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Influence of Dielectric Constant of Medium on Chemical Speciation of Co(II), Ni(II) and Cu(II) Complexes with 5-Hydroxysalicylic acid in DMF-Water Mixtures.

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ABSTRACT

Speciation of Co(II), Ni(II) and Cu(II) complexes with 5-Hydroxysalicylic acid (5-HSA) in the presence of N, N'-Dimethyl formamide-water mixtures(0.0-60% v/v) at an ionic strength of 0.16 mol dm^{-3} and temperature 303 K were investigated pH metrically. The existence of different binary complex species was established from modeling studies using the computer program MINIQUAD75. The increased stability of the complexes with increasing DMF was explained by electrostatic forces. The influence of the DMF on the chemical speciation is discussed based on the dielectric constant of the medium. Distribution diagrams of various species of the complexes in relation to pH are presented.

Keywords: 5-Hydroxysalicylic acid; Speciation; DMF-Water; Binary complexes; Dielectric constant.

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INTRODUCTION

Classical curve-fitting methods that use the least-squares methods [1, 2] are applied to estimate the number of species simultaneously present at equilibrium, their stoichiometries, and their stability constants. Bioavailability of a particular metal depends on its complex chemical reactions of dissolution, binding and complexation with the constituents of the environmental aquatic phase [3]. The metal complexes can be more active than the free ligands and some side effects may decrease upon complexation. In addition, the complexes can exhibit bioactivities which are not shown by the free ligand. The speciation study of essential metal ion complexes is useful to understand the role played by the active site cavities in biological molecules and the bonding behavior of drug residues with the metal ion [4, 5]. The species refined and their relative concentrations under the experimental conditions represent the possible forms of drugs in bio-fluids.

Speciation analysis, the determination of the concentrations of separate and unique atomic and molecular forms of an element instead of its total concentration in a sample is important in human biology, nutrition, toxicology and in clinical practice [6-8].Cobalt is essential for the production of red blood cells. It acts as coenzyme in several biochemical processes. Cobalt in the form of vitamin B12 is essential for animals. Vitamin B12 is synthesized only by microorganisms, in particular anaerobic bacteria. Nickel is associated with several enzymes [9-11] and any variation in its concentration leads to metabolic disorders. Copper is largely rejected from cells but outside the cell, it is essential for the metabolism of many hormones and connective tissue. The biological functions include electron transfer, dioxygen transport, oxygenation, oxidation, reduction and disproportionation [12, 13].

The aim of the present study is to understand the role of metal ions at active site cavities in bioactive molecules like drugs, enzymes and proteins to know the effect of dielectric constant of the medium on the chemical speciation of the title systems. 5-HSA has been taken as a model compound for drug residues, since the dielectric constant at the active site cavities is very small compared to that at bio-fluids, low dielectric constant is mimicked by using a water soluble organic solvent like N,N' Dimethyl Formamide (DMF).

EXPERIMENTAL

Chemicals

5-HSA (TCI, India) solution (0.05 mol L^{-1}) was prepared in triple-distilled deionised water by maintaining 0.05 mol L^{-1} hydrochloric acid concentration to increase the solubility. DMF (Qualigens, India) was used as received. 2 mol L^{-1} sodium chloride (Qualigens, India) was prepared to maintain the ionic strength in the titrand. 0.1 mol L^{-1} aqueous solutions of Co(II), Ni(II) and Cu(II) chlorides were prepared by dissolving G.R. Grade (E-Merck, India) salts in triple-distilled water maintaining 0.05 mol L^{-1} hydrochloric acid to suppress the hydrolysis of metal salts. 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 [14, 15]. The strengths of alkali and mineral acid were determined using the Gran plot method [16, 17]

Apparatus

The titrimetric data were obtained using EQUIPTRONICS (Model EQ 614 A) pH meter (readability 0.01), which was calibrated with 0.05 mol L^{-1} potassium hydrogen phthalate in acidic region and 0.01 mol L^{-1} borax solution in basic region. The glass electrode was equilibrated in a well stirred DMF-water mixture containing the inert electrolyte. All the titrations were carried out in the medium containing varying concentrations of DMF-water mixtures (0.0-60% v/v) by maintaining an ionic strength 0.16 mol L^{-1} with sodium chloride at 303.0 ± 0.1 K. The effect of variation in asymmetry potential, liquid junction potential, activity coefficient, sodium ion error and dissolved carbon dioxide on the response of glass electrode was accounted for in the form of correction factor [18].

