

## Potentiometry, Effect of Solvent and Thermodynamics of Novel Carbohydrazone and Its Transition Metal(II) Complexes

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The ligand (2E,2'E)-2,2'-(carbonylbis(hydrazine-2-yl-1-ylidene))dipropionic acid (CBHP) had been synthesized and characterized using different tools of analysis. Protonation constants of the novel (2E,2'E)-2,2'-(carbonylbis(hydrazine-2-yl-1-ylidene))dipropionic acid (CBHP) ligand and its corresponding metal-CBHP stability constants with Cu(II), Ni(II), Co(II) and Zn(II) ions were measured in aqueous solution at ionic strength (I) of 0.1 mol.dm<sup>-3</sup> NaNO<sub>3</sub>. The order of stability for the formed complexes with reference to the metal ions complies with this order Cu(II) > Ni(II) > Co(II) > Zn(II) in harmony with the Irving-Williams stability order. The speciation of different species in solution has been assessed as a function of pH. The thermodynamic parameters were calculated and discussed. The effect of solvent on the protonation equilibria of the ligand was also discussed.

**Keywords:** Carbohydrazone; Complex; speciation; Thermodynamics; Nickel, Potentiometry.

### 1. INTRODUCTION

Carbohydrazones are adaptable ligands in coordination to metals because of their simplicity of synthesis and variety in addition to structural possibilities. They act also as intense antimicrobial, antioxidant, anticonvulsant, cytotoxic, catalytic and pharmacological agents [1-4]. Carbohydrazones have gigantic biological applications because of their N- and O-donor sites. Carbohydrazones exist in balance of different tautomers because of special structural features which significantly influence their chelating capacity [5]

Determination of the protonation constants of a certain substance play a crucial role in preparative chemistry and can also provide a serious data about drug features like solubility, lipophilicity, acidity, basicity [6,7], binding to receptors [7-9] and porousness [10].

In order to understand the physiochemical behavior of novel compounds, their protonation constants were required to ascertain the concentration of the ionized species of these compounds at any pH [11] using different systems, for example, potentiometry, conductometry and spectrophotometry. Here, a potentiometric procedure was utilized on the grounds that it has the greatest region of applicability and reliability [12-14].

Recently, the attention paid the conceivable variable biological activities of hydrazones and their metal complexes however studies dealing with protonation and complex formation equilibria of hydrazones and their complexes are still uncommon.

Thus, taking into consideration, the above mentioned facts and in pursuit of the research program [15-27], we have attached a great importance to the study of bio-ligands and their complexes, we have synthesized a novel carbohydrazone Schiff base, (2E,2'E)-2,2'-(carbonylbis(hydrazine-2-yl-1-ylidene))dipropionic acid (CBHP) ligand (Scheme 1) and carried out a systematic study on its interactions with the some bivalent transition metals at  $I = 0.1 \text{ mol.dm}^{-3} \text{ NaNO}_3$  and different temperatures in aqueous solution employing potentiometric technique. We report herein the protonation constant of the carbohydrazone, the effect of both solvent temperature, the stability constants of the complexes and the thermodynamics associated with the reactions under study.

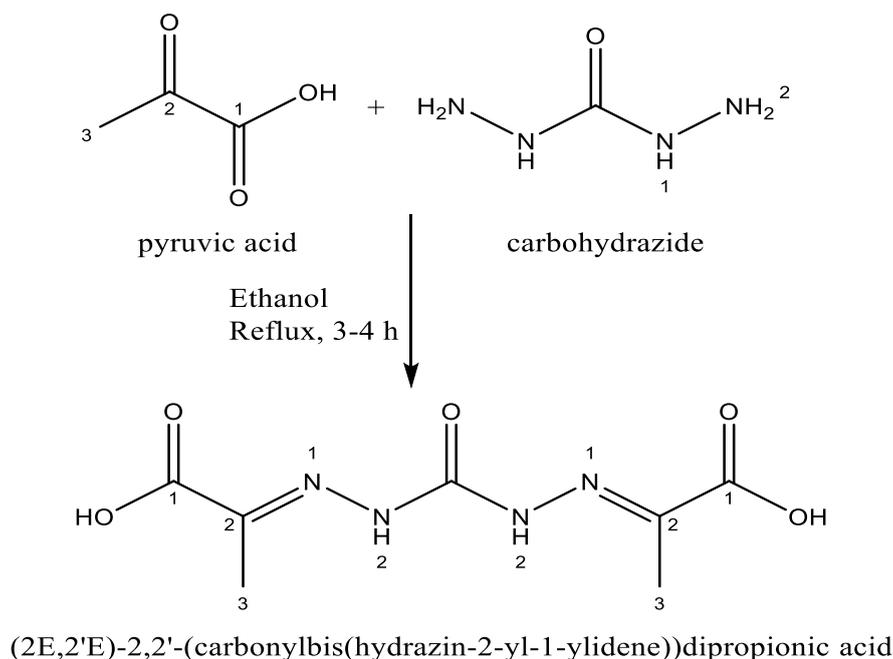
## 2. EXPERIMENTAL

### 2.1. Materials and reagents

The utilized chemicals were used as provided from the chemical companies (BDH and Aldrich) without further purification including  $\text{HNO}_3$ ,  $\text{NaOH}$ ,  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ ,  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ ,  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ,  $\text{ZnCl}_2$ , dioxane and ethanol.

### 2.2. Synthesis of (2E,2'E)-2,2'-(carbonylbis(hydrazine-2-yl-1-ylidene))dipropionic acid (CBHP) ligand.

The ligand, (2E,2'E)-2,2'-(carbonylbis(hydrazin-2-yl-1-ylidene))dipropionic acid (CBHP) was prepared by adding of pyruvic acid (13.90 ml, 2 mole) is added to ethanolic solution of carbohydrazide (9.0086 g, 1 mole) and the mixture is refluxed for 3-4 h (Scheme 1). The produced white precipitate washed by absolute ethanol followed by diethyl ether and checked by TLC. The melting points of the ligand, CBHP found to be 172 °C (yield 92%).



**Scheme 1.** Synthesis of CBHP carbohydrazone ligand.

### 2.3. Instruments and potentiometric titrations

Potentiometric measurements were made utilizing a Metrohm 848 Titrino equipped with a Dosimat unit (Switzerland-Herisau). Potentiometric titrations were carried out as given in literature [28-31].

The proton association constants of the carbohydrazone ligand were determined potentiometrically utilizing ( $1.25 \times 10^{-3}$  mol.dm<sup>-3</sup>) of the CBHP-ligand solution (40 cm<sup>3</sup>). The stability constants of the M(II)-CBHP complexes were assessed utilizing potentiometric data obtained from (40 cm<sup>3</sup>) mixture containing MCl<sub>2</sub>.nH<sub>2</sub>O ( $1.25 \times 10^{-3}$  mol.dm<sup>-3</sup>) + CBHP ( $1.25 \times 10^{-3}$  mol.dm<sup>-3</sup>/2.5 × 10<sup>-3</sup> mol.dm<sup>-3</sup>).

