

Ternary Complexes of some Divalent Metal Ions with Potentially Tridentate Ligands in Dioxane-Water Mixtures

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Received 25 October 2011, revised 20 April 2012, accepted 26 July 2012.

ABSTRACT

Chemical speciation of mixed ligand complexes of Ca(II), Mg(II) and Zn(II) with L-histidine and L-glutamic acid have been studied in varying concentrations (0.0–60.0 % v/v) of 1, 4-dioxane-water mixtures maintaining an ionic strength of 0.16 mol L⁻¹ sodium chloride at 303.0 K. Titrations were carried out in the presence of different relative concentrations (M:L:X = 1.0:2.5:2.5, 1.0:2.5:5.0, 1.0:5.0:2.5) of metal (M) to L-histidine (L) to L-glutamic acid (X) with sodium hydroxide. Stability constants of ternary complexes were refined with MINIQUAD75. The best-fit chemical models were selected based on statistical parameters and residual analysis. The predominant species detected were ML₂XH₂, MLXH₂ and MLX₂ for Ca(II), Mg(II) and Zn(II). The formation and distribution of different species with relative concentrations of metal and ligands with varying pH are represented in the form of distribution diagrams. The influence of the solvent on the speciation is discussed in terms of the dielectric constant of the medium.

KEYWORDS

Speciation, mixed ligand complexes, L-histidine, L-glutamic acid, essential metals, dioxane.

1. Introduction

Most metabolic reactions are catalyzed by metal-containing enzymes, the activity of which is due to metal-enzyme-substrate complexes. The active site of the enzymes has a lower polarity than biofluids. The specificity and selectivity of enzyme-substrate reactions can be achieved by manipulating the equivalent solution dielectric constants (ESDC) at the active site.¹ The ESDC at the active sites in bovine carbonic anhydrase and carboxy peptidase were estimated to be 35 and 70, respectively. Hence, modelling studies of ternary complexes have gained popularity in different aqua-organic mixtures with different dielectric constants.^{2–6} The aim of the present study was to understand the role of metal ions at active site cavities. Histidine (His) and glutamic acid (Glu) have been studied in this work as model compounds for amino acid residues. The low dielectric constant of the medium is mimicked by using a water soluble polar organic solvent, namely, dioxane (DOX).

L-Histidine is present at the active sites of many enzymes and biomolecules. L-Glutamic acid acts as a neurotransmitter and as a precursor of γ -aminobutyric acid.^{7–9} Calcium and magnesium are essential mineral nutrients for life.^{10,11} In animals and plants different cell types maintain different concentrations of magnesium.^{12–16} The Lewis acidity of the Zn²⁺ ion, flexibility of its coordination sphere and kinetic lability of coordinated ligands are responsible for its broad utility within proteins of the body.^{17–19} Hence, the speciation of ternary complexes of Ca(II), Mg(II) and Zn(II) with His and Glu has been studied in dioxane-water mixtures and reported in this communication. The protonation constants²⁰ of His and Glu and their binary complexes^{21,22} with Ca(II), Mg(II) and Zn(II) in DOX-water mixtures were reported earlier.

2. Experimental

All the chemicals used in this work were of analytical reagent (AR) grade with a minimum assay of 99.9 % and were obtained

from E-Merck and Qualigens, India. They were used without further purification. Solutions of 0.05 mol L⁻¹ His and Glu (Merck, India) were prepared in triple-distilled deionized water by maintaining 0.05 mol L⁻¹ hydrochloric acid to increase the solubility. Solutions of 0.2 mol L⁻¹ hydrochloric acid and 2.0 mol L⁻¹ sodium chloride (Qualigens, India) were prepared to maintain the acidity and ionic strength in the titrand, respectively. Solutions of 0.1 mol L⁻¹ of Ca(II), Mg(II) and Zn(II) chlorides (G.R. Grade, Merck, India) were prepared in triple-distilled water maintaining 0.05 mol L⁻¹ HCl to suppress the hydrolysis of the metal ions. A 0.4 mol L⁻¹ sodium hydroxide (Qualigens, India) solution was used as the titrant. The sodium hydroxide was standardized by standard solutions of oxalic acid and potassium hydrogen phthalate. Hydrochloric acid was standardized by standard borax solution and standardized sodium hydroxide solution. The concentrations of Ca(II), Mg(II) and Zn(II) solutions were determined complexometrically by titrating against a standard solution of EDTA using Eriochrome Black T as the indicator and NH₄OH/NH₄Cl buffer to maintain the pH at 10.0. The data were subjected to analysis of variance of one-way classification²³ to assess the errors that might have crept into the determination of the concentrations. The strengths of alkali and mineral acid were determined using the Gran plot method.^{24,25}

