mL). To allow for the complete dissolution of the amino acid, NaOH was added (80.0 mg; 2.00 mmol). The solution was magnetically stirred for 30 min. Picolinic acid (123.0 mg; 1.00 mmol) was added to the Ni (II)-phe mixture, upon which the green solution turned light blue. A solution of NaOH (5%) was added dropwise, to adjust the pH of the Ni(II)-Hpic-ser system to approximately 6.2, thus observing the precipitation of a light blue solid. The mixture was stirred for 30 min. The solid was filtered off, washed with cold water (3 portions of 2 mL each) acetone (5 mL) and diethyl ether (5 mL), and dried on air. Characterization was performed on this solid. The mother liquor was reserved on a Petri dish, to allow for the slow crystallization of the compound. After a few days, dark blue rectangular crystals were obtained. Yield of the solid: 291.3 mg, 84%. Anal. Calc. for $C_{15}H_{14}N_2NiO_4{\cdot}C_3H_6O{\cdot}2H_2O$: C, 49.24; H, 5.51; N, 6.38. Found: C, 51.05; H, 5.42; N, 6.49. ^{1}H NMR (300.2 MHz, DMSO d_6, 25 °C): δ [ppm] = 54.23 (br), 51.51 (br), 44.19 (br), 15.48 (br), 6.94 (br). IR (KBr disk, ν in cm^{-1}): 3355 *br*, 3087 *m*, 3064 *m*, 3029 *m*, 2929 *m*, 1592 *s*, 1497 *m*, 1453 *m*, 1406 *s*, 1349 *m*, 1102 *m*, 1067 *m*, 752 *m*, 728 *m*, 698 *s*, 656 *m*, 601 *m*, 576 *m*, 547 *m*. UV–Vis (DMSO, λ_{max} in nm): 617.

2.5. Computational details

All structures were optimized using DMol^3 [23,24]. This DFT based program allows for the determination of the relative stability of all studied species based on their electronic structure. The calculations were performed using the Kohn–Sham Hamiltonian with the PBE gradient correction [25] and the double-zeta plus (DNP) numerical basic set [23,24,26]. The All Electron core treatment was used for all the atoms. Frequency calculations of all structures showed that the values were positive indicating that all structures are real minima. The presence of chemical bonds, has been analyzed using the quantum theory of atoms in molecules (QTAIM) [27] and the AIM-UC code [28]. The solvent was considered explicitly by the addition of molecules of water and DMSO to the complexes. The Lewis acid and basic sites could be identified, and their strength quantified, by means of the electrostatic potential (V(r)). Mapping V(r) values onto colors over an isosurface of the electron density (0.001 a.u.), allowed for the identification of the acid sites (zones were the nuclear contribution dominates) and the basic sites (zones were the electronic contribution dominates) [29,30].

3. Results and discussion

3.1. Speciation studies for the studied ligands and the ternary systems Ni(II)-HPic-L (L = serine, threonine, methionine, phenylalanine)

The ionization constants of the studied ligands were determined potentiometrically. Fig. 1 shows, as an example, the Z_C *vs* pH data of the H^+ - ser system and the protonation constants (Table 1) in 1.0 mol.dm^{-3} NaCl ionic medium. These results are in good agreement with the literature values, considering the differences in ionic strength and ionic medium [12,13]. In Fig. 2, the species distribution diagram for this system is shown. The Z_C *vs* pH graphics and speciation diagrams for the other ligands studied are provided as Supporting information.

The protonation constants of the ligand were studied using the same experimental conditions set for the ternary systems. In Fig. 1, the Z_C(pH) data is given for the H^+-Hser system. A good agreement between the experimental data (points) and the theoretical curve (the line) can be observed. The species distribution diagram given

Table 1
Values of $\log_{10}\beta_{pr}$ and pK_i for the ligands studied (25 °C, I = 1.0 mol.dm^{-3} NaCl ionic medium).

Equilibrium	pic	ser	$\log_{10}\beta_{pr}$ thr	met	phe
$L^- + H^+ \rightleftharpoons HL$	5.22 (1)	8.952(9)	8.81(2)	9.04(1)	8.95(2)
	5.32[a]	9.04[a]	8.91[a]	9.12[a]	9.21[a]
$L^- + 2H^+ \rightleftharpoons H_2L^+$	6.83(2)	11.16(2)	10.97(2)	11.19(2)	11.23(4)
	6.22[a]	11.17[a]	11.06[a]	11.34[a]	11.13[a]
Dispersion (σ)	0.015	0.014	0.017	0.018	0.032
pKa_1	1.69	2.21	2.16	2.15	2.31
pKa_2	5.34	8.952	8.81	9.04	8.95

Values in parentheses are standard deviations [$3\sigma(\log_{10}\beta)$] on the last significant figure.
[a] Reported values of $\log_{10}\beta_{pr}$ can be found in Ref. [13] and were studied under the following conditions: pic: $NaNO_3$ 1.0 mol.dm^{-3}, 20 °C; ser, thr and met: KCl 0.2 mol.dm^{-3}, 25 °C; phe: $NaClO_4$ 0.2 mol.dm^{-3}, 25 °C.

