A pH METRIC DETERMINATION OF PROTONATION CONSTANTS OF MERCAPTOSUCCINIC ACID IN DIMETHYLFORMAMIDE AND ACETONITRILE -WATER MIXTURES

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ABSTRACT

The protonation constants values of mercaptosuccinic acid were determined in Dimethyl formamide and Acetonitrile - water mixtures (0–60% v/v) at 303.0 K at an ionic strength of 0.16 M using pH-metric technique. The protonation constants were calculated with the computer program MINIQUAD75 and selection of the best fit chemical models was based on the statistical parameters. The log K values were found to be an increase with increase of the organic solvent content. The linear variations of the protonation constants with the reciprocal of the dielectric constant of the medium have been attributed to the dominance of electrostatic forces. Distribution of species, protonation equilibria and effect of influential parameters on the protonation constants have also been presented.

Keywords: Mercaptosuccinic acid, Dimethylformamide, Acetonitrile, protonation constant, dielectric constant

INTRODUCTION:

Mercaptosuccinic acid as a ligand, has been of interest because of its versatility in coordinate modes due to two carboxylic acids and sulfhydryl groups (1). More recently, it has been used in the synthesis of novel polyanionic inhibitor of HIV and other viruses (2).Thiomalic acid is used as a brightening agent of metal plating.

Mercaptosuccinic acid (MSA) or thiomalic acid (HOOC-CH(SH)-CH_2-COOH) is a dicarboxylic acid containing a thiol functional group (-SH group) instead of an -OH group in malic acid (3). It is an important organic compound with multifunctional intermediate in organic synthesis. It is widely used in the synthesis of various biologically active sulfur containing compounds such as the antileukemic spiro [indoline-3,2'-thiazolidine]-2,4'-diones (4), antimicrobial (5,6) and antitubercular 4-thiazolidinones. It is also used as a building block in the synthesis of novel polyanionic inhibitors of human immunodeficiency virus and other viruses (7) and as a starting material in the synthesis of isocysteine, an important non-proteinogenic amino acid in a potent peptide inhibitor of stromelysin (8). In addition, sodium salt of the anionic Au (I) complex of 2-mercaptosuccinic acid is an effective antiarthritic drug (9). MSA is widely applied in industry and technology as corrosion inhibitor, electrolyte for electroplating bath and components of bleach-fixing baths for photographic films and as active materials for depilatories and hair straightening (10).

The composition and stability of zinc complexes of thiomalic acid was studied by using potentiometer and conductivitymeter (11).
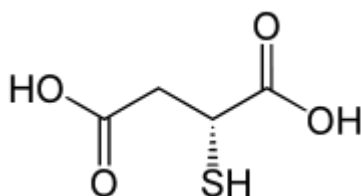

Fig: Structure of 2-mercaptosuccinic acid

The dicarboxylic reductant, MSA was one of the thiols chosen since there are three species existing in solution with different charges over the pH range. It may exist as double or singly protonated form or as the dianion having the two carboxylates deprotonated (12). The determination of protonation constants of MSA is important in understanding its physico-chemical behavior and its an interaction with metals under low dielectric constants in organic solvent-water mixtures, because it is known

that such mixed solvents produce a solvent with quite different properties, both physically (dielectric, density and viscosity) and chemically (acid-base and donor-acceptor properties) and provide a better model for *in vivo* reactions (13-14). In this experiment, the protonation constants of mercaptosuccinic acid have been determined pH-metrically in aqueous solutions containing Dimethylformamide (DMF) and Acetonitrile (AN), which are binary mixtures used as a solvent frequently in pharmaceutical industry and biochemistry)

AN is a weak base (15) and a much weaker acid (16) than water. Anions have lower solvation energies in AN than in water, except in those cases where there is specific interaction with the solvent, thus cations are reduced at considerably more positive potential (17) in AN than in water. It is a protophobic dipolar aprotic solvent and it does not form any hydrogen bond with solute species. The protophobic character of AN may arise from the possible formation of dimers which are shown to exist from IR studies (18). Acid-base equilibria and dissociation behavior of various acids in acetonitrile medium have been studied using spectrophotometer and conductivitymeter (19). Proton acceptor power and homo conjugation of mono- and diamines in acetonitrile as solvent was studied (20). Dielectric constants of water + acetonitrile have been measured from 308.15 to 278.15 K over the entire composition range. Their deviations from ideality have been determined (21).