2.1. Procedure

An ELICO (Model LI 120, India) pH meter, of 0.01 readability (pH 0–14), in conjunction with a glass combination pH electrode was used to monitor the pH. Potassium hydrogen phthalate (0.05 mol L⁻¹) and borax (0.01 mol L⁻¹) solutions were used to calibrate and to preliminarily check the response of the glass electrode in acidic (pH = 4.01) and basic (pH = 9.18) regions. The calibration was linear in the pH range of refinement. The effect of variations in asymmetry, liquid junction potential, activity coefficient, sodium ion error and dissolved carbon dioxide on the response of glass electrode was accounted for in the form of a correction factor (log F),²⁶ in the present electrometric titrations.

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Table 1 Total initial concentrations of ingredients (in mmol) for mixed-ligand titrations in DOX-water mixtures.
[NaOH] = 0.4 mol L⁻¹; V₀ = 50.0 cm³; temperature = 303.0 K;
Ionic strength = 0.16 mol L⁻¹; [HCl] = 1 mmol.

% v/v DOX	Ca(II)			Mg(II)			Zn(II)			M:L:X
	TM ₀	TL ₀		TM ₀	TL ₀		TM ₀	TL ₀		
		His	Glu		His	Glu		His	Glu	
00.00	0.0819	0.2495	0.2510	0.1198	0.2495	0.2510	0.0927	0.2495	0.2510	1:2.5:2.5
		0.3742	0.3765		0.3742	0.3765		0.3742	0.3765	1:2.5:5.0
		0.4990	0.5020		0.4990	0.5020		0.4990	0.5020	1:5.0:2.5
10.00	0.0819	0.2500	0.2495	0.1198	0.2500	0.2495	0.0927	0.2500	0.2495	1:2.5:2.5
		0.3750	0.3742		0.3750	0.3742		0.3750	0.3742	1:2.5:5.0
		0.5000	0.4990		0.5000	0.4990		0.5000	0.4990	1:5.0:2.5
20.00	0.0819	0.2500	0.2500	0.1198	0.2500	0.2500	0.0927	0.2500	0.2500	1:2.5:2.5
		0.3750	0.3750		0.3750	0.3750		0.3750	0.3750	1:2.5:5.0
		0.5000	0.5000		0.5000	0.5000		0.5000	0.5000	1:5.0:2.5
30.00	0.0819	0.2500	0.2500	0.1198	0.2500	0.2500	0.0927	0.2500	0.2500	1:2.5:2.5
		0.3750	0.3750		0.3750	0.3750		0.3750	0.3750	1:2.5:5.0
		0.5000	0.5000		0.5000	0.5000		0.5000	0.5000	1:5.0:2.5
40.00	0.0819	0.2500	0.2500	0.1198	0.2500	0.2500	0.0927	0.2500	0.2500	1:2.5:2.5
		0.3750	0.3750		0.3750	0.3750		0.3750	0.3750	1:2.5:5.0
		0.5000	0.5000		0.5000	0.5000		0.5000	0.5000	1:5.0:2.5
50.00	0.0819	0.2495	0.2495	0.1198	0.2495	0.2495	0.0927	0.2495	0.2495	1:2.5:2.5
		0.3742	0.3742		0.3742	0.3742		0.3742	0.3742	1:2.5:5.0
		0.4990	0.4990		0.4990	0.4990		0.4990	0.4990	1:5.0:2.5
60.00	0.0819	0.2500	0.2500	0.1198	0.2500	0.2500	0.0927	0.2500	0.2500	1:2.5:2.5
		0.3750	0.3750		0.3750	0.3750		0.3750	0.3750	1:2.5:5.0
		0.5000	0.5000		0.5000	0.5000		0.5000	0.5000	1:5.0:2.5

TM₀ is the initial number of mmols of metal ion, TL₀ is the initial number of mmols of ligand, M is metal ion, L is the primary ligand (His) and X is the secondary ligand (Glu).

