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RESEARCH ARTICLE

Influence of Anionic Micelles on Protonation Equilibria of L-Dopa and Catechol

T.V.S.P.V.SATYA GURU[1], V. RAVI KUMAR[2] and G.NAGESWARA RAO[3,*]

[1]Department of Chemistry, Vignan's Institute of Information Technology, Duvvada, Visakhapatnam, India
[2]Department of Chemistry, Mrs.A.V.N College, Visakhapatnam- 530003, India
[3]Department of Inorganic and Analytical Chemistry, Andhra University Visakhapatnam-530 003, India

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Abstract:
The impact of sodium lauryl sulphate (SLS) on the protonation equilibria of L-Dopa and catechol has been studied in various concentrations (0.0-2.5% w/v) of SLS solution maintaining an ionic strength of 0.16 mol L^{-1} at 303 K. The protonation constants have been calculated with the computer program MINIQUAD75 and the best fit models have been selected based on statistical parameters. The trend of log values of step-wise protonation constants with mole fraction of the medium has been explained based on electrostatic and non-electrostatic forces operating on the protonation equilibria. The effects of errors on the protonation constants have also been presented.

Keywords: Protonation equilibria, MINIQUAD75, sodium lauryl sulphate, L-Dopa, Catechol.

Introduction

L-Dopa (L-3,4-dihydroxyphenylalanine) is a naturally occurring dietary supplement and psychoactive drug found in certain kinds of food and herbs, and is synthesized from the essential amino acids L-phenylalanine and L-tyrosine in the mammalian body and brain. Dopa is the precursor to the neurotransmitters dopamine, nor-epinephrine (noradrenaline) and epinephrine (adrenaline). Dopa is used as a prodrug to increase dopamine levels in the treatment of Parkinson's disease[1,2] since it is able to cross the blood-brain barrier where as dopamine cannot.

Catechol (1,2-dihydroxybenzene) is used as a reagent for photography, dyeing fur, rubber, plastic production and in the pharmaceutical industry.[3] Catechols are intermediary products in the degradation of aromatic compounds and lignin by microorganism.[4]

In humans and mammals, catechols can occur as metabolites in the degradation of benzene or estrogens or as endogenous compounds, such as neurotransmitter and their precursors.[5] Hence, protonation constants of L-dopa and Catechol have been determined in micellar media which achieve compartmentalization of biofluids.

Sodium lauryl sulfate (SLS) is an anionic surfactant and profoundly influences the bulk properties of physiological systems. They can solubilise, concentrate and compartmentalize ions and molecules.[6] Several studies have reported on protonation constants of α-amino acids in anionic micellar media.[7-9] Protonation constants of L-dopa and catechol were determined in various media.[10, 11]

2. Experimental

2.1. Materials

Solutions (0.05 mol L^{-1}) of L-dopa (Loba, India) and catechol (Finar, India) were prepared in triple distilled water by maintaining 0.05 mol dm^{-3} acid (HCl) concentration to increase the solubility. Analytical reagent grade sodium lauryl sulphate (SLS) obtained from Qualigens was used as received. Sodium chloride (Qualigens, India) of 2 mol L^{-1} was prepared to maintain the ionic strength in the titrant. Sodium hydroxide (Qualigens, India) of 0.4 mol L^{-1} was prepared. Acid and alkali 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 analysis of variance of one way classification (ANOVA).[12] The strengths of alkali and mineral acid were determined using the Gran plot method.[13]

2.2. Alkalimetric titration

Alkalimetric titrations were carried out in media containing varying compositions of SLS-water (0.5–2.5% w/v) maintaining an ionic strength of 0.16 mol L^{-1} with sodium chloride at 303 ± 0.05K. An Elico LI-120 pH meter was used. Potassium hydrogen phthalate (0.05 mol L^{-1}) and borax (0.01 mol L^{-1}) solutions were used to calibrate the pH meter. In each titration, the titrand consisted of approximately 1 mmol of hydrochloric acid. The amounts of the ligands in the titrands ranged between 0.25 and 0.50 mmols. The glass electrode was equilibrated in a well stirred SLS-water mixture containing inert electrolyte for several days. At regular intervals strong acid was titrated against alkali to check the complete equilibration of the glass electrode. The calomel electrode was refilled with SLS-water mixture of equivalent composition as that of the titrand. The details of experimental procedure and titration assembly have been detailed elsewhere.[14]

2.3. Modeling strategy

The approximate protonation constants of L-dopa and catechol were calculated with the computer program SCPHD.[15] The best fit chemical model for each system investigated was arrived at using MINIQUAD75.[16] The variation of stepwise protonation constants was analyzed on electrostatic grounds on the basis of solute-solute and solute-solvent interactions.

