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Acido-Basic Equilibria of L-Phenylalanine and Maleic Acid in Neutral Micellar Medium

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ABSTRACT

Protonation equilibria of L-phenylalanine and maleic acid have been studied in varying concentrations (0.0-2.5% v/v) of Triton X-100 (TX100) solution maintaining an ionic strength of 0.16 mol dm^{-3} at 303K using pH metric method. The protonation constants have been calculated with the computer program MINIQUAD75 and the best fit models are arrived at based on statistical grounds employing crystallographic R factor, skewness, χ^2 and kurtosis. These protonation constants values have been found to shift in micellar media as compared to those in pure water. The differences in the values have been attributed to the solvent properties of the interfacial and bulk phases involving contribution from the micellar surface potential in the case of charged micelles. The trend of log values of step-wise protonation constants with mole fraction of the medium have been explained based on electrostatic and non-electrostatic forces operating on the protonation equilibria. Distributions of species, protonation equilibria and effect of influential parameters on the protonation constants have also been presented.

Keywords: Protonation equilibria, MINIQUAD75, Triton X-100, L-phenylalanine and Maleic acid.

INTRODUCTION

The acid–base equilibria of a number of phenols, amines and carboxylic acids in aqueous micellar solutions have been examined [1]. A number of studies have been reported on protonation constants of α-amino acids in different media [2–5]. Acidity and basicity of a molecule is governed by its structure and solvent effects [6, 7]. The present work is an attempt to study the effects of non-ionic micellar solution on the dissociation equilibria of the two biologically or industrially useful acids, viz., phenylalanine and maleic acids in the surfactant TX100. TX100 is a nonionic surfactant and profoundly influences the bulk properties of physiological systems. They can solubilise, concentrate and compartmentalize ions and molecules [8]. Amphiphilic molecules, containing both hydrophobic and hydrophilic moieties, associate in water above a certain concentration to form colloidal particles called micelles [9]. Micellar systems can shift acid-base equilibria. This shift can be explained in terms of differences between the properties of the bulk solvent and of the interfacial region and perturbation of the acid-base equilibria by the electrostatic field effect of the charged interface. The dissociation equilibria of substituted benzoic acids in cationic and

anionic micelles have been investigated potentiometrically [10]. It was shown that their pKa values shift to about 0.5-3.0 in anionic micelles.

L-phenylalanine (LPA) is an α-amino acid. This is essential and non polar amino acid because of the hydrophobic nature of the benzyl side chain. LPA is one of the twenty common amino acids used to biochemically form proteins, coded for by DNA. The codons for L-phenylalanine are UUU and UUC. LPA is biologically converted into L-tyrosine. L-tyrosine in turn is converted into L-DOPA, which is further converted into dopamine, nor epinephrine and epinephrine . LPA is converted to cinnamic acid by the enzyme phenylalanine ammonia-lyase [11]. Phenylalanine uses the same active transport channel as tryptophan to cross the blood-brain barrier and in large quantities, interferes with the production of serotonin. The quantity of L-phenylalanine produced commercially has been increased by genetically engineering E.coli, such as by altering the regulatory promoters or amplifying the number of genes controlling enzymes responsible for the synthesis of the amino acid. Phenylalanine is found naturally in the breast milk of mammals. It is used in the manufacture of food and drink products and sold as a nutritional supplement for its reputed analgesic and antidepressant effects. It is a direct precursor to the neuromodulator phenyl ethylamine a commonly used dietary supplement.

