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The determination of the stability constants of complexes of 1,2,4-triazoles and biologically relevant ligands with M(II) by potentiometric titration in aqueous solution

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Potentiometric equilibrium measurements have been performed at $25 \pm 0.1^{\circ}C$ and $I = 0.10\,mol\,dm^{-3}$ $NaNO_3$ for the interaction of 1,2,4-triazole and M(II) [Cu, Co, Ni, and Zn] with some biologically important ligands (glycine, α-alanine, DL-valine, *n*-valine, DL-leucine, serine, aspartic acid, histidine, and asparagine). Ternary complexes are formed by a stepwise mechanism. The relative stabilities of the ternary complexes are compared with those of the corresponding binary complexes in terms of $\Delta \log K$, $\log X$, and % R.S values. The concentration distribution curves of the various binary and ternary species in a solution were evaluated as a function of pH.

Keywords: Equilibriums; Binary complexes; Ternary complexes; Stability constants; Distribution curves

1. Introduction

Metal coordination complexes have been extensively used in clinical applications as enzyme inhibitors [1], anti-bacterial [2, 3], antiviral [4–6], and anti-cancer agents [7–9]. Different metals have been employed in these complexes, including platinum, gold, vanadium, iron, molybdenum, cobalt, tin, gallium, copper, and many others [10]. 1,2,4-Triazole (1,2,4-TRZ) and its derivatives constitute a promising class of ligands that are widely used in the synthesis of various complexes [11]. Complexes of triazoles play a significant role in biological processes [12–15], such as anti-inflammatory, antimycobacterials [16], and anticonvulsants [17]. Metal complexes of triazoles are used to produce pharmaceutical compounds to inhibit tumor growth and cancer in mammals [18–21]. Such compounds are also used to treat viral as well as bacterial infections [22–24]. In living systems, almost all biochemical processes proceed in the solution phase where several metal ions are present in trace quantities. Whenever a metal ion exists in a solution together with two or more different ligands, the formation of various

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simple as well as ternary complexes is always possible, depending on the pH of the system. The actual complex-formation depends on the affinity of the metal ion towards the various ligands present, and the relative concentrations thereof. In this study, the stability constants of mixed complexes from 1,2,4-TRZs and biologically relevant ligands (glycine, α-alanine, DL-valine, *n*-valine, DL-leucine, serine, aspartic acid, histidine, and asparagine) were determined using potentiometric method at 25°C and $I = 0.10\,\text{mol}\,\text{dm}^{-3}$ $NaNO_3$. The concentration distributions of the various complex species were evaluated.

2. Experimental

2.1. *Materials*

Metal nitrate (BDH) solutions were standardized complexometrically. Carbonate-free sodium hydroxide (titrant, prepared in $0.10\,\text{mol}\,\text{dm}^{-3}$ $NaNO_3$ solution) was standardized potentiometrically with KH phthalate (Merck AG). pH-metric titrations were performed with NaOH (Aldrich) standard solution. 1,2,4-TRZ (Sigma) and the bioligands (BDH) were used as received. A nitric acid solution ($\approx 0.04\,\text{mol}\,\text{dm}^{-3}$) was prepared and used after standardization. Sodium hydroxide, nitric acid, and sodium nitrate were from Merck p.a. All solutions used throughout the experiments were prepared freshly in ultra pure water with a resistivity of $18.3\,\text{mol}\,\text{L}^{-1}\,\Omega\,\text{cm}$. All the aqueous solution samples were prepared gravimetrically.

2.2. *pH-metric measurements*

pH-measurements were performed using a 702 titroprocessor equipped with a 665 dosimat (Switzerland) made by Metrohm. The electrodes were calibrated in both acidic and alkaline regions by titrating $0.01\,\text{mol}\,\text{dm}^{-3}$ nitric acid with standard sodium hydroxide under the same experimental conditions. The concentration of free hydrogen ion, C_{H+} at each point of the titration is related to the measured E of the cell by the Nernst equation:

$$E = E^0 + Q \log C_{H^+} \tag{1}$$

where E^0 and Q are parameters of refinement and represent the standard electrode potential and slope; C_{H+} represents the hydrogen ion concentration. The value of E^0 for the electrode was determined from a Gran plot derived from a separate titration of nitric acid with a standard NaOH solution under the same temperature and medium conditions as those for the test solution titration. The results so obtained were analyzed by nonlinear least-squares computer program (GLEE, glass electrode evaluation) [25] to refine E^0 and the autoprotolysis constant of water, K_W. During these calculations, K_W was refined until the best value for Q was obtained. The results obtained indicated reversible Nernstian response of the glass electrode used. The investigated solutions were prepared (total volume $50\,\text{cm}^3$) and titrated potentiometrically against standard CO_2 free NaOH ($0.10\,\text{mol}\,\text{dm}^{-3}$) solution. A stream of nitrogen was passed throughout the course of the experiment to exclude the adverse effect of atmospheric

carbon dioxide. For the determination of binary systems (one ligand and M(II)), solution containing ligand (1,2,4-TRZ or bioligand) and M(II) were titrated at 1 : 1–1 : 6 metal : ligand ratio and for ternary systems, the ratios used were 1 : 1 : 1 and 1 : 2 : 2. The concentration of ligand solutions in the titrated samples were always the same, 0.001 mol dm^{-3}. Measurements were conducted in a stream of nitrogen, at ionic strength 0.1 mol dm^{-3} $NaNO_3$, using CO_2-free NaOH solution as a titrant. Titrations were performed up to pH $\approx$ 11. Each set of titrations were performed at least four times to check the reproducibility of the data.

