

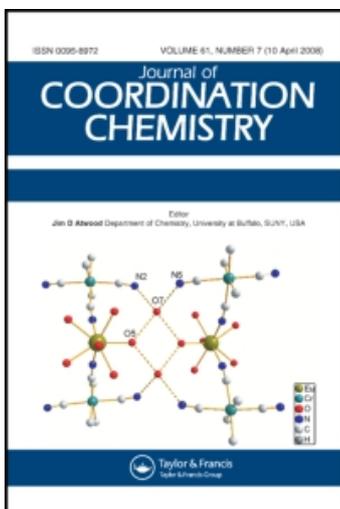
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BINDING ABILITY OF OXINE-LIKE LIGANDS. POTENTIOMETRIC AND POLAROGRAPHIC STUDY ON Ni(II), Co(II), Zn(II) AND Cd(II) COMPLEXES OF 9-HYDROXYPYRIDO(1,2- α)PYRIMIDIN-4-ONE

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BINDING ABILITY OF OXINE-LIKE LIGANDS. POTENTIOMETRIC AND POLAROGRAPHIC STUDY ON Ni(II), Co(II), Zn(II) AND Cd(II) COMPLEXES OF 9-HYDROXYPYRIDO(1,2,-*a*)PYRIMIDIN-4-ONE

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Potentiometric and polarographic studies of metal ion coordination with 9-hydroxypyrido[1,2-*a*]pyrimidin-4-one (HPP) with Ni(II), Zn(II), Co(II) and Cd(II) ions have been carried out. For comparison, stability constants with 8-hydroxy-imidazo[1,2-*a*]pyridine (HIP) were also measured. Due to the low solubility of the latter ligand complexes, measurements were made also in dioxan/water solutions. In the case of both ligands the coordination mode is the same. The oxine-like binding *via* {N, O⁻} donor set leads to formation of stable ML and ML₂ complexes. Stability constants clearly indicate that both ligands are very effective and the HPP, having a more favourable position of the electron pair on nitrogen, forms stronger complexes with smaller metal ions *i.e.*, Ni(II), Zn(II) and Co(II). Cd(II) is better fitted to the HIP donor set.

KEYWORDS: Pyrimidones, oxines, complexes, stability constants

INTRODUCTION

Recent studies have shown that substituted imidazopyridines behave like structural analogues of oxine, and coordinate metal ions *via* the oxine-type of donor set, {N, O⁻}.^{1,2} This type of coordination leads to the formation of very strong complexes although the unfavourable position of the electron pair on nitrogen in the 5-membered imidazole ring makes these ligands distinctly less effective than oxine itself. Biological tests have shown that there is a mutual influence of metal ions and ligands on toxicity. Complex formation may decrease or increase toxicity depending on the ligand and metal ion used.²

In this work we present data obtained for Ni(II), Co(II), Zn(II) and Cd(II) complexes with 8-hydroxy-imidazo(1,2-*a*)pyridine (**I**, HIP) and 9-hydroxypyrido(1,2-*a*)pyrimidin-4-one (**II**, HPP). The latter is a close structural

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analogue of oxine. Proton dissociation constants of both donors are, however, distinctly different than those of oxine.

EXPERIMENTAL

Synthesis of 9-hydroxypyrido[1,2-a]pyrimidin-4-one

9-Hydroxypyrido[1,2-a]pyrimidin-4-one was prepared by condensation of 2-amino-3-hydroxypyridine with isopropylidene aminomethylenemalonate as described earlier.^{3,4} HIP was synthesized as described.² Purity of both ligands was checked by elemental analysis, spectroscopic methods²⁻⁴ and potentiometric titrations.

Potentiometric titrations

Potentiometric titrations were performed with an assembly consisting of a Radiometer PHM 64 pH-meter, an automatic Hamilton burette and a 5 cm³ titration vessel thermostatted at 25°C. The pH meter and a double electrode (Radiometer GK232) were adjusted in terms of activity against standard buffers (phthalate acid, pH 4.005 and borax, pH 9.138). The relation between activity and concentration of H⁺ was evaluated by titration of strong acid against NaOH. All titrated solutions contained 0.1 mol dm⁻³ KNO₃ and a known concentration of HCl to fully protonate the ligands. The systems were titrated in water and water/dioxan solution (50/50, v/v) to compare with previous results.