The simulated acid-base titration data (pHCi) calculated by means of the SCPHD²⁷ program was used to compute the log F for each of the solvent compositions. The log F value is used to convert pH meter dial reading into the logarithm of the reciprocal of the hydrogen ion concentration (pHEi) according to Equation 1.

$$\log F = \text{pHCi} - \text{pHEi} \quad (1)$$

For the determination of stability constants of ternary species, initially strong acid was titrated against alkali at regular intervals to check the complete equilibration of the glass electrode. Then, the calomel electrode was refilled with the DOX-water mixture of equivalent composition to that of the titrand. All the titrations were performed pH metrically in a medium containing varying concentrations (0.0–60.0 % v/v) of DOX-water mixtures at 303.0 ± 0.1 K. Dioxane is completely miscible with water in all proportions. The excess molar volumes for binary mixtures of dioxane and water at 303.0 K have been taken from the literature²⁸ and the necessary volume corrections were made. In each of the titrations, the titrand consisted of approximately 1.0 mol L⁻¹ mineral acid in a total volume of 50.0 mL. Titrations were carried out in the presence of different relative concentrations of the metal (M), His (L) and Glu (X) (M:L:X = 1.0:2.5:2.5, 1.0:2.5:5.0, 1.0:5.0:2.5) with 0.4 mol L⁻¹ sodium hydroxide. The analytical concentrations of the ingredients are given in Table 1. The details of the experimental procedure and titration assembly are given elsewhere.²⁹ The best-fit chemical model for each system investigated was arrived at using a non-linear least squares analysis program MINQUAD75,³⁰ which exploits the advantage of the constrained least squares method in the initial refinement

and reliable convergence of undamped, unconstrained Marquardt algorithm.

3. Results and Discussion

3.1 Modelling of Chemical Speciation

A preliminary investigation of the alkalimetric titrations of mixtures containing different mole ratios of His and Glu in the presence of mineral acid and inert electrolyte inferred that no condensed species were formed. The best fit models were chosen based on the statistical parameters like χ^2 , R-factor, skewness and kurtosis given in Table 2. The ternary complex species detected are ML₂XH₂, MLXH₂ and MLX₂ for Ca(II), Mg(II) and Zn(II). A very low standard deviation (SD) in log values of the overall stability constants (log β) indicates the precision of these parameters. The small values of U_{corr} (sum of squares of deviations in the concentrations of the metal, ligands and the hydrogen ion at all experimental points corrected for degrees of freedom) indicate that the models represent the experimental data. Small values of the mean, standard deviation and mean deviation for the systems corroborate that the residuals are around a zero mean with little dispersion. For an ideal normal distribution, the values of kurtosis and skewness should be three and zero, respectively. If the calculated kurtosis is less than three, the peak of the error distribution curve is flat (platykurtic) and if the kurtosis is greater than three, the distribution shall have sharp peak (leptokurtic). The kurtosis values in the present study indicate that most of the residuals are greater than three and so the distribution of the residuals has a sharp peak (leptokurtic) pattern in the majority and a few form platykurtic

Table 2 Parameters of the best fit chemical models for the Ca(II), Mg(II) and Zn(II)- His-Glu ternary complexes in DOX-water mixtures.