Procedure

For the determination of stability constants of metal-ligand binary species, initially titrations of strong acid with alkali were carried out at regular intervals to check whether complete equilibration was achieved. In

each of the titrations, the titrand consisted of approximately 1 mmol mineral acid in a total volume of 50 mL. Titrations with different ratios (1:2.5, 1:3.75 and 1:5.0) of metal-to-ligand were carried out using 0.4 mol L^{-1} Sodium hydroxide. Other experimental details are given elsewhere [19, 20].

Modeling Strategy

The computer program SCPHD [21, 22] was used to calculate the correction factor. By using the pH-metric titration data, the binary stability constants were calculated with the computer program MINIQUAD75 [23, 24], which exploit the advantage of the constrained least-squares method in the initial refinement and reliable convergence of Marquardt algorithm. During the refinement of binary systems, the correction factor and the protonation constants of 5-HSA were fixed. The variation of stability constants with the dielectric constant of the medium was analyzed on electrostatic grounds on the basis of solute-solute and solute-solvent interactions.

RESULT AND DISCUSSION

The results of the final best-fit models that contain the stoichiometry of the complex species and their overall formation constants along with some of the important statistical parameters are given in Table 1. Very low-standard deviation in overall stability constants (log β) signifies the precision of these constants. The small values of U$_{corr}$ (sum of squares of deviations in concentrations of ingredients at all experimental points) corrected for degrees of freedom, small values of mean, standard deviation and mean deviation for the systems are validated by the residual analysis [25].

Residual Analysis

In data analysis with least squares methods, the residuals (the differences between the experimental data and the data simulated based on model parameters) are assumed to follow Gaussian or normal distribution. When the data are fit into the models, the residuals should ideally be equal to zero. If statistical measures of the residuals and the errors assumed in the models are not significantly different from each other, the model is said to be adequate. Further, a model is considered adequate only if the residuals do not show any trend. Respecting the hypothesis that the errors are random, the residuals are tested for normal distribution. Such tests are χ^2, Skewness, Kurtosis and R-factor [26]. These statistical parameters show that the best-fit models portray the metal-ligand species in DMF-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 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 different values are obtained for models containing different number of species, 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 -1.47 and 0.40 for Co(II), -1.06 and 0.92 for Ni(II) and -0.11and 1.61 for Cu(II). 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 platykurtic pattern for Co(II), leptokurtic pattern in the case of Ni(II) and Cu(II).

Table 1. Parameters of best fit chemical models of Co(II), Ni(II) and Cu(II) – 5-HSA complexes in DMF-water mixtures. Temp= 303 K, Ionic strength=0.16 mol dm^{-3}.

