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# Solution Equilibria of Ternary Systems Involving Transition Metal Ions, Hydroxamic Acids, and Bioligands

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The formation of ternary complexes of the Cu(II), Co(II), Ni(II), and Zn(II) metal ions with some hydroxamic acids (acetohydroxamic acid, Aha; benzohydroxamic acid, Bha; salicylhydroxamic acid, Sham; and *N*-phenylbenzohydroxamic acid, *N*-PhBha) and some bioligands (α-alanine, α-ala; L-valine, L-val; norvaline, norval; aspartic acid, aspart; glutamic acid, glut; asparagines, asperg; histamine, Him; and imidazole, imid) was investigated using the potentiometric technique at 25 °C and $I = 0.10\ \text{mol}\cdot\text{dm}^{-3}$ $NaNO_3$. The stability constants of these ternary systems were calculated. The order of stability of the ternary complexes in terms of the nature of metal ions, hydroxamic acids, and bioligands was investigated and discussed as well as the values of $\Delta \log K$ and $\log X$ for the ternary systems. The concentration distribution curves of the various binary and ternary complex species in solution were evaluated. The effect of temperature of the medium on both the ionization process of Aha, Sham, aspart, and glut and the complex formation with Cu(II), Co(II), and Ni(II) for 1:1:1 ternary systems in the range of (15 to 45) °C and $I = 0.10\ \text{mol}\cdot\text{dm}^{-3}$ $NaNO_3$ in an aqueous medium has been studied. The thermodynamic parameters are calculated and discussed. Evaluation of the effect of ionic strength was carried out in $NaNO_3$ as a supporting electrolyte $I$ [(0.10 to 0.50) $\text{mol}\cdot\text{dm}^{-3}$]. The dependence on ionic strength of the stability constants of the binary and ternary complexes was analyzed. In addition, the chelation mode of the ternary complexes was ascertained by conductometric titrations. Also, confirmation of the formation of ternary complexes in aqueous solutions has been done using cyclic voltammetry measurements.

## Introduction

Hydroxamic acids ($RC(=O)N(OH)R'$) have been employed as chelating agents since long ago,[1] and their study still attracts much attention.[2,3] These compounds possess diverse biochemical activities in antibiotics, growth factors, antibiotic antagonists, and tumor inhibitors,[4−9] many of which are due to the properties of their complexes with transition metal ions.[10−12]

In most metal complexes formed with hydroxamic acids, coordination occurs by deprotonation of the OH group and subsequent O,O coordination of the carbonyl oxygen and deprotonated OH. Much of their biological activity is related to their capability to form very stable chelates with various metal ions.[13,14]

Amino acids are important low molecular weight ligands in humans[15−18] and other biosystems.[19,20] The reactivity of amino acids and other small organic molecules is often modified when they are coordinated to metal ions.[21,22] Since most of the processes in biological systems include metal ion interaction to several different ligands, studying mixed-ligand complexation is of considerable importance.

Here we report results of a study on the solution equilibria involved in the formation of ternary complexes of divalent transition metal ions (Cu(II), Co(II), Ni(II), and Zn(II)) containing the aliphatic and aromatic hydroxamic acids (acetohydroxamic acid, Aha; benzohydroxamic acid, Bha; salicylhydroxamic acid, Sham; and *N*-phenylbenzohydroxamic acid, *N*-PhBha) and the bioligands (α-alanine, α-ala; L-valine, L-val; norvaline, norval; aspartic acid, aspart; glutamic acid, glut; asparagines, asperg; histamine, Him; and imidazole, imid). This study was performed to investigate the complexation behavior of these ternary systems and to determine the stability constants of the complexes formed in solution, using glass electrode potentiometric measurements. In addition, the chelation mode of ternary complexes was ascertained by conductometric titrations. Also, confirmation of the formation of ternary complexes in aqueous solution has been done using cyclic voltammetry measurements.

## Experimental Section

***Materials and Solutions.*** Aha and Bha were Sigma products. Sham was purchased in a pure form from Nasr Pharmaceutical Chemicals Co., Egypt. *N*-PhBha was a Fluka product. The purity of the hydroxamic acids and the concentrations of the stock solutions were determined using Gran's method. The bioligands used were analytical grade (BDH) products with high purity. Metal ion solutions were prepared from Analar metal salt samples (BDH) in bidistilled water and standardized with ethylenediaminetetraacetic acid (EDTA). Carbonate-free sodium hydroxide (titrant, prepared in 0.10 $\text{mol}\cdot\text{dm}^{-3}$ $NaNO_3$ solution) was standardized potentiometrically with KH phthalate (Merck AG). A nitric acid solution ($\approx 0.04\ \text{mol}\cdot\text{dm}^{-3}$) was prepared and used after standardization. Sodium hydroxide, nitric acid, and sodium nitrate were from Merck p.a. Dioxane, of high purity, was from BDH.

***Apparatus and Procedure.*** pH measurements were performed using a 702 titroprocessor equipped with a 665 dosimat (Switzerland) made by Metrohm. The electrode was calibrated in terms of the hydrogen ion concentration by titrating HCl with NaOH solution[23] using a computer program (GLEE, glass electrode evaluation).[24] This program provides an estimate of the carbonate concentration of the base, the pseudo-Nernstian

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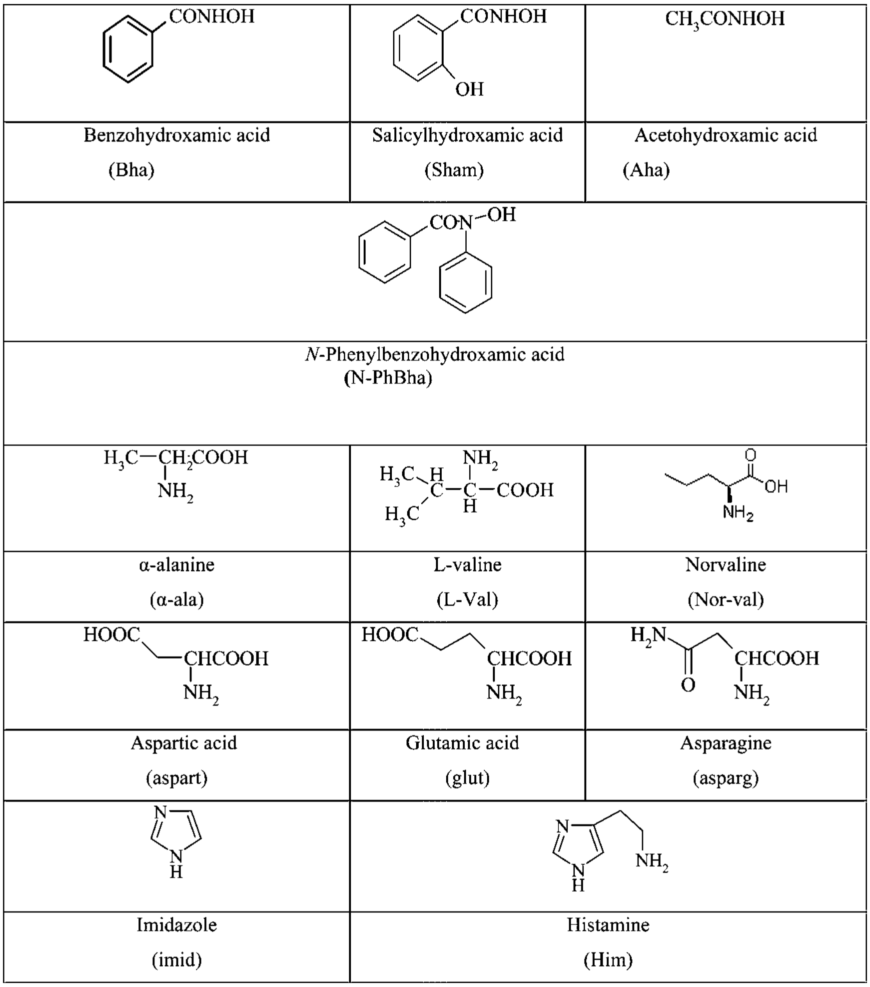
**Scheme 1**



