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

Ch. Nageswara Rao, Bogi Srinu, V. Gowri Kumari and B. B. V. Sailaja

Department of Inorganic & Analytical Chemistry, Andhra University, Visakhapatnam, India

ABSTRACT

Chemical speciation of binary complexes of Pb(II) and Cd(II) ions with maleic acid have been studied pHmetrically in the concentration range of 0–50% v/v ethylene glycol (EG)–water mixtures maintaining an ionic strength of 0.16 molL−1 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 ML₂, ML₃, and ML₂H for Pb(II) and Cd(II). The chemical speciation, metal bioavailability, and transportation are explained based on the distribution diagrams.

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
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. 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 mol L\(^{-1}\)) was prepared in triple-distilled deionized water by maintaining 0.05 mol L\(^{-1}\) 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 mol L\(^{-1}\) 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 mol L\(^{-1}\) 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. The strengths of alkali and mineral acid were determined using the Gran plot method.

**Instrumentation**

The titrimetric data were obtained using ELICO (Model Li-120) pH meter (readability 0.01), which 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 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 mol L\(^{-1}\) with sodium nitrate at 303.0 ± 0.1 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 mmol mineral acid in a total volume of 50 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 mol L\(^{-1}\) sodium hydroxide. Other experimental details are given elsewhere.

**Modeling strategy**

The approximate complex stability constants were calculated using the computer program SCPHD. 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 MINIQUAD75.

**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 \(U_{corr}\) (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. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | \(\log \beta_{MLH}\) (SD) | \(\%\) v/vEG | \(ML_2\) | \(ML_3\) | \(ML_2H\) | NP | \(U_{corr}\) | Skewness | \(\chi^2\) | R-factor | Kurtosis | pH-range |
| Pb(II)          |                 |                |       |       |       |     |          |        |         |          |          |         |
| 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(25)      | 14.07(10) | 78   | 1.87  | −0.18| 38.93 | 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  |
| Cd(II)          |                 |                |       |       |       |     |          |        |         |          |          |         |
| 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 | 39.93 | 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: \(U_{corr} = U/(NP \times m) \times 10^6\), where \(m = \text{number of experimental points} \); \(SD = \text{Standard deviation}\).
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$_2$H, 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$_2$H 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 | ML$_2$ | ML$_2$H | ML$_3$ |
|----------|---------|--------|---------|--------|
| 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(53) |
|          | +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) |
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 acts 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.

\[
ML^+ + L = ML_2H^+ + H^+ 
\]

(3) \[
M(II) + 2LH_2^+ = ML_2H^+ + 3H^+ 
\]

(4) \[
ML_2H_2 = ML_2 + 2H^+ 
\]

(5) 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 acts 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.
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 ML₂, ML₃, and ML₂H 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.

Notes on contributors

Ch. Nageswara Rao, the co-author, holds a MSc degree in Chemistry from the Andhra University, India. He works as a lecturer in DVN College, Anakapalle, Visakhapatnam, India. He has published over nine scientific and proceedings publications. His research interests are in chemical speciation and water analysis.

Bogi Srinu, the co-author, holds a MSc degree in Chemistry from the Andhra University, India. He is a research scholar at Andhra University, India. He has published over six scientific and proceedings publications. His research interests are in chemical speciation and water analysis.

V. Gowri Kumari, the co-author, holds a MPhil degree in Chemistry from the Andhra University, India. She is a research scholar at Andhra University, India. She has published over seven scientific and proceedings publications. Her research interests are in chemical speciation and water analysis.

B.B.V. Sailaja, the corresponding author, holds a PhD degree in Chemistry from the Andhra University, India. She works as an assistant professor at Andhra University, India. She has published over 35 scientific and proceedings publications. Her research interests are in chemical speciation and water analysis.

References

[1] Leggett J, editor. Computational methods for the determination of formation constants. New York (NY): Plenum Press; 1985.
[2] Di Toro DM. Biotic ligand model of the acute toxicity of metals. 1. Technical basis. Environ. Toxicol. Chem. 2001;20:2383–2396.
[3] West DX, Padhye SB, Sonawane PB. Structure and bonding. Vol. 76. New York (NY): Springer-Verlag; 1991. p. 1–49.
[4] Beraldo H, Gambino D. The wide pharmacological versatility of semicarbazones, thiosemicarbazones and their metal complexes. Mini. Rev. Med. Chem. 2004;4:31–39.
[5] May PM, Linder PW, Williams DR. Computer simulation of metal-ion equilibria in biofluids: models for the low-
molecular-weight complex distribution of calcium(II), magnesium(II), manganese(II), iron(III), copper(II), zinc(II), and lead(II) ions in human blood plasma. J. Chem. Soc., Dalton Trans. 1977;44:588–595.

