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Potentiometric Studies on Binary and Ternary Complexes of Ni(II) and Cu(II) Ions with L-Valine and Paracetamol

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Abstract: The protonation constants of the free ligands and the stability constants of binary and ternary complexes of bivalent metal ions of Ni(II) and Cu(II) with a biologically important amino acid of L-valine, *Val*, and paracetamol, *Para*, were studied potentiometrically in aqueous solutions at 313.15 ± 0.1 K and a fixed ionic strength of I = 0.10 M NaCl. The complexation model for each system was established using the Irving-Rossotti equation. The formation of the 1:2 or 1:1 binary complexes and 1:1:1 ternary complexes in which the amino acid *Val* was used as the primary ligand and *Para* as the secondary ligand, as inferred from the corresponding potentiometric pH-metric titration curves, and their relative stabilities compared to the corresponding ML and ML_2 binary complexes are expressed in terms of statistical parameters ΔlogK, $\log K_1$ and $\log K_2$. The complex stability was found to follow the order of Cu(II) > Ni(II). Through these diagnostic studies, it was possible to give the general formula of compounds prepared from amino acids and paracetamol. Amino acid binds to the central ion through oxygen in the hydroxyl group and nitrogen atom in the amine group ($-NH_2$), whereas paracetamol forms a unipolar bond by binding to the concentrated ion through the oxygen atom in the hydroxyl group. Most of the nickel complexes had octahedral symmetry with valine and paracetamol ligands, while the copper complexes had square or hierarchical to square base symmetry.

Keywords: Binary complexes; L-Valine; Paracetamol; Potentiometric method; Stability constant; Ternary complexes

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1. INTRODUCTION

Mixed-ligand metal complexes are a branch of biological inorganic chemistry and have important implications for many other sciences, ranging from medicine to environmental science. Studies on the roles of metal ions in biological systems often involve the development of relevant chemistry (1-3). Metal-ligand complexes consist of a central metal, known as Lewis acid, that is bound to ligands, commonly known as Lewis bases, which can either be ions, atoms, or neutral molecules (1-3). When a ligand contains two or more donor atoms close to each other, the formed metal complex is said to be a chelate, and the process is referred to as chelating. Cu(II), among essential transition metals, is important for many enzymes, particularly those catalyzing physiologically important reactions. Copper has a strong ability to form complexes with proteins, peptides, and enzymes in living organisms (4, 5). Examples of copper-containing compounds are tyrosinase, ferroxidase and haemocyanin (4). Ni(II) is important because of its ability to replace other metal ions in enzymes and proteins, as well as to bind to cellular compounds containing O, S and N atoms, such as enzymes and nucleic acids. Nickel is essential for the healthy life of humans and animals, and its deprivation profoundly impairs intestinal absorption of iron and thus causes anaemia. It has been reported that 90% of both glucose and glycogen concentrations in the liver and serum were reduced by nickel depletion (6).

Among various bioactive ligands, amino acids have special importance compared to other chemical compounds because they are regarded as the foundation stones of living organisms. Therefore, it is necessary to study their chemical properties to explain their behavior and potential applications. Among these properties are the stability constants and the thermodynamics of complexes they form with various metals (7, 8). Amino acids can act as coordinating agents through their amino (NH_2) and carboxyl (COO^-) groups. These groups provide a

more diverse coordination activity towards heavy metal ions and thus can be used to isolate heavy metal ions and obtain safer drugs or antidotes against metal poisoning.

L-Val (Fig. 1) is an α-amino acid used in the biosynthesis of proteins (9). Because L-*Val* is an essential amino acid that is not synthesized by the body, it must be obtained from food or supplements. *L-Val* plays an important role in synthesis and maintenance of muscles, stress management, growth in children, and support of the immune system as well as the functioning of the nervous system. Earlier studies have shown that *L-Val* may help to manage nervousness and insomnia because it has a role in forming the myelin sheaths that cover nerve cells. Valine, like other branched-chain amino acids, is associated with insulin resistance; higher levels of valine are observed in the blood of diabetic humans (9-11).

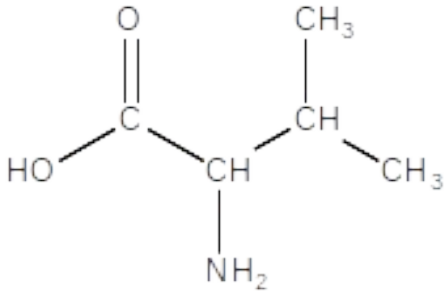


Figure 1: Structure of *L-Val* (2-amino-3-methylbutanoic acid).

Paracetamol *(Para)* (Fig. 2) is most widely used in the world today and leads the list of the World Health Organization (WHO) as the most important, safe, and effective medicine for the health care system (1, 2, 12-20). It is used as a treatment for headache, toothache, migraine attacks, moderate strength cases of arthritis, as well as to reduce postvaccination fever in children (1, 2, 12-21). In addition, it is used instead of aspirin, especially in patients with infectious diseases such as gastric ulcers (13, 14). Although *Para* is used to treat inflammatory pain, it is not generally classified as a nonsteroidal anti-inflammatory drug (NSAID) because it exhibits only weak anti-inflammatory activity (1, 2, 12-22).

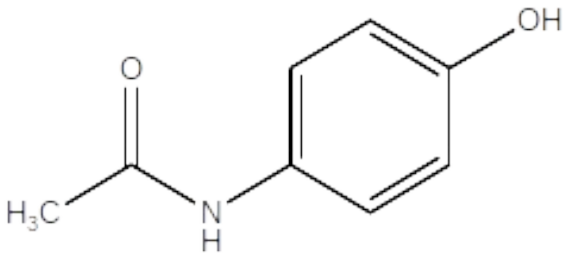


Figure 2: Structure of para(N-(4-hydroxyphenyl)acetamide)

Singh and coworkers studied the interaction of transition metal ions with N-benzoyl-*Val*, N–benzoyl, glycol-*Val,* and isovaleric acid (23). They adopted the pH titration technique to evaluate stability constants at 25, 35 and 45 °C and an ionic strength of 0.15 M (KNO_3) in 50 % (v/v) water-dioxane medium. Their study reported that only 1:1 metal complexes were formed with stability.