3. Results and Discussion

3.1. Secondary Formation Functions

Secondary functions like average number of protons bound per mole of ligand ($\bar{n}H$) and number of moles of alkali consumed per mole of ligand (**a**) are useful to detect the number of equilibria. Plots of $\bar{n}H$ versus pH for different concentrations of ligand (formation curves) should overlap if there is no formation of polymeric species. Overlapping formation curves for dopa and catechol (Figure 3) rule out the polymerization of the ligand molecules. The pH values at half integral values of $\bar{n}H$ correspond to the protonation constants of the ligands. Three half integrals (2.5, 1.5 and 0.5) in the case of dopa (Figure 1A), and one half integral (0.5) in the case of catechol (Figure 1B) emphasize the presence of three and one protonation-deprotonation equilibria in the pH range of present study.

The plots of pH versus **a** are given in Figure 2. The negative values of **a** correspond to the number of moles of free acid present in the titrand and the number of associable protons. The positive values of **a** indicate the number of dissociable protons in the ligand molecules. The maximum value of **a** (Figure 2B) is +1, which clearly infers that catechol has one dissociable proton. The corresponding value for dopa (Figure 2A) is +2, which indicates that dopa has two dissociable (one carboxyl and one phenolic) protons.

Dopa contains two ionizable phenolic protons (catecholate) in addition to carboxylic and amino protons. Its neutral ligand form is a tribasic acid, H_3L, with four potential co-ordination centers. So dopa possesses four protonation constants corresponding to four protons in H_4L^+ form. The first proton has a very high affinity for L^{3-} ion to coordinate phenolate ion (log K~13). The next two protons coordinate to the other phenolate oxygen and the amine nitrogen. These two formation reactions overlap. The fourth proton to coordinate is the carboxyl proton (log K~2). From spectroscopic evidence Martin[17,18] and Gergely et al[19] concluded that the amine group has higher affinity for protons than the second phenolate oxygen which was criticized by Jameson.[20] He interpreted that the phenolate oxygen protonated first (log K_{OH} = 9.76) followed by the amine nitrogen (log K_{NH3+} = 8.93). The uncertainty was resolved by a proton NMR study in D_2O solution.[21] This study identified the second phenolic group of dopa to be more acidic (log K_{OH} = 8.78) than the amino group (log K_{NH3+} = 9.76). Other literature values reported[22–28] allowed the calculation of recommended protonation constants at 25°C and I = 0.1 to 0.2 M to be log K_{HL} = 13.4, log K_{H2L} = 9.84, log K_{H3L} = 8.77 and log K_{H4L} = 2.21.

The best fit models that contain the type of species and log values of overall formation constants (log β) along with some of the important statistical parameters of the present study are given in Table 1. A very low standard deviation (SD) in log β values, U_{corr} (sum of the squares of deviations in concentrations of ligand and hydrogen ion at all experimental data points corrected for degree of freedom) indicate that the experimental data can be represented by the model. Small values of mean, standard deviation and mean deviation for the systems

corroborate that the residuals are around a zero mean with little dispersion.

3.2. Residual Analysis[29]

In data analysis with least squares methods, the residuals (the differences between the experimental data and the data simulated based on the model parameters) are assumed to follow Gaussian or normal distribution. When the data are fit into the models, the residuals should be ideally equal to zero. Further, a model is considered adequate only if the residuals do not show any trend. Respecting the hypothesis of the least squares analysis, the residuals are tested for normal distribution. Such tests are χ^2, skewness, kurtosis and R-factor. These statistical parameters of the present data show that the best fit models portray the acido-basic equilibria of dopa and catechol in SLS-water mixtures, as discussed below.

χ^2 test

χ^2 is a special case of gamma distribution whose probability density function is an asymmetrical function. This distribution measures the probability of residuals forming a part of standard normal distribution with zero mean and unit standard deviation. If χ^2 calculated is less than the table value, the model is accepted.