% v/v DOX	log β_{MLXH} (SD)			pH-range	NP	$U_{corr} \times 10^8$	Skewness	Kurtosis	χ^2	R-factor
	ML_2XH_2	$MLXH_2$	MLX_2							
Ca(II)										
00.0	29.41(8)	26.65(4)	9.67(8)	3.0–10.0	94	5.08	-0.23	4.95	31.19	0.0116
10.0	27.85(6)	24.27(8)	8.28(9)	2.2–10.0	153	5.77	0.57	3.58	128.94	0.0101
20.0	28.65(10)	25.90(5)	9.45(8)	2.5–10.0	157	5.97	0.11	3.46	67.38	0.0123
30.0	28.53(16)	26.06(6)	9.23(11)	2.8–10.0	124	9.97	0.36	3.06	81.94	0.0154
40.0	29.22(8)	25.97(6)	10.46(6)	3.0–10.0	117	4.80	-1.30	3.95	92.22	0.0105
50.0	29.39(9)	26.32(5)	10.96(7)	3.0–10.0	103	8.56	-0.28	2.92	11.18	0.0134
60.0	31.11(9)	26.25(8)	11.19(13)	3.0–10.0	110	3.93	-0.47	2.75	26.52	0.0102
Mg(II)										
00.0	28.98(8)	25.94(5)	9.39(8)	2.9–10.0	97	10.96	-0.59	7.27	48.04	0.0167
10.0	28.32(12)	25.61(7)	9.48(12)	2.7–10.0	123	3.32	0.39	3.38	12.78	0.0139
20.0	28.91(10)	25.89(5)	9.76(9)	2.7–10.0	106	20.19	-0.23	3.13	19.17	0.0205
30.0	28.30(11)	25.47(5)	9.08(9)	3.0–10.0	106	18.54	-0.37	3.62	31.40	0.0204
40.0	28.99(6)	25.54(5)	10.33(5)	3.0–10.0	111	8.31	-0.80	4.81	65.55	0.0134
50.0	29.57(8)	26.20(5)	10.60(8)	3.0–10.2	108	21.24	-0.14	2.85	27.56	0.0209
60.0	31.99(5)	26.35(5)	12.04(8)	3.0–10.0	111	5.34	0.58	2.97	27.57	0.0120
Zn(II)										
00.0	31.40(8)	24.75(24)	18.45(20)	4.0–8.0	58	2.64	-1.59	6.61	27.45	0.0085
10.0	31.74(9)	25.40(24)	18.87(29)	4.0–8.0	59	3.54	-0.94	6.38	17.63	0.0095
20.0	32.18(7)	25.42(22)	17.11(22)	4.0–8.0	60	0.20	-0.66	4.73	14.29	0.0034
30.0	33.31(6)	26.79(6)	19.13(15)	4.0–8.0	65	1.45	-0.13	6.44	36.06	0.0058
40.0	34.51(9)	27.75(9)	21.51(14)	4.0–8.0	69	3.32	-0.28	5.88	22.67	0.0088
50.0	32.93(7)	26.28(6)	18.24(41)	4.0–8.0	66	0.72	-0.24	2.05	16.48	0.0040
60.0	34.31(24)	27.67(19)	22.35(25)	4.0–7.0	72	13.49	-0.01	2.45	48.28	0.0177

$U_{corr} = U/(NP-m)$, m is the number of species; NP is the number of experimental points; SD is the standard deviation.

patterns. The values of skewness recorded in Table 2 are between -1.59 and 0.58. These data provide evidence that the residuals form part of a normal distribution; hence, the least squares method can be applied to the present data. The sufficiency of the model is further evident from the low crystallographic R-values recorded.

3.2. Effect of Dielectric Constant on Stability of Ternary Complexes

Addition of DOX to water decreases the dielectric constant of the medium. The dielectric constants of DOX at different percentages (0.0–60.0 % v/v) of water were taken from literature.³¹ The change in overall stability constants or change in Gibbs energy with change in co-solvent depends on two factors: electrostatic and non-electrostatic. As the basicity³² of DOX is lower than that of water, the non-electrostatic effect seems to decrease the proton accepting power of the ligand. Addition of more DOX removes water molecules from the coordination sphere of the metal ion making it more susceptible to react with the ligand. According to Born's³³ equation the energy of electrostatic interaction is related to the dielectric constant of the medium and $\log \beta$ versus $1/D$ (D is the dielectric constant of the medium) should be linear.

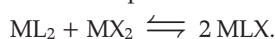
The trends of the stability constant ($\log \beta$) values of the ternary complexes with $1/D$ of the DOX-water mixtures are given in Fig. 1. The trend is almost linear which indicates that either the dielectric constant or the long range interactions are responsible for the trend in stability. This linear increase in $\log \beta$ values indicates the dominance of the structure-forming nature of DOX over the complexing ability.

3.3 Stability of Ternary Complexes

The stability of the ternary complexes as compared to their binary analogues was quantified^{34–37} based on the disproportionation constant ($\log X$) given by Equation 2.

$$\log X = 2\log K_{MLX}^M - \log K_{ML_2}^M - \log K_{MX_2}^M, \quad (2)$$

which corresponds to the equilibrium



Under these equilibrium conditions one can expect 50 % ternary complexes and 25 % each of the binary complexes to be formed and the value of $\log X$ was reported³⁸ to be 0.6. A value greater than this accounts for the extra stability of MLX .

