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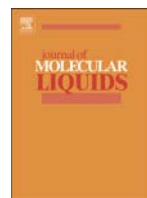**13** PUBLICATIONS **3** CITATIONS

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Solution equilibria and stabilities of binary and ternary Nickel(II) complexes with picolinic acid and small blood serum bioligands

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ABSTRACT

The binary and ternary complexes of Nickel(II) with picolinic acid (Hpic) as a primary ligand and the small blood serum bioligands lactic acid (Hlac), oxalic acid (H_2ox), citric acid (H_3cit) and phosphoric acid (H_3PO_4) as biologically relevant secondary ligands were studied. The acidity constants of the ligands selected were determined potentiometrically and used for determining the stability constants of the complexes formed in aqueous solution at 25 °C and using an ionic strength I = 1.0 mol dm^{-3} (NaCl). The analysis of the potentiometric data by means of the computational least-squares program LETAGROP indicates the Ni(II)–Hlac system in the formation of the complexes [NiL]$^+$ and [NiL(OH)$_2$]$^-$. The Ni(II)–H_3cit system indicates the formation of the species [NiL]$^-$, [Ni(HL)L]$^{3-}$ and [NiL$_2$]$^{4-}$. In the Ni(II)–H_3PO_4 system the complexes [NiH$_2$L]$^+$, NiHL and [NiL]$^-$ were detected. In the case of the ternary systems we observed in the Nickel(II)–Hpic–Hlac system the formation of the complexes Ni(pic)(L), [Ni(pic)(L)(OH)]$^-$ and [Ni(pic)(L)(OH)$_2$]$^{2-}$. In the Nickel(II)–Hpic–H_2ox system the species [Ni(pic)(L)]$^-$, [Ni(pic)(L)(OH)]$^{2-}$ and [Ni(pic)$_2$(L)]$^{2-}$ were observed. In the Nickel(II)–Hpic–H_3cit system the complexes [Ni(pic)(HL)]$^-$, [Ni(pic)(L)]$^{2-}$ and [Ni(pic)(L)(OH)]$^{3-}$ were detected. Finally, in the Nickel(II)–Hpic–H_3PO_4 system the complexes Ni(pic)(H$_2$L), [Ni(pic)(HL)]$^-$ and [Ni(pic)(L)]$^{2-}$ were observed. Species distribution diagrams as a function of pH were briefly discussed.

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1. Introduction

The importance of pyridinecarboxylic acid systems from their presence in many natural products such as alkaloids, vitamins, and coenzymes is discussed. These compounds are of particular interest to medicinal chemists because of their wide variety of physiological properties displayed by natural and synthetic acids. Moreover, many of the pyridinecarboxylates are versatile ligands and their complexes with some metal ions have found use in medicine and in quantitative analysis. Pyridinecarboxylic acid metal complexes are, therefore, especially interesting model systems [1].

Ni(II) performs biological role through hydrogen oxidation. It seems that nickel undergoes changes in oxidation state indicating that the nickel core is the active part of the enzyme called hydrogenase [2], which is also present in methyl CoA reductase enzyme and other charged nucleic acid repair [3,4].

The effect of metallopicolinate complexes with the first transition metals was examined and the effect of complexes that are more active than an insulin-mimetic leading compound such as oxovanadium(IV)–picolinate complex and VO(pa)$_2$ was developed.

Different metallopicolinate complexes were prepared, and their in vitro insulinomimetic and in vivo antidiabetic activities were evaluated [5].

The idea is that after oral administration of these complexes, they may encounter many other potential Ni(II) binding molecules present in extracellular or intracellular biological fluids. These latter ligands may partially or completely displace the original Nickel(II) carrier molecules from the coordination sphere of the metal. Accordingly, ternary complex formation should be taken into account in a speciation description of these complexes in biological fluids. Such ternary complexes might be of great importance in the absorption and transport processes of the Nickel(II) complexes and even in their physiological activity [6].

