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Protoletic Equilibria of L-Phenylalanine and Maleic Acid in DMF-Water Mixture

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Abstract: Protonation equilibria of L-phenylalanine and maleic acid have been studied in various concentrations (0.0-50% v/v) of DMF-water solution maintaining an ionic strength of 0.16 mol dm⁻³ at 303 K. The protonation constants have been calculated using the computer program MINQUAD75 and the best fit models are arrived at based on statistical grounds employing crystallographic R factor, χ^2 , skewness and kurtosis. 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. The chemical speciation was explained based on the distribution diagrams drawn using HYSS HYPERQUAD.

Keywords: protonation equilibria, MINQUAD75, HYSS HYPERQUAD, DMF, L-phenylalanine and maleic acid

I. INTRODUCTION

L-phenylalanine is nonpolar α -amino acid because of the hydrophobic nature of the benzyl side chain with the formula C₆H₅CH₂CH(NH₂)COOH.

This is essential amino acid, one of the 20 common amino acids used to form proteins biochemically. L-phenylalanine is biologically converted into L-tyrosine. L-tyrosine in turn is converted into L-DOPA, which is further converted into dopamine, norepinephrine, and epinephrine. Phenylalanine is converted to cinnamic acid by the action of enzyme phenylalanine ammonia lyase [1].

L-Phenylalanine (LPA) actively participates in acido-basic equilibria especially in physiological pH conditions. LPA has two functional groups and one is protonated, amino group followed by one carboxylic group. Hence, LPA has bidentate behavior resulting in five membered ring structures. Nitrogen donor atoms can associate with hydrogen ions in physiological pH ranges [2].

Maleic acid is industrially derived by hydrolysis of maleic anhydride, maleic anhydride is produced by oxidation of benzene or butane.

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 [3].

Maleic acid (MA) is a dicarboxylic acid and acts as bidentate ligand resulting in seven membered ring structures. There is often significant competition between hydrogen and metal ion for the donor sites. This situation results in the simultaneous existence of a number of equilibria, producing an array of successively protonated complexes [4].

Protonation constants of LPA calculated from solutions of low ionic strength [5] will almost certainly suffer from significant changes in activity during the course of the titrations.

Hence values quoted for the constants must be suspect. For reasonably precise values for formation constants, pH measurements should be precise to at least 0.01 pH units. So, an understanding of the protonation-deprotonation equilibria of LPA and MA is necessary before an attempt is made to investigate the metal-ligand equilibria associated with LPA and MA.

N, N-Dimethylformamide (DMF) is an organic compound and a common solvent for chemical reactions which is miscible with water and the majority of organic liquids.

It is a polar aprotic solvent with a high boiling point which facilitates reactions that follow polar mechanisms. It can be hydrolyzed by strong acids and bases, especially at elevated temperatures [6].

In the present study, protonation/deprotonation of L-phenylalanine and maleic acid were reported in the presence of DMF as a co-solvent.

II. METHODOLOGY

A. Experimental

- 1) *Chemicals and Standard Solutions:* All the chemicals used in this investigation were of analytical reagent grade purity. Solutions of 0.05 mol dm^{-3} L-phenylalanine (GR grade, Loba, India), 0.05 mol dm^{-3} maleic acid (GR grade, Loba, India), 0.2 mol dm^{-3} Hydrochloric acid (Merck, India), 0.4 mol dm^{-3} of sodium hydroxide (Merck, India) and DMF (Qualigens, India) were prepared. Sodium chloride (Merck, India) of 2.0 mol dm^{-3} was prepared to maintain the ionic strength in the titrand. Triple-distilled deionised water was used for preparation of all the solutions. All the solutions were standardized by standard methods. To assess the errors that might have crept into the concentrations, the data were subjected to analysis of variance of one-way classification (ANOVA) using the computer program COST [7]. The strength of the prepared carbonate-free sodium hydroxide solution was determined by titrating it against nitric acid solution using the Gran plot method [8].
- 2) *Alkalimetric Titrations:* The pH measurements of the proton–ligand systems were carried out in aqueous media containing varying compositions of organic solvent (DMF) in the range of 0–50% v/v maintaining an ionic strength of 0.16 mol dm^{-3} with sodium chloride at 303.0 K using a digital pH meter ELICO-LI120 type (readability 0.01). 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 L-phenylalanine, maleic acid (ligands) in the titrand are in the range of 0.25–0.50 mmol. The glass electrode was equilibrated in a well stirred DMF–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. In these titrations, the titrand consisted of mineral acid and ligand, in a total volume of 50mL. Titrations were performed by adding each time 0.1 cm^3 portions of 0.4 mol dm^{-3} sodium hydroxide to the titrand. The pH meter reading was recorded only after a constant value was displayed. Typical duplicate titrations showed that equilibration was fast and titration data did not differ by more than 0.02 units [9].
- 3) *Modeling strategy:* The approximate protonation constants of L-phenylalanine and maleic acid were calculated with the computer program SCPHD [10]. The best fit chemical model for each system investigated was arrived at using non-linear least squares computer program, MINQUAD75, which exploits 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 [11].