standard potential and slope of the electrode, and optionally the concentration of the base and p$K_w$. For the determination of the binary systems (one ligand and M(II)), solutions containing ligand (hydroxamic acid or bioligand) and M(II) ion were titrated at a 1:1 or 1:6 metal/ligand ratio, and for ternary systems, the ratios used were 1:1:1 and 1:2:2. The concentration of the ligand solutions in the titrated samples were always the same and varied in the range ($1.10^{-3}$ to $6.10^{-3}$) $\text{mol}\cdot\text{dm}^{-3}$. To account for the differences in acidity, basicity, dielectric constant, and anion activities for partially aqueous solutions relative to pure aqueous ones, the pH values of the former solutions were corrected by making use of the procedure described by Douheret.[25] Measurements were conducted in a stream of nitrogen, at an ionic strength of 0.1 $\text{mol}\cdot\text{dm}^{-3}$ $NaNO_3$, using $CO_2$-free NaOH solution as a titrant. Titrations were performed up to pH $\approx$ 10.50. Each set of titrations was performed at least four times to check the repeatability of the data.

All calculations were made with the aid of a computer program based on an unweighted linear least-squares fit. The stoichiometries and stability constants of the complexes formed were determined by examining various possible composition models for the systems studied. The model selected was that which gave the best statistical fit. In addition, the calculations were not performed for pH regions where experimental findings showed the possibility of hydrolysis (a continuous decrease in the pH or the formation of a precipitate).

Each of the investigated solutions was thermostatted at the required temperature with a precision of ± 0.10 °C, and the solutions were left to stand at this temperature for about 15 min before titration. Magnetic stirring was used during all titrations. The calculations were performed using 100 to 120 experimental data points for each titration taking into account only the part of the titration curve when there was no precipitation in the solution.

***Conductometric Measurements.*** Conductometric titrations were followed with a HANNA conductivity meter HI-98304. The following mixture was titrated conductometrically against 0.10 $\text{mol}\cdot\text{dm}^{-3}$ NaOH solution: 0.01 $\text{mol}\cdot\text{dm}^{-3}$ Cu(II) (10 mL) + 0.01 $\text{mol}\cdot\text{dm}^{-3}$ hydroxamic acids (10 mL) + 0.01 $\text{mol}\cdot\text{dm}^{-3}$ aspart (10 mL).

***Cyclic Voltammetry Measurements.*** Cyclic voltammetric measurements were collected using a potentiostat/galvanostate wenking PGS 95 with a single compartment voltammetric cell equipped with a platinum working electrode (area = 0.50 $\text{cm}^2$), a Pt-wire counter electrode, and a saturated calomel electrode as a reference electrode.[26] In a typical experiment, a sample volume of 25 $\text{cm}^3$ containing the free metal ion $1\cdot10^{-3}$ $\text{mol}\cdot\text{dm}^{-3}$ Cu(II) (a), $1\cdot10^{-3}\text{mol}\cdot\text{dm}^{-3}$ Cu(II) + $1\cdot10^{-3}$ $\text{mol}\cdot\text{dm}^{-3}$ hydroxamic acid (b), $1\cdot10^{-3}\text{mol}\cdot\text{dm}^{-3}$ Cu(II) + $1\cdot10^{-3}\text{mol}\cdot\text{dm}^{-3}$ bioligand (c), and $1\cdot10^{-3}\text{mol}\cdot\text{dm}^{-3}$ Cu(II) + $1\cdot10^{-3}\text{mol}\cdot\text{dm}^{-3}$ hydroxamic acid + $1\cdot10^{-3}\text{mol}\cdot\text{dm}^{-3}$ bioligand (d) was used. The ionic strength of the studied solutions was adjusted to 0.10 $\text{mol}\cdot\text{dm}^{-3}$ using a $NaNO_3$ solution. All solutions were investigated in water at 25 °C. The solutions were purged with nitrogen for 120 s, and then the potential was scanned at the scan rate 25 $\text{mV}\cdot\text{s}^{-1}$ from (+ 0.20 to −0.60) V.

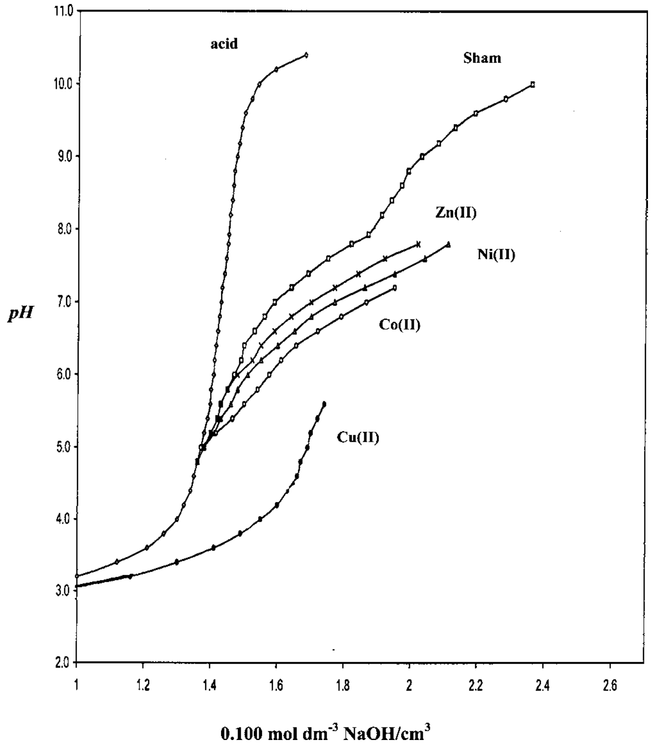


**Figure 1.** Potentiometric pH titration curves for the Sham and its metal complexes system at 1:2 metal to ligand ratios; $C_{\text{Sham}} = 1.10^{-3}$ mol·dm$^{-3}$, 25 °C, and $I = 0.10$ mol·dm$^{-3}$ $NaNO_3$.

## Results and Discussion

***Dissociation Constants of the Free Ligands.*** The formulas of the investigated ligands are shown in Scheme 1. The values of the protonation constants for the hydroxamic acids (Aha, Bha, and Sham) together with a detailed discussion about the acid−base properties of these ligands can be found in our earlier published work.[27] Over the wide pH range of 2 to 10.5, the values of the protonation constants for the bioligands were determined and are in good agreement with the ones reported.[28]

Because of the low solubility of *N*-PhBha in aqueous media,[29] the pH metric titrations were carried out in a 40 % dioxane−water medium. Its measured p$K_a$ value of (8.56 ± 0.02) is also in good agreement with the related literature data.[30,31]

The dissociation constants of the investigated hydroxamic acids in 0.10 mol·dm$^{-3}$ $NaNO_3$ are compared to those in presence of 0.10 mol·dm$^{-3}$ KCl, and the values are shown. It is obvious that replacement of 0.10 mol·dm$^{-3}$ $NO_3^-$ by 0.10 mol·dm$^{-3}$ $Cl^-$ does not cause any significant change in the acid−base properties of these molecules, and the trend remains the same.[35]

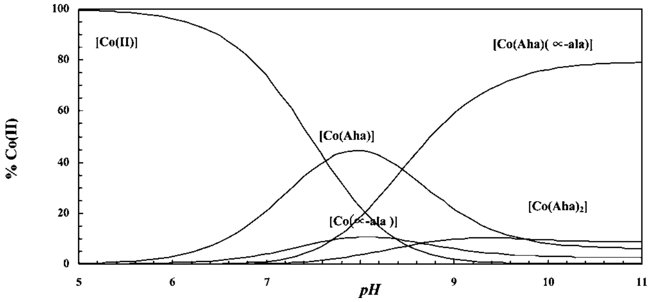


**Figure 2.** Representative concentration distribution curves as a function of pH calculated for Co(II)−Aha−α-ala system in the ratio 1:2:2 at 25 °C, $I = 0.10$ mol·dm$^{-3}$ $NaNO_3$, and $C_{\text{ligand}} = 1.10^{-3}$ mol·dm$^{-3}$.

