

Effect of Ethylene Glycol on Chemical Speciation of Ternary Complexes of Phenylalanine and Maleic Acid with Ca(II), Mg(II) and Zn(II) Metal Ions

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Abstract: The stability constants of ternary complexes of Ca(II), Mg(II) and Zn(II) ions with Phenylalanine and Maleic acid were determined pH metrically in the presence of 0.0–60.0 % v/v ethylene glycol-water mixtures maintaining an ionic strength of 0.16 mol L⁻¹ at 303.0 K. Alkali metric titrations were carried out in different relative concentrations [M:L:X=1.0:2.5:2.5, 1.0:2.5:5.0, 1.0:5.0:2.5 for Ca(II), Mg(II) and Zn(II) of metal (M) to Phenylalanine (L) to Maleic acid (X)]. Stability constants of ternary complexes were calculated and various models were refined with MINQUAD75. The best fit chemical models were selected based on statistical parameters and residual analysis. The species detected are MLXH and ML₂XH for Ca(II), Mg(II) and Zn(II). The relative stabilities of the mixed ligand complexes were compared with those of the binary complexes. The enhanced stability associated with the ternary complex is attributed to chelate effect, stacking interactions and hydrogen bonding.

Keywords: Stability constants, Mixed-ligand complexes, Phenylalanine, Maleic acid, Metals and Ethylene glycol.

1. Introduction

Metals can be involved in a series of complex chemical and biological interactions [1-3]. The most important factors which affect their mobility are pH, sorbent nature, presence and concentration of organic and inorganic ligands, including humic and fulvic acids and nutrients [4]. Calcium metal is used as a reducing agent in preparing other metals such as thorium and uranium. It is also used as an alloying agent for aluminium, beryllium, copper, lead and magnesium alloys. Calcium compounds are widely used. There are vast deposits of limestone (calcium carbonate) used directly as a building stone and indirectly for cement. When limestone is heated in kilns it gives off carbon dioxide gas leaving behind quicklime (calcium oxide). This reacts vigorously with water to give slaked lime (calcium hydroxide). Slaked lime is used to make cement, as a soil conditioner and in water treatment to reduce acidity, and in the chemicals industry. It is also used in steel making to remove impurities from the molten iron ore. When mixed with sand, slaked lime takes up carbon dioxide from the air and hardens as lime plaster. Gypsum (calcium sulfate) is used by builders as a plaster and by nurses for setting bones, as 'Plaster of Paris' [5-10]. Magnesium is the seventh most abundant element by mass and eighth by molarity. It is found in large deposits in the form of magnesite, dolomite and other minerals. The daily intake of magnesium in normal human being should be 0.3-0.4 g. It is primarily absorbed in the small intestines. It is the main intracellular earth metal cation with a free concentration in the cytosol around 0.5 mmol/ L. Zinc metalloenzymes are involved in the formation or hydrolysis of each of the major classes of endogenous compounds (proteins, lipids, carbohydrates, etc.) and includes representatives from each of the six categories of enzymes of the International Union of Biochemistry. The crystal structure has been identified for