Table 2
Equilibrium constants ($\log_{10}\beta_{pqrs}$) for the Nickel(II) – pic^- – L^- systems (L = ser, thr, met, phe; 25 °C, I = 1.0 mol.dm^{-3} NaCl ionic medium).

Equilibrium	$\log_{10}\beta_{pr}$			
	ser	thr	met	phe
$Ni^{2+} + pic^- + L^- \rightleftharpoons Ni(pic)(L)$	15.94(5)	15.50(3)	15.37(4)	15.11(8)
$Ni^{2+} + pic^- + L^- + H_2O \rightleftharpoons [Ni(pic)(L)(OH)]^- + H^+$	8.5(1)	–	7.5(1)	7.2(1)
$Ni^{2+} + pic^- + 2L^- \rightleftharpoons [Ni(pic)(L)_2]^-$	20.8(2)	20.68(6)	19.9(2)	18.7(4)
Dispersion	0.073	0.035	0.061	0.090

Values in parentheses are standard deviations [$3\sigma(\log_{10}\beta_{pqrs})$] on the last significant figure.

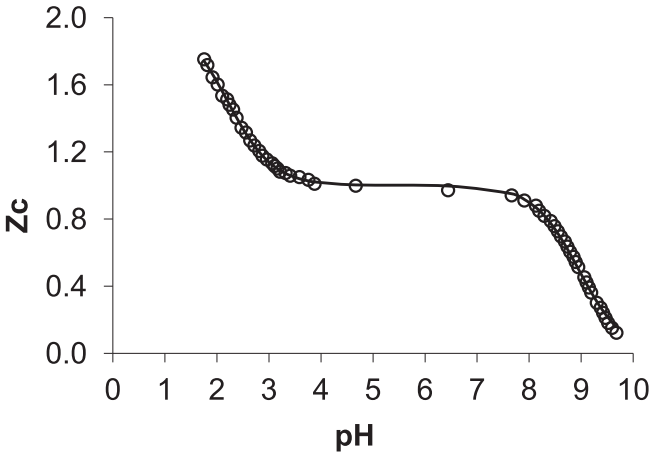


Fig. 1. Z_C, average number of mole of H^+ associate per mole of Serine *vs.* pH, in 1.0 mol.dm^{-3} NaCl at 25 °C. The line represents the theoretical curve calculated with the equilibrium constants of Table 1.

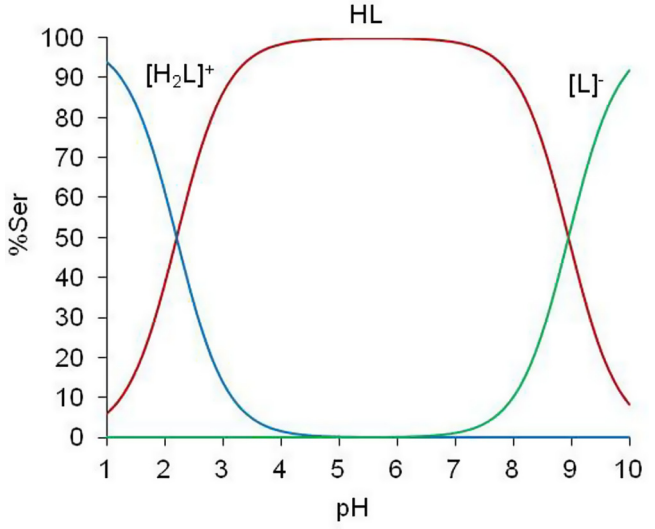


Fig. 2. Species distribution diagram as a function of pH for the Serine system in 1.0 mol.dm^{-3} NaCl at 25 °C considering the conditions Serine = 2 mmol.dm^{-3}.

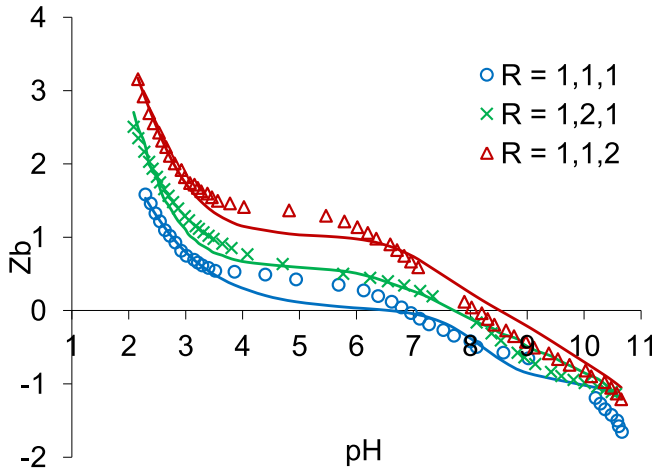


Fig. 3. Z_B, average number of mole of H^+ associate per mole of Nickel(II) *vs.* pH of the Nickel(II) – Hpic – Hser system, in 1.0 mol.dm^{-3} NaCl at 25 °C. The lines represent theoretical curves calculated with the equilibrium constants of Table 2.