Enamullah and coworkers determined the proton-ligand and metal-ligand formation constants of phthalamic acid with transition metal ions such as Zn(II), Ni(II), and Cd(II) (1, 2, 24). It has been found that the metal ions Zn(II) and Cd(II) formed complexes at low ionic strength, I = 0.1 M. At higher ionic strengths, such as I = 0.15 M, these ions seem to be inactive towards the ligand. Some chelates of penicillamine with different metal ions have been studied (25-27). Chakravarti et al. studied the formation of biological chelates of divalent metal ions with a cephalosporin by the pH-metric method (1, 2, 28). In their study, it was found that the stability constants follow the order Cu(II) > Zn(II) > Co(II) > Ni(II) > Cd(II) > Mg(II) > Mn(II). In addition, the logK values are less negative than -0.6, suggesting favored formation of ternary complexes.

As part of our interest in studying the coordination chemistry of transition metal (29-35), this paper addresses the determination of the stability constants of new ternary complexes formed by Ni(II) and Cu(II) with *Val* and *Para* (first report), using a potentiometric pH method in the presence of 0.1 M (NaCl) ionic strength at the bodily temperature of 313.15 ± 0.1 K. The method of Calvin-Bjerrum (36, 37) as adopted by Irving and Rossotti (38, 39) was used to determine logK values.

2. MATERIALS AND METHODS

2.1 Materials

All chemicals utilized in this investigation were of analytical reagent grade (AR) quality and highest purity. *Val* (>99%) and *Para* (99.5%) were purchased from Fluka and CCM (Malaysia), respectively. Metal salts, including $CuCl_2.2H_2O$ (≥ 99.99%), were obtained from T-Baker lab chemicals, and $NiCl_2.6H_2O$ (98%) was obtained from Surechem Products. Sodium hydroxide (98.8%) was purchased from Shandong, hydrochloric acid (36%) from Scharlau-chemise and sodium chloride (99.7%) from BDH Chemicals. The most of metal cation-EDTA complexes have a relatively high formation constant, which is the main factor driving the widespread use of EDTA in the standardization of metal cation solutions. A complexometric indicator is needed to identify the endpoint of metal cation titrations carried out with EDTA. The most common indication for this use is a blue dye called Eriochrome Black T (Erio-T). When complexed with metal ions, Erio-T is utilized in EDTA titration, which results in a color change from blue to pink at the endpoint. In the complexometric titration, an ammoniacal buffer solution of pH 10 (mixture of ammonium chloride and ammonium hydroxide) is used because all metal–EDTA reactions are pH-dependent.

2.2 Solutions

A hydrochloric acid stock solution was prepared and titrated against standardized sodium hydroxide. The stock solution of 0.004 M *Val* was freshly prepared before use by accurately dissolving 0.04686 g of *Val* powder with a minimum quantity of deionized distilled water. A fresh stock solution of 0.02 M *Para* was prepared daily by dissolving 0.30234 g of *Para*

in deionized distilled water. Carbonate-free sodium hydroxide solution was prepared and standardized against standard oxalic acid solution before starting an experiment. The stock solution of each metal salt was prepared by dissolving the required quantities (0.47542 g of Ni(II) and 0.34096 g of Cu(II)) in deionized distilled water. The stock solution of metal salt was standardized by ethylenediaminetetraacetic acid (EDTA) titrations.

2.3 Apparatus

Potentiometric titration was performed using a Thermo Electron Corporation Orion 3-Star pH Benchtop (accuracy ± 0.002) instrument with a glass and calomel electrode assembly. The pH-meter was standardized before each titration with a buffer solution of pH 4.01, 7 and 10. The temperature was constantly maintained (± 0.1 K) by Gant Instruments (Cambridge) Ltd. Thermostated Water Bath: Model SUB28.

2.4 Procedure

The experimental procedure involved the potentiometric titration of the following sets of solutions:

1) Acid titration: HCl (0.1 M, 10 mL)
2) Ligand titration: HCl (0.1 M, 10 mL) + *Val* (0.004 M, 10 mL).
3) Metal(II) + ligand titration: HCl (0.1 M, 10 mL) + *Val* (0.004 M, 10 mL) + metal(II) (0.004 M, 10 mL).
4) Metal(II) + ligand titration: HCl (0.1 M, 10 mL) + *Para* (0.004 M, 10 mL) + metal(II) (0.004 M, 10 mL).
5) Metal(II) + mixed ligand titration: HCl (0.1 M, 10 mL) + *Val* (0.004 M, 10 mL) + metal(II) (0.004 M, 10 mL) + *Para* (0.004 M, 10 mL).

The total volume used in each cell was 50 mL in the absence and presence of 0.1 M NaCl for the ionic strength study and at a temperature of 313.15 ± 0.1 K. Titration curves were obtained from the plots of pH versus volume of alkali required, and the four curves are referred to as (i) acid, (ii) ligand, (iii) complex, and (iv) mixed ligand complex (Fig. 3).

3. RESULTS AND DISCUSSION

3.1 Collection of Literature Data

The protonation constants and stability constant of the binary complexes of the drugs paracetamol and the amino acid L-Valine had previously been determined and are reported in various literature reports. According to the temperature and the type of solvent, it was observed that the values of these constants varied (see Tables 1 and 2).

Moreover, there was also a variety of salts (KNO_3, $NaNO_3$, NaCl and $NaClO_4$) that were added to the aqueous medium as an ionic force. Furthermore, the values of these constants were affected by the ionic strengths of several salts (KNO_3, $NaNO_3$, NaCl, and $NaClO_4$). Since these values will be utilized to determine the stability constants of the ternary complexes, it was necessary to re-determine these constants.

3.2 Protonation Constants of Paracetamol and L-Valine Ligands

A critical study of the literature data was conducted because there are various studies dealing with the protonation constant of the L-Valine amino acids and paracetamol ligands. The most relevant references are those shown in Table 1, the values are in good agreement (40). L-Valine exists as zwitterions in aqueous solution, the carboxyl group is deprotonated in acidic media at pH 2 to 3, whereas the amino group is protonated in basic solutions at pH 9 to 10. The two dissociation mechanisms are thus entirely distinct from one another. In the case of paracetamol, its pK_a is 9.38, at this pH, the paracetamol molecules are in the protonated form, while the deprotonated form will be mostly present when $pH > 9.24$ (41).