***Stability Constants of Binary Complexes.*** Representative pH metric titration curves of metal ion Sham with 1:2 stoichiometry are shown in Figure 1. In the metal complex curves, there are significant differences in the pH effects caused by complex formation with various metal ions which clearly reveals the differences in the stability of the complexes. The stability constants of the corresponding binary complexes are listed in Table 1. Although the stability constants of 1:1 and 1:2 binary complexes of the M(II) with bioligands or hydroxamic acids have been reported earlier by others,[32−34] we have redetermined these constants as it is preferable to determine the binary and ternary constants under the same experimental conditions.[35] However, the present results agree well with those from the literature.[32−34] It is worth mentioning that the *N*-PhBha binary complexes were so insoluble[30] that they precipitated immediately on mixing; therefore, those binary complexes could not be detected under the experimental conditions, and the corresponding stability constant values could not be evaluated.

***Stability Constants of Ternary Complexes.*** In our study, hydroxamic acids (A) are considered as primary ligands and the bioligands (L) as secondary ligands with all investigated metal ions, except in the case of the ternary systems involving the bioligands: aspart, glut, Him, or imidazole and the investigated hydroxamic acids in which the former ligands act as primary ligands and the latter as secondary ligands with the metal ions: Co(II), Ni(II), and Zn(II).

A better analysis of the results is provided by the speciation diagrams (formation percentage, calculated with respect to M(II), versus pH) plotted in Figures 2 and 3 (the speciation data was obtained using the SPECIES program, and predicts the percentage distribution of various forms of the metal at different pH values based upon input stability constants contained in a thermodynamic database[36]). By analyzing the distribution diagram for the Co(II)−Aha−α-ala ternary complex system, it can be seen that the extent of complex formation is pH-dependent. The mixed-ligand species starts to form at pH ≈

**Table 1. Stability Constants for 1:1 and 1:2 Binary Complexes of Hydroxamic Acids and Bioligands at 25 °C and $I = 0.10$ mol·dm$^{-3}$ $NaNO_3$**

| | Cu(II) | | Co(II) | | Ni(II) | | Zn(II) | |
|---|---|---|---|---|---|---|---|---|
| ligand | log $K_1$ | log $K_2$ | log $K_1$ | log $K_2$ | log $K_1$ | log $K_2$ | log $K_1$ | log $K_2$ |
| Aha | 8.20 ± 0.03 | 5.89 ± 0.03 | 4.86 ± 0.03 | 3.47 ± 0.01 | 5.62 ± 0.05 | 4.57 ± 0.02 | 5.71 ± 0.02 | 4.72 ± 0.05 |
| Bha | 7.60 ± 0.02 | 3.34 ± 0.01 | 4.81 ± 0.05 | 3.38 ± 0.03 | 5.10 ± 0.04 | 3.67 ± 0.01 | 5.07 ± 0.01 | 4.32 ± 0.02 |
| Sham | 13.10 ± 0.01 | 3.42 ± 0.01 | 6.37 ± 0.05 | 4.55 ± 0.04 | 6.08 ± 0.02 | 3.92 ± 0.02 | 5.94 ± 0.03 | 3.99 ± 0.03 |
| α-ala | 7.64 ± 0.01 | 6.94 ± 0.03 | 4.44 ± 0.02 | 3.35 ± 0.02 | 6.60 ± 0.02 | 4.44 ± 0.01 | 5.37 ± 0.02 | 5.16 ± 0.05 |
| L-val | 7.88 ± 0.02 | 4.73 ± 0.01 | 5.22 ± 0.04 | 3.73 ± 0.01 | 6.68 ± 0.01 | 4.55 ± 0.02 | 5.91 ± 0.01 | 5.45 ± 0.03 |
| norval | 7.80 ± 0.05 | 4.70 ± 0.02 | 4.80 ± 0.02 | 3.65 ± 0.01 | 5.70 ± 0.03 | 4.70 ± 0.02 | 5.30 ± 0.02 | 4.34 ± 0.01 |
| aspart | 8.64 ± 0.02 | 7.06 ± 0.05 | 6.10 ± 0.01 | 4.31 ± 0.05 | 7.50 ± 0.03 | 4.26 ± 0.03 | 7.36 ± 0.02 | 4.04 ± 0.02 |
| glut | 8.60 ± 0.02 | 6.59 ± 0.02 | 4.63 ± 0.02 | 3.62 ± 0.01 | 5.90 ± 0.01 | 5.37 ± 0.02 | 5.91 ± 0.05 | 4.04 ± 0.01 |
| asparag | 6.91 ± 0.02 | 5.12 ± 0.03 | 4.03 ± 0.05 | 3.95 ± 0.02 | 5.36 ± 0.03 | 4.04 ± 0.04 | 4.47 ± 0.04 | 3.71 ± 0.06 |
| imid | 4.15 ± 0.03 | 3.47 ± 0.04 | 2.40 ± 0.01 | | 3.03 ± 0.02 | | 2.51 ± 0.05 | |
| Him | 9.55 ± 0.05 | 6.55 ± 0.01 | 5.35 ± 0.03 | 4.45 ± 0.02 | 6.85 ± 0.02 | 6.56 ± 0.01 | 6.66 ± 0.02 | 5.82 ± 0.01 |

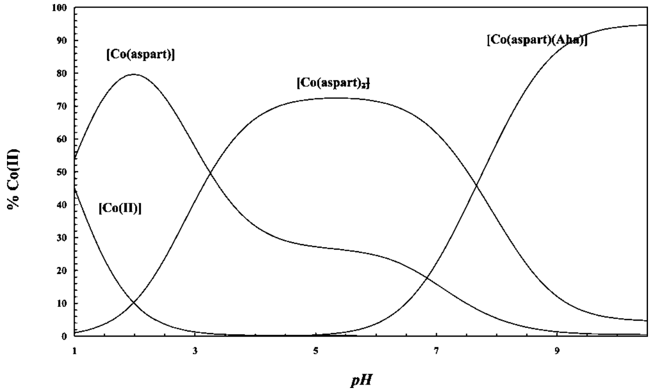


**Figure 3.** Representative concentration distribution curves as a function of pH calculated for Co(II)−Aha−aspart system in the ratio 1:2:2 at 25 °C, $I = 0.10$ mol·dm$^{-3}$ NaNO$_3$, and $C_{\text{ligand}} = 1.10^{-3}$ mol·dm$^{-3}$.