Stability constant values were calculated adopting the Irving and Rossotti technique [26, 27]. Computations related to the estimation of stability constants were performed by regression analysis of titration curves using a computer program based on an unweighted linear least-squares fit. The stoichiometries and stability constants of complexes formed were determined by examining various possible composition models for the studied systems. The model selected was that which gave the best statistical fit. 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). The concentration distribution diagrams were obtained with the program SPECIES [28] under the experimental conditions used.

Each of the investigated solutions was thermostated at the required temperature with an accuracy of $\pm 0.10^{\circ}$C, and the solutions were left to stand at this temperature for 15 min before titration. Magnetic stirring was used during all titrations. About 100–140 experimental data points were available for evaluation in each system. The titration was repeated at least four times for each titration curve. A summary of the experimental details for the potentiometric measurements is given in table 1.

3. Results and discussion

The formulas of the investigated ligands are shown in scheme 1. The values of the protonation constants for the 1,2,4-TRZ together with a detailed discussion about the acid–base properties of these ligands can be found in our published work [29]. In the pH range 2–11, values of the protonation constants for the bioligands were in good agreement with the ones reported [30]. The formation constants of the binary complexes were previously reported [31–44]. We have redetermined these constants (tables 2–11) under the prevailing experimental conditions as those utilized for determining the stability constants of the mixed-ligand complexes.

Accordingly, 1,2,4-TRZ is expected to have two ionization constants relevant to the following ionization steps:

$$H_2L^+ \rightleftharpoons HL + H^+ \tag{2}$$

$$HL \rightleftharpoons L^- + H^+ \tag{3}$$

First, ionization constant for the cationic 1,2,4-TRZ is very low (<2.4) [35] and dissociates in strongly acidic solutions. Therefore, these values could not be measured and were not used in the calculations.

Table 1. Summary of experimental parameters for potentiometric measurements.

Systems	*Protonation processes of ligands*: 1,2,4-TRZ and the bioligands (glycine, α-alanine, DL-valine, *n*-valine, DL-leucine, serine, aspartic acid, histidine, and asparagine) in aqueous medium at 25°C and 0.10 mol dm^{-3} $NaNO_3$. *Binary*: • 1,2,4-TRZ with Cu(II), Co(II), Ni(II), and Zn(II) metal ions in aqueous medium at 25°C and 0.10 mol dm^{-3} $NaNO_3$. • Bioligands with Cu(II), Co(II), Ni(II), and Zn(II) metal ions in aqueous medium at 25°C and 0.10 mol dm^{-3} $NaNO_3$. *Ternary*: 1,2,4-TRZ and Bioligands with the Cu(II), Co(II), Ni(II), and Zn(II) metal ions in aqueous medium at 25°C and 0.10 mol dm^{-3} $NaNO_3$.
Solution composition	[ligand] 1×10^{-3} mol dm^{-3}; metal/ligand ratio ranging from 1 : 1 to −1 : 6 for the binary system of the ratios 1 : 1 : 1 and 1 : 2 : 2 for ternary systems; at 25°C and $I = 0.10$ mol dm^{-3} $NaNO_3$.
Experimental method	*pH*-metric titration of 50 cm^3 samples.
Instrument	SM 702 Metrohm automatic titrator with a combined pH glass electrode equipped with a 665 dosimat and a magnetic stirrer (Switzerland).
Calibration	By periodic titrations of HNO_3 solution (at the same temperature and ionic strength) with the use of a computer program (GLEE, glass electrode evaluation) [–].
T (°C)	25°C
I (mol dm^{-3})	0.10 mol dm^{-3} $NaNO_3$
n_{tot}[a]	100–140
n_{tit}[b]	4–6
Method of calculation	Computer program based on unweighted linear least-square fit.

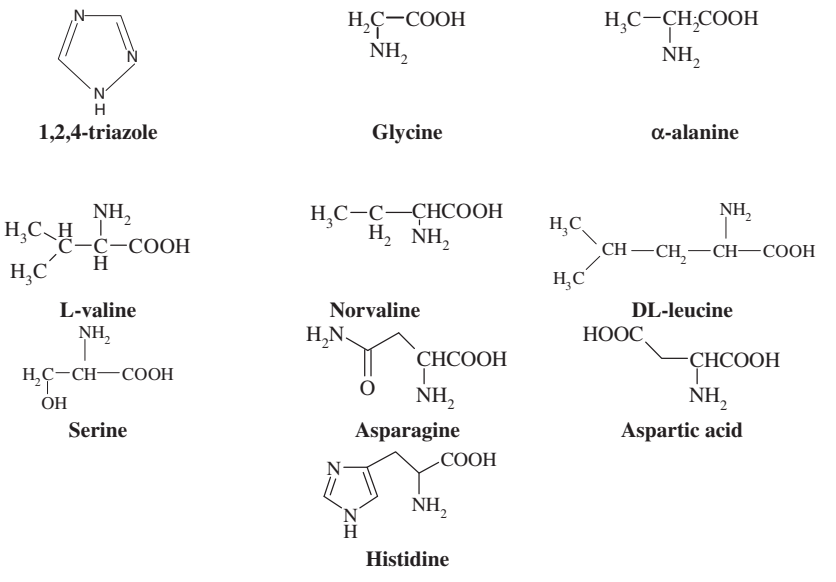
[a]Number of titration points per titration.
[b]Number of titrations per titration curve.

