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Complexation equilibria of Zn(II) complexes contain pyridoxine HCl and some bioligands: pH-metric studies

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Mixed ligand complexes (MC) of pyridoxine HCl drug as ligand [P] with Zn(II) in the occurrence of some bioligands (amino acids or peptides) as ligands [L] have been studied using pH-metric measurements in aqueous solution at 25 °C and ionic strength I = 0.10 mol dm^{-3} ($NaNO_3$). The obtained complexes and their formation constants were established on basis of computer analysis potentiometric data, using specific program model (HYPERQUAD). Complexes mixed-ligand were formed by a simultaneous mechanism. The parameter Δlog K, log X, and % R.S. were evaluated and discussed. The determination of the pH of solutions was executed through finding the percentage of the distribution of several species.

Keywords: Complexes; Formation constant; Drug; Amino acids; Peptides; Potentiometric titration.

1. INTRODUCTION

Complexes of mixed bioligands are known for their biological activity which lead to them to be incorporated in different biochemical processes [1–4], considered as enzymatic model complexes, and play an important role in the biochemical reactions catalyzed by the enzyme metal [5]. Furthermore, these types of complexes perhaps exist in biological fluids which contains various M^{n+} ions and many ligands. The stability analysis of mixed ligand complexes help to understan the driving forces behind the formation of these complexes in the biological systems.

Medicinally important drugs such as amino acids, and peptides have notable medicinal and biological importance which recently manage grab the attention to study the biological importance of mixed ligand complexes of transition metals with pharmaceutical molecules. Pyridoxine hydrochloride is chemically known as (2-methyl-1-hydroxy-4,5-bis (hydroxylmethyl)pyridinium chloride (*Scheme 1*), also known as VB6. Pyridoxine has significant role for human body functions such as; metabolism, nervous system (both central and peripheral)traditional functioning, co-enzyme to help other enzymes

to act as non-oxidative exchange of amino acids, helps in the exchange of some amino acids (tryptophan, methionine, cysteine, glutamic and other), and helps the regulation of lipid metabolism [6]. The potency of drugs is lower than that of their metal complexes [7]. This makes them crucial for catalytic processes, transportation also detoxification.

Some biological activity such as; antidiabetic, antimicrobial, anticonvulsant, and antiproliferative–antitumor, and anti-inflammatory were reported for various zinc complexes [8-11]. In the present research work, mixed ligand complex formation equilibria of Zn(II) with pyridoxine drug (P) and some bio-relevant ligands (L) will be determined by potentiometric titration technique in aqueous solution at T= 25 °C and I = 0.10 mol dm^{-3} ($NaNO_3$). Mixed-ligand complexes have been set in a comparison with binary complexes terms of stability.

2. EXPERIMENTAL

2.1. Chemicals

Amino acids and peptides investigated are: glycine, valine, L-ornithine, alanine, cysteine, histidine HCl, glycylglycine, glycyl-L-alanine, and glycyl-L-leucine were purchased as pure analytical grad from Sigma chem. Pyridoxine HCl was obtained from Merck. Stocks solutions of $Zn(NO_3)_2 \cdot 6H_2O$, $NaNO_3$, and HNO_3 were prepared from analytical reagent grade chemicals obtained from BDH-Biochemicals Ltd Poole and standardized by titration with EDTA. CO_2-free sodium hydroxide, which is a titrant was prepared and standardized using KHP pH-metrically. The ionic strength was kept fixed at 0.10 mol dm^{-3} with $NaNO_3$ in all titrations.

2.2. Experimental techniques and instrumentation

The following mixtures were prepared and titrated potentiometrically using a 0.05 mol dm^{-3} NaOH solution:

(A) forty mL solution include $NaNO_3$ in the concentration of 0.10 mol dm^{-3} and a ligand at a concentration of 1.25×10^{-3} mol dm^{-3} (peptide, drug, or amino acid).

(B) forty mL solution include 1.25×10^{-3} mol dm^{-3} Zn(II) ion and 0.10 mol dm^{-3} $NaNO_3$.

(C) forty mL solution include 1.25×10^{-3} mol dm^{-3} Zn(II), 0.10 mol dm^{-3} $NaNO_3$, and 3.75×10^{-3} mol dm^{-3} of the ligand drug (amino acid or peptide).