12 zinc enzymes [16] including alcohol dehydrogenase, carboxy peptidases A and B, alkaline phosphatase and carbonic anhydrases I and II. The zinc binding sites vital to catalysis include three amino acid residues and an activated water molecule. The amino acids can include combinations of histidine, glutamine, aspartate or cysteine [17]. The coordination geometry has been found to depend on the type of ligand that is bound to Zn(II) and the solvent accessibility of the metal binding site [18]. Another critical function of zinc in biological systems is the regulation of DNA and RNA synthesis [18-22]. In the brain, zinc appears to be involved in neurotransmission, the formation of micro tubules and is bound to hormones [23] such as insulin and 7-S-nerve growth factor. Zinc plays a modulating role in synaptic transmission by interacting with specific sites on ionotropic neurotransmitter receptor proteins. Celentano et al [24]. have demonstrated in spinal cord neurons that extracellular zinc inhibits γ -amino butyric acid (GABA) receptor function by an allosteric mechanism. Zinc has also been shown to interact with the NMDA receptor at a unique extracellular site distinct from other modulators like magnesium or glycine [25]. Phenylalanine is the starting compound used in the flavonoid_biosynthesis. Lignan is derived from phenylalanine and from tyrosine. Phenylalanine is converted to cinnamic acid by the enzyme Phenylalanine ammonia-lyase [26]. Maleic acid is transformed into fumaric acid through the process of heating the maleic acid in 12 M hydrochloric acid solution. Reversible addition (of H⁺) leads to free rotation about the central C-C bond and formation of the more stable and less soluble fumaric acid. Maleic acid is an industrial raw material for the production of glyoxylic acid by ozonolysis [27].

The present work is carried out to understand (i) the role played by the active site cavities in biological molecules, (ii)

the type of ternary complexes formed and (iii) the bonding behavior of the protein residues with the metal ions. The types of complexes formed and their relative concentrations under the present experimental conditions represents the possible forms of metal ions in the biological fluids and speciation represents the biological activity of these metals in the presence of different complexing agents. Since the dielectric constant at active site cavities is small compared to biofluids, the authors tried to mimic low dielectric constant by using a water soluble organic solvent like ethylene glycol. Although the binary complexes of metals Ca(II), Mg(II) and Zn(II) with Phenylalanine and Maleic acid are have been studied previously [28-31].

2. Experimental

Solutions of 0.1 mol L⁻¹ Ca(II), Mg(II) and Zn(II) chlorides G.R. Grade (E-Merck, Germany) were prepared by dissolving them in triple distilled water 0.05 mol L⁻¹ aqueous solutions of Phenylalanine (Phe) and Maleic acid (Mal) (E-Merck, Germany) were also prepared. To increase the solubility of the ligands and to suppress the hydrolysis of metal salts, 0.05 mol L⁻¹ hydrochloric acid (Qualigens, India) was maintained in the solutions. Ethylene glycol (Qualigens, India) was used as received. The strength of alkali was determined using the Gran plot method [32, 33]. Errors in the concentrations of the ligands, metal ions and alkali were subjected to analysis of variance of one way classification [34]. The titrations were carried out in the medium containing varying concentrations of EG maintaining an ionic strength of 0.16 mol L⁻¹ with sodium chloride (Merck, India) at 303.0 K. The measurements were made with an ELICO (Model LI-120) pH meter of 0.01 readability in conjunction with a glass and calomel electrode. The pH meter was calibrated with 0.05 mol L⁻¹ potassium hydrogen phthalate in acidic region and 0.01 mol L⁻¹ borax solution in basic region. The glass electrode was equilibrated in a well stirred EG-water mixtures containing inert electrolyte. The effect of variations in asymmetry potential, liquid junction potential, activity coefficient, sodium ion error and dissolved carbon dioxide on the response of glass electrode were accounted for in the form of correction factor (log F) which was computed from the experimental and simulated acid-base titration data by SCPHD program [35]. A correction was applied to the pH meter dial readings to account for the solvent effect on pH. Titration of strong acid with alkali was carried out at regular intervals to check whether complete equilibration was achieved. The calomel electrode was refilled with EG-water mixture of equivalent composition as that of the titrand. In each of the titrations, the titrand consisted of 1 mmol of hydrochloric acid in a total volume of 50 cm³. Titrations were carried out in the presence of different relative concentrations of the metal (M) to Phe (L) to Mal (X) [M:L:X = 1.0:2.5:2.5, 1.0:2.5:5.0, 1.0:5.0:2.5 in the case of Ca(II), Mg(II) and Zn(II)] with 0.4 mol L⁻¹ NaOH. The details of experimental procedure and titration assembly are given elsewhere [36]. The best-fit chemical model for each

system investigated was arrived at using a non-linear least squares analysis program MINQUAD75 [37], which exploits the advantage of constrained least squares method in the initial refinement and reliable convergence of undamped, unconstrained Marquardt algorithm. The analytical concentrations of the ingredients are given in Table 1.