1,2,4-TRZ was titrated in the presence and absence of M(II). The titration curve of the M(II) complex is lower than that of the free 1,2,4-TRZ curve (figures 1–3), indicating complex formation associated with the release of hydrogen ions. The formation constants were determined by fitting potentiometric data on the basis of possible composition models. The selected model with the best statistical fit consisted of M(A) and M(A_2) complexes. The stability constants of their complexes are given in table 2.

The stability constants of 1 : 1 binary complexes of 1,2,4-TRZ [31–44] were refined separately using the titration data of these systems in a 1 : 1 to 1 : 6 metal : ligand ratio at 25°C and $I = 0.10$ mol dm^{-3} $NaNO_3$ and they were in good agreement with the reported values [31–44]. The stepwise stability constants, $\log K_1$ and $\log K_2$, derived from the computed values of $\log \beta$, according to equations $\log K_1 = \log \beta_1$ and $\log K_2 = \log \beta_2 - \log K_1$, show how tightly selected ligands are bound to M(II) (tables 2–11). In addition, $\log K_2$ values are lower than those of $\log K_1$, as expected from the steric hindrance. The stepwise equilibria corresponding to stability constants $\log K_1$ and $\log K_2$ can be represented as follows:

$$M + AMA \rightleftharpoons K_1 = \frac{[MA]}{[M][A]} \tag{4}$$

$$MA + A \rightleftharpoons MA_2 K_2 = \frac{[MA_2]}{[MA][A]} \tag{5}$$



Scheme 1. Structures of the studied ligands.

Table 2. Dissociation constant of TRZ, stability constants of 1 : 1 and 1 : 2 binary complexes at 25°C and $I = 0.10\,\text{mol dm}^{-3}$ ($NaNO_3$).

Cation	pK_{a2} (this work)	pK_{a2} [Ref.]	$\log K^{M}_{ML}$ (this work)	$\log K^{M}_{ML}$ [Ref.]	$\log K^{ML}_{ML_2}$	$\Delta\log K'$
H	10.20 ± 0.03	9.95 [34]				
Cu^{II}			9.19 ± 0.01	9.14 [34]	7.03 ± 0.03	−2.16
Ni^{II}			7.01 ± 0.03	6.93 [34]	4.56 ± 0.02	−2.45
Co^{II}			6.18 ± 0.01	6.10 [34]	4.14 ± 0.01	−2.04
Zn^{II}			6.41 ± 0.03		4.24 ± 0.04	−2.17

Table 3. Dissociation constant of glycine, stability constants of 1 : 1 and 1 : 2 binary complexes and 1 : 1 : 1 ternary complexes involving TRZ at 25°C and $I = 0.10\,\text{mol dm}^{-3}$ ($NaNO_3$).

Cation	pK_{a2} (this work) pK_{a2} [Ref.]	$\log K^{M}_{ML}$ (this work) $\log K^{M}_{ML}$ [Ref.]	$\log K^{ML}_{ML_2}$	$\Delta\log K'$	$\log K^{MA}_{MAL}$	$\Delta\log K''$	$\log \beta^{M}_{MAL}$	% R.S	$\log X$
H	9.63 ± 0.02 9.80 [31]								
Cu^{II}		7.93 ± 0.06 8.23 [32]	6.93 ± 0.04	−1.00	7.57 ± 0.04	−0.36	16.76	−4.54	2.44
Ni^{II}		6.82 ± 0.04 5.85 [30]	$4.55 \pm 0.034.96$ [30]	−2.27	6.63 ± 0.05	−0.19	13.64	−2.79	4.34
Co^{II}		5.45 ± 0.02	4.03 ± 0.03	−1.42	5.83 ± 0.03	0.38	12.01	6.97	4.22
Zn^{II}		6.31 ± 0.04	5.47 ± 0.07	−0.84	6.30 ± 0.07	−0.01	12.71	−0.16	2.99

Table 4. Dissociation constant of α-alanine, stability constants of 1 : 1 and 1 : 2 binary complexes and 1 : 1 : 1 ternary complexes involving TRZ at 25°C and $I = 0.10\,\text{mol dm}^{-3}$ ($NaNO_3$).

