



The Impact of Mixed Solvents on Protonation Equilibria of Mercaptosuccinic Acid in Ethylene Glycol – Water Media

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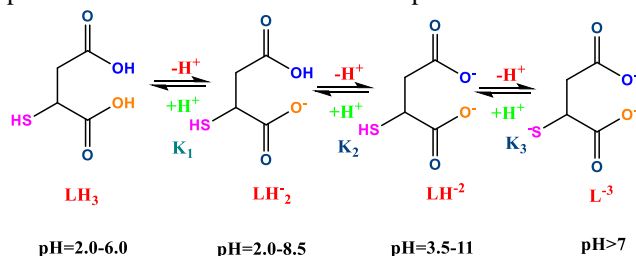
MINIQUAD75

Protonation constant

dielectric constant

ABSTRACT

The protonation constants values of mercaptosuccinic acid were determined in ethylene glycol and water media (0-60% v/v) at 303.0 K at ionic strength of 0.16 M using pH metric technique. The protonation constants were calculated with the computer program MINIQUAD 75 and selection of the best fit chemical models were arrived based on the statistical parameters. The log K values were found to 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 has also been reported.



Protonation deprotonation equilibria of Mercapto Succinic Acid

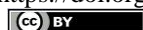
1. Introduction

The protonation constants of physiologically active ligands in various media will be informative. Identifying the pH range where the compounds ionise the least allows you to isolate a substance with maximum yield. Protonation of a newly formed molecule can reveal its structure. The proposed structure may be valid if theoretical protonation constants match experimental values. The protonation constants are needed to make pH buffers[1].

They are determined using conductometry, spectrophotometry, and potentiometry [2,3,4]. This method can also be used to calculate complex stability constants of physiologically active metal ligands[5]. Calculating ionised species concentrations at any pH requires knowledge of chemical equilibrium constants. 2-Sulfonylbutanedioic acid (2-Mercaptosuccinic acid or MSA) is a dicarboxylic acid differs from malic acid by having a thiol functional group (-SH group), as illustrated

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in Figure 1a [6]. Organic synthesis relies heavily on this important organic compound, which is used as a multifunctional intermediate. The two carboxyl groups allow MSA to act as a reducing agent, while the thiol derivative allows it to act as a capping agent[7]. Another feature of MSA is its use as a sulfur-containing ligand in

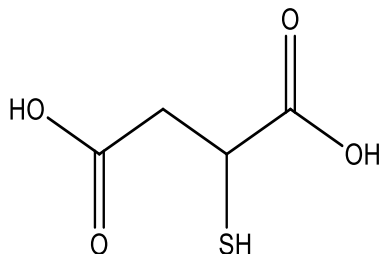


Figure - 1a. Structure of mercaptosuccinic acid

pH-metric investigations of several binary and ternary metal complexes [8-17]. MSA works best at physiological pH. MSA has two carboxylic and one thiol functional groups. They are protonated thiol first, then two carboxylic groups.

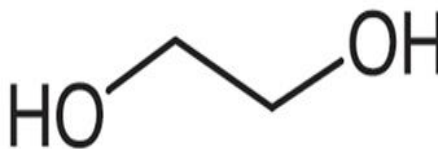


Figure 1b. Structure of ethyleneglycol

There is a wealth of information on bioligand protonation and stability constants[18-31]. But mixed solvent research could add to the body of knowledge on bioligand chemistry in water. Water-organic solvent mixtures are popular due of their versatility. Synthesis, titrations, and liquid chromatographic separations all use these solvent combinations. As proton carriers, solvent molecules are vital in chemical and biological reactions. Data on protonation constants will help us comprehend biology. So, studies in non-water media should help understand bioligand chemistry in living systems.

Aqueous solutions containing Ethylene glycol (EG), a binary mixture commonly used as a solvent in industries, were used to determine the protonation-deprotonation equilibrium of MSA pH-metrically. Enzyme and protein active site cavities can be studied using this type of research.