The equilibrium constants estimated from the titration data are defined by Eqs. (2) and (3), where M, L and H represent the metal(II) ion, carbohydrazone ligand and H<sup>+</sup>, respectively.

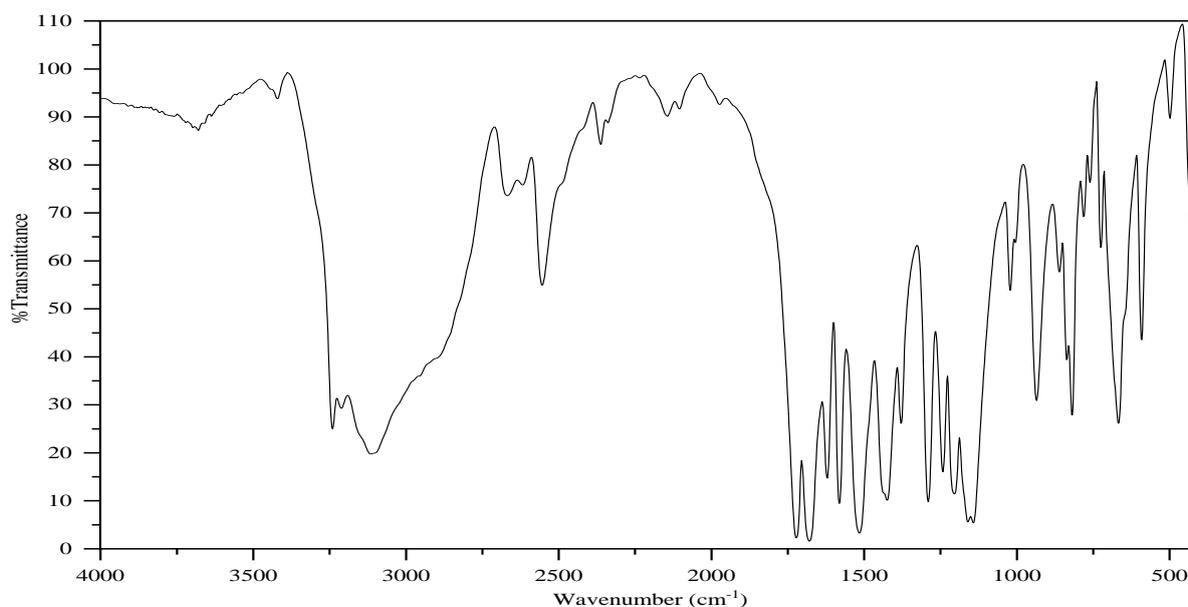


$$\beta_{pqr} = \frac{[M_p(L)_q(H)_r]}{[M]^p [L]^q [H]^r} \quad (3)$$

The calculations and speciation diagrams were carried out using MINIQUAD-75 [36] and the program SPECIES [37] respectively.

### 3. DISCUSSION

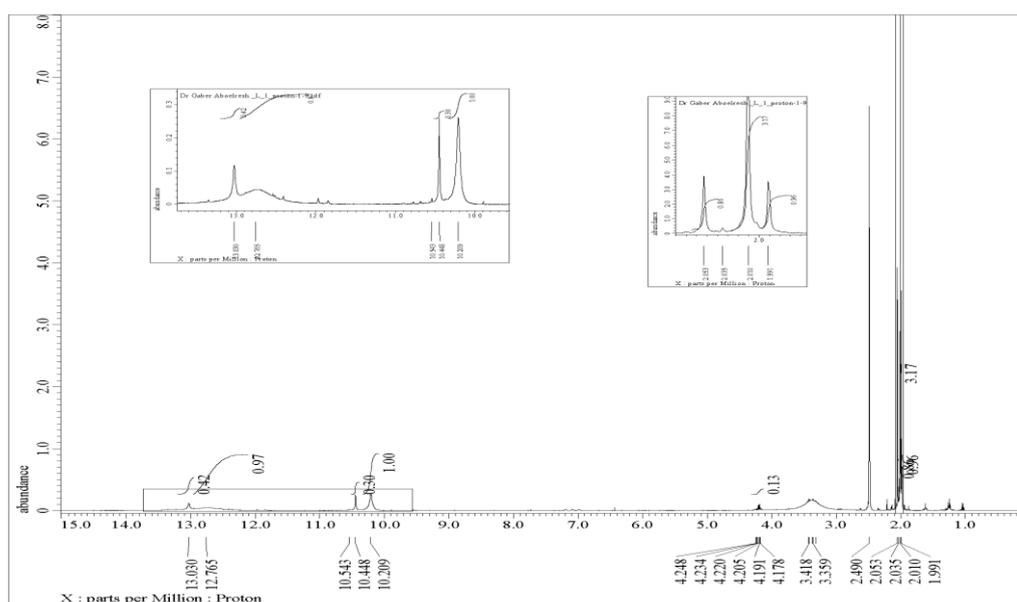
#### 3.1. FT-IR spectrum of ligand, CBHP



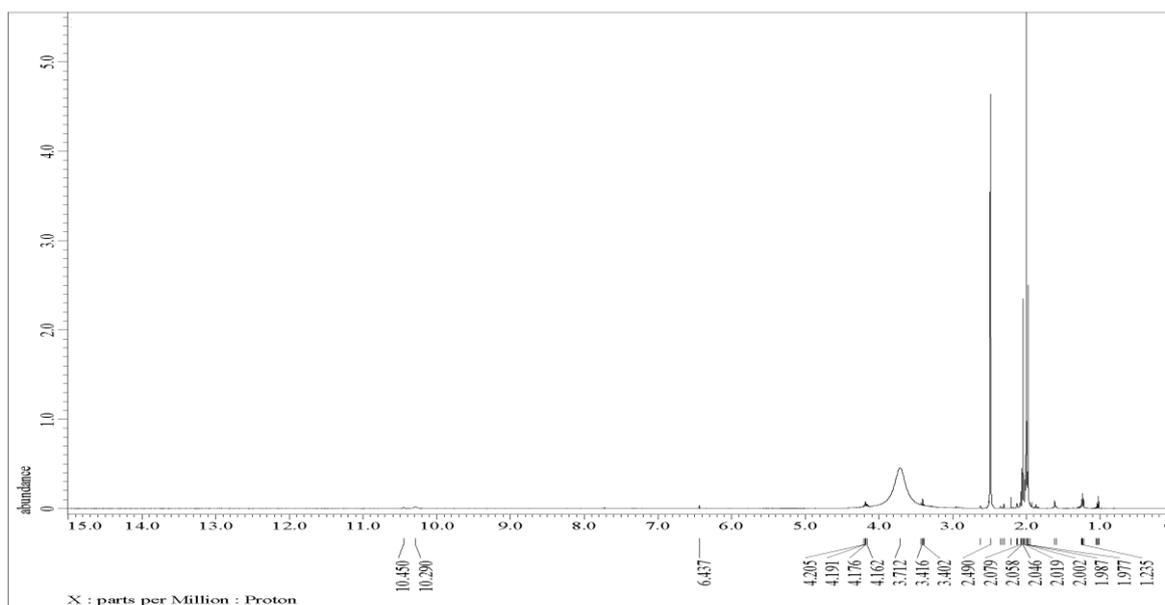
**Figure 1.** FT-IR spectrum of CBHP hydrazone ligand.