Cation	pK_{a2} (this work) pK_{a2} [Ref.]	$\log K^{M}_{ML}$ (this work) $\log K^{M}_{ML}$ [Ref.]	$\log K^{ML}_{ML_2}$	$\Delta\log K'$	$\log K^{MA}_{MAL}$	$\Delta\log K''$	$\log \beta^{M}_{MAL}$	% R.S	$\log X$
H	9.69 ± 0.04 9.82 [37]								
Cu^{II}		7.64 ± 0.04 8.33 [37]	6.48 ± 0.03	−1.16	7.43 ± 0.02	−0.21	16.62	−2.75	1.95
Ni^{II}		5.48 ± 0.02	4.13 ± 0.05	−1.35	6.70 ± 0.01	1.22	13.71	22.26	3.67
Co^{II}		4.63 ± 0.05	3.57 ± 0.02	−1.06	6.88 ± 0.03	1.21	12.02	26.13	3.25
Zn^{II}		$5.37 \pm 0.034.62$ [37]	5.16 ± 0.05	−0.21	5.84 ± 0.05	1.51	13.29	28.12	3.68

Table 5. Dissociation constant of *n*-valine, stability constants of 1 : 1 and 1 : 2 binary complexes and 1 : 1 : 1 ternary complexes involving TRZ at 25°C and $I = 0.10\,\text{mol dm}^{-3}$ ($NaNO_3$).

Cation	pK_{a2} (this work) pK_{a2} [Ref.]	$\log K^{M}_{ML}$ (this work) $\log K^{M}_{ML}$ [Ref.]	$\log K^{ML}_{ML_2}$	$\Delta\log K'$	$\log K^{MA}_{MAL}$	$\Delta\log K''$	$\log \beta^{M}_{MAL}$	% R.S	$\log X$
H	±0.04								
Cu^{II}		8.12 ± 0.01	6.81 ± 0.01	−1.31	7.42 ± 0.01	−0.70	16.61	−8.62	2.07
Ni^{II}		5.27 ± 0.02	4.38 ± 0.03	−0.89	6.46 ± 0.02	1.19	13.47	22.58	5.72
Co^{II}		4.15 ± 0.03	3.47 ± 0.01	−0.68	6.83 ± 0.04	1.69	12.02	40.72	6.10
Zn^{II}		4.42 ± 0.02	4.10 ± 0.03	−0.32	5.84 ± 0.03	2.41	13.24	54.52	7.31

Table 6. Dissociation constant of DL-valine, stability constants of 1 : 1 and 1 : 2 binary complexes, and 1 : 1 : 1 ternary complexes involving TRZ at 25°C and $I = 0.10\,\text{mol dm}^{-3}$ ($NaNO_3$).

Cation	pK_{a2} (this work) pK_{a2} [Ref.]	$\log K^{M}_{ML}$ (this work) $\log K^{M}_{ML}$ [Ref.]	$\log K^{ML}_{ML_2}$	$\Delta\log K'$	$\log K^{MA}_{MAL}$	$\Delta\log K''$	$\log \beta^{M}_{MAL}$	% R.S	$\log X$
H	9.57 ± 0.03 9.57 [35]								
Cu^{II}		7.88 ± 0.03 8.05 [38]	4.73 ± 0.01	−3.15	7.50 ± 0.02	−0.38	16.69	−4.82	4.55
Ni^{II}		6.68 ± 0.01 5.32 [30]	4.55 ± 0.02	−2.13	6.72 ± 0.01	0.04	13.73	0.60	4.66
Co^{II}		5.22 ± 0.02	3.73 ± 0.03	−1.49	5.92 ± 0.05	0.01	12.33	0.17	2.65
Zn^{II}		5.91 ± 0.03	5.45 ± 0.04	−0.46	6.74 ± 0.03	1.52	12.92	29.12	6.57

When a solution contains two different ligands and a metal ion, they may exist in equilibria in which either (i) both the ligands combine with the metal ion simultaneously or (ii) the two ligands may be combined one by one at different pH. The formation of ternary complexes was inferred from the pH-metric curves. It was deduced that 1,2,4-TRZ acts as a primary ligand in the ternary complexes involving glycine, α-alanine,

Table 7. Dissociation constant of DL-leucine, stability constants of 1 : 1 and 1 : 2 binary complexes and 1 : 1 : 1 ternary complexes involving TRZ at 25°C and $I = 0.10\,mol\,dm^{-3}$ ($NaNO_3$).

Cation	pK_{a2} (this work) pK_{a2} [Ref.]	$\log K^{M}_{ML}$ (this work) $\log K^{M}_{ML}$ [Ref.]	$\log K^{ML}_{ML_2}$	$\Delta\log K'$	$\log K^{MA}_{MAL}$	$\Delta\log K''$	$\log \beta^{M}_{MAL}$	% R.S	$\log X$
H	9.66 ± 0.02 9.81 [38]								
Cu^{II}		8.26 ± 0.01 8.10 [38]	3.27 ± 0.02	−4.99	7.60 ± 0.05	−0.66	16.79	−7.99	5.38
Ni^{II}		5.33 ± 0.02	3.38 ± 0.04	−1.95	6.80 ± 0.05	1.47	13.81	27.58	7.34
Co^{II}		4.49 ± 0.03	3.58 ± 0.02	−0.91	5.92 ± 0.08	1.43	12.10	31.85	5.81
Zn^{II}		4.73 ± 0.02	4.57 ± 0.05	−0.16	6.62 ± 0.02	1.89	13.03	39.96	6.11

Table 8. Dissociation constant of serine, stability constants of 1 : 1 and 1 : 2 binary complexes and 1 : 1 : 1 ternary complexes involving TRZ at 25°C and $I = 0.10\,mol\,dm^{-3}$ ($NaNO_3$).

