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## Computer-augmented modeling studies of Pb(II) and Cd(II) complexes with maleic acid in ethylene glycol–water mixture

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### ABSTRACT

Chemical speciation of binary complexes of Pb(II) and Cd(II) ions with maleic acid have been studied pH metrically in the concentration range of 0–50% v/v ethylene glycol (EG)–water mixtures maintaining an ionic strength of 0.16 molL<sup>-1</sup> at 303 K. Alkalimetric titrations were carried out in different relative concentrations of metal and maleic acid. Stability constants of various models of binary complexes were refined with MINIQUAD75. The best-fit chemical models were selected based on statistical parameters and residual analysis. The species detected are ML<sub>2</sub>, ML<sub>3</sub>, and ML<sub>2</sub>H for Pb(II) and Cd(II). The chemical speciation, metal bioavailability, and transportation are explained based on the distribution diagrams.

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### KEYWORDS

Binary complexes; maleic acid; ethylene glycol (EG); stability constants

### Introduction

Classical curve-fitting methods that use the least-squares methods [1] are applied to estimate the number of species simultaneously present at equilibrium, their stoichiometries, and their stability constants. Bioavailability of a particular metal depends on its complex chemical reactions of dissolution, binding, and complexation with the constituents of the environmental aquatic phase.[2] The metal complexes can be more active than the free ligands and some side effects may decrease upon complexation. In addition, the complexes can exhibit bioactivities which are not shown by the free ligand. The mechanism of action can involve binding to a metal ion *in vivo* or the metal complex may be a vehicle for activation of the ligand as the cytotoxic agent. Moreover, coordination may lead to significant reduction of drug resistance.[3,4]

In biological fluids, the metal ions exist in non-exchangeable form as metalloproteins or loosely bound to some biological ligands as in metal-activated proteins. The loosely bound metal ions are in equilibrium with similar metal ions present in the bio-fluids. These simultaneous equilibria involving a variety of metal ions and ligands are important in biological fluids.[5] Hence, the chemical speciation of ligands with metal ions has been studied in this laboratory.[6–10]

Maleic acid is a dicarboxylic acid. It is the *cis* isomer of butenedioic acid, whereas fumaric acid is the *trans* isomer. It is soluble in water and moderately toxic. Inhalation causes irritating of nose and throat. Contact with eyes or skin causes irritation. It is used to make other chemicals and for dyeing and finishing naturally occurring fibers.

Speciation profoundly influences both the toxicity and bioavailability of an element. The speciation studies of toxic metal ion complexes are useful for understanding the role played by active site cavities in biological molecules and the binding behavior of protein residues with the metal ions and helpful to understand the interaction with other ligands commonly exist in biological fluids. Chemical speciation of metals is important for the understanding of their distribution, mobility, bioavailability, toxicity, and for setting environmental quality standards. Bioavailability of a particular metal depends on its complex chemical reactions of dissolution, binding, and complexation with the constituents of the environmental aquatic media. To reveal the solvent effects on equilibrium processes involving charged species, we have studied the complex formation of maleic acid with Pb(II), Pb(II), and Cd(II) as a good example in modeling of the bonding modes of dicarboxylic acids to toxic metal ions in mixtures containing ethylene glycol (EG) and water. Heavy metals such as lead, cadmium, and mercury are toxic substances which exert adverse effects on neurological, reproductive, renal, and hematological systems in humans and animals. Organo-lead compounds exhibit toxic effect on the central nervous system.[11] Similarly, cadmium exhibits various chronic and acute disorders like testicular atrophy, hypertension, damage to kidneys and bones, anemia and Itai-Itai.[12–16] Hence, the stability constants of the binary complexes of Pb(II) and Cd(II) have been determined using pH meter. These values are potentially useful to environmental and biological problems.[17,18] In this study, water was substituted

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by ethylene glycol that has lower dielectric constant to mimic the permittivity of bio-active sites. Thus, the water-EG mixtures produce the conditions that exist at the active sites of enzymes and side chains of proteins. [19–23] The present paper describes the complexation of Pb(II) and Cd(II) with maleic acid in EG–water media.

