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Coordination properties of dehydroacetic acid - binary and ternary complexes

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Coordination properties of dehydroacetic acid − binary and ternary complexes

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Complex formation equilibria of dehydroacetic acid with Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+} and Mn^{2+} and the ternary complexes involving Cu^{2+}, dehydroacetic acid and some amino acids containing different functional groups are investigated. Stoichiometry and stability constants for the complexes are estimated at 25°C and 0.1 M ionic strength in 25% dioxane-water mixtures. The concentration distribution diagrams of the complexes were evaluated. The effect of temperature and organic solvent on the acid dissociation constant of dehydroacetic acid and the formation constant of Cu^{2+} complex was studied and thermodynamic parameters calculated.

1. Introduction

Dehydroacetic acid (HD), (3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one), is widely used as fungicide [1], herbicide and as a preservative that has powerful antimicrobial effect against bacteria, yeast and particularly molds [2].

The complex of dehydroacetic acid with Cu^{2+} is more active than either HD alone or the copper salts [3]. Also, it has been shown that complexes of dehydroacetic acid with zinc and with several other transition metal cations are fungistatic [4]. Dehydroacetic acid is also used as an antienzyme agent in tooth paste to reduce pickle bloating [5], and widely used in food technology *i.e.* to enhance vitamin C stability and protect vegetables during food processing [6].

Despite these biological activities, reactivity of dehydroacetic acid toward metal ions have found comparatively limited study. Because of possible complexation of HD either taken as residual fungicides on fruits or introduced to the body through tooth paste or food additives with metal ions in body fluids, the reactivity of HD toward metal ions seems of value. With the above in mind and in conjunction with our previous studies

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of metal complexes of biological significance [7–11], the present investigation is concerned with complex formation equilibria of dehydroacetic acid with Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+} and Mn^{2+} and ternary complexes of Cu^{2+} with amino acids.
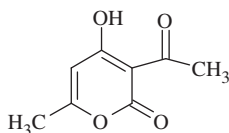
HD

2. Experimental

2.1. *Materials and reagents*

Dehydroacetic acid was obtained from Aldrich Chem. Co. The amino acids: glycine, alanine, proline, valine, β-phenylalanine, iso-leucine, histamine dihydrochloride and histidine monohydrochloride, were provided by Sigma Chem. Co. Metal salts in the form of nitrates were provided by BDH.

The metal ion content of solutions was determined by complexometric EDTA titrations [12]. Carbonate-free NaOH (titrant) was prepared and standardized against potassium hydrogen phthalate solution. All solutions were prepared in deionized H_2O.

2.2. *Apparatus and measuring techniques*

Potentiometric measurements were made using a Metrohm 686 titroprocessor equipped with a 665 Dosimat (Switzerland-Herisau). The titroprocessor and electrode system were calibrated with standard buffer solutions, prepared according to NBS specification [13]. All titrations were carried out at $25 \pm 0.1°C$, in a double-walled glass cell, through the outer jacket of which water was circulated from a constant temperature bath.

The acid-dissociation constants of the ligands were determined potentiometrically by titrating the ligand ($40\,cm^3$) solution (1.25 or 2.50 mmoles) at constant ionic strength 0.1 M (adjusted with $NaNO_3$) in 25% dioxane–water mixture. The stability constants of the binary complexes were determined by titrating $40\,cm^3$ of solutions of Cu^{2+} (0.625 or 1.25 mmoles), the ligand (1.25 or 2.50 mmoles) and $NaNO_3$ (0.1 M) in 25% dioxane–water mixtures. The conditions for measuring stability constants of the ternary complexes were the same as those adopted for the binary ones, however, the solutions contained equivalent amounts of Cu^{2+}, dehydroacetic acid (HD) and the amino acids in a concentration ratio of $1:1:1$ (1.25 mmoles). All titrations were performed in a purified N_2 atmosphere using aqueous 0.05 M NaOH (in 0.1 M $NaNO_3$). Values of pK_w in dioxane–water mixtures and at different temperatures were determined as described previously [14]. Various amounts of standard NaOH solution were added to a 0.10 M $NaNO_3$ solution. $[OH^-]$ was calculated from the amount of base added; $[H^+]$ was calculated from the pH value. The values obtained in this way at 25°C for $-\log[H^+][OH^-]$, pK_w, are 13.85, 14.23, 14.92, 15.12 and 15.63 for 12.25, 25.0, 50.0, 62.5 and 75.0%, respectively. The values obtained for 25% dioxane–water mixtures are 14.54, 14.38, 14.23, 14.07 and 13.91 for 15, 20, 25, 30 and 35°C, respectively.