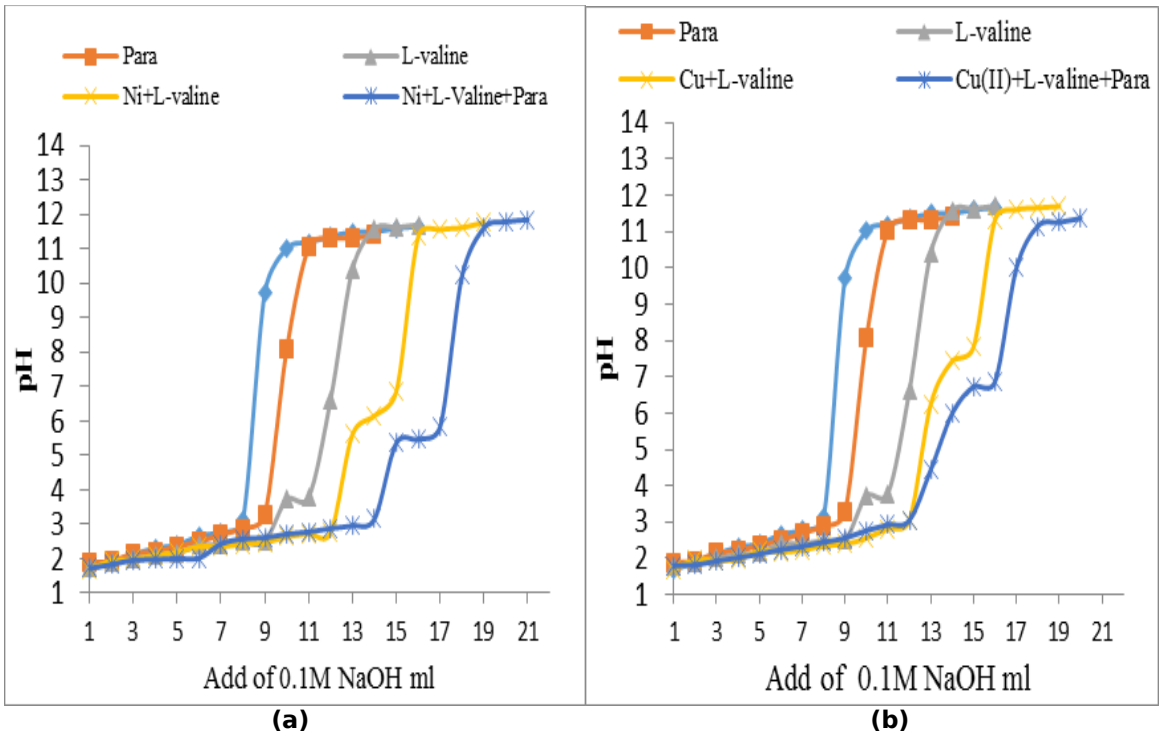
Stability constants for the nickel and copper complexes of L-Valine amino acid can readily be obtained with pH-metry. Tentative values of the stability constants for the nickel and copper binary system are listed in Table 2. The values obtained are in agreement, and they are given as recommended values.

Many authors have reported the study of stability constant of L-Valine with Cu and Ni metal complexes as seen in Table 2. However, few data on the stability constant of binary paracetamol–Cu(II) or binary paracetamol-Ni(II) complexes have been reported in literature and for the mixed ligands complexes have not been reported elsewhere in literature, to the best of our knowledge. Therefore, the present study is aimed at determining the stability constant of ternary para-L-Val-Cu(II) para-L-Val-Ni(II)and complexes using pH-metry method.

3.3 Potentiometric Measurements of Binary and Ternary Complexes

3.3.1 Binary Complexes

The proton dissociation constants of *Para* and *L*-Valine and their complexes with Ni(II) and Cu(I) were determined in aqueous medium at 313.15 K in the absence of I = 0.1 mol/L NaCl. The formation constants of binary complexes were obtained using Irving - Rossotti equations by calculating the values of the average number of ligand molecules attached per metal ion (ñ) and free ligand exponent (pL) (Irving and Rossotti, 1953, 1954). The titration curves (Fig. 3) indicate that the ligand curves are slightly shifted to the high pH value of the acid titration curve.



(a) **(b)**

Figure 3: Potentiometric titration curves of **(a)** *Val - Para* - Ni(II) complexes and **(b)** *Val-Para* - Cu(II) complexes at 313.15 K.

Table 1: Protonation constants (logK^H) of free ligands (Literature Values)

ligand	$\log K_1^H$	$\log K_2^H$	Condition	Ref.
L-Valine	9.41	2.95	25 °C, $NaNO_3$ (0.1 M), 40% ethanol-water	(42)
	9.62	2.32	25 °C, aq, KNO_3(0.1M)	(43)
	9.50	2.36	25 °C, aq, $NaClO_4$(0.1M)	(44)
	9.405	2.292	37 °C, aq,	(45)
	9.805	2.298	37 °C, aq, (NaCl 0.1 M)	(46)
	9.47	2.25	25 °C, aq, (KNO_3 0.11M)	(47)
	9.49	2.26	30 °C, aq, ($NaClO_4$ 0.1M)	(48)
	9.60	2.31	30 °C, aq, ($NaClO_4$ 0.2M)	(49)
Paracetamol	9.24	-	37 °C, aq, ($NaNO_3$ 0.1M)	(50)
	9.50	-	25 °C, aq	(51)
	9.47	-	37 °C, aq,	(46)
	9.67	-	37 °C,(KNO_3 0.1 M), 40% Ethanol-water	(52)

Table 2: Stability constants of Cu and Ni binary metal complexes of L-Valine amino acids and paracetamol ligands (Literature Values)

Complexes	$\log K_1$	Condition	Ref.
Ni(II)-Para	5.59	25 °C, aq, $NaClO_4$(0.1 M)	(53)
	3.30	KNO_3 (0.1),40%ethanol-water	(52)
Cu(II)-Para	1.54	37 °C, aq, $NaNO_3$ (0.1 M)	(50)
Ni(II)-L-Val	9.71	30 °C, aq, $NaClO_4$ (0.1 M)	(48)
	8.98	30 °C, aq, $NaClO_4$ (0.2 M)	(49)
	9.72	25 °C, aq,	(54)
	9.53	25 °C, aq, KNO_3 (0.15 M)	(55)
	9.02	40 °C, aq, KNO_3 (0.15 M)	(55)
Cu(II)-L-Val	11.54	25 °C, aq, $NaNO_3$ (0.1 M), 40%ethanol-water	(42)
	14. 76	25 °C, aq, KNO_3 (0.15 M)	(55)
	14.28	35 °C, aq, KNO_3 (0.15 M)	(55)