Cation	pK_{a2} (this work) pK_{a2} [Ref.]	$\log K^{M}_{ML}$ (this work) $\log K^{M}_{ML}$ [Ref.]	$\log K^{ML}_{ML_2}$	$\Delta\log K'$	$\log K^{MA}_{MAL}$	$\Delta\log K''$	$\log \beta^{M}_{MAL}$	% R.S	$\log X$
H	9.05 ± 0.05 9.12 [31]								
Cu^{II}		7.02 ± 0.02 7.95 [33]	5.39 ± 0.04	−1.63	7.40 ± 0.07	0.38	16.59	5.41	4.55
Ni^{II}		5.38 ± 0.05	4.12 ± 0.05	−1.26	5.85 ± 0.02	0.47	12.86	8.74	4.65
Co^{II}		4.26 ± 0.04	3.76 ± 0.03	−0.50	4.39 ± 0.02	0.13	10.57	3.05	2.80
Zn^{II}		4.81 ± 0.06	3.93 ± 0.02	−0.88	5.54 ± 0.03	0.73	11.95	15.18	4.51

Table 9. Dissociation constant of histidine,[a] stability constants of 1 : 1 and 1 : 2 binary complexes and 1 : 1 : 1 ternary complexes involving TRZ at 25°C and $I = 0.10\,mol\,dm^{-3}$ ($NaNO_3$).

Cation	pK_{a1} pK_{a2} pK_{a1} [Ref.] pK_{a2} [Ref.]	$\log K^{M}_{ML}$ (this work) $\log K^{M}_{ML}$ [Ref.]	$\log K^{ML}_{ML_2}$	$\Delta\log K'$	$\log K^{MA}_{MAL}$	$\Delta\log K''$	$\log \beta^{M}_{MAL}$	% R.S	$\log X$
H	6.28 ± 0.04 9.53 ± 0.02								
Cu^{II}		10.03 ± 0.04 10.50 [36]	4.74 ± 0.04	−5.29	9.18 ± 0.02	−0.01	19.21	−0.11	5.28
Ni^{II}		8.46 ± 0.02 8.30 [36]	6.73 ± 0.02	−1.72	8.37 ± 0.01	1.36	16.83	19.40	3.09
Co^{II}		6.96 ± 0.05 6.40 [36]	5.76 ± 0.05	−1.20	7.55 ± 0.03	1.37	14.51	22.17	2.57
Zn^{II}		7.15 ± 0.03	6.10 ± 0.03	−1.05	7.11 ± 0.05	0.70	14.26	16.92	1.75

[a]Histidine acts as a primary ligand (A) and hydroxamic acids act as secondary ligands (L).

Table 10. Dissociation constant of asparagine, stability constants of 1 : 1 and 1 : 2 binary complexes and 1 : 1 : 1 ternary complexes involving TRZ at 25°C and $I = 0.10\,\text{mol dm}^{-3}$ ($NaNO_3$).

Cation	pK_{a1}	$\log K^{M}_{ML}$	$\log K^{ML}_{ML_2}$	$\Delta\log K'$	$\log K^{MA}_{MAL}$	$\Delta\log K''$	$\log \beta^{M}_{MAL}$	% R.S	$\log X$
H	8.82 ± 0.02								
Cu^{II}		6.20 ± 0.02	5.12 ± 0.03	−1.79	7.53 ± 0.05	1.33	16.72	21.45	5.91
Ni^{II}		5.77 ± 0.01	4.04 ± 0.04	−1.32	6.05 ± 0.05	0.28	13.06	4.85	4.74
Co^{II}		3.50 ± 0.05	3.59 ± 0.02	−0.44	4.48 ± 0.08	0.98	10.66	28.00	3.91
Zn^{II}		4.60 ± 0.04	3.71 ± 0.06	−0.76	5.28 ± 0.02	0.68	11.69	14.78	4.42

Table 11. Dissociation constant of aspartic acid,[a] stability constants of 1 : 1 and 1 : 2 binary complexes and 1 : 1 : 1 ternary complexes involving TRZ at 25°C and $I = 0.10\,\text{mol dm}^{-3}$ ($NaNO_3$).

Cation	pK_{a1} pK_{a2} pK_{a1} [Ref.] pK_{a2} [Ref.]	$\log K^{M}_{ML}$ (this work) $\log K^{M}_{ML}$ [Ref.]	$\log K^{ML}_{ML_2}$	$\Delta\log K'$	$\log K^{MA}_{MAL}$	$\Delta\log K''$	$\log \beta^{M}_{MAL}$	% R.S	$\log X$
H	3.88 ± 0.03 9.52 ± 0.03 3.67 [35] 9.68 [35]								
Cu^{II}		7.67 ± 0.05 8.50 [36]	4.34 ± 0.05	−3.33	8.60 ± 0.04	−0.59	16.24	−6.42	4.31
Ni^{II}		6.14 ± 0.03	4.26 ± 0.03	−1.88	7.55 ± 0.02	0.54	13.69	7.70	5.41
Co^{II}		4.60 ± 0.06	3.53 ± 0.05	−1.07	5.56 ± 0.03	−0.62	10.16	−10.03	1.87
Zn^{II}		5.36 ± 0.02	4.04 ± 0.02	−1.32	6.60 ± 0.02	2.36	11.98	2.96	3.87

[a]Aspartic acid acts as a primary ligand (A) and hydroxamic acid.