3. Results and Discussion

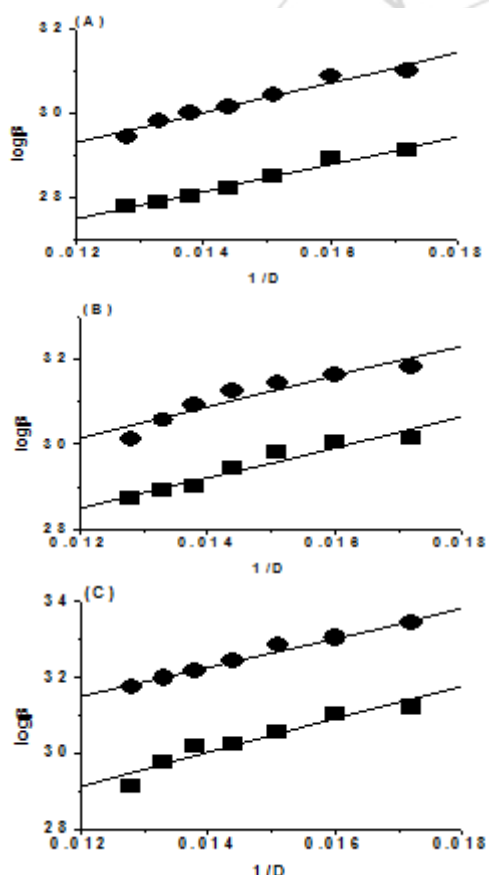
A preliminary investigation of alkalimetric titrations of mixtures containing different mole ratios of Phe and Mal in the presence of hydrochloric acid and inert electrolyte inferred that no condensed species were formed. The protonation [38, 39] constants and the stability constants of the binary [28-31] metal complexes of these ligands were fixed in refining of ternary complexes and in testing various chemical models using MINQUAD75. 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 MLXH and ML₂XH for Ca(II), Mg(II) and Zn(II). A very low standard deviation (SD) in 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 metal, ligands and hydrogen ion at all experimental points corrected for degrees of freedom) indicate that the models represent the experimental data. Small values of SD 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. The kurtosis values in the present study indicate that most of the residuals are greater than three and their distributions have sharp peak (platykurtic) pattern in majority of the systems. The values of skewness recorded in Table 2 are in between -0.37 and 1.92. These data evince that the residuals form a part of normal distribution; hence, least-squares method can be applied to the present data. The authenticity of the model is further evident from the low crystallographic R-values recorded.

Effect of Solvent

EG is a protophilic dipolar protic solvent and acts as a structure former. Ethylene glycol with two hydroxyl groups has properties distinctly different from monohydric alcohols. EG is more acidic (less basic) than water due to electron withdrawing effect of CH₂ groups. Hence, it removes water from coordination sphere of metal ions, making them more reactive towards the ligands. As a result, the stability of the complexes is expected to increase. At the same time, it is a coordinating solvent and competes with the ligands for coordinating the metals. This decreases the stability of the complexes. Hence, the stability of complex is expected to either increase or decrease.

Table 1: Total initial concentrations of ingredients (in mmol) for mixed ligands (Phe and Mal) titrations in EG-water mixtures. $[\text{NaOH}] = 0.4 \text{ mol L}^{-1}$; $V_0 = 50 \text{ cm}^3$; Temperature = 303.0 K; Mineral acid = 1.0 mmol; $\mu = 0.16 \text{ mol L}^{-1}$