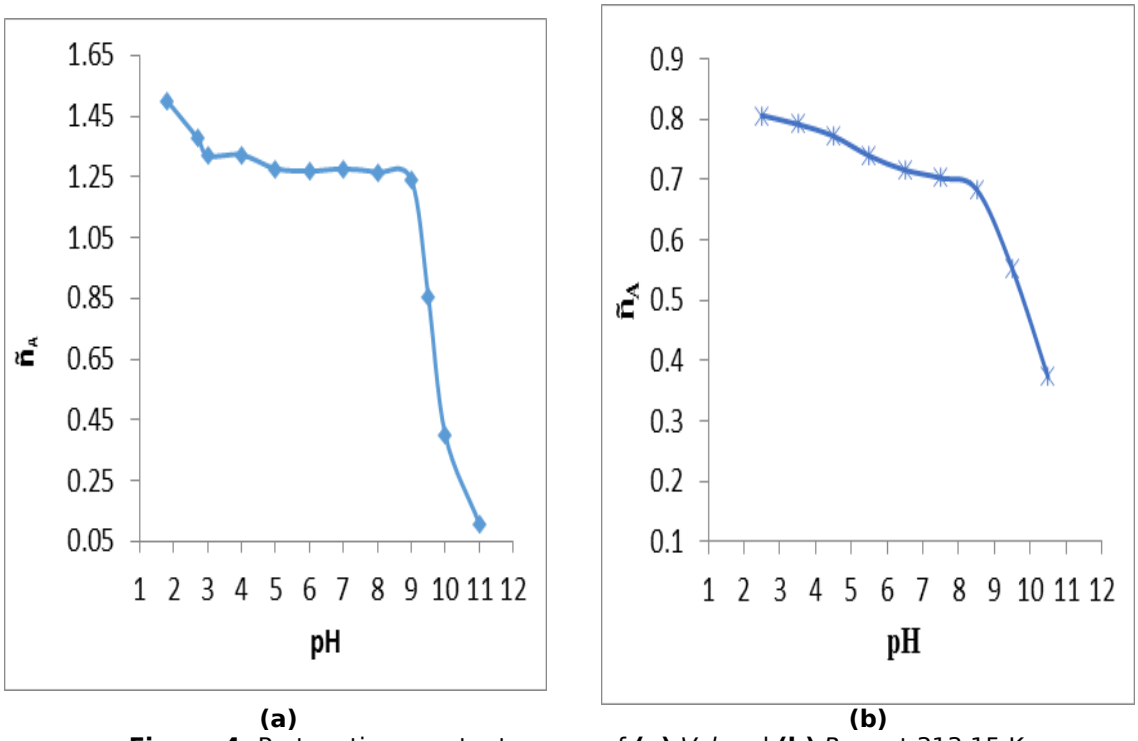
The shift is due to the interaction of protons with the ligand and subsequently with the metal ion. The values of n_A (the degree of formation of the proton complex) were calculated using the following equation:

$$n_A = Y + \frac{\left[(V' - V'') \times (N + E^0)\right]}{\left[(V^0 + V') \times T_L^0\right]} \quad \text{(Eq. 1)}$$

where Y = number of replaceable hydrogen ions, V°

= total volume (50 mL), V' = volume of alkali required by the acid, V" = volume of alkali used by acid and ligand, N = concentration of alkali, E° = total strength of acid and T_{L° = total concentration of ligand (37, 39).

The proton ligand formation curve was obtained by plotting the degree of formation (n_A) of the proton complex against pH values. The values of $\log K_1^H$ and $\log K_2^H$ were determined from the curves corresponding to n_A values of 0.5 and 1.5 (Fig. 4). The protonation constants at 313.15 ± 0.1 K were calculated (39, 56) and are summarized in Table 3.



(a) **(b)**

Figure 4: Protonation constant curves of **(a)** *Val* and **(b)** *Para* at 313.15 K.

Table 3: Protonation constants of *Val* and *Para* and stability constants of their complexes in the absence of 0.1 M NaCl (ionic strength) at 313.15 K.

Metal ions	M(*Val*)	M(*Val*)	M(*Para*)	$\log K^{M(L-Val)}_{M(L-Val)(Para)}$	Δ log*K*
	$\log K_1^H$	$\log K_2^H$	$\log K_1^H$		
H⁺	10.123	2.314	9.8773	------	------
Ni(II)	8.856	2.866	3.8250	5.9594	+ 2.1345
Cu(II)	9.342	2.995	4.0767	6.3943	+ 2.3176

The values of ñ (average number of ligand molecules attached per metal ion) were calculated using Equation 2:

$$\tilde{n} = \frac{\left[(V''' - V'') \times (N + E^0)\right]}{\left[(V^0 + V'') \times n_A \times T^0_M\right]} \qquad \text{(Eq. 2)}$$

where V"' = volume of alkali used for acid + ligand + metal ion, T_{M° = total concentration of the metal ion, while the other terms are defined as in Equation 1. The free ligand exponent, pL, was calculated using Equations 3a and 3b as given below:

$$pL = \log_{10}\left\{\sum_{j=0}^{j=J} {}^{0}\beta_j^H \frac{[H]^j}{(T_L - n T_M)}\right\} \qquad \text{(3a)}$$

$$pL = \log\left[\frac{1 + pK_1^H(1/anti\log B) + pK_1^H \times pK_2^H(1/anti\log B)^2}{T_L - \tilde{n} T_M} \times \frac{V + V'''}{V}\right] \qquad \text{(3b)}$$

where β_j^H = proton ligand stability constant and the rest of the terms are similarly defined as in Equations 1 and 2 (38, 39). Values of $\log K_1$ and $\log K_2$ were obtained using the Bjerrum half-integral

method (37, 39) and interpolation at half n values calculation method using the following equations:

$$\log K_1 = pL \quad (4a)$$

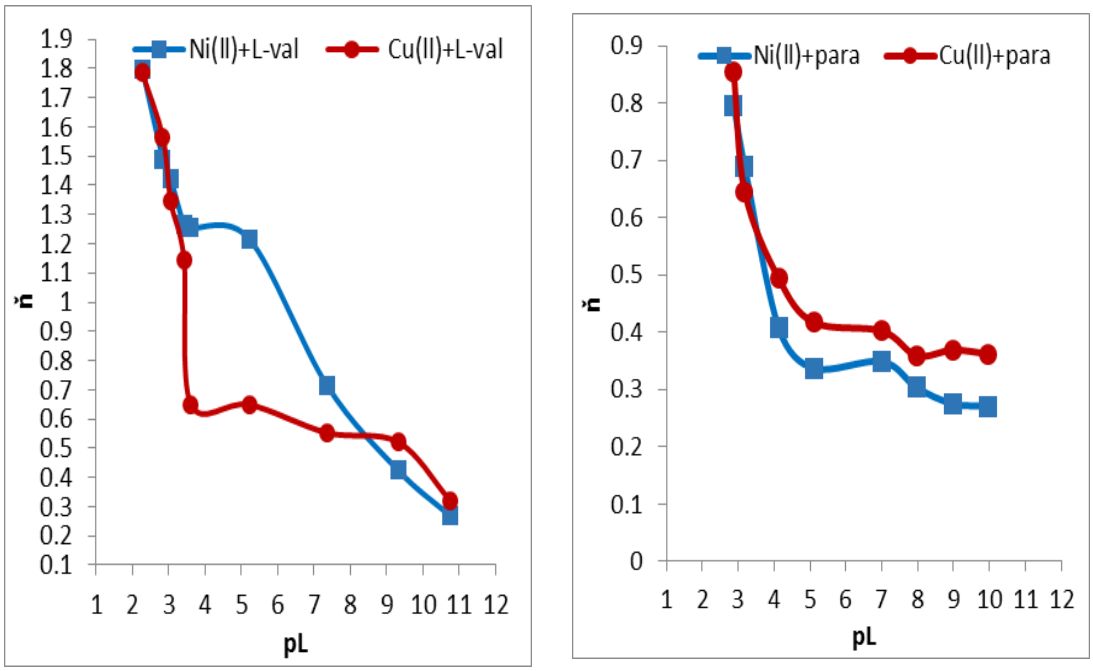
$$\log K_2 = pL \quad (4b)$$

By plotting a graph of ñ against pL and determining the corresponding values of pL at ñ equal to 0.5 and 1.5, the respective values of $\log K_1$ and $\log K_2$ were obtained. The values of n obtained for the metal-ligand system indicate the formation of either 1:1 or 1:2 complexes (Fig. 5). The overall order of stability (logβ) is Cu(II)>Ni(II) and is in good agreement with the Irving-Williams order of stability (38). The values listed in Table 3 are related to the following equilibrium:

$$HL \leftrightarrow H^+ + L^- \qquad K_1=[H^+][L^-]/[HL] \quad (5a)$$

$$H_2L \leftrightarrow H^+ + HL^- \qquad K_2= [H^+][HL^-]/[H_2L] \quad (5b)$$

The attachment of a proton to the NH_2-group (A is the primary ligand) is associated with the $\log K_1$ value in *Val*, and the protonation of an α-carboxylate group (L is the second ligand) corresponds to the $\log K_2$ value in *Val* and the $\log K_1$ value in *Para*.



(a) **(b)**

Figure 5: Formation curves of binary metal ion complexes with **(a)** M(II) + *Val* and **(b)** M(II) + *Para* at 313.15 K

The obtained results show the same logarithm to the formation constants for all types of complexes, which have been identified using potentiometric titration as given by the following equilibria:

$$M+L \leftrightarrow ML \qquad K_1= [ML]/[M][L] \quad (6a)$$

$$\text{or } M+2\,L \leftrightarrow ML_2 \qquad K_2= [ML2]/[M][L]^2 \quad (6b)$$

3.3.2 Ternary Complexes

The potentiometric titration curves for ternary complexes (metal–*Val*-*Para*), representing typical titration curves for the metal–*Val*–*Para* system, studied in a 1:1:1 molar ratio at 313.15 K and in the absence of 0.1 M NaCl are shown in Fig. 3. The primary complex curve (free acid + M(II) + *Val*) and mixed ligand curve (free acid + M(II) + *Val* + *Para*) overlap with each other up to pH 3. This result indicates that within this pH range, the combination of secondary ligands does not take place when the primary ligand combines with the metal. Above pH 3, the two curves start to diverge from each other, signifying the starting point of occurrence for the combination of the secondary ligand with the primary complex (1, 2, 57-61).

In the calculation, ternary complexes were assumed to form in two steps. Initially, the primary ligand (A), with a higher formation constant in the binary complex, reacts with the metal ion to form a binary complex with formula MA. The binary ligand then coordinates to the second ligand (L) to form a mixed ligand complex in the form of MAL. The primary ligand can also be determined by comparing the titration curves of binary systems.

The complex that reached the highest pH before precipitation of the metal hydroxide was considered to be the first complex formed in mixed ligand systems, and the corresponding ligand was the primary ligand in a ternary complex. The formation of a ternary complex can be represented by the stepwise equilibrium below:

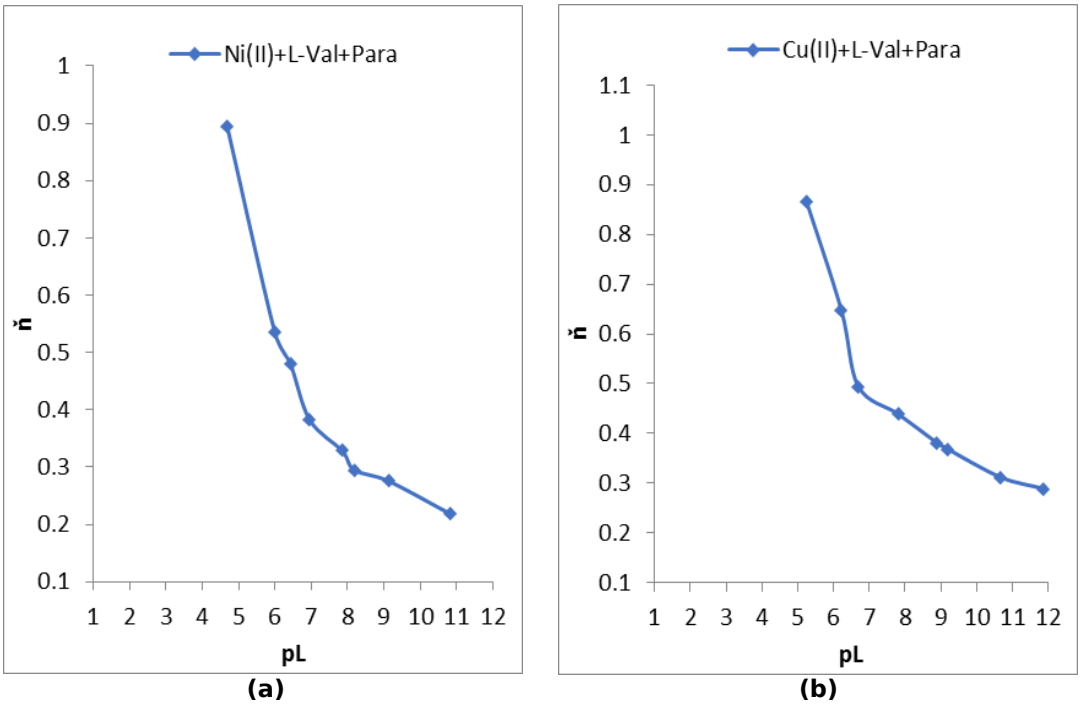
$$M + A \Leftrightarrow MA \qquad K_{MA}^{M} = \frac{[MA]}{[M][A]} \quad (7a)$$

$$MA + L \Leftrightarrow MAL \qquad K_{MAL}^{MA} = \frac{[MAL]}{[MA][L]} \quad (7b)$$

