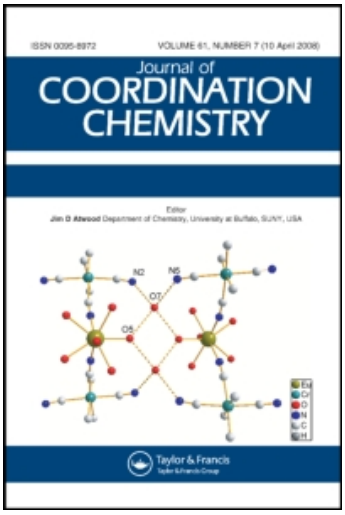

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Histidine and Ornithine as Ligands Towards Zinc(II)

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HISTIDINE AND ORNITHINE AS LIGANDS TOWARDS ZINC(II)

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The equilibria occurring in the systems zinc(II)–histidine and zinc(II)–ornithine have been studied at 25°C in 1.00 M NaCl as constant ionic medium by measuring the electromotive force of galvanic cells containing zinc amalgam and glass electrodes. The experimental data for both systems were accounted for by assuming the existence of the species ZnL^+, ZnL_2, $ZnHL^{2+}$, $ZnHL_2^+$, $ZnH_2L_2^{2+}$ and ZnH_2L^{3+}, where L indicates the uninegative ligand anion (histidine or ornithine). For all the proposed species the stability constants have been determined. The protonation constants of histidine and ornithine were determined under the same experimental conditions, by using a H_2 electrode. The validity of the results is supported by the good agreement between experimental data and calculated values.

Keywords: Histidine, ornithine, zinc(II), complexes, bioavailability.

INTRODUCTION

The equilibria occurring in aqueous solutions between aminoacids and cations play an important role in many respects. The presence of metals in natural water, in soil or in fruits for example can be dangerous to human health. The mechanism of action of toxicity can be strongly dependent on the equilibria in which metals participate.[1–5]

On the other hand the therapeutic activity of complexes between cations and aminoacids has been recognized by many authors.[6–8] For example, zinc(II) seems to activate important metalloenzymes and to be fundamental in protein synthesis,[9–11] while zinc(II) deficiency has been shown to occur in patients with liver disease.[12–16] Zinc(II) sulfate has often been used for supplementing patients with cirrhosis[14] and improvement was reported,[17] although it was lower[18] than that reported by other authors using the complex zinc(II)–histidine (1:2) for the same purpose.[19]

All these reasons led us to study the behaviour of aqueous solutions containing zinc(II) and histidine in a wide range of hydrogen ion concentration. In fact, bioavailability of zinc(II) from the complex with histidine seems strongly dependent on the time of its ingestion after, during or before a meal;[19] this is probably connected with variations of acidity in the stomach. Recently, equilibria between zinc(II) and aspartate and glutamate have been studied.[20] These two ligands contain two carboxylic groups and one amino group, whereas histidine has one carboxylic and one amino group together with an imidazole ring. All three ligands are potentially terdentate. Besides histidine, ornithine has also been studied because the length of its carbon atom chain is comparable to that of glutamate, aspartate and

histidine, but it has a further amino group in the side chain. The comparison between the stability of complexes formed also seems to be interesting with respect to bioavailability of zinc(II).

In the literature,[21,22] some studies have been reported on this subject, but they do not agree with each other, probably because they were carried out over a narrow concentration range and are not complete. Very little has been reported on the formation of protonated complexes.

For histidine Perrin and Sharma[23] assumed the existence of ZnL, ZnL_2, and ZnHL (where L indicates the anion of histidine) to explain their e.m.f. measurements carried out by means of a glass electrode at 37°C and in 0.15 M KNO_3. Pettit and Swash[24] found the species ZnL, ZnL_2, ZnHL, $ZnHL_2$, and ZnH_2L_2, but Brookes and Pettit[25] did not detect ZnH_2L_2.

Complex formation between zinc(II) and ornithine has been less studied. Rebertus[26] has proposed a value for the stability constant of ZnL, while Albert[27] has reported a global stability constant for ZnL_2. Clarke and Martell[28] explain their experimental data (glass electrode, 25°C and 1.00 M KNO_3) by assuming only the presence of ZnHL and ZnH_2L_2. A considerable disagreement attends the values for protonation constants of ornithine, as well. The aim of the present paper was to investigate aqueous solutions containing zinc(II) and histidine or ornithine over a wide range of concentration of reagents in order to verify the presence of species of the type $Zn_qH_pL_r$, without any preliminary hypothesis. The possibility of existence of polynuclear species ($q > 1$), protonated complexes ($p > 0$), complexes formed with loss of protons ($p < 0$) would also be examined.