Maleic acid (MA) is a dicarboxylic acid. Maleic acid is the cis isomer of butenedioic acid, whereas fumaric acid is the trans isomer. It is mainly used as a precursor to fumaric acid and relative to its parent maleic anhydride. Maleic acid is a less stable molecule than fumaric acid. The difference in heat of combustion is 22.7 $kJ.mol^{-1}$. The heat of combustion is -1355 $kJ.mol^{-1}$. Maleic acid is more soluble in water than fumaric acid. The melting point of maleic acid (139–140^{0}C) is also much lower than that of fumaric acid (287^{0}C). Both properties of maleic acid can be explained on account of the intramolecular hydrogen bonding that takes place in maleic acid at the expense of intermolecular interactions and that are not possible in fumaric acid. In industry, maleic acid is derived by hydrolysis of maleic anhydride, the latter being produced by oxidation of benzene or butane. Maleic acid is an industrial raw material for the production of glyoxylic acid by ozonolysis. The major industrial use of maleic acid is its conversion to fumaric acid. Maleic acid and fumaric acid do not spontaneously interconvert because rotation around a carbon carbon double bond is not energetically favorable. However, conversion of the cis isomer into the trans isomer is possible by photolysis in the presence of a small amount of bromine.

MATERIALS AND METHODS

Reagents: Solutions (0.05 mol dm^{-3}) of L-phenylalanine (Loba, India) and maleic acid (Loba, India) were prepared in triple-distilled water by maintaining 0.05 mol dm^{-3} nitric acid concentration to increase the solubility. TX (Merck, India) was used as received. Nitric acid (Merck, India) of 0.2 mol dm^{-3} was prepared. Sodium nitrate (Merck, India) of 2 mol dm^{-3} was prepared to maintain the ionic strength in the titrand. Sodium hydroxide (Merck, India) of 0.4 mol dm^{-3} was prepared. 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 analysis of variance of one way classification (ANOVA) [12-15]. The strengths of alkali and mineral acid were determined using the Gran plot method [16, 17].

Alkalimetric Titrations: Alkalimetric titrations were carried out in media containing varying compositions of TX (0-2.5% v/v) maintaining an ionic strength of 0.16 mol dm^{-3} with sodium nitrate at 303 ± 0.05K. An Elico LI-120 pH meter was used. Potassium hydrogen phthalate (0.05 mol dm^{-3}) and borax (0.01 mol dm^{-3}) solutions were used to calibrate the pH meter. In each titration, the titrand consisted of approximately 1 mmol of nitric acid. The amounts of the ligands in the titrands ranged between 0.25 and 0.50 mmol. The glass electrode was equilibrated in a well stirred TX-water mixture containing inert electrolyte for several days. At regular intervals the strong acid was titrated against alkali to check the complete equilibration of the glass electrode. The calomel electrode was refilled with TX-water mixture of

equivalent composition as that of the titrand. The details of experimental procedure and titration assembly have been detailed elsewhere [18]. The initial concentrations of ingredients are given in table 1.

Table 1. Total initial concentrations of ingredients (in mmol) in proton - ligand titrations in TX100-water mixtures. [NaOH] = 0.4 mol dm^{-3}; V_0 = 50 cm^3; Temperature = 303 K, Mineral acid = 1.0 mmol; μ = 0.16 mol dm^{-3}.

% v/v TX100	No. of titration curves	TL0	
		L-phenylalanine	Maleic acid
0.0	3	0.2494 0.3741 0.4988	0.2498 0.3747 0.4996
0.5	3	0.2495 0.3742 0.4990	0.2493 0.3739 0.4986
1.0	3	0.2505 0.3757 0.5010	0.2483 0.3724 0.4966
1.5	3	0.2489 0.3733 0.4878	0.2494 0.3741 0.4988
2.0	3	0.2503 0.3754 0.5006	0.2488 0.3732 0.4976
2.5	3	0.2484 0.3726 0.4968	0.2478 0.3717 0.4956

Modeling Strategy: The approximate protonation constants of phenylalanine and maleic acid were calculated with the computer program SCPHD [19-22]. The best fit chemical model for each system investigated was arrived at by using non-linear least-squares computer program, MINIQUAD75 [23], which exploit the advantage of constrained least-squares method in the initial refinement and reliable convergence of Marquardt algorithm. The variation of stepwise protonation constants (log K) with the mole fraction of the medium was analyzed on electrostatic grounds for the solute-solute and solute-solvent interactions.