EG% v/v	TM0			TL0	TX0	TM0:TL0:TX0
	Ca(II)	Mg(II)	Zn(II)	Phe	Mal	
0.0	0.100	0.099	0.102	0.2500	0.2495	1:2.5:2.5
				0.2500	0.4996	1:2.5:5.0
				0.5005	0.2495	1:5.0:2.5
10.0	0.100	0.099	0.102	0.2525	0.2515	1:2.5:2.5
				0.2525	0.5060	1:2.5:5.0
				0.5025	0.2515	1:5.0:2.5
20.0	0.100	0.099	0.102	0.2515	0.2510	1:2.5:2.5
				0.2515	0.5030	1:2.5:5.0
				0.5020	0.2510	1:5.0:2.5
30.0	0.100	0.099	0.102	0.2584	0.2545	1:2.5:2.5
				0.2584	0.5065	1:2.5:5.0
				0.5015	0.2545	1:5.0:2.5
40.0	0.100	0.099	0.102	0.2530	0.2563	1:2.5:2.5
				0.2530	0.5045	1:2.5:5.0
				0.5065	0.2563	1:5.0:2.5
50.0	0.100	0.099	0.102	0.2510	0.2504	1:2.5:2.5
				0.2510	0.5014	1:2.5:5.0
				0.5016	0.2504	1:5.0:2.5
60.0	0.100	0.099	0.102	0.2501	0.2515	1:2.5:2.5
				0.2501	0.5014	1:2.5:5.0
				0.5019	0.2515	1:5.0:2.5

**Figure 1:** Variation of stability constant values of Phe and Mal complexes with reciprocal of dielectric constant ($1/D$) of Ca(II) (A); Mg(II) (B) and Zn(II) (C); (■) $\log \beta_{\text{MLXH}}$; (●) $\log \beta_{\text{ML2XH}}$; in EG-water mixtures.

The variation of overall stability constant values or change in free energy with co-solvent content depends upon two factors, viz., electrostatic and non-electrostatic. Born's classical treatment [40] accounts for the electrostatic contribution to the free energy change. According to this treatment, the energy of electrostatic interaction is related to dielectric constant. Hence, the $\log \beta$ values should vary linearly as a function of reciprocal of the dielectric constant of the medium which is observed in the present study (Figure 1). The linear variation indicates that electrostatic forces dominate the equilibrium process under the present experimental conditions. The linear increase indicates the dominance of the structure forming nature of EG over its complexing ability. The cation stabilizing nature of co-solvents, specific solvent-water interactions, charge dispersion and specific interactions of co-solvents with solute account for little deviation from the linear relationship.

Effect of systematic errors on best-fit model

In order to rely upon 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 influential parameters like concentrations of alkali, mineral acid, ligand and metal (Table 3). The order of the ingredients that influence the magnitudes of stability constants due to incorporation of errors is alkali>acid>ligands>metal>volume> $\log F$. Some species are even rejected when errors are introduced in the concentrations. This study confirms the appropriateness of the chosen best-fit models. This study also indicates the relative sensitivities of model parameters.

Table 2: Best fit chemical models of Ca(II), Mg(II) and Zn(II) complexes with Phenylalanine and Maleic acid in EG-water mixtures