2.RESULTS AND DISCUSSION

2.1.Protonation Equilibria

Stepwise protonation constants and equilibrium numbers were estimated using secondary formation functions (typical number of protons bound to a mole of ligand). To calculate the protonation constants of a ligand, divide the number of equilibrium states by the number of half integrals in the pH range of interest. Three half integrals (0.5, 1.5, and 2.5) vs pH for MSA confirm three protonation–deprotonation equilibria. There are three protons bounded per one MSA molecule in the studied pH range as revealed from Figure 2. Figure 3 shows the presence of LH_3 , LH_2^- , LH^- , and L^{3-} for MSA using the best fit protonation constants from Table 1. The protonation – deprotonation equilibria of MSA in 0-60% v/v EG-Water mixture were developed and shown in Figure 4.

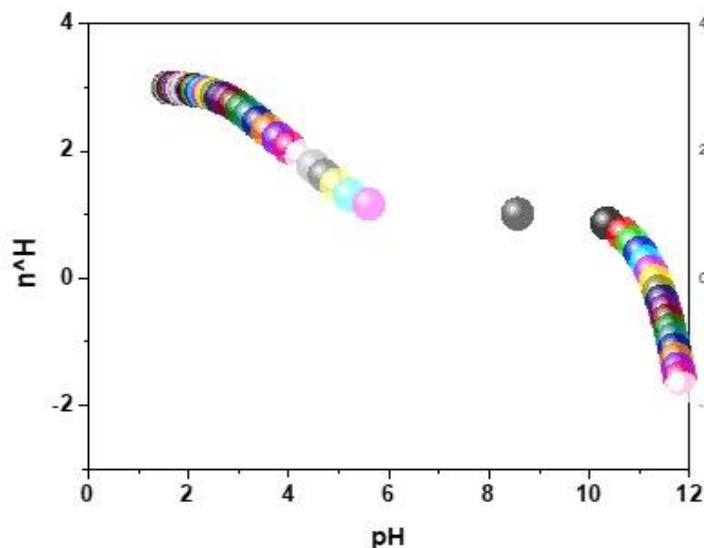


Figure 2. Formation function plots of MSA in 40.0% v/v EG-water mixture

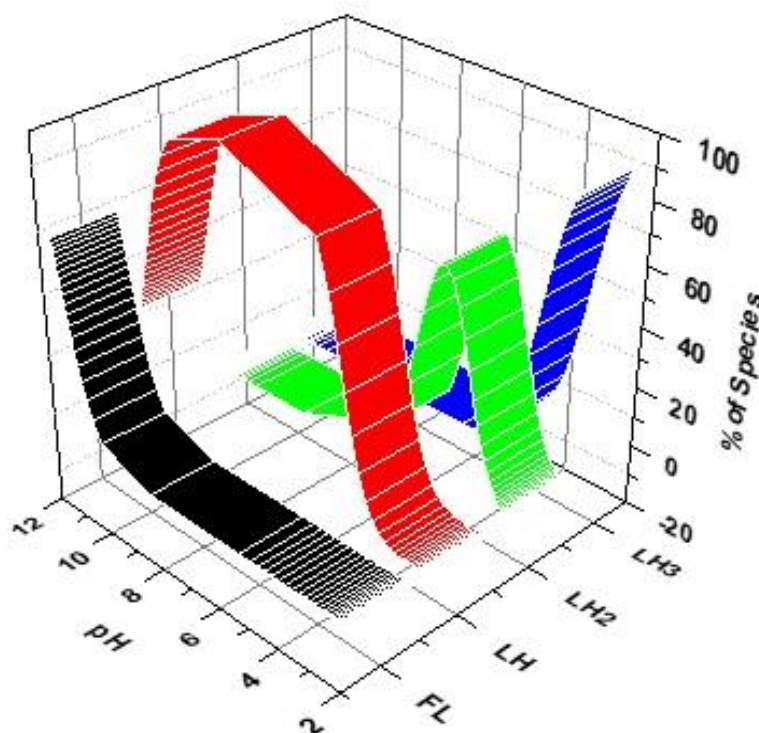


Figure 3. Distribution of diagram of protonated and deprotonated species for MSA in 40.0% v/v EG-water mixture

2.2. Effect of solvent

Equilibrium constants vary depending on the reaction media and must be considered. For acid-base equilibria, electrostatic and non-electrostatic effects are usually explored [38,39,40]. The solvent's structure, effect on protonation constants, and microscopic factors may account for protonation constant fluctuation. With organic solvent concentration, both electrostatic and non-electrostatic variables contribute to protonation constant deviation. Born's equation [41] states that electrostatic energy is inversely proportional to dielectric constant.