In this work we report the results on mixed ligand complex formation in the Ni(II)–picolinic acid–ligand B systems, where ligand B was the most important low molecular mass (l.m.m.) component. Ni(II) binders present in blood serum include: lactic acid (Hlac), oxalic acid (H$_2$ox), phosphoric acid (H$_3PO_4$) and citric acid (H$_3$cit). The study of the binary Ni(II) complexes formed with ligand B was included in this work. The pH-potentiometry technique was used to determine the stoichiometries and stability constants of the complexes formed in aqueous solution.

Until now, there are no reports on the speciation of the ternary complexes of Nickel(II)–Hpic and the ligand B Hlac, H$_2$ox, H$_3PO_4$ and H$_3$cit [7,8].

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2. Experimental

2.1. Reagents

NiCl$_2$·6H$_2$O (Merck p.a.), picolinic acid (Hpic) (Merck p.a.), ligands Hlac, Na$_2$ox, Na$_3$PO$_4$ and Na$_3$cit (Merck p.a.), Na$_2$EDTA·2H$_2$O (Merck p.a.), and bromopyrogallol red (Merck p.a.) were used as indicators in order 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 an indicator, and the HCl solution was standardized with NaOH solution of known concentration [9]. The solutions were prepared using triply glass-distilled water, boiled before preparation of the solutions in order to remove dissolved CO$_2$. To prevent hydrolysis of the NiCl$_2$ stock solution, it contained 100 mmol dm^{-3} HCl. NiCl$_2$ is hygroscopic and must be weighed as fast as possible. For that reason it is necessary to standardize the NiCl$_2$ stock solution using a Na$_2$EDTA·2H$_2$O solution (0.01 mol dm^{-3}) in a buffer media (pH = 10) using bromopyrogallol red as an indicator [10]. The acidity of the NiCl$_2$ stock solution was determined by the Gran method [11]. Potentiometric measurements were carried out in aqueous solution using 1.0 mol dm^{-3} NaCl as ionic medium. Nitrogen free O$_2$ and CO$_2$ were used.

2.2. Methods

The potentiometric measurements were done using the following instruments: Thermo Orion model 520A pH meter, Metrohm EA 876-20 titration vessel, and 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 maintained at (25.0 ± 0.1) °C by constant circulation of water from the thermostat bath.

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 [12]. 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 ligand B under study were added and finally an aliquot of the Nickel(II) stock solution was added sequentially. And, 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 molar ratios R = 1, 2 and 4 for the Ni^{2+}–ligand B systems and for the Nickel(II):Hpic:ligand B molar ratios R = 1:1:1, 1:1:2 and 1:2:1.

The systems Ni^{2+}–ligand B (H$_i$L) were studied according to the reaction scheme:

$$pH_2O + qNi^{2+} + rH_iL \rightleftharpoons [Ni_q(OH)_p(H_iL)_r] + pH^+, \beta_{p,q,r}.$$

The systems Ni^{2+}–Hpic–ligand B (H$_i$L) were studied according to the reaction scheme:

$$pH_2O + qNi^{2+} + rHpic + sH_iL \rightleftharpoons [Ni_q(OH)_p(Hpic)_r(H_iL)_s] + pH^+, \beta_{p,q,r,s}$$
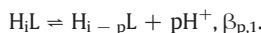
where H$_i$L represents the ligand B: Hlac, H$_2$ox, H$_3$PO$_4$ and H$_3$cit, $[Ni_q(OH)_p(Hpic)_r(H_iL)_s]$ is the ternary (p,q,r,s) complex (the charges were omitted for simplicity) and β_{pqrs} is the respective stability constant.