Crystallographic R-test

Hamilton's R factor ratio test[30] is applied in complex equilibria to decide whether inclusion of more species in the model is necessary or not. In pH-metric method the readability of pH meter is taken as the R_{limit} which represents the upper boundary of R beyond which the model bears no significance. When these are different number of species the models whose values are greater than R-table are rejected. The low crystallographic R-values given in Table 1 indicate the sufficiency of the model.

Skewness

It is a dimensionless quantity indicating the shape of the error distribution profile. A value of zero for skewness indicates that the underlying distribution is symmetrical. If the skewness is greater than zero, the peak of the error distribution curve is to the left of the mean and the peak is to the right of the mean if skewness is less than zero. The values of skewness recorded in Table 1 are between –0.13 and 2.13. These data evince that the residuals form a part of normal distribution; hence, least-squares method can be applied to the present data.

Kurtosis

It 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). 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 the residuals form leptokurtic pattern in dopa and catechol.

3.3. Effect of systematic errors on best fit model

Any variation in the concentrations of ingredients like alkali, mineral acid and ligand affects the magnitudes of protonation constants. Such parameters are called influential or dangerous parameters. 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. The results of a typical system given in Table 2 emphasize that the errors in the concentrations of alkali and mineral acid affect the protonation constants more than that of ligand.

3.4. Effect of micelles

The effect of dielectric constant on the protonation equilibria of dopa in dioxan-water mixture was reported[31] where the log values of protonation constants of dopa increased linearly with decreasing dielectric constant of the medium. The apparent shift in the magnitude of protonation constants in micellar media compared to aqueous solution (Figure 3) was attributed to the creation of concentration gradient of protons between the interface and the bulk solution.[32] Further the presence of micelles is known to alter the dielectric constant of the medium, which has direct influence on the protonation deprotonation equilibria.[33-35]

The variation of protonation constant 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.[36] According to this treatment, the energy of electrostatic interaction or the logarithm of step-wise protonation constant (log K) should vary linearly as a function of the mole fraction of the medium. Such linear variation of the protonation constants of dopa (Figure 3A) in SLS-water mixture shows the dominance of electrostatic interactions.

Many workers were of the opinion that both electrostatic and non-electrostatic effects should be considered even in the case of simple acido-basic equilibria; one dominates the other, depending upon the nature of solute and solvent.[37–39] The log K value of catechol decrease linearly with mole fraction of the medium (Figure 3B). This may be because catechol has no associable protons. Since it has no polar groups, specific solvent-water interaction, charge dispersion, and specific interaction of co-solvent with solute (indicated by the changes in the solubility of different species in the aqua-organic

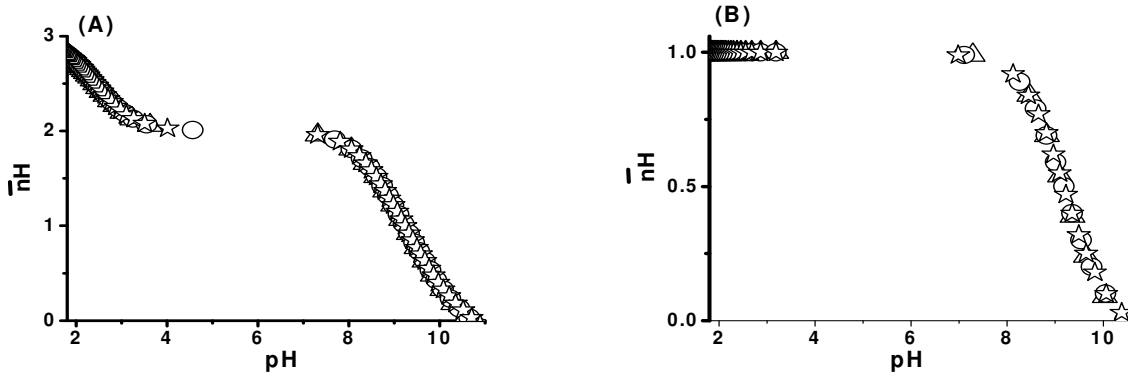

Figure 1: Plots of $\bar{n}H$ versus pH in 1.5% w/v SLS-water mixture, (A) dopa (B) catechol.