For this purpose, it was decided to carry out this study in a constant ionic medium[29] (1.00 M NaCl) by means of e.m.f. measurements of galvanic cells containing glass and zinc amalgam electrodes at 25°C. It was also necessary to determine the protonation constants of histidine and ornithine anions because these are not known under the selected experimental conditions. The results are discussed with respect to the bioavailability of the zinc(II).

EXPERIMENTAL

Methods

All measurements were performed at 25°C and in 1.00 M NaCl as constant ionic medium. Solutions (S) were prepared by adding an excess of NaCl with respect to the reagents so that, as according to Biedermann and Sillèn,[29] activity coefficients could be assumed as being constant and concentrations could replace activities in all calculations. The general composition of solutions S was the following: B M in Zn(II), H M in H^+, A M in L, (1-2B-H)M in Na^+, 1.00 M in Cl^-, where B and A indicate the total concentration of zinc(II) and ligands, respectively, whereas H is the analytical excess of hydrogen ions.

The e.m.f. of the following two cells:

$$(-)\,\mathrm{Zn(Hg)/Solution\ S/R.E.}\ (+) \qquad \text{(I)}$$

$$(-)\,\mathrm{R.E./Solution\ S/G.E.}\ (+) \qquad \text{(II)}$$

was measured. R.E. (Ag, AgCl/1.00 M NaCl saturated with AgCl/1.00 M NaCl) and

G.E. are the reference and glass electrodes, respectively, whereas Zn(Hg) represents the zinc amalgam.

The e.m.f. of cells(I) and (II) at 25°C and in mV units can be expressed as follows:

$$E_{\mathrm{I}} = E^0_{\mathrm{I}} - 29.58 \log b - E_{\mathrm{j}}$$

$$E_{\mathrm{II}} = E^0_{\mathrm{II}} + 59.16 \log h + E_{\mathrm{j}}$$

E^0_{I} and E^0_{II} are two constants determined in the first part of each measurement in the absence of the ligands, and b and h are the free concentrations of zinc(II) and hydrogen ions, respectively. E_{j} is the liquid junction potential, which, under the chosen experimental conditions, is $E_{\mathrm{j}} = -60\,\mathrm{h}$.

For each experimental point, b and h were obtained by a procedure similar to that described previously.[30] For each measurement, B and H were kept constant, while A and $-\log h$ were increased gradually. Measurements were continued to $-\log h \leqslant 9$. To explain the experimental data in terms of complex formation it was necessary to determine the protonation constants of the ligands, relative to the equilibria.

$$n\mathrm{H}^+ + \mathrm{L} \rightleftharpoons \mathrm{H}_n\mathrm{L}$$

and defined by the relationship

$$[\mathrm{H}_n\mathrm{L}] = k_n h[\mathrm{H}_{n-1}\mathrm{L}] \text{ (charges omitted)}$$

where n can be 1, 2 or 3. The determination of the values of k_n was carried out by measuring the e.m.f. of cell(III)

$$(-)\,\mathrm{Pt},\ \mathrm{H_2}/\text{Solution T/R.E. } (+)\ \text{(III)}$$

at 25°C and in 1.00 M NaCl, as a function of H ($0 \leqslant H \leqslant 0.1$ M) and A ($0.010 \leqslant A \leqslant 0.050$ M). Solution T had the following general composition: H M in H^+, A M in L, (1 − H) M in Na^+, 1 M in Cl^-.