Calculations were performed using the computer program [15] MINIQUAD-75 on an IBM computer. The accepted model gave the best statistical fit and was chemically consistent with the titration data without any system bias in residuals [15]. The formation constants of the general species MDLH, where M, D, L and H refer to metal, dehydroacetic acid, amino acids and proton, respectively, are listed in tables 1–3. The concentration distribution diagrams were obtained using the program SPECIES (L. Pettit, Personal communication) under the experimental conditions described.

3. Results and discussion

The acid dissociation constant (pK_a) of dehydroacetic acid was determined by direct potentiometric measurements as 5.53 ± 0.01. The proton may be released from the

Table 1. Protonation constants of dehydration and formation constants (log values) of its Cu^{2+} complex in dioxane–water solution of different composition at 25°C and 0.1 M ionic strength.

Equilibrium	12.5%[a]	25%	50%	62.5%	75%
$H^+ + D^- \rightleftharpoons HD$	5.18(0.01)[b]	5.53(0.01)	6.04(0.01)	6.35(0.01)	6.61(0.01)
$Cu^{2+} + D^- \rightleftharpoons CuD^+$	5.85(0.04)	6.38(0.03)	7.87(0.03)	8.75(0.03)	9.88(0.04)
$Cu^{2+} + 2D^- \rightleftharpoons CuD_2$	9.26(0.06)	10.71(0.03)	12.59(0.04)	13.92(0.04)	15.74(0.03)
$Cu^{2+} + D^- + OH^- \rightleftharpoons CuD(OH)$	12.05(0.06)	13.47(0.04)	14.76(0.07)	16.03(0.04)	15.98(0.05)

[a]Percentage of dioxane (v/v); [b]standard deviation is given in parentheses.

Table 2. Formation constants (log values) for binary complexes of dehydroacetic acid in 25% (v/v) dioxane–water solution at 25°C and 0.1 M ionic strength.

Equilibrium	Cu^{2+}	Ni^{2+}	Co^{2+}	Zn^{2+}	Mn^{2+}
$M^{2+} + OH^- \rightleftharpoons M(OH)^+$	7.36(0.07)	5.81(0.09)	6.57(0.06)	7.27(0.07)	8.82(0.03)
$M^{2+} + 2OH^- \rightleftharpoons M(OH)_2$	14.64(0.05)	11.07(0.08)	13.52(0.08)	13.70(0.06)	14.81(0.07)
$M^{2+} + D^- \rightleftharpoons MD^+$	6.38(0.03)	4.13(0.03)	3.62(0.03)	3.89(0.03)	2.87(0.08)
$M^{2+} + 2D^- \rightleftharpoons MD_2$	10.71(0.03)	7.86(0.01)	6.83(0.05)	6.64(0.01)	5.66(0.06)
$M^{2+} + D^- + OH^- \rightleftharpoons MD(OH)$	13.47(0.04)	10.93(0.05)	11.52(0.04)	13.47(0.04)	12.39(0.03)

Table 3. Formation constants of binary and ternary complexes of Cu^{2+} involving dehydroacetic and amino acids in 25% (v/v) dioxane–water solutions at 25°C and 0.1 M ionic strength.[a]