The values of ň (average number of secondary ligand molecules attached to the primary complex (M-*Val*)) were calculated from the following equation:

$$\tilde{n} = \frac{(V''' - V'') \times (N + E)}{(V - V'') \times T_M \times \tilde{n}_A} \quad \text{(Eq. 8)}$$

where T_M° = initial total metal ion concentration, V''' = the differences in the volume of alkali added between the (free acid + metal+ *Val* + *Para*) curve and (free acid + metal + *Val*) curve, and V'' = the differences in the volume of alkali added between the (free acid) curve and (free acid + *Para*) curve (1, 2, 57-61). The free secondary ligand exponent, pL, was calculated using Equation 3b and is shown in Fig. 6. The horizontal distance between the (free acid) curve and (free acid + *Para*) curve, V'', indicates the protons released as a result of self-dissociation of the secondary ligand, whereas the difference between the (free acid + M(II) + *Val*) curve and (free acid + M(II) + *Val* + *Para*) curve, V''', indicates the sum of protons released due to the self-dissociation of secondary ligand and protons released due to the formation of mixed ligand complex. Thus, (V''-V'') accounts for the total protons released due to the formation of the mixed ligand complex. The formation of the ternary complex M-(*Val*)-(*Para*) shifts the buffer region of the ligands to lower pH values, which indicates that the ternary complex is more stable than the binary complex.



(a) **(b)**

Figure 6: Formation curves of **(a)** Cu(II)-*Val*-*Para* and **(b)** Ni(II)-*Val*-*Para* complexes at 313.15 K.

To compare the stabilities of the ternary complex species with those of the parent binary complexes, the difference between the stabilities of the binary and ternary complexes values, Δlog*K*, were determined using Equation 9 and are summarized in Table 3.

$$\Delta \log K = \log K^{M(L-Val)}_{M(L-Val)(Para)} - \log K^{M}_{M} \quad (9)$$

It was determined that the Δlog *K* values were positive in terms of stability, and a statistical increase is shown in the value of stability constants of the mixed ligand complex. Based on the results in Table 3, the values of the ternary stability constants are found to decrease in the order of Cu(II) > Ni(II).

The complex formation equilibrium of the ternary metal ion complexes and the overall stability constants were calculated using the equations below:

$$M + (Val) + Para \leftrightarrow M(Val)(Para) \quad (10a)$$

$$K^{M}_{M(Val)(Para)} = \frac{[M(Val)(Para)]}{[M][Val][Para]} = K^{M(Val)}_{M(Val)(Para)} \times K^{M}_{M(Val)} \quad (10b)$$

3.4 Effect of Ionic Strength on Binary and Ternary Complex Formation

The interfering effects of ionic strength on the strength of metal ions, *Val*, and *Para* were studied in the presence and absence of ionic strength (0.1 M NaCl) at 313.15 K and 0.004 M of metal ions.

The titration curves of metal complexes in the presence of 0.1 M NaCl (Fig. 7) indicated that there was no precipitate formed in the solutions. This implies that there was no tendency to form hydroxo complexes either because the number of moles of

NaOH consumed was equivalent to the number of moles of HCl or because the interfering effects of hydroxo complexes are negligible. Based on Fig. 8, it can be concluded that metal ions with *Val* or *Para* form a 1:1 or 1:2 ratio of metal-ligand complexes.