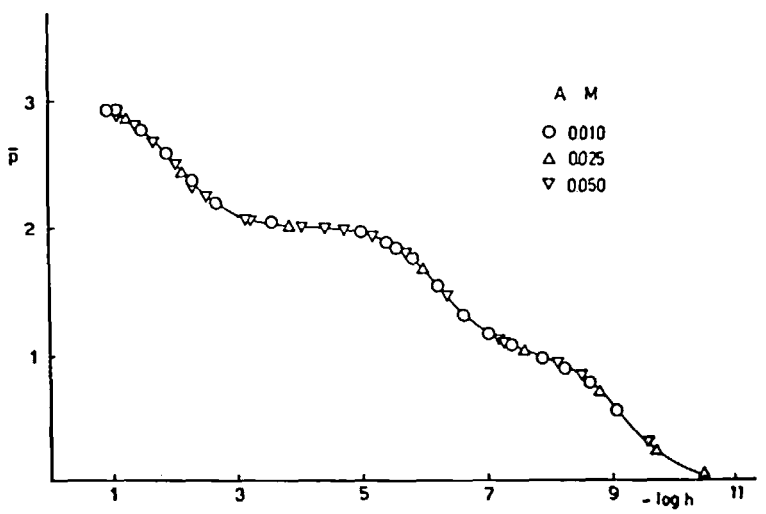

FIGURE 1 Protonation function of histidine. The curve is the normalized best fit.

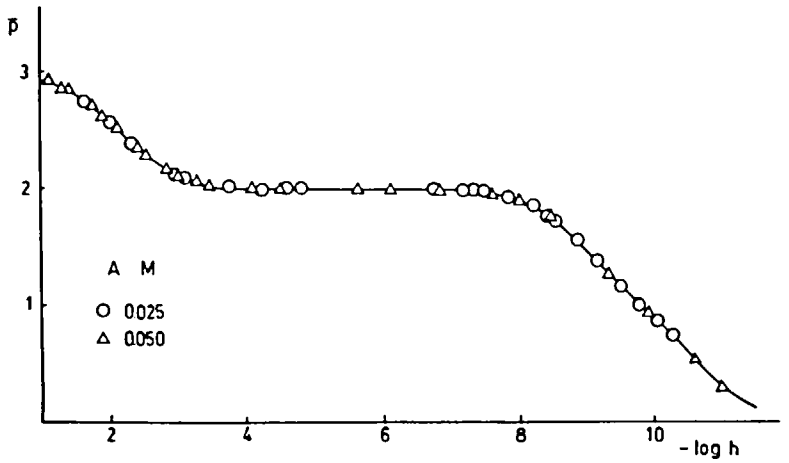

FIGURE 2 Protonation function of ornithine. The curve is the normalized best fit.

The protonation functions of histidine and ornithine anions $\{\bar{p} = \Sigma n\,[H_nL]\,(1 + \Sigma\,[H_nL])^{-1}\}$ are shown in Figures 1 and 2, respectively. The values $\log k_1 = 9.21 \pm 0.01$, $\log k_2 = 6.27 \pm 0.02$ and $\log k_3 = 2.00 \pm 0.06$ were obtained for histidine and $\log k_1 = 10.66 \pm 0.03$, $\log k_1k_2 = 19.66 \pm 0.02$ and $\log k_3 = 2.17 \pm 0.06$ for ornithine. The limits of error correspond to the maximum shift possible between the normalized curve[31] and experimental points for which agreement was still acceptable.

Materials and analysis

NaCl, HCl and NaOH were prepared and analysed as described previously.[32] A stock solution of zinc(II) chloride was prepared by dissolving a weighed amount of zinc metal (Koch Light, 99.9999%) in a slight excess of distilled HCl. After the complete dissolution of the zinc, the excess HCl was stripped off and the residue topped up with bidistilled water so as to obtain a weakly acid solution ($H \sim 10^{-4}$ M). H was determined by Gran's method.[33] The total zinc(II) content was checked by means of precipitation as phosphate;[34] results agreed to within $\pm 0.1\%$.

L-Histidine and *L*-ornithine hydrochlorides (both C. Erba RP) were recrystallized twice by adding acetone dropwise (C. Erba RP) to a saturated and filtered aqueous solution of *L*-histidine or *L*-ornithine hydrochloride, respectively. The solids obtained were then dried at 110°C. The absence of water and the stoichiometric compositions were checked by thermoanalysis and by argentometry, according to Volhard.

The zinc amalgam ($\sim 5 \times 10^{-3}\%$ weight) was prepared *in situ* in the measurement vessel, by reducing coulometrically the calculated amount of zinc(II) on a mercury cathode. We have proved that the response of the zinc amalgam electrode prepared in such a way obeys the Nernst equation in our solutions. The E_1 values remained constant within ± 0.02 mV for two hours and within ± 0.10 mV overnight. As the values of E_1 have a slight drift as $-\log h \leqslant 3$, no measurements were performed in this range. This limitation was not very important because complexes do not form appreciably at high acidity in both cases. Further details on e.m.f. measurements are given in previous papers.[30,32]

RESULTS AND DISCUSSION

Both systems were studied by performing several series of e.m.f. measurements at different H (0.025, 0.050, 0.070 and 0.100 M) and B values (0.5, 1.0 and 2.0×10^{-3} M). By arranging the values of b and h obtained from cells (I) and (II) with B and H, it was possible to calculate η ($=\log (B/b)$) and to plot the data in the form η ($-\log h$)$_{H,B}$.