DMF was first prepared in 1893 by the French chemist Albert Verley. It is a compound formed by the substitution of the hydroxyl group of formic acid with dimethylamino group and the molecular formula $HCON(CH_3)_2$. It is a clear, transparent and high-boiling point liquid with a light amine flavor and a relative density of 0.9445 (25°C). It is soluble in water and most of the organic solvents (22) that are used as a common solvent for chemical reactions. In Petroleum Industry DMF can be used as a gas absorbent for separating and refining gases. In Pesticide and Pharmaceutical industries DMF finds application as an intermediate of organic synthesis. It is also used as a catalyst in carboxylation reactions, in organic synthesis, as a quench and cleaner combination for hot-dipped tin parts (e.g., for high-voltage capacitors), as an industrial paint stripper and in inks and dyes in printing and fibre-dyeing applications (23-24).

EXPERIMENTAL:
Chemicals and Standard Solutions

All the chemicals used in this investigation were of Analytical Reagent grade purity. Triple distilled deionized water was used for the preparation of all the solutions. 0.05 M Solution of mercaptosuccinic acid (HIMEDIA) was prepared by maintaining 0.05 M Hydrochloric acid concentration to increase the solubility. DMF and AN (Merck, India) were used as received. 0.2 M Hydrochloric acid (Merck, India) solution was prepared. 2.0 M Sodium chloride (Merck, India) was prepared to maintain the ionic strength in the titrand, 0.4 M Sodium hydroxide (Merck, India) was used as titrant.

The acid and base solutions were standardized by standard methods. Thus, the concentration of the alkali was determined by titrating it with standard oxalic acid and potassium hydrogen phthalate solutions, while the normality of hydrochloric acid was determined using standardized sodium hydroxide and the primary standard borax solutions. The concentration of the carbonate-free sodium hydroxide solution was determined by titrating it against hydrochloric acid solution using the Gran plot method (25).

Titration:
The pH measurements of proton-ligand system was carried out in aqueous media containing varying compositions of organic solvent (DMF or AN) in the range of 0–60% v/v maintaining an ionic strength of 0.16 M with sodium chloride at 303.0 ± 0.1 K using a Digital pH meter Elico - MKVI type (readability 0.01) with mechanical stirring carried by a teflon stirrer. The pH metric titration assembly consisted of a double walled spoutless pyrex glass vessel of 100 ml capacity fitted with a perspex lid through which the glass combination pH electrode, gas inlet-outlet tubes and burette tip were admitted. Potassium hydrogen phthalate (0.05 mol) and borax (0.01mol) solutions were used to calibrate the pH meter. In each titration, the titrand consisted of approximately 1 mmol of hydrochloric acid in a total volume of 50 ml. The amounts of MSA in the titrands ranged between 0.25 and 0.50 mmols. The glass electrode was equilibrated in a well stirred organic solvent-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 details of the experimental procedure and titration assembly used in our laboratory have been given elsewhere (26).

RESULTS AND DISCUSSION:
BEST FIT MODELS
The computer program SCPHD (27) was used to calculate the correction factor applied to pH meter dial reading to calculate approximate protonation constants of mercaptosuccinic acid. The best fit chemical model for each system investigated was arrived at using non-linear least-squares computer program, MINIQUAD75 which exploits the advantage of constrained least squares method in the initial refinement and reliable convergence of Marquardt algorithm (28-29). The variation of stepwise protonation constants was analyzed mainly on electrostatic grounds on the basis of solute-solute and solute-solvent interactions.

The results of best fit models that contain the type of species and overall protonation constants of MSA along with some important statistical parameters are given in Table 1. A low standard deviation in logβ values indicates the precision of these parameters. The small values of Ucorr (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 system confirm 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 leptokurtic patterns. The values of skewness recorded in the table are between -0.04 and 2.43. These data evince that the residuals form part of a 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.

Thus, the statistical parameters show that the best fit models represent the acid-base equilibria of MSA acid in both DMF and AN-water mixtures.