[6] Ramaanaiah M, Goutham Sri S, Sailaja BBV. Effect of non ionic micelles on the chemical speciation of binary complexes of Pb(II), Cd(II) and Hg(II) with L-phenylalanine. Chem. Speciation Bioavailability 2013; 25:285–290.

[7] Ramaanaiah M, Goutham Sri S, Sailaja BBV. Chemical speciation of Pb(II), Cd(II) and Hg(II) binary complexes of L-phenylalanine in CTAB-water mixtures. J. Indian Chem. Soc. 2014;91:351–357.

[8] Chandra leela A, Swaroopa rani R, Rao GN. Solvent effect on protonation equilibria of L-aspartic acid and ethylenediamine in dioxan-water mixtures. Proc. Natl. Acad. Sci. 2012;82:197–204.

[9] Ramaanaiah M, Goutham Sri S, Sailaja BBV. Formation of binary complexes of Pb(II), Cd(II) and Hg(II) with maleic acid in CTAB-water mixtures. Chem. Speciation Bioavailability 2014;26:231–239.

[10] Veeraswami B, Bhushanavathi P, Viplavaprasad U, Rao GN. Chemical speciation of L-proline complexes of Ca(II), Zn(II) and Mn(II) in acetonitrile–water mixtures. Chem. Speciation Bioavailability 2013;25:147–151.

[11] Chang LW. The neurotoxicology and pathology of organomercury, organolead, and organotin. J. Toxicol. Sci. 1990;15:125–151.

[12] Nakagawa H, Tabata M, Morikawa Y, et al. High mortality and shortened life-span in patients with itai-itai disease and subjects with suspected disease. Arch. Environ. Health 1990;45:283–287.

[13] Jacobs RM, Spiveryfo MR, Aldridge MH. Changes in plasma proteins associated with anemia produced by dietary cadmium in Japanese quail. J. Nutr. 1969;99:119–128.

[14] Schroeder HA. Cadmium as a factor in hypertension. J. Chronic Dis. 1965;18:647–656.

[15] Bui TH, Lindsten J, Nordberg GF. Chromosome analysis of lymphocytes from cadmium workers and itai-itai patients. Environ. Res. 1975;9:187–195.

[16] Drash GA. Increase of cadmium body burden for this century. Sci. Total Environ. 1993;67:75–76.

[17] Ramamoorthy S, Manning PG. Equilibrium studies of metal-ion complexes of interest to natural waters—II: Simple and mixed complexes of dl- and meso-tartaric acid with Cu(II) ions. J. Inorg. Nucl. Chem. 1972;34:1989–1996.

[18] Manning PG, Ramamoorthy S. Equilibrium studies of metal-ion complexes of interest to natural waters – III. J. Inorg. Nucl. Chem. 1972;34:1997–2005.

[19] Rees DO. Experimental evaluation of the effective dielectric constant of proteins. J. Mol. Biol. 1980;141:323–326.

[20] Rogers NK. Electrostatic interactions in globular proteins: calculation of the pH dependence of the redox potential of cytochrome c. J. Mol. Biol. 1985;182:613–616.

[21] Sigel H, Martin RB, Tribolet R, et al. An estimation of the equivalent solution dielectric constant in the active-site cavity of metalloenzymes. Eur. J. Biochem. 1985;152:187–193.

[22] Akerlof G, Short OA. The dielectric constant of dioxane-water mixtures between 0 and 80 degrees-correction. J. Am. Chem. Soc. 1953;75:6357.

[23] Sigel H. Hydrophobic interactions in biological systems: some background information based on ligand-ligand interactions in metal ion complexes. Pure Appl. Chem. 1989;61:923–932.

[24] Rao GN. Complex equilibria of some biologically important metal ions in aquo-organic media [PhD thesis]. Visakhapatnam: Andhra University; 1989.

[25] Gans P, Sabatini A, Vacca A. An improved computer program for the computation of formation constants from potentiometric data. Inorg. Chim. Acta 1976;18:237–239.

[26] Nageswara Rao CH, Gowri Kumari V, Sailaja BBV. Solvent effect of protonation equilibria of L-asparagine and maleic acid in dimethyl sulfoxide. J. Indian Chem. Soc. 2014;91:1021–1027.