6.77 and is dominant above pH ≈ 10. With increasing pH, its concentration increases reaching a maximum of 78.99 % at pH 10.82. The ternary complex formed with the aspart ligand in Co(II)−Aha−aspart (Figure 3) is more favored; the ternary species reaches a maximum of approximately 93.37 % at pH 9.79. This behavior is mainly based on the fact that the aspart is much more prone to complex formation than α-alanine.

Potentiometric pH titration curves were constructed within the pH range of 2 to 10.5. However, the stability constants of binary and ternary complex species were determined successfully at lower pH values. The formation of monohydroxo complexes could not be detected; the formation constants of the corresponding complex species were rejected by our computer program. All side reactions due to hydrolysis of the M(II) ion have not been included in our calculations. Also, in our investigations, measurements were carried out over a wide range of ligand/metal molar ratios to reach high pH values.[37]

Examination of stability constant values of the same metal ion ternary complexes (Tables 2, 3, 4, and 5) reveals the following: (i) A comparison of the overall stability constants of M(II)−A−L ternary systems indicates the higher stabilities of the ternary complexes containing dicarboxylic amino acid

**Table 2. Stability Constants for Cu(II) Ternary Complexes at 25 °C and $I = 0.1$ mol·dm$^{-3}$ NaNO$_3$**

| | $\log K^{\text{MA}}_{\text{MAL}}$ | | | $\log \beta^{\text{M}}_{\text{MAL}}$ | | | $\Delta \log K$ | | | $\log X$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ligand | Aha | Bha | Sham | Aha | Bha | Sham | Aha | Bha | Sham | Aha | Bha | Sham |
| α-ala | 7.56 ± 0.02 | 8.28 ± 0.01 | 8.98 ± 0.03 | 15.76 | 15.88 | 22.08 | −0.08 | 0.64 | 1.34 | 2.29 | 6.28 | 7.60 |
| L-val | 7.50 ± 0.07 | 8.26 ± 0.02 | 8.96 ± 0.05 | 15.53 | 15.89 | 22.02 | −0.38 | 0.38 | 1.08 | 4.47 | 8.28 | 14.97 |
| norval | 7.24 ± 0.05 | 8.12 ± 0.02 | 8.73 ± 0.06 | 15.44 | 15.72 | 21.83 | −0.56 | 0.32 | 0.93 | 3.89 | 8.20 | 9.34 |
| aspart | 9.30 ± 0.02 | 9.38 ± 0.07 | 10.10 ± 0.02 | 17.50 | 16.98 | 23.20 | 0.46 | 0.54 | 1.26 | 5.65 | 8.36 | 9.72 |
| glut | 8.80 ± 0.01 | 8.96 ± 0.03 | 9.35 ± 0.01 | 17.40 | 16.56 | 22.45 | 0.20 | 0.36 | 0.75 | 5.12 | 7.99 | 8.69 |
| asparag | 6.02 ± 0.05 | 6.97 ± 0.08 | 7.05 ± 0.02 | 14.22 | 14.57 | 20.15 | −0.89 | 0.06 | 0.14 | 1.03 | 5.48 | 5.48 |
| imid | 3.97 ± 0.03 | 4.04 ± 0.04 | 5.42 ± 0.03 | 12.17 | 11.64 | 18.52 | −0.18 | −0.11 | 1.27 | −1.42 | 1.28 | 3.95 |
| Him | 9.59 ± 0.03 | 9.73 ± 0.03 | 10.11 ± 0.03 | 17.79 | 17.33 | 23.21 | 0.04 | 0.18 | 0.56 | 6.74 | 9.57 | 10.25 |

**Table 3. Stability Constants for Co(II) Ternary Complexes at 25 °C and $I = 0.1$ mol·dm$^{-3}$ NaNO$_3$**

| | $\log K^{\text{MA}}_{\text{MAL}}$ | | | $\log \beta^{\text{M}}_{\text{MAL}}$ | | | $\Delta \log K$ | | | $\log X$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ligand | Aha | Bha | Sham | Aha | Bha | Sham | Aha | Bha | Sham | Aha | Bha | Sham |
| α-ala | 4.38 ± 0.03 | 4.81 ± 0.03 | 6.21 ± 0.05 | 9.24 | 9.62 | 12.58 | −0.06 | 0.37 | 1.77 | 1.94 | 2.89 | 4.52 |
| L-val | 5.12 ± 0.01 | 5.24 ± 0.01 | 6.17 ± 0.07 | 10.05 | 9.99 | 12.76 | −0.10 | 0.02 | 0.95 | 2.72 | 3.02 | 5.46 |
| norval | 5.08 ± 0.05 | 5.12 ± 0.04 | 6.11 ± 0.08 | 9.94 | 9.93 | 12.48 | −0.28 | 0.32 | 1.31 | 3.04 | 3.21 | 4.02 |
| aspart | 5.68 ± 0.01 | 5.98 ± 0.06 | 6.38 ± 0.02 | 11.82 | 12.12 | 13.52 | 0.82 | 1.17 | 0.01 | 3.58 | 4.27 | 3.90 |
| glut | 5.14 ± 0.04 | 5.91 ± 0.02 | 5.98 ± 0.02 | 9.64 | 10.41 | 10.48 | 0.28 | 1.10 | −0.39 | 3.19 | 4.82 | 3.79 |
| asparag | 4.44 ± 0.05 | 4.86 ± 0.03 | 5.55 ± 0.01 | 9.30 | 9.67 | 11.92 | 0.41 | 0.83 | 2.34 | 1.46 | 2.39 | 4.24 |
| imid | 3.45 ± 0.02 | 3.56 ± 0.06 | 3.80 ± 0.023 | 8.85 | 5.96 | 6.20 | −1.41 | −1.25 | −2.57 | | | |
| Him | 6.05 ± 0.06 | 6.20 ± 0.01 | 7.32 ± 0.03 | 11.40 | 11.55 | 12.671 | 1.19 | 1.39 | 0.55 | 4.18 | 4.57 | 5.64 |

**Table 4. Stability Constants for Ni(II) Ternary Complexes at 25 °C and $I = 0.1$ mol·dm$^{-3}$ NaNO$_3$**

| | $\log K^{\text{MA}}_{\text{MAL}}$ | | | $\log \beta^{\text{M}}_{\text{MAL}}$ | | | $\Delta \log K$ | | | $\log X$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ligand | Aha | Bha | Sham | Aha | Bha | Sham | Aha | Bha | Sham | Aha | Bha | Sham |
| α-ala | 6.02 ± 0.03 | 6.89 ± 0.04 | 7.50 ± 0.05 | 11.64 | 11.99 | 13.58 | −0.58 | 0.29 | 0.90 | 3.03 | 5.67 | 6.61 |
| L-val | 5.98 ± 0.02 | 6.40 ± 0.04 | 6.95 ± 0.03 | 11.68 | 11.45 | 12.97 | −0.70 | −0.28 | 0.27 | 1.70 | 3.02 | 4.74 |
| norval | 5.82 ± 0.04 | 6.25 ± 0.02 | 6.98 ± 0.06 | 11.44 | 11.35 | 13.06 | 0.12 | 0.55 | 1.28 | 2.37 | 4.13 | 5.34 |
| aspart | 6.20 ± 0.03 | 7.3 ± 0.02 | 7.79 ± 0.02 | 12.34 | 13.44 | 13.93 | 0.58 | 2.20 | 1.71 | 3.57 | 6.67 | 6.88 |
| glut | 5.98 ± 0.01 | 6.08 ± 0.01 | 6.18 ± 0.02 | 12.18 | 12.28 | 12.38 | 0.36 | 0.29 | 0.10 | 2.02 | 3.12 | 2.55 |
| asparag | 5.59 ± 0.03 | 5.65 ± 0.02 | 5.98 ± 0.03 | 11.21 | 10.75 | 12.06 | 0.23 | 0.20 | 0.62 | 2.57 | 3.59 | 3.48 |
| imid | 3.53 ± 0.05 | 3.87 ± 0.06 | 4.20 ± 0.01 | 6.56 | 6.90 | 7.23 | −2.09 | −1.23 | −1.88 | | | |
| Him | 6.80 ± 0.01 | 7.32 ± 0.02 | 7.78 ± 0.02 | 13.15 | 14.17 | 14.43 | 1.18 | 2.22 | 1.70 | 2.47 | 4.41 | 4.56 |