RESULTS AND DISCUSSION

Residual Analysis [24-27]: 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 shows that the best fit models portray the acido-basic equilibria of L- phenylalanine and maleic acid in TX100-water mixtures, as discussed below.

χ2 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 the χ2 calculated is less than the table value, the model is accepted.

Crystallographic R-test: Hamilton's R factor ratio test 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 numbers of species the models whose values are greater than R-

table are rejected. The low crystallographic R-values given in Table 2 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 2 are between -1.02 and 0.69. 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 the case of both L-phenylalanine and maleic acid. Alkalimetric titration data are simulated using the model parameters given in table 2. These data are compared with the experimental alkalimetric titration data, to verify the sufficiency of the models. The overlap of the typical experimental and simulated titrations data given in the figure 1 indicates that the proposed models represent the experimental data.

Table 2. Best fit chemical model of acido-basic equilibria of L-phenylalanine and Maleic acid in TX-100 water mixtures. Temp= 303 K, Ionic strength= 0.16 mol dm^{-3}.

% v/v. TX100	Log β_1 (SD)	Log β_2 (SD)	NP	U_{corr}	Skewness	Kurtosis	χ^2	R
L-Phenylalanine (pH ranges 2.0-11.00)								
0.0	9.27(1)	11.48(1)	72	1.86	-0.17	3.27	1.22	0.0096
0.5	9.47(1)	11.93(2)	84	6.59	0.69	5.27	23.43	0.0164
1.0	8.72(2)	12.17(7)	23	10.95	-0.33	3.34	6.17	0.0292
1.5	9.26(1)	11.69(1)	79	2.73	0.55	4.18	4.63	0.0113
2.0	9.69(1)	12.55(2)	43	5.12	0.00	3.83	8.88	0.0158
2.5	9.56(1)	12.30(2)	63	5.41	0.17	3.52	9.11	0.0187
Maleic acid (pH ranges 1.8 -10.00)								
0.0	6.15(1)	7.93(2)	102	6.80	-0.29	4.94	7.45	0.0151
0.5	5.95(1)	7.91(2)	59	3.86	0.35	3.74	47.83	0.0159
1.0	6.08(1)	8.30(2)	19	1.18	-1.02	4.14	4.11	0.0078
1.5	6.19(1)	8.31(2)	87	6.35	-0.81	4.09	5.86	0.0174
2.0	6.22(1)	8.93(1)	22	2.00	-0.03	4.13	2.55	0.0089
2.5	6.25(1)	8.86(2)	35	6.97	-0.27	2.46	1.77	0.0175

U_{corr} = U/ (NP-m) X 10^8; NP = Number of points; m = number of protonation constants; SD = Standard deviation.

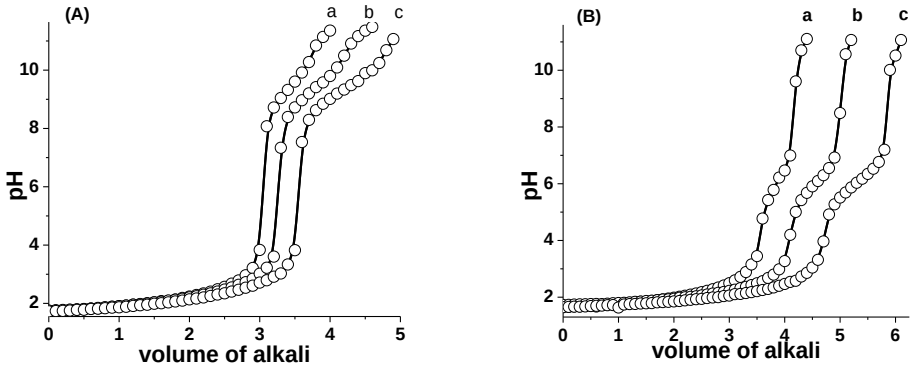

Fig. 1: Simulated (o) and experimental (solid line) alkalimetric titration curves in 0.5% v/v TX100-water mixtures: **(A)** L-phenylalanine **(B)** Maleic acid; (a) 0.25, (b) 0.375 and (c) 0.50 mmol, respectively.

