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Speciation of binary complexes of Pb(II), Cd(II) and Hg(II) with L-dopa in Acetonitrile-water mixtures

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Abstract
Speciation of binary complexes of Pb(II), Cd(II) and Hg(II) with L-3,4-DIhydroxyphenylalanine (dopa) in (0-60% v/v) acetonitrile-water mixtures have been studied pH-metrically at a tempature of 303 K at an ionic strength of 0.16mol L^{-1}. The models for binary species contain ML_2H for Pb(II), MLH, ML_2H for Cd(II) and MLH, ML_2H_2 for Hg(II). The trend in the variation of stability constants with the mole fraction of acotonitrile was explained on the basis of electrostatic and non electrostatic forces. Distribution of the species with pH at different compositions of acetonitrile-water media was also presented.

Keywords: binary complexes, stability constants, dopa, speciation, acetonitrile

Introduction
L-dopa (3,4-DIhydroxy –L-phenylalanine) is a drug related compound, found in certain kinds of food and herbs and is made from L-tyrosine [1], which is an amino acid naturally occurring in the human body. It is the natural precursor of dopamine, and is the most effective and effective frequently prescribed therapy for controlling the symptoms of Parkinson's diseases [2].

Heavy metals such as lead, cadmium and mercury are toxic substances which exert adveres effects on neurological, reproductive, renal and hematological systems in humans and animals. Organo- mercury and lead compounds exhibit toxic effect on the central nervous system [3]. Similarly cadmium exhibits various chronic and acute disorders like testicular atropy, hypertension, damage to kidney and bones, anemia and Itai-Itai [4, 8]. Hence, the stability constants of the binary complexes of Pb(II), Cd(II) and Hg(II) have been determined using pH metry. These values are potentially useful to environmental and biological problems [9, 11].

The present paper describes the complexation of Pb(II), Cd(II) and Hg(II) with L-dopa in Acetonitrile-water media.

Acetonitrile (AN) is a colorless polar aprotic solvent [12]. It behaves as a weaker base [13] and as a much weaker acid [14] than water. It has a dielectric constant of 36 and autoprotolysis constant of 33.6. AN also acts as a strongly differentiating solvent with a modest solvating power for many polar ionic solutes [15].

Materials and Methods
Reagents and preparation
L-dopa (dopa), nitrates of lead, cadmium and mercury, Acetonitrile, mineral acid (HNO_3), sodium hydroxide and sodium nitrte were of analytical grade reagents. Acetonitrile was used as received. Aquoes solutions of dopa, metal salt solutions, nitric acid, a carbonate free sodium hydroxide and sodium nitrate were prepared by dissolving samples in triple distilled

Sodium hydroxide and sodium nitrate were of analytical grade reagents. Acetonitrile was used as received. Aqueous solutions of dopa, metal salt solutions, nitric acid, a carbonate free sodium hydroxide and sodium nitrate were prepared by dissolving samples in triple distilled water. To increase the solubility of dopa and to suppress the hydrolysis of metal salts, the nitric acid concentration was maintained at 0.05 mol L^{-1}. The solutions were standardized by employing standard methods. The data were subjected to ANOVA [16], to assess the errors that might have crept into the determination of the concentrations. Gran plot [17] method was employed to determine the strength of the alkali.

Apparatus
Elico LI 120 pH meter was used for the pH measurements. Potassium hydrogen phthalate solution (0.05 mol L^{-1}) in the acidic region and borax solution (0.01 mol L^{-1}) in the basic region were used to calibrate the pH meter. The pH meter was equilibrated in a well-stirred Acetonitrile water mixture containing inert electrolyte. The effects of variations in the asymmetry potential, liquid junction potential, activity coefficient, sodium ion error and dissolved carbon dioxide on the response of the glass electrode were accounted for in the form of correction factors [18, 19].