In Figures 3 and 4 the dependence of η on $-\log h$ is shown for histidine and ornithine, respectively. In all cases η is independent of B because points obtained at different B, but at the same H, fall on the same curve. It can be assumed that polynuclear species in zinc(II) are negligible ($q = 1$), and the prevailing species can be indicated by ZnH_pL_r with the relative stability constants $\beta_{1,p,r}$ (defined by the relationship $[ZnH_pL_r] = \beta_{1,p,r} b h^p a$).

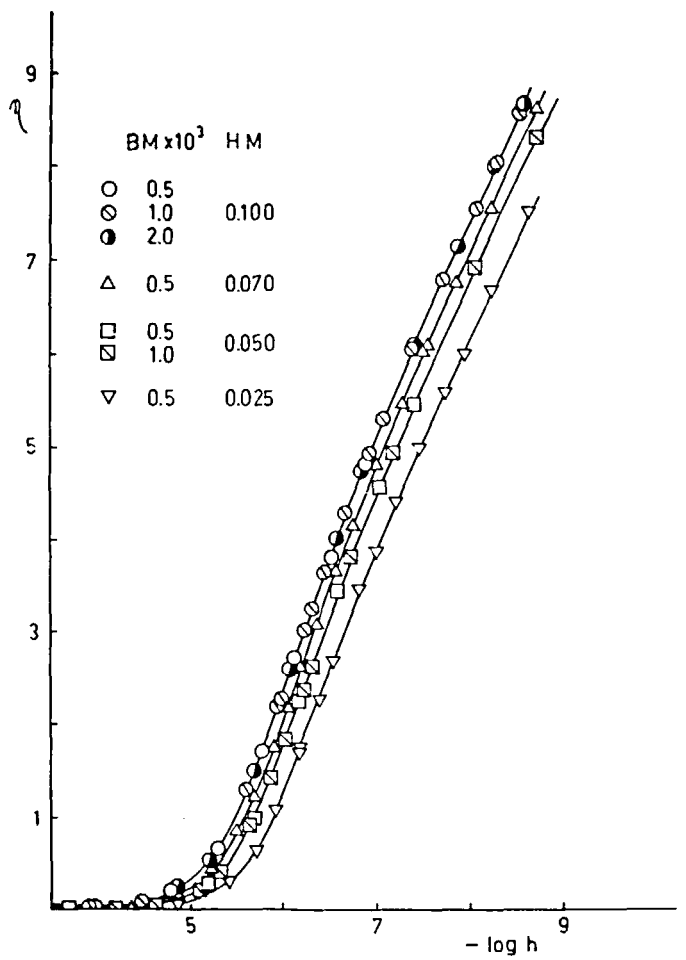

FIGURE 3 The dependence of η ($=\log (B/b)$) on $-\log h$ for the system zinc(II)—histidine. Curves are calculated by using the values of Table I.

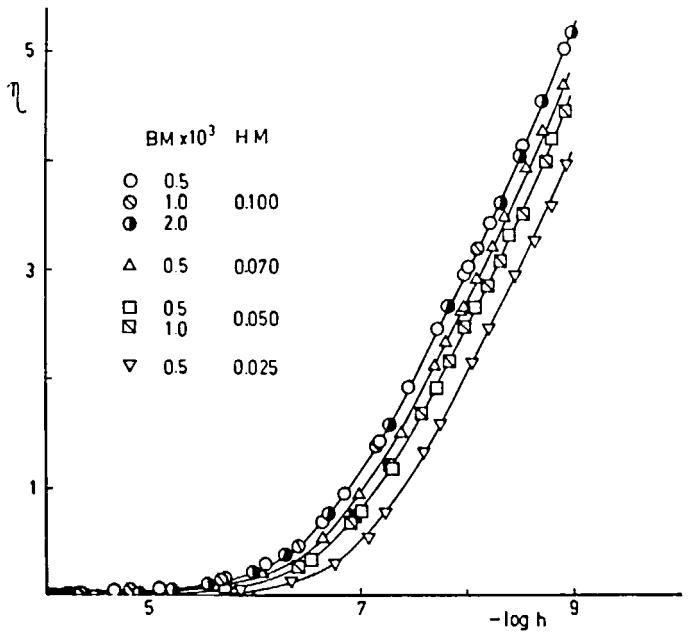

FIGURE 4 The dependence of η (= log (*B*/*b*)) on −log *h* for the system zinc(II)—ornithine. Curves are calculated by using the values of Table I.