The FT-IR spectrum of the ligand, CBHP (Fig. 1) displayed strong bands at 3240 and 1722  $\text{cm}^{-1}$  assigned to  $\nu(\text{OH})$  and  $\nu(\text{C}=\text{O})$  of the carboxylic group. Also, the bands at 3115 and 1679  $\text{cm}^{-1}$  belong to the  $\nu(\text{NH})$  and  $\nu(\text{C}=\text{O})$  of the hydrazone moiety. The bands at 1621 and 1021  $\text{cm}^{-1}$  attributed to  $\nu(\text{C}=\text{N})_{\text{azomethine}}$  [38] and  $\nu(\text{N}-\text{N})$  [39], respectively.

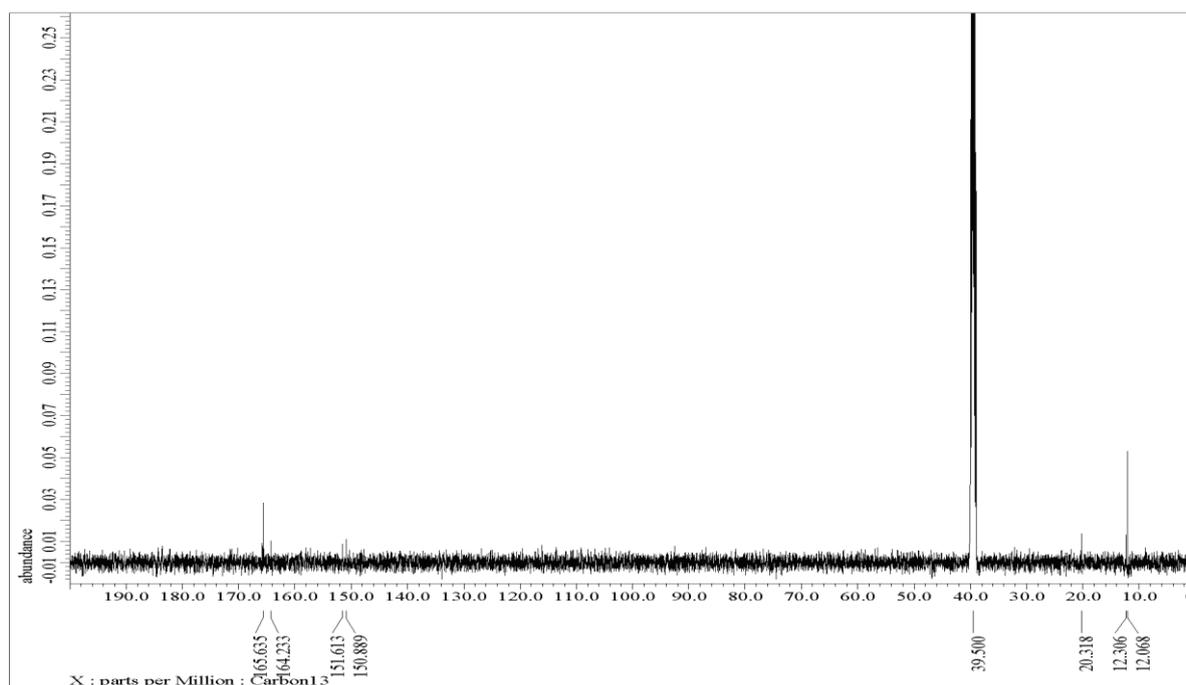
#### 3.2. $^1\text{H}$ and $^{13}\text{C}$ -NMR spectra of CBHP hydrazone ligand



**Figure 2.**  $^1\text{H}$ -NMR spectrum of CBHP hydrazone ligand in  $\text{d}_6$ -DMSO.



**Figure 3.**  $^1\text{H}$ -NMR spectrum of CBHP hydrazone ligand in  $d_6$ -DMSO with addition of  $\text{D}_2\text{O}$ .

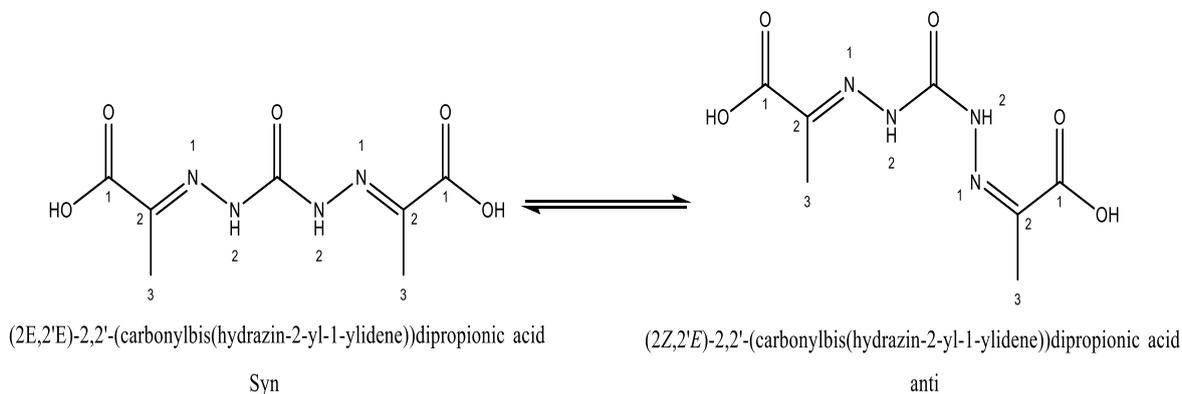


**Figure 4.**  $^{13}\text{C}$ -NMR spectrum of CBHP hydrazone ligand in  $d_6$ -DMSO.

The  $^1\text{H}$ -NMR spectrum in  $d_6$ -DMSO (Fig. 2) displayed two signals at  $\delta = 10.448$  and  $10.209$  ppm in respect to TMS assignable to (OH) of carboxylic group and (NH) protons, respectively which disappear after addition of  $\text{D}_2\text{O}$  (Fig. 3).