The potentiometric data were analyzed using the program LETAGROP [13,14], in order to minimize the function $Z_B = (h - H) / M_T$, where Z_B is

Table 1
Values of log β_{pr} and pK_i for the ligands studied (25 °C, I = 1.0 mol dm^{-3} NaCl ionic medium). Considering the general reaction:

$$H_iL \rightleftharpoons H_{i-p}L + pH^+, \beta_{p,1}.$$

Species	Hpic	H$_2$ox	Hlac	H$_3$cit	H$_3$PO$_4$
(p,1)	log β_{pr}	log β_{pr}	log β_{pr}	log β_{pr}	log β_{pr}
(1,1)	1.01(4)				
(−1,1)	−5.22(1)	−1.22(2)	−3.60(1)	−2.82(2)	−2.08(4)
(−2,1)		−4.75(2)		−6.96(3)	−8.39(3)
(−3,1)				−12.20(3)	−19.00(5)
Dispersion σ (Z)	0.014	0.016	0.013	0.016	0.035
pK_i					
H$_2$L$^+$–HL	1.01				
HL–L$^-$	5.22		3.60		
H$_3$L–H$_2$L				2.82	2.08
H$_2$L–HL		1.22		4.14	6.31
HL–L		3.53		5.24	10.61

Values in parentheses are standard deviations [3σ(log β)] on the last significant figure.

the average number of mole of H$^+$ dissociates per mole of metal, 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 was calculated at the ionic strength of 1.0 mol dm^{-3} NaCl to be 13.69 (±0.01). The equilibria corresponding to the formation of the hydroxo complexes of Nickel(II) were considered in the calculation of the stability constants of ternary complexes. The following species [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 $\beta_{4,-4} = -27.73(3)$ [15] were assumed. The binary Nickel(II)–Hpic [15] and the Nickel(II)–H$_2$ox systems [16] 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 fixed during the analysis. The aim was to find a complex or complexes giving the lowest sum of the errors squared, $U = \sum (Z_B^{exp} - Z_B^{calc})^2$, the fittings were done by testing different (p,q,r) and (p,q,r,s) combinations.

The species distribution diagrams were done with the computer program HYSS [17], yielding the β_{pqr} and β_{pqrs} values, which are summarized in Tables 2–3.

3. Results

3.1. Ionization constants of the studied ligands

The ionization constants (Table 1) in the ionic medium 1.0 mol dm^{-3} NaCl are in good agreement with the literature values, considering the differences in ionic strength and ionic medium [7,8].
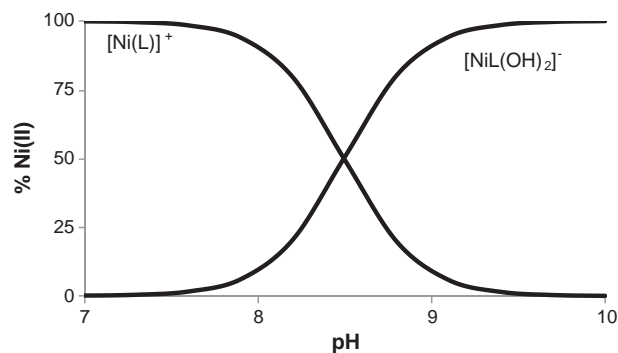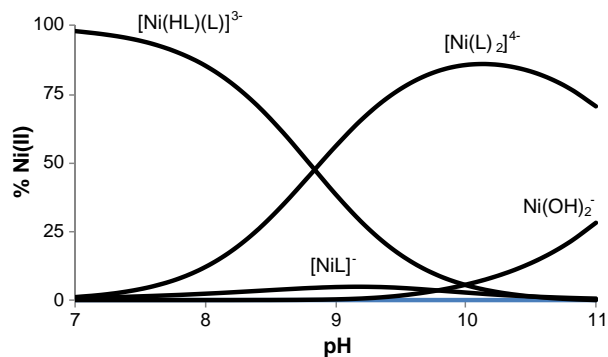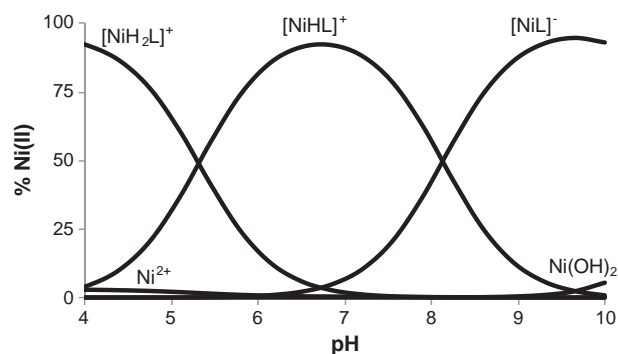

Fig. 1. Species distribution diagrams as a function of pH for the Nickel(II)–Hlac system in 1.0 mol dm^{-3} NaCl at 25 °C considering the conditions $M_T = 2$ mmol dm^{-3} and molar ratio R = 2.