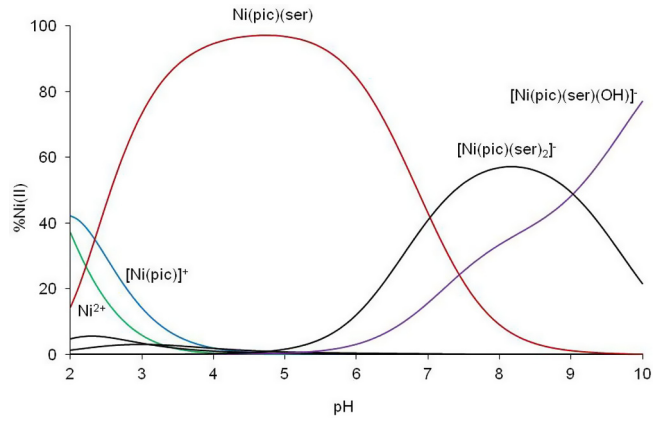


Fig. 4. Species distribution diagram as a function of pH for the Nickel(II) – Hpic – Hser system in 1.0 mol.dm^{-3} NaCl at 25 °C considering the conditions M_T = 2 mmol.dm^{-3} and molar ratio R = 1:1:2.

in Fig. 2 shows that the anionic (L^-) form of this amino acid predominates at pH > 9, the zwitterionic form (HL) is very important in the range 2.2 < pH < 8.95 and the protonated form of the serine (H_2L^+) is the major species formed at pH > 2.2.

The formation of the ternary Nickel (II) complexes was also studied. Fig. 3 shows the Z_B(pH) data, which is given as an example of the ternary complexes studied in this work. In this case, the Ni (II) – Hpic – Hser system is presented, and in Fig. 4 the species distribution diagram is shown. For this system the conditions are: M_T = 2 mmol.dm^{-3} and molar ratio R = 1:1:2, considering the stability constants summarized in Table 2. The data for the other ternary systems (Z_B(pH) and speciation diagrams for the other molar ratios) studied are provided as Supporting information.

As an example of the ternary systems, the potentiometric data analysis for the Nickel(II)-Hpic-Hser system performed with the program LETAGROP [18,19] is given. The analysis indicates the formation of the mononuclear complexes Ni(pic)(ser), [Ni(pic)(ser)(OH)]$^-$ and [Ni(pic)$(ser)_2$]$^-$. The same speciation was obtained for the Nickel(II)-Hpic-Hmet and Nickel(II)-Hpic-Hphe systems. In the case of the Nickel(II)-Hpic-Hthr only two complexes Ni(pic)(thr) and [Ni(Pic)$(thr)_2$]$^-$ were considered. The behavior observed for the Ni(II)-Hpic-Hthr system was mainly due to the fact that at pH > 8 the nickel species precipitates. The species distribution

diagram for the system Nickel(II) – Hpic – Hser at a molar ratio of 1:1:2, is given in Fig. 4. It can be observed that in the range 2.5 < pH < 7 the most important species is the ternary complex Ni(pic)(ser), while between 7 < pH < 9 the major species is the complex $[Ni(pic)(ser)_2]^-$ and at pH > 9 the species $[Ni(pic)(ser)(OH)]^-$ predominates.

The relative stability of the ternary complexes, in comparison with the binary ones, can be obtained from the Δ log K″ value, where Δ log K″ is calculated considering the reactions:

$$[Ni(pic)]^+ + [Ni(ser)]^+ \rightleftharpoons [Ni(pic)(ser)] + Ni^{2+}, \Delta \log K'' = +0.76$$

$$[Ni(pic)]^+ + [Ni(thr)]^+ \rightleftharpoons [Ni(pic)(thr)] + Ni^{2+}, \Delta \log K'' = +0.18$$

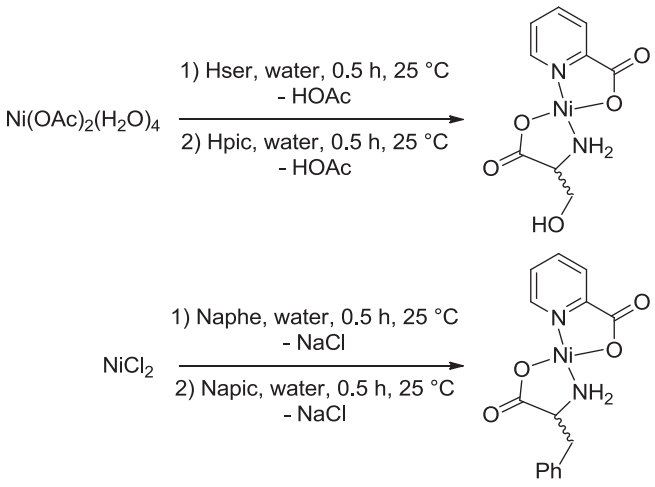
$$[Ni(pic)]^+ + [Ni(met)]^+ \rightleftharpoons [Ni(pic)(met)] + Ni^{2+}, \Delta \log K'' = +0.74$$