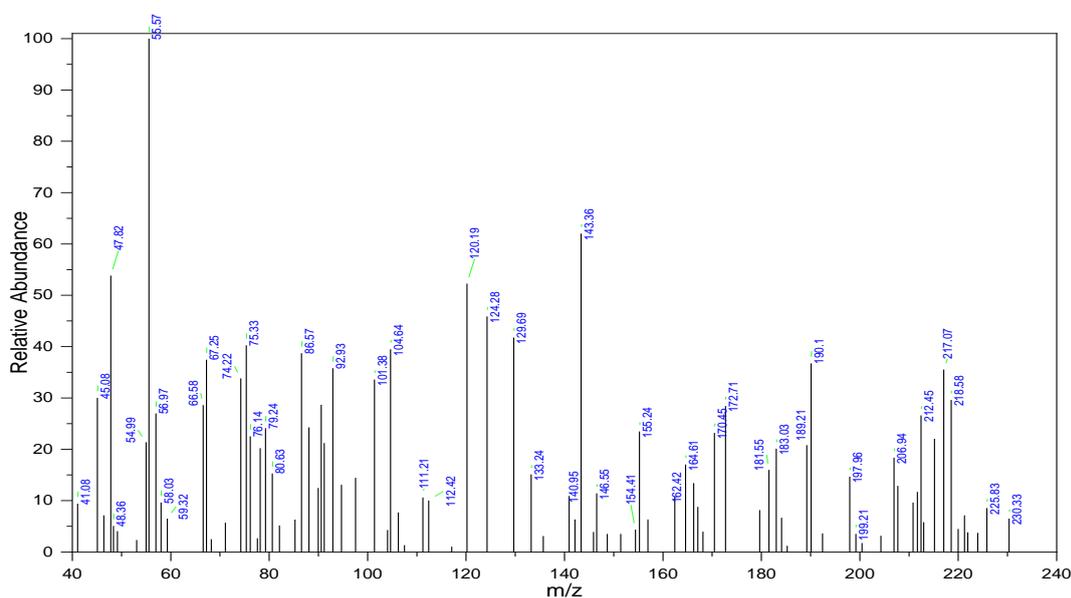
In the  $^{13}\text{C}$ -NMR spectrum (Fig. 4), the multiplier number of carbon signals suggested that the presence of ligand structure in different structures such as syn and anti (Scheme 2) which belong to the

position of carboxylic groups. The signals belong to the  $(C=O)_{\text{carboxylic}}$  appeared at 166.635 and 164.233 ppm. Also, the  $(C=O)$  signals of hydrazone moiety appeared at 151.613 ppm. While the  $(C=N)$  signals lies at 150.889 ppm. Finally, the strong signals at 12.068 and 12.306 assigned to the  $(CH_3)$  groups.

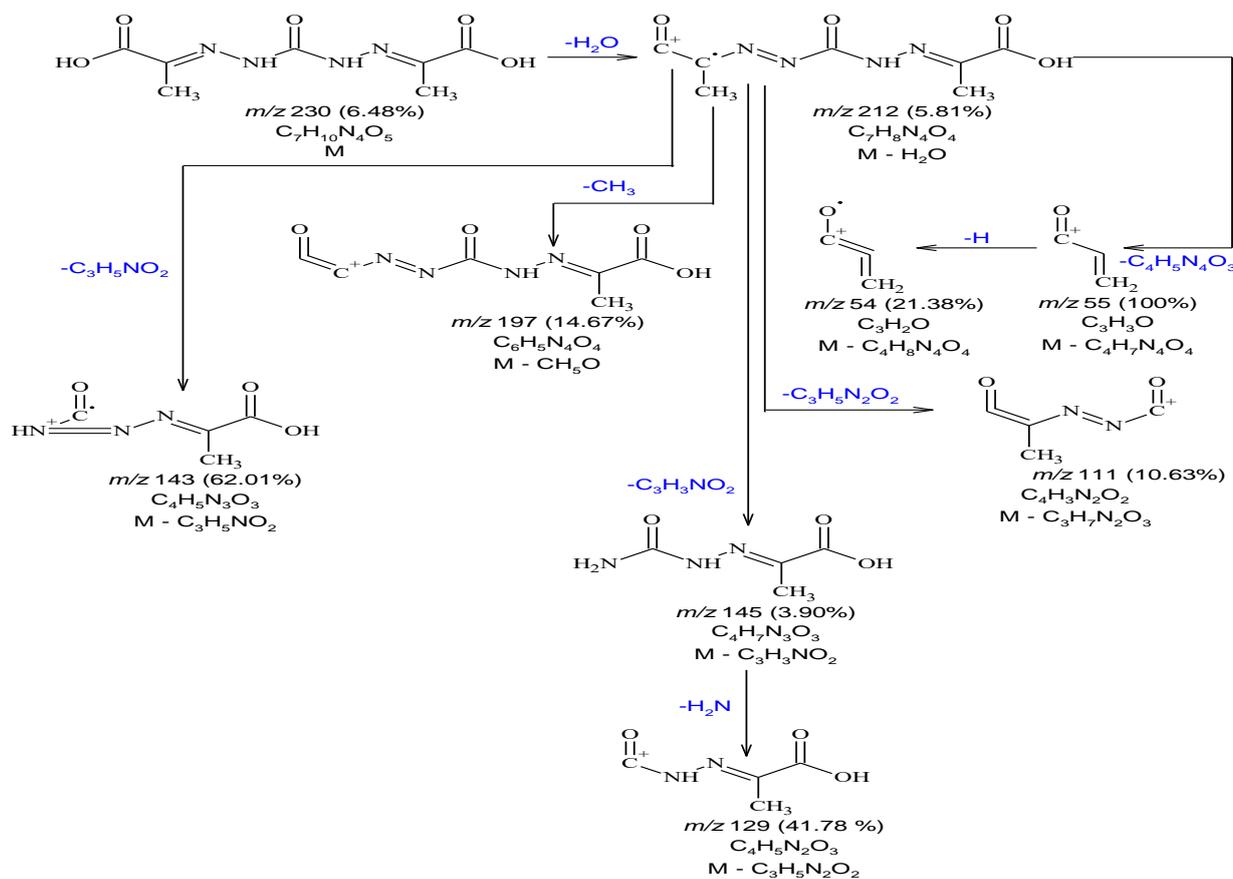


**Scheme 2.** Syn and anti- tautomer of carbohydrazone ligand.

### 3.3. Mass spectrum of CBHP hydrazone ligand



**Figure 5.** Mass spectrum of CBHP hydrazone ligand.



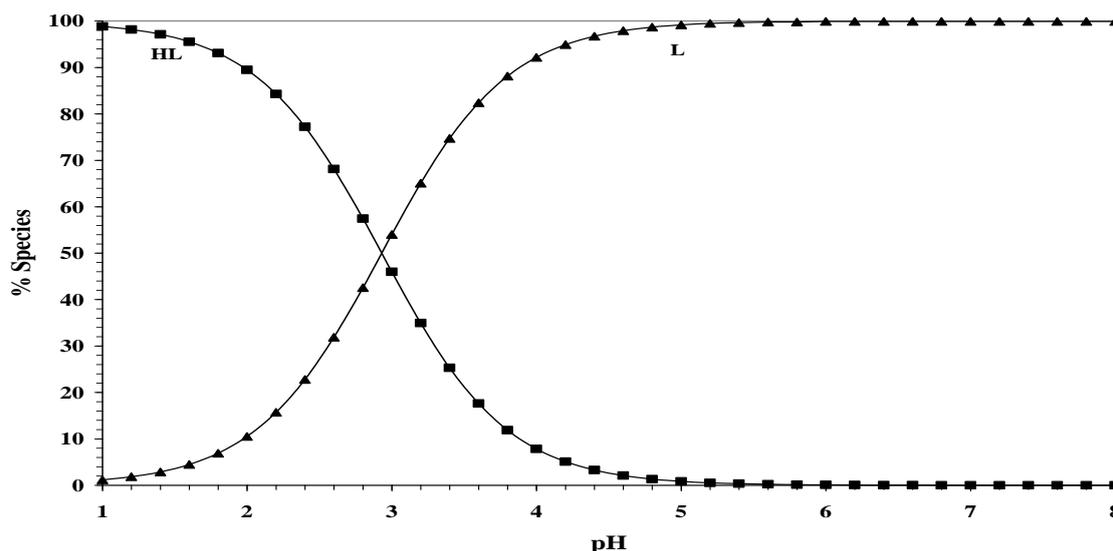
The mass spectrum of CBHP is given in Fig. 5 shows the molecular ion peak for CBHP at  $m/z = 230.33$  (6.48%) corresponding to  $(C_7H_{10}N_4O_5)$  [40]. The fragmentation path of CBHP is given in scheme 3 [41, 42].