**Table 5. Stability Constants for Zn(II) Ternary Complexes at 25 °C and $I = 0.1$ mol·dm$^{-3}$ NaNO$_3$**

| | $\log K^{\text{MA}}_{\text{MAL}}$ | | | $\log \beta^{\text{M}}_{\text{MAL}}$ | | | $\Delta \log K$ | | | $\log X$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ligand | Aha | Bha | Sham | Aha | Bha | Sham | Aha | Bha | Sham | Aha | Bha | Sham |
| α-ala | 5.75 ± 0.01 | 5.82 ± 0.03 | 6.18 ± 0.02 | 11.50 | 10.89 | 12.12 | 0.38 | 0.45 | 0.81 | 1.62 | 2.16 | 3.21 |
| L-val | 5.74 ± 0.04 | 5.80 ± 0.01 | 5.98 ± 0.05 | 11.49 | 10.75 | 11.86 | −0.17 | −0.11 | 0.07 | 1.17 | 0.93 | 2.50 |
| norval | 5.25 ± 0.02 | 5.44 ± 0.02 | 5.84 ± 0.02 | 10.96 | 10.51 | 11.78 | −0.05 | 0.14 | 0.54 | 1.44 | 2.22 | 3.35 |
| aspart | 6.02 ± 0.02 | 6.09 ± 0.04 | 7.32 ± 0.03 | 11.38 | 11.45 | 12.68 | 0.31 | 1.02 | 1.38 | 3.28 | 3.82 | 6.61 |
| glut | 5.92 ± 0.01 | 5.98 ± 0.02 | 7.28 ± 0.03 | 11.83 | 11.89 | 13.19 | 0.21 | 0.91 | 1.34 | 3.08 | 3.60 | 6.53 |
| asparag | 5.42 ± 0.03 | 5.63 ± 0.01 | 5.80 ± 0.02 | 11.13 | 10.70 | 11.74 | 0.95 | 1.16 | 1.33 | 2.41 | 3.23 | 3.90 |
| imid | 3.50 ± 0.02 | 3.72 ± 0.03 | 5.09 ± 0.01 | 6.01 | 6.23 | 6.60 | −2.21 | −1.35 | −1.85 | | | |
| Him | 6.06 ± 0.02 | 6.52 ± 0.01 | 7.19 ± 0.02 | 12.72 | 13.18 | 13.85 | 0.35 | 1.45 | 1.25 | 1.58 | 2.90 | 4.57 |

**Table 6. Thermodynamic Quantities Associated with the Dissociation of Some Hydroxamic Acid or Bioligand and the Interaction of Metal Ions with the Ligands at 1:1 and 1:1:1 Molar Ratios and $I = 0.10\ \mathrm{mol \cdot dm^{-3}}$ $NaNO_3$**

| | | p*K*'s or log *K* | | | |
|---|---|---|---|---|---|
| ligand or complex | cation | $t$/°C = 15 | 25 | 35 | 45 |
| Aha | H | 9.57 ± 0.03 | 9.40 ± 0.01 | 9.21 ± 0.04 | 9.13 ± 0.01 |
| (1:1) binary complex of Aha | Cu(II) | 8.51 ± 0.01 | 8.20 ± 0.02 | 8.08 ± 0.01 | 7.94 ± 0.03 |
| | Ni(II) | 5.66 ± 0.04 | 5.62 ± 0.01 | 5.58 ± 0.03 | 5.48 ± 0.01 |
| | Co(II) | 4.89 ± 0.03 | 4.86 ± 0.01 | 4.78 ± 0.01 | 4.75 ± 0.02 |
| Sham | H | 8.18 ± 0.01 | 7.40 ± 0.02 | 6.85 ± 0.01 | 6.53 ± 0.02 |
| | H | 9.85 ± 0.02 | 9.78 ± 0.01 | 9.69 ± 0.02 | 9.63 ± 0.03 |
| (1:1) binary complex of Sham | Cu(II) | 14.09 ± 0.02 | 13.10 ± 0.01 | 12.98 ± 0.01 | 12.75 ± 0.02 |
| | Ni(II) | 6.36 ± 0.01 | 6.08 ± 0.02 | 5.94 ± 0.03 | 5.82 ± 0.01 |
| | Co(II) | 6.68 ± 0.03 | 6.37 ± 0.05 | 6.30 ± 0.01 | 6.06 ± 0.03 |
| aspart | H | 3.87 ± 0.01 | 3.80 ± 0.01 | 3.72 ± 0.02 | 3.60 ± 0.03 |
| | H | 9.85 ± 0.02 | 9.77 ± 0.02 | 9.62 ± 0.03 | 9.48 ± 0.01 |
| (1:1) binary complex of aspart | Cu(II) | 8.87 ± 0.02 | 8.64 ± 0.02 | 8.46 ± 0.02 | 8.27 ± 0.01 |
| | Ni(II) | 7.69 ± 0.01 | 7.50 ± 0.03 | 7.33 ± 0.01 | 7.17 ± 0.04 |
| | Co(II) | 6.27 ± 0.01 | 6.10 ± 0.01 | 6.01 ± 0.02 | 5.90 ± 0.03 |
| glut | H | 4.15 ± 0.02 | 4.02 ± 0.02 | 3.96 ± 0.02 | 3.89 ± 0.01 |
| | H | 9.87 ± 0.01 | 9.79 ± 0.03 | 9.66 ± 0.01 | 9.60 ± 0.04 |
| (1:1) binary complex of glut | Cu(II) | 8.75 ± 0.01 | 8.60 ± 0.02 | 8.38 ± 0.01 | 8.17 ± 0.01 |
| | Ni(II) | 6.01 ± 0.02 | 5.90 ± 0.01 | 5.81 ± 0.02 | 5.73 ± 0.03 |
| | Co(II) | 4.72 ± 0.02 | 4.63 ± 0.02 | 4.57 ± 0.02 | 4.52 ± 0.02 |
| (1:1:1) ternary complex of Sham and aspart | Cu(II) | 10.43 ± 0.03 | 10.10 ± 0.02 | 9.75 ± 0.01 | 9.39 ± 0.03 |
| | Ni(II) | 8.02 ± 0.02 | 7.79 ± 0.02 | 7.52 ± 0.02 | 7.28 ± 0.04 |
| | Co(II) | 6.55 ± 0.01 | 6.38 ± 0.02 | 6.16 ± 0.01 | 6.00 ± 0.01 |
| (1:1:1) ternary complex of Aha and aspart | Cu(II) | 9.57 ± 0.04 | 9.30 ± 0.02 | 9.16 ± 0.02 | 8.84 ± 0.02 |
| | Ni(II) | 6.33 ± 0.01 | 6.20 ± 0.03 | 6.03 ± 0.03 | 5.88 ± 0.01 |
| | Co(II) | 5.82 ± 0.01 | 5.68 ± 0.01 | 5.62 ± 0.01 | 5.52 ± 0.03 |
| (1:1:1) ternary complex of Sham and glut | Cu(II) | 9.76 ± 0.01 | 9.35 ± 0.01 | 9.18 ± 0.02 | 8.90 ± 0.01 |
| | Ni(II) | 6.37 ± 0.03 | 6.18 ± 0.02 | 6.06 ± 0.03 | 5.95 ± 0.02 |
| | Co(II) | 5.91 ± 0.04 | 5.98 ± 0.02 | 5.66 ± 0.01 | 5.56 ± 0.02 |
| (1:1:1) ternary complex of Aha and glut | Cu(II) | 9.08 ± 0.02 | 8.80 ± 0.01 | 8.53 ± 0.02 | 8.32 ± 0.02 |
| | Ni(II) | 6.07 ± 0.02 | 5.98 ± 0.01 | 5.87 ± 0.02 | 5.78 ± 0.01 |
| | Co(II) | 5.22 ± 0.03 | 5.14 ± 0.04 | 5.10 ± 0.01 | 5.02 ± 0.03 |