% v/v DMF	log β_{mlh} (SD)			pH-Range	NP	U_{corr}	χ^2	Skewness	Kurtosis	R-factor
	ML$_2$H$_2$	ML$_2$H$_3$	ML$_2$H$_4$							
				Co (II)						
0.0	27.67(12)	35.40(37)	37.51(40)	2.0-11.5	101	28.26	9.58	-0.06	2.75	0.03518
10	27.38(16)	35.29(35)	37.86(48)	2.0-11.5	38	25.02	4.74	0.40	2.50	0.04425
20	26.98(16)	34.84(21)	38.05(11)	2.0-11.5	31	11.82	13.58	0.01	3.99	0.02965
30	26.64(22)	34.40(33)	38.47(73)	2.0-11.5	45	37.14	3.25	0.28	2.91	0.04881
40	26.40(38)	34.09(52)	38.79(93)	2.0-11.5	48	69.55	44.67	-1.47	6.31	0.07852
50	26.90(39)	33.89(64)	38.97(90)	2.0-11.5	15	33.58	4.60	0.09	2.07	0.04434
60	26.11(43)	33.54(47)	39.21(58)	2.0-11.5	19	24.12	6.12	0.22	2.54	0.03544
				Ni (II)						
0.0	27.31(09)	34.88(36)	36.79(40)	2.0-11.5	102	24.24	8.88	-0.09	3.09	0.03369
10	27.01(08)	35.18(23)	36.99(39)	2.0-11.5	84	18.76	27.17	0.12	3.81	0.03372
20	26.89(11)	35.45(28)	37.25(48)	2.0-11.5	57	23.70	41.35	0.25	3.46	0.04010
30	26.53(22)	35.74(32)	37.65(54)	2.0-11.5	56	28.86	31.62	-1.06	6.50	0.05324
40	27.16(23)	35.98(58)	37.87(27)	2.0-11.5	27	21.12	7.99	-0.74	3.76	0.05120
50	26.16(12)	36.20(40)	38.10(36)	2.0-11.5	32	20.41	21.50	0.76	2.93	0.08985
60	25.89(13)	36.58(41)	38.46(52)	2.0-11.5	36	34.75	22.01	0.92	3.01	0.07546
				Cu (II)						
0.0	26.32(13)	31.87(37)	34.98(40)	2.0-11.5	99	34.16	15.65	-0.11	4.61	0.03952
10	26.68(50)	32.11(61)	35.39(65)	2.0-11.5	56	22.83	5.71	0.09	3.45	0.03642
20	26.99(31)	32.46(45)	35.83(47)	2.0-11.5	75	22.36	10.13	0.69	3.59	0.02583
30	27.32(30)	32.84(46)	36.14(55)	2.0-11.5	11	24.50	5.55	0.93	3.38	0.03493
40	27.62(35)	33.18(37)	36.53(45)	2.0-11.5	43	22.55	25.23	1.61	6.05	0.09702
50	27.97(54)	33.54(41)	36.94(38)	2.0-11.5	37	16.73	14.05	0.36	3.92	0.09257
60	28.24(27)	33.89(72)	37.31(62)	2.0-11.5	41	66.31	11.24	0.82	3.52	0.07582

U_{corr} = U/ (NP − m); m = number of species; NP = number of experimental points; SD = standard Deviation.

Effect of Systematic Errors on Best Fit Model

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 undertaken by introducing pessimistic errors in the influential parameters like concentrations of alkali, mineral acid, ligand, metal, log F and volume in Table 2. The order of the ingredients that influence the magnitudes of stability constants due to incorporation of errors is alkali > acid > metal > ligand > volume > log F. Some species were even rejected when errors were introduced in the concentrations. The rejection of some species and increased standard deviations in the stability constants on introduction of errors confirm the suitability of the experimental conditions (concentrations of ingredients) and choice of the best-fit models.

Table 2. Effect of errors in influential parameters on Ni(II) and 5-HSA complex stability constants in 20 % v/v DMF-water mixture.

Ingredient	% Error	Log β_{mlh}(SD)		
		122	123	124
	0	26.99(31)	32.46(45)	35.83(47)
Acid	-5	24.86(105)	Rejected	37.12(75)
	-2	25.62(99)	31.15(85)	Rejected
	+2	26.12(98)	33.11(89)	36.88(98)
	+5	27.32(106)	33.54(92)	Rejected
Alkali	-5	Rejected	33.41(41)	37.12(62)
	-2	25.88(79)	34.21(97)	Rejected
	+2	26.38(107)	31.62(99)	38.12(97)
	+5	Rejected	31.20(102)	33.99(97)
Ligand	-5	26.13(47)	33.12(85)	33.15(52)
	-2	27.31(89)	32.26(46)	34.28(68)
	+2	25.74(95)	32.89(79)	36.87(46)
	+5	25.24(46)	33.47(94)	39.88(42)
Metal	-5	26.25(38)	33.01(49)	34.75(53)
	-2	26.78(46)	32.59(68)	35.12(47)
	+2	27.45(81)	31.97(94)	34.88(62)
	+5	25.64(94)	32.65(86)	33.95(56)
Volume	-5	24.12(51)	33.41(37)	35.66(75)
	-2	25.31(39)	32.33(33)	36.01(65)
	+2	26.21(45)	33.95(91)	35.32(48)
	+5	26.85(71)	31.68(36)	35.74(61)
Log F	-5	26.88(38)	31.25(54)	Rejected
	-2	28.21(62)	32.73(81)	34.58(45)
	+2	27.11(79)	31.66(24)	35.06(68)
	+5	26.64(57)	30.52(22)	36.21(49)