$$[Ni(pic)]^+ + [Ni(phe)]^+ \rightleftharpoons [Ni(pic)(phe)] + Ni^{2+}, \Delta \log K'' = -0.39$$

which means that the ternary complexes formed with the amino acids ser, thr and met are more stable than their binary analogues, while in the case of the ternary complex formed with phe, the species formed is less stable than the binary complexes [31]. These studies do not provide information on the coordination modes of the amino acids or the picolinate on the studied systems, although from the stability constants it might be proposed that these are bonded in a chelating fashion. Previous reports on the coordination mode of picolinic acid support this proposal, given the fact this ligand usually coordinates as an N,O-chelate [3,5,32], although other coordination modes have been identified [32].

3.2. Isolation of the ternary complexes Ni(pic)(L) (L = ser, phe)

The wide pH range in which the ternary complex Ni(pic)(ser) is the major species in solution (2.5 < pH < 7, 94% of total nickel) suggests that, under the appropriate conditions, attempts of isolation of this species could be performed. A similar situation was observed for the Ni(II)-pic-phe system (at pH = 6.2 87% of total nickel was the ternary species) and, thus, these were the complexes of choice to study their synthesis and isolation in the solid state. The Ni(pic)(L) complexes were prepared from Nickel(II) acetate or Nickel(II) chloride in two consecutive steps as depicted in Scheme 1. In the first step, one equivalent of the corresponding amino acid is added and the picolinic acid is incorporated afterwards. With this protocol, light blue solids were obtained in moderate yields.



Scheme 1. Synthesis of Ni(pic)(ser) (top) and Ni(pic)(phe) (bottom). Stereochemistry is omitted for clarity purposes.

The solubility of the isolated light blue solids was studied in water (Ni(pic)(ser) slightly soluble, Ni(pic)(phe) sparingly soluble), dimethylformamide (both solids are insoluble) and dimethyl sulfoxide (Ni(pic)(ser) and Ni(pic)(phe) slightly soluble). These compounds are insoluble in most of the other common organic solvents. The poor solubility of the complexes made their characterization in solution quite difficult. Since DMSO gave the best solubility for both compounds, the UV–vis and NMR studies were performed in this solvent.

The UV–Vis absorption spectra of Ni(pic)(phe) in DMSO shows a maximum at 617 nm in the visible range of the spectrum (see Supporting information). For the Ni(pic)(ser) compound in DMSO a maximum at 619 nm was observed (see Supporting information). For this compound the molar attenuation coefficient, ε = 5.95 L mol^{-1} cm^{-1}, was measured according to the Beer-Lambert Law (see Supporting information). The magnitude of ε is consistent with a *d-d* transition in a relatively centro-symmetric compound. Unfortunately, for the complex Ni(pic)(phe) ε could not be reliably measured due to its poor solubility in common solvents. The maximum of absorption in the visible range (orange) is in agreement with the observed color (light blue) of the isolated compounds.

The ^1H NMR spectrum of Ni(pic)(ser) in a "classical" spectral width (SW = 16 to −4) returned only the solvent residual resonance (D_2O) and a broad signal at 2.53 ppm. The spectrum was recorded again in a wider window (SW = 200 to −200, see Supporting information) and changing the relaxation delay (d1). The best spectrum (better signal/noise ratio and resolution) was obtained with a relatively short d1 (0.500 s vs. default d1 = 1.000 s). A new set of six broadened resonances were observed in the range of 55 to 14 ppm. As expected, $^{13}C\{^1H\}$ resonances were not properly resolved. This behavior in solution indicates that the complex Ni(pic)(ser) has an important paramagnetic character. For Ni(pic)(phe) the ^1H NMR spectrum in DMSO d_6 features a set of five broadened resonances between 55 and 6 ppm. The experimental conditions were the same than those for Ni(pic)(ser) (SW = 400 ppm, O1P = 0 ppm, d1 = 0.500 s). For comparison, the binary complexes $Ni(pic)_2$, $Ni(ser)_2$ and $Ni(phe)_2$ were intentionally prepared based on reported protocols [33] and their ^1H NMR spectra in DMSO d_6 were recorded (see Supporting information). The species $Ni(pic)_2$, exhibits four broad signals, while the NiL_2 (L = ser, phe) systems only show two resonances. Details about the spectra as well as their qualitative comparison can be found in the Supporting information.

Thermogravimetric analysis of the Ni(pic)(L) (L = ser, phe) complexes were performed (plots of TGA can be consulted in the Supporting information). The assignment of the different decomposition steps is given in Table 3.