Table 2
Equilibrium constants (log β_{pqr}) for the binary Nickel(II)–H_iL systems (25 °C, I = 1.0 mol dm^{-3} NaCl ionic medium). According to the following reaction scheme:

$$pH_2O + qNi^{2+} + rH_iL \rightleftharpoons [Ni_q(OH)_p(H_iL)_r] + pH^+, \beta_{p,q,r}.$$

Species	log β_{pqr}			
(p,q,r)	Hlac	H_2ox[a]	H_3cit	H_3PO_4
(−1,1,1)	5.31(5)	3.41(2)		2.1(1)
(−2,1,1)		0.96(2)		−3.21(7)
(−3,1,1)	−11.68(5)	−8.49(6)	−5.9(1)	−11.34(9)
(−4,1,2)		−0.78(1)		
(−5,1,2)			−4.22(6)	
(−6,1,2)			−13.06(6)	
Dispersion (σ)	0.117	0.033	0.053	0.078

Values in parentheses are standard deviations [3σ(log β_{pqr})] on the last significant figure.
[a] REF = 16.

3.2. Binary Nickel(II) complexes

3.2.1. Nickel(II)–Hlac system

In Fig. 1 the species distribution diagrams for this system are given for the following conditions: M_T = 2 mmol dm^{-3} and molar ratio R = 2, considering the stability constants summarized in Table 2.

3.2.2. Nickel(II)–H_3cit system

In Fig. 2 the species distribution diagrams are given for this system for the following conditions: M_T = 2 mmol dm^{-3} and molar ratio R = 2, considering the stability constants summarized in Table 2.

3.2.3. Nickel(II)–H_3PO_4 system

In Fig. 3 the species distribution diagrams for this system are shown for the following conditions: M_T = 2 mmol dm^{-3} and molar ratio R = 2, considering the stability constants summarized in Table 2.

3.3. Ternary Nickel(II) complexes

3.3.1. Nickel(II)–Hpic–Hlac system

In Fig. 4 the species distribution diagrams for this system are given for the following conditions: M_T = 2 mmol dm^{-3} and molar ratio R = 1:1:1, considering the stability constants summarized in Table 3.

3.3.2. Nickel(II)–Hpic–H_2ox system

In Fig. 5 the species distribution diagrams for this system are given for the following conditions: M_T = 2 mmol dm^{-3} and molar ratio R = 1:2:1, considering the stability constants summarized in Table 3.

3.3.3. Nickel(II)–Hpic–H_3cit system

In Fig. 6 the species distribution diagrams for this system are shown for the following conditions: M_T = 2 mmol dm^{-3} and molar ratio R = 1:1:1, considering the stability constants summarized in Table 3.

3.3.4. Nickel(II)–Hpic–H_3PO_4 system

In Fig. 7 the species distribution diagrams for this system are given for the following conditions: M_T = 2 mmol dm^{-3} and molar ratio R = 1:1:1, considering the stability constants summarized in Table 2.

In the Ni(II)–Hlac system the analysis made of the potentiometric data indicated the formation of the complexes $[NiL]^+$ and $[NiL(OH)_2]^-$. The species distribution diagrams are given in Fig. 1, and the complex $[NiL]^+$ predominates at pH values between 7 and 8.5, and the complex $[NiL(OH)_2]^-$ predominates at pH >8.5.