## Experimental

### Materials

Maleic acid (Qualigens, India) solution ( $0.05 \text{ molL}^{-1}$ ) was prepared in triple-distilled deionized water by maintaining  $0.05 \text{ molL}^{-1}$  nitric acid concentration to increase the solubility. Ethylene Glycol (Merck, India) was used as received. Two moles per liter sodium nitrate (Qualigens, India) was prepared to maintain the ionic strength in the titrand.  $0.05 \text{ molL}^{-1}$  aqueous solutions of Cd (II) and Pb(II) nitrates were prepared by dissolving G.R. Grade (E-Merck, Germany) salts in triple-distilled water maintaining  $0.05 \text{ molL}^{-1}$  nitric acid to suppress the hydrolysis of metal salts. All the solutions were standardized by standard methods. To assess the errors that might have crept into the determination of the concentrations, the data were subjected to the analysis of variance of one way classification.[24] The strengths of alkali and mineral acid were determined using the Gran plot method. [25,26]

### Instrumentation

The titrimetric data were obtained using ELICO (Model Li-120) pH meter (readability 0.01), which was calibrated with  $0.05 \text{ molL}^{-1}$  potassium hydrogen phthalate in acidic region and  $0.01 \text{ molL}^{-1}$  borax solution in basic region. The glass electrode was equilibrated in a well-stirred ethylene glycol–water mixture containing the inert electrolyte. All the titrations were carried out in the medium containing varying concentrations of EG–water mixtures (0–50% v/v) by maintaining an ionic strength of  $0.16 \text{ molL}^{-1}$  with

sodium nitrate at  $303.0 \pm 0.1 \text{ K}$ . The effect of variation in asymmetry potential, 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 correction factor.

### Analytical procedures

For the determination of stability constants of metal–ligand binary species, initially titrations of strong acid with alkali were carried out at regular intervals to check whether complete equilibration was achieved. Then the calomel electrode was refilled with ethylene glycol–water mixture of equivalent composition as that of titrand. In each of the titrations, the titrand consisted of approximately  $1 \text{ mmol}$  mineral acid in a total volume of  $50 \text{ ml}$ . Titrations with different ratios 1:2.5, 1:3.75, and 1:5.0 in the case of Cd(II) and Pb(II) of metal-to-ligand were carried out with  $0.4 \text{ molL}^{-1}$  sodium hydroxide. Other experimental details are given elsewhere.[27]

### Modeling strategy

The approximate complex stability constants were calculated using the computer program SCPHD.[28] By following some heuristics in the refinement of the stability constants, the best-fit chemical models for each system were arrived at using the computer program MINIQAD75.[29]

## Results and discussion

The results of the best-fit models that contain the stoichiometry of the complex species and their overall formation constants along with some of the important statistical parameters are given in Table 1. A very low standard deviation in  $\log \beta$  values indicates the precision of these parameters. The small values of  $U_{\text{corr}}$  (the sum of squares of deviations in concentrations of reactants at all

**Table 1.** Parameters of best-fit chemical models of M(II)–maleic acid complexes in EG–water medium.

% v/vEG	$\log \beta_{\text{MLH}}(\text{SD})$			NP	$U_{\text{corr}}$	Skewness	$\chi^2$	R-factor	Kurtosis	pH-range
	$\text{ML}_2$	$\text{ML}_3$	$\text{ML}_2\text{H}$							
<i>Pb(II)</i>										
0	7.90(19)	10.73(15)	13.38(15)	75	4.82	0.40	12.62	0.0166	2.35	2.0–7.0
10	7.56(59)	10.59(38)	13.37(18)	78	5.02	1.73	38.68	0.0599	8.95	2.0–7.0
20	7.51(68)	10.34(21)	13.27(16)	29	9.15	1.85	39.99	0.0392	9.31	2.0–6.5
30	7.51(22)	10.00(26)	13.66(08)	83	5.39	1.80	40.83	0.0292	11.66	2.0–7.0
40	7.63(38)	10.02(53)	14.07(10)	78	1.87	−0.18	10.38	0.0357	2.31	2.0–8.0
50	7.74(47)	10.29(22)	13.05(16)	46	5.42	−1.25	92.03	0.0883	7.15	2.0–8.0
<i>Cd(II)</i>										
0	6.91(19)	9.57(86)	12.52(61)	41	87.07	3.36	114.33	0.1086	13.37	3.0–8.5
10	7.42(55)	10.76(40)	13.28(21)	87	4.98	4.24	184.52	0.0719	23.15	2.0–8.0
20	8.16(39)	10.68(45)	14.33(15)	76	7.26	1.84	35.79	0.0545	9.72	2.0–8.0
30	8.37(85)	11.91(24)	14.98(14)	80	8.54	1.45	29.93	0.0663	7.06	2.0–7.5
40	10.00(58)	12.42(75)	15.96(36)	85	3.20	1.76	37.55	0.0692	9.03	2.0–7.9
50	11.50(48)	14.47(43)	17.96(31)	68	3.40	0.24	34.75	0.0451	4.29	2.0–8.0