(D) forty mL solution include 1.25×10^{-3} mol dm^{-3} Zn(II), 1.25×10^{-3} mol dm^{-3} (drug), 1.25×10^{-3} mol dm^{-3} (amino acid or peptide), and 0.10 mol dm^{-3} $NaNO_3$.

The acid dissociation constant (pKa) of ligands was analysed potentiometrically using titrating mixture (A). Performing a titration of the mixture allowed the estimation of Zn(II) hydrolysis constants (B). The binary Zn(II) complexes formation constants of were detected by titrating mixture (C). Stability constants of Peptide and amino acid mixed complexes were calculated after obtaining the mixture's potentiometric data (D).

The performance of potentiometric titrations were carried out at a temperature of 25±0.1°C using Griffin pH J-300-010 G Digital pH meter. The electrode and the standard buffer solutions were calibrated at pH 4.0, and pH 10.0. The equilibrium constant determination volume used was 40 ml at *I*=0.10 mol dm^{-3} ($NaNO_3$) under a nitrogen atmosphere. The hydroxyl groups [OH] values were calculated using a pK_w value of 13.87±0.05 at 25°C.

2.3. Data processing

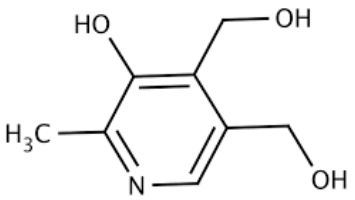
The HYPERQUAD computer program was used to obtain pKa of ligands and log β for complexes from potentiometric data [12]. The complexation between Zn (II) and P and L can be calculated using the following equations:

$$m(Zn) + p(P) + l(L) + h(H) \rightleftharpoons [(Zn)_m(P)_p(L)_l(H)_h] \quad (1)$$

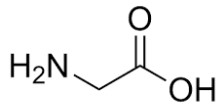
$$\beta_{mplh} = \frac{[Zn_m P_p L_l H_h]}{[Zn]^m [P]^p [L]^l [H]^h} \quad (2)$$

Where *m, p, l, and h* are the coefficients for metal ion, ligand P, ligand amino acids or peptides, and H-atoms, respectively. The different complex species concentration distribution diagrams were performed in solution as a function of the pH were obtained using the program HYSS [13].

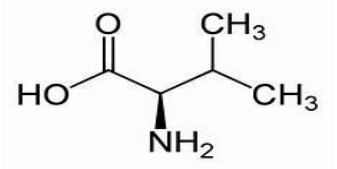
HCl



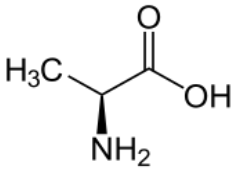
Pyridoxine hydrochloride



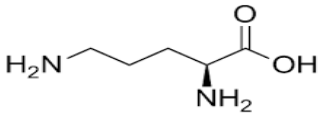
Glycine



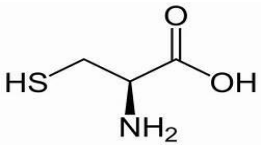
Valine



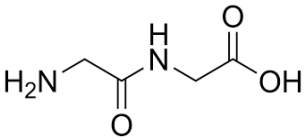
L-Alanine



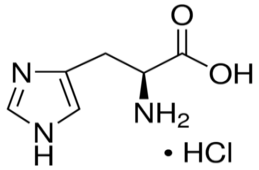
L-Ornithine



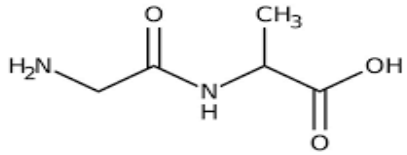
Cysteine

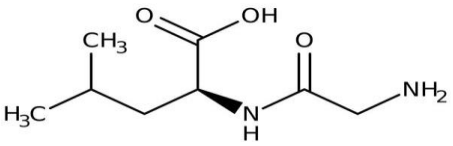


Glycyl-glycine



Histidine





Glycyl-L-alanine Glycyl-L-leucine

Scheme 1. The structural formula of ligands.

