

EFFECT OF PROPYLENE CARBONATE ON CHEMICAL SPECIATION OF L-HISTIDINE COMPLEXES WITH SOME ESSENTIAL TRACE METALS

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ABSTRACT

Computer simulation models have been developed to investigate the possible forms of amino acids in bio-fluids. The distribution of Ni(II), Cu(II) and Co(II) among the L-Histidine in propylene carbonate - water mixtures (0-14% v/v) at 303 K temperature and 0.16 mol L⁻¹ ionic strength has been investigated pH metrically. ML₂H₂, ML₂H, ML₂ and MLH are the detected species for all the three metals Ni(II), Cu(II) and Co(II). The models containing different numbers of species were refined by using the computer program MINIQUAD75. Based on statistical parameters, best-fit chemical models were tabulated. The trend in variation of stability constants of the complexes with reciprocal of dielectric constant of the medium is explained based on electrostatic and non-electrostatic forces. The distribution of species and possible equilibria for the obtained species were also described.

Keywords: L-Histidine, MINIQUAD75, Propylene carbonate, stability constants, statistical parameters.

INTRODUCTION

Metal-ligand interactions are central to understand the contaminant pathways (uptake, metabolism and excretion) and bio-availability¹. In vivo, distribution of metal ions involves transport as complexes of amino acids, peptides, proteins or other natural ligands such as citrate². For example, Ni²⁺ and Cu²⁺ bound to the protein human-serum albumin, by the amino acid L-Histidine(His)¹⁰. Being associated with so many enzymes, a minor change in the concentration of Ni(II), Cu(II) and Co(II) results in several disorders⁵.

When it comes to **Cobalt**, complexing with glycyglycine and histidine function as reversible oxygen carriers. Divalent cobalt has a role of enzyme activator for carbonic anhydrase or carboxy peptidase¹¹. It is worth mentioning the corrinoid ring systems known as cobalamines and presence of stable carbon-cobalt bond in vitamin B₁₂ which largely accounts for catalytic function⁶. **Nickel** has become a major player in bioinorganic chemistry, particularly in microorganisms, having impacts on both environmental settings and human pathologies. At least nine classes of enzymes are now known to require nickel in their active sites, including catalysis of redox and non-redox chemistries. In addition, the dark side of nickel has been illuminated in regard to its participation in microbial pathogenesis, cancer, and immune responses³. One of the examples is nickel subsulphide is the most potent carcinogenic metal compounds in experimental animals⁶. Apart from **copper** being essential for utilization of iron in haemoglobin formation in higher animals, blue copper proteins widely occurring in nature play a major role as oxygen carriers in blood plasma and brain⁴. Binary and ternary complexes of copper are present in small concentrations in blood serum, they play a significant role in the transport of metal ion across the membrane. Any disturbance in copper transport was characterized by Menkens disease¹².

Besides being an essential amino acid, **L-Histidine** plays an important role in citric acid cycle. Neutral histidine is a common coordinating ligand for all transition metals and because of its rich chemistry and pH sensitivity in the physiologically relevant range, it act as an active site for many enzymes and biomolecules like superoxide dismutase, ferritin, iron uptake regulation protein-FUR, ceruloplasmin, hemoglobin, metallothionein and cysteine dioxygenase⁷⁻⁹. In all these proteins, the

major binding group for metal ions is the imidazole group of histidine. **Propylene carbonate (PC)** is an odourless, clear liquid with a low vapour pressure at room temperature^{13,14}. Some clinical studies says a 20% solution of propylene carbonate to undiluted propylene carbonate caused moderate skin irritation, whereas $\leq 0.1\%$ to 5% aqueous solutions produced no such harm, infact it can be widely used in cosmetic products¹⁵.

Our experiment model is complex formation of L-Histidine with Ni(II), Cu(II) and Co(II) in Propylene carbonate-water media, through this we are able to explain the study of complex equilibria in aqua-organic media and its solute-solvent interactions¹⁹⁻²⁰. The species refined and their relative concentrations under the experimental conditions represent the possible forms of amino acids in bio-fluids.