| ligand or complex | cation | $\Delta H^{o}$ $\mathrm{kJ \cdot mol^{-1}}$ | $\Delta G^{o}$ $\mathrm{kJ \cdot mol^{-1}}$ | $\Delta S^{o}$ $\mathrm{J \cdot mol^{-1} \cdot K^{-1}}$ |
|---|---|---|---|---|
| Aha | H | 26.83 | 53.65 | −89.97 |
| (1:1) binary complex of Aha | Cu(II) | −34.65 | −46.80 | 42.12 |
| | Ni(II) | −8.96 | −32.08 | 77.16 |
| | Co(II) | −7.89 | −27.74 | 67.01 |
| Sham | H | 97.44 | 42.24 | −183.22 |
| | H | 13.24 | 55.82 | −142.71 |
| (1:1) binary complex of Sham | Cu(II) | −43.10 | −43.71 | 8.60 |
| | Ni(II) | −20.42 | −42.35 | 73.80 |
| | Co(II) | −18.79 | −21.25 | 9.07 |
| aspart | H | 15.62 | 20.69 | −20.13 |
| | H | 22.54 | 56.28 | −110.90 |
| (1:1) binary complex of aspart | Cu(II) | −20.56 | −28.83 | 27.87 |
| | Ni(II) | −16.55 | −25.02 | 28.09 |
| | Co(II) | −11.40 | −20.35 | 30.22 |
| glut | H | 14.68 | 22.95 | −27.56 |
| | H | 16.60 | 55.88 | −131.46 |
| (1:1) binary complex of glut | Cu(II) | −20.32 | −28.69 | 27.98 |
| | Ni(II) | −16.28 | −19.69 | 58.02 |
| | Co(II) | −5.31 | −15.45 | 34.36 |
| (1:1:1) ternary complex of Sham and aspart | Cu(II) | −30.86 | −33.70 | 8.86 |
| | Ni(II) | −21.98 | −25.99 | 12.93 |
| | Co(II) | −16.71 | −21.29 | 14.94 |
| (1:1:1) ternary complex of Aha and aspart | Cu(II) | −25.30 | −31.03 | 19.70 |
| | Ni(II) | −9.41 | −20.41 | 36.70 |
| | Co(II) | −8.76 | −18.95 | 34.36 |
| (1:1:1) ternary complex of Sham and glut | Cu(II) | −24.80 | −31.20 | 22.00 |
| | Ni(II) | −24.61 | −20.69 | 35.04 |
| | Co(II) | −10.23 | −19.30 | 30.22 |
| (1:1:1) ternary complex of Aha and glut | Cu(II) | −22.63 | −29.36 | 22.31 |
| | Ni(II) | −8.69 | −19.95 | 37.61 |
| | Co(II) | −5.59 | −17.43 | 38.82 |

(aspart and glut). This behavior can be mainly ascribed to the fact that the dicarboxylic acids are much more prone to complex formation than (α-ala, norval, and asparag) as a result of the large difference in their basic strengths as well as their tendency to act as ONO tridentate ligands. Furthermore, with respect to the dicarboxylic amino acids, it is evident that the stability of binary or mixed ligand complexes containing aspart is higher than that of the corresponding one containing glut. This behavior can be interpreted in terms of the effective basicity of the free conjugate base of the aspart.[38] (ii) The stability of ternary complexes involving α-ala are found to be lower than those containing glycine.[27] This behavior does not follow their basicities as expected, probably because the p$K_{a2}$ values of the amino acids are so similar. It is suggested that steric hindrance, caused by the presence of a methyl group on the carbon bearing the amino group (α-ala), is responsible for the lower stability of its ternary complexes.[39] (iii) The observed low stabilities of the ternary complexes containing asparag has been described elsewhere.[40] (iv) Analysis of the titration results for the mixed-ligand complexes containing α-amino acids showed the formation of 1:1:1 ternary complexes with stability constants higher than those of the corresponding monodentate imidazole complexes. This indicates that amino acids bind through the amino and carboxylate groups.[39] (v) The order of stability of the ternary systems with respect to the metal ions studied follows the Irving−Williams series.[40] (vi) The higher stability of ternary complexes involving His[27] or Him than those of α-amino acids reveals that His or Him interacts with the metal ion by the amino and imidazole nitrogen atoms.

The $\beta^{M}_{MAL}$ constant expresses the stability of the mixed-ligand species, and it does not represent the binding strength between L and M(II) ions directly in the presence of A. This effect is much better reflected by the equilibrium constant, $K^{MA}_{MAL}$ calculated according to eq 1.

$$\log K^{MA}_{MAL} = \log \beta^{M}_{MAL} - \log K^{M}_{MA} \qquad (1)$$

Different methods[35,41] are known to estimate the formation of mixed ligand complexes. The Δ log *K* value is defined as the constant due to the equilibrium MA + ML $\rightleftharpoons$ MAL + M[41] and provides an insight into the various factors responsible for the formation and stabilization of ternary complexes in the solution, as defined by eq 2

$$\Delta \log K = \log K^{MA}_{MAL} - \log K^{M}_{ML} \qquad (2)$$

In the case of ternary complex formation, negative Δ log *K* values can be explained on the basis of the presence of a fewer number of coordination sites on the MA monocomplexes than on the aquated metal ion. Thus, the secondary ligand (L) is expected to bind the MA complex with a smaller stability constant than that with an aquated metal ion, generally between −0.50 and −2.0.[42−44] In general, positive Δ log *K* values were obtained, indicating a significant stabilization of the ternary systems (Tables 2 to 5). The higher values of Δ log *K*, for the ternary systems involving the aromatic hydroxamic acids (Sham or Bha) than for the aliphatic hydroxamic acid, Aha, may be attributed to the presence of an aromatic ring.[43,44] Δ log *K* values in general for the ternary systems involving Cu(II) were less positive than for the corresponding other metal ion systems; this observation is in agreement with the different coordination geometries of these metal ions. Contrary to Δ log *K*, the values of log *X* (the constant due to the equilibrium [$MA_2$] + [$ML_2$] $\rightleftharpoons$ 2[MAL],[35] the appropriate constants are given in Tables 2 to 5) are much higher for the Cu(II) ion than other M(II) ions; this is due to the relatively small value of log $K_2$ (Table 1). The values of log *X* are higher than that expected on a statistical basis (0.60).[45,46] This means that the formation of mixed complexes is favored in these systems.