% v/v EG	log β _{mlxh} (SD)		NP	U _{corr}	χ ²	Kurtosis	Skewness	R-factor	pH-range
	1111	1211							
Ca(II)									
0.0	27.79(1)	29.43(1)	92	8.38	10.26	3.23	-0.25	0.0046	1.8-7.7
10.0	27.88(1)	29.82(2)	91	9.68	14.20	3.42	-0.37	0.0423	1.8-7.7
20.0	28.01(3)	29.99(3)	89	2.02	11.56	2.36	-0.03	0.0356	1.8-7.7
30.0	28.22(3)	30.14(3)	59	6.26	5.22	3.34	-0.12	0.0194	1.8-7.7
40.0	28.51(2)	30.42(3)	57	9.78	8.07	3.49	-0.04	0.0245	1.8-7.7
50.0	28.92(2)	30.88(1)	55	6.16	7.94	4.23	1.03	0.0075	1.8-7.7
60.0	29.11(1)	31.01(1)	77	3.08	13.40	2.90	-0.31	0.0315	1.8-7.7
Mg(II)									
0.0	28.7(1)	30.12(1)	110	1.04	22.76	3.34	-0.28	0.0026	1.8-7.7
10.0	28.91(4)	30.56(4)	58	1.23	12.98	4.28	1.92	0.0035	1.8-7.7
20.0	29.02(1)	30.92(2)	55	1.60	19.42	3.53	-0.05	0.0339	1.8-7.7
30.0	29.44(2)	31.25(2)	55	3.82	5.16	2.61	-0.08	0.0159	1.8-7.7
40.0	29.82(1)	31.44(1)	52	7.29	8.69	2.52	1.00	0.0243	1.8-7.7
50.0	30.04(2)	31.62(2)	62	3.49	17.71	2.00	0.01	0.0194	1.8-7.7
60.0	30.14(3)	31.82(1)	61	2.16	7.32	2.12	-0.09	0.0391	1.8-7.7
Zn(II)									
0.0	29.12(1)	31.75(1)	100	6.62	10.40	3.69	-0.31	0.0036	1.8-7.7
10.0	29.75(1)	31.98(1)	98	5.67	11.09	4.93	1.02	0.0986	1.8-7.7
20.0	30.19(2)	32.16(2)	109	1.01	26.35	3.67	0.15	0.0490	1.8-7.7
30.0	30.25(1)	32.42(1)	86	2.59	46.93	2.90	1.67	0.0032	1.8-7.7
40.0	30.56(2)	32.86(2)	95	2.99	17.98	6.81	1.67	0.0307	1.8-7.7
50.0	31.02(2)	33.04(2)	103	6.74	8.58	5.27	1.51	0.0430	1.8-7.7
60.0	31.22(3)	33.42(4)	92	7.11	39.30	3.40	1.00	0.0443	1.8-7.7

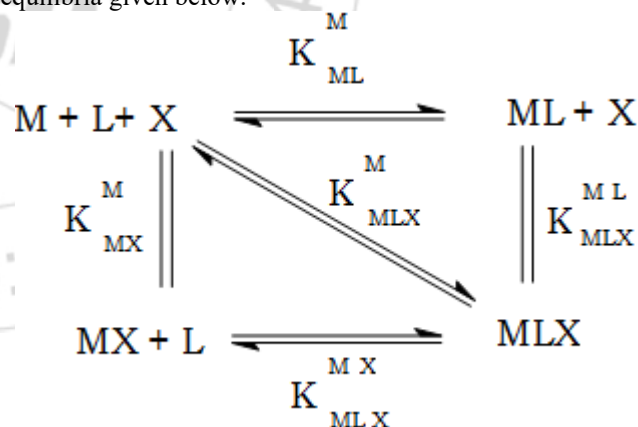
U_{corr} = U/ (NP-m) X 10⁸; where m = number of species; NP = Number of experimental points.

Table 3: Effect of errors in influential parameters on Phe-Ca(II)-Mal complexes stability constants in 40% v/v EG-water mixture