In the Ni(II)–H_3cit system the analysis indicates the formation of the species $[NiL]^-$, $[Ni(HL)L]^{3-}$ and $[NiL_2]^{4-}$. The species distribution diagrams (Fig. 2) show that the $[Ni(HL)L]^{3-}$ is abundant at pH <8.8, the complex $[NiL]^-$ is formed in low quantity, and the complex $[NiL_2]^{4-}$ predominates at pH >8.8.

In the Ni(II)–H_3PO_4 system, the formation of the complexes $[NiH_2L]^+$, NiHL and $[NiL]^-$ was observed. The species distribution diagrams are given in Fig. 3, and show that the $[NiH_2L]^+$ is abundant at pH <5, the acidic complex NiHL is present between pH 5 and 8 and the species $[NiL]^-$ is the most important complex at pH >8.

The potentiometric data analysis for the Nickel(II)–Hpic–Hlac system performed with the program LETAGROP [13,14] indicates the formation of the mononuclear complexes Ni(pic)(L), $[Ni(pic)(L)(OH)]^-$ and $[Ni(pic)(L)(OH)_2]^{2-}$. The species distribution diagrams are given

Fig. 3. Species distribution diagrams as a function of pH for the Nickel(II)–H_3PO_4 system in 1.0 mol dm^{-3} NaCl at 25 °C considering the conditions M_T = 2 mmol dm^{-3} and molar ratio R = 2.

Fig. 2. Species distribution diagrams as a function of pH for the Nickel(II)–H_3cit system in 1.0 mol dm^{-3} NaCl at 25 °C considering the conditions M_T = 2 mmol dm^{-3} and molar ratio R = 2.
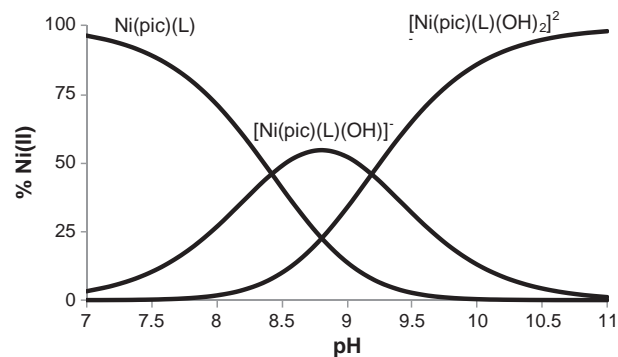

Fig. 4. Species distribution diagrams as a function of pH for the Nickel(II)–Hpic–Hlac system in 1.0 mol dm^{-3} NaCl at 25 °C considering the conditions M_T = 2 mmol dm^{-3} and molar ratio R = 1:1:1.

Table 3
Equilibrium constants (log β_{pqrs}) for the ternary Nickel(II)–Hpic–H_iL systems (25 °C, I = 1.0 mol dm^{-3} NaCl ionic medium). According to the following reaction scheme:

$$pH_2O + qNi^{2+} + rHpic + sH_iL \rightleftharpoons [Ni_q(OH)_p(Hpic)_r(H_iL)_s] + pH^+, \beta_{p,q,r,s}.$$
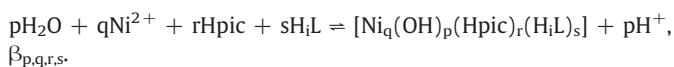
Complexes	log β_{pqrs}			
	Hlac	H_2ox	H_3cit	H_3PO_4
[Ni(pic)HL]			2.37(7)	−0.92(6)
[Ni(pic)L]	8.43(3)	5.53(5)	−2.09(6)	−10.3(1)
[Ni(pic)L(OH)]	0.01(9)	−4.32(8)	−12.53(9)	
[Ni(pic)L(OH)$_2$]	−9.18(5)			
[Ni(pic)$_2$L]		4.89(8)		
Dispersion (σ)	0.073	0.065	0.078	0.071

Values in parentheses are standard deviations [$3\sigma(\log \beta_{pqrs})$] on the last significant figure. The charges of the complexes were omitted for simplicity.

in Fig. 4, and we see that the most important species is the ternary complex Ni(pic)(L) at pH <8.4, the species $[Ni(pic)(L)(OH)]^-$ is formed between 8.4 < pH < 9.2 and the species $[Ni(pic)(L)(OH)_2]^{2-}$ is present at pH >9.2.