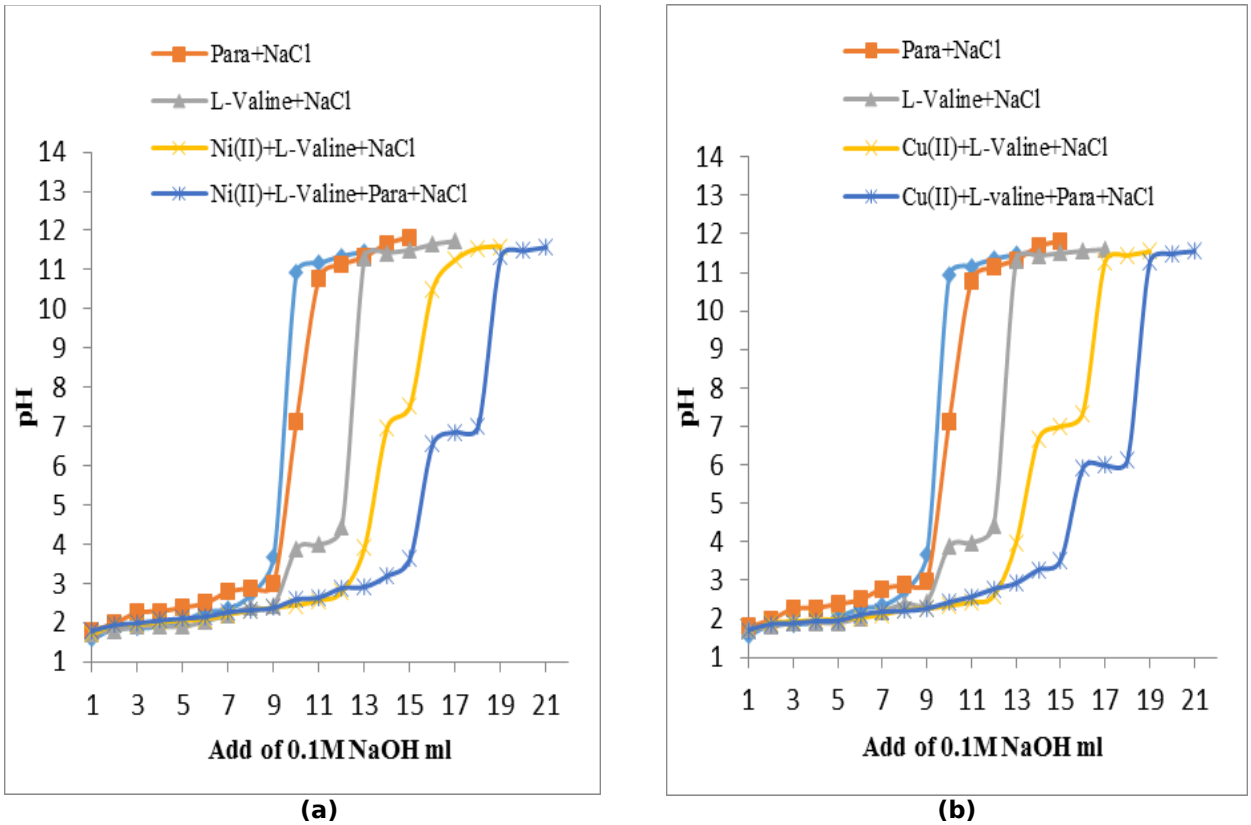


Figure 7: Potentiometric titration curves of **(a)** *Val*-*Para*-Ni(II) complexes and **(b)** *Val*-*Para*-Cu(II) complexes at 313.15 K and 0.1 M NaCl ionic strength.

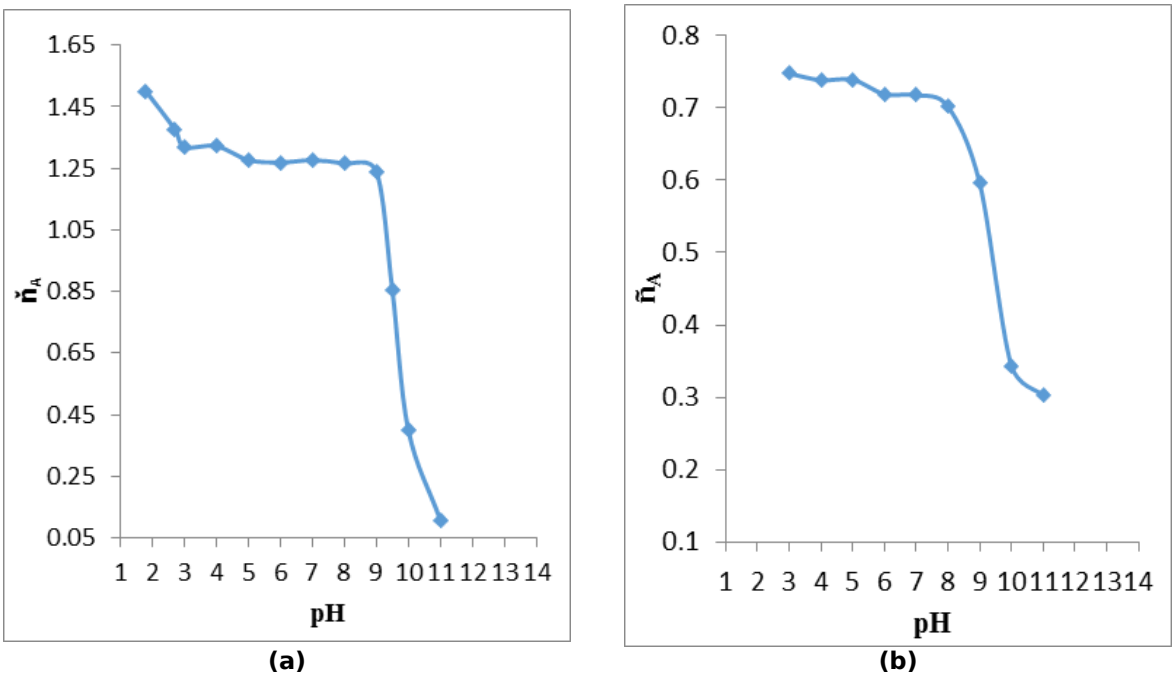
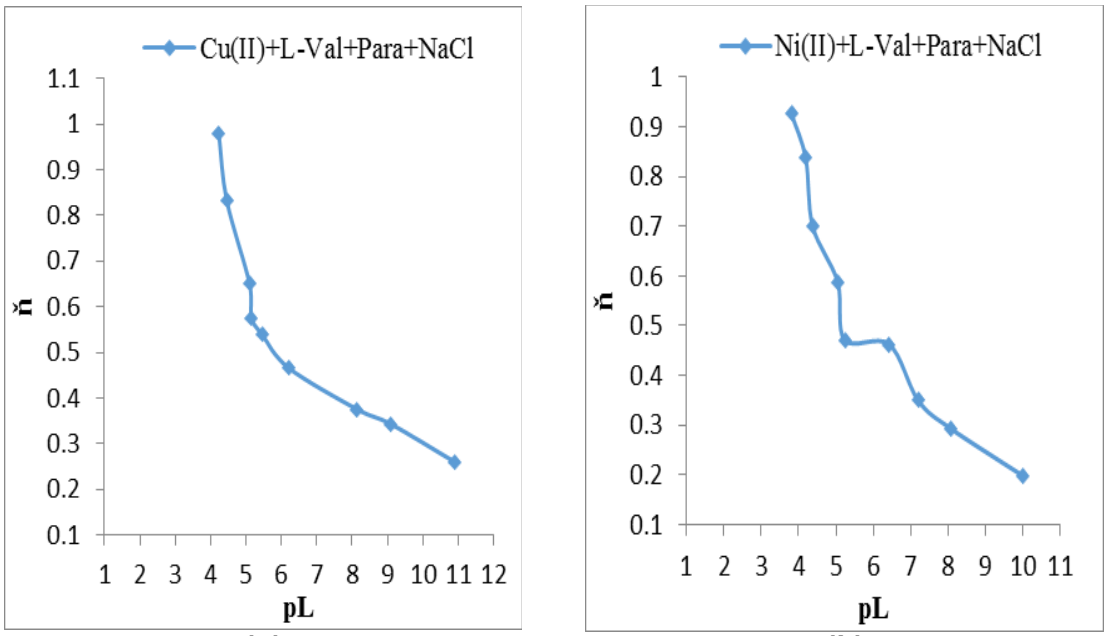


Figure 8: Protonation constant curves of **(a)** *Val* and **(b)** *Para* at 313.15 K.

It was also noted that the presence of NaCl during the complexation reaction causes an increase in pH (Fig. 9) as a result of the decrease in the protonation constant of *Val* for configuring the binary complex (M-*Val*) and the decrease in the protonation constant of *Para* for configuring the ternary complex (M-*Val*-*Para*), as shown in Fig. 8 and Table 4.



(a) **(b)**

Figure 9: Formation curves of ternary M(II)–Val-*Para* complexes at 313.15 K in the presence of 0.1 M NaCl and 0.004 M of **(a)** Cu(II) and **(b)** Ni(II).