### 3.4. Protonation constants of CBHP hydrazone ligand

The protonation constant ( $\log K^H$ ) of the ligand has been utilized for the calculation of the stability constant of the M-CBHP complexes.  $pK$  values for CBHP ligand at different temperatures were listed in Table 1. This carbohydrazone Schiff base ligand acts as monoprotic acid.

**Table 1.** Protonation constants and thermodynamics of of CBHP carbohydrazone ligand in aqueous solution at different temperatures and  $I = 0.1 \text{ mol dm}^{-3} \text{ NaNO}_3$ .

System	$T(^{\circ}\text{C})$	q	$r^a$	$\log_{10}\beta^b \pm \sigma$	$S^c$	$\Delta H^{\circ} (\text{kJ mol}^{-1})$	$\Delta S^{\circ} (\text{JK}^{-1} \text{ mol}^{-1})$	$\Delta G^{\circ} (\text{kJ mol}^{-1})$
CBHP	15	1	1	$3.01 \pm 0.04$	$1.5 \text{ E-}7$	-14.39	8.60	-16.91
	20	1	1	$3.01 \pm 0.05$	$3.4 \text{ E-}6$			
	25	1	1	$2.97 \pm 0.04$	$5.6 \text{ E-}7$			
	30	1	1	$2.93 \pm 0.05$	$4.9 \text{ E-}7$			



**Figure 6.** Species distribution diagram of CBHP hydrazone ligand as a function of pH.

The  $\log_{10}K$  value is related to the attachment of  $H^+$  to the carboxylate group and this is also illustrated in the speciation of the CBHP ligand as a function of pH as given in Fig. 6. In the case of CBHP ligand, if the solution's pH changes near 2.9, it causes a large change in the presence of CBHP ligand. When the pH is 2.0, about 90 % exist as protonated CBHP carbohydrazone ligand molecules, but at a pH of 4.2, over 90 % exists as deprotonated ligand. The  $\log K_{\text{carboxylate}}$  values ranges from (2.89-3.01) is similar to that found in literature for the carboxylate group (2.45-3.33) [43, 44].

### 3.5. Stability constants of the carbohydrazone complexes

The stability constants of M(II)-CBHP carbohydrazone Schiff base complexes were determined in aqueous solution. Comparison of the titration curve of the free CBHP carbohydrazone ligand with those of the complexed CBHP ligand demonstrates that the ML complex curve is lower than the corresponding free CBHP ligand indicating a more release of  $H^+$ .

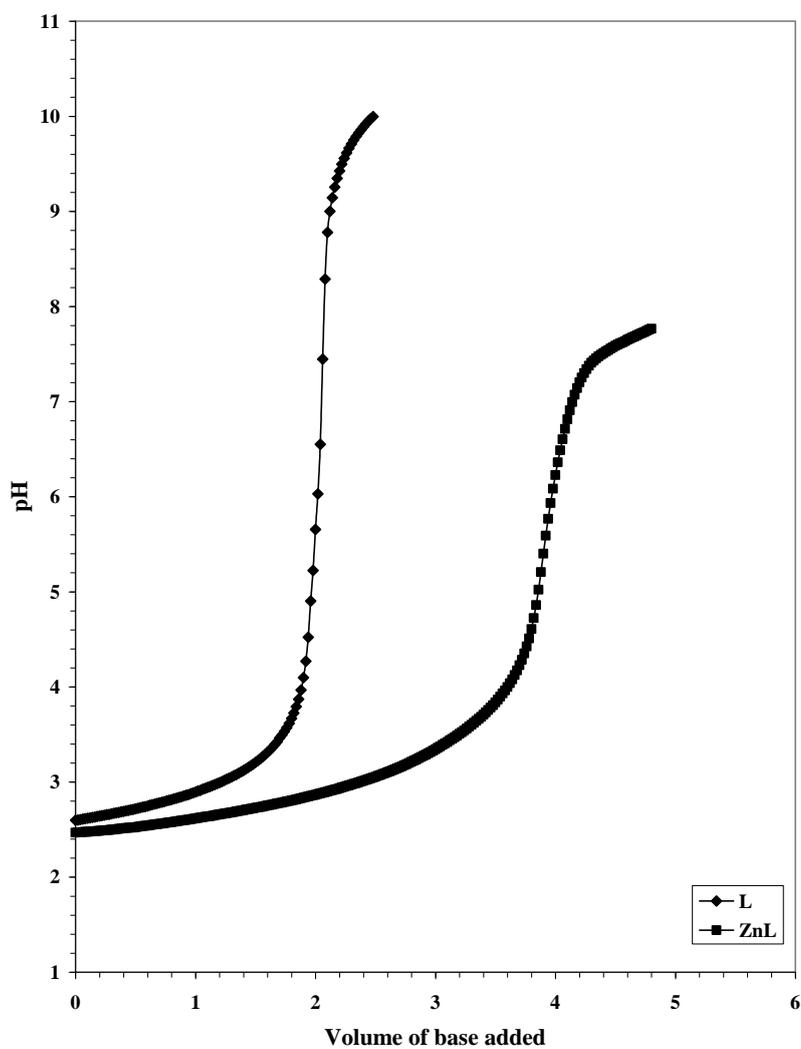
**Table 2.** Stability constants of M(II)-CBHP carbohydrazone ligand in aqueous solution at different temperatures and  $I = 0.1 \text{ mol dm}^{-3} \text{ NaNO}_3$ .

System	$T(^{\circ}\text{C})$	p	q	r	$\log_{10}\beta$	S
Cu-CBHP	15	1	1	0	$11.66 \pm 0.04$	$1.7\text{E-}7$
	20	1	1	0	$11.50 \pm 0.05$	$3.4\text{E-}7$
	25	1	1	0	$11.35 \pm 0.04$	$4.9\text{E-}7$
	30	1	1	0	$11.19 \pm 0.04$	$2.4\text{E-}7$
Ni-CBHP	15	1	1	0	$9.92 \pm 0.06$	$3.8\text{E-}7$
	20	1	1	0	$9.78 \pm 0.05$	$1.4\text{E-}7$
	25	1	1	0	$9.63 \pm 0.04$	$9.1\text{E-}7$

	30	1	1	0	9.51±0.04	2.5E-7
Co-CBHP	15	1	1	0	6.64±0.04	6.4E-7
	20	1	1	0	6.54±0.03	3.8E-7
	25	1	1	0	6.46±0.05	1.9E-7
	30	1	1	0	6.38±0.05	3.7E-7
Zn-CBHP	15	1	1	0	5.01±0.04	2.1E-7
	20	1	1	0	4.93±0.06	7.6E-7
	25	1	1	0	4.85±0.05	5.4E-7
	30	1	1	0	4.78±0.05	2.8E-7

Definitions of stability constants:

$K_{110} = K_{ML} = [ML] / [M][L]$ ; (L = carbohydrazone ligand); (Charges are omitted for simplicity).