3. RESULTS AND DISCUSSION

3.1. The Determination of ligands protonation constants

Table 1 provides the protonation constants pKa for all ligands (open formulae of the ligands selected are provided in Scheme 1). pK's were obtained according to the following equations:

$H_2L \rightleftharpoons H + HL$ $[H][HL] = Ka_1[H_2L]$, (3)

$HL \rightleftharpoons H + L$ $[H][L] = Ka_2[HL]$. (4)

The pKa of amino acids and peptides were proved to be in matching the previously reported [14-18]. For the α-amino acids or peptides, pKa_1= α-carboxyl group, pKa_2 = α-ammonium ion, and pKa_3 = side-chain group. (*See Table1*).

Table 1. pK's of the ligands at 25 °C and I = 0.10 mol dm^{-3} ($NaNO_3$).

Ligands	pK's of Ligands		
	pK_{a1} **±SD**	pK_{a2} **±SD**	pK_{a3}**±SD**
Pyridoxine (P)	4.60 ±0.03	9.20 ±0.01	
Glycine	2.23 ±0.01	9.52 ±0.01	
Valine	2.32 ±0.01	9.21 ±0.02	
Ornithine	1.96 ±0.01	10.76 ±0.03	8.65 ±0.02
Alanine	2.13 ±0.02	9.76 ±0.01	
Cysteine	1.92±0.02	9.77 ±0.03	6.90 ±0.02
Histidine	1.82±0.06	9.11 ±0.01	6.06 ±0.04
Glycyl-glycine	3.21 ±0.01	8.04 ±0.02	
Glycyl-L-alanine	2.91±0.01	7.62 ±0.01	
Glycyl-L-leucine	4.29 ±0.01	9.27 ±0.01	

Note. pK_{a1}: coincide to 11 species (i.e., $L^- + H^+ \rightleftharpoons LH$); pK_{a2} coincide to 12 species (i.e., $LH + H^+ \rightleftharpoons LH_2^+$). Uncertainties are indicated as ± one standard deviation.

The protonation constants values for the pyridoxine HCl are pKa_1=9.20 and pKa_2=4.60 for the phenol and pyridine respectively. Fig. 1. The graphical distribution species diagram displayed that the protonated species H_2P^+ began to form at low acidic conditions (pH < 2.5). Upon increasing the pH, the ligand (H_2P^+) started to lose its ability to form protons (HP), which is the predominant type in the pH range 5.6–8.2. The increases in pH leads to deprotonation of the second proton to produce deprotonated types (P) which is the principal types at pH ≥10.

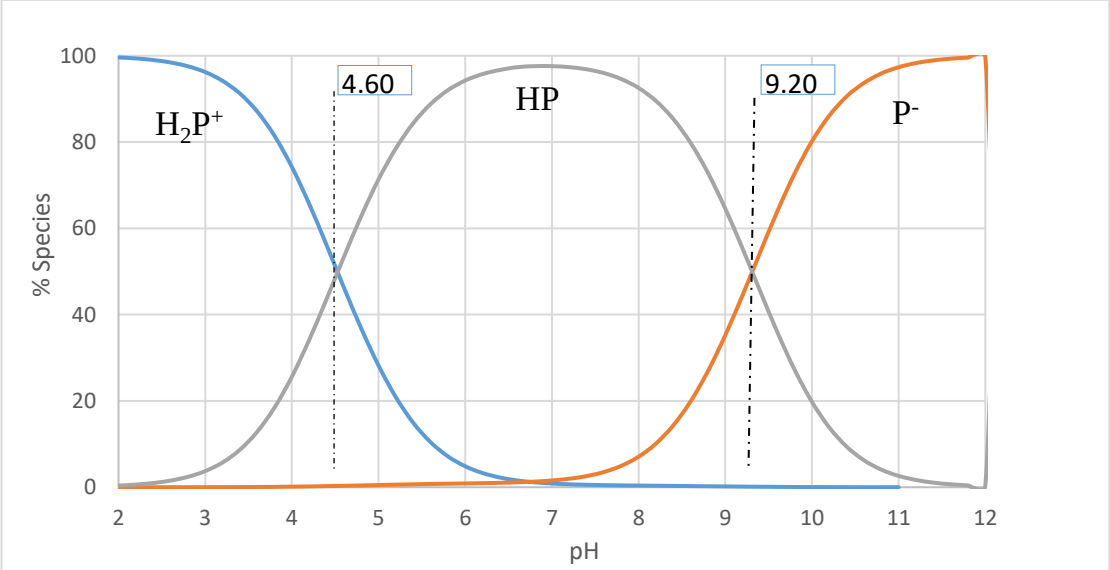


Figure 1. Percentage of species distribution as a function of pH in the P system.