| Ligand	$\log\beta_{0011}$	$\log\beta_{0012}$	$\log\beta_{1010}$	$\log\beta_{1020}$	$\log\beta_{1110}$
Glycine	9.49(0.01)	11.57(0.04)	8.18((0.01)	15.23(0.01)	13.36(0.06)
Alanine	9.92(0.01)	13.75(0.01)	9.22(0.03)	16.24(0.04)	13.99(0.01)
Proline	10.02(0.01)	13.17(0.06)	8.99(0.01)	16.52(0.02)	14.09(0.08)
β-phenylalanine	9.06(0.01)	11.22(0.05)	8.64(0.01)	15.76(0.02)	13.89(0.07)
Valine	9.41(0.01)	11.37(0.07)	8.29(0.01)	15.63(0.02)	13.75(0.07)
Iso-leucine	9.49(0.01)	11.41(0.08)	8.17(0.01)	15.33(0.02)	13.43(0.06)
Histidine	9.26(0.01)	15.04(0.01)	10.07(0.02)	18.52(0.05)	16.36(0.04)
Histamine	9.81(0.01)	15.92(0.01)	9.37(0.01)	15.56(0.03)	15.48(0.05)

[a]$\log\beta_{CuDLH}$, where M, L, D and H are the coefficients of copper, dehydroacetic acid, amino acids and protons, respectively.

hydroxyl group as shown below:
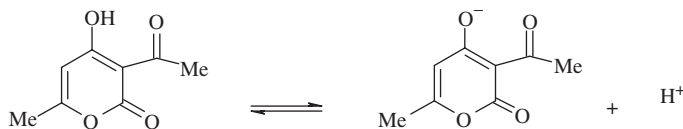
3.1. *Binary complexes of dehydroacetic acid*

The stability of binary complexes of Cu^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+} and Zn^{2+} with dehydroacetic acid was studied applying potentiometric measurements. The stability constants of their complexes are shown in tables 1 and 2. The potentiometric titration curves for Cu^{2+}, Ni^{2+}, Mn^{2+}, Zn^{2+} or Co^{2+} with HD are significantly lower than the HD titration curve, corresponding to formation of a complex through release of a proton. The potentiometric data are fitted well assuming formation of $M(D)^+$ (1100), $M(D)_2$ (1200) and $M(D)(OH)$ (110-1), where D^- stands for the ionized form of dehydroacetic acid (scheme 1). This model was tested by comparing the experimental titration data points and the theoretical curve calculated from the values of acid dissociation constants of HD and formation constants of the Cu^{2+} complex, taken as a representative (figure 1). The good fit is an indication of the validity of the complex formation model.
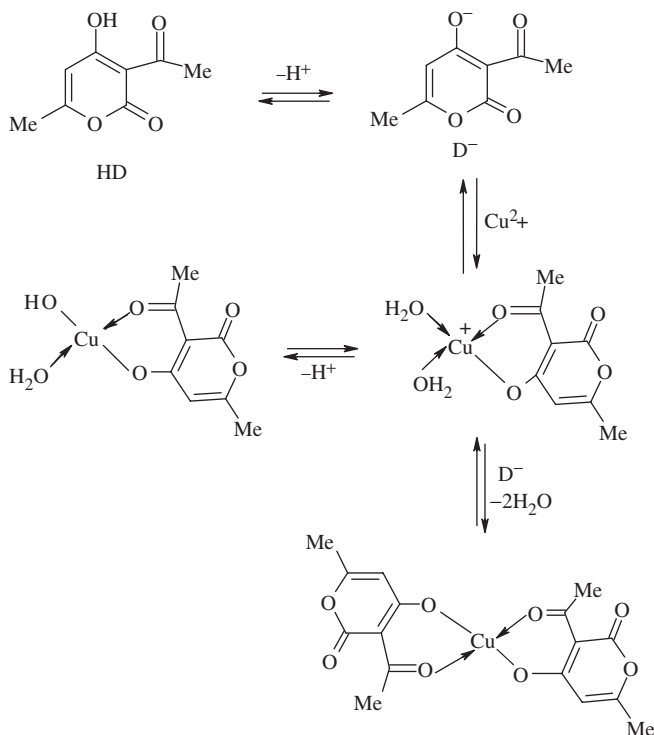
Scheme 1. Complex formation equilibria of Cu^{2+} with dehydroacetic acid.