Ingredi-Ents	% of error	log β _{mlxh} (SD)	
		MLXH	ML ₂ XH
	0	28.51(2)	30.42(3)
Alkali	-5	30.25(35)	Rejected
	-2	29.43(23)	31.54(32)
	+2	29.36(33)	31.35(21)
	+5	30.31(23)	Rejected
Acid	-5	30.35(21)	Rejected
	-2	29.35(25)	30.22(36)
	+2	29.02(16)	30.36(27)
	+5	Rejected	31.21(12)
Ligand(L)	-5	29.75(12)	31.04(10)
	-2	28.86(8)	30.78(9)
	+2	28.52(9)	30.55(6)
	+5	29.65(16)	31.08(12)
Ligand(X)	-5	29.78(14)	31.26(10)
	-2	29.46(9)	31.62(6)
	+2	28.25(8)	30.22(5)
	+5	29.38(12)	31.66(14)
Metal	-5	29.73(8)	31.20(9)
	-2	28.70(6)	30.16(7)
	+2	28.69(9)	30.14(8)
	+5	29.72(12)	31.18(9)
log F	-5	28.68(6)	30.12(8)
	-2	28.66(5)	30.11(6)
	+2	28.67(8)	30.13(7)
	+5	28.69(6)	30.14(8)
Volume	-5	29.65(8)	30.12(6)
	-2	28.64(7)	30.10(5)
	+2	28.66(5)	30.13(6)
	+5	29.67(6)	30.14(8)

4. Stability of Ternary Complexes

The formation of mononuclear unprotonated binary and ternary complexes from a mixture of metal ion (M(II)) and primary (L) and secondary (X) ligands can be shown as the equilibria given below.



The change in stability of the ternary complexes as compared to their binary analogues was quantified [41-43] based on the disproportionation constant (log X) given by Equation 1. Which corresponds to the equilibrium

$$\log X = 2 \log K_{MLX}^M - \log K_{ML}^M - \log K_{MX}^M \dots (1)$$

$$ML_2 + MX_2 \rightleftharpoons 2 MLX$$

Under these equilibrium conditions one can expect 50% ternary complex and 25% each of the binary complexes to be formed and the value of log X was reported [44] to be 0.6. A value greater than this accounts for the extra stability of MLX. Another approach [43-45] to quantify the stability of ternary complexes was based on the difference in stability

($\Delta \log K$) for the reactions ML with X and $M_{(aq)}$ with L and X, where L is primary ligand (Phe) and X is the secondary ligand (Mal). It is compared with that calculated purely on statistical grounds. Equation 2 can be formulated based on the properties of the cyclic systems reported earlier, from which it is clear that both the ligands in the ternary complex influence mutually to the same extent.

$$\Delta \log K = \log K_{MLX}^M - \log K_{ML}^M - \log K_{MX}^M \dots (2)$$

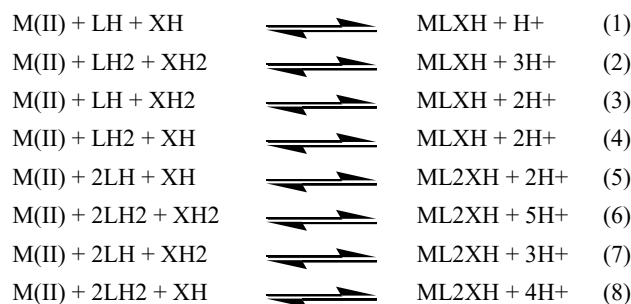
The electrostatic theory of binary complex formation and statistical arguments suggest the additional coordination positions of given multivalent hydrated metal ion available for the first ligand than for the second. Hence, the usual order of stability $K_{ML}^M > K_{MLX}^M$ applies. This suggests that $\Delta \log K$ should be negative, although several exceptions [46] have been found. The statistical values of $\Delta \log K$ for bidentate L and X are -0.4, -0.6 and between -0.9 and -0.3 for octahedral, square planar and distorted octahedral complexes, respectively. Negative values of $\Delta \log K$ can be understood as the secondary ligand forms a more stable complex with hydrated metal ion than with ML. Whenever the experimental values of $\Delta \log K$ exceed the statistical values, it can be inferred that the ternary complex is formed as a result of interaction of ML with X or MX with L. $\Delta \log K$ values of ternary complexes containing bipyridyl as the primary ligand are positive for O-donors (malonic acid, pyrocatechol etc.), negative for N-donors (ethylene diamine) and intermediate or negative for amino acids with both N and O co-ordination sites. However, a very high negative value (-2.3) for Cu(en) (iminodiacetic acid) and a positive value (0.82) for Cu(ophen)-(6,7-dihydroxynaphthalene-2-sulfonate) was also observed [43].