Table 4: Protonation constants of *Val* and stability constants of its complexes at 313.15 K in the presence of 0.1 M NaCl (ionic strength).

Metal ions	M(*Val*)	M(*Val*)	M(*Para*)	$\log K^{M(Val)}_{M(Val)(Para)}$	Δ log *K*
	$\log K_1^H$	$\log K_2^H$	$\log K_1^H$		
H⁺	9.914	2.151	9.4058	-----	------
Ni(II)	8.683	2.811	3.0561	5.1567	+ 2.1006
Cu(II)	9.166	2.900	3.6011	5.7567	+ 2.1556

Moreover, it is noted that the values of stability constants of the formed complexes in the presence of NaCl are lower than the corresponding values in the absence of NaCl. The order of stability constants of the metal-para complexes formed (Table 4) shows a good agreement with the Irving–Williams order of Cu(II) > Ni(II) (62).

3.5 Effect of Ni(II) & Cu(II) Metal Ions on the Structure of Used Ligands

3.5.1 L-Valine

In order to comprehend how metals and proteins interact in biological systems, it is important to study metal complexes of physiologically active ligands such as amino acids. The stability constants of these complexes will also aid in identifying the atoms or groups that are in charge of forming the bonds with the metal ions. Metal ions have a number of distinguishing characteristics that make them able to perform out a wide variety of biofunctions as their small size, positive charge, and electron spin configuration (63, 64). Due to their acidic-basic nature, amino acids function as bidentate ligands to bind through (N, O) donor atoms. Amino acids are regarded as zwitterions, in which they include the positively charged NH_3^+ group or the negatively charged COO^- group (64).

The main goals of this investigation are to report the stability constants of the Cu(II) and Ni(II) complexes of *L-Val* along with to investigate the method in which *L-Val* interacts with the respective metal cations in aqueous environment. A copper(II) complex that exhibits a broad affinity for L-amino acids was described by Leach and Angelici (65). With L-leucine, L-phenylalanine, alanine, L-serine, and valine, copper(II) forms stronger complexes than with the corresponding antipodes, according to a set of stability constants determined using potentiometry. Noori et al. (66) had synthesized complexes of Mn(II), Fe(II), Co(II), Ni(II), Cu(II), and Cd(II) ions with L-Valine as a primary ligand and 1,10-phenanthroline as a secondary ligand. The work indicated that nickel has an octahedral geometry. Fayad et al. (67) reported the synthesis of six novel mixed ligand complexes of metals (II), using saccharin and L-Valine as primary and secondary ligands, respectively (67). The complexes with the formulas $[M(Val)_2(Sac)_2]$, M(II) = Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) were obtained. Based on the results, it could be concluded that L-Valine coordinated to metal ions as a bidentate ligand through the nitrogen of the amine group and the oxygen of the carboxylate group (See Fig. 10).

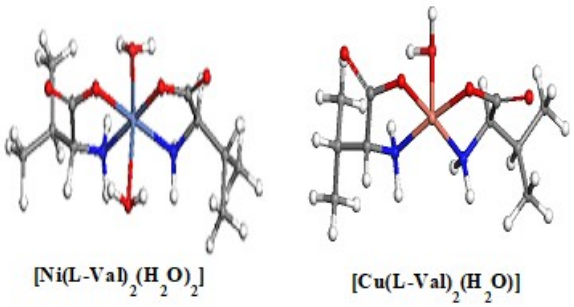


Figure 10: Suggested geometric structures of L-Valine complex.

3.5.2 Paracetamol Complexes

Metal complexes are playing a bigger role in the development of pharmaceuticals. This has prompted extensive research on metal drug complexes, in which pharmaceutical substances function through chelation to understand how metal binding affects the behaviors of biological processes in the human body (1, 2). Since paracetamol has two functional groups (NH amide and OH phenol), it is bound to metal ions once it enters the body. Refat et al. (68, 69) synthesized paracetamol complexes with Mn(II), Co(II), Fe(III), Zn(II), and Cu(II). Paracetamol behaves as a monobasic bidentate ligand in these complexes, and the structures of those complexes have been validated by elemental analysis, FT-IR spectroscopy, and thermal analysis. Obaleye et al. prepared and investigated complexes of Co(II), Ni(II), and Fe(III) with paracetamol (70, 71). According to research, paracetamol ligand acts as a bidentate chelating agent in which the oxygen of the hydroxyl and amide groups are coordinated (Fig. 11). Babamale et al. synthesized mixed metal complexes of aspirin and ascorbic acid involving the ions Fe(II), Co(II), Ni(II), Cu(II), and Zn(II) (72). According to the physical and spectroscopic studies, paracetamol's amide nitrogen and carbonyl oxygen were responsible for the metal's coordination. Based on the results, it could be concluded that paracetamol coordinated as a monodentate through the nitrogen atom (See Fig. 11).

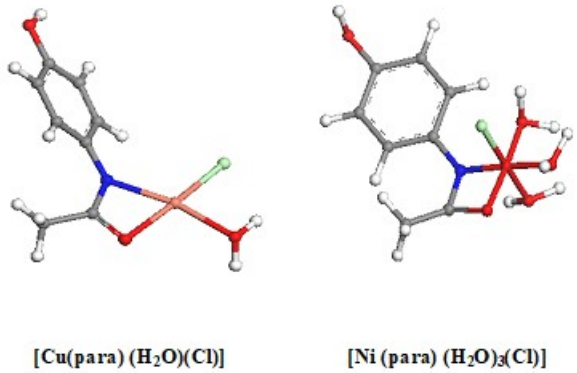


Figure 11: Suggested geometric structures of paracetamol complexes.

4. CONCLUSION

The stability constants for the ternary metal complexes of *Val* and *Para* with Ni(II) and Cu(II), formed with *Val* as the primary ligand and *Para* as the secondary ligand with metal ions, were computed from potentiometric titrations. The concentration of metal ions was kept constant at 0.004 M, and the ratio of metal ions: *Val*: *Para* was kept at 1:1:1. The stability constants in the absence of 0.1 M NaCl ionic strength were found to be higher than the stability constants in the presence of 0.1 M NaCl ionic strength. The order of stability is in accordance with the Irving-Williams order of stability: Cu(II) > Ni(II). The calculated values of the ΔlogK parameters showed the effect of the bound primary ligand on an incoming secondary ligand. The positive values of ΔlogK parameters indicate the higher stability of ternary complexes than the corresponding binary ones.

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