Measurements
All measurements were carried out at 303 K and at an ionic strength of 0.16 mol dm-3 which was maintained with sodium nitrate. The electrode was kept usually for 2-3 days, in the required solvent system for equilibration. To verify whether the electrode was equilibrated or not, a strong acid was titrated with an alkali every day until no appreciable differences were observed between the pH values of two titrations at the corresponding volumes of the titrant. Then the electrode was said to be equilibrated. Free acid-base titrations were performed to calculate the correction factor. In each of the titrations, the titrand consists of 1-3 mmol of mineral acid in a total volume of 50 cm^3. Titrations with different metal to ligand ratios (1:2.5, 1:3.75, 1:5) for Pb(II) and Cd(II), (1:5,

1:7.5, 1:10) for Hg(II) were carried out with 0.40 mol L^{-1} sodium hydroxide. The analytical concentrations of the ingredients are given in Table 1. Other experimental details are given elsewhere [20].

Modeling strategy

The approximate complex stability constants were calculated using the computer program SCPHD [21]. By following some heuristics in the refinement of the stability constants, the bestfit chemical models for each system were arrived at using the computer program MINIQUAD75 [22].

Results and Discussion

Alkalimetric titration curves in Acetonitrile-water mixtures reveal that the acido-basic equilibria of dopa are active in the pH range of 2.00 – 10.00.

Table 1: Total concentrations of ingradients(in mmol) of titrands in Acetonitrile-water (NaOH)=0.4 mol dm-$_3$;V_0=50 cm^3; temp=303 K; ionic strength= 0.16 mol dm-3; mineral acid= 1-3 mmol

%v/v Acetonitrile	TM0		TL0	TL0:TM0	TM0	TL0	TL0:TM0
	Pb(II)	Cd(II)	L-dopa		Hg(II)	L-dopa	
0.00	0.0998	0.0906	0.250	2.50	0.045	0.250	5.0
			0.375	3.75		0.375	7.5
			0.500	5.00		0.500	10.0
10.0	0.0998	0.0906	0.250	2.50	0.045	0.250	5.0
			0.375	3.75		0.375	7.5
			0.500	5.00		0.500	10.0
20.0	0.0998	0.0906	0.250	2.50	0.045	0.250	5.0
			0.375	3.75		0.375	7.5
			0.500	5.00		0.500	10.0
30.0	0.0998	0.0906	0.250	2.50	0.045	0.250	5.0
			0.375	3.75		0.375	7.5
			0.500	5.00		0.500	10.0
40.0	0.0998	0.0906	0.250	2.50	0.045	0.250	5.0
			0.375	3.75		0.375	7.5
			0.500	5.00		0.500	10.0
50.0	0.0998	0.0906	0.250	2.50	0.045	0.250	5.0
			0.375	3.75		0.375	7.5
			0.500	5.00		0.500	10.0
60.0	0.0998	0.0906	0.250	2.50	0.045	0.250	5.0
			0.375	3.75		0.375	7.5
			0.500	5.00		0.500	10.0

Table 2: Parameters of best-fit chemical models of Pb(ll), Cd(ll) and Hg(ll) –dopa complexes in acetonitrile-water mixture.(No. of titrations in each percentage=3, Temp=303 K,

%v/v AN	Log βmlh(SD)				NP	U_{corr}	Skewness	Kurtosis	χ^2	R-Factor	pH range
	1 1 1	1 2 1	1 1 2	1 2 2							
	Pb(ll)										
0			22.17		109	16.32	-0.37	9.82	137.6	0.0162	1.5-6.3
10			23.05(19)		96	18.17	-0.80	4.60	51.78	0.0148	1.8-5.5
20			22.22(37)		17	6.49	-1.80	10.25	54.88	0.0143	2.5-5.8
30			22.61(27)		35	8.96	1.01	3.74	57.82	0.0143	2.0-5.8
40			22.79(20)		51	7.72	0.91	4.05	59.76	0.0118	2.09-6.0
50			22.81(36)		48	15.48	0.66	3.53	48.67	0.0169	2.09-6.0
60			22.97(18)		48	12.86	-0.64	5.97	41.00	0.0089	1.5-2.5
	Cd(ll)										
0	15.92(18)	21.83(17)			29	7.92	-1.26	5.09	11.48	0.018	3.0-8.5
10	15.32(24)	21.34(20)			45	2.16	0	5.32	26.01	0.0074	2.5-8.0
20	14.40(25)	20.83(15)			77	6.90	-1.94	5.85	170.9	0.0111	2.0-8.0
30	14.41(25)	20.87(15)			26	6.39	1.04	3.96	24.77	0.0146	3.1-8.0
40	13.56(42)				88	93.05	0.10	2.89	21.70	0.048	2.0-10.0
50	14.72(36)	21.87(26)			15	8.33	1.56	5.07	17.76	0.0154	4.0-10.0
60		22.70(31)			13	14.4	1.38	4.46	28.49	0.0198	4.0-8.5
	Hg(ll)										
0	19.09			25.67(81)	109	15.66	3.10	17.43	197.4	0.0149	1.5-9.0
10	19.49(50)			39.07(10)	141	50.79	1.07	5.66	84.97	0.025	1.6-9.5
20	19.32(32)				146	79.02	1.72	6.53	133.1	0.0318	1.76-9.9
30	19.60(11)			32.49(32)	71	15.58	-2.19	7.48	66.47	0.0191	1.8-10.0
40	20.20(15)			33.69(12)	114	5.14	-0.52	4.42	26.75	0.0091	1.8-9.9
50	20.47(10)			33.82(44)	103	17.7	0.34	4.13	13.20	0.0173	1.8-9.5
60	18.08(23)			35.82(24)	39	1.44	1.61	7.00	70.69	0.0056	2.5-6.5