Effect of Solvent

The dielectric constant is one of the characteristics of liquid. The metal-ligand stability 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 changed or has a dipole. Variations in the relative strengths of acids and bases with changing solvents should be a function of the charge, the radius of the ion and the dielectric constants of the medium.

When the ionization of an acid gives a net increase of ions, a decrease in the dielectric constant of the solvent should be accompanied by an increase in the stability constant of a weak acid dissolved in it. The variation of stability constant or change in free energy with co-solvent content depends upon two factors, viz, electrostatic and non-electrostatic forces. Born's classical treatment holds good in accounting for the electrostatic contribution to the free energy change [27]. According to this treatment, the energy of electrostatic interaction or stability constants should vary linearly as a function of the reciprocal of the dielectric constant (1/D) of the medium. Such linear variation of stability constants of 5-HSA in DMF-water mixtures shows the dominance of electrostatic interactions and the trend is showed in Figure 1.

A plot of log β versus 1/D (D is dielectric constant) should be linear if Born's classical treatment holds good indicating that electrostatic forces alone operate. The values of Co(II), Ni(II) and Cu(II) complexes of 5-HSA with 1/D reveals that the electrostatic forces are dominating the equilibrium process under the present experimental conditions. The solute-solvent interactions, relative thermodynamic stabilities and kinetic liabilities are also expected to play an important role.
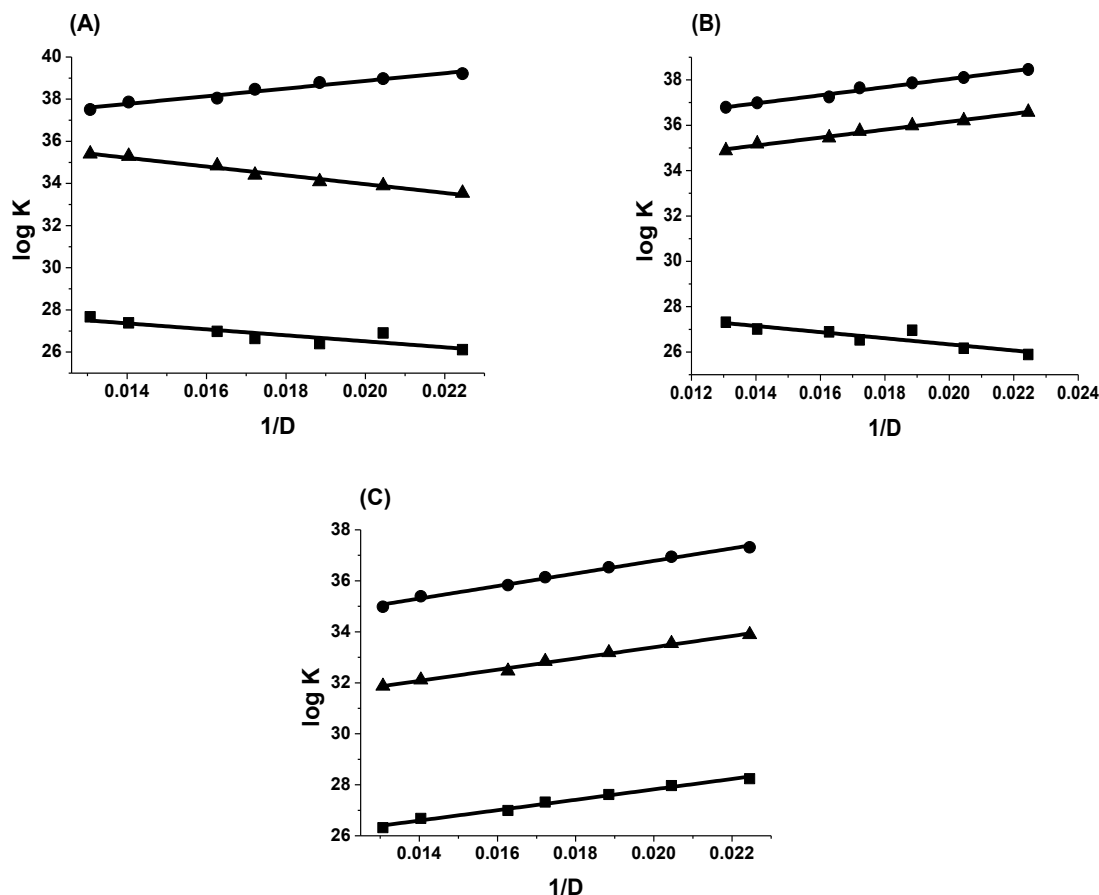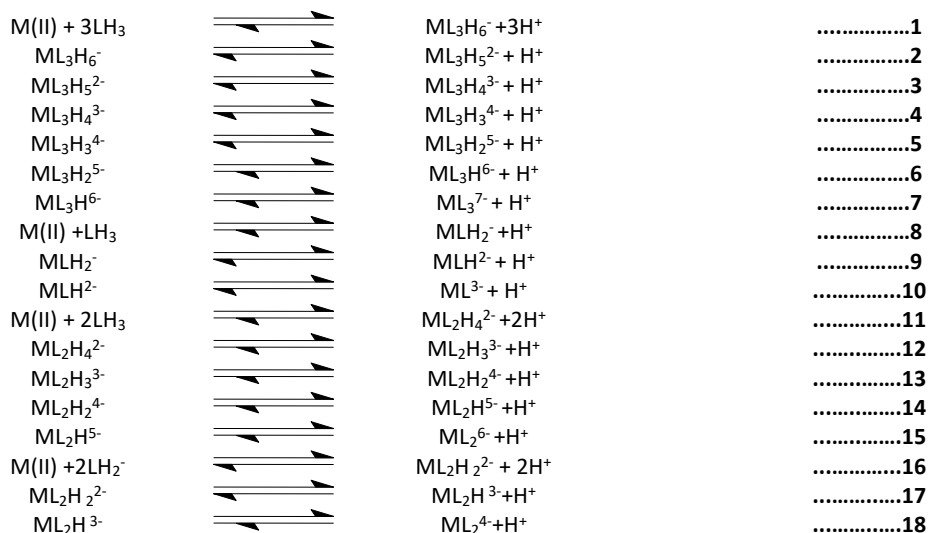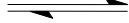
Figure 1. Variation of overall stability constant values of metal-5-HSA complexes with 1/D of DMF-water mixtures (a) Co(II); (b) Ni(II); (c) Cu(II); (■)log β_{ML2H2}; (▲) log β_{ML2H3}; (●) log β_{ML2H4}.

Distribution Diagrams

5-HSA is a tridentate ligand, it has one carboxyl (–COOH) and two hydroxyl (-OH) groups. The different forms of 5-HSA are LH_3, LH_2^-, and LH^{2-} in the pH range 1.5-6.5, 1.5-11.5 and 5.5-11.5 respectively. Hence, the plausible binary metal-liga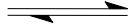nd complexes can be predicted from these data. The present investigation reveals the existence of ML_2H_2, ML_2H_3, and ML_2H_4 for Co(II), Ni(II) and Cu(II). The formation of various 5-HSA complex species is shown in the following equilibria.