Metal chlorides (Prolabo) were used as metal ion sources. Metal ion stock solutions (~0.1 mol dm⁻³) in 0.01 M HCl were standardized against EDTA. Stock solutions of ligands with concentration of about 10⁻³ were prepared by dissolving a weighed amount of ligand in strong acid. The exact ligand and free proton concentrations were calculated from potentiometric titration data; 1/1 to 1/4 metal to ligand molar ratios were used for titrations.

The γ and pK_w parameters for mixed solvents were calculated by comparison of the experimental and theoretical curves obtained for strong acid titrations. For the solvents used they were slightly higher than those for pure water *i.e.*, $\gamma = -0.3$ and pK_w = 14.15 for water/dioxan and $\gamma = -0.065$ and pK_w = 13.75 for pure water.

Calculations of stability constants were made with the aid of the SUPERQUAD computer program⁵ which allows the simultaneous refinement of stability constants together with total ligand and total hydrogen concentrations. Standard deviations quoted were computed by SUPERQUAD and refer to random errors only. This gives, however, a good indication of the importance of particular species in the equilibrium.

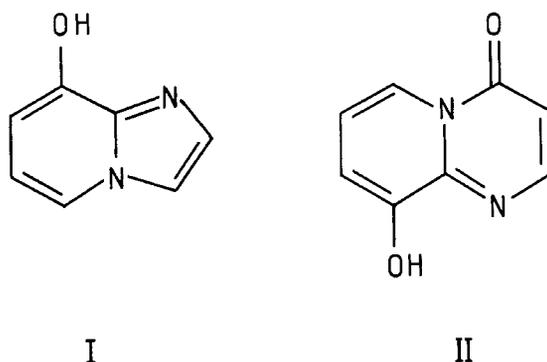
Polarographic measurements

Electrode processes were studied by DC (direct current) and DPP (differential pulse) polarography using a dropping mercury electrode as working electrode (drop time 3.95 s and a height of 55 cm). A saturated calomel reference electrode was connected to a polarographic cell *via* a salt bridge filled with saturated sodium perchlorate. All measurements were performed at 25°C at ionic strength 0.1 mol dm⁻³ (NaClO₄) for Ni(II) and 0.5 mol dm⁻³ for Cd(II) solutions; pH was

adjusted with NaOH or HClO₄. Argon was bubbled through the solutions to remove oxygen. All stock solutions were prepared from analytical reagent grade chemicals. The concentrations of Ni(II) and Cd(II) were 10⁻⁴ and 5 × 10⁻⁵ mol dm⁻³, respectively; ligand concentration varied from 5 × 10⁻⁵ to 7 × 10⁻⁴ mol dm⁻³. The resulting current was measured as the difference between the total current and the residual current (supporting electrolyte and ligand currents at the same potential).

RESULTS AND DISCUSSION

Potentiometric titrations show that ligand II, Scheme, behaves as LH₂ with two protonation constants pK₁ = 3.36 and pK₂ = 7.19 (assigned to nitrogen and phenolic oxygen deprotonations, respectively; Table 1). Both these values indicate that this ligand contains a much more acidic donor set when compared to oxine or other substituted imidazopyridines, e.g., 8-hydroxyimidazo[1,2-*a*]pyridine, I (Table 1). This results mostly from the presence of the quinone group *trans* to nitrogen (Scheme).



The titration curves obtained for metal ions clearly indicate the formation of complex species in all solutions. The base consumption as well as calculations based on potentiometric data suggest the same set of complexes for all metal ions with both ligands HIP and HPP. Except for Cu(II), which gives precipitates both in water and water/dioxan solutions with HPP, all other metal ions form two complexes under the conditions used, ML and ML₂ (Table 1). Stability constants show that HPP is a very effective chelating agent. Comparison of stabilities for complexes with HIP and HPP in water/dioxan solutions shows that, except for Cd(II), all metal ions form considerably stronger complexes with HPP although they are still much less stable than those of oxine. Cd(II), however, is an exception. The stabilities of its complexes with HIP are distinctly higher than those with HPP. The reason could be due to a much larger ionic radius of Cd(II) (~1.0 Å) in comparison to Zn(II) (0.74 Å), Ni(II) (0.69 Å) or Co(II) (0.74 Å). The large radius of Cd(II) fits better to an {N, O⁻} donor set of the imidazopyridine which is hindered for smaller ions due to the unfavourable position of lone pair

Table 1 Stability constants ($\log \beta$) of metal complexes obtained from potentiometric and polarographic data. Standard deviations are given in parentheses.