Thus, the logarithm of stepwise protonation constants ($\log K$) should be directly related to the reciprocal of the medium's dielectric constant. The $\log K$ values rise linearly with increasing of percentage of organic content in pure water [42,43,44,45]. Figure 5 show how electrostatic interactions dominate $\log K$ values in mixtures. Increasing solvent basicity (acidity) causes the linear increase. The variation in $\log K$ values with percentage of solvent for MSA have been calculated using the formula (Eq. 1) and results are tabulated in Table – 3.

$$\begin{aligned}
 \log K_1 &= \log \beta_3 - \log \beta_2 \\
 \log K_2 &= \log \beta_2 - \log \beta_1 \quad \text{-----(1)} \\
 \log K_3 &= \log \beta_1
 \end{aligned}$$

Table 3. The variation of $\log K$ values of MSA in 0-60% v/v EG -Water mixtures

% of Solvent	$\log K_1$	$\log K_2$	$\log K_3$
0	2.89	4.36	10.96
10	2.93	4.39	11.12
20	2.99	4.40	11.28
30	3.04	4.43	11.48
40	3.06	4.52	11.62
50	3.08	4.55	11.85
60	3.14	4.57	12.06

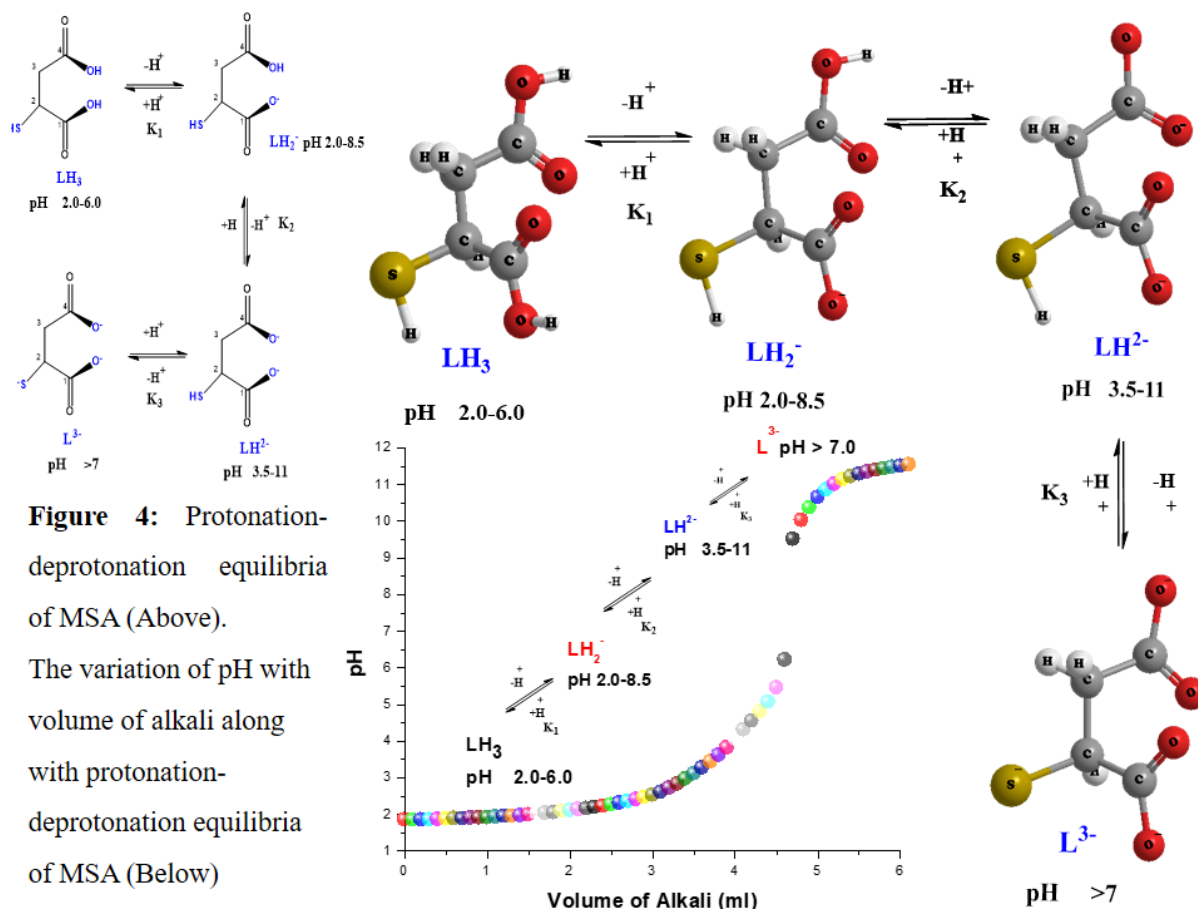


Figure 4: Protonation-deprotonation equilibria of MSA (Above). The variation of pH with volume of alkali along with protonation-deprotonation equilibria of MSA (Below)

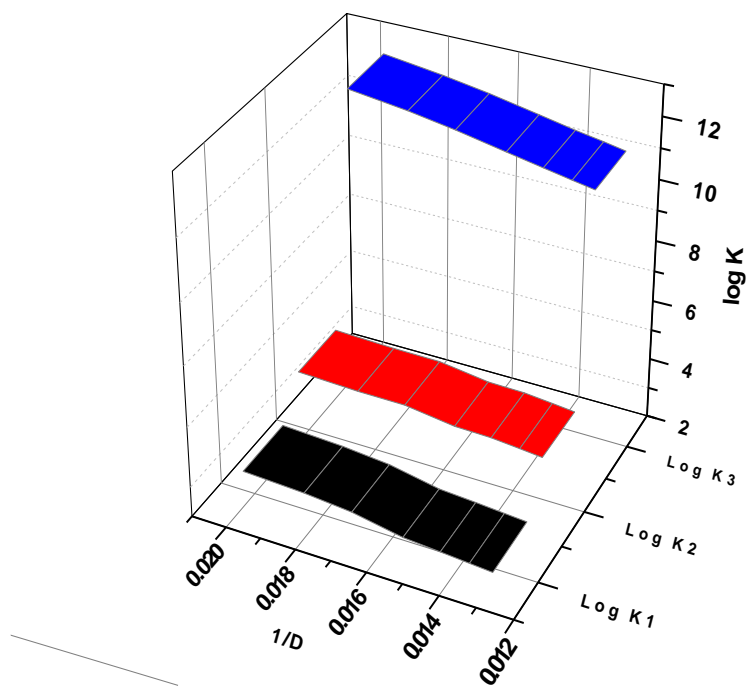


Figure 5. Variation of stepwise protonation constant ($\log K$) of MSA with reciprocal of dielectric constant

3. Experimental

3.1. Preparation of experimental solutions and standardization