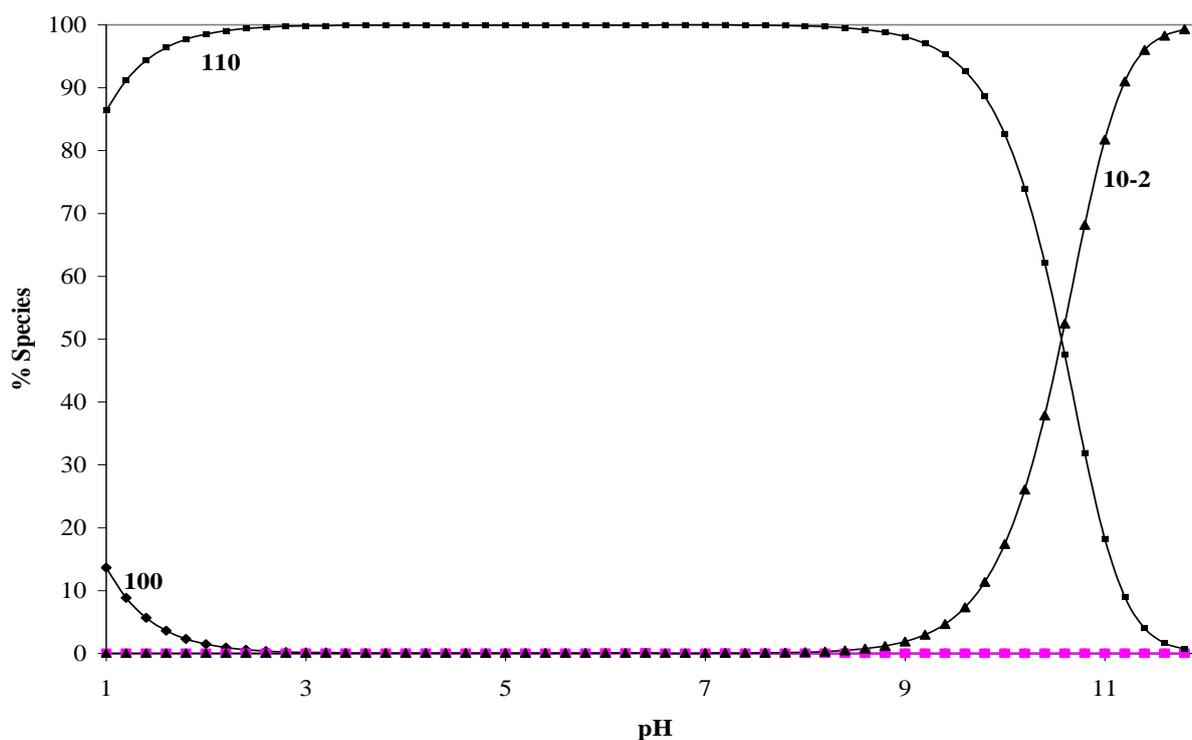


**Figure 7.** Potentiometric titration curve of Zn-CBHP complex.

The potentiometric titration curve of  $Zn^{(II)}$ -CBHP as a representative case of metal(II)-CBHP complexes was given in Fig. 7.

The stoichiometric stability constants of M(II)-CBHP complexes were determined in aqueous solution at various temperatures and these constants are given in Table 2. The data also demonstrated the formation of the M(II)-CBHP complexes with stoichiometric coefficients 1:10.

The species distribution is an integral asset for the appraisal of the concentrations of the species present as a function of pH. It indicates the best conditions of pH, concentration and metal:ligand proportion for synthesis of the complex in the solid state. In order to investigate change in the concentration of the metal(II) complexes with pH, the species distribution diagram for Cu-CBHP system is examined (Fig. 8) as a representative case of metal(II)-CBHP complexes.



**Figure 8.** Species distribution diagram of Cu-CBHP complex species as a function of pH.

Copper(II) ion was found to bind easily with CBHP-ligand to form deprotonated Cu-CBHP complexes. The Cu-CBHP distribution diagram demonstrated that the deprotonated Cu-CBHP complex is formed with most extreme percent of 100 % at pH 5.8.

### 3.6. The relationship between the properties of central metal ion and stability of complexes

So as to clarify why a given ligand prefers binding to one metal rather than another metal, the relation between the periodic table properties [45] and the stability constants of complexes was examined. In this study, it was found that, the stability of M(II)-CBHP carbohydrazone complexes

obeyed this order:  $Zn^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+}$  which is in accordance with Irving-Williams' order [46, 47].

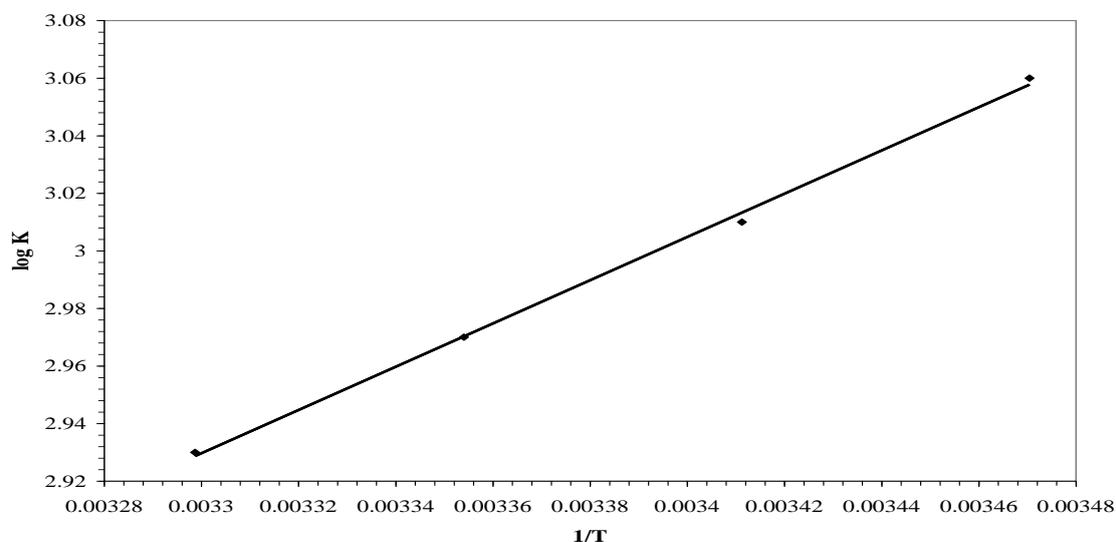
The correlation between the  $\log_{10}K_{ML}$  and the electronegativities of the metal ions under investigation indicates that as the electronegativity of metals increases ( $Zn^{2+}$  (1.65) <  $Co^{2+}$  (1.88) <  $Ni^{2+}$  (1.91) <  $Cu^{2+}$  (2.0)), the difference in electronegativity between the metal atom and the donor atom of the ligand decreases and hence the metal-ligand bond ought to have progressively covalent character, prompting increment the level of stability of complexes.