Table 1: Best fit model of protonation equilibria of MSA in 0-60% AN- and DMF-water mixtures

%V/V AN	Log βMLXH(SD)			NP	$U_{Corr} \times 10^8$	Skewness	Kurtosis	χ^2	R-Factor	pH Range
	LH₃	LH₂	LH							
In AN										
0.0	18.60(4)	15.68(4)	10.79(4)	228	2.00	-0.43	4.56	64	0.005	1.55-10.5
10	20.26(5)	16.63(5)	11.16(2)	169	1.40	-0.04	8.2	65.24	0.01	2.00-10.5
20	19.09(2)	15.95(2)	10.98(2)	210	0.94	-0.05	3.48	19.77	0.006	2.00-10.5
30	18.82(3)	15.48(2)	10.60(2)	268	1.74	2.43	11.36	124	0.009	1.8-10.5
40	19.91(4)	16.21(3)	11.04(2)	326	2.91	-1.21	11.82	92	0.01	1.5-11.5
50	20.61(5)	16.59(4)	11.18(2)	334	3.25	-1.17	11.98	87	0.01	1.67-11.5
60	21.35(1)	16.90(9)	11.18(7)	364	5.81	2.25	7.27	67	0.02	1.47-11.0
In DMF										
0.0	18.60(4)	15.68(4)	10.79(4)	228	2.00	-0.43	4.56	64	0.005	1.55-10.5
10	18.90(7)	15.27(6)	10.46(3)	186	3.7	1.86	5.18	147	0.01	1.58-11.00
20	18.88(3)	15.39(2)	10.50(1)	184	1.6	1.29	6.11	50	0.008	1.58-11.00
30	18.64(6)	15.06(5)	10.11(3)	163	3.05	-0.49	4.72	83	0.018	1.8-10.5
40	18.52(6)	15.00(5)	10.12(3)	202	3.6	-1.05	4.28	102	0.02	1.7-11.5
50	22.41(1)	17.80(7)	11.66(7)	153	4.49	0.57	4.15	43	0.024	1.67-11.5
60	24.38(1)	18.85(1)	11.30(4)	104	8.22	0.28	3.28	13.08	0.044	1.47-11.0

The primary alkalimetric titration data were simulated and compared with the experimental alkalimetric titration data, to verify the sufficiency of the model. The overlap of the typical experimental and simulated titrations data given in Figure 1 indicates that the proposed models correctly represent the experimental data collected from the refinements carried in the pH rang of 1.5 to 11.5
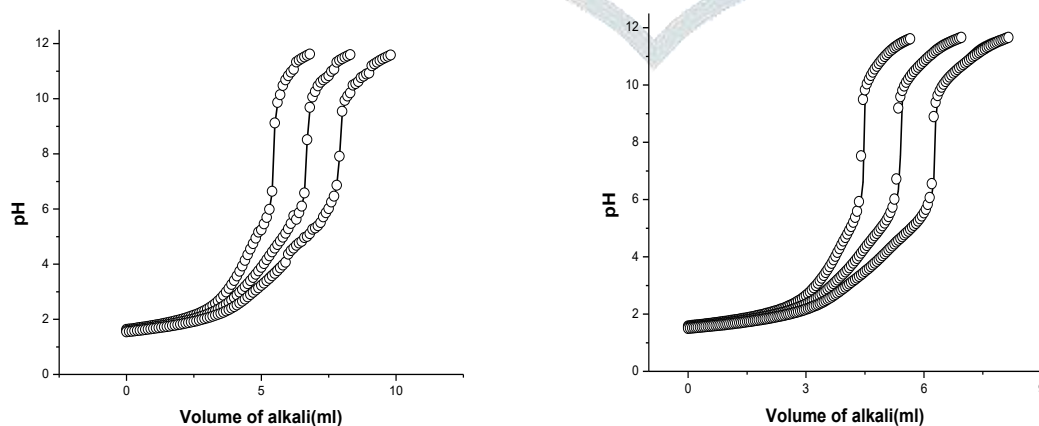

Figure 1. Simulated (o) and experimental (solid line) alkalimetric titration curves of MSA in 30% v/v organic solvent; (A) AN and (B) DMF: (a) 0.25, (b) 0.375 and (c) 0.50 mmol, respectively