Note:  $U_{\text{corr}} = U/(\text{NP} \cdot m) \times 10^8$ , where  $m$  = number of species; NP = Number of experimental points; SD = Standard deviation.

experimental points) corrected for degrees of freedom, indicate that the model can represent the experimental data. Small values of mean, standard deviation, and mean deviation for the systems corroborate that the residuals are around a zero mean with little dispersion. Kurtosis is a measure of the peakedness of the error distribution near a model value. For an ideal normal distribution, kurtosis value should be three (mesokurtic).[30] If the 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 the residuals form leptokurtic as well as platykurtic patterns and very few form mesokurtic patterns. The values of skewness recorded in Table are between  $-1.25$  and  $4.24$ . These data suggest that the residuals form a part of normal distribution. Hence, least-squares method can be applied to the present data. The sufficiency of the model is further evident from the low crystallographic  $R$ -values. These statistical parameters thus show that the best-fit models portray the metal–ligand species in EG–water mixture.

### Effect of systematic errors on best-fit model

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 undertaken by introducing pessimistic errors in the influential parameters like concentrations of alkali, mineral acid, ligand, and metal (Table 2). The order of the components that influence the magnitudes of stability constants due to incorporation of errors is alkali > acid > ligand > metal. Some species were even rejected when errors are introduced

in the concentrations. The rejection of some species and increased standard deviations in the stability constants on introduction of errors confirm the suitability of the experimental conditions (concentrations of components) and choice of the best-fit models.

### Effect of solvent

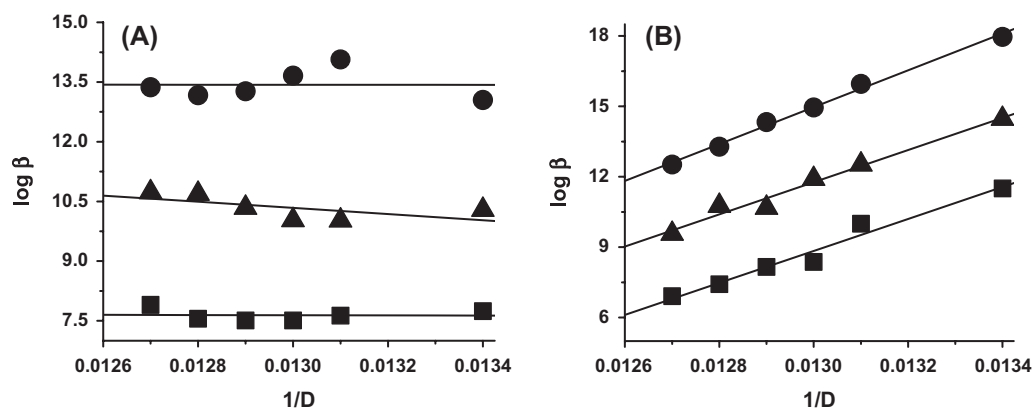
The variation of stability constants or change in free energy with co-solvent content depends upon two factors, viz., electrostatic and non-electrostatic. Born's classical treatment holds good in accounting for the electrostatic contribution to the free energy change (Born, 1920). According to this treatment, the energy of electrostatic interaction is related to dielectric constant. Hence, the logarithm of overall stability constant ( $\log \beta$ ) should vary linearly as a function of the reciprocal of the dielectric constant ( $1/D$ ) of the medium. These plots (Figure 1) in EG–water mixtures show that the  $\log \beta$  values are linearly vary with decreasing dielectric constant values.