Although the species ML_2XH_2 , $MLXH_2$ and MLX_2 have been found in the present study, the $\log X$ values of all these species could not be calculated due to the absence of some of the binary species required for this calculation. The $\log X$ values of $MLXH_2$ have been calculated as given in Table 3 due to the availability of the corresponding binary species given in the footnote of Table 3. The $\log X$ values are in the range of 2.02–15.15 for Ca(II), 2.02–14.51 for Mg(II) and 1.27–9.82 for Zn(II) and all the values are higher than those expected on a statistical basis (0.6). These higher values account for the extra stability of the ternary complexes. The reason^{39,40} for the extra stability may be due to interactions outside the coordination sphere such as the formation of hydrogen bonds between the coordinated ligands, charge neutralization, chelate effect and stacking interactions.

3.4. Effect of Influential Parameters on Stability Constants

Any variation in the parameters like concentrations of ingredi-

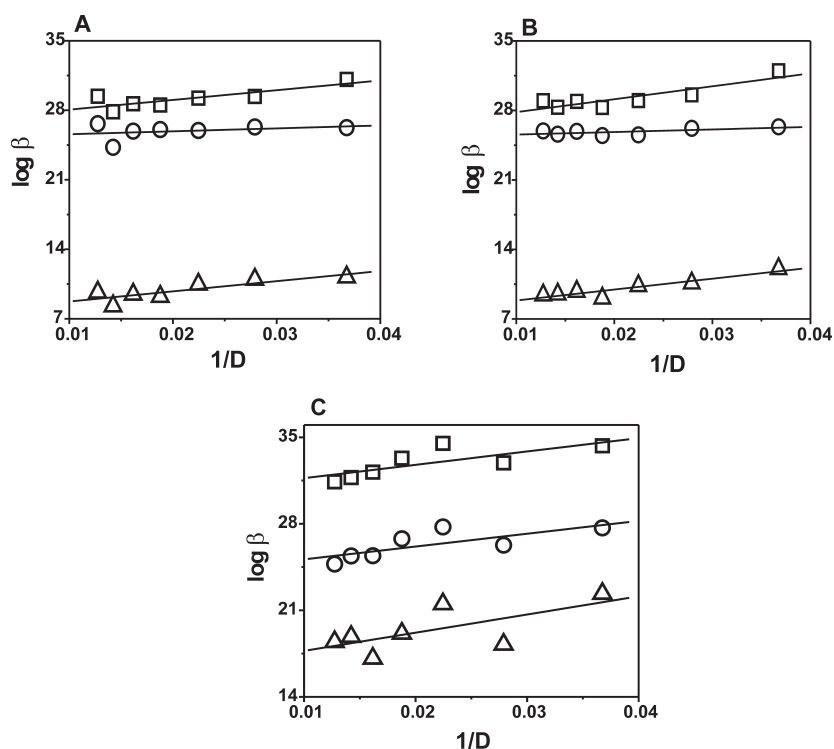


Figure 1 Variation of the magnitude of the stability constants ($\log \beta$) of the ternary complexes of (A) Ca(II), (B) Mg(II) and (C) Zn(II) with His and Glu with the reciprocal of the dielectric constant ($1/D$) of DOX-water mixtures: (\square) $\log \beta_{ML_2XH_2}$, (\circ) $\log \beta_{MLXH_2}$ and (\triangle) $\log \beta_{MLX_2}$.

Table 3 $\log X$ values of $MLXH_2$ of Ca(II), Mg(II) and Zn(II)-His and Glu in DOX-water mixtures calculated using various possible equations given below.