Effect of systematic errors on best fit model :

Any variation in the concentrations of ingredients like alkali, mineral acid and the ligand affects the magnitudes of protonation constants. Such parameters are termed as an influential parameters. MINIQUAD75 does not have provision to study the effect of systematic errors in the influential parameters 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 mineral acid, alkali, and ligand volume. 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 the ligand and volume of the solution. Increased standard deviations in the protonation constants with increased errors in the concentrations of the ingredients corroborate the appropriateness of the experimental conditions. Statistically the best chemical models that represent acid-base equilibria under study should have very low standard deviation in their protonation constant (log β) values that indicate the precision of the parameters. The increased standard deviation in protonation constants and even rejection of some species on the introduction of errors confirms the correctness of the proposed models. This type of investigation is significant as the data acquisition was done under varied experimental conditions with different accuracies.

Table-2: Effect of errors an influential parameters on protonation constants of L-Dopa in 30%v/v Acetonitrile-water and DMF-water mixtures.

Ingredient	%of error	MSA in Acetonitrile			MSA in DMF		
		β1(SD)	β2(SD)	β3(SD)	β1(SD)	β2(SD)	β3(SD)
Alkali	**0**	10.60(02)	15.48(02)	18.82(03)	10.16(03)	15.86(05)	18.64(06)
	-5	10.71(04)	15.66(05)	19.06(05)	10.23(03)	15.18(05)	18.82(06)
	-2	10.64(02)	15.55(03)	18.91(03)	10.19(03)	15.10(04)	18.72(05)
	2	10.57(02)	15.43(03)	18.75(03)	10.13(04)	15.02(06)	18.58(07)
	5	10.53(03)	15.36(04)	18.65(05)	10.10(05)	14.97(07)	18.50(09)
Acid	**0**	10.60(02)	15.48(02)	18.82(03)	10.16(03)	15.86(05)	18.64(06)
	-5	10.54(03)	15.40(03)	18.67(04)	10.12(05)	15.00(07)	18.53(08)
	-2	10.58(02)	15.45(02)	18.76(03)	10.14(04)	15.03(05)	18.60(07)
	2	10.63(02)	15.52(03)	18.89(04)	10.17(03)	15.08(04)	18.69(05)
	5	10.67(04)	15.60(05)	19.01(05)	10.20(03)	15.13(04)	18.77(05)
Ligand	**0**	10.60(02)	15.48(02)	18.82(03)	10.16(03)	15.86(05)	18.64(06)
	-5	10.58(02)	15.45(03)	18.78(03)	10.14(04)	15.03(05)	18.61(06)
	-2	10.59(02)	15.47(02)	18.81(03)	10.15(03)	15.05(05)	18.63(06)
	2	10.61(02)	15.50(02)	18.84(03)	10.17(05)	15.07(05)	18.66(06)
	5	10.63(02)	15.53(03)	18.87(03)	10.18(03)	15.09(04)	18.68(05)

Protonation equilibria:

The step-wise protonation constants and number of equilibria can be determined from the secondary formation functions such as average number of protons bound per mole of ligand ($\bar{n}_H$). The pH values at half integral values of $\bar{n}_H$ correspond to the protonation constants of the ligand and the number of half integrals in the pH range of the study corresponds to the number of equilibria. Thus, three half integrals (0.5, 1.5 and 2.5) in the versus pH curve of Figure 2 conform the presence of three protonation-deprotonation equilibria. The maximum value of in the formation curve of Figure 2 is three, which clearly shows that MSA has three bound protons per molecule.