The extra stability in the ternary complexes can be measured by other parameters such as Δ*H*°, Δ*S*°, and Δ*G*°, the thermodynamic parameters associated with the dissociation of ligands as well as metal ligand complexes as evaluated by studying the stability constants of binary and ternary systems of the Aha, Sham, aspart, and glut acid ligands with the Cu(II), Co(II), and Ni(II) metal ions at (15 to 45) °C and *I* = 0.10 mol·dm$^{-3}$ NaNO$_3$. In both binary and ternary complexes, stability constants decrease with an increase in temperature (Table 6). The slope of the plot (p$K_a$ or log *K* vs 1/*T*) was applied to evaluate the enthalpy change (Δ*H*°) for the dissociation or complexation process, respectively. The thermodynamic parameters of the dissociation process are recorded in Table 6. The enthalpy changes for the formation of binary systems are exothermic, and the entropy values are positive (Table 6), which confirm that complex formation is entropically favored.[47] Also, the higher entropy value in all binary systems further supports the bidentate nature of the ligands in the binary complexes.

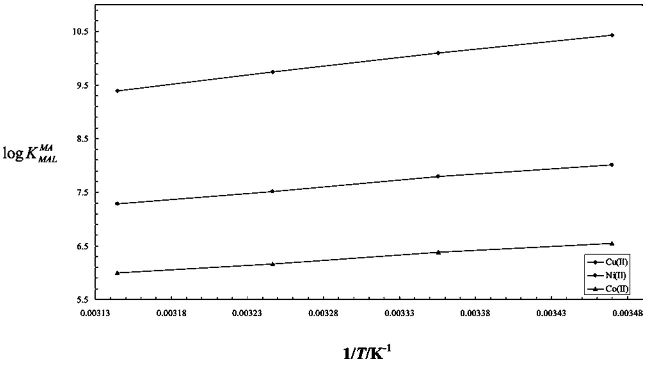


**Figure 4.** Plot of log $K^{MA}_{MAL}$ for the M(II)−Sham−aspart ternary system vs 1/*T* at *I* = 0.10 mol·dm$^{-3}$ NaNO$_3$.

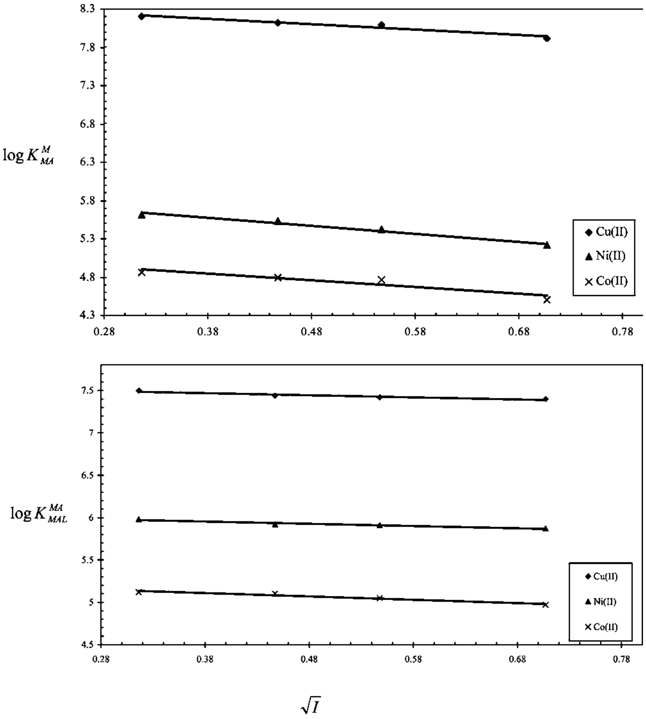


**Figure 5.** Plot of log $K^{M}_{MA}$ and log $K^{MA}_{MAL}$ values for the M(II)−Aha binary and M(II)−Aha−L-val ternary systems vs $I^{1/2}$ at 25 °C.

Figure 4 shows a plot of log $K^{MA}_{MAL}$ for the M(II)−Sham−aspart ternary system versus 1/*T* at *I* = 0.10 mol·dm$^{-3}$ NaNO$_3$. The enthalpy changes for the 1:1:1 mixed ligand complex formation are more negative (more exothermic) than those of the corresponding 1:1 M(II)−A, indicating that the higher negative enthalpy changes favor 1:1:1 mixed ligand complex formation and are responsible for higher stabilities. However, an inverse behavior was observed in case of the Cu(II)−Sham (Table 1) binary system compared to its corresponding ternary ones (Table 6). This may be due to the fact that some more water molecules may still be attached to the metal ion in 1:1 binary systems

**Table 7. Dissociation Constants of Aha and L-val and Stability Constants of Their 1:1 Binary and 1:1:1 Ternary Complexes at 25 °C and Different Ionic Strengths**

| ionic strength, $I$ NaNO$_3$ | p$K_a$ | | log $K_1$[a] | | | log $K_1$[b] | | | log $K^{MA}_{MAL}$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Aha | L-val | Cu(II) | Ni(II) | Co(II) | Cu(II) | Ni(II) | Co(II) | Cu(II) | Ni(II) | Co(II) |
| 0.00 | 9.43 ± 0.02 | 9.76 ± 0.01 | 8.43 ± 0.01 | 5.97 ± 0.02 | 5.18 ± 0.04 | 8.26 ± 0.02 | 7.08 ± 0.04 | 5.39 ± 0.01 | 7.57 ± 0.01 | 6.08 ± 0.03 | 5.26 ± 0.01 |
| 0.10 | 9.35 ± 0.01 | 9.65 ± 0.04 | 8.20 ± 0.03 | 5.62 ± 0.05 | 4.86 ± 0.03 | 7.88 ± 0.05 | 6.68 ± 0.05 | 5.22 ± 0.05 | 7.50 ± 0.07 | 5.98 ± 0.07 | 5.12 ± 0.07 |
| 0.20 | 9.31 ± 0.03 | 9.59 ± 0.01 | 8.12 ± 0.02 | 5.53 ± 0.03 | 4.80 ± 0.05 | 7.75 ± 0.02 | 6.51 ± 0.02 | 5.15 ± 0.03 | 7.44 ± 0.01 | 5.92 ± 0.01 | 5.10 ± 0.03 |
| 0.30 | 9.29 ± 0.02 | 9.56 ± 0.03 | 8.09 ± 0.04 | 5.42 ± 0.05 | 4.77 ± 0.03 | 7.62 ± 0.03 | 6.33 ± 0.03 | 5.10 ± 0.04 | 7.42 ± 0.02 | 5.91 ± 0.05 | 5.05 ± 0.03 |
| 0.50 | 9.25 ± 0.05 | 9.51 ± 0.03 | 7.92 ± 0.03 | 5.22 ± 0.02 | 4.51 ± 0.07 | 7.43 ± 0.05 | 6.18 ± 0.06 | 5.01 ± 0.04 | 7.40 ± 0.04 | 5.87 ± 0.03 | 4.97 ± 0.05 |

[a] log $K_1$ = log $K^{M(II)}_{M(II)-Aha}$. [b] log $K_1$ = log $K^{M(II)}_{M(II)-L-val}$.