% v/v DOX	$\log X_{MLXH_2}$ (T1)	$\log X_{MLXH_2}$ (T2)	$\log X_{MLXH_2}$ (T3)	$\log X_{MLXH_2}$ (T4)	$\log X_{MLXH_2}$ (T5)
Ca(II)					
00.0	7.14	3.74	8.61	15.15	13.95
10.0	5.44	2.45	6.58	11.64	12.01
20.0	8.22	5.56	8.10	13.95	13.72
30.0	6.18	3.16	6.95	12.58	12.43
40.0	5.58	2.02	5.88	11.04	10.58
50.0	7.68	4.75	8.05	13.37	12.49
60.0	6.19	3.17	6.33	11.13	11.58
Mg(II)					
00.0	6.67	3.54	8.13	14.51	11.89
10.0	6.75	3.89	8.19	13.85	10.96
20.0	6.97	3.76	7.58	13.11	11.53
30.0	6.71	3.92	7.34	13.17	11.15
40.0	5.23	2.02	5.65	10.63	10.03
50.0	6.49	3.51	6.89	11.70	11.51
60.0	7.00	4.44	7.08	12.20	12.04
Zn(II)					
00.0	2.20	1.27	2.57	5.11	5.19
10.0	4.20	2.40	3.19	5.44	6.70
20.0	3.45	1.78	2.45	4.47	6.11
30.0	5.40	3.42	4.11	6.10	8.15
40.0	5.68	3.84	5.16	6.46	8.78
50.0	3.65	1.79	3.17	4.29	6.41
60.0	6.27	4.56	4.90	6.41	9.82

$$\log X_{MLXH_2} = 2\log \beta_{MLXH_2} - \log \beta_{ML_2} - \log \beta_{MX_2H_4} \quad (T1)$$

$$= 2\log \beta_{MLXH_2} - \log \beta_{ML_2H} - \log \beta_{MX_2H_3} \quad (T2)$$

$$= 2\log \beta_{MLXH_2} - \log \beta_{ML_2H_2} - \log \beta_{MX_2H_2} \quad (T3)$$

$$= 2\log \beta_{MLXH_2} - \log \beta_{ML_2H_3} - \log \beta_{MX_2H} \quad (T4)$$

$$= 2\log \beta_{MLXH_2} - \log \beta_{ML_2H_4} - \log \beta_{MX_2} \quad (T5)$$

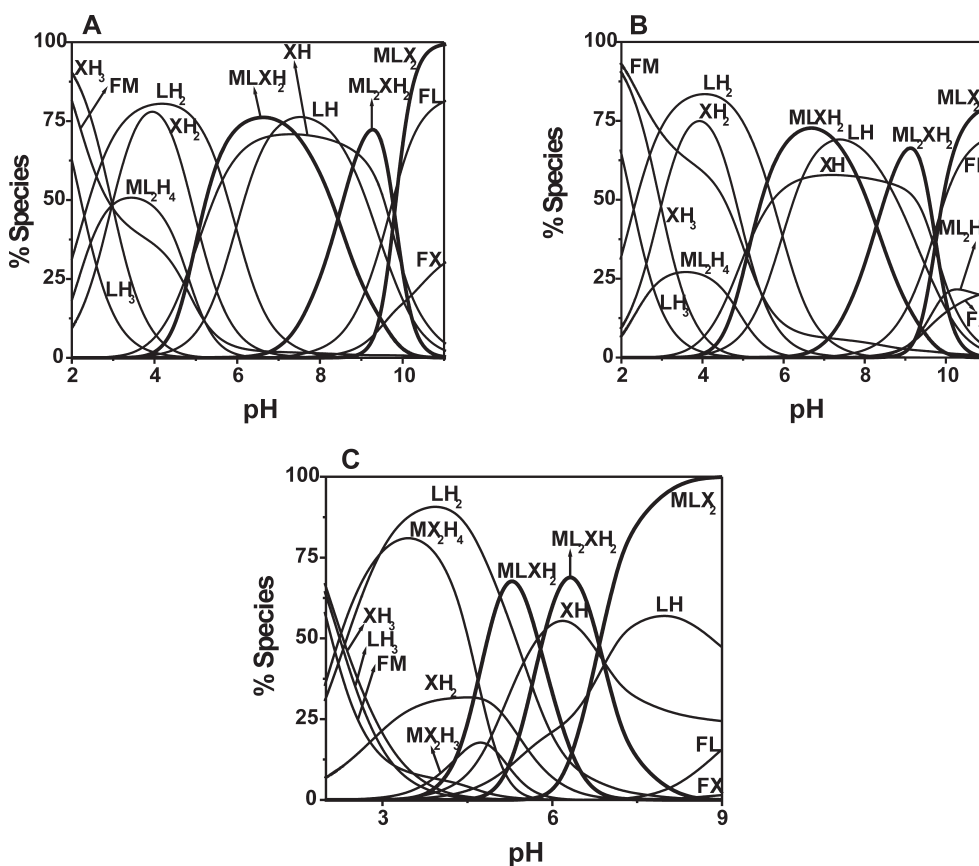


Figure 2 Species distribution diagrams of ternary complexes of His and Glu in a 40 % DOX-water mixture: (A) Ca(II), (B) Mg(II) and (C) Zn(II).