From the material balance relative to zinc(II), by taking into account the mass action law, equation (*1*) can be derived.

$$\eta = \log(B/b) = \log(1 + \Sigma_p\Sigma_r\beta_{1,p,r}h^p a^r) \qquad (1)$$

To find the prevailing values of p and r and then the $\beta_{1,p,r}$ values, it was necessary to have the free concentration of the ligands, a. This can be calculated from the material balance of H, (*2*).

$$H = h + k_1 ha + 2k_1k_2h^2a + 3k_1k_2k_3h^3a + \Sigma_p\Sigma_r p\beta_{1,p,r}bh^p a^r \qquad (2)$$

In (*1*) and (*2*) and in the equations that follow, hydrolyzed species of zinc(II) are neglected on the basis of the values of b and h measured and the results of Biedermann.[35] To calculate a, equations can be derived using the approach applied by Osterberg.[36] Values of log a calculated by means of this procedure or by neglecting the last term of (*2*) coincide within ± 0.02, because of the concentration range of B and $H(B \leqslant 0.02\,H)$. Figures 5 and 6 show the dependence of η on $-\log a$ for zinc(II)-histidine and for zinc(II)-ornithine, respectively. As for both systems η is an increasing function of H, complexes with additional protons ($p \geqslant 0$) are present. To obtain values of p and r and the relative $\beta_{1,p,r}$ values, a procedure similar to that described previously[20] was applied. For both the systems, the experimental data could be accounted for by the assumption of the species ZnL, ZnL_2, ZnHL, $ZnHL_2$, ZnH_2L_2 and ZnH_2L. In Table I, the relative stability constants $\beta_{1,p,r}$ are collected. There is no evidence for species at higher p/r ratio (for instance ZnH_3L or ZnH_4L). The values of the stability constants in Table I have been used to calculate

the curves drawn in Figures 3 to 6. The agreement between points and curves is good and supports the validity of our results.

As expected, polynuclear complexes are not present in any appreciable quantity, whereas both ligands are able to form complexes with additional protons. By comparing the results of this work on histidine with those in the literature,[21-25] it appears that the presence of the species ZnL, ZnL_2, ZnHL, $ZnHL_2$, ZnH_2L_2 and ZnH_2L found by Pettit and Swash[24] is confirmed, even if the values proposed for the stability constants are different. We also detect the presence of ZnH_2L.

TABLE I

Proposed values for stability constants (log $\beta_{1,p,r}$) for the zinc(II)-histidine and zinc(II)-ornithine systems (25°C, I = 1(NaCl)).

Species	Zinc(II)-histidine	Zinc(II)-ornithine
ZnL	6.17 ± 0.05	7.34 ± 0.04
ZnL_2	11.65 ± 0.04	10.97 ± 0.10
ZnHL	11.58 ± 0.05	14.66 ± 0.08
$ZnHL_2$	17.73 ± 0.05	19.15 ± 0.15
ZnH_2L_2	22.60 ± 0.07	28.63 ± 0.06
ZnH_2L	15.10 ± 0.15	19.78 ± 0.10