DL-valine, *n*-valine, DL-leucine, serine, and asparagine, whereas 1,2,4-TRZ behaves as a secondary ligand in ternary systems containing aspartic acid and His. The ternary complex formation could be considered in stepwise complexation equilibria:

$$\text{M(II)} + \text{A} \rightleftharpoons \text{M(II)} - \text{A}, \quad K^{\text{M(II)}}_{\text{M(II)}-\text{A}} = \frac{[\text{M(II)} - \text{A}]}{[\text{M(II)}][\text{A}]} \tag{6}$$

$$\text{M(II)} - \text{A} + \text{L} \rightleftharpoons \text{M(II)} - \text{A} - \text{L}, \quad K^{\text{M(II)}-\text{A}}_{\text{M(II)}-\text{A}-\text{L}} = \frac{[\text{M(II)} - \text{A} - \text{L}]}{[\text{M(II)} - \text{A}][\text{L}]} \tag{7}$$

The overall stability constant β^{M}_{MAL} may be represented by the following equation:

$$\text{M} + \text{A} + \text{L} \rightleftharpoons \text{MAL}, \quad \beta^{\text{M}}_{\text{MAL}} = \frac{[\text{MAL}]}{[\text{M}][\text{A}][\text{L}]} = K^{\text{MA}}_{\text{MAL}} \times K^{\text{M}}_{\text{MA}} \tag{8}$$

where M(II) is Cu(II), Co(II), Ni(II), or Zn(II), A represents the primary ligand, and L represents the secondary ligand (amino acid or TRZ in the case of aspartic acid, and histidine). For instance, examining figure 2, one observes that the curves obtained for the different 1 : 2 : 2 ternary complex solutions (curve f) overlap with the titration curve of the 1 : 1 binary Co(II)–aspartic acid (curve c) at low pH and a divergence of the ternary complex titration curve from that of the binary Co(II)–TRZ is observed at higher pH. This shows the coordination of TRZ to the Co(II)–aspartic acid binary complex in a stepwise manner as represented by the Equations (6) and (7).

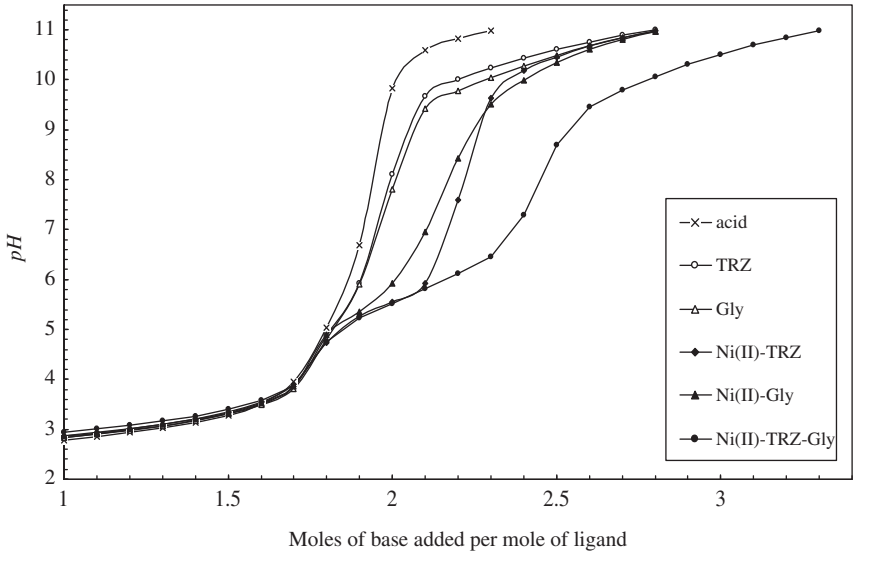


Figure 1. Potentiometric titration curve of the Ni–TRZ–gly system.