U_{corr}=U/ (NP-m) X10^8;NP= Number of points; m= number of protonation constants; SD= Standard deviation.

Table 3: Effect of errors in influential parameters on the complex stability constants in 30% (v/v) aceto nitrile-water mixture(L-dopa)

Ingradient	% of error	MLH	ML_2H_2
Acid	-2	21.49(06)	Rejected
	+2	Rejected	Rejected
	-5	Rejected	Rejected
	+5	Rejected	Rejected
	0	19.60(11)	32.49(32)
Alkali	-2	20.87(06)	Rejected
	+2	Rejected	Rejected
	-5	13.18(81)	Rejected
	+5	Rejected	Rejected
Ligand	-2	18.74(20)	31.74(42)
	+2	19.79(08)	32.63(20)
	-5	20.55(07)	Rejected
	+5	19.99(09)	32.67(26)
Metal	-2	19.26(11)	32.20(25)
	+2	19.65(13)	32.41(42)
	-5	18.95(17)	32.13(26)
	+5	19.47(15)	32.21(47)

Based on the active forms of the ligand in this pH range, models containing various numbers and combinations of complex species were generated using an expert system package CEES [23]. These models were inputted to MINIQUAD75 along with the alkalimetric titration data. The best-fit model was selected using the statistical parameters of the least square residuals. The final values of the stability constants of the complex are given in Table 2.

Effect of systematic errors on best-fit model

In order to rely upon the best-fit model for critical evaluation and application under varied experimental conditions with different accuracies of data acquisitions, a study was made by mineral acid, ligand and metal (Table 3). The order of the constituents that influence the magnitude s of the stability constants due to incorporation of errors are alkali> acid> ligand>metal. The rejection of some species and increased standard deviations in the stability constants on introduction of errors confirm the appropriateness of the best-fit models. This study supports that the experimental concentrations are appropriate and the proposed models are adequate for the experimental data.