From the concentration distribution curve of Cu^{2+} complex, figure 2, $Cu(D)^{+}$ species dominates at low pH and has a maximum concentration of 84.1% at pH $\approx$ 3.5. The $Cu(D)_2$ species dominates in the pH range 4–8, *i.e.* it is the main species in the physiological pH range (maximum concentration of 66.0% at pH $=$ 6.4). The monohydroxo species (CuDOH) exists at higher pH range and has a maximum concentration of 68.1% at pH $\approx$ 8.9.

The electronic absorption spectra of aqueous Cu^{2+} and a solution of Cu^{2+} and HD prepared at pH $\sim$ 4 and in different molar ratios are compared.

The broad band at 805 nm of free Cu^{2+} ($^2B_{1g} \leftarrow {}^2A_{1g}$ transition [16]) undergoes a blue shift to 724 and 690 nm in the spectra of solution mixtures of Cu^{2+} and HD with molar ratios of 1:1 and 1:2 (Cu^{2+}:HD), respectively. The first shift indicates coordination of one HD and the second shift is due to coordination of the second HD.

3.2. *Relation of stability constant with metal ion properties*

The stability constant of metal ion complexes is affected by the metal properties.
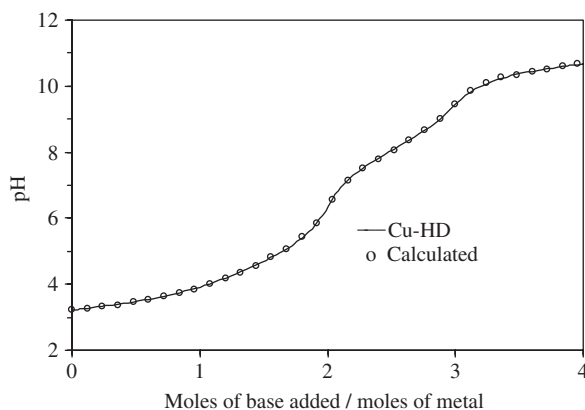

Figure 1. Potentiometric titration curve of 0.625 mmoles of Cu^{2+} and 1.25 mmoles of HD.
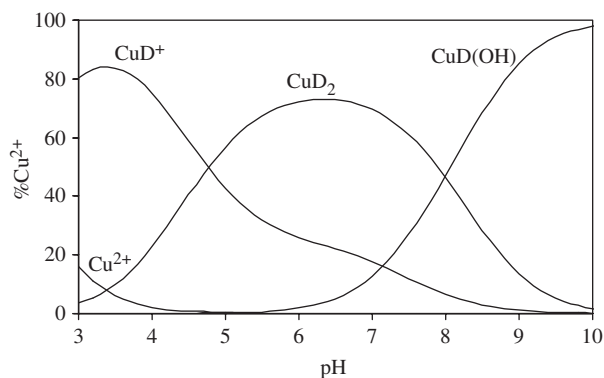

Figure 2. Concentration distribution of various species as a function of pH in the Cu-(HD) system at concentration of 0.625 and 1.25 mmol L^{-1} for Cu^{2+} and HD, respectively.

3.3. *Atomic number and ionic radius (R)*

The stability constants increase with increasing atomic number reaching a maximum in the case of Cu^{2+} followed by a decrease for Zn^{2+} as shown by the following sequence (figure 3): $Mn^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$, the Irving–William's order [18] for divalent 3d metals. Figure 3 reflects a linear relation between $\log \beta_{110}$ and $1/R$ [19], explained on the grounds that interaction of metal and ligand is electrostatic and the stability constant for complexes of the same charge should be inversely proportional to metal ion radii.