Ni(pic)(ser) was thermally decomposed in four successive decomposition steps within the studied temperature range (25–500 °C). The first decomposition step corresponds to an estimated mass loss of 9.72% (37.03 uma) within the temperature range 77–115 °C and might be attributed to the liberation of the two water molecules (hydrate). The second decomposition steps takes place within the temperature range 122–322 °C with an estimated mass loss of 11.29% (43.02 uma), which can be accounted for the removal of one CO_2. The picolinate ligand (pic) and the acetic acid solvate were removed in the third step within the temperature range 388–442 °C (mass loss of 48.31%. 184.05 uma). The remaining residue consists of decarboxylated serine (1,2-ethanolamine) bonded to Ni(II) as XX ligand (residue of 30.68%, 116.86 uma). The compound Ni(pic)(phe) decomposes in two consecutive steps within the measured temperature range (25–500 °C). The first decomposition occurs within 115–141 °C, with a mass loss of 7.99% (35.09 uma), possible due to the release of two water molecules. During the next step, in the range 308–405 °C, the concomitant elimination of the acetone solvate with the ligands (mass loss

Table 3
Thermal analytical data for the ternary complexes Ni(pic)(L) (L = ser, phe).

Molec. Formula	Decomp. Temp. (°C)	Mass Loss (%)	Molec. Mass Found	Eliminated Species	Solid Residue (%)
Ni(pic)(ser)·$C_2H_4O_2$·$2H_2O$	77–115	9.72	37.03	2 H_2O	
$C_{11}H_{18}N_2NiO_9$	122–322	11.29	43.02	CO_2	
M. W. 380.96 g/mol	338–442	48.31	184.05	$C_8H_9NO_4$	
	450–500	30.68	116.86		C_2H_5NNiO (30.68)
Ni(pic)(phe)·C_3H_6O·$2H_2O$	115–141	7.99	35.09	2 H_2O	
$C_{18}H_{24}N_2NiO_7$	308–405	75.16	330.02	$C_{18}H_{22}N_2O_4$	
M. W. 439.09 g/mol	420–500	16.85	73.98		NiO (16.85)

of 75.16%, 330.02 uma) takes place, leaving only NiO as the residue (residue of 16.85%, 73.98 uma).

Finally, the pale blue solid isolated from the synthesis of the compound Ni(pic)(phe) was finely grounded and subjected to XRD analysis. Also, the binary complexes $Ni(pic)_2$ and $Ni(phe)_2$ were studied by this technique. The qualitative comparison of the diffractograms (see Supporting information) further proves the isolation of the ternary complexes under the specified reaction conditions.

3.3. Theoretical studies

Due to the difficulties of crystallizing the Ni(pic)(phe) ternary complex, theoretical calculations were performed in order to propose its possible structure, including the constitution in water and DMSO. These types of studies have been previously performed by other authors to assess on the stabilities and geometries of ternary Ni(II) complexes [3,34].

In this case, several conformations were considered, but only the most stable ones will be displayed below. In Fig. 5, the most stable conformation for the Ni(pic)(phe) complex in water is presented. In addition to the intrinsic bonds of the complex, interactions between this compound and the solvent water molecules are also presented. These interactions are corroborated by the topological analysis of the electron density (QTAIM). Results and theoretical support of this methodology, as well as the EDD technique, are presented in the Supporting information. In this figure the square pyramidal conformation around the Ni atom can be seen. In the base of the pyramid, two O and two N atoms from the picolinic acid and the phenylalanine are coordinated forming a square base with the Ni, and in the upper vortex a water molecule completes the pyramidal conformation. In a previous work from Sankaralingam et al. [3] a distorted octahedral coordination geometry which could be in equilibrium with a square pyramidal conformation was proposed for a Ni (II) complex. Starting from the square pyramidal conformation, 12 water molecules were added. This procedure was done to complete the octahedral conformation with another water molecule, which could be located in an antisymmetric position to the other water ligand in the upper vortex of the pyramid. Despite several calculations changing the number and conformation of the water molecules, this octahedral geometry could not be reached.

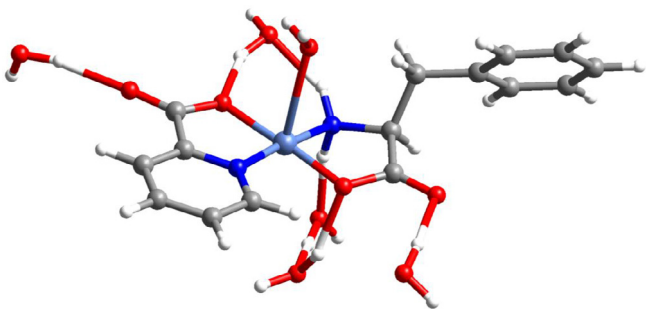


Fig. 5. Most stable conformation for the penta-coordinated mode of the Ni atom in the Ni(pic)(phe) complex. Light blue, dark blue, red, gray and white spheres represent the Ni, N, O, C and H atoms, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In Fig. 6, the mapping of the electrostatic potential over an isosurface of electronic density for the dehydrated complex, is presented. The geometry of Fig. 5 was kept in order to localize the most acid and basic zones surrounding the complex. A color scale which increases in acidity from red (most basic zones), following green and yellow, to reach blue (most acid zones) was established. This figure has two images, which correspond to both faces, above and below, of the Ni (II) square planar geometry. It can be clearly observed that the most acidic zone is located over the hydrogen atom bonded to the phenylalanine nitrogen atom. On the other face the proton acidity of the ligand is still stronger than that of the Ni atom. This explains why this hydrogen atom is the preferred site of interaction with an oxygen atom of an additional water molecule, instead of the less acid Ni atom. In this sense, a water molecule reacts first with this proton, thus making the Ni atom accessible for a second water molecule.