III. RESULTS AND DISCUSSION

The best fit models that contain the type of species and 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 the squares of deviations in concentrations of ligand and hydrogen ion at all experimental points) corrected for degrees 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.

For an ideal normal distribution, the values of kurtosis and skewness should be three and zero, respectively. The kurtosis values in the present study indicate that the residuals form nearer to leptokurtic as well as very few are platykurtic patterns. The values of skewness given in Table 1 are between -0.17 and 0.59 for LPA and -0.29 and 0.66 for MA.

These data evince that the residuals form a part of normal distribution; hence, the least squares method can be applied to the present data.

The sufficiency of the model is further evident from the low crystallographic R-values.

The statistical parameters thus show that the best fit models portray the acid–base equilibria of L-phenylalanine and maleic acid in DMF–water mixtures.

Table 4. 1: Best fit chemical models of acido-basic equilibria of LPA and MA in DMF-water mixture.

Temp= 303 K, Ionic strength=0.16 moldm⁻³

L-PHENYLALANINE (pH range 1.6 -11.5)								
% of DMF	011	012	NP	U _{corr} x10 ⁸	Skewness	Kurtosis	χ ²	R-factor
	Log β ₁ (SD)	log β ₂ (SD)						
0.0	9.27(1)	11.48(1)	72	1.857	-0.17	3.27	1.22	0.0096
10.0	8.80(2)	12.08(5)	25	10.43	0.24	2.88	2.16	0.0281
20.0	8.75(1)	11.86(2)	21	3.15	-0.05	2.87	2.95	0.0132
30.0	8.64(1)	11.59(3)	23	2.85	0.10	1.55	9.30	0.0142
40.0	8.71(2)	12.18(4)	47	15.11	0.59	3.57	5.40	0.0336
50.0	8.66(4)	12.85(8)	52	48.6	0.43	3.51	4.62	0.0582
MALEIC ACID (pH range 1.5 -10.00)								
0.0	6.15(1)	7.93(2)	102	6.8	-0.29	4.94	7.45	0.0151
10.0	6.73 (2)	10.07(4)	30	7.5	0.00	2.86	3.47	0.0227
20.0	6.48(2)	10.27(4)	48	1.30	0.43	3.09	8.17	0.0353
30.0	6.36(2)	9.91(3)	43	11.70	0.40	3.30	1.63	0.0306
40.0	6.13(1)	9.65 (3)	44	9.76	0.20	4.04	6.36	0.0293
50.0	6.13(3)	9.65(6)	48	3.5	0.66	2.99	1.33	0.0529

U_{corr} = U/ (NP-m) x 108; NP = number of points; m = number of protonation constants; SD = standard deviation.

A. Effect of Systematic Errors on Best fit Model

MINIQUAD75 does not have provision to study the effect of systematic errors in the influential parameters such as concentrations of reactants and electrode calibration on the magnitude of protonation constant. 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 concentrations of alkali, mineral acid and the ligands. The results of a typical system given in Table 2 emphasize that the errors in the concentrations of alkali affect the protonation constants more than the others.

Table 2: Effect of errors in influential parameters on the protonation constants in 20% v/v DMF-water mixture.