3.4. *Electronegativity*

With respect to increasing electronegativity of the metals, the electronegativity difference between a metal atom and donor atom of the ligand will decrease; hence
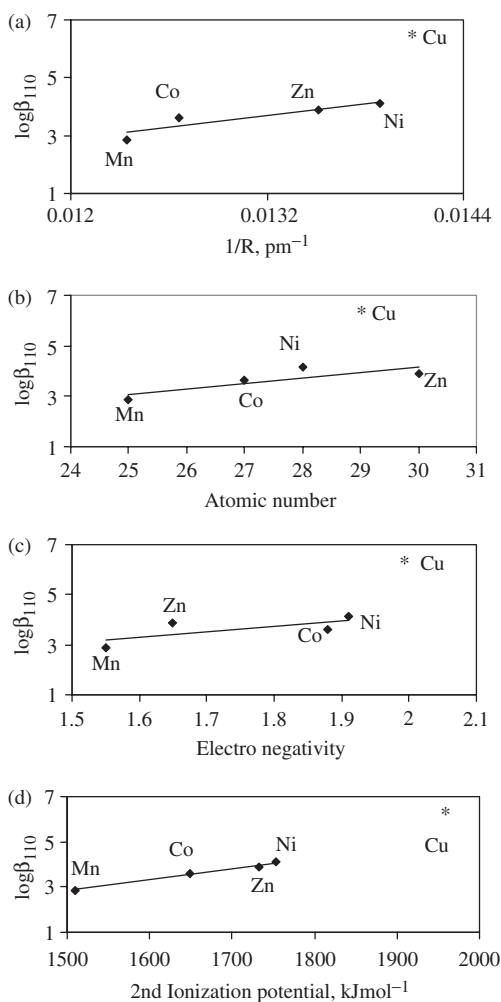

Figure 3.   Effect of metal ion properties on the stability constants of metal complexes.

the metal–ligand bond would have more covalent character resulting in greater stability of the metal chelate. Plotting $\log \beta_{110}$ values against electronegativity [17] of the metal atoms gives a straight line as shown in figure 3.

3.5. *The ionization potential*

A linear correlation has been obtained between $\log K_1$ and second ionization potentials of bivalent metal ions studied, confirming the validity of the Van Panthaleon-Van Ech equation [19]:

$$\log K_1 = P(I - q)$$

where I is the ionization potential, P and q are constants depending on the ligand and the experimental conditions but independent of the metal ion. P depends on the number of the donor groups and q is the number of electrons involved. Plotting $\log \beta_{110}$ values against the ionization potential of the metal atoms gives a straight line as shown in figure 3.

　　The stability constant of the Cu^{2+} complex is quite large compared to the other metals. The ligand field will give Cu^{2+} some extra stabilization due to tetragonal distortion of the octahedral symmetry [20]. Thus, $\log K_1$ value for the Cu^{2+} deviates significantly when $\log K_1$ values of metal chelates are plotted against properties of the metal ions.

3.6. *Effect of temperature*

The values obtained for $\Delta H°$, $\Delta S°$ and $\Delta G°$ associated with protonation of HD, equation (1) and complex formation with Cu^{2+}, equations (2) and (3) were calculated from the temperature dependence of the data in table 4; $\Delta H°$ and $\Delta S°$ were obtained by a linear least square fit of $\ln K$ *versus* $1/T$ ($\ln K = -\Delta H°/RT + \Delta S°/R$).

$$D^- + H^+ \rightleftharpoons HD \tag{1}$$

$$CU^{2+} + D^- \rightleftharpoons CuD^+ \tag{2}$$

$$CuD^+ + D^- \rightleftharpoons CuD_2 \tag{3}$$

　　The results obtained are summarized in table 5 and can be interpreted as follows:

(1) The neutralization reaction is exothermic; desolvation is an endothermic process.
(2) The protonation of D^- has positive entropy due to increased disorder as a result of desolvation and breaking of hydrogen bonds.

Table 4.　Log formation constants for binary complexes of (HD) with Cu^{2+} at different temperatures.[a]

Equilibrium	15°C	20°C	25°C	30°C	35°C
$H^+ + D^- \rightleftharpoons HD$	5.59(0.01)	5.57(0.01)	5.53(0.01)	5.48(0.01)	5.45(0.01)
$Cu^{2+} + D^- \rightleftharpoons CuD^+$	6.81(0.05)	6.59(0.02)	6.38(0.03)	6.21(0.02)	6.12(0.02)
$Cu^{2+} + 2D^- \rightleftharpoons CuD_2$	11. 21(0.06)	10.96(0.03)	10.71(0.03)	10.50(0.02)	10.36(0.06)
$Cu^{2+} + D^- + OH^- \rightleftharpoons CuD(OH)$	14.10(0.07)	13.76(0.03)	13.47(0.04)	13.19(0.04)	12.99(0.08)

[a]Standard deviations are given in parentheses.