Secondary Formation Functions: Secondary formation functions like average number of protons bound per mole of ligand ($\overline{n_H}$) and number of moles of alkali consumed per mole of ligand (**a**) are useful to detect the number of equilibria. Plots of $\overline{n_H}$ versus pH for different concentrations of the ligand should overlap if there is no formation of polymeric species. Overlapping formation curves for Phenylalanine and maleic acid (figure 2) rule out the polymerization of the ligand molecules. The pH values at half integral values of $\overline{n_H}$ correspond to the protonation constants of the ligands. Two half integrals 1.5 and 0.5 in the case of phenylalanine figure 2(A) and maleic acid figure 2(B) emphasize the presence of two protonation-deprotonation equilibria in the pH range of present study. The number of plateaus in the formation curves corresponds to the number of these equilibria.

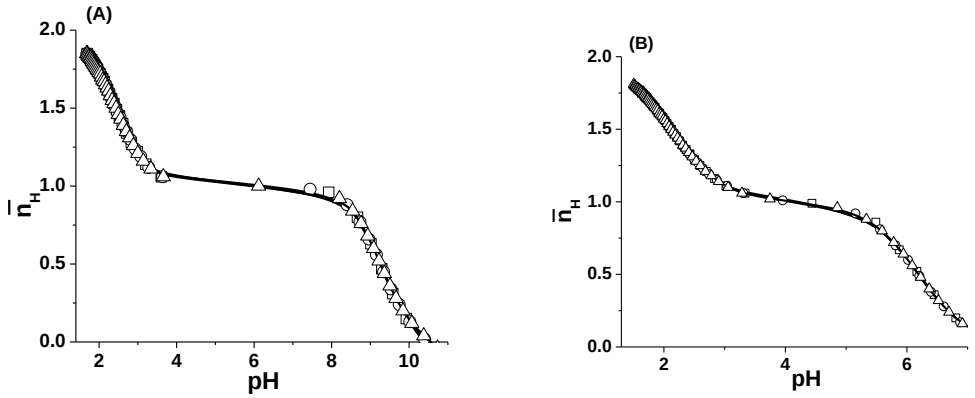

Fig. 2 Plots of $\overline{n_H}$ versus pH in 1.5 % v/v TX100-water mixture: (**A**) L - phenylalanine (**B**) Maleic acid, (Δ) 0.25, (○) 0.375, and (□) 0.50 mmol, respectively.

The plots of **a** versus pH are given in Fig. 3. The negative values of **a** corresponds 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** in figure 3(A) is +1, which indicates that phenylalanine has one dissociable (one carboxyl) proton. The corresponding value for maleic acid figure 3(B) is +2, which clearly infers that maleic acid has two dissociable (two carboxyl) protons.