Ingredient	% Error	Log β (SD)			
		LPA		MA	
		LH	LH ₂	XH	XH ₂
Acid	0	8.75(1)	11.86(2)	6.48(2)	10.27(4)
	-5	Rejected	11.52(16)	5.80(13)	8.95(18)
	-2	8.59(42)	11.93(14)	6.00(12)	9.38(14)
	+2	8.84(10)	12.45(15)	Rejected	Rejected
	+5	9.04(40)	12.86(18)	6.48(13)	10.35(15)
Alkali	-5	Rejected	12.86(18)	6.65(13)	10.60(16)
	-2	8.86(12)	12.45(15)	6.33(12)	10.01(14)
	+2	8.57(12)	11.93(14)	5.94(12)	Rejected
	+5	8.35(13)	Rejected	5.67(14)	Rejected
Ligand	-5	8.67(12)	12.19(15)	5.99(12)	9.44(15)
	-2	8.70(12)	12.19(14)	6.07(12)	9.57(14)
	+2	8.73(12)	12.19(14)	6.19(11)	9.73(13)
	+5	8.76(12)	12.19(14)	6.28(11)	9.85(13)

B. Effect Of Dielectric Constant Of Solvent On Protonation Equilibria

Ligand protonation constants are strongly affected by the dielectric constant of the medium because of the fact that at least one of the constituents is charged and other is either charged or has a dipole moment [12]. Seleem *et al.* [13] and others [14] reported the effect of the reaction medium on protonation equilibria of different ligands. The change in dielectric constant varies the relative contributions of electrostatic and non-electrostatic interactions.

The apparent shift in the magnitude of protonation constants in organic media compared to aqueous solution was attributed to the creation of concentration gradient of protons between the interface and the bulk solution [15]. Furthermore, the presence of DMF is known to alter the dielectric constant of the medium, which has a direct influence on the protonation-de protonation equilibria [16,17,18]. In the present study, log Ks of both LPA and MA increased linearly (Fig. 1) as a function of the reciprocal of the dielectric constant (1/D) of DMF-water mixtures.

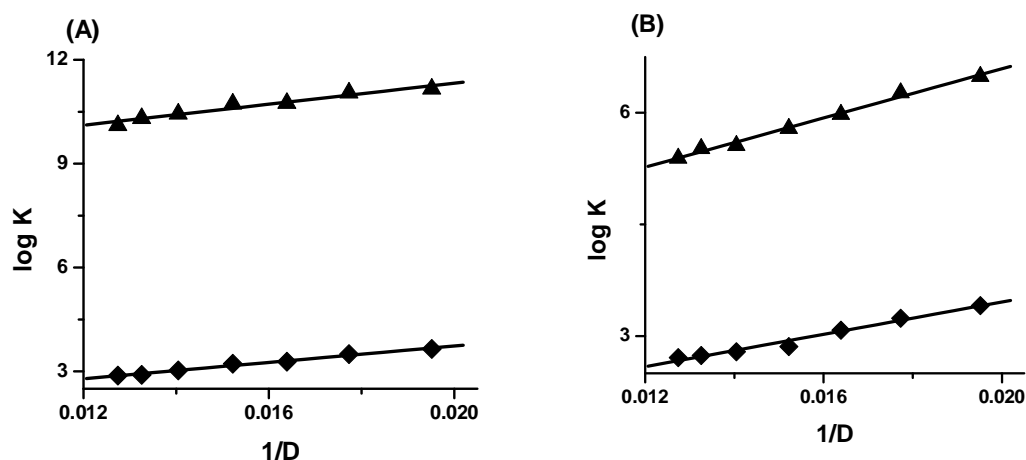


Fig.1: Variation of stepwise protonation constant (log K) with reciprocal of dielectric constant (1/D) of solvent. (A) LPA and (B) MA in DMF-water mixture (◆) log K₁ and (▲) log K₂.

C. Formation Functions

The protonation constants and number of equilibria (Figure 4) could be determined from the secondary formation functions like average number of protons bound per mole of ligand \bar{n}_H . Plots of \bar{n}_H versus pH for different concentrations of the ligand should overlap if there is no formation of polymeric species. The overlapping of formation curves for L-phenylalanine and maleic acid (Figure 4A and 4B) rule out the polymerization of the ligand molecules.