An aqueous solution of MSA (Merck India) of concentration 0.05 mol L⁻¹ was prepared. In order to increase the solubility of the compound an acidic medium of 0.05M was maintained using HCl. We utilized Ethylene Glycol (Merck, India) as received. Standard approaches were used for preparation and standardization of all solutions. To identify any concentration determination mistakes, data were subjected to ANOVA[32]. These were calculated using the Gran plot approach[33,34].

3.2. Titrations arrangement

During each titration, the titrand was around 1mmol of HCl in 50ml. As for MSA, ranged from 0.25 to 0.50 mmols each. The pH of the resultant solution in aqueous media with organic solvent 0-60% (EG) was measured at 303K, using an Metrohm 877 titrino plus auto-titrator (readability 0.001) combined with pH electrode and a Teflon stirrer. To keep the ionic strength of 0.16 M, a 2M NaCl was used. It was necessary to perform periodic titrations of the strong acid and alkali to ensure that the glass electrode was completely equilibrated before proceeding with the experiment. The details of our laboratory's experimental

procedure and titration assembly were taken from literature[35]

3.3. Best suited model

The protonation constants of MSA were calculated using the MINIQUAD75[36]. The Marquardt algorithm's dependable convergence resulted to the chemical model that suit best for each system studied[37]. Interactions between solutes and solvents helped us understand how stepwise constants changed over time. Best-fit models for MSA in EG-water mixtures are shown in Table 1. The experimental data are accurately represented by Ucorr (sum squares of variations at all experimental sites), corrected for degrees of freedom. Low mean, standard deviation, and mean deviation confirm near-zero residuals with limited dispersion.