The stepwise stability constants of the complexes formed at different temperatures were calculated and the average values are included in table 4. These values decrease with increasing temperature, indicating that complexation is more favorable at lower temperatures. From these results the following conclusions can be made:

(1) All values of ΔG° for complexation are negative, indicating the spontaneity of the coordination process.
(2) The negative values of ΔH° show that the coordination process is exothermic, indicating that the complexation reactions are favored at low temperatures.
(3) ΔG° and ΔH° values for the 1 : 1 complexes are more negative than those of the 1 : 2 complexes, table 5, attributed to both the steric hindrance produced by the entrance of a second ligand and charge neutralization.

The ΔS° values for all investigated complexes are positive, except for the formation of CuD^{+} species, indicating increase in entropy by release of bound solvent is greater than the decrease resulting from coordination itself.

3.7. *Effect of solvent*

The effect of dioxane as a solvent on the acid-base and Cu^{2+} complex formation equilibria with dehydroacetic acid was investigated. The results (table 2 and figure 5) show an increase of pK_a of HD with increase in concentration of dioxane (decreasing dielectric constant). As the dielectric constant decreases, the ion-ion interaction involving the proton and the anionic oxygen donor of the ligand increases, consequently the pK_a increases [21].

The medium effect on the equilibrium constant of Cu^{2+}–dehydroacetic acid complex formation (table 1 and figure 4) reveals an increase of formation constant upon addition of dioxane. This can be explained as a result of increasing electrostatic forces between Cu^{2+} ion and anionic oxygen of the ligand, leading to extra complex stability.

3.8. *Ternary complexes of Cu^{2+}, HD and amino acids*

The potentiometric data of the ternary complexes involving simple amino acids best fits assuming a complex of stoichiometric coefficient 1110. The stability constant values ($\log \beta_{1110}$) of simple amino acid complexes show the proline complex has the highest value, due to the highest basicity of the proline amino group. The concentration distribution diagram of glycine complex (figure 6) shows the ternary complex (1110) attains its maximum formation of 42.5% at $pH \approx 7.3$. This means that in the physiological pH range interaction between dehydroacetic acid and amino acid is quite feasible.

Table 5. Thermodynamic parameters for the equilibria of Cu(İİ) and HD complexes.

Equilibrium	$\Delta H^{\circ a}$ (kJ mol^{-1})	ΔS° (JK^{-1} mol^{-1})	ΔG° (kJ mol^{-1})
1. $D^{-} + H^{+} \rightleftharpoons HD$	−12.6(0.5)	63.6(0.8)	−31.5(0.7)
2. $Cu^{2+} + D^{-} \rightleftharpoons CuD^{+}$	−59.9(0.8)	−78.3(0.9)	−36.6(0.7)
3. $CuD^{+} + D^{-} \rightleftharpoons CuD_2$	−13.6(0.5)	37.3(0.7)	−24.7(0.6)
4. $CuD^{+} + OH^{-} \rightleftharpoons CuD(OH)$	−35.0(0.7)	18.1(0.4)	−40.4(0.7)

[a]Standard deviations are given in parentheses.

Histidine forms the ternary complex 1110. Its stability constant value is higher than those of simple amino acids and in fair agreement with that of histamine, indicating that histidine coordinates by the amino and imidazole groups, similar to histamine. The concentration distribution diagram, depicted in figure 7, showed that the predominant species is 1110 over a wide pH range of 4–11, with a maximum formation of $\approx 86\%$.
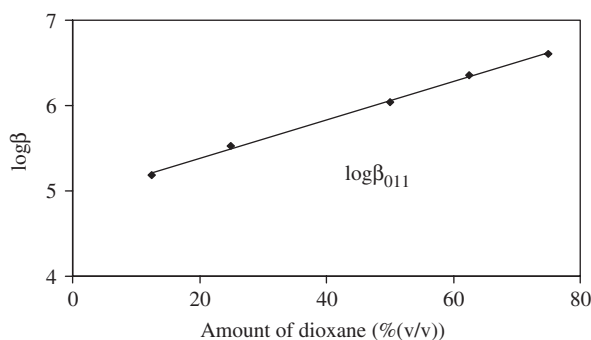