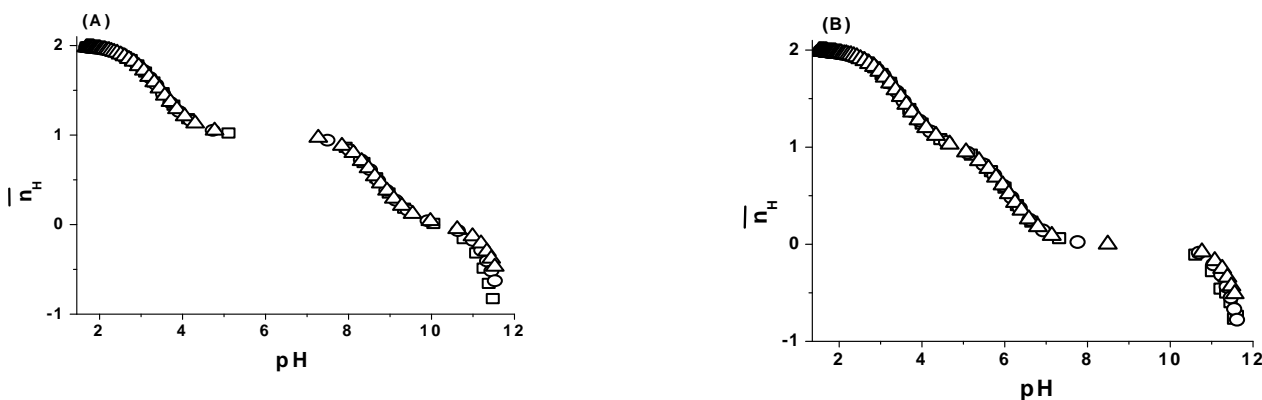


Fig.2: Formation curves of (A) LPA, (B) MA in 20% v/v DMF. Ligand concentrations (in mmol) 0.25 (□-□), 0.375(○-○) and 0.50 (Δ-Δ).

The number of moles of alkali consumed per mole of the ligand denoted by a , is another secondary formation function like $\overline{n_H}$. A curve of a versus pH gives the number of equivalents of alkali consumed per mole of ligand. The negative values of a correspond to the excess of mineral acid present in the titrand and the number of associable protons, whereas the positive values correspond to the dissociable protons. The maximum value of a is 2 for MA and 1 for LPA which indicates that maleic acid has two dissociable protons and phenylalanine has 1 dissociable proton.

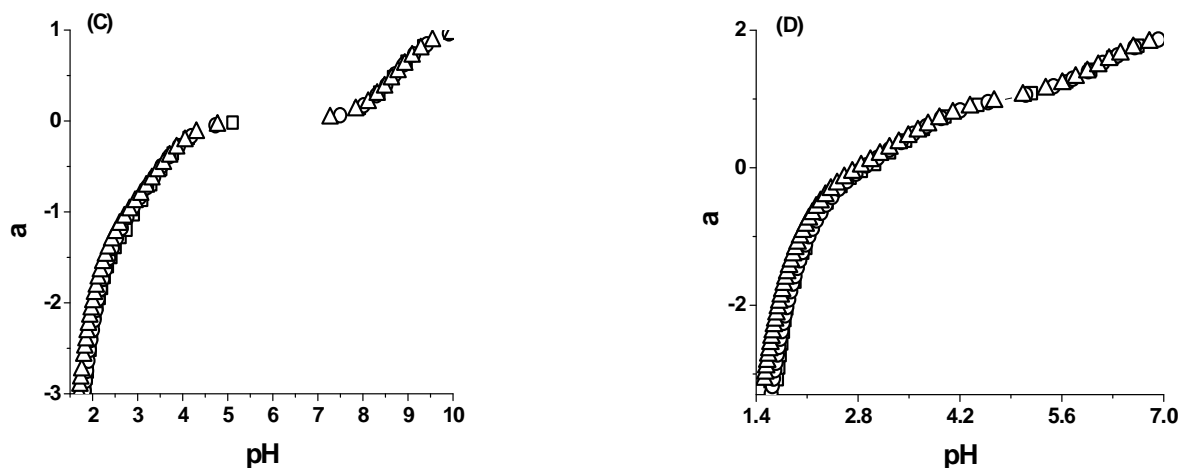


Fig.3: Number of moles of alkali versus pH curves of (C) LPA, (D) MA in 20% v/v DMF. Ligand concentrations (in mmol) 0.25 (□-□), 0.375(○-○) and 0.50 (Δ-Δ).