The $\Delta \log K$ and $\log X$ values calculated for MLXH from binary and ternary complexes are included in Table 4. $\Delta \log K$ and $\log X$ values for ML_2XH could not be calculated due to the absence of relevant binary species. In the present study, the $\Delta \log K$ and $\log X$ values range for MLXH species from 13.65 to 18.39 and 22.45 to 29.03 respectively in EG-water mixtures. Some $\Delta \log K$ and $\log X$ values are found to be more than the theoretical values which account for the extra stability of the ternary complexes. The reason [47, 48] for the extra stability of these complexes 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.

5. Distribution Diagrams

The mixed-ligand species of Phe (L) and Mal (X) detected are MLXH and ML_2XH for Ca(II), Mg(II), and Zn(II) in EG - water mixtures. A perusal of the distribution diagrams (Figure. 2) reveals that at very low pH the concentrations of the mixed ligand complexes are less than those of protonated ligands. The concentrations of the ternary species increase with pH. The protonated ternary species, MLXH and ML_2XH are distributed at lower pH. The concentrations of binary species are less compared to the ternary species due to more stable ternary complexes. The ternary species of Ca(II), Mg(II) and Zn(II) exist in the pH range 4.0-10.0. The

formation of the complex species can be represented by the following equilibria.



Distribution diagrams drawn using the formation constants of the best fit model are shown in Figure. 2. Mixed ligand complexes of Ca(II), Mg(II), and Zn(II) are detected in the pH range 4.0-10.0. MLXH is the predominant species formed in the pH range 4.0-8.0 by the interaction of M(II) with protonated ligands (LH, LH_2 , XH and XH_2) (Equilibria 1-4). The ML_2XH species is formed at the pH range 7.0-10.0. ML_2XH species may be formed from the Equilibria 5-8. Suggested structures for ternary complexes of Phe and Mal, where M = Ca(II), Mg(II) and Zn(II) in EG-water are given in Figure 3.

Table 4: $\Delta \log K$ and $\log X$ values of ternary complexes of Ca(II), Mg(II) and Zn(II)-Phe and Mal in EG-water mixtures.

% v/v EG	$\Delta \log K$	$\log X$
	1111	1111
Ca(II)		
0.0	18.01	26.20
10.0	15.68	23.87
20.0	15.48	23.34
30.0	13.83	22.45
40.0	14.07	23.38
50.0	14.45	24.63
60.0	13.65	22.57
Mg(II)		
0.0	18.39	29.03
10.0	16.79	25.40
20.0	15.61	26.45
30.0	14.13	25.86
40.0	14.95	27.45
50.0	15.77	28.13
60.0	14.59	26.60
Zn(II)		
0.0	17.93	28.30
10.0	16.26	27.48
20.0	15.72	27.64
30.0	14.42	26.08
40.0	15.92	27.02
50.0	16.28	28.36
60.0	14.18	25.62

