

Potentiometric and Thermodynamic Studies for Binary and Mixed Ligand Complexes of Some Transition Metal Ions with Hydrazone and Phenylalanine

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Binary and ternary complex formation equilibria of M(II) with SAH-hydrazone ligand (2-((2-phthalazin-1-yl)hydrazono)methyl)phenol) in presence of phenylalanine (Phe) as a representative example of amino acids have been studied using the pH-metric titrations. The pH-titrations of the reaction mixtures have been shown 1:1:1 (M: SAH: Phe) ternary complex formation. The stability constants and stoichiometries of the formed binary and ternary complexes have been calculated at $I = 0.1 \text{ mol dm}^{-3}$ NaCl in 60% (v/v) DMSO-water solution. The stability order of complexes with reference to the metal ions has been followed this order $\text{Cu(II)} > \text{Ni(II)} > \text{Co(II)} > \text{Mn(II)}$ in concord with the Irving-Williams stability order. The stability of mixed-ligand complexes was quantitatively matched with the stability of the binary complexes with reference to $\Delta \log_{10}K$, $\Delta \log_{10}\beta$ and $\log_{10}X$ parameters. The speciation of different species in solution has been evaluated as a function of pH. Additionally, the effect of temperature on protonation of ligands and formation of mixed-ligand complexes (M-SAH-Phe) was investigated. The thermodynamics were calculated and discussed.

Keywords: Cu(II); Potentiometry; Protonation; Species; Hydrazone, Phenyl alanine; Complex formation.

1. INTRODUCTION

Ternary complexes become of paramount significance in biological chemistry [1] due to the fact that mixed chelation occurs generally in biological fluids as millions of potential ligands are

probably to compete for metal ions *in vivo* [2]. Also, metal complexes are quite known to speed up drug effectuation and the performance of a therapeutic agent can be promoted upon coordination with a metal ion [3,4]. Specially, the ternary complexes derived from the bio-relevant ligands containing N,O donor bonding sites with M(II) ions are utilized in several fields such as biological, analytical, industrial and therapeutic applications [5,6].

Hydrazones compounds form an environment similar to biological systems by binding through atoms of oxygen and nitrogen. Coordination chemistry of hydrazone complexes of has received a considerable attention as a result of their wide biological activities and their effective inhibition of enzymes action. Moreover, most of hydrazone compounds form stable complexes with transition metals so this type of ligands has become one of the most important types of coordination compounds and played significant role in developing the coordination chemistry [7]. Hydrazone derivatives have various biological activities like analgesic [8], antipyretic [9], antibacterial [10] and antitumor [11] activities. Also, metal ions are essential elements for healthy life to human and higher animals [12] particularly the late first row transition metals such as, cobalt, nickel, copper and zinc are biologically relevant metals as they are associated with various biomolecules related to essential physiological activities.

On the other hand, amino acids possess specific significance among the other molecules since they are the structural units of proteins found in tissues of the human body. Also, the reaction between metal ions and amino acids is of worthy concern as a model for metal-protein interactions and different biological systems [13]. Amino acids and their ternary complexes are used in various fields like biology, pharmacy, and industry [14]. They are involved in several activities in the human body like neurotransmitter function, pH-setting, transamination, cholesterol metabolism, pain treatment, toxins removal and inflammation control. Metallic complexes including hydrazones and amino acids bearing the importance of both amino acids and hydrazones and has become of immense biological importance. Also, calculations of stability constants of the complex formation of biologically active ligands with metal ions in addition to calculations of the concentration of each species at any pH are very important for the whole understanding of the physiochemical manner of such compounds [15], require determination of their protonation constants. Additionally, protonation constants are of paramount importance in pharmaceutical studies particularly for the discovery and evaluation of novel compounds that could be effective drugs. In continuation of our previously work [16-23] and to extend the research domain of investigation on the coordination chemistry of hydrazones and amino acids, we report here the solution equilibrium studies of the mixed-ligand complexes including some transition metal ions (Cu^{2+} , Co^{2+} , Ni^{2+} and Mn^{2+}), (SAH) as the primary ligand (L^1) (Figure 1) and L-phenylalanine (2ry ligand) are carried out potentiometrically in 60 % (v/v) DMSO-water mixture at $I = 0.1 \text{ mol dm}^{-3}$ (NaCl). The thermodynamic parameters were calculated and discussed.

2. EXPERIMENTAL

2.1. Materials

All chemicals utilized in this investigation were of the analytical reagent grade (AR) quality and of highest purity. They included salicylaldehyde (Aldrich, $\geq 99.0\%$), hydralazine (Aldrich, 99 %) and phenylalanine (Phe, Aldrich, 99 %). Metal salts including $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (Aldrich, $\geq 99.99\%$), $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (Sigma-Aldrich, 98 %), $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (Aldrich, 99.9 %) and $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ (Sigma-Aldrich, $\geq 99\%$). DMSO was provided by Aldrich Chemicals Company. The metal content of solutions was established using complexometric EDTA titrations [24]. Carbonate free NaOH solution was prepared from a Titrisol solution (Merck) and its concentration was periodically checked versus standard phthalic acid monopotassium salt solution.