Cation	Water				Water/dioxan (50/50)			
	LH ₂	LH	ML	ML ₂	LH ₂	LH	ML	ML ₂
(I)								
H ⁺					15.34 (0.01)	9.61 (0.01)		
Cu(II) ^a							9.48 (0.01)	17.71 (0.01)
Ni(II) ^a							6.59 (0.09)	11.40 (0.04)
Co(II)							5.88 (0.06)	10.88 (0.10)
Zn(II)							6.55 (0.05)	12.04 (0.07)
Cd(II)							6.84 (0.05)	13.04 (0.08)
(II)								
H ⁺	10.55 (0.02)	7.19 (0.01)			10.60 (0.09)	7.75 (0.04)		
Cu(II)				^p				
Ni(II)			7.50 (0.02)	14.19 (0.04)			8.50 (0.04)	14.98 (0.04)
			7.85*	14.00*				
Co(II)			6.54 (0.05)	12.75 (0.05)			6.97 (0.01)	12.94 (0.02)
Zn(II)			6.30 (0.04)	11.89 (0.05)			7.50 (0.03)	13.70 (0.05)
Cd(II)			4.94 (0.12)	10.60 (0.09)			5.90 (0.09)	11.83 (0.13)
			4.60*	9.40*				

^a Data obtained from ref. 2. * Values obtained from polarographic measurements. ^p Cu(II) complexes precipitate both in aqueous and mixed solvent solutions.

at the imidazole nitrogen.² Thus, in the case of smaller metal ions, steric effects are more important for complex stabilities than the protonation constants of the donor atoms.

The results collected in Table 1 show, however, than in pure water the order of stability constants of ligand II, Ni(II) > Co(II) \approx Zn(II) > Cd(II), agrees well with the Irving Williams order. This is also pronounced in the case of mixed solvent solutions although complexes of Co(II) and Zn(II) are very close in stability to each other and addition of dioxan changes this order; Zn(II) complexes become slightly more stable than those of Co(II) (Table 1).

The constants obtained for metal-HIP systems in mixed solvents are ordered in a rather different way than those discussed above, (Cd > Zn \approx Ni > Co). The strongest species are formed in the case of Cd(II) while the weakest are those of Ni(II) and Co(II). This results most likely from the fact that metal ion radius is a major factor in influencing coordination.

Polarographic measurements could be carried out for the Cd(II) and Ni(II) systems in aqueous solutions.

Cd(II)-containing solutions

Reduction of Cd(II) in the presence of the ligands usually exhibits one reduction wave shifted to more negative potential in comparison to the free metal system. In the case of HPP, DC polarographic reduction is much more complicated. The reduction wave obtained consists the reduction wave of the free metal ion and reduction waves of complexes. Reduction potentials of all these waves are very close to each other and their separation is very difficult. This suggests slow kinetics between species formed in solution. In DPP ($\Delta E = 20$ mV, $t = 2$ s), three reduction peaks are obtained at -0.554 (free Cd(II) ion), -0.660 and -0.780 V for complexed metal ion (Fig. 1). Evaluation of stability constants is rather difficult but by use of variation of the height of the reduction peak of the free metal at different ligand concentrations, two values were obtained, $\log \beta_1 = 4.60$ and $\log \beta_2 = 9.4$. Both values are lower than those obtained from potentiometric data but they support the model obtained from the pH titrations discussed above.