It has been shown that Ni(II) species have a strong preference to form distorted octahedral complexes [3,9]. Also, the relative stability between octahedral and square pyramidal conformations has been studied [3]. In this sense, to investigate on the possibility of stabilizing an octahedral Ni(II) complex, preliminary calculations were performed for the Ni(II) system with picolinic acid and alanine as model amino acid. This resulted in an octahedral coordination for the ternary complex. In this conformation the picolinic acid and the amino acid are not in the same plane, as they are in the square planar conformation. For the octahedral conformation, the oxygen atom from the picolinic acid ligand is twisted in 90 degrees (thus coordinating in an axial position), and two water molecules complete the coordination sphere. In Fig. 7, the analogous optimized geometry for this type of coordination for the Ni(pic)(phe) complex is presented, showing the six bonds of the Ni atom with the picolinic acid ligand, the phenylalanine and two water molecules. The topological analysis of the electron density was also applied to this complex, in order to corroborate the existence of these interactions. Results are displayed in Fig. S34 (Supporting information). Even when this conformation can be adopted by the complex Ni(pic)(phe), it is less stable than the pentacoordinated one by 21 kcal/mol due to the internal stress induced by the presence of the phenyl ring. For the calculations of the energy differences, water molecules were only considered if they were interacting with the Ni atom, taking care of always keeping the mass balance. In the case of structures presented in Figs. 5 and 7, six water molecules were considered for the optimization of the tetrahedral structure and only two water molecules were considered for the octahedral type (the energy of 4 water molecules was added). For the formation of the square pyramidal conformation at least 6 water molecules were needed, because the acidity of

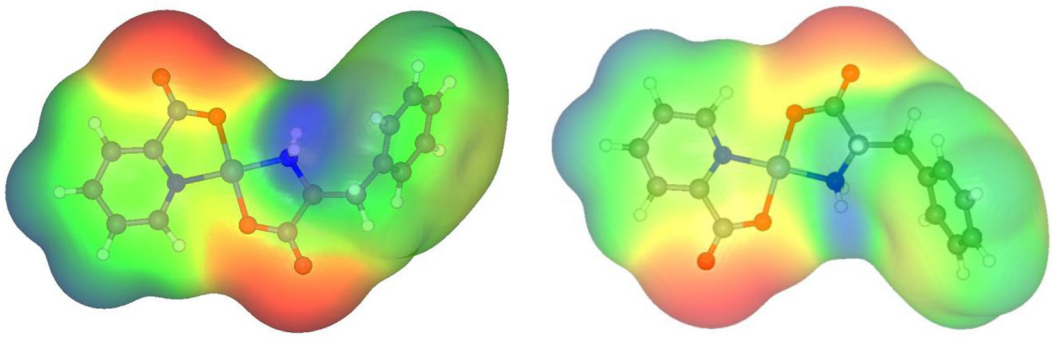


Fig. 6. Electrostatic potential mapping over an isosurface of electron density for the dehydrated penta-coordinated mode presented in Fig. 5. Light blue, dark blue, red, gray and white spheres represent the Ni, N, O, C and H atoms, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

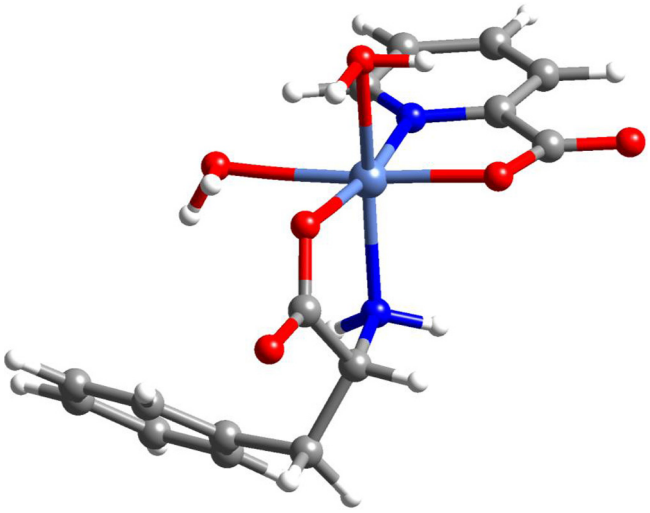


Fig. 7. Most stable conformation for the *hexa*-coordinated mode of the Ni atom in the Ni(pic)(phe) complex. Light blue, dark blue, red, gray and white spheres represent the Ni, N, O, C and H atoms, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