Reagents and Solutions

All the reagents used in this experiment were purity - grade analytical reagents and were standardized by standard methods. 0.1 mol L⁻¹ concentration of Ni(II), Cu(II) and Co(II) chlorides were prepared in triple distilled water and to suppress the hydrolysis of metal salts 0.05M concentration of hydrochloric acid was added. Also to increase the solubility of the Histidine, hydrochloric acid of 0.05M concentration was added in preparing the solution of L-Histidine. Propylene carbonate was used as it is. Sodium chloride was prepared to maintain the ionic strength in the titrand. Sodium hydroxide of 0.4M and hydrochloric acid of 0.2M were prepared. The concentration of the metal ions were determined by complexometric titration. Through the Gran plot method^{22,23}, strengths of alkali and mineral acid were determined.

Equipment and Method

With different ratios of 1:2.5, 1:3.75, 1:5 for Ni(II),Cu(II) and Co(II) individually of metal to ligand, Alkalimetric titration were carried. These titrations were performed in the medium containing varying concentrations (0.0-14.0 % v/v) of Propylene carbonate in water at an ionic strength of 0.16M with sodium chloride at 303 K \pm 0.1 K using a 905 Titrando Metrohm type-Auto titrator (readability 0.001) with a Teflon stirrer mechanical agitation. Before carrying actual experiment, for every percentage the glass electrode was calibrated in Propylene carbonate-water mixtures containing inert electrolyte for 10-15 days. Neutralization reactions at regular intervals were performed to confirm the strength of Alkali.

Modelling strategy

The computer program SCPHD⁶, is used to calculate the correction factor. By using pH metric titration data, the binary stability constants were calculated with the computer program MINQUAD75²¹. The values of correction factor and protonation constants of L-Histidine were fixed, during the refinement of binary systems. The variation of stability constants with the mole fraction of the medium was analyzed on the basis of electrostatic, non- electrostatic, solute- solute and solute- solvent interactions.

RESULTS AND DISCUSSION

The results from best fit models that contain the type of species and overall formation constants along with the important statistical parameters are given in Table 1. The low standard deviation in log β values indicates the accuracy of the models obtained. U_{corr} values are small, the values of kurtosis are >3 , 3.0 and <3 indicates that the residuals form leptokurtic as well as platykurtic patterns and very few are nearer to mesokurtic patterns and skewness values in Table 1 are between -0.04 and 1.13 indicating normal distribution; hence, least squares method can be applied to the present data. Further extending about the low crystallographic R-values, these statistical parameters support the best fit models of our metal-ligand species in Propylene carbonate-water mixtures.

Table 1: Parameters of best fit chemical models, of L-Histidine complexes of Ni(II),Cu(II) and Co(II) in Propylene carbonate-water mixtures. (Temperature =303K, Ionic strength =0.16 mol dm⁻³)