3.2. The complexes formation constants Determination

3.2.1. Binary complexes

Amino acids and peptides formation constant values of the binary complexes (Table 2) showed contrast values with which published in literature [19, 20]. Potentiometric titration of pyridoxine (P) was performed with and/or without the existence of Zn(II) ion in aqueous solution at ratios ranging from 1:1 to 1:3 stoichiometry, at a temperature of 25 °C, and ionic strength of I = 0.10 mol dm^{-3} ($NaNO_3$).

The Zn(II) with the P curve value was lower than the value of the P titration curve, this is an indication of a complex formation through the release of a proton. The selection of the most statistically-suitable model shows that it contains [Zn (II)-P] 1100, [Zn(II)-$(P)_2$] 1200, [Zn(II)-(P)(H_{-1})] 110-1 and [Zn(II)-(P)$(H_{-2})_2$] 120-2 species. The pH function of different species is displayed in a diagram that shows their distribution in multiple concentration values in Fig. 2. All Zn–P species concentrations showed parallel increases with pH increasing, attaining a maximum of 29.7.3% at pH 5.0. A reduction of the species Zn-P concentration is noticed after the increase of pH in addition to elevation in the Zn(II)-$(P)_2$ concentration . Table 2 displays the complexes' constants of stability.

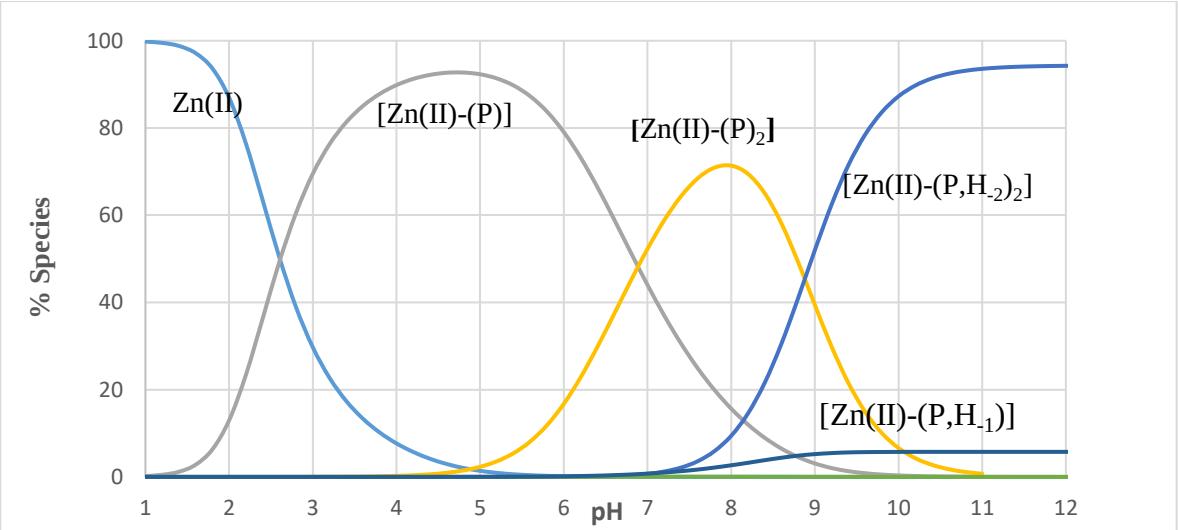


Figure 2. Percentage of species distribution as a function of pH in the Zn(II)-P system.

Table 2. *log β* of binary complexes at 25 °C and I = 0.10 mol dm^{-3} ($NaNO_3$).