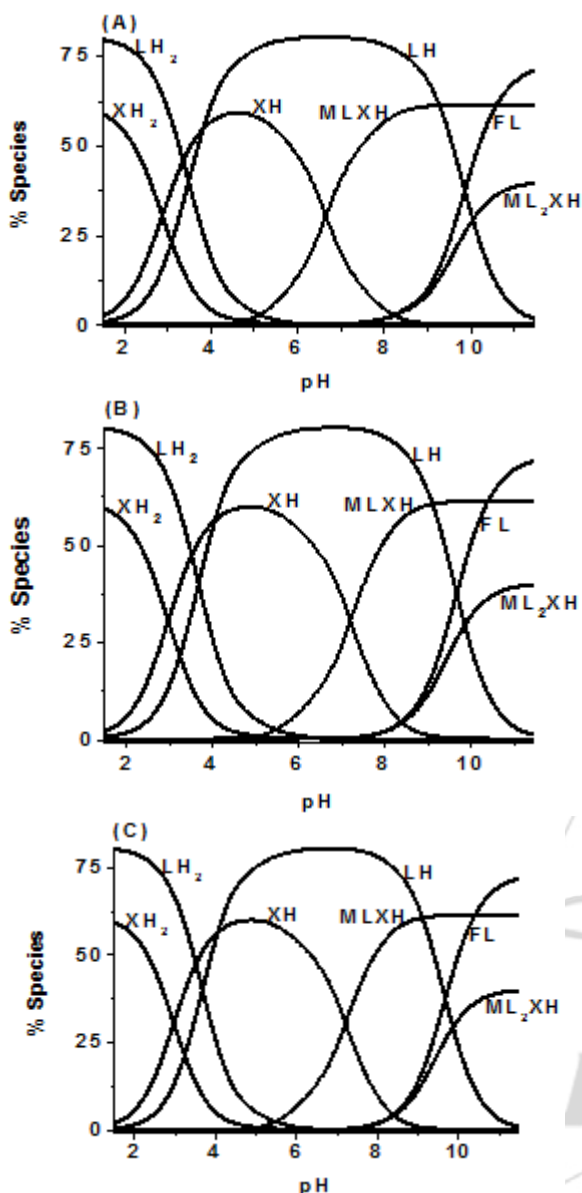


Figure 2: Distribution diagrams of Phe-M(II)-Mal ternary complexes in 30% PG-water mixtures; (A) Ca(II), (B) Mg(II) and (C) Zn(II).

6. Conclusions

The following conclusions have been drawn from the modeling studies of the ternary complexes of Ca(II), Mg(II) and Zn(II) with Phe and Mal in EG–water mixtures.

- 1) The mixed-ligand complex species detected are MLXH and ML_2XH for Ca(II), Mg(II) and Zn(II), where L = Phe and X = Mal.
- 2) The values of $\Delta \log K$ and $\log X$ indicate that the ternary species have enhanced stability compared to their binary species, may be due to the 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 on coordinated charge groups of the ligands.
- 3) The linear variation of stability constants as a function of $1/D$ of the medium indicates the dominance of electrostatic forces over non-electrostatic forces. The linear increasing trend with EG content supports the

predominance of the structure forming nature of EG over its complexing ability.

- 4) The magnitudes of the stability constants for mixed ligand complexes are affected by the errors in the influential parameters like the concentrations of the ingredients. The order of influence is alkali>acid>ligands>metal>volume>log F.

The study also gives an insight into the metal availability or metal transport in biofluids. The ternary complexes are more amenable for “metal transport” because of their extra stability.

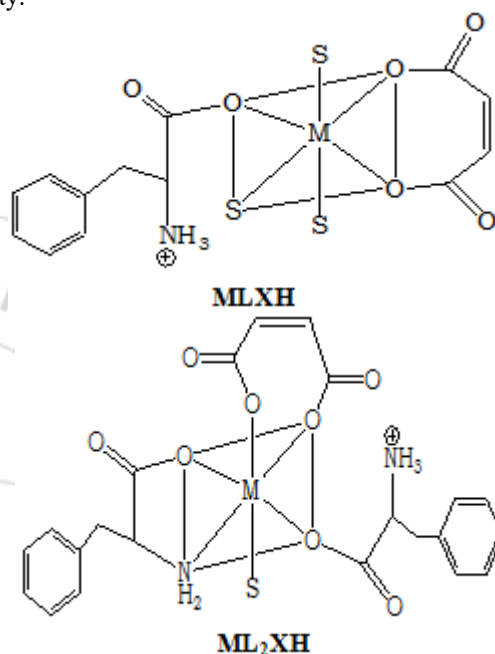


Figure 3: Proposed structures of ternary complexes of Ca(II), Mg(II) and Zn(II), where S is either solvent or water molecules.

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