In the Nickel(II)–Hpic–H_2ox system the complexes $[Ni(pic)(L)]^-$, $[Ni(pic)(L)(OH)]^{2-}$ and $[Ni(pic)_2(L)]^{2-}$ were detected. The species distribution diagrams are shown in Fig. 5, and we see that the ternary complex $[Ni(pic)(L)]^-$ is formed 60% in the range 2.1 < pH < 3.5, the species $[Ni(pic)_2(L)]^{2-}$ is very abundant at pH >3.5 and the species $[Ni(pic)(L)(OH)]^{2-}$ is present at pH >9.

In the Nickel(II)–Hpic–H_3cit system the complexes $[Ni(pic)(HL)]^-$, $[Ni(pic)(L)]^{2-}$ and $[Ni(pic)(L)(OH)]^{3-}$ were observed. The distribution diagrams shown in Fig. 6 indicate that the complex $[Ni(pic)(HL)]^-$ predominates at pH <4.2, the $[Ni(pic)(L)]^{2-}$ is the most important species in the system and predominates between the pH values 4.2 and 10 and the ternary complex $[Ni(pic)(L)(OH)]^{3-}$ predominates at pH >10.

In the Nickel(II)–Hpic–H_3PO_4 system the complexes $Ni(pic)(H_2L)$, $[Ni(pic)(HL)]^-$ and $[Ni(pic)(L)]^{2-}$ were observed. The distribution diagrams shown in Fig. 7 indicate that the complex $Ni(pic)(H_2L)$ is formed at pH <3.5, the species $[Ni(pic)(HL)]^-$ is very abundant between the pH 3.5 and 9 and the complex $[Ni(pic)(L)]^{2-}$ is abundant at pH >9.

4. Conclusions

The analysis of the potentiometric data of the binary systems indicates the formation of complexes with stoichiometry 1:1, and the species with composition 2:1 $[Ni(HL)L]^{3-}$ and $[NiL_2]^{4-}$ are only formed in the Ni(II)–H_3cit system.
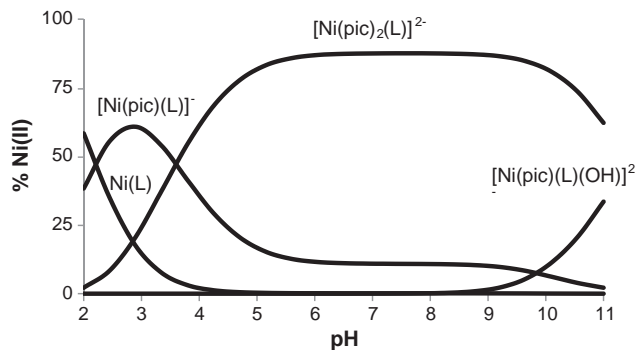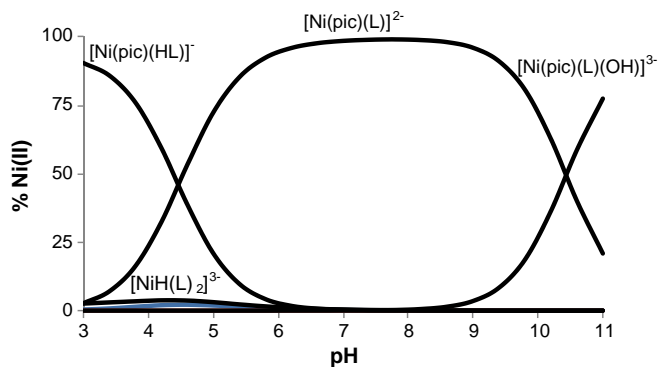