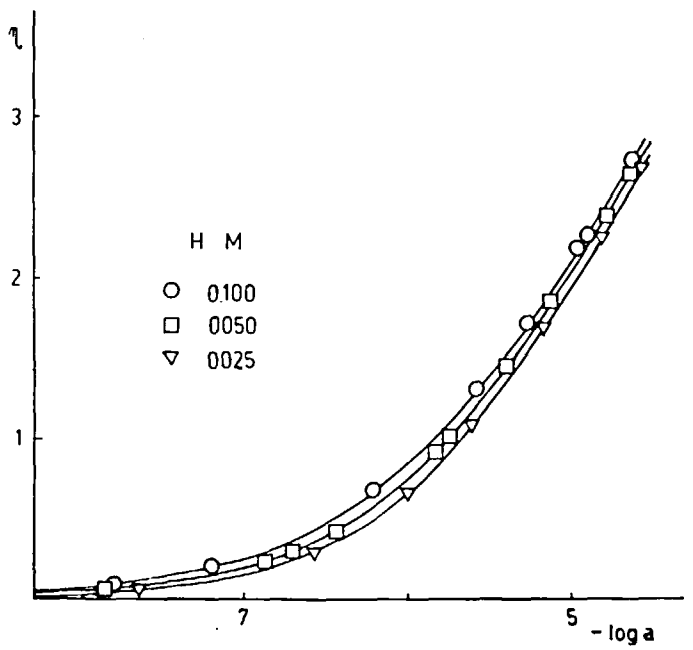

FIGURE 5 Experimental data obtained for the zinc(II)-histidine system at different H values, reported in the form η $(-\log a)_{B,H}$. Curves are calculated by using the values of Table I.

In the case of ornithine our results can be compared partially with those obtained by Clarke and Martell.[28] These authors explained their data by assuming only the presence of ZnHL and $Zn(HL)_2$ and consequently the values found for the equilibrium constants are different with respect to those proposed here. The other results present in the literature refer to a very restricted range of concentration.

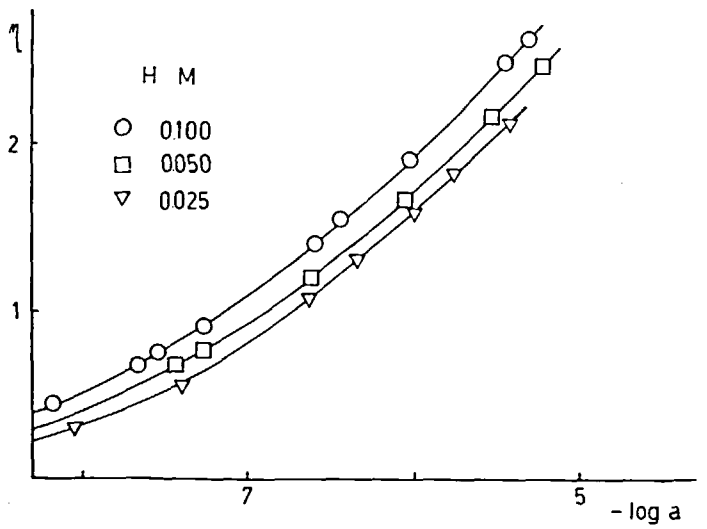

FIGURE 6 Experimental data obtained for the zinc(II)–ornithine system at different H values, reported in the form η $(-\log a)_{B,H}$. Curves are calculated by using the values of Table I.

The determination of the protonation constants of both ligands is also taken into account. The high value of $\log k_1$ for both ligands, involves measurements of $-\log h$ in alkaline solutions ($-\log h \geqslant 9$) at 1 M Na^+, where deviations of the response of G.E. are not negligible. In this work a H_2 electrode was employed so that its response can be assumed as being correct even at $-\log h \geqslant 11$.

The comparison between histidine and ornithine seems interesting. From the values collected in Table I ornithine appears as a stronger ligand than histidine towards zinc(II). All values of the third column (except that relative to ZnL_2) are higher than those of the second. However, it is important to remember that ornithine is a stronger base than histidine so that at the same $-\log h$ value, the free concentration of the latter (able to bond Zn^{2+}) is higher than the former. This means that even if the $\beta_{1,0,1}$ value relative to the complex formed by ornithine is higher than that of histidine, the formation of ZnL begins at lower $-\log h$ for histidine than for ornithine and, at the same $-\log h$, the quantity of zinc(II) bound to histidine is more than that bond to ornithine.

By using the values of the constants of Table I, distribution curves for the species found for both systems were calculated as a function of $-\log h$ at $A = 0.025$ and 0.100 M and are plotted in Figures 7 and 8, respectively. At $-\log h \sim 5$ and $A =$ 0.100 M, the quantity of free zinc(II) is about 80% in the case of ornithine while it is less than 30% in the presence of histidine. Near 100% of the zinc(II) is present as a complex in the case of histidine at $-\log h \sim 6.5$ (even at $A = 0.025$ M) while, for the same $-\log h$, about 40% of zinc(II) is not bound to ornithine.