Figure 4.   Effect of solvent on $\log \beta$ of (HD).
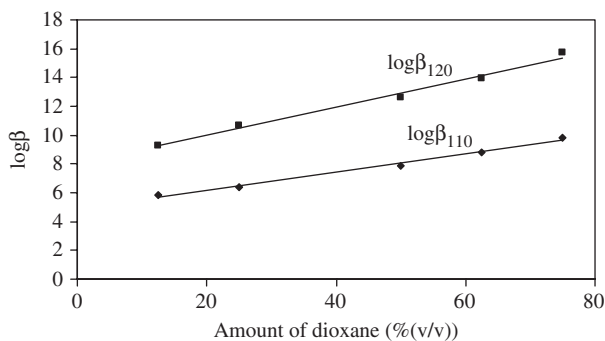

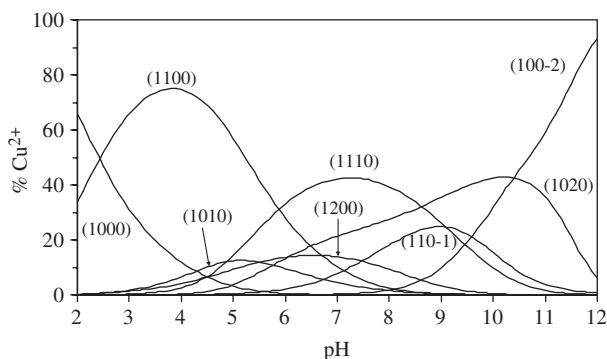Figure 5.   Effect of solvent on $\log \beta$ of Cu–HD complex.

Figure 6.   Concentration distribution of various species as a function of pH in the Cu–HD–glycine system at concentrations of $1.25 \, \text{mmol} \, \text{L}^{-1}$ for each of Cu^{2+}, HD and glycine.
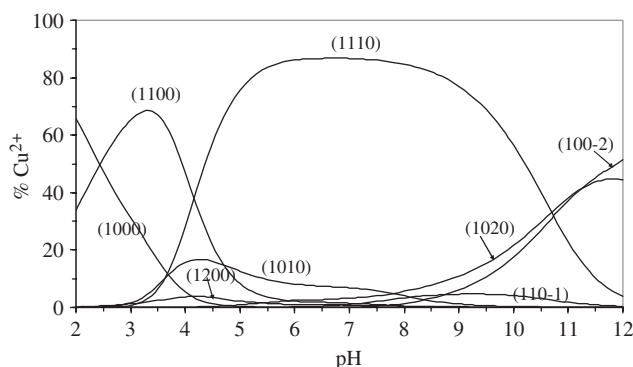
Figure 7. Concentration distribution of various species as a function of pH in Cu–HD–histidine system at concentrations of $1.25 \, mmol \, L^{-1}$ for Cu^{2+}, HD and histidine.

4. Conclusion

The present investigation describes the complex formation equilibria of dehydroacetic acid with some selected metal ions of biological significance. Stability constant data of such metal complexes allow calculation of the equilibrium distribution of dehydroacetic acid in biological fluids where the metal ions are present, giving a basis for understanding the mode of action of such metal species under physiological condition.

Traditionally, water has been considered as the solvent to represent biological conditions. Although this is generally true, a lower polarity has been detected in some bio-chemical micro-environments, such as active site of enzymes and side chains in proteins [22–26]. It was suggested that these properties can be simulated by water/ dioxane mixtures. Consequently, a study of the Cu^{2+}-dehydroacetic acid complex formation equilibria in dioxane-water solutions of different compositions could be of biological significance. The formation of dehydroacetic acid complexes would be more favored in biological environments of lower dielectric constant.

Amino acids form stable mixed-ligand complexes with Cu^{2+} and dehydroacetic acid. The mixed ligand complexes are formed in the physiological pH range, indicating that interaction between Cu^{2+}, dehydroacetic acid and protein is quite feasible.

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