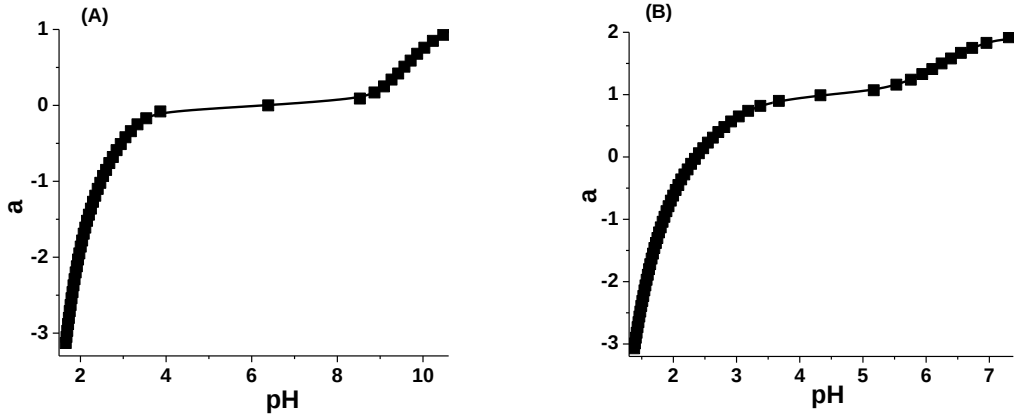

Fig. 3 Variation of a with pH in 2.5 % v/v TX100-water mixture: (**A**) L-phenylalanine **(B**) Maleic acid, respectively.

Distribution Diagrams: Typical distribution plots produced by DISPLOT [28] using protonation constants from the best fit models are shown in Figure 4. A single representative plot is shown for each system at a particular TX-water concentration. The zwitterion of phenyl alanine, LH, is present to an

extent of 98% in the pH range 2.0-11.0. The distribution plot of phenylalanine in figure 4(A) is shows the existence of LH_2^+, L^-. In the case of maleic acid, LH^- is present to an extent of 90% in the pH range 1.5-10. The distribution plots of maleic acid in figure 4(B) show the existence of LH_2, L^{2-}. The corresponding protonation-deprotonation equilibria are shown in figure 5.

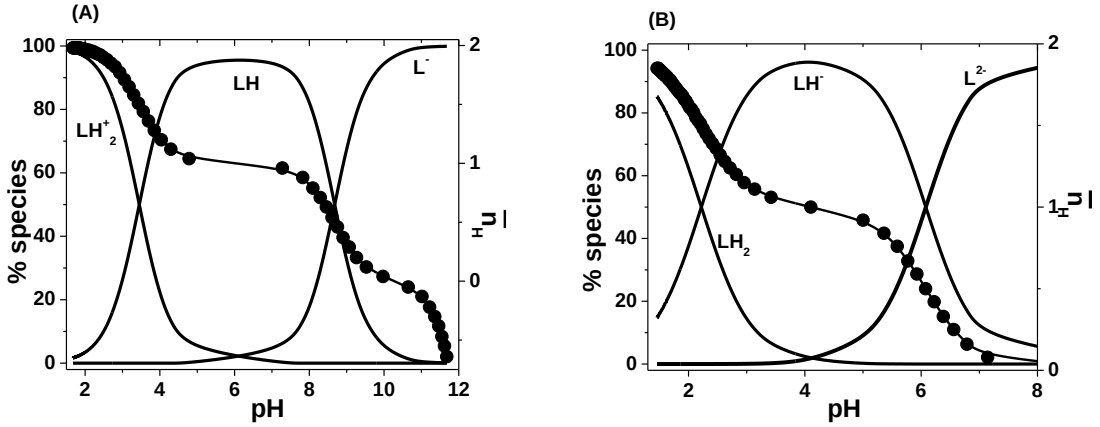

Fig. 4. Formation functions (●) and Species distribution diagrams of (**A**) L-phenylalanine (**B**) Maleic acid in 1.0% v/v TX100-water mixture.