%v/v PC	Log β_{min} (SD)				NP	U _{corr} x 10 ⁸	χ^2	Skew ness	Kurto sis	R-Factor	pH range
	1 1 1	1 2 0	1 2 1	1 2 2							
Ni(II)											
0	14.102(401)	16.939(284)	21.002(982)	27.141(243)	37	9.8362	34.51	0.35	7.10	0.013	3.5-5.8
2	13.885(164)	16.014(143)	20.901(271)	26.018(203)	39	3.5779	4.23	0.14	2.81	0.007	3.5-5.8
4	14.189(428)	16.945(324)	21.219(349)	27.153(284)	37	9.8315	31.34	0.37	7.09	0.013	3.5-5.8
6	13.306(471)	15.600(330)	-	26.061(327)	30	5.7621	18.62	-0.13	1.88	0.030	3.5-5.6
8	13.247(529)	14.822(529)	19.977(144)	25.468(626)	32	6.1122	17.17	-0.20	3.15	0.031	3.8-5.9
10	12.947(171)	14.016(145)	19.409(378)	25.150(187)	40	1.1235	4.13	0.01	2.90	0.013	3.5-6.0
12	13.290(485)	15.069(367)	19.918(296)	25.641(432)	39	5.5691	30.49	-0.11	0.94	0.031	3.5-6.0
14	12.694(144)	13.565(125)	19.046(265)	24.626(200)	40	8.3006	2.00	0.06	2.94	0.011	3.5-6.0
Cu(II)											
0	14.102(401)	16.939(284)	21.002(982)	27.141(243)	37	9.8362	34.51	0.35	7.10	0.013	3.5-5.8
2	-	18.140(143)	21.443(271)	26.803(203)	29	2.1108	8.17	-0.07	2.45	0.017	3.0-4.2
4	13.613(223)	18.195(123)	22.724(191)	26.208(753)	45	7.6270	4.56	0.47	5.15	0.011	3.2-5.5
6	13.860(185)	16.901(160)	22.821(139)	26.720(206)	46	5.2266	8.09	-0.32	3.35	0.009	3.2-7.0
8	13.397(119)	16.917(065)	22.610(056)	26.806(049)	46	1.0162	24.78	-0.39	3.96	0.004	3.2-7.0
10	13.618(173)	18.111(099)	22.790(132)	26.440(339)	41	3.8322	7.15	0.46	4.41	0.007	3.2-5.6
12	13.416(081)	18.055(188)	22.250(211)	26.558(114)	46	3.4603	3.91	0.65	4.14	0.007	3.2-5.6
14	13.275(216)	17.530(095)	22.288(131)	26.366(121)	44	3.3999	3.76	0.39	2.80	0.007	3.3-6.0
Co(II)											
0	14.273 (562)	15.270 (558)	20.305 (805)	25.319 (279)	30	1.1068	9.91	0.05	2.17	0.013	4.5-6.0
2	13.293 (176)	14.670 (143)	19.212 (518)	24.907 (177)	42	2.5961	16.73	1.13	6.68	0.007	3.5-6.0
4	13.227 (135)	14.350 (111)	19.350 (216)	24.622 (176)	40	1.6146	12.80	0.70	5.07	0.005	3.5-6.0
6	13.160 (127)	14.092 (104)	19.260 (182)	24.430 (197)	39	1.4908	8.47	0.49	4.49	0.005	3.5-6.0
8	13.055 (122)	13.714 (100)	19.096 (159)	24.159 (243)	37	1.5096	10.01	0.03	3.22	0.005	3.5-6.0
10	13.003 (132)	13.513 (107)	18.990 (171)	24.015 (308)	36	1.7895	9.33	-0.04	2.78	0.005	3.5-6.0
12	12.905 (148)	13.205 (119)	18.768 (192)	23.876 (345)	36	2.4448	10.81	-0.09	2.52	0.006	3.5-6.0
14	12.440 (207)	13.176 (130)	17.865 (975)	23.787 (340)	40	7.9474	4.67	-0.12	2.60	0.011	3.5-6.0

$U_{corr} = U/(NP-m) \times 10^8$, m –number of species: NP= number of experimental points

Effect of systematic errors on best fit models

In order to obtain the best fit chemical model for critical evaluation and application, effect of systematic errors under varied experimental conditions with different accuracies of data introduced pessimistic errors in the influential parameters like concentrations of alkali, mineral acid, ligand and metal given in Table 2. The order of the ingredients that influence the magnitudes of stability constants after introducing errors^{24,25} is alkali>acid>ligand>metal. The rejection of some species in the stability constants on introduction of errors confirm the suitability of our experimental conditions and our choice of the best fit models can be accepted.

Table 2: Effect of errors in concentrations of ingredients on stability constants of Cu(II) – L-Histidine complexes in 10% v/v Propylene carbonate-water mixtures