ents affects the magnitudes of equilibrium constants. Such parameters are called influential or dangerous parameters. In order to obtain the best chemical model for critical evaluation and application under varied experimental conditions with different accuracies of data acquisition, an investigation was made by introducing pessimistic errors in the concentrations of alkali, mineral acid, ligands, metal and log F. It was found that errors in the acid and alkali concentrations affect the stability constants more than those in the concentrations of the ligands, metal and log F.

3.5. Distribution Diagrams

Various possible equilibria for the formation of the ternary complexes refined in the present study have been proposed based on the existence of free metal, various forms of the ligands and the binary complexes in the pH range of existence of the ternary complexes, as found in the distribution diagrams (Fig. 2). Some typical distribution diagrams in a 40 % DOX-water mixture were drawn by using the formation constants of the best fit model and are shown in Fig. 2. They contain protonated and unprotonated species like ML_2XH_2 , $MLXH_2$ and MLX_2 for Ca(II), Mg(II) and Zn(II). The active forms of these ligands are LH_3^{2+} , LH_2^+ , LH and L^- for His and XH_3^+ , XH_2 , XH^- and X^{2-} for Glu. The binary complex species of His are ML_2 , ML_2H , ML_2H_2 , ML_2H_3 and ML_2H_4 and Glu are MX_2 , MX_2H , MX_2H_2 , MX_2H_3 and MX_2H_4 for Ca(II), Mg(II) and Zn(II). The distribution diagrams indicate the relative abundance of various forms of metal (chemical speciation) at different pH and dielectric conditions. A stable ternary complex will be responsible for metal ion transportation in biological systems and the weak binary metal complexes make the essential metals bioavailable. The increased concentrations of complexing agents make the essential metal ions unavailable

due to the formation of stable binary metal complexes. The formation of the ternary complex species can be represented by the following equilibria. The charges of the species are omitted for clarity.

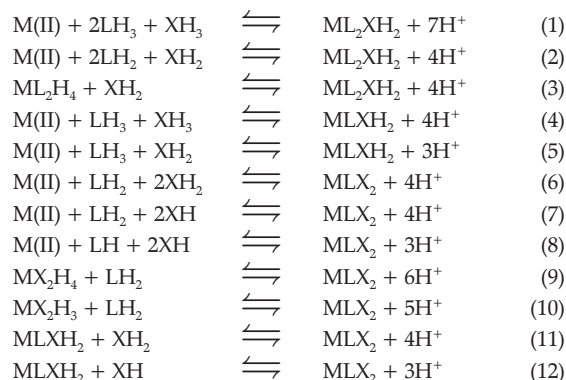


Figure 2A represents the distribution of various His-Ca(II)-Glu complexes. ML_2XH_2 is formed by the interaction of free metal ion with LH_3 and XH_3/LH_2 and XH_2 or by the reaction of ML_2H_4 with XH_2 (Equilibria 1–3). The $MLXH_2$ species is formed by the interaction of free metal ion with LH_3 and XH_3/LH_3 and XH_2 (Equilibria 4 and 5). The MLX_2 species is formed by the reaction of free metal ion with LH and XH or by the interaction of $MLXH_2$ with XH (Equilibria 8 and 12). Figure 2B represents the formation of His-Mg(II)-Glu complexes. ML_2XH_2 is formed by the interaction of free metal ion with LH_2 and XH_2 or by the reaction of ML_2H_4 species with XH_2 (Equilibria 2 and 3). The $MLXH_2$ species is formed by the interaction of free metal ion with LH_3 and XH_3 (Equilibrium 4). Interaction of $MLXH_2$ with XH or free metal ion with LH and XH/LH_2 and XH gives the MLX_2 species (Equilibria