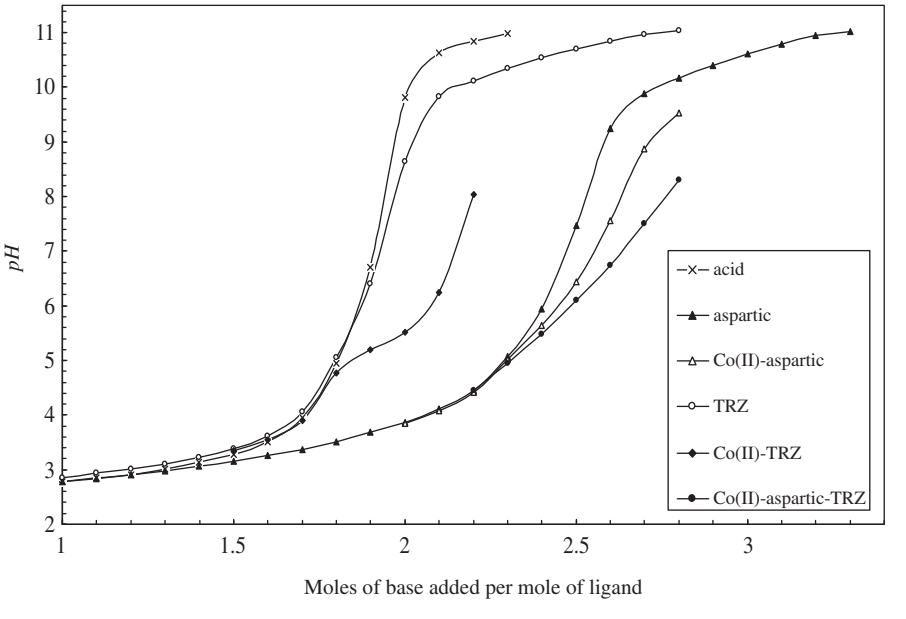


Figure 2. Potentiometric titration curve of the Co–aspartic–TRZ-system.

Examination of stability constant values of the same metal ion ternary complexes (tables 2–11) reveals:

(1) The stabilities of the aspartate complexes are greater than those of glycine, α-alanine, L-valine, norvaline, and asparagine as a result of large difference in their basic strengths as well as their tendency to act as ONO tridentate ligands.

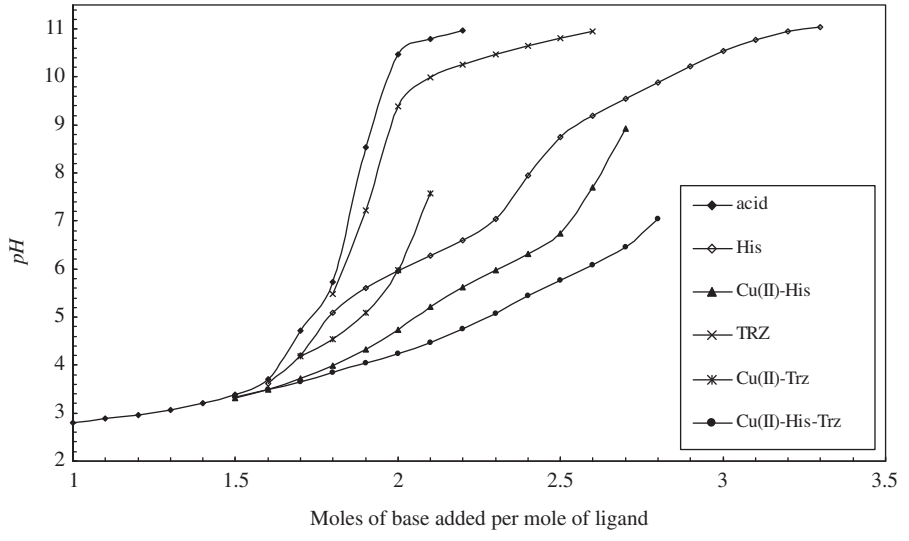


Figure 3. Potentiometric titration curve of the Cu–His–TRZ-system.

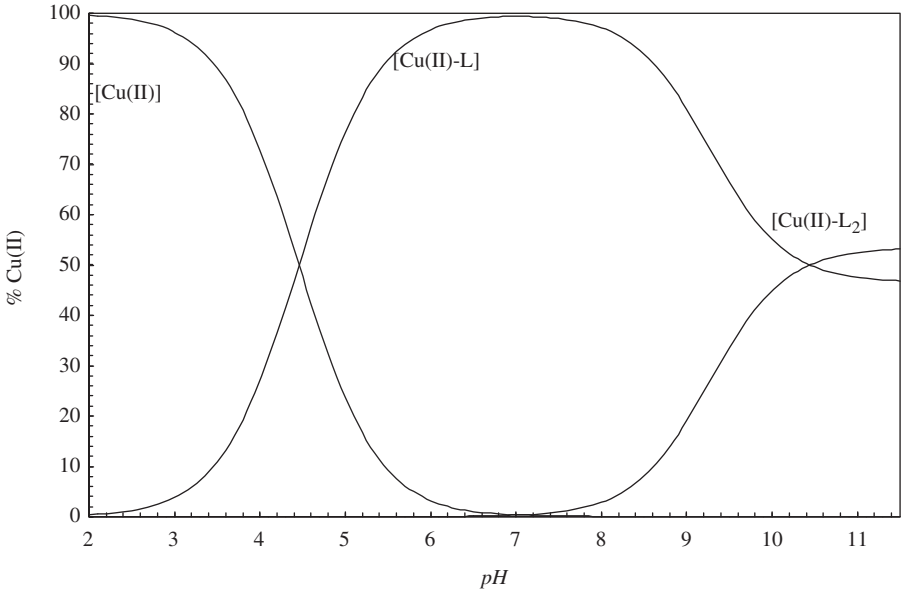


Figure 4. Representative concentration distribution curves as a function of pH calculated for Cu(II)–DL-leucine system in the ratio 1 : 4 at 25°C, $I = 0.10\,\text{mol dm}^{-3}$ $NaNO_3$ and $C_{\text{ligand}} = 0.001\,\text{mol dm}^{-3}$.