Systems	**m**	**p**	**l**	**h**[r]	***log β***[b] **± SD**
$Zn(H_2O)_6^{+2}$	1	0	0	-1	-7.43 ±0.01
	1	0	0	-2	-15.09 ±0.01
Zn(II)-Pyridoxine (P)	1	1	0	0	2.89 ±0.02
	1	2	0	0	8.04 ±0.06
	1	1	0	-1	-2.34 ±0.02
	1	2	0	-2	-7.30 ±0.04
Zn(II)-Glycine	1	0	1	0	3.03 ±0.01
	1	0	2	0	7.23 ±0.02
Zn(II)-Valine	1	0	1	0	3.38 ±0.01
	1	0	2	0	7.23 ±0.02
Zn(II)- Ornithine	1	0	1	0	4.29 ±0.02
	1	0	2	0	8.71 ±0.02
Zn(II)- Alanine	1	0	1	0	3.12 ±0.01
	1	0	2	0	7.10 ±0.04
Zn(II)-Cysteine	1	0	1	0	4.44 ±0.02
	1	0	2	0	8.25 ±0.01
Zn(II)-Histidine	1	0	1	0	4.21 ±0.01
	1	0	2	0	8.13 ±0.01
Zn(II)-Glycyl-glycine	1	0	1	0	4.00 ±0.01
	1	0	1	-1	2.43 ±0.01
Zn(II)-Glycyl-L-alanine	1	0	1	0	3.64 ±0.01
	1	0	1	-1	2.23 ±0.01
Zn(II)- Glycyl-L-leucine	1	0	1	0	4.35 ±0.02
	1	0	2	0	8.71 ±0.01
	1	0	1	-1	2.86 ±0.03

[r] *m, p, l, and h* are the stoichiometric constants. Uncertainties are expressed as ± one standard deviation

3.2.2. Mixed-ligand complexes

3.2.2.1. Amino acids

Amino acids L with drug P were used to form mixed ligand complexes to yield a potentiometric data, this data fitted with another model assuming that P and L ligation will occur simultaneously according to the equilibrium seen below (5), charges being removed to avoid complexity.

$$Zn + P + L + H \rightleftharpoons [Zn(P)(L)(H)] \quad (5)$$

Upon Computer analysis of pH titration data the result shown the formation of the species: [Zn(P)(L)] (1110) and [Zn(P, H−1)(L)] (111-1). Histidine and ornithine forms, in addition to the 1110 and 111-1, the protonated (1111) species [21]. The equation below is used to estimate the pK_a of protonated species.

$$pK_a = \log \beta_{1111} - \log \beta_{1110} \quad (6)$$

Histidine complex have pK_a = 5.32 which is lower than pK_a of amino group NH_3^+ (pK_a = 9.11), but nearer in value to the pK_a of the imidazole group (6.06), which suggests that the protonated complex proton are occurs on the imidazole group. The formation constant of ornithine complex is greater than α-amino acids, which reflects that the ornithine is ligating through two amino groups [21]. The acid dissociation constants pK_a values of the [Zn(P, H_{-1}) L] complexes ($\log\beta_{1110}$–$\log\beta_{111\text{-}1}$) obtained with glycine, valine, L-ornithine, alanine, cysteine, histidine are 5.92, 6.09, 6.40, 6.19, 5.95 and 5.72 respectively. 111–1 species corresponds to the deprotonation of OH of pyridoxine (P).

Formation constants $\log K^{Zn(P)}_{Zn(P)(L)}$ and $\log K^{Zn(L)}_{Zn(P)(L)}$ (as shown in Table 3) were calculated for every mixed ligand system. It can be seen that P & L acts as the primary and secondary ligand respectively in all systems. Amino acids were represented by valine complexes speciation diagram in Figure 3 at pH value of 8.6, the maximum concentration 33% was achieved by the complex species of [Zn(p)(L)], So it's behavior in the physiological pH range is predominate. through simultaneous mechanism MC was formed and its relative stability was compared to those of the corresponding binary complexes and expressed in terms of Δlog K, % R.S and log X. Δ log K can define by the following equation:

$$\Delta \log K = logK^{ZnP}_{ZnPL} - (logK^{Zn}_{ZnL}) = logK^{ZnL}_{ZnPL} - (logK^{Zn}_{ZnP}) \quad (7)$$

Results in table 3 reported positive values of Δ log K, indicating that the amino acids (L) produce Better stable complexes with Zn(II)-P than with Zn (II). This result can be used as indication to a stacking interaction between the drug and the amino acids [22]. To measure the quantity of ternary complex stability, the percent relative stabilization (% RS) is outlined [23]:

$$\%\ R.S. = \left[\frac{(log\, K^{Zn(P)}_{Znu(P)L} - logK^{Zn}_{Zn(L)}}{logK^{Zn}_{Zn(L)}}\right] \times 100 \quad (8)$$

All systems parameters values percentage of R.S are positive (Table 3), which can be the proof of stability improvement, these values were agreed with the Δ log K values.