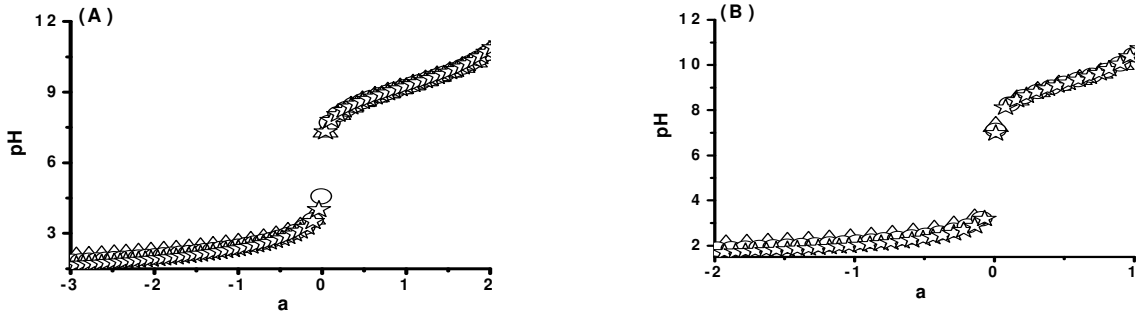

Figure 2: Plots of pH versus a in 1.5% w/v SLS-water\ mixture, (A) dopa (B) catechol.

Table 1: Best fit chemical models of acido-basic equilibria of L-Dopa and Catechol in SLS- water mixtures. Temp = 303K, Ionic strength = 0.16 mol L^{-1}.

% w/v of SLS	log β_{mlh} (SD) 011	012	013	NP	U_{corr}	Skew-ness	Kurtosis	χ^2	R-factor
			L- Dopa (pH range 1.6-3.5 & 7.0-10.5)						
0.0	9.91(9)	18.74(1)	21.10(1)	145	1.70	0.90	5.46	39.16	0.004
0.5	9.70(1)	18.41(1)	20.74(1)	108	2.45	0.65	4.86	22.45	0.005
1.0	9.89(1)	18.71(1)	21.54(2)	110	2.52	1.41	6.69	47.42	0.007
1.5	9.76(1)	18.48(1)	20.90(2)	156	6.56	0.19	4.25	74.36	0.009
2.0	9.73(1)	18.43(1)	21.20(2)	153	2.80	0.50	5.00	28.59	0.006
2.5	9.63(1)	18.21(1)	20.93(4)	145	3.08	-0.13	3.04	30.31	0.006
			Catechol (pH range 8.0-10.0)						
0.0	9.25(9)	-	-	28	2.16	1.94	7.71	14.57	0.016
0.5	9.22(8)	-	-	28	2.01	1.48	5.36	5.36	0.015
1.0	9.19(7)	-	-	30	1.40	2.13	8.09	8.09	0.013
1.5	9.17(9)	-	-	28	2.63	1.73	6.24	6.24	0.017
2.0	9.14(9)	-	-	27	2.04	1.19	4.15	4.15	0.015
2.5	9.12(9)	-	-	28	2.52	0.77	3.76	3.76	0.017

U_{corr} = U/ (NP - m) X 10^8; where m = number of species , NP = number of experimental points and SD = standard deviation.

Table 2: Effect of errors in influential parameters on the protonation constants of dopa and catechol in 1.5% w/v SLS-water mixtures.

Ingredient	% Error	log β (SD)			
		L- Dopa			catechol
		LH	LH_2	LH_3	LH
	0	9.76(1)	18.48(1)	20.90(2)	9.17(9)
Acid	-5	9.54(1)	18.04(2)	20.04(3)	8.94(2)
	-2	9.67(1)	18.30(2)	20.55(2)	9.08(1)
	+2	9.85(1)	18.65(1)	21.27(2)	9.27(7)
	+5	9.97(1)	18.91(1)	21.84(3)	9.41(1)
Alkali	-5	10.10(2)	19.07(2)	21.78(4)	9.47(1)
	-2	9.90(2)	18.71(2)	21.24(1)	9.29(6)
	+2	9.62(1)	18.62(1)	20.59(2)	9.06(1)
	+5	9.42(1)	17.94(2)	20.15(3)	8.88(3)
Ligand	-5	9.63(1)	18.35(1)	20.86(2)	9.12(1)
	-2	9.71(1)	18.43(1)	20.88(2)	9.15(1)
	+2	9.81(1)	18.53(1)	20.92(2)	9.20(8)
	+5	9.88(1)	18.61(2)	20.95(2)	9.23(7)
logF	-5	9.74(1)	18.44(2)	20.70(3)	9.15(9)
	-2	9.75(1)	18.46(2)	20.82(3)	9.17(9)
	+2	9.77(1)	18.49(1)	20.98(2)	9.18(9)
	+5	9.78(1)	18.52(1)	21.09(2)	9.20(9)
Volume	-5	9.76(1)	18.48(1)	21.03(2)	9.17(9)
	-2	9.76(1)	18.48(1)	20.96(2)	9.17(9)
	+2	9.76(1)	18.48(2)	20.84(3)	9.17(9)
	+5	9.76(2)	18.48(2)	20.76(3)	9.17(9)