Ingredient	% of error	Log β_{mlh} Cu -His			
		MLH	ML ₂	ML ₂ H	ML ₂ H ₂
Acid	-5	14.617 (581)	20.262 (426)	23.690 (967)	28.154 (333)
	-2	14.047 (201)	18.968 (122)	23.258 (202)	27.021 (246)
	0	14.120 (401)	16.939 (284)	21.002 (982)	27.141 (243)
	+2	13.087 (272)	17.268 (125)	22.315 (118)	26.152 (293)
	+5	12.638 (233)	15.669 (578)	21.799 (069)	Rejected
Alkali	-5	Rejected	15.979 (235)	21.725 (068)	26.038 (083)
	-2	13.202 (212)	17.336 (111)	22.389 (105)	26.233 (245)
	+2	13.984 (207)	18.851 (125)	23.169 (207)	26.824 (361)
	+5	14.583 (442)	20.032 (330)	23.613 (738)	27.806 (296)
Ligand	-5	13.447 (222)	17.715 (132)	22.622 (139)	25.958 (926)
	-2	13.557 (188)	17.951 (111)	22.726 (134)	26.254 (500)
	+2	Rejected	18.157 (086)	22.378 (176)	26.959 (062)
	+5	13.724 (144)	18.505 (076)	22.915 (131)	26.853 (140)
Metal	-5	Rejected	18.236 (093)	22.293 (249)	26.930 (072)
	-2	13.616 (182)	18.203 (099)	22.790 (145)	26.495 (318)
	+2	13.618 (166)	18.017 (100)	22.785 (122)	26.386 (361)
	+5	13.617 (159)	17.874 (102)	22.772 (112)	26.311 (397)

Effect of Solvent

Propylene carbonate is a polar aprotic solvent. With increasing propylene carbonate concentration, the dielectric constant of the propylene carbonate-water mixture decreases and these solutions are supposed to imitate physiological conditions where the definition of the equivalent dielectric solution constant is applicable to protein cavities. The dielectric constants of propylene carbonate at different percentages (0.0-14.0 v/v %) of water were taken from literature¹⁶⁻¹⁸. The linear variation (Fig 1) of stability constants of L-Histidine complexes of Ni(II), Cu(II) and Co(II) in Propylene carbonate-water mixtures with 1/D (where D is dielectric constant of the medium) indicates that non electrostatic forces²⁶ dominate the electrostatic forces^{27,28}. It is observed that the stability constant of ML₂ species of Cu(II) with L-Histidine only decreases with the decrease of dielectric constant.

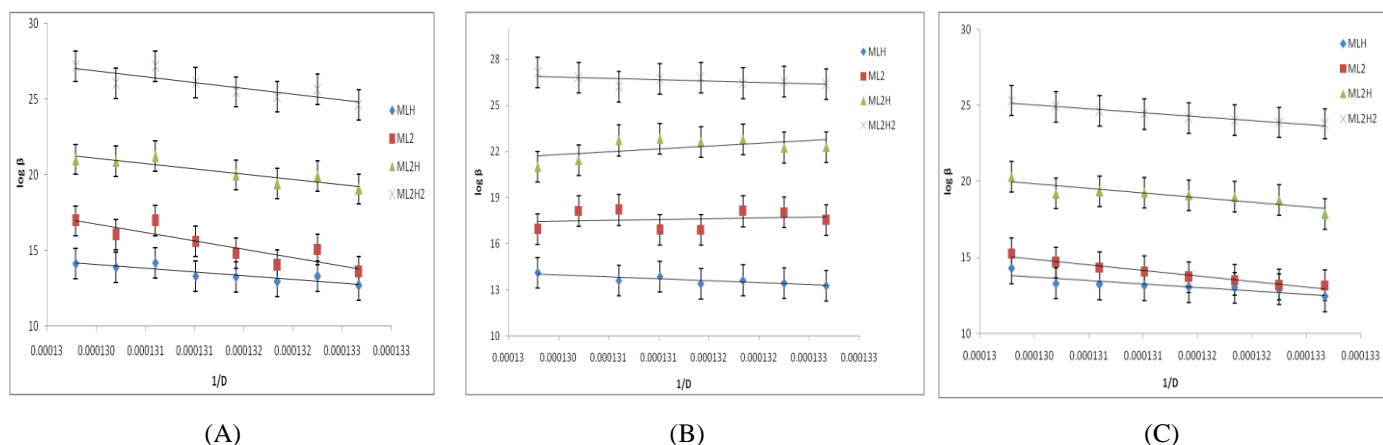


Fig. 1: Variation of $\log \beta$ with reciprocal of dielectric constant of Propylene carbonate–water mixtures (A) Ni(II), (B) Cu(II) and (C) Co(II)