Fig. 6. Species distribution diagrams as a function of pH for the Nickel(II)–Hpic–H_3cit system in 1.0 mol dm^{-3} NaCl at 25 °C considering the conditions M_T = 2 mmol dm^{-3} and molar ratio R = 1:1:1.
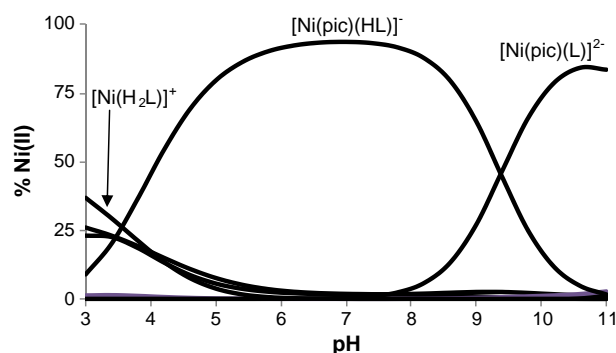

Fig. 7. Species distribution diagrams as a function of pH for the Nickel(II)–Hpic–H_3PO_4 system in 1.0 mol dm^{-3} KCl at 25 °C considering the conditions M_T = 2 mmol dm^{-3} and molar ratio R = 1:1:1.

In the case of the ternary systems, the complexes with composition $[Ni(pic)(L)]$ were observed, and a complex with composition $[Ni(pic)_2(L)]^{2-}$ was only observed in the Nickel(II)–Hpic–H_2ox system. The complex $[Ni(pic)(L)]^{2-}$ is only formed 100% in the Nickel(II)–Hpic–H_3cit system at pH = 7.

References

[1] M.M. Khalil, A.E. Attia, J. Chem. Eng. Data 45 (2000) 1108.
[2] A.F. Kolodziej, Prog. Inorg. Chem. 41 (1994) 493.
[3] S.J. Lippard, Science 268 (1995) 996.
[4] E. Jabri, M.B. Carr, R.P. Hausinger, Science 268 (1995) 998.
[5] N. Yasumatsu, Y. Yoshikawa, Y. Adachi, H. Sakurai, Bioorg. Med. Chem. 15 (2007) 4917.
[6] E. Kiss, E. Garribba, G. Micera, K. Kiss, H. Sakurai, J. Inorg. Biochem. 78 (2000) 97.
[7] A.E. Martell, M. Smith, R.J. Motekaitis, NIST Critical Stability Constants of Metal Complexes Database, US Department of Commerce, Gaithersburg, MD, 1993.
[8] K.J. Powell, L.D. Pettit, IUPAC Stability Constants Database, Academic Software, Otley (U.K.), 1997.
[9] I.M. Kolthoff, V.A. Stenger, Volumetric Analysis, vol. IIInterscience Publishers, New York, 1947. 94.
[10] G.H. Jeffery, J. Bassett, J. Mendham, R.C. Denney, Vogel's Textbook of Quantitative Chemical Analysis, 5th edn Longman Scientific and Technical, UK, 1989. 327.
[11] G. Gran, Analyst 77 (1952) 661.
[12] G. Biedermann, L.G. Sillén, Ark. Kem. 5 (1953) 425.

Fig. 5. Species distribution diagrams as a function of pH for the Nickel(II)–Hpic–H_2ox system in 1.0 mol dm^{-3} NaCl at 25 °C considering the conditions M_T = 2 mmol dm^{-3} and molar ratio R = 1:2:1.

[13] 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 (6) (2005) 501.
[14] L.G. Sillén, B. Warnqvist, Ark. Kem. 31 (1969) 315.
[15] L. Veliz, J.D. Martínez, M.L. Araujo, F. Brito, G. Lubes, M. Rodríguez, V. Lubes, Av. Quím. 6 (2011) 3.
[16] J. Peñuela, J.D. Martínez, M.L. Araujo, F. Brito, G. Lubes, M. Rodríguez, V. Lubes, J. Coord. Chem. 64 (2011) 2698.
[17] L. Alderighi, P. Gans, A. Ienco, D. Peters, A. Sabatini, A. Vacca, Coord. Chem. Rev. 184 (1999) 311.