$M(II) + 3LH_3$	$ML_3H_6^- + 3H^+$	1
$ML_3H_6^-$	$ML_3H_5^{2-} + H^+$	2
$ML_3H_5^{2-}$	$ML_3H_4^{3-} + H^+$	3
$ML_3H_4^{3-}$	$ML_3H_3^{4-} + H^+$	4
$ML_3H_3^{4-}$	$ML_3H_2^{5-} + H^+$	5
$ML_3H_2^{5-}$	$ML_3H^{6-} + H^+$	6
ML_3H^{6-}	$ML_3^{7-} + H^+$	7
$M(II) + LH_3$	$MLH_2^- + H^+$	8
MLH_2^-	$MLH^{2-} + H^+$	9
MLH^{2-}	$ML^{3-} + H^+$	10
$M(II) + 2LH_3$	$ML_2H_4^{2-} + 2H^+$	11
$ML_2H_4^{2-}$	$ML_2H_3^{3-} + H^+$	12
$ML_2H_3^{3-}$	$ML_2H_2^{4-} + H^+$	13
$ML_2H_2^{4-}$	$ML_2H^{5-} + H^+$	14
ML_2H^{5-}	$ML_2^{6-} + H^+$	15
$M(II) + 2LH_2^-$	$ML_2H_2^{2-} + 2H^+$	16
$ML_2H_2^{2-}$	$ML_2H^{3-} + H^+$	17
ML_2H^{3-}	$ML_2^{4-} + H^+$	18

$$ML_2H_2{}^{2-} \rightleftharpoons ML_2{}^{4-} + 2H^+ \quad \text{..............19}$$

$$M(II) + LH_2{}^- \rightleftharpoons MLH + H^+ \quad \text{..............20}$$

$$MLH \rightleftharpoons ML^- + H^+ \quad \text{..............21}$$

$$M(II) + 3LH_2{}^- \rightleftharpoons ML_3H_6{}^{3-} + 3H^+ \quad \text{..............22}$$

$$ML_3H_6{}^{3-} \rightleftharpoons ML_3H_5{}^{4-} + H^+ \quad \text{..............23}$$

$$ML_3H_5{}^{4-} \rightleftharpoons ML_3H_4{}^{5-} + H^+ \quad \text{..............24}$$

$$ML_3H_4{}^{5-} \rightleftharpoons ML_3H_3{}^{6-} + H^+ \quad \text{..............25}$$

$$ML_3H_3{}^{6-} \rightleftharpoons ML_3H_2{}^{7-} + H^+ \quad \text{..............26}$$

$$ML_3H_2{}^{7-} \rightleftharpoons ML_3H^{8-} + H^+ \quad \text{..............27}$$

$$ML_3H^{8-} \rightleftharpoons ML_3{}^{9-} + H^+ \quad \text{..............28}$$

Some typical distribution diagrams in DMF-water mixtures are shown in Figure 2. They indicate that the binary complexes of Co(II), Ni(II) and Cu(II) are formed in the pH range 1.5-12.0. ML_2H_4, ML_2H_3 and ML_2H_2 are simultaneously formed with the increasing pH. ML_2H_3, ML_2H_2 species percentage successively increases with increasing pH. Successive deprotonation of ML_2H_4 forms ML_2H_3 beyond a pH 4.0. The percentage of the ML_2H_2 species increases successively with increasing in pH up to 11.8. The concentration of ML_2H_4 species decreased, while the concentration of ML_2H_3 and ML_2H_2 increased in the pH range 4.0-11.0. ML_2H_2 formed at higher pH with high percentage in the case of Co(II), Ni(II) and Cu(II).