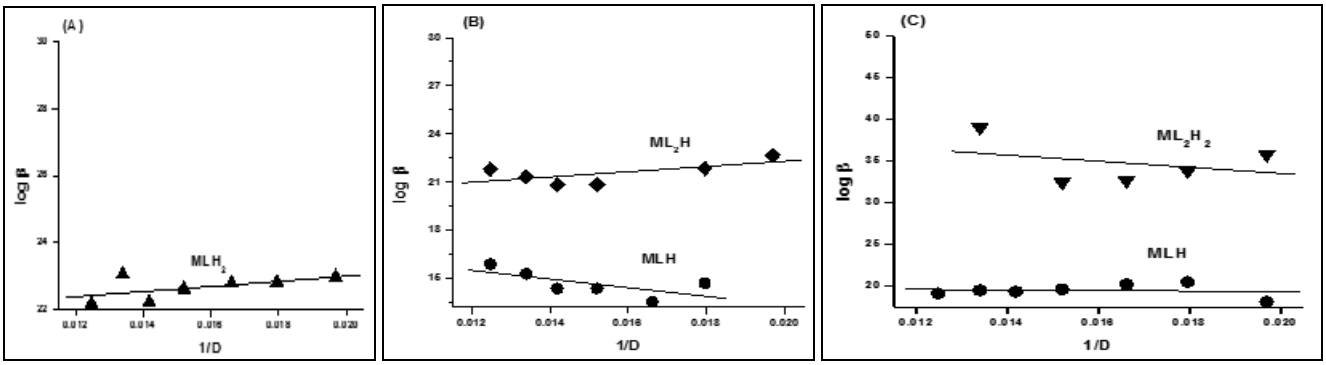

Fig 1: Vriation of stability constant values of (A) Pb(II); (B) Cd(II); (C) Hg(II)-Dopa complexes with reciprocal of dielectric constant (1/D) in Acetonitrili-water mixtures; (▲)log β 112; (●) log β 111; (♦) log β 121. (▼) log β 122;

Effect of dielectric constant

Addition of Acetonitrile to water decreases the dielectric constant of the medium. The dielectric constants of the medium at different percentages (0-60%) of AN were taken from literature [24]. The change in overall stability constants or change in free energy with change in co-solvent depends on two factors, viz., electrostatic and non-electrostatic. As basicity of AN is lower than that of water, the non-electrostatic effect seems to decrease proton accepting power of the ligand. Addition of more AN removes water molecules from hydration sphere of metal ion making it more susceptible to react with the ligand. According to Born's equation [25] the energy of electrostatic interactions is related to dielectric constant of the medium and log β versus 1/D (D is the dielectric constant of the medium) should be linear. So log β should increase/decrease linearly with decrease in dielectric constant of the medium (with increase in AN content) if the interaction between metal ion and ligand is electrostatic in nature. The linear variation of log β values of Dopa complexes of Pb(II), Cd(II) and Hg(II) with 1/D (Figure 1) indicates that the electrostatic solute-solvent interactions are predominant. The cation stabilizing nature of co-solvent, specific solvent-water interactions, charge dispersion and specific interactions, charge dispersion and specific interactions of co-solvent with the solute may be responsible for small deviation from the linear realationship. This study is helpful to understand the co-solvent effect at a molecular level [26, 28] and provide useful information in aiding in the rational drug design, medicinal chemistry, biochemistry and molecular biology.

The species distribution diagrams were obtained using the computer program DISPLOT [29]. Dopa has two ionisable phenolic protons in addition to carboxyl and amino protons and its various forms are LH_3^+, LH_2, LH^- in the pH ranges 2.0-8.0, 2.0-11.0, 5.0-11.8 and greater than 9, respectively [30]. The plausible refined species are MLH_2 for Pb(II), MLH, ML_2H for Cd(II) and Hg(II) for MLH and ML_2H_2 in AN-water mixture. The formation of various binary complexes is shown in the following equilibria:

$$M(II) + LH_3^+ \rightleftharpoons MLH_2^+ + H^+ \quad \text{.....(1)}$$

$$M(II) + 2LH_3^+ \rightleftharpoons MLH^+ + 4H^+ \quad \text{.....(2)}$$

$$MLH^+ + LH_3^+ \rightleftharpoons ML_2H_2 + H^+ \quad \text{.....(3)}$$

$$MLH^+ + LH_2 \rightleftharpoons ML_2H_2 + H^+ \quad \text{.....(4)}$$

$$MLH^+ + LH_2 \rightleftharpoons ML_2H^- + H^+ \quad \text{.....(5)}$$

The plausible refined species are ML_2H^- for Pb(II), MLH^+ and MLH_2^+ for Cd(II), and MLH^+, ML_2H_2 for Hg(II). Typical distribution diagrams of Pb(II), Cd(II) and Hg(II) in AN-water mixture are shown in Figure 2. In the case of Pb(II) ML_2H^- by the equilibrium 5. In case of Cd(II) MLH_2^+ is formed by the interaction of protonated ligand with metal ion in Equilibrium1 and MLH^+ formed in equilibrium 2. In the case of Hg(II) ML_2H_2 species is formed by equilibria 3 and 4 and the MLH^+ species the interaction of protonated ligand with metal ion in Equilibrium2.