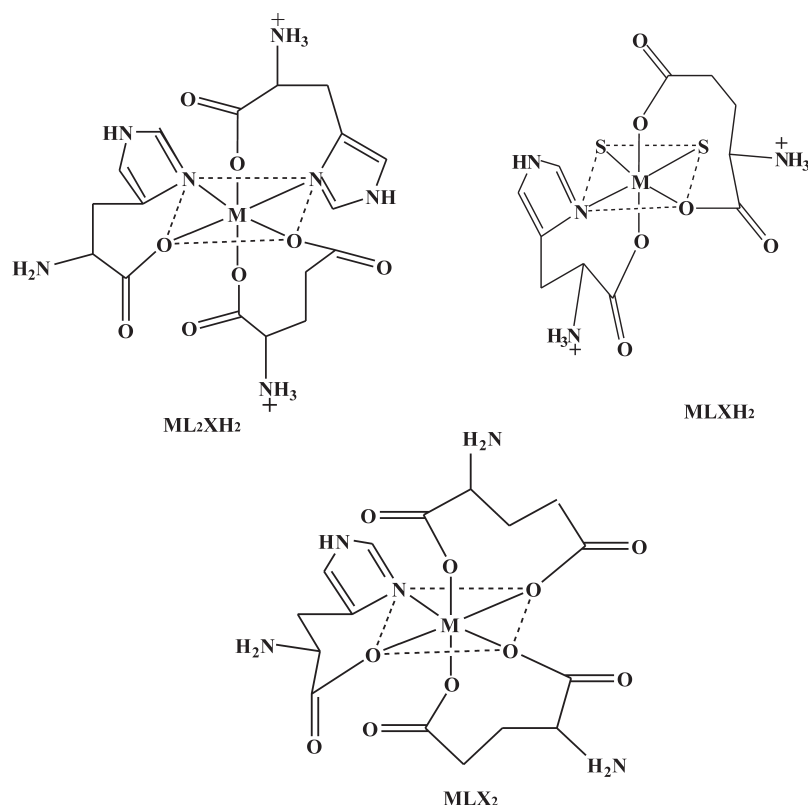


Figure 3 Proposed structures of His-M(II)-Glu ternary complexes, where S is either a solvent or water molecule.

7, 8 and 11). Figure 2C represents the formation of His-Zn(II)-Glu complexes. ML_2XH_2 is formed by the interaction of free metal ion with LH_3 and XH_3 or LH_2 and XH_2 (Equilibria 1 and 2). The $MLXH_2$ species is formed by the interaction of free metal ion with LH_3 and XH_3 (Equilibrium 4). MLX_2 is formed by the interaction of free metal ion with LH_2 and XH_2 , MX_2H_4 and MX_2H_3 with LH_2 or interaction of $MLXH_2$ with XH_2 (Equilibria 6, 9–11). During the stability constant refinement process, the MLX species was not refined. This may be due to its instability and interaction of protonated ternary complexes with XH or XH_2 to form the more stable MLX_2 species (Equilibria 6–12). Based on the protonation and deprotonation equilibria of His and Glu, and depending on the coordinating sites in the ligands and the nature of the metal ions, and basic coordination chemistry principles, possible structures of the ternary complexes are proposed as shown in Fig. 3.

4. Conclusions

A study of the speciation of ternary complexes of Ca(II), Mg(II) and Zn(II) with His and Glu in DOX water media reveals the compartmentalization of metabolic reactions. The following conclusions have been drawn from the modelling studies:

The predominant species detected are ML_2XH_2 , $MLXH_2$ and MLX_2 for Ca(II), Mg(II) and Zn(II). The active forms of the ligands (protonated and deprotonated forms that participate in the formation equilibria) are LH_3^{2+} , LH_2^+ , LH and L^- for His and XH_3^+ , XH_2 , XH^- and X^{2-} for Glu. The values of $\log X$ indicate that the ternary species have extra stability compared to their binary species. This may be due to interactions outside the coordination sphere, such as the formation of hydrogen bonds between the coordinated ligands, charge neutralization, chelate effect, stacking interactions and the electrostatic interaction between the non-coordinated charged groups of the ligands. The linear increase in the stabilities of ternary complexes with decreasing dielectric constants is due to the dominance of

electrostatic forces. The study also gives an insight into the metal availability/metal transport in biofluids and toxicity of these metals. The ternary complexes are more amenable for 'metal transport' because of their extra stability and the binary complexes make the 'metal available' in biological systems due to their decreased stability.

Acknowledgements

The authors (BAK, SR and KBKN) thank the University Grants Commission, New Delhi, India, for financial support in the form of a Fellowship under the Faculty Development Programme.

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