Generally, it is seen that  $Cu^{2+}$  complex has a large with respect to the other metals. The ligand field had given  $Cu^{2+}$  further stability because of tetragonal distortion of the octahedral symmetry [48-50]. Likewise, this can be ascribed to the way that, the reduction of charge density on the central metal ion diminishes the electrostatic attraction between the cation and the ligand and hence the stability of complexes decreases.

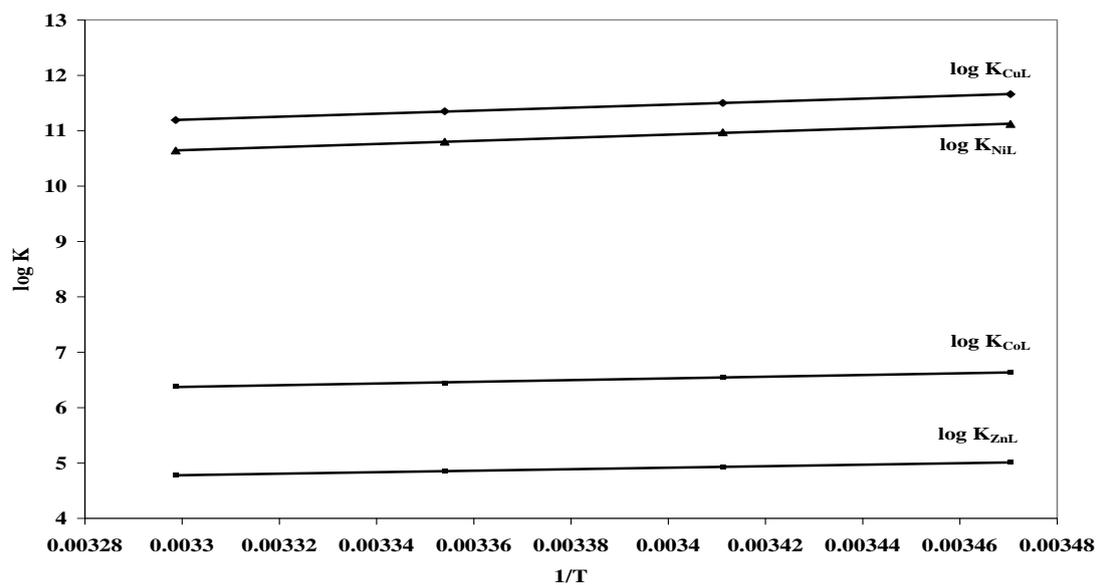
### 3.7. Effect of temperature and thermodynamics

Estimation of the thermodynamic parameters that are identified with the protonation of hydrazone and their metal(II) complexes have been determined from the temperature dependent data given in Table 3. Estimations of  $\Delta H$  and  $\Delta S$  were obtained by drawing the relation between  $\ln K$  versus  $1/T$  ( $\ln K = -\Delta H/RT + \Delta S/R$ ) leading to an intercept  $\Delta S/R$  and a slope  $-\Delta H/R$  (Figs. 9 and 10). Main conclusions were outlined as follows:

- The protonation reaction of the CBHP hydrazone is exothermic
- The net free energy of the reaction is negative  $\Delta G$  (Table 3).
- Formation constants of M-CBHP carbohydrazone complexes at various temperatures decrease with rising of temperatures, indicating that complex formation is favored at low temperature.



**Figure 9.** Effect of temperature on the dissociation constant of CBHP ligand.



**Figure 10.** Effect of temperature on the formation constants of M(II)–CBHP complexes.

**Table 3.** Thermodynamic functions for ML complexes of CBHP carbohydrazone ligand in aqueous solution at different temperatures and  $I = 0.1 \text{ mol dm}^{-3} \text{ NaNO}_3$ .

$M^{n+}$	T/K	$\Delta G$	$\Delta H$	$\Delta S$
$Zn^{2+}$	15	-27.6	-26.2	5.0
	20	-27.7		
	25	-27.7		
	30	-27.8		
$Co^{2+}$	15	-36.6	-28.5	28.0
	20	-36.7		
	25	-36.9		
	30	-37.0		
$Ni^{2+}$	15	-54.7	-45.7	31.2
	20	-54.9		
	25	-55.0		
	30	-55.2		
$Cu^{2+}$	15	-64.3	-52.2	42.1
	20	-64.6		
	25	-64.8		
	30	-65.0		

\* As it is realized that metal(II) ions exist in solution as octahedral hydrated species [51]. So the values of  $\Delta S$  and  $\Delta H$  can be considered as the sum of both the liberation of water molecules and formation of bonds between the metal and ligand. From these outcomes the following conclusions can be derived:

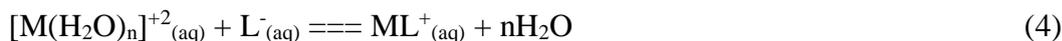
\* Inspection of the data reveals that M(II)-CBHP complexes are formed in the molar proportion 1:1 while 1:2 complexes were not formed. This might be ascribed to the way that steric hindrance results from the addition of the second bulky ligand prevents formation of the  $ML_2$  (1:2) species.

\* For the same ligand at constant temperature, the stability of the chelates is in accordance with stability order of the binary complexes and Irving–Williams order [52-54]. It is observed that the stability of the Cu(II)-CBHP complex is large in comparison with the other metals ( $\log K_{[Cu(CBHP)]} = 11.35 > \log K_{[Ni(CBHP)]} = 9.63 > \log K_{[Co(CBHP)]} = 6.44 > \log K_{[Zn(CBHP)]} = 4.85$ ). Under the effect of both the polarizing ability of the metal ion [55] and the ligand field [51],  $Cu^{2+}$  will get some additional stability because of tetragonal distortion of octahedral symmetry in its complexes. The more prominent stability of  $Cu^{2+}$  complexes is created by the notable Jahn-Teller effect [56].

\* All negative values of  $\Delta G$  associated with the process of M(II)-CBHP complexes show the spontaneity of complexation process.

\* Negative values of  $\Delta H$  and demonstrated that formation of M(II)-CBHP carbohydrazone complexes is exothermic and chelation process is preferred at low temperatures.

\* Positive values of  $\Delta S$  for M(II)-CBHP carbohydrazone complexes (Table 3), affirming that the complexation is entropically favourable [57] and depends on  $H^+$  liberation and the release of  $H_2O$  molecules [58]. During formation of metal chelates,  $H_2O$  molecules from the primary hydration sphere of the metal ion are displaced by coordination of CBHP carbohydrazone causing increase of the randomness of the system as appeared in Eq. 4.



\* In general, the unusual higher +ve values of  $\Delta S$  for all the M(II)-CBHP complexes are consistent with the hypothesis that a large number of  $H_2O$  molecules are liberated upon complexation with probability of change for the coordination number [59].