The typical distribution plots (Figure 2) produced using the protonation constants from the best fit models given in Table I show the existence of, and *L* species. The *LH2* species is predominant at low pH and its amount decreases exponentially and becomes almost zero around pH 6, and exists in the pH ranges 2.0–9.0. The most predominant species, form of mercaptosuccinic acid is present to an extent of 90% starting around pH 3.0. The free ligand (*L*) concentration progressively increases starting from around pH 9.0 and attains its maximum at higher pH in both the media. The plotting percent of species vs. pH could be also used to approximate protonation constants because at the upper intersections where the points [LHn] =[LHn-1] occurs at a pH values equal to the protonation constants.
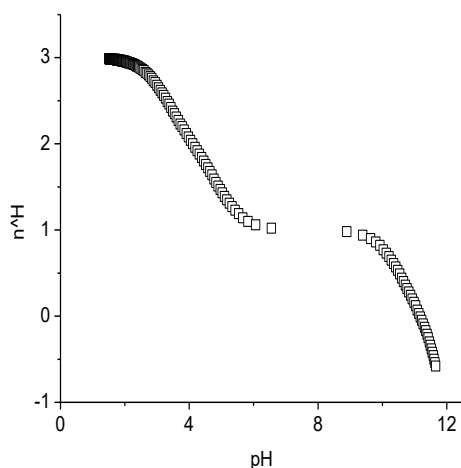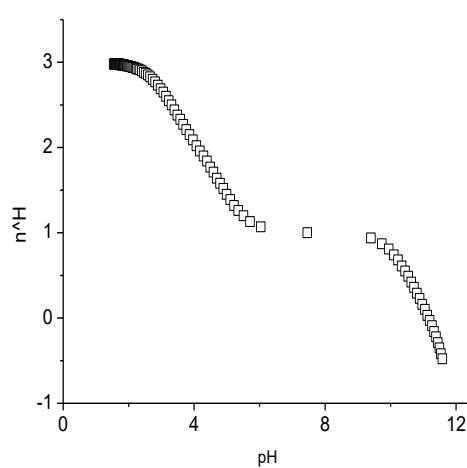
<center>Fig-2(a)   Fig-2(b)</center>

Figure-2: Formation function plots of protonated and deprotonated MSA species in 30.0% v/v AN-water [2(a)] and DMF-water mixtures [2(b)]
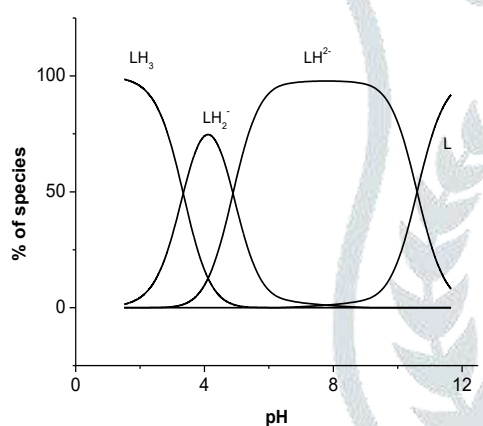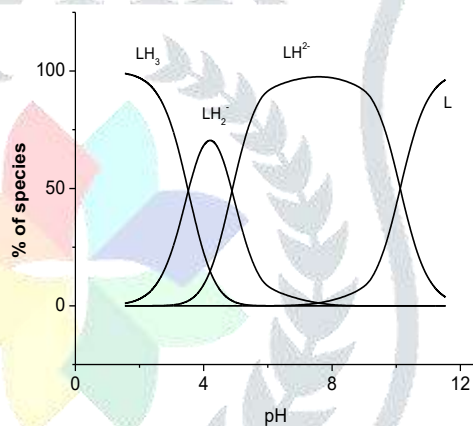

<center>Fig-3(a)   Fig-3(b)</center>

Figure-3: Distribution diagrams of protonated and deprotonated MSA species in 30.0% v/v AN-water [3(a)] and DMF-water mixtures [3(b)]

The protonation-deprotonation equilibria of MSA and pH ranges of existence of the species are shown in Figure 4 in which MSA loses carboxylic and thiol protons successively as the amount of alkali added increases.
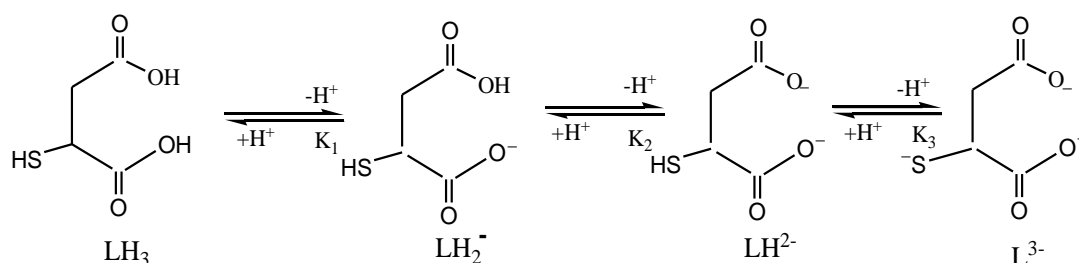