### Distribution diagrams

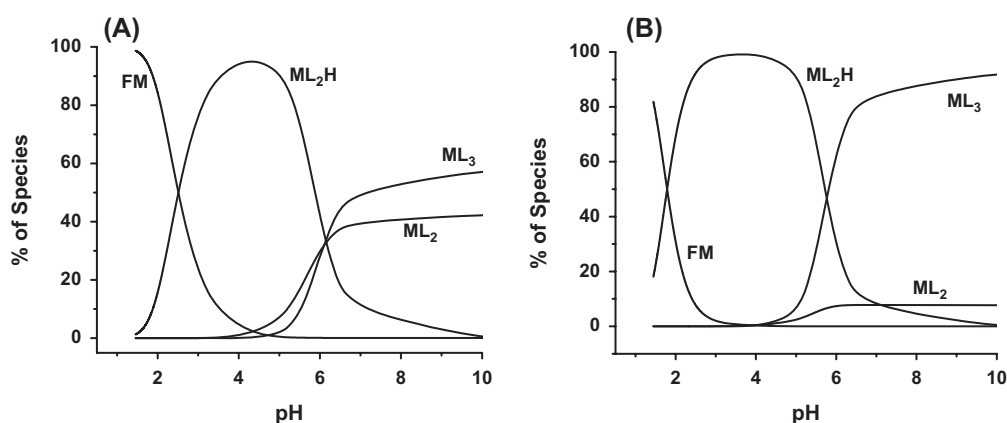
Maleic acid is a bidentate ligand that has two dissociable (carboxyl groups) protons. The different forms of maleic acid are  $LH_2$ ,  $LH^-$ , and  $L^{2-}$  in the pH range 1.5–3.5, 3.5–8.0, and 4.0–8.0, respectively. Hence, the plausible binary metal–ligand complexes can be predicted from these data. The present investigation reveals the existence of  $ML_2H$ ,  $ML_2$ , and  $ML_3$  for Pb(II) and Cd(II). The  $ML_2$  species is the predominant species (Figure 2) at higher pH and  $ML_2H$  is the predominant species at lower pH among all the binary complexes. Low concentration of free metal ion (FM) indicates the strong complexing nature of maleic acid. The formation of various binary complex

**Table 2.** Effect of errors in influential parameters on the stability constants of Cd(II)–maleic acid complexes in 40% v/v EG–water medium.

Reactant	% Error	$\log \beta$ (SD)		
		$ML_2$	$ML_3$	$ML_2H$
Acid	0	10.00(58)	12.42(75)	15.96(36)
	–5	Rejected	19.23(53)	20.93(08)
	–2	11.64(62)	14.43(45)	17.42(55)
	+2	7.91(62)	10.21(91)	14.05(25)
	+5	Rejected	5.77(72)	Rejected
Base	–5	Rejected	Rejected	Rejected
	–2	6.90(30)	Rejected	13.16(24)
	+2	11.91(94)	15.22(79)	17.70(68)
	+5	Rejected	21.34(40)	21.41(39)
Ligand	–5	10.70(72)	13.78(65)	16.50(48)
	–2	10.32(64)	13.01(68)	16.23(42)
	+2	9.65(53)	11.79(99)	15.69(31)
	+5	8.48(31)	Rejected	14.59(21)
Metal	–5	10.45(57)	13.00(65)	16.44(37)
	–2	10.15(56)	12.61(71)	16.12(36)
	+2	9.84(56)	12.23(77)	15.81(34)
	+5	9.52(52)	11.81(84)	15.46(28)

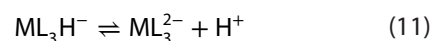
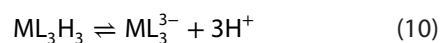
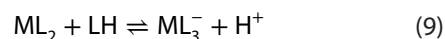
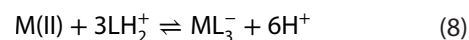
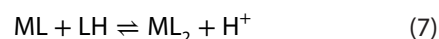
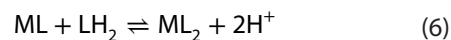
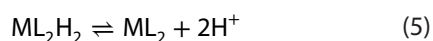
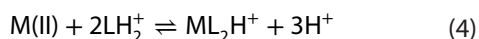
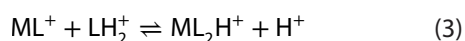
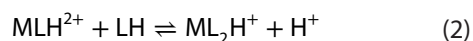
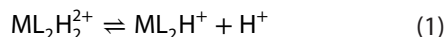


**Figure 1.** Variation of overall stability constant values of metal-maleic acid complexes with EG-water mixtures (A) Pb(II) and (B) Cd(II); (■)  $\log \beta_{ML_2}$ ; (▲)  $\log \beta_{ML_3}$ ; (●)  $\log \beta_{ML_2H^+}$