Both ligands are able to form protonated complexes, but in this aspect ornithine prevails over histidine. It can be seen from Figures 7 and 8 that the highest percentage of protonated complexes is about 75% for histidine (at $-\log h \sim 5.5$) whereas for ornithine it reaches about 85%, at $-\log h \sim 7.5$. It is remarkable that at $-\log h \sim 7$, in the case of histidine, ZnL_2 represents 80–85% of the total zinc(II),

and $ZnHL_2$ about 10–15%. At the same $-\log h$ value in the case of ornithine, the species ZnL_2 does not exist, but ZnL, ZnH_2L_2 and ZnHL are present.

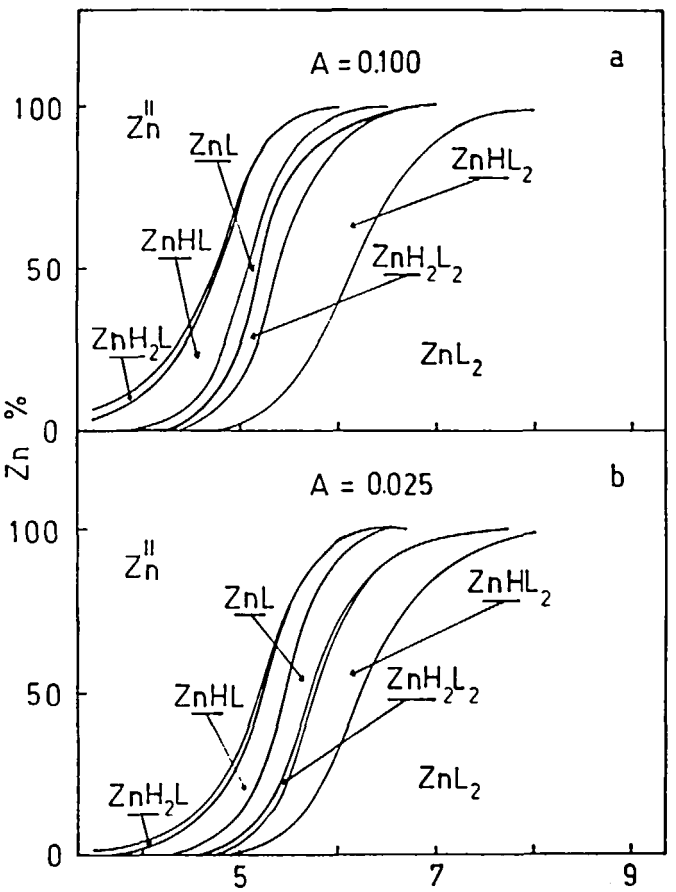

FIGURE 7 Distribution curves depending on $-\log h$ at $A = 0.100$ M (a) and 0.025 M (b) for the system zinc(II)–histidine. Curves are calculated for $B = 0.5 \times 10^{-3}$ M. Curves calculated for all values of B practically coincide.

Complexes with a high r/p ratio are favoured by high A, while relatively little $ZnHL_2$ (~5%) is present for ornithine. For both ligands, ZnH_2L, not reported before, is present at low $-\log h$, as expected, and reaches ~5% of total zinc(II), for histidine and more than 10% for ornithine, at $A = 0.100$ M. It is surprising to observe that about 70% of the total zinc(II) in solutions of zinc(II)–ornithine at $-\log h \sim 7$ and $A = 0.100$ M is present in the form ZnH_2L_2.

It seems interesting to compare the behaviour of histidine and ornithine with that of aspartate and glutamate. Table II collects species and relative constants proposed for the systems zinc(II)–aspartate, glutamate, histidinate and ornithinate. Histidine and ornithine are stronger ligands toward zinc(II) than are aspartate and glutamate.