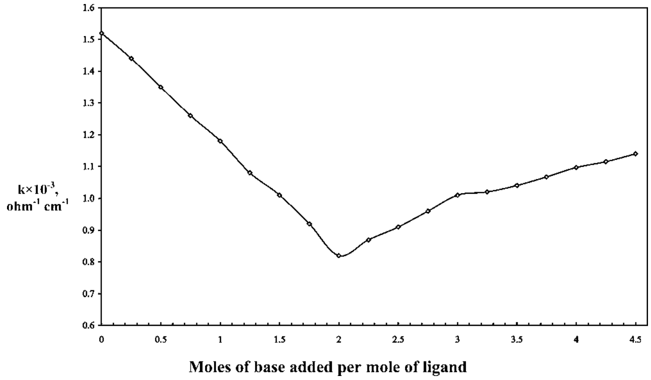


**Figure 6.** Conductometric titration curve for the Cu(II)−Aha−aspart system.

and, when a 1:1:1 complex is formed, more energy is needed in the bond breaking process.[48] The values of $\Delta S^o$ substantiate the suggestion that the different binary and ternary complexes are formed due to coordination of the ligand anion to the metal cation. Furthermore, the positive values of $\Delta S^o$ suggest also a desolvation of the ligands, resulting in weak solvent−ligand interactions, to the advantage of the metal ion−ligand interaction.[49]

The ternary systems M(II)−valine−Aha (M(II) = Co(II), Ni(II), and Cu(II)) were chosen for studying the effect of ionic strength on the dissociation of the ligands as well as the stability of the 1:1 binary and 1:1:1 ternary complexes. Linear plots were obtained when log $K^{M}_{MA}$ and log $K^{MA}_{MAL}$ values were plotted against $I^{1/2}$ (Figure 5) in accordance with the Debye−Hückel equation. The thermodynamic equilibrium constants (at $I = 0.0$) were determined by applying linear regression analysis. The results obtained are reported in Table 7.

The conductometric titration curve for the Cu(II)−Aha−aspart ternary system, taken as a representative curve (Figure 6), shows an inflection at $a = 2$ ($a$ = moles of base added per mole of ligand). This probably corresponds to the neutralization of 2H$^+$ ions resulting from the formation of the Cu(II)−aspart complex. Between $2 < a < 3$, the conductance increases slightly, supposedly because of the formation of the ternary complex, and is associated with the release of one proton from Aha. Beyond $a = 3$, the conductance rapidly rises with further addition of NaOH because of the large conductivity of the hydroxyl ion. According to the above findings, the mode of chelation is in accordance with the results obtained by potentiometric pH titrations.

The addition of ligands caused a slight shift of the cathodic peak to a more negative potential, indicating the formation of binary and ternary complexes in solution. Figure 7 shows the cyclic voltammograms recorded at a platinum electrode for the systems Cu(II)−Sham−aspart, Cu(II)−Sham−glut, Cu(II)−Aha−aspart, and Cu(II)−Aha−glut at scan rate of 25 mV·s$^{-1}$, pH = 3.50, 25 °C, and $I$ = 0.10 mol·dm$^{-3}$ NaNO$_3$. The voltamograms show that the half-wave potentials

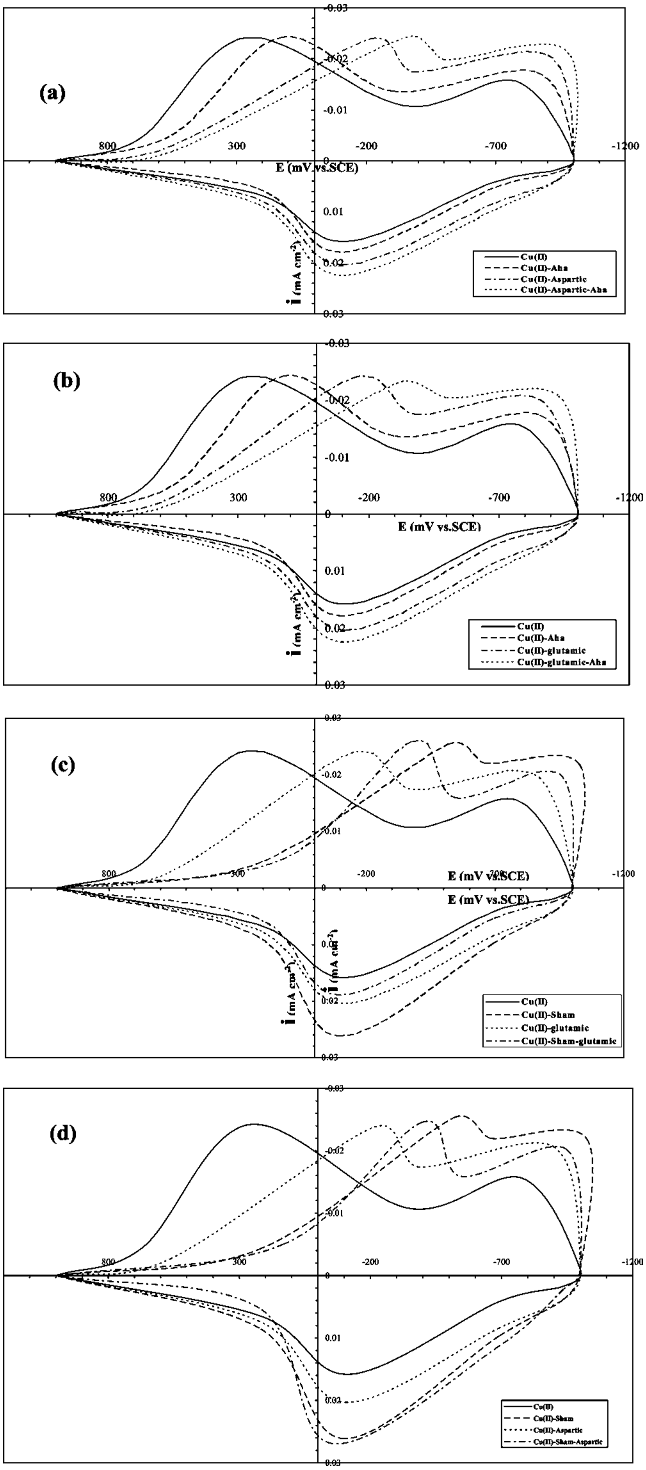


**Figure 7.** Cyclic voltammograms for the ternary systems (a−d) at 25 °C, $I$ = 0.10 mol·dm$^{-3}$ NaNO$_3$, and pH 3.5 with a scan rate of 25 mV·s$^{-1}$.

depend on the stability constants of the complex species,[50] as defined by eq 3

$$(E_{1/2})_{\mathrm{C}} = E_{1/2} - \frac{RT}{nF}\ln K_{\mathrm{f}} - \frac{RT}{nF}\ln a_{\mathrm{L}} \qquad (3)$$

where $(E_{1/2})_{\mathrm{C}}$ and $E_{1/2}$ are the half-wave potentials for the complexed and uncomplexed cation, respectively, and $K_{\mathrm{f}}$ is the stability constant of the complex. It is quite clear that the cyclic voltammograms of the binary and ternary complexes are quite different, and the cathodic peaks are slightly shifted to more negative potentials as well, indicating the formation of the ternary complexes in solution. The main features of the voltammograms are a two-electron oxidation step at positive potentials and a two-electron reduction step at negative potentials for the Cu(II) binary and ternary complexes of the above-mentioned systems.

The irreversibility phonomenon increases according to the following sequence:

Cu(II)−Aha−glut → Cu(II)−Sham−glut →
Cu(II)−Aha−aspart → Cu(II)−Sham−aspart

## Conclusions

The values of the stability constants of the mixed-ligand complexes investigated were discussed. The relative stability of the mixed-ligand complex was compared with that of the binary complex. The mode of chelation was ascertained by conductometric measurements. In addition, the formation of ternary complexes was confirmed by using cyclic voltammetric measurements.

Finally, we concluded that the high stability of mixed-ligand complexes occurs in the ternary systems: transition metal ion/hydroxamic acid/bioligand, which must be taken into account when modeling the process proceeding in biological systems with the participation of the metal ion and the investigated ligands.

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