Figure-4 Protonation-deprotonation equilibria of 2-mercaptosuccinic acid

Effect of Solvent:

The reaction medium is one of the most important influencing factors in determining the equilibrium constants. The solvent effect on protonation constants could be explained on the basis of dielectric constant of the medium, solvent structure, preferential solvation, and microscopic parameters(30-32). The variation of protonation constant or change in free energy with the organic solvent content depends up on two factors: electrostatic one, which can be estimated by the Born's equation(33) and non-electrostatic one, which includes specific solute-solvent interactions. When the electrostatic effects dominate the equilibrium

proceeds, according to Born's equation, the energy of electrostatic interaction is related inversely to dielectric constant(34) Hence, the logarithm of step-wise protonation constant (log K) should vary linearly as a function of the reciprocal of the dielectric constant ($1/D$) of the medium.

It is observed that in both the media the log K values of mercaptosuccinic acid increase linearly as the content of organic solvent increases. The result is in agreement with those reported in the literature for the media containing pure water as solvent(35-37) but the small differences are possibly due to the different experimental procedures, temperature and different background electrolytes used. In this study, the linear variation of log K values as a function of 1/D (Figure 4) in both AN- and DMF- water mixtures shows the dominance of electrostatic interactions. This linear increase can be attributed to ion-association reaction, solute-solvent interactions, proton-solvent interactions and solvent basicity (acidity) effects.
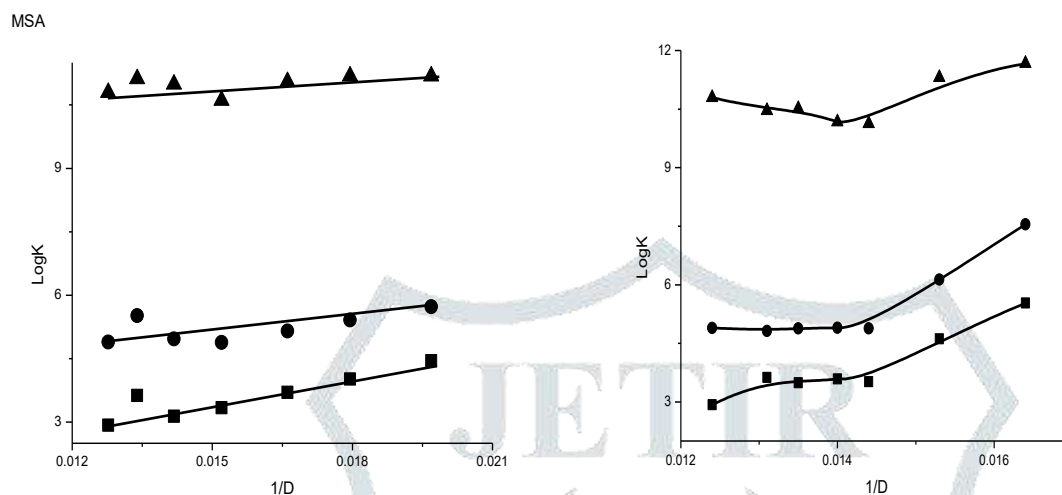

Figure 5. Variation of step-wise protonation constant (log K) of MSA with reciprocal of dielectric constant (1/D) in AN-water 5(a) & DMF-water mixture 5(b): (■) log K_1, (●) log K_2 and (▲) log K_3

CONCLUSIONS :

Mercaptosuccinic acid has three dissociable protons *exists* in LH$_3$ form at low pH and gets deprotonated with the formation of L^{3-}, and species, successively, with increase in pH. The linear variation of log values of stepwise protonation constants with decreasing dielectric constant of the media confirms the dominance of electrostatic forces in the protonation-deprotonation equilibria of MSA acid. The effect of systematic 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 those in the concentration of ligand and volume of the solution.

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