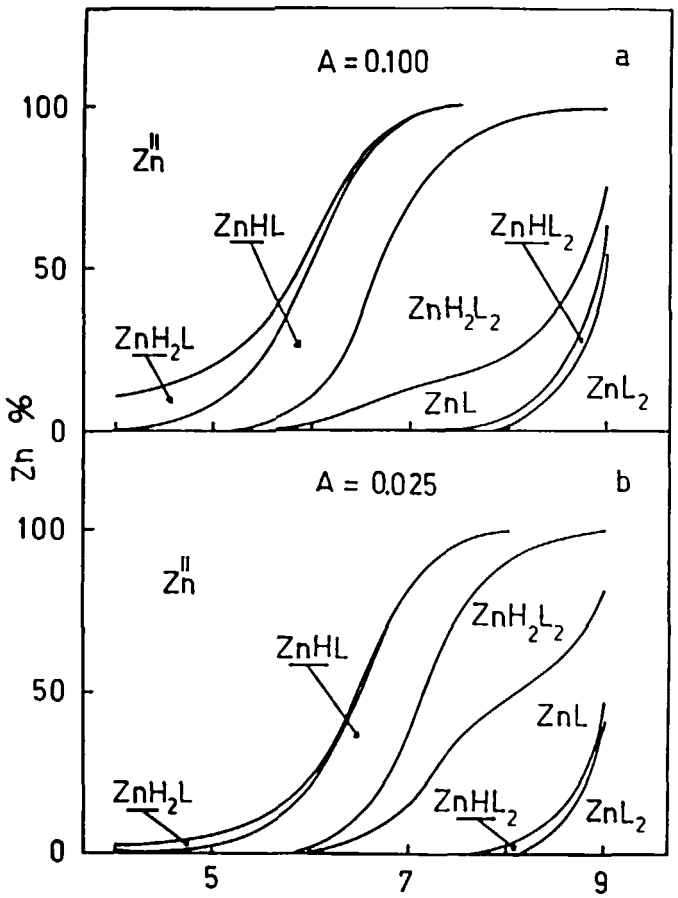

FIGURE 8 Distribution curves depending on $-\log h$ at $A = 0.100$ M (a) and 0.025 M (b) for the system zinc(II)-ornithine. Curves are calculated for $B = 0.5 \times 10^{-3}$ M. Curves calculated for all values of B practically coincide.

TABLE II

Comparison between the values of log $\beta_{1,p,r}$ for aspartate,[20] glutamate,[20] histidine and ornithine as ligands towards zinc(II) at 25°C.

Species	Aspartate (1 M $NaClO_4$)	Glutamate (1 M $NaClO_4$)	Histidine (1 M NaCl)	Ornithine (1 M NaCl)
ZnL	5.64	4.53	6.17	7.34
ZnL_2	9.62	7.79	11.65	10.97
ZnL_3	12.38	9.41		
ZnHL	10.49	10.25	11.58	14.66
ZnH_2L	13.37	evidence	15.10	19.78
$ZnHL_2$	16.12	15.44	17.73	19.15
ZnH_2L_2	20.55		22.60	28.63
$ZnHL_3$	19.87	18.90		
ZnH_2L_3	26.50	25.08		

This result could be expected if the greater affinity of zinc(II) for the amino group than the carboxylic group is considered. From a comparison of the stabilities of ZnL_2, it can be deduced that histidine is the strongest ligand. Glutamate and aspartate are also able to form complexes with a ratio 1:3 between zinc(II) and ligand, while this is not possible for histidine and ornithine. Histidine and ornithine show more distinctive terdentate character than any other aminoacid component of proteins and consequently form stable ZnL_2 complexes with little tendency to form ZnL_3.

An X-ray crystallographic study[37] of zinc(II)-histidine complexes has shown that in the solid state coordination is primarily through the tertiary imidazole nitrogen and the α-amino nitrogen, so that in ZnL_2 the nitrogens form a distorted tetrahedral array around the zinc ion. The distance 2.8–2.9 Å between the zinc ion and an oxygen atom of a carboxyl group indicates that zinc(II) has to be considered as being loosely coordinated to the latter. Similar considerations may be extended to solution.

A competition occurs between zinc ions and protons for the ligand. At low $-\log h$, protons bind more easily, than zinc(II), especially in the case of ornithine whose amino nitrogen is more basic than an imidazole nitrogen atom. The existence of this competition explains why at $-\log h \leqslant 5$ the quantity of zinc(II) bound to the ligand is slight.

Inspection of the distribution curves for the system zinc(II)–histidine at $A = 0.025$ M can explain the fact that bioavailability[19] depends on experimental conditions. The $-\log h$ value seems to be crucial to establish in which form zinc(II) is present in aqueous solutions containing histidine. At $-\log h \sim 8$, total zinc(II) is present as ZnL_2, but even in an excess of histidine ($A = 0.025$) if $-\log h$ decreases (for example to $-\log h \sim 5$) only 30% of zinc(II) is bound to histidine in the form ZnL ($\sim 15\%$) or as protonated complexes ($\sim 15\%$). By decreasing $-\log h$, histidine is protonated and zinc(II) tends to be present as the free ion. Probably, the competitive equilibria with protons explain the results obtained by Schœlmerich *et al.*[19] concerning the importance of the mode of application of ZnL_2 to treat liver diseases.

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