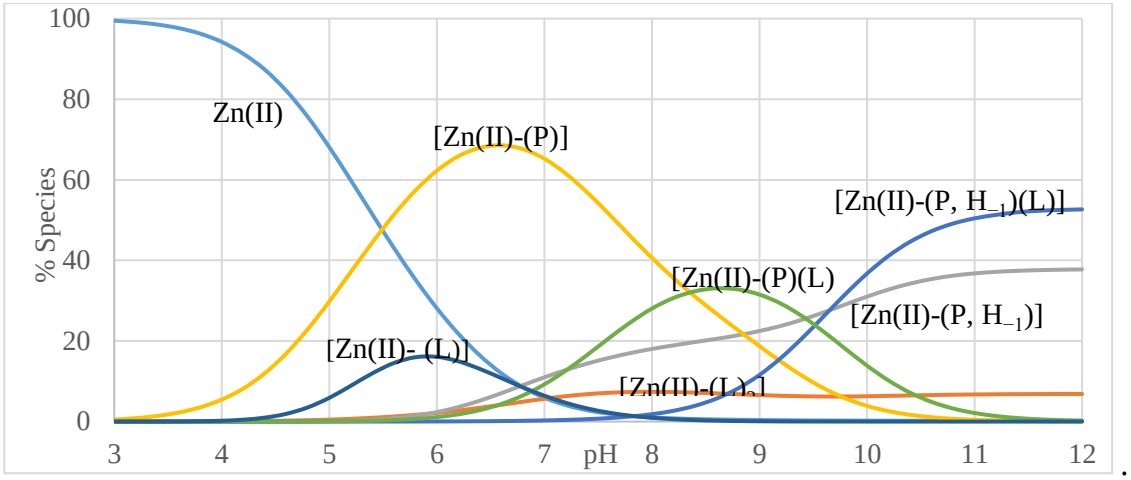


Figure 3. Percentage of species distribution as a function of pH in the Zn(II)-P-Valine system.

Table 3. log β and other parameters of mixed ligand complexes involving amino acids at 25 °C and *I* = 0.10 mol dm^{-3} ($NaNO_3$).

Systems	**m**	**p**	**l**	**h**[r]	***log β***[b] **± SD**	$log\ K^{Zn(P)}_{Zn(P)L}$	$log_{10}\ K^{Zn(L)}_{Zn(P)(L)}$	***Δ log K***	***%R. S***	***log X***
Zn(II)-P-Glycine	1	1	1	0	8.65 ±0.05	5.76	5.62	2.73	90.39	2.03
	1	1	1	-1	2.73 ±0.01					
Zn(II)-P-Valine	1	1	1	0	8.11 ±0.02	5.22	4.73	1.84	54.43	0.95
	1	1	1	-1	2.02 ±0.01					
Zn(II)-P-Ornithine	1	1	1	0	10.75±0.01	7.86	6.46	3.57	83.21	4.75
	1	1	1	-1	4.35±0.06					
	1	1	1	1	16.30±0.03					
Zn(II)-P-Alanine	1	1	1	0	8.52 ±0.01	5.63	5.40	2.51	80.44	1.90
	1	1	1	-1	2.33 ±0.01					
Zn(II)-P-Cysteine	1	1	1	0	10.05 ±0.01	7.16	5.61	2.72	61.26	3.81
	1	1	1	-1	4.10 ±0.01					
Zn(II)-P-Histidine	1	1	1	0	10.23 ±0.01	7.34	6.02	3.13	74.35	4.29
	1	1	1	-1	4.51±0.01					
	1	1	1	1	15.55±0.03					

[r] *m*, *p*, *l* and *h* are the stoichiometric coefficient. Uncertainties are expressed as ± one standard deviation.

Disproportionate constant X of mixed ligand complexes [24] can be defined by Eqs. 9 and 10 (Table 3):

$$Zn(P)_2 + Zn(L)_2 \rightleftharpoons 2Zn(P)(L) \qquad X= \frac{[Zn(P)(L)]^2}{[Zn(P)_2][Zn(L)_2]} \qquad (9)$$

$$\log X = 2\log \beta^{Zn}_{Zn(P)L} - \left(\log\beta^{Zn}_{Zn(P)_2} + \log \beta^{Zn}_{Zn(L)_2}\right) \qquad (10)$$

Statistical grounds expected of log X is + 0.6 for all geometries [25]. Obtaining of positive values higher than those expected statistically, pointed to the noticeable stabilities of ternary complexes.