An ideal normal distribution has three kurtosis and zero skewness. The study's kurtosis findings suggest the residuals are leptokurtic. Table-1 shows skewness values from -1.5 to 3.01. They show that residuals have a normal distribution, allowing for least squares. The low crystallographic R values also show the model's sufficiency. Thus, the best-fit model accurately depicts MSA acid-base equilibrium in EG-water.

Table 1. Model that suit best for protonation study of MSA in 0-60% EG -water mixture

% V/V EG	log β(SD)			NP	U _{Corr} X10 ⁸	Skewness	Kurtosis	χ ²	R-Factor
	LH	LH ₂	LH ₃						
	In EG			pH Range – 1.5 – 11.00					
0.0	10.96(9)	15.32(9)	18.21(6)	120	0.6	0.16	7.39	29.69	0.0034
10	11.12(2)	15.51(5)	18.44(5)	114	0.71	-0.24	3.95	16.09	0.0024
20	11.28(2)	15.68(2)	18.67(2)	125	1.61	1.72	7.62	12.07	0.0061
30	11.48(2)	15.91(2)	18.95(3)	104	0.23	0.88	3.82	16.41	0.0022
40	11.62(2)	16.14(3)	19.20(4)	114	2.84	-0.89	3.04	12.85	0.0014
50	11.85(2)	16.40(4)	19.48(5)	128	1.94	-0.62	2.86	10.24	0.0018
60	12.06(7)	16.63(9)	19.77(1)	134	1.52	0.24	7.14	20.29	0.0024

Influence of methodical inaccuracies on refined data
Changes in alkali, mineral acid, or ligand concentration impact protonation constants. They can influence other aspects. MINIQUAD75 cannot quantify systematic errors in influential parameters, hence it cannot examine their influence on a protonation constant. With varying data acquisition accuracy and negative error in mineral acid, alkali, and ligand concentrations, the best-fit chemical model was determined.

Lesser deviations in component concentrations confirm the experimental circumstances, as seen in Table 2. The protonation constant (log K) values of the best chemical models should have a low standard deviation. Even with errors, higher protonation constant standard deviation causes rejection. It's vital because the data was obtained under varying experimental circumstances.

Table 2. Influence of errors on protonation constants of MSA in 40%v/v EG-water mixture

Ingredient	% of error	MSA in EG		
		log β_1 (SD)	log β_2 (SD)	log β_3 (SD)
Alkali	0	11.79(09)	16.14(09)	18.97(06)
	-5	11.61(17)	16.08(21)	18.71(09)
	-2	11.69(22)	16.11(31)	18.88(14)
	2	11.77(04)	16.16(08)	18.98(27)
	5	11.81(19)	16.21(14)	-
Acid	0	11.79(09)	16.14(09)	18.97(06)
	-5	11.72(11)	16.08(14)	-
	-2	11.75(21)	16.11(18)	18.94(11)
	2	11.80(09)	16.16(08)	18.99(27)
	5	11.84(17)	16.28(17)	19.08(15)
Ligand	0	11.79(09)	16.14(09)	18.97(06)
	-5	11.77(13)	16.11(18)	18.84(09)
	-2	11.75(16)	16.13(08)	18.92(16)
	2	11.80(08)	16.18(08)	18.99(07)
	5	11.81(07)	16.20(07)	19.03(14)

4. Conclusions

MSA has three dissociable protons exists in LH₃ form at low pH and gets deprotonated with the formation of LH₂, LH²⁻ and L³⁻ 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 the electrostatic forces in the protonation-deprotonation equilibria of MSA.

Acknowledgements

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