(2) Stability of ternary complexes involving α-alanine are lower than those containing glycine [45]. This behavior does not follow their basicities as expected, probably because the pK_{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

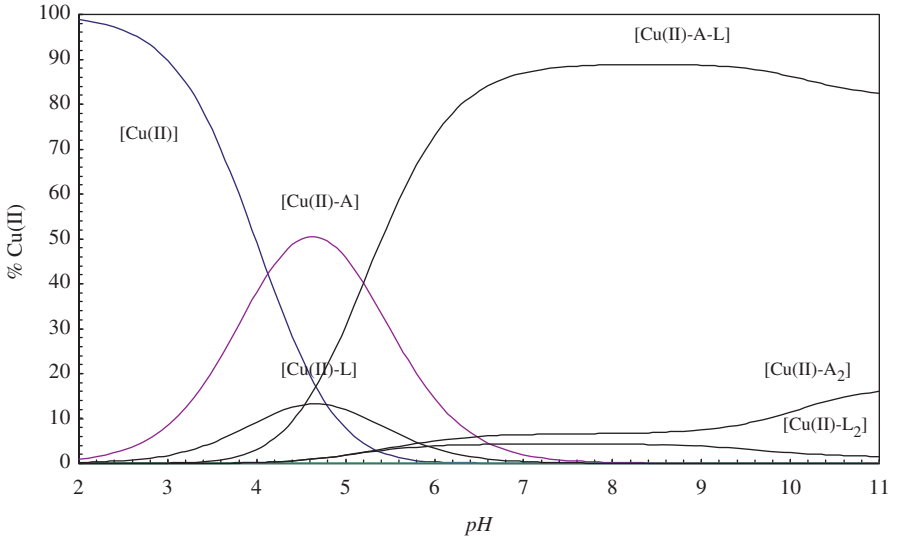


Figure 5. Representative concentration distribution curves as a function of pH calculated for Cu(II)–TRZ–gly system in the ratio 1 : 2 : 2 at 25°C, $I = 0.10\,\text{mol dm}^{-3}$ $NaNO_3$ and $C_{\text{ligand}} = 0.001\,\text{mol dm}^{-3}$.

amino group (α-alanine), is responsible for the lower stability of its ternary complexes.

(3) The observed lower stabilities of the ternary complexes containing asparagine can be mainly attributed to the low basicity of asparagine-free conjugate base ($pK_{a2} = 8.82 \pm 0.02$).
(4) The complex stability of the ternary systems with respect to the metal ion is Zn(II) < Cu(II) > Ni(II) > Co(II). The order of stability follows the Irving-Williams series.
(5) The higher stability of ternary complexes involving His than those of α-amino acids reveals that His interacts with the metal ion by the amino and imidazole nitrogens.

The concentration distribution of the various species as a function of pH provides a useful description of metal ion binding in the biological system. In all distribution curves the concentration of the formed complex increases with increasing pH, thus making the complex formation more favored in the physiological pH range. In all Cu : aa (aa: represents the amino acid) species distribution diagrams, ML species are formed early (pH around 3) due to the great affinity between Cu(II) and the amino group, which has its proton displaced to complex. In figure 4 the species distribution diagram of [Cu(II)-DL-leucine] is shown as an example. The mixed ligand species [Cu(II)-TRZ-gly] starts to form at pH ~ 3.5 and with increasing pH (figure 5), its concentration increases reaching a maximum of 88.68% at pH 7.8. Further increase of pH is accompanied by a decrease in ternary complex concentration and an increase of Cu(II)–A_2 complex concentrations.

Different methods [46–49] are known to estimate the formation of mixed ligand complexes. $\Delta \log K$ value provides an insight into the various factors responsible for the formation and stabilization of ternary complexes in solution, as defined by

Equation (9):

$$\Delta \log K = \log K^{MA}_{MAL} - \log K^{M}_{ML} \quad (9)$$

In the case of ternary complex formation, negative $\Delta \log K$ 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 [47, 48]. In general, positive $\Delta \log K$ values indicate a significant stabilization of the ternary systems (tables 2–11). The higher values of $\Delta \log K$, for the ternary systems involving His than the aliphatic amino acids, may be attributed to the presence of an aromatic ring [48, 49]. $\Delta \log K$ values, in general, for ternary systems involving Cu(II) were less than for the corresponding other metal ion systems, in agreement with different coordination geometries of these metal ions. Contrary to $\Delta \log K$ and the values of $\log X$ (the constant due to the equilibrium $[MA_2] + [ML_2]2[MAL]$) [47], the appropriate constants given in tables 2–11 are much higher for Cu(II) than other M(II) ions due to the relatively small value of $\log K_2$ (tables 2–11). The values of $\log X$ are higher than that expected on a statistical basis (0.60) [49, 50], indicating that the formation of mixed complexes is favored in these systems.

4. Conclusions

The present investigation describes the formation equilibria of binary and ternary complexes of M(II) involving TRZ and various biologically relevant ligands containing different functional groups. The ternary complexes of α-amino acids are formed in a stepwise process, whereby binding of M(II) to *A* is followed by the ligation of L. The stability constants of complexes in solution have been calculated and their concentration distributions are evaluated.

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