The highest values of the thermodynamic functions for the Cu-CBHP complexes is ascribed to the  $3d^9$ -configuration of Cu(II) which undergoes Jahn-Teller distortion.

### 3.8. Effect of solvent

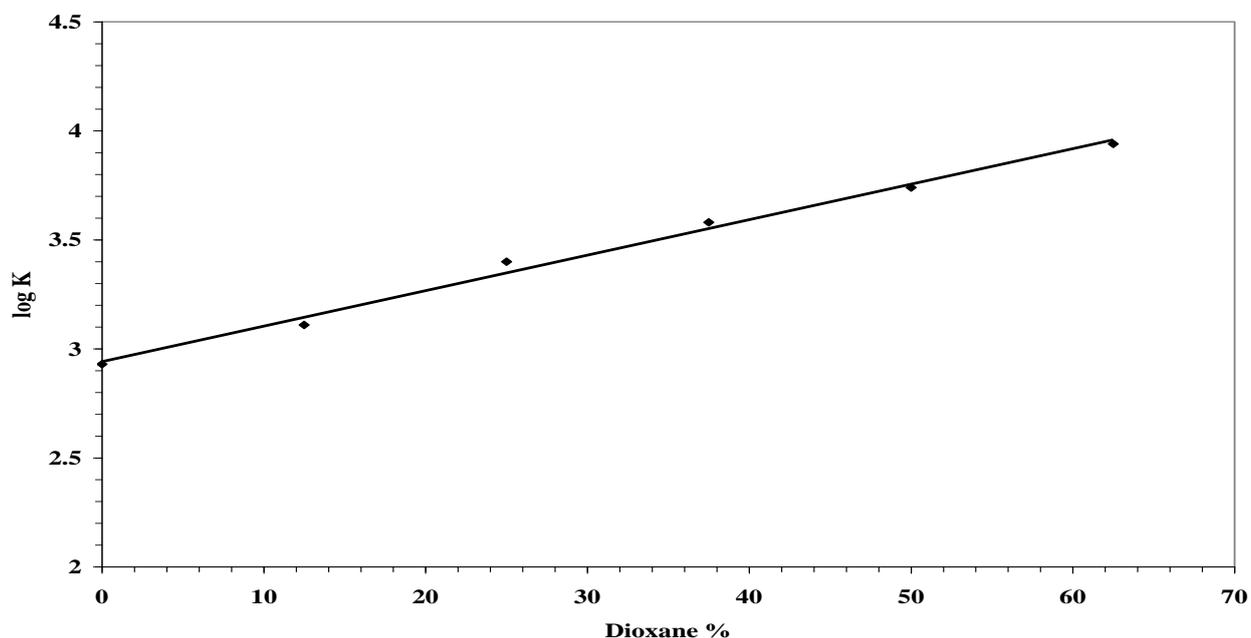
As it is realized that, simulation for the dielectric constant of the active site cavities of enzymes can be studied using aqueous solutions containing dioxane-water solutions of different compositions in range from 30 to 70 [60-64]. Cautious investigation of media effects on the equilibrium constants (Table 4) shows the following features.

-The stoichiometric protonation constant of CBHP carbohydrazone ligand is identified with the following equilibrium:



This protonation constant is identified with the protonation of the carboxylate group (Fig. 11).

In case of compounds containing O-H group, as the % of organic solvent in the medium of the reaction increases, the dielectric constant decreases and hence the ion-ion interaction between the  $H^+$  and the anionic oxygen donor of the ligand increases more than the ion-dipole interaction between the  $H^+$  and the solvent molecule causing more stability of these compounds [65]. In this way, the  $pK_a$  of carboxylic group increases linearly as the % of organic solvent increases in the medium i.e. the solvent of low dielectric constant increases the electrostatic forces between the ions and support formation of the molecular species. A similar pattern was observed for the  $pK_a$ 's of phosphoric acid (P-OH) groups of IMP [66] and HMI [32] and IMA [65].



**Figure 11.** Effect of dioxane concentration (Vol-%) on the dissociation constant of CBHP ligand.

**Table 4.** Negative logarithm of the acidity constants of CBHP carbohydrazone in dependence on the amount of dioxane added to water at  $I = 0.1 \text{ mol}\cdot\text{dm}^{-3}$  ( $\text{NaNO}_3$ ) and  $25^\circ\text{C}$ .

% (V/V) Dioxane	pK
0	2.93
12.5	3.11
25	3.40
37.5	3.58
50	3.74
62.5	3.94

The data given in Table 4 demonstrated that the  $pK_a$  of COOH group increases as the % of organic solvent increases. This might be ascribed to increase the electrostatic forces between the ions and facilitate formation of the molecular species by the decrease of the dielectric constant of the medium.

**Table 5.** Protonation constants of CBHP carbohydrazone ligand in aqueous solution and 50% water-solvent mixture at  $I = 0.1 \text{ mol dm}^{-3} \text{ NaNO}_3$ .

System	q	r <sup>a</sup>	pK $\pm\sigma$	S <sup>c</sup>
Aqueous	1	1	2.93 $\pm$ 0.04	5.6E-7
50% Water-Ethanol	1	1	3.11 $\pm$ 0.09	3.9E-7
50% Water-Dioxane	1	1	3.75 $\pm$ 0.07	2.4E-7

In this examination, investigation of the acid dissociation constant of the CBHP carbohydrazone ligand on various solvents like ethanol and dioxane. It was seen that the pK<sub>a</sub> follow the following order (Table 5)

$$pK_{\text{COOH}}(\text{dioxane}) < pK_{\text{COOH}}(\text{ethanol})$$

A difference between the calculated values of pK<sub>COOH</sub> equal to 0.64 is observed when going from ethanol to dioxane. The difference between the values of pK is due to the difference in polarity of the two solvents, in addition to hydrogen bonds between the solvent and the carboxylic OH group. This is in agreement with the previous literature studies [67, 68].

#### 4. CONCLUSIONS

In the present study, protonation and complex formation equilibria of M(II), with novel carbohydrazone Schiff base were investigated in aqueous, dioxane-water and ethanol-water mixtures at ionic strength of  $0.1 \text{ mol.dm}^{-3}$  using  $\text{NaNO}_3$ . Each of the following points was concluded:

1. The protonation constants and stability of M(II)-CBHP complexes were determined
2. Carbohydrazone Schiff base (CBHP) has one dissociable proton of COOH.
4. Protonation and complexation processes are spontaneous and exothermic.
5. The obtained data will be a noteworthy commitment to specialists carrying out mechanistic studies in biological media.
6. The pK<sub>a</sub> of COOH group increases as the % of organic solvent in the medium increases.
7. pK<sub>COOH</sub> (in dioxane) < pK<sub>COOH</sub> (in ethanol)

#### ABBREVIATIONS

CBHP: (3E,3'E)-3,3'-(ethane-1,2-diylbis(azaneylylidene))bis(N-(pyridin-2-yl)butanamide)

IMP: Inosine-5'-monophosphate

IMA: imidazole acetic acid

HMI: 4-Hydroxymethyl-imidazole

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