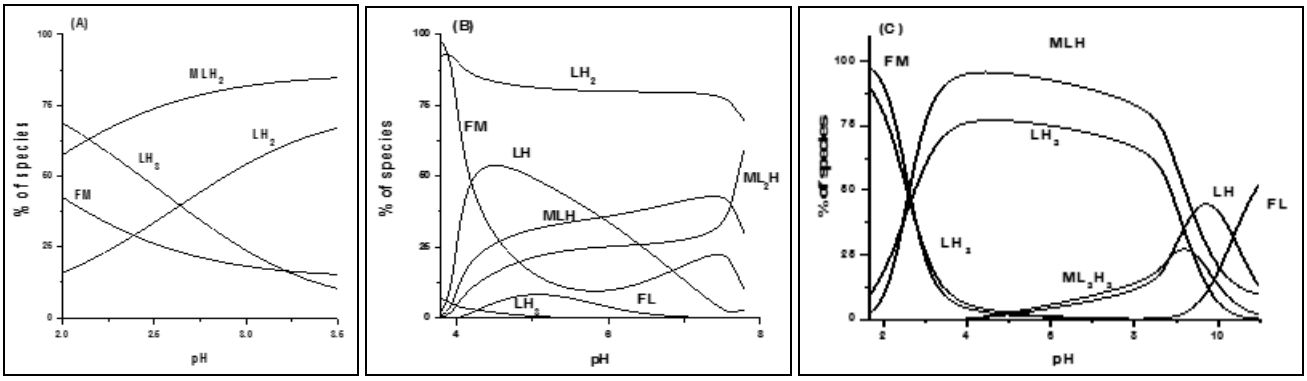

Fig 2: Distribution diagrams of (A) Pb(II); (B) Cd(II); (C) Hg(II)-dopa complexes in 30% v/v AN-water mixture

Structures of binary complexes

Dopa has tendency to chelate with essential or toxic metal ions either to compete with metallo enzymes or toxic ions from living systems. L-Dopa has two sets of chelating groups: the amino carboxylate side chain donors (N, O) and the catecholate donors (O, O). The distribution diagrams of Dopa with toxic metal ions (Figure2) demonstrate that these ligands coordinate via the side chain donors at lower pH but via the catecholate group at higher pH. Of course, there is a possibility of the simultaeneous ligand coordination to both bonding sites in the case of ligand excess, which are observed at intermediate pH. Although it is not possible to elucidate or confirm the structures of compexes pH metrically, they can proposed based on the literature reports and chemical knowledge [31]. Amino nitrogen atoms can associate with hydrogen ions in physiological pH range and the amino group is protonated at pH less than 9.0. It is observed that the maximum concentration of the protonated complex is at a pH more than 5 (Figure 2), and is concluded that the amino group is protonated complexes but not carboxyl group. The plausible structures of the complexes are shown in Figure 3.

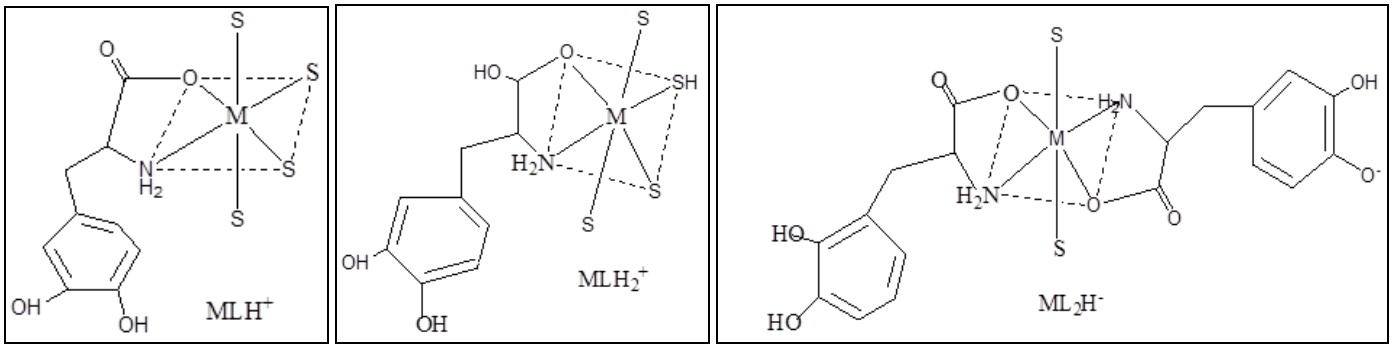

Fig 3

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