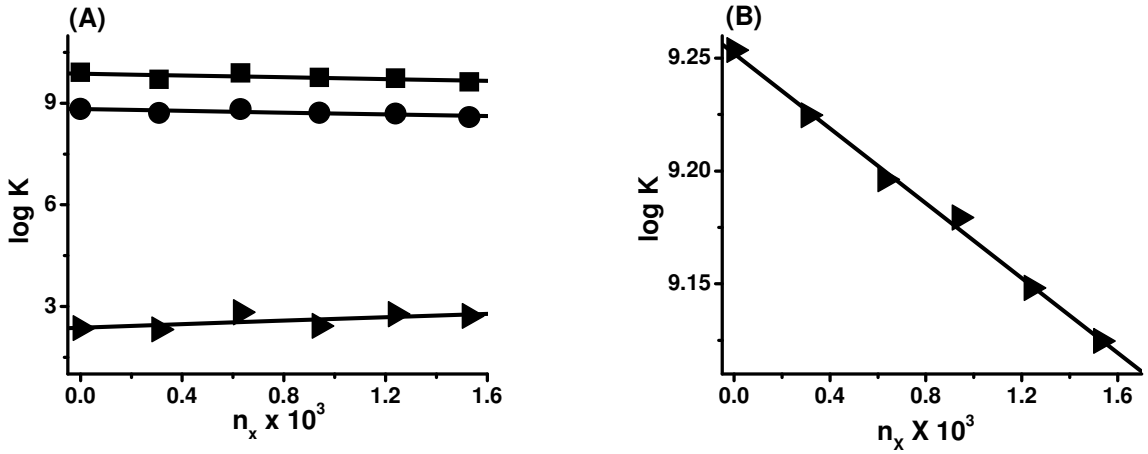

Figure 3: Variation of stepwise protonation constant (log K) with mole fraction of SLS in SLS-water mixtures. (A) Dopa, (B) Catechol (►) log K_1, (●) log K_2, (■) log K_3.

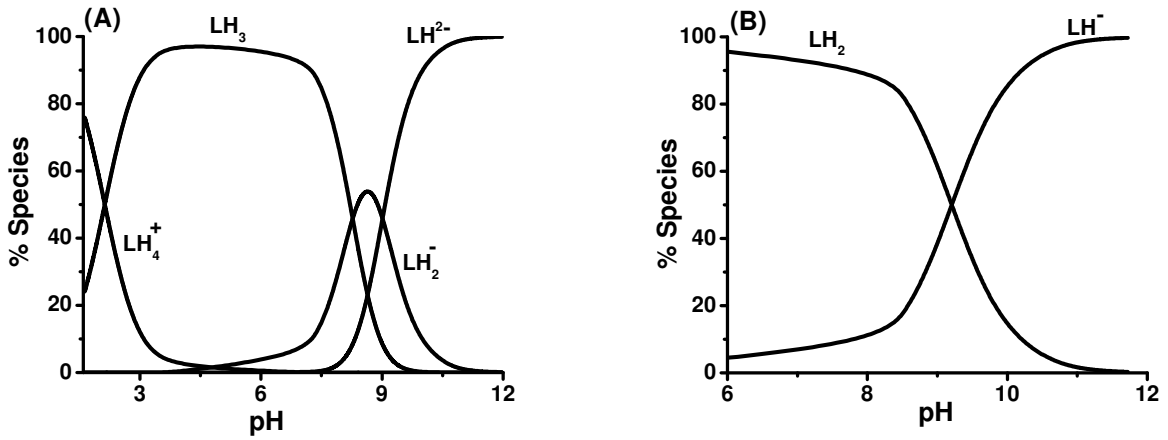

Figure 4: Species distribution diagrams of (A) dopa, (B) catechol in 1.0% w/v SLS-water mixture.