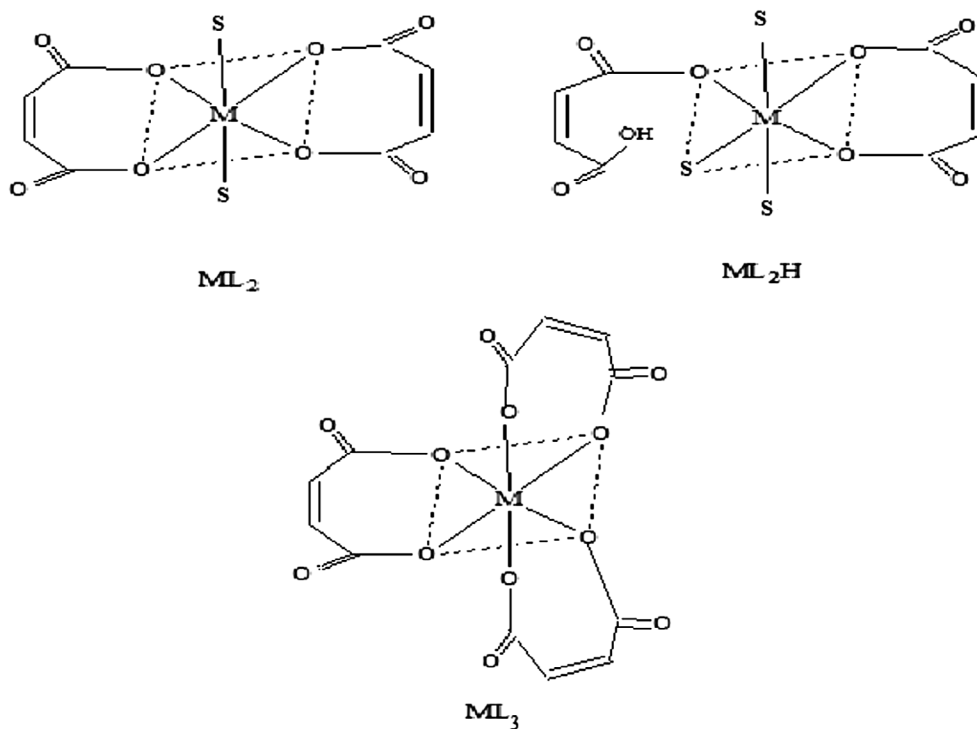
**Figure 2.** Distribution diagrams of maleic acid complexes in 30% v/v EG-water mixture. (A) Pb(II) and (B) Cd(II).

species is shown in the following equilibria. Some typical distribution diagrams of EG-water media are shown in Figure 2. The species of  $ML_2H$ ,  $ML_3$ , and  $ML_2$  are formed in the pH range of 1.5–10.0 for Pb(II) and Cd(II), respectively.  $ML_2H$  is formed at lower pH and  $ML_2$ ,  $ML_3$  are formed with the increasing pH.  $ML_3$  and  $ML_2$  species percentage successively increases with an increasing pH. Successive deprotonation of  $ML_2H_2$ ,  $MLH$ , and  $ML$  forms  $ML_2H$  [Equilibria (1), (2) and (3)].  $ML_2$  formed at higher pH. [Equilibria (5), (6), and (7)]. The percentage of the  $ML_2$  species increases successively with an increase in the pH. The concentration of  $ML_2H$  species decreased, while the concentration of  $ML_2$  and  $ML_3$  increased in the pH range.



### Structures of complexes

Depending upon the nature of the ligands and the metal ions, the basic chemical knowledge the structures of the binary complexes were proposed as shown in Figure 3. These structures indicate that maleic acid act as bidentate ligands depending upon the pH conditions. Octahedral structures are proposed to the complexes of all the metal ions. The VSEPR theory suggests that Pb(II) and Cd(II) complexes shall be octahedral, because there are six outer electron pairs.



**Figure 3.** Structures of maleic acid complexes (*S* is either solvent or water molecules).

## Conclusions

The following conclusions have been drawn from the modeling studies of the maleic acid complexes of Pb(II) and Cd(II) in EG–water mixture

- (1) The common species of  $ML_2$ ,  $ML_3$ , and  $ML_2H$  formed due to the interaction of maleic acid with the toxic metals of Pb(II) and Cd(II). These models are validated by statistical treatment of data.
- (2) 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 dominance of the structure forming nature of EG over its complexing ability
- (3) The order of components influencing the magnitudes of stability constants due to incorporation of errors in their concentrations is alkali > acid > ligand > metal.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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