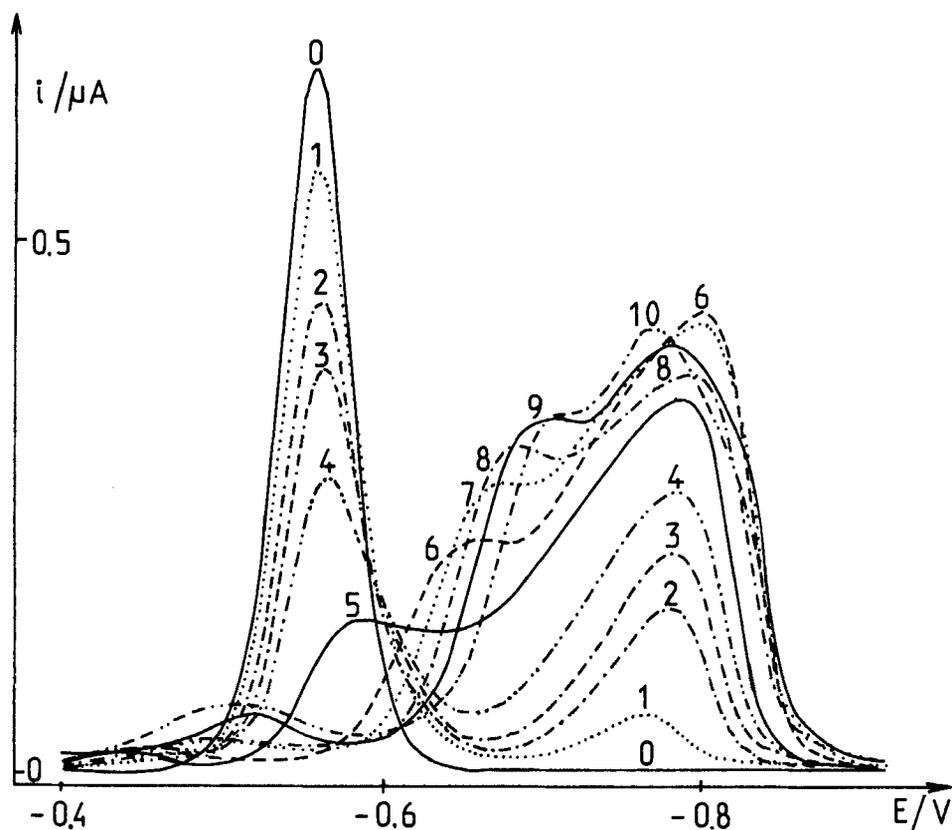


Figure 1 Differential pulse polarograms in the Cd(II)/9-hydroxypyrido[1,2-*a*]pyrimidin-4-one system at pH 6.78 in 0.5 M NaClO₄; $\Delta E = 20$ mV, $t_1 = 2$ s, $[Cd(II)] = 5.10 \cdot 10^{-5}$ mol dm⁻³. Concentration of ligand: (0) 0, (1) 0.03, (2) 0.05, (3) 0.07, (4) 0.10, (5) 0.14, (6) 0.20, (7) 0.30, (8) 0.40, (9) 0.50, (10) 0.70 mmol dm⁻³.

Ni(II)-containing solutions

In DC polarography Ni(II) in 0.1 M NaClO₄ exhibits one irreversible, two-electron reduction wave at -0.98 V. In the presence of HPP at low ligand concentrations (10⁻⁵ to 10⁻⁴ mol dm⁻³) at pH 2.5–4.5 two reduction waves are observed. The wave at -0.81 V increases with ligand concentration while the free metal wave decreases to zero at a ligand concentration of about 3 × 10⁻⁴ mol dm⁻³. Increase of pH above 4.5 leads to a considerable decrease of the complex reduction wave and its shift to more negative potentials, suggesting that a second, perhaps square-planar, species is formed. This shift of potential causes overlap of complex and ligand reduction waves. To evaluate complex formation in this system, measurements were performed at pH 4.30 at a ligand concentration of 1 × 10⁻⁵–4 × 10⁻⁴ mol dm⁻³. Reduction waves and their parameters are collected in Figure 2 and Table 2.

In DPP (ΔE = 50 mV, t = 2s) two reduction peaks are observed for complex species at -0.735 and -0.862 V (Fig. 3). Since the former peak is observed at low ligand concentrations, it corresponds to the reduction of the NiL species while the second one describes the reduction of the NiL₂ complex.

Analysis of the limiting currents of both reduction waves according to procedures described earlier,^{6–8} indicates that the first complex is indeed NiL (evaluated average ligand number is 1, Fig. 4). The reduction wave of the complex is of diffusion character. This indicates that the dissociation rate of the NiL complex is so slow that limiting current is proportional to equilibrium concentrations of the complexes which are reduced at the electrode. The evaluated rate constant was