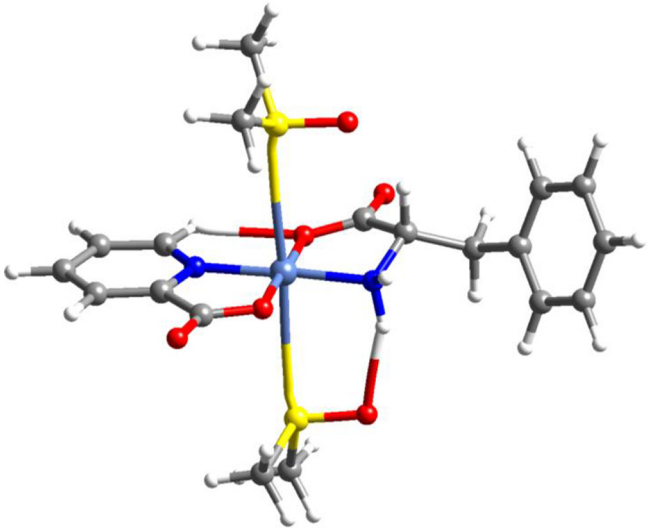


Fig. 8. Octahedral coordination for the Ni(pic)(phe) complex when the solvent is DMSO. Light blue, dark blue, red, yellow, gray and white spheres represent the Ni, N, O, S, C and H atoms, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the Ni atom is not sufficiently attractive for the first five water molecules.

The relative stability of the binary and ternary complexes was also investigated by means of computational calculations. In the gas phase, the binary species $Ni(phe)_2$ is the most stable compared to the other two compounds Ni(pic)(phe) and $Ni(pic)_2$. The ternary complex Ni(pic)(phe) is only 2.5 kcal/mol less stable than $Ni(phe)_2$. However, this value is very close to the experimental error and, then, almost non significant. The binary compound $Ni(pic)_2$ is 27 kcal/mol less stable than $Ni(phe)_2$. In solution, the potentiometric data analysis for this particular system (amino acid phenylalanine) indicates that the ternary species is less stable than the binary complexes. Further theoretical studies on the ternary system Ni (II)-picolinic acid-amino acid will be discussed in future reports.

In DMSO, the octahedral conformation is also possible. In Fig. 8, this geometrical arrangement is displayed. O atoms of both solvent molecules, are pointing towards the most acid zones of the complex, allowing the S atoms to be located over the Ni atom. The topological analysis of the electron density was also applied to this complex, in order to corroborate the presence of these interactions. Results are displayed in Fig. S35 of the Supporting information.

4. Conclusions

The analysis of the potentiometric data by means of the computational least-squares program LETAGROP, indicates that in the Nickel(II)-Hpic-Hser, Nickel(II)-Hpic-Hmet and Nickel(II)-Hpic-Hphe systems the complexes Ni(pic)(L), $[Ni(pic)(L)(OH)]^-$ and $[Ni(pic)(L)_2]^-$ are formed. In the Nickel (II)-Hpic-Hthr system, only the complexes Ni(pic)(L) and $[Ni(pic)(L)_2]^-$ were identified. The analysis of the ternary complexes stability compared to the binary ones using the Δ log K″ value indicates that the ternary complex formed with the amino acids ser, thr and met are more stable. In the case of the ternary complex with phe, it is less stable than the binary complexes. The synthesis of two of the Ni(pic)(L) (L = ser, phe) complexes was achieved and both elemental analysis and TGA show that the solids are obtained as hydrates. Crystallization of these solids was attempted, revealing differences in stability which seem to favor the binary picolinate complex rather than the ternary species. Theoretical calculations indicate that it is possible to obtain two conformations for the Ni(pic)(phe) ternary complex in water, the most stable one which is pentacoordinated, and the octahedral one. In DMSO it is also possible to obtain an octahedral arrangement.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ica.2017.11.017.