The protonation-deprotonation equilibria of LPA and MA are shown with the pH ranges of existence of the species in Fig.4. In these equilibria LPA can exist in anionic, zwitterionic and cationic forms, whereas MA can exist in only anionic or neutral form at different pH ranges. These observations can be explained as follows. When LPA and MA are successively protonated, the charge of the species is decreased and low dielectric medium favors the protonation reaction, due to dominant electrostatic interactions. Thus, decrease in dielectric constant of the medium increased the protonation constants.

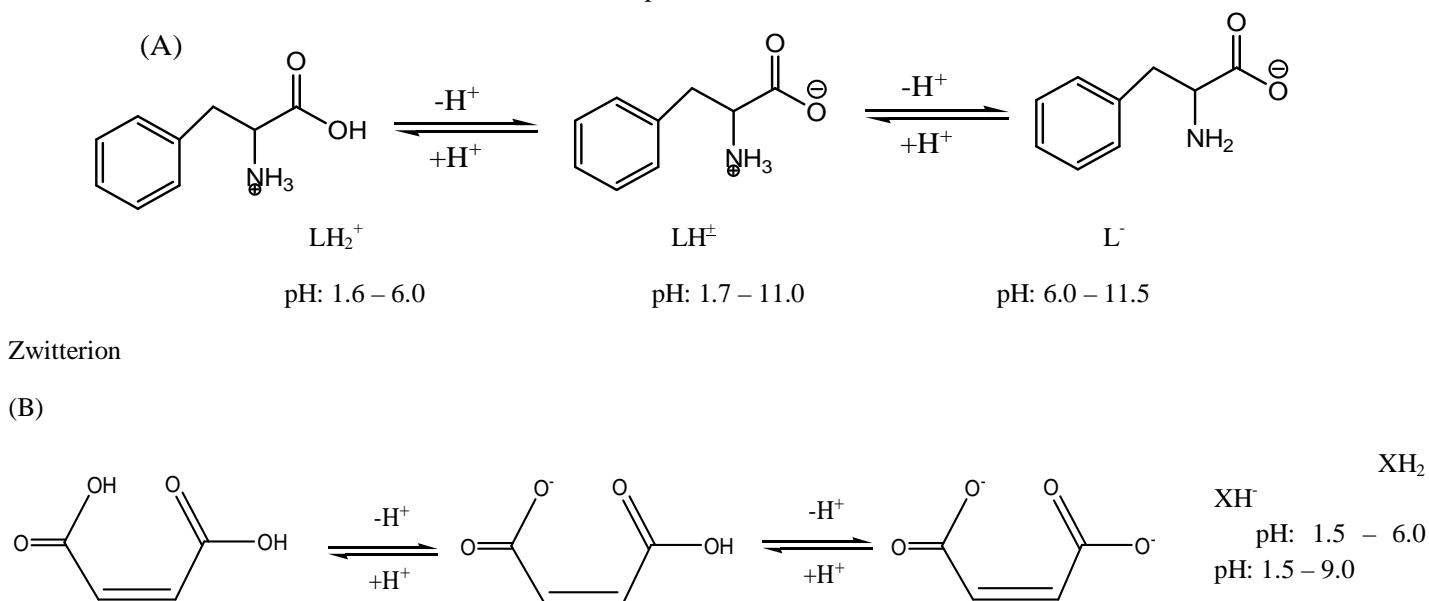


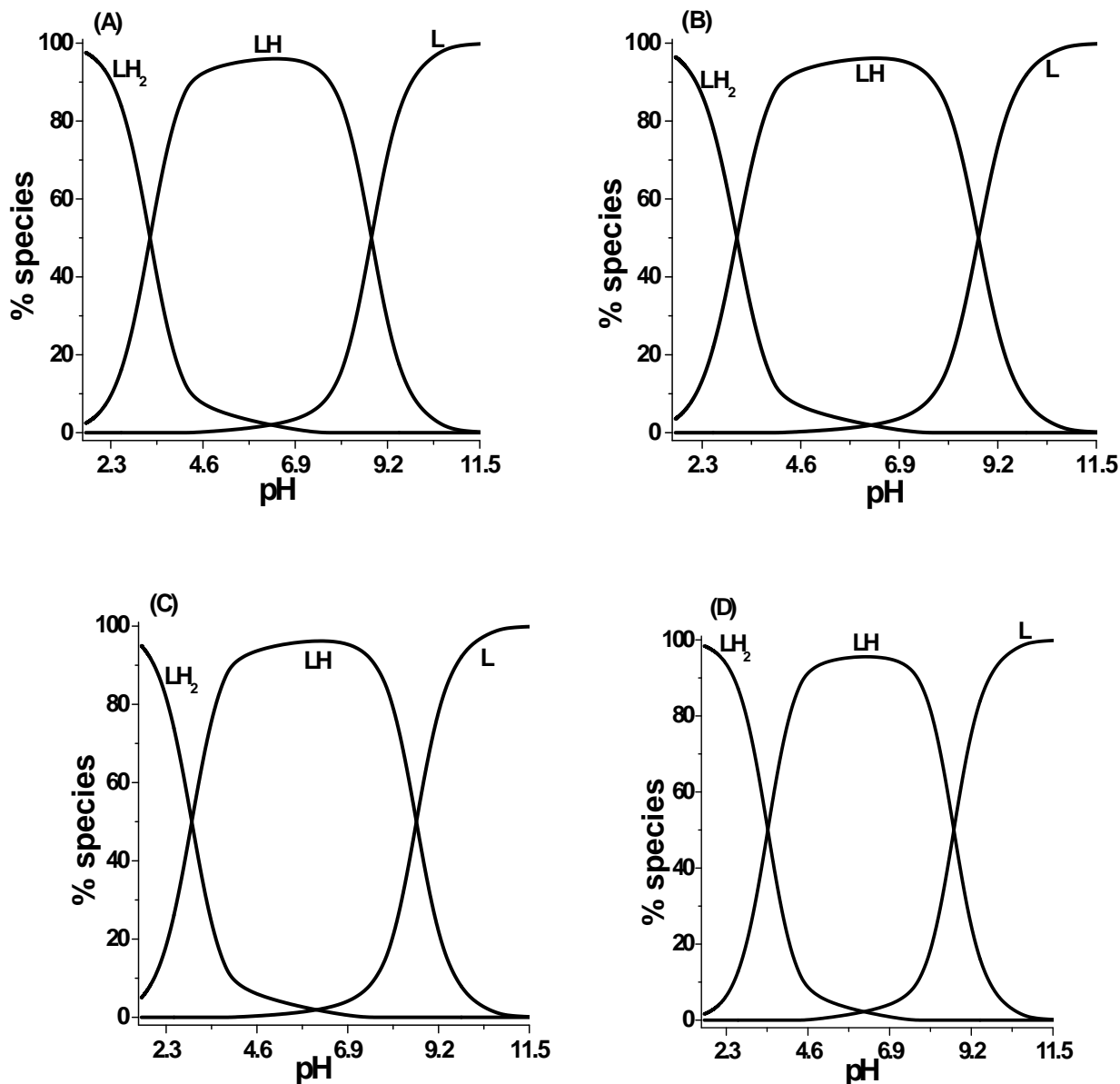
Fig.4: Protonation-deprotonation equilibria of (A) LPA and (B) MA

D. Distribution Diagrams

Distribution diagrams-plots of percentage or fraction of species as a function of free concentrations of ingredients (pH, pL or pM) are not only of theoretical interest but find practical utility in a variety of chemical problems.

L-Phenylalanine has one dissociable proton and one amino group which can associate with a proton. It exists as LH_2^+ at low pH and gets deprotonated with the formation of LH and L^- successively with increase in pH.

Maleic acid has two dissociable protons. It exists as XH_2 at low pH and gets deprotonated with the formation of XH^- and X^{2-} successively with increase in pH. Typical distribution plots in DMF- water mixtures given in Fig.2 and 3 show the existence of LH_2^+ , LH and L^- for LPA and XH_2 , XH^- and X^{2-} for MA respectively. In the case of LPA, the zwitterionic form LH^\pm is present to an extent of 80-90% in the pH ranges 1.7–11.0. The XH^- form MA is present to an extent of 80-90% in the pH range 1.5–9.0.