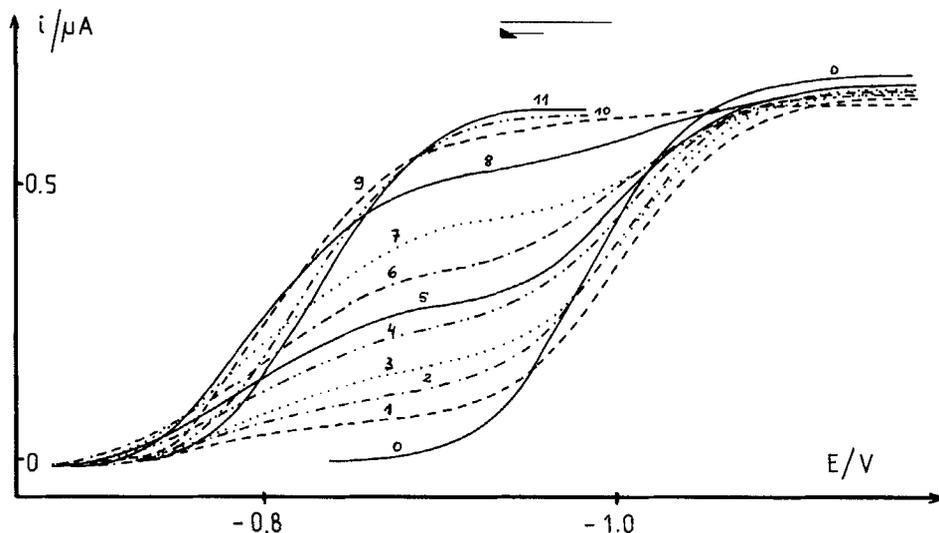


Figure 2 DC polarograms of 1 × 10⁻⁴ mol dm⁻³ Ni(II) in 0.1 M NaClO₄ in the presence of various concentration of 9-hydroxypyridido[1,2-*a*]pyrimidin-4-one: (0) 0, (1) 0.01, (2) 0.02, (3) 0.03, (4) 0.04, (5) 0.05, (6) 0.07, (7) 0.10, (8) 0.14, (9) 0.20, (10) 0.30, (11) 0.40 mmol dm⁻³ at pH 4.30; t₁ = 3.95 s.

Table 2 Values of limiting currents (i) and dissociation rate constants (k_b) for different ligand concentrations in Ni(II)/9-hydroxypyrido[1,2-*a*]pyrimidin-4-one solutions at pH 4.3 in 0.1 M NaClO₄, drop time 3.95 s, [Ni(II)] = 0.0001 mol dm⁻³.

No	c_{tot} (mol dm ⁻³)	i_l (10 ⁻⁸ A)	i_k (10 ⁻⁸ A)	i_d^M (10 ⁻⁸ A)	k_b (s ⁻¹)
0				69.76	
1	0.00001	65.60	6.08	59.52	0.3628
2	0.00002	67.84	11.20	56.64	0.2877
3	0.00003	66.56	16.64	49.92	0.3054
4	0.00004	67.84	21.76	46.08	0.2872
5	0.00005	67.84	27.20	40.64	0.3055
6	0.00007	66.24	34.56	31.68	0.2787
7	0.00010	64.96	44.16	20.80	0.2900
8	0.00014	65.60	52.80	12.80	0.3086
9	0.00020	64.00	57.60	6.40	0.4140
10	0.00030	62.08	62.08	0.00	
11	0.00040	63.04	63.04	0.00	

Here, c_{tot} corresponds to total ligand concentration, i_l to total limiting current, i_k to limiting current of the complex reduction wave and i_d^M to limiting current of the nickel aquo ion.