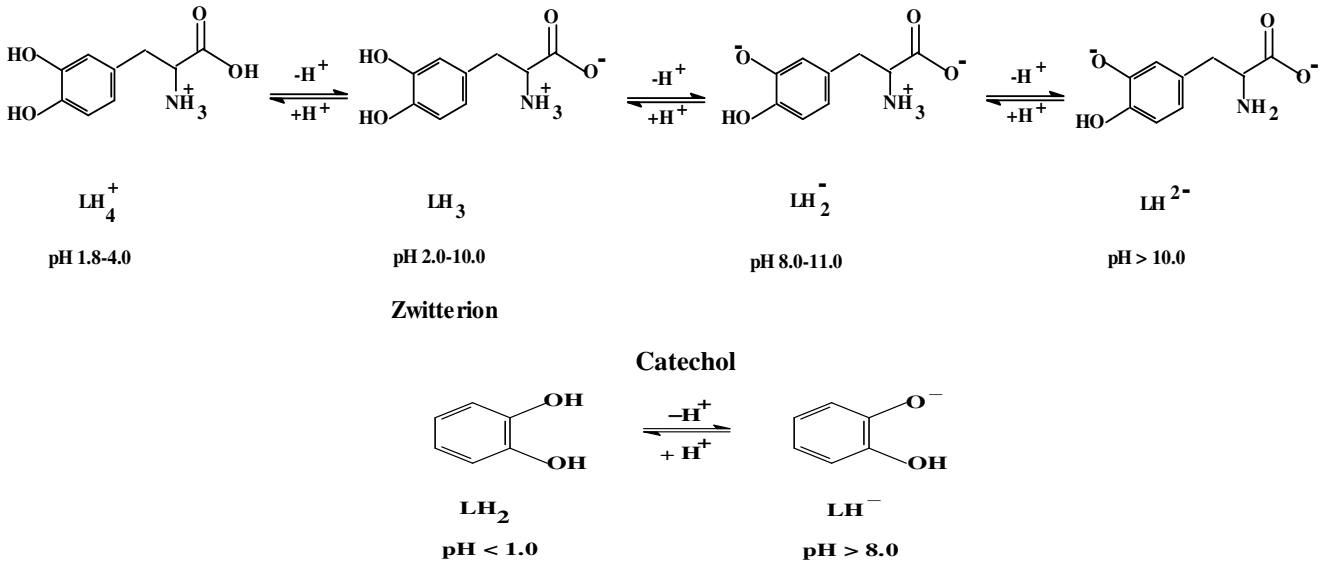

Figure 5. Protonation-deprotonation equilibria of dopa and catechol.

mixtures) account for the deviation of classical linear relationship of log K with mole fraction (n_x).

3.5. Distribution diagrams

The distribution plots (Figure 4) produced using the protonation constants from the best fit models (Table 1) show the existence of LH_4^+, LH_3, LH_2^- and LH^{2-} in the case of dopa and LH_2 and LH^- in the case of catechol in different pH ranges. The corresponding protonation-deprotonation equilibria are shown in Figure 5. As the alkali is added to the titrand containing the ligands, the protonated forms of the ligands lose their protons. In the pH range of study, dopa loses carboxylic, phenolic and amino protons successively. The second phenolic proton is lost at pH greater than 12.0. Hence, under present experimental conditions the most deprotonated form of dopa is LH^{2-}.

Similarly the second phenolic proton of catechol is lost at pH greater than 12.0. In the present study, the pH range is 8.0-10.0 and so only one protonation constant is reported.

4. Conclusions

1. L-Dopa has three dissociable protons and one amino group which can associate with a proton. It exists as LH_4^+ at low pH and gets deprotonated with the formation of LH_3, LH^-_2 and LH^{2-} successively with increase in pH.
2. Catechol has two dissociable protons. It exists as LH_2 at low pH and gets deprotonated with the formation of LH^- with increase in pH.
3. The linear variation of dopa and catechol with mole fraction of SLS–water mixtures indicates the dominance of electrostatic forces in the protonation–deprotonation equilibria
4. The effect of systematic errors in the influential parameters shows that the errors in the concentrations

of alkali and ligand will affect the protonation constants more than that of the mineral acid.

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