ML_2H_4 species is formed at pH less than 2.0 (Equilibrium 11) by interacting LH_3 with free metal, which might have been quickly deprotonated to ML_2H_3 (Equilibrium 12) and ML_2H_2 (Equilibrium 13) or the Free metal interacts with $LH_2{}^-$ to form ML_2H_2 (Equilibrium 16) at pH more than 4.0 for Co(II), Ni(II) and Cu(II).
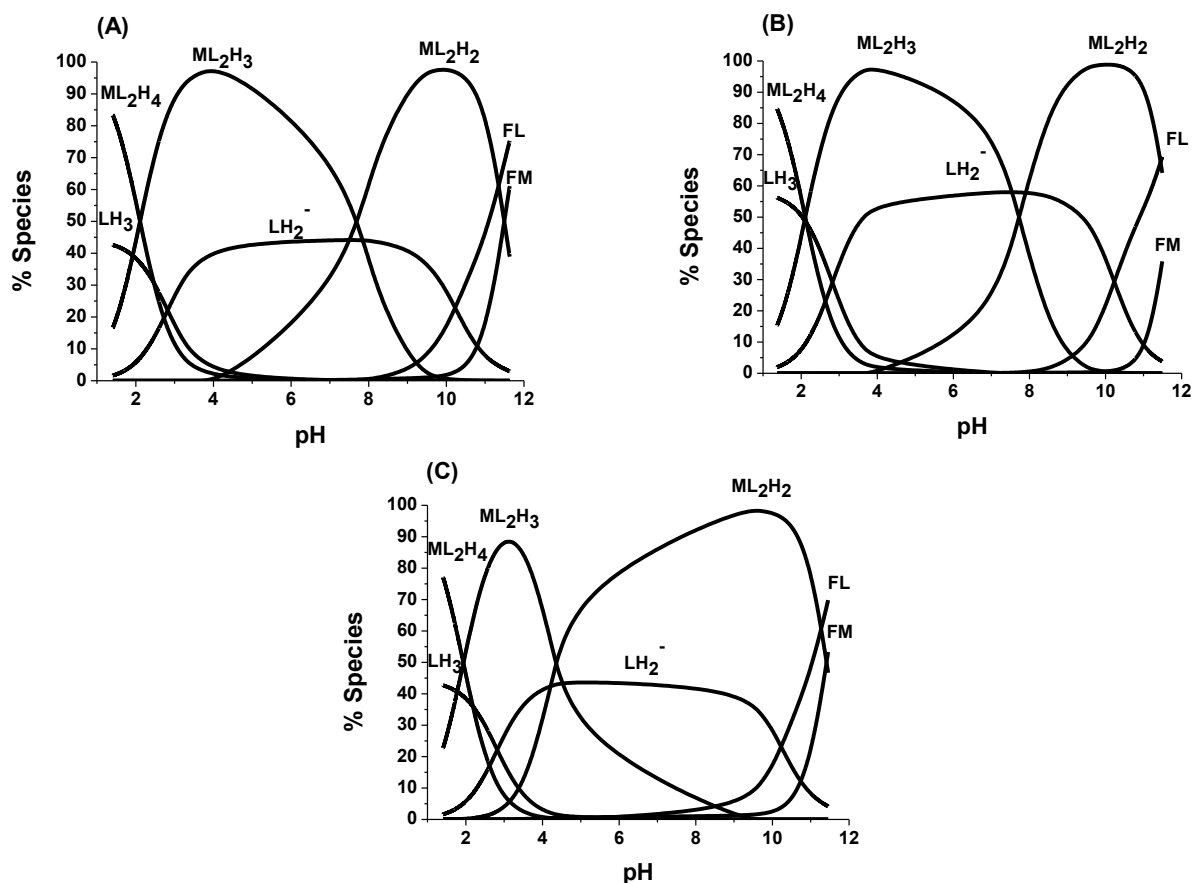

Figure 2: Distribution diagrams of binary complexes of 5-HSA in 10% v/v DMF-water mixture: (a) Co(II), (b) Ni(II) and (c) Cu(II).