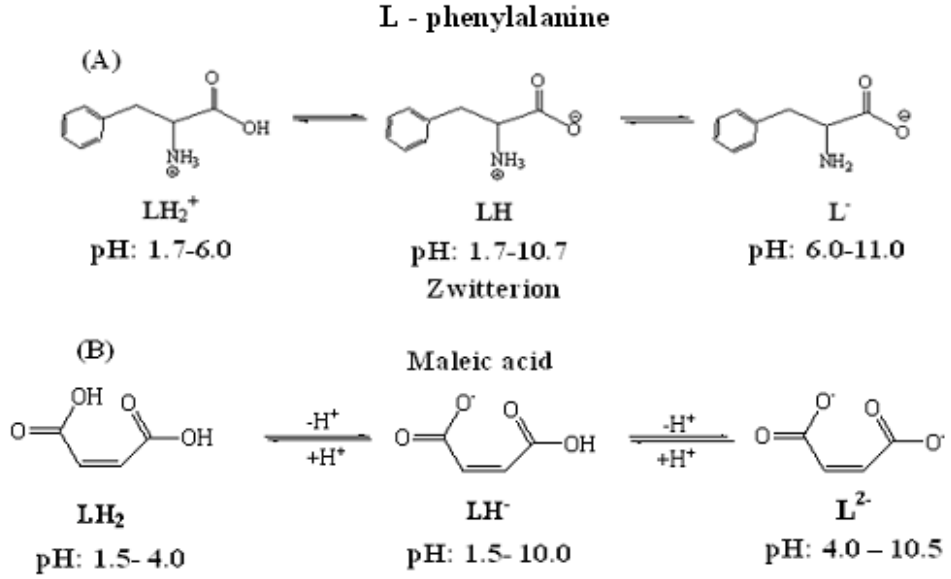

Fig. 5 Protonation-deprotonation equilibria of (**A**) L - phenylalanine (**B**) Maleic acid.

Effect of surfactant: In the presence of non-ionic surfactant TX100 the acid dissociates even lesser as compared to that in pure water. The TX100 molecule contains large number of electron releasing polyoxyethylene head groups. Due to negative inductive effect, the electron density on the carbon atom in the acid molecule increases which in turn increases the electron density on the adjoining C-OH bond. The overall effect is that of an increase in electron density in the O-H bond. This leads to difficulty in the release of proton by the acid molecule causing lower dissociation of the acid and higher p*K*a values. In the absence of any strong electrostatic effect in case of non-ionic surfactants, the polarity effect is expected to play a larger role. The dielectric constant of the micellar phase is smaller than that of water and so when the acid is solubilised at this phase the dissociation equilibrium is shifted to the left, thereby increasing the

p*K*a value. It is also possible that the presence of several ethoxylated oxygen atoms should increase the number of hydrogen bonds, and therefore promote dissociation. According to the results observed, it seems that hydrogen bonding outweigh the possibility the inductive and dielectric factors causing an overall increase in dissociation. Hence protonation constants are slightly increased in the present study.

The appreciable change in the magnitude of protonation constants in non-ionic miceller media compared to aqueous solution (Figure 6) was attributed to the creation of concentration gradient of protons between the interface and the bulk solution [29]. Further the presence of micelles is known to alter the dielectric constant of the medium, which has direct influence on the protonation-de protonation equilibria [30].

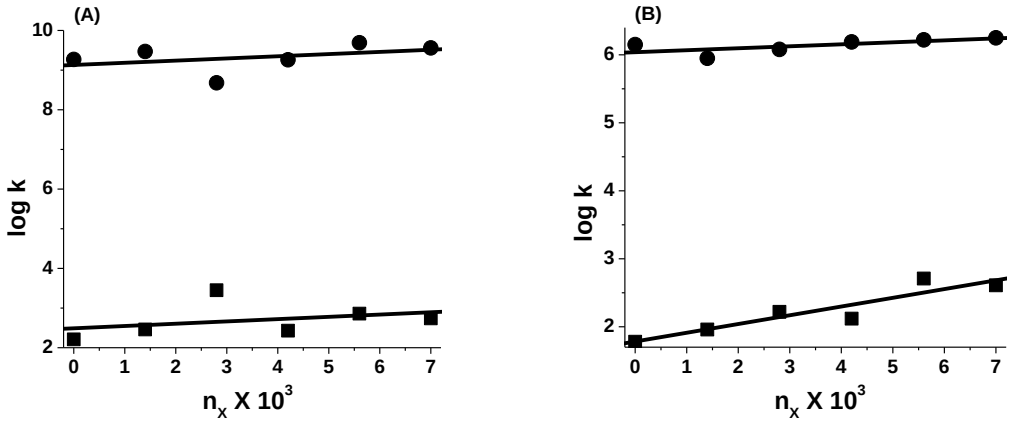

Fig. 6 Variation of stepwise protonation constant (log **K**) with mole fraction of TX100 in TX100-water mixtures. (**A**) L-phenylalanine (**B**) Maleic acid (■) log $\mathbf{K}_1$ (●) log $\mathbf{K}_2$.