3.2.2.2. peptides

The peptides may form the [Zn(P)(L)] or [Zn(P)(LH$_{-1}$)] complexes by organization through the amine and carbonyl groups. A switch to amide nitrogen from the initial oxygen of carbonyl should occur at sites of coordination following the increase of pH [26]. The amide groups experience deprotonation and the [Zn(PH$_{-1}$)LH$_{-1}$ complexes were formed. Two pKa values obtained with glycyl-glycine, glycyl-L-alanine and glycyl-L-leucine complexes, the pKa$_1$ (logβ_{1110}–log$\beta_{111\text{-}1}$) are 4.8,4.52 and 5.97 and pK_{a2} (log$\beta_{111\text{-}1}$–log$\beta_{111\text{-}2}$) are 8.75, 9.18 and 8.97 respectively. The species 111–1 resembles to the deprotonation of OH of P as for the Zn(P, H$_{-1}$)–amino acid complexes. The pK_{a2} of the [Zn(P, H$_{-1}$)-pipteds, H−1] (111$_{-2}$) corresponds to amide ionization. The pK$_{a2}$ (log$\beta_{111\text{-}1}$–log$\beta_{111\text{-}2}$) of the glycyl-L-alanine complex was greater than glycyl-glycine and glycyl-L-leucine. The formation of a slightly less favored and more strained chelate ring with seven members explains this phenomenon. The distribution curves concentrations in all types of the formed complex 1110 were increases with increasing the pH, so it make the formation of the complex (in the physiological pH range) are more favorable.

Table 4. *log β* and ***Δ log K*** of mixed ligand complexes involving peptides at 25 °C and I = 0.10 mol dm^{-3} ($NaNO_3$).

Systems	**m**	**p**	**l**	**h^r**	***log β^b* ± SD**	***Δ log K***
Zn(II)-P-Glycyl-glycine	1	1	1	0	9.65 ±0.02	-0.47
	1	1	1	-1	4.85 ±0.03	
	1	1	1	-2	-3.90 ±0.02	
Zn(II)-P- Glycyl-L-alanine	1	1	1	0	9.47 ±0.01	-0.17
	1	1	1	-1	4.95 ±0.01	
	1	1	1	-2	-4.23 ±0.02	
Zn(II)-P- Glycyl-L-leucine	1	1	1	0	9.18 ±0.01	-2.54
	1	1	1	-1	3.21 ±0.02	
	1	1	1	-2	-4.76 ±0.04	

^{r}*m*, *p*, *l*, and *h* are the stoichiometric coefficient. Uncertainties are expressed as ± one standard deviation.

The concentration of the (111−1*)* complex increases, while the concentration of the 1110 complex is reduced upon the increase in pH. When the pH increases further, the concentration of the 111–1 complex decrease and an increase of the concentration of the (111–2) complex is observed. in Table 4 contains the Δ log K values representing the complexes' relative stabilities. The Δ log K value for the induced deprotonated peptide complexes were calculated using Eq 11.

$$\Delta \log K = log\beta_{111-1} - log\beta_{1100} - log\beta_{101-1} \quad (11)$$

Δlog K values of the induced deprotonated mixed ligand complexes were negative, this shows that the formation of the binary amide complexes is more preferable than ternary ones. Built on the information that Δlog K values rely on the metal ion and the ligands coordination number, the change in Δlog K values found could be referred to the alteration in the geometry of the complex [27].

4. CONCLUSION

The current work exploration explain the equilibrium formation of Zn(II) complexes using pyridoxine HCl drug in addition to some other bioligands containing different functional groups. FC of the complexes formed in solution were estimated at T= 25 °C and *I*= 0.10 mol dm^{-3} ($NaNO_3$). The results indicate that the mixed ligand complex formation was carried out using a simultaneous mechanism. The calculated stabilization parameter (Δ log K, log X, log X, and % R.S) values of the amino acids mixed ligand complexes are higher in stabilities than their binary complexes.

Due to the specific characteristic of the hetero-aromatic N-base, the Δ log K values for peptide systems are negative, accordingly the peptide could have π -accepting qualities with a better effect on the stability of the complexes, and thus the mixed ligand complexes formed have lower stability than binary complexes. Finally, the concentration distribution illustrations of ligands and other binary and ternary complexes obtained were evaluated.

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