Distribution diagrams

Histidine is a tridentate ligand that has one dissociable (carboxylate group) and two associable (amino, imidazole) protons. The different forms of Histidine are LH_3^{+2} , LH_2^+ , LH and L^- in the pH ranges <4.0, 2.0-7.0, 6.0-10.0 and > 9.0, respectively. The present investigation reveals the existence of ML_2H_2 , ML_2H , ML_2 and MLH for Ni(II), Cu(II) and Co(II). The formation of various L-Histidine complex species is shown in the following equilibria below. Distribution diagrams were drawn for various complex species using the formation constants of the best-fit models as shown in Fig 2. These diagrams indicate that the percentage of ML_2H_2 , ML_2H and MLH species of Ni(II), Cu(II) and Co(II) decreases with the increase of pH. The percentage species of ML_2 increases for the present experimental conditions. Depending upon the active sites in the ligand and the nature of the metal ions, the structures were proposed for the species detected as shown in Fig 3.

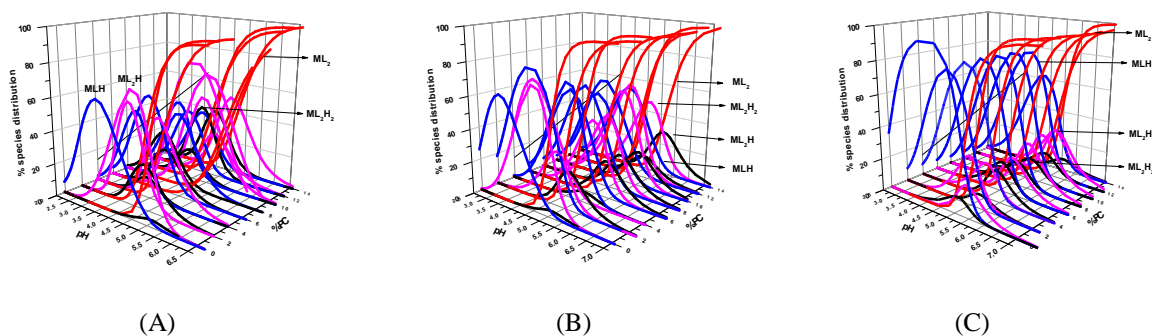
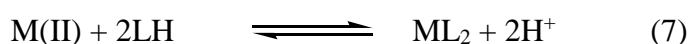
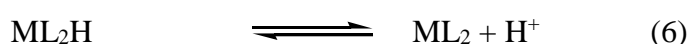
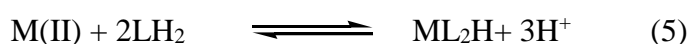
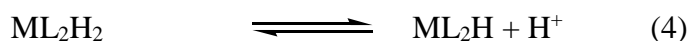
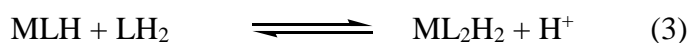
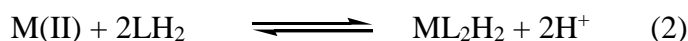
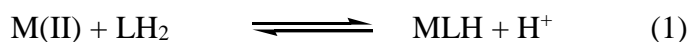


Fig. 2: Species distribution diagrams of L-Histidine complexes (0-14 % v/v) in Propylene carbonate–water mixture. (A) Cu (II), (B) Ni (II) and (C) Co(II)