References

[1] A.A. Soliman, A.A. El-Sherif, M.A. Amin, J. Solut. Chem. 44 (2015) 77–99.
[2] C. Jubert, A. Mohamadou, C. Gérard, S. Brandes, A. Tabard, J.-P. Barbier, Inorg. Chem. Commun. 6 (2003) 900–907.
[3] M. Sankaralingam, P. Vadivelu, E. Suresh, M. Palaniandavar, Inorg. Chim. Acta 407 (2013) 98–107.
[4] M. Melchior, K.H. Thompson, J.M. Jong, S.J. Rettig, E. Shuter, V.G. Yuen, Y. Zhou, J.H. McNeill, C. Orvig, Inorg. Chem. 38 (1999) 2288–2293.
[5] N. Yasumatsu, Y. Yoshikawa, Y. Adachi, H. Sakurai, Bioorg. Med. Chem. 15 (2007) 4917–4922.
[6] K. Fukui, Y. Fujisawa, H. Ohya-Nishiguchi, H. Kamada, H. Sakurai, J. Inorg. Biochem. 77 (1999) 215–224.
[7] a) E.P. Broering, P.T. Truong, E.M. Gale, T.C. Harrop, Biochemistry 52 (2013) 4–18;
b) D.P. Barondeau, C.J. Kassmann, C.K. Bruns, J.A. Tainer, E.D. Getzoff, Biochemistry 43 (2004) 8038–8047;
c) J.L. Wuerges, Y.-I. Yim, H.-S. Yim, S.-O. Kang, K.D. Carugo, Proc. Natl. Acad. Sci. U.S.A. 101 (2004) 8569–8574.
[8] S.K. Chatterjee, R.C. Maji, S.K. Barman, M.M. Olmstead, A.K. Patra, Angew. Chem. Int. Ed. 53 (2014) 10184–10189.
[9] D. Árus, Á. Dancs, N.V. Nagy, T. Gajda, Dalton Trans. 42 (2013) 12031–12040.
[10] D.P. Martínez, M.L. Araujo, F. Brito, A. Pérez, L. Hernández, V. Lubes, J. Mol. Liq. 220 (2016) 681–686.
[11] D. Gallardo, K. Puche, A. Pérez, E. Del Carpio, L. Hernández, V. Lubes, J. Mol. Liq. 230 (2017) 370–373.
[12] A.E. Martell, M. Smith, R.J. Motekaitis, NIST Critical Stability Constants of Metal Complexes Database, US Department of Commerce, Gaithersburg, MD, 1993.
[13] K.J. Powell, L.D. Pettit, IUPAC Stability Constants Database, Academic Software, Otley (U.K.), 1997.
[14] I.M. Kolthoff, V.A. Stenger, Volumetric Analysis, vol. II, Interscience Publishers, New York, 1947, p. 94.
[15] G. Gran, Analyst 77 (1952) 661–671.
[16] R.K. Harris, E.D. Becker, S.M.C. de Menezes, R. Goodfellow, P. Granger, Solid State Nucl. Magn. Reson. 22 (2002) 458–483. Pure App. Chem. 73 (2001) 1795–1818.
[17] G. Biedermann, L.G. Sillén, Ark. Kemi. 5 (1952) 425–540.
[18] F. Brito, M.L. Araujo, V. Lubes, A. D'Ascoli, A. Mederos, P. Gili, S. Domínguez, E. Chinea, R. Hernández-Molina, M.T. Armas, E.J. Baran, J. Coord. Chem. 58 (2005) 501–512.
[19] L.G. Sillén, B. Warnqvist, Ark. Kemi. 31 (1969) 315–339.
[20] L. Veliz, J.D. Martínez, M.L. Araujo, F. Brito, G. Lubes, M. Rodríguez, V. Lubes, Av. Quím. 6 (2011) 3–11.
[21] D. Gallardo, Estudio de la formación de complejos ternarios de níquel (II) con ácido dipicolínico y los aminoácidos ser, thr, met y phe Undergraduate Degree Project, Coordinación de Lic. Química, Universidad Simón Bolívar, Venezuela, 2014.
[22] L. Alderighi, P. Gans, A. Ienco, D. Peters, A. Sabatini, A. Vacca, Coord. Chem. Rev. 184 (1999) 311–318.
[23] DMol^3 is available as part of Material Studio San Diego, USA, 2010.
[24] B. Delley, J. Chem. Phys. 92 (1990) 508–517.
[25] J.P. Perdew, K. Burke, M. Ernzerhof, Phys. Rev. Lett. 77 (1996) 3865–3868.
[26] B. Delley, J. Chem. Phys. 113 (2000) 7756–7764.
[27] R.F.W. Bader, Atoms in Molecules—a Quantum Theory, Clarendon Press, Oxford, 1990.
[28] D. Vega, D. Almeida, J. Comput. Methods Sci. Eng. 14 (2014) 131–136.
[29] P. Sjoberg, P. Politzer, J. Phys. Chem. 94 (1990) 3959–3961.
[30] D.S. Coll, A. Vidal, J. Rodríguez, E. Ocando, R. Añez, A. Sierraalta, Inorg. Chim. Acta 436 (2015) 163–168.
[31] M.M. Khalil, A.E. Attia, J. Chem. Eng. Data 44 (1999) 180–184.
[32] K. Ma, Q. Shi, M. Hu, X. Cai, S. Huang, Inorg. Chim. Acta 362 (2009) 4926–4930.
[33] Ni(pic)$_2$: (a) O. Tamer, D. Avcı, Y. Atalay, J. Mol. Struct. 1098 (2015) 12–20;
. Ni(ser)$_2$: (b)S. Mandal, G. Das, H. Askari, J. Mol. Struct. 1081 (2015) 281–292;
. Ni(phe)$_2$: (c)Md.E. Hossain, Md.M. Hasan, M.E. Halim, M.Q. Ehsan, M.A. Halim, Spectrochim. Acta, Part A 138 (2015) 499–508;
(d) S. Mandal, G. Das, H. Askari, J. Chem. Inf. Model. 54 (2014) 2524–2535.
[34] A.M. Rayan, M.M. Ahmed, M.H. Barakat, A.T. Abdelkarim, A.A. El-Sherif, J. Coord. Chem. 68 (2015) 678–703.