Effect of Systematic Errors in Best Fit Model: MINIQUAD75 does not have provision to study the effect of systematic errors in the influential parameters like the concentration of ingredients and electrode calibration on the magnitude of protonation constant. In order to rely upon the best fit 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 concentration of alkali, mineral acids and the ligands. The results of a typical system given in table 3 emphasize that the errors in the concentrations of alkali and mineral acid affects the protonation constants more than that of the ligand.

Table 3. Effect of errors in influential parameters on the protonation constants in 1.5% (v/v) TX100-water mixture.

		L-Phenylalanine		Maleic acid	
Ingredient	% Error	log β_1	log β_2	log β_1	log β_2
	0	9.26(1)	11.69(1)	6.19(1)	8.31(2)
Acid	-5	8.90(3)	11.00(4)	5.82(2)	7.57(3)
	-2	9.12(1)	11.42(2)	6.04(1)	8.02(1)
	+2	9.40(1)	11.98(1)	6.34(2)	8.61(3)
	+5	9.61(2)	12.40(3)	6.58(4)	9.07(6)
Alkali	-5	9.68(2)	12.39(3)	6.80(7)	9.29(9)
	-2	9.43(1)	11.96(1)	6.42(3)	8.68(4)
	+2	9.10(1)	11.43(2)	5.98(1)	7.96(2)
	+5	8.85(3)	11.05(5)	5.66(4)	7.43(6)
Ligand	-5	9.20(1)	11.68(1)	6.02(1)	8.07(2)
	-2	9.24(1)	11.69(1)	6.12(1)	8.22(2)
	+2	9.28(1)	11.70(1)	6.26(2)	8.41(2)

	+5	9.32(1)	11.71(1)	6.36(2)	8.54(3)
Volume	-5	9.26(1)	11.74(1)	6.19(1)	8.38(2)
	-2	9.27(1)	11.71(1)	6.19(1)	8.34(2)
	+2	9.26(1)	11.68(1)	6.20(1)	8.28(2)
	+5	9.26(1)	11.65(1)	6.20(1)	8.24(2)
log F	-5	9.26(1)	11.68(1)	6.19(1)	8.30(2)
	-2	9.26(1)	11.69(1)	6.19(1)	8.31(2)
	+2	9.26(1)	11.70(1)	6.19(1)	8.32(2)
	+5	9.26(1)	11.70(1)	6.19(1)	8.32(2)

APPLICATIONS

The present work is expected to mimic the physiological conditions where the concept of the equivalent solution dielectric constant for protein cavities is applicable. The studies carried out on these systems under the present experimental conditions are useful to understand the role played by the active site cavities in biological molecules.

CONCLUSIONS

1. L- Phenylalanine has one dissociable proton and one amino group which can associate with a proton. L-phenylalanine forms LH_2^+ at low pH and gets deprotonated with the formation of LH and L^- successively with increase in pH.
2. Maleic acid has two dissociable protons. Maleic acid form LH_2 at low pH and gets deprotonated with the formation of LH^- and L^{2-} successively with increase in pH.
3. Secondary formation functions-number of moles of alkali per mole of the ligand and average number of moles of protons bound per mole of the ligands are useful in detecting the number of protonation equilibria and in guessing the approximate protonation constants.
4. The log values of protonation constants of L-phenylalanine and maleic acid increased almost linearly with increasing mole fraction of TX100-water mixtures indicating the dominance of electrostatic forces in the protonation-deprotonation equilibria and hydrogen bonding in TX100.
5. The effect of systematic errors in the influential parameters shows that the errors in the concentrations of alkali and mineral acids will affect the protonation constants more than that of the ligand, volume of acid and log F.

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