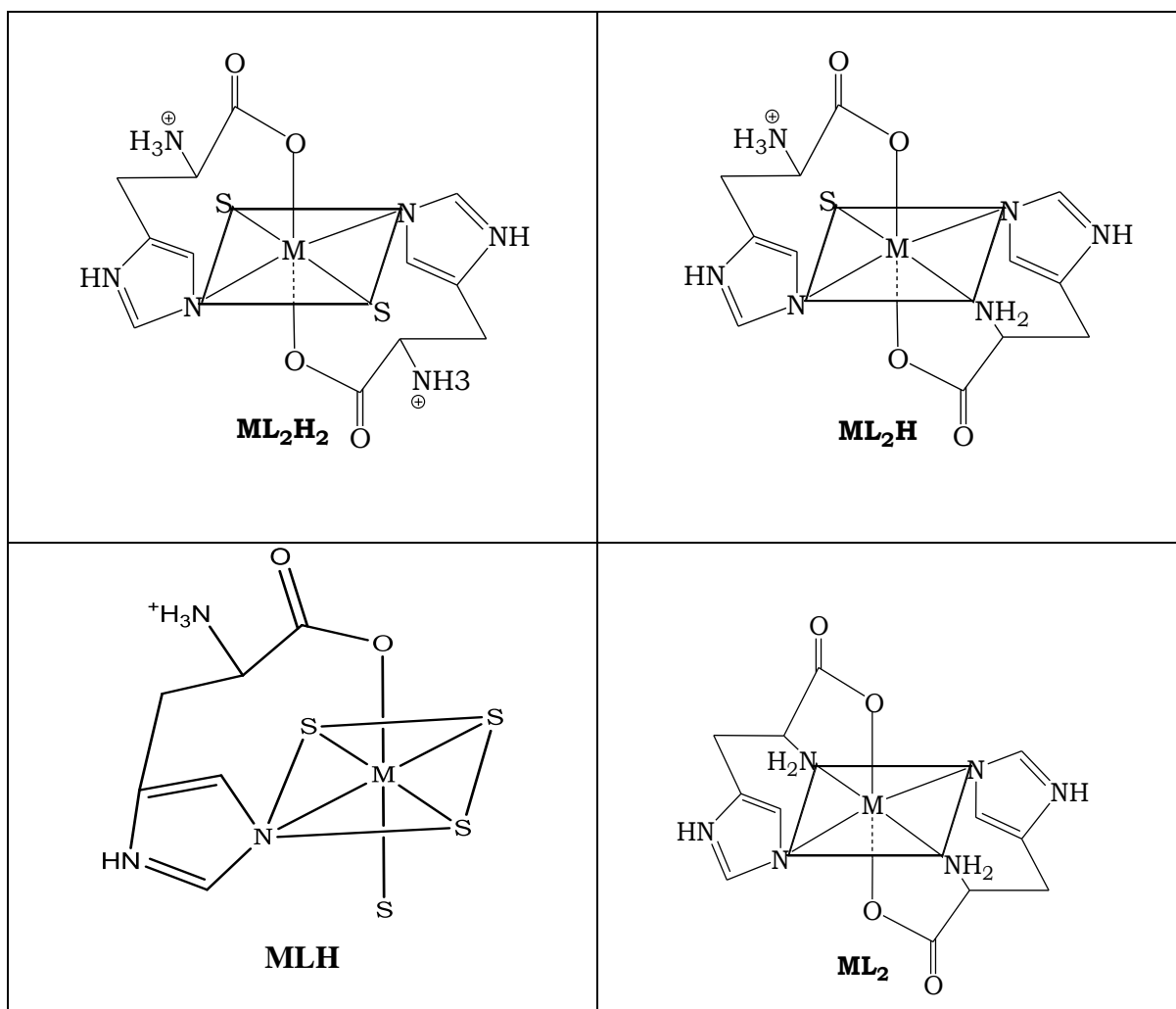


Fig. 3: Structures of Metal – His complexes where M= Ni, Cu and Cd; L= L-Histidine and S is either solvent or water molecule.

CONCLUSIONS

1. Our present speciation studies of transition metal ion complexes with L-Histidine in Propylene carbonate-water mixtures indicate the formation of protonated complexes in acidic pH.
2. As pH increases, the nitrogen atoms are deprotonated and coordinated with metals.
3. The species formed due to the interaction of L-Histidine with the metals are MLH, ML₂, ML₂H and ML₂H₂ for all the three metals.
4. The linear decrease in log β values with the inverse of dielectric constant (1/D) of the medium indicates the dominance of non-electrostatic forces over electrostatic forces.
5. The influence of errors in the concentration of the ingredients on the magnitudes of the stability constants is alkali > acid > ligand > metal.

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