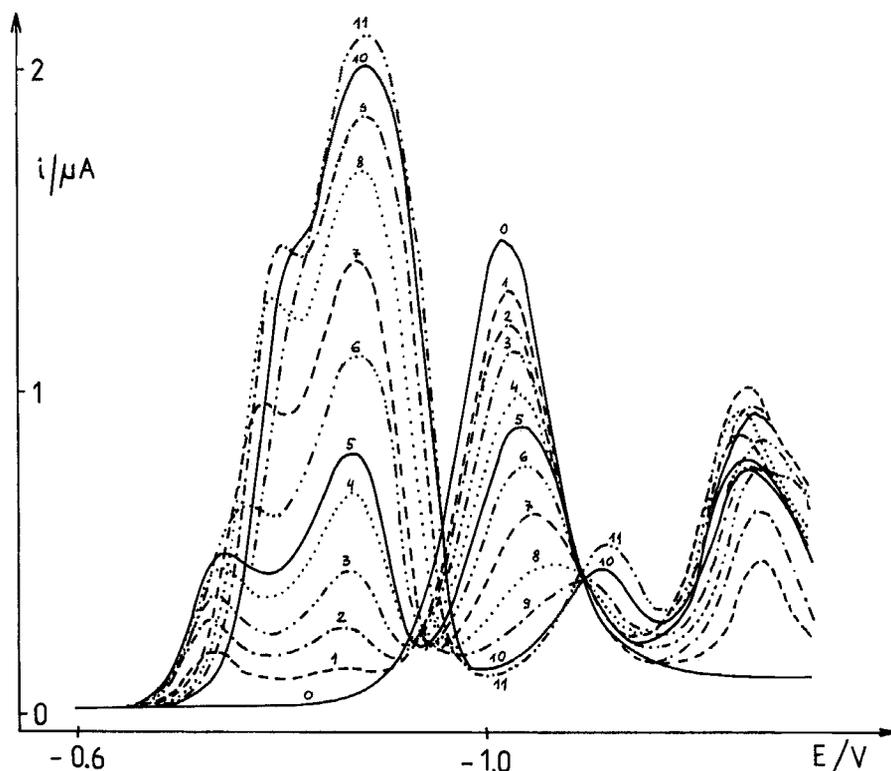


Figure 3 Differential pulse polarograms of Ni(II)/9-hydroxypyrido[1,2-*a*]pyrimidin-4-one solutions at different concentration of ligand: (0) 0, (1) 0.01, (2) 0.02, (3) 0.03, (4) 0.04, (5) 0.05, (6) 0.07, (7) 0.10, (8) 0.14, (9) 0.20, (10) 0.30, (11) 0.40 mmol dm⁻³ in 0.1 M NaClO₄ at pH 4.30; [Ni(II)] = 1.10⁻⁴ mol dm⁻³, ΔE = 50 mV, t_d = 2s.

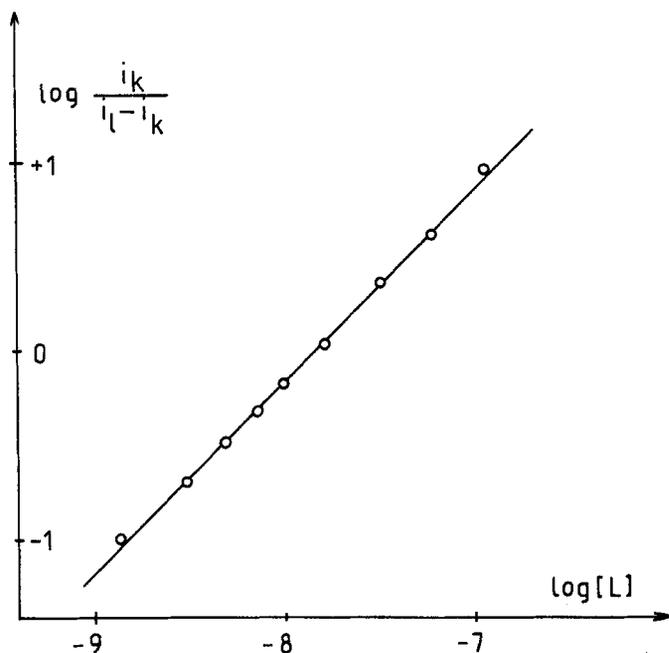
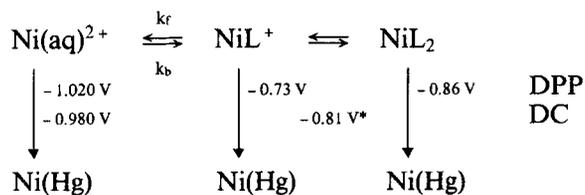


Figure 4 Plot of $\log \frac{i_k}{i_l - i_k}$ vs $\log[L]$ for the Ni(II)/9-hydroxypyrido[1,2-*a*]pyrimidin-4-one system.

estimated to be 0.295 s^{-1} (Table 2). The general scheme of polarographic reaction is shown below.



(*one reduction wave is observed in DC polarography)

The evaluated stability constants are $\log \beta_1 = 7.85$ and $\log \beta_2 = 14.00$. Both these values are very close to those obtained from potentiometric data (Table 1). These results clearly support the model obtained from pH metric measurements.

CONCLUSIONS

Comparison of the data obtained for HPP with those obtained for imidazopyridine has shown that a very important factor in complex stability is the position of the electron pair on the heterocyclic nitrogen involved in metal ion coordination. Its

position in the imidazole ring is unfavourable; metal ion radius is then a major factor with respect to complex stability. Metal ions like Cd(II) are better fitted to bind strongly to this type of ligand.

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