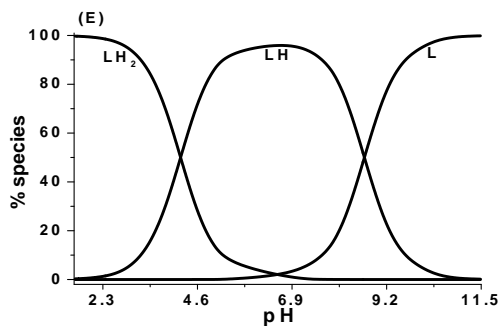


Fig.5: Distribution diagrams of LPA in DMF-water mixtures % v/v.

(A) 10, (B) 20, (C) 30, (D), 40 and (E) 50

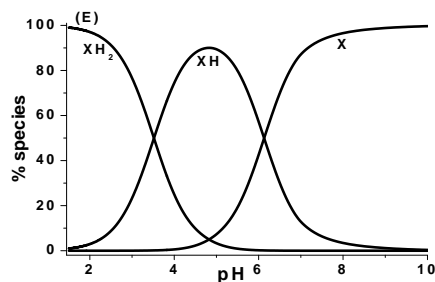
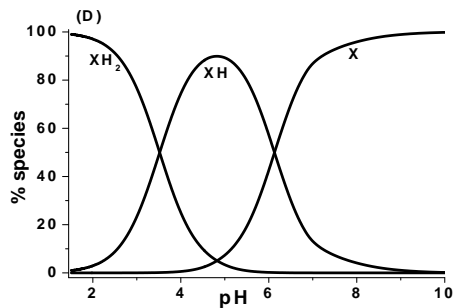
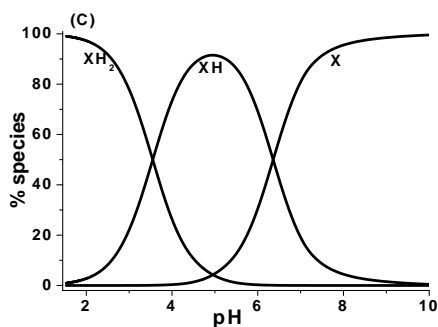
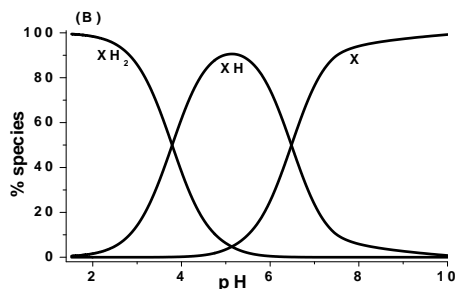
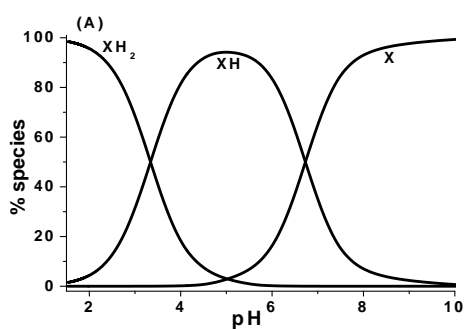


Fig.6: Distribution diagrams of MA in DMF-water mixtures % v/v.

(A) 10, (B) 20, (C) 30, (D) 40, and (E) 50.

IV. CONCLUSIONS

L-phenylalanine forms LH^{2+} at low pH and get deprotonated with the formation of LH and L^- successively with increase in pH. Maleic acid also forms XH_2 at low pH gets deprotonated with the formation of XH^- and X^{2-} with increase in pH. The linear variation of log values of stepwise protonation constants with mole fraction of DMF in DMF–water mixtures indicates the dominance of electrostatic forces in protonation and deprotonation equilibria. The log Ks of both LPA and MA increased linearly as a function of the reciprocal of the dielectric constant ($1/D$) of DMF-water mixtures. The protonation constants and number of equilibria could be determined from the secondary formation functions like average number of protons bound per mole of ligand nH and number of moles of alkali consumed per mole of ligand (a). The effect of errors in the influential parameters on the protonation constants shows that the errors in the concentrations of alkali and mineral acid affect the protonation constants more than that of the ligand.

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