Structures of complexes

5-HSA has three functional groups such as one -COOH and two –OH groups, and is helpful to form different complexes with Co(II), Ni(II) and Cu(II). Octahedral structures are proposed to the complexes of all

the metal ions. The VSEPR theory suggests that Co(II), Ni(II) and Cu(II) complexes shall be octahedral because, there are six outer electron pairs. This argument supports the structures of complexes proposed in Figure 3.
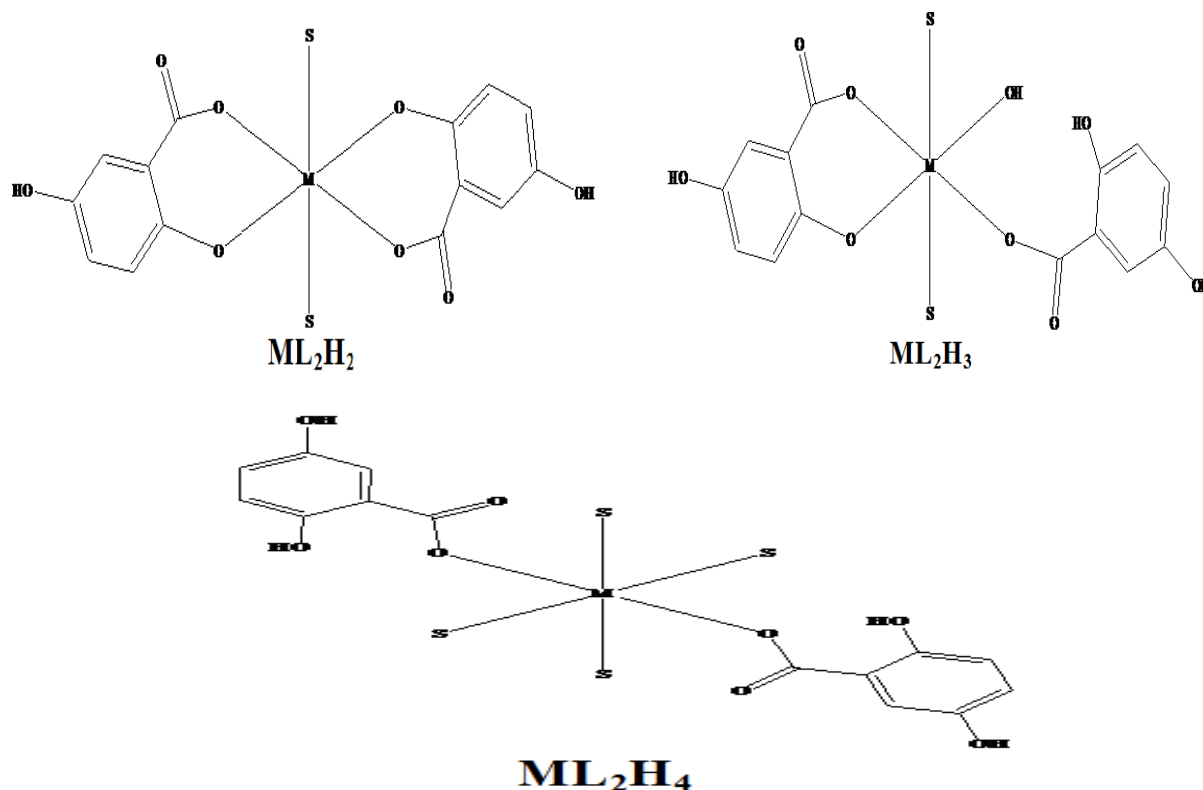

Figure 3: Structure of 5-HSA complexes, where S is either solvent or water molecules.

CONCLUSIONS

The following conclusions have been drawn from the modeling studies of 5-HSA complexes of Co(II), Ni(II) and Cu(II) in DMF-water mixtures.

1. 5-HSA forms both protonated and unprotonated complexes under pH range 2.0–12.0
2. The complex species formed due to interaction of 5-HSA with the essential metals are ML_2H_2, ML_2H_3 and ML_2H_4.
3. The linear variation of the stability constants with 1/D of the DMF indicates the dominance of electrostatic forces over non-electrostatic forces.
4. The order of the components in influencing the magnitudes of the stability constants due to incorporation of errors is alkali > acid > ligand > metal > volume > Log F.
5. Some species are stabilized due to electrostatic interactions and some are destabilized due to the decreased dielectric constant.

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