2.2. Synthesis of (SAH) ligand

The hydrazone compound (SAH) (Figure 1) was prepared as reported in the scientific literature [25], by mixing ethanolic solution of salicylaldehyde SAH containing 1.22 g (0.01 mol) with 1.96 grams (0.01 mol) of hydralazine in the same volume of ethanol under reflux conditions for 3 hours. The precipitate has been collected by filtration process via buchner, recrystallized from ethanol and dried at room temperature. The percent yield of the precipitate reaches 85 %.

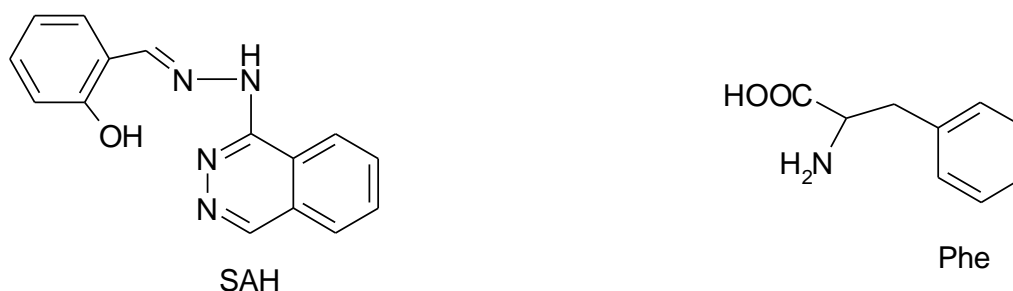
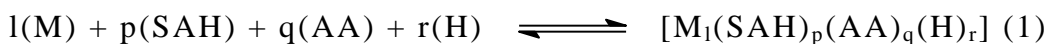


Figure 1. Structural formulae of SAH and Phe compounds.

2.3. Potentiometric titrations

The protonation constants of the ligands and stability of complex formation were measured potentiometrically using earlier described method [19]. pH-metric titrations were carried out by using of Metrohm 686 titroprocessor equipped with a 665 Dosimat. Double-wall glass titration cell equipped with a magnetic stirring system was used. The cell solution was stirred continuously at constant speed during the titration using magnetic stirring system. The glass electrode was calibrated using 0.05 m of both phosphate and potassium hydrogen buffer solutions [26]. The titration reaction was investigated in presence of purified N₂ atmosphere using standard solution of 0.05 mol dm⁻³ sodium hydroxide free from carbon dioxide. The titration cell was cleaned with distilled water and dried with a tissue before

and after the experiment. Covered cell calibration lid contains four holes for Metrohm glass electrode, glass tubing for nitrogen injection, thermometric probe and plastic tube for alkali solution. Before filling of a tube with alkali solution, the tube was washed several times with distilled water and then washed with alkali solution at least 4 times. Also, the air bubbles were avoided to leak in the tube in order to get accurate results for the measured volumes. Stock solution of metal salts was prepared and standardized using complexometric EDTA titrations [24]. In order to avoid probable hydrolysis of SAH ligand in aqueous solution, potentiometric titration was carried out in 60%-40% DMSO-water mixture. The pH-meter readings were converted into $[H^+]$ concentration as given in literature [27] using Van Uitert and Hass equation [28]. To keep the ionic strength (I) constant during the titration process, supporting electrolyte of sodium chloride was used. The ionic product ($K_w = [H^+][OH^-]$) was calculated at $I = 0.10 \text{ mol dm}^{-3}$ using sodium chloride in 60 %-40 % DMSO-water solutions based on measurements of $[OH^-]$ and pH in several series of experiments [29]. The pK_w value obtained in this medium is 15.58. The protonation constants of the SAH and amino acids were investigated potentiometrically by titration of SAH-solution ($1.0 \times 10^{-3} \text{ mol dm}^{-3}$) or Phe amino acid solution (50 ml). The stability constants of the binary complexes were investigated potentiometrically by titration using metal salt ($1.0 \times 10^{-3} \text{ mol dm}^{-3}$) + (SAH or Phe) (1.0×10^{-3} and $2.0 \times 10^{-3} \text{ mol dm}^{-3}$). The stability constants of the ternary complexes were investigated using potentiometric data obtained from mixtures of M^{II} , SAH and Phe. The stoichiometries and stability constants of the complex species were determined by examination of various probable composition models as 1:1:1, 1:1:2 and 1:2:1 (M^{II} : SAH: Phe) for the studied systems according to the following equilibria:



$$\beta_{lpqr} = \frac{[M_l(SAH)_p(AA)_q(H)_r]}{[M]^l [SAH]^p [AA]^q [H]^r} \quad (2)$$

The protonation and formation constants were calculated using the MINIQUAD-75 computer program [30] and the speciation diagrams were obtained by the program SPECIES [31].

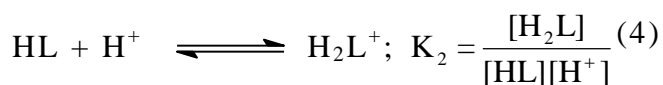
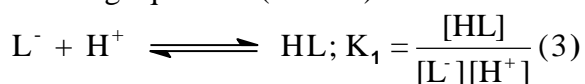
3. RESULTS AND DISCUSSION

3.1. Equilibrium studies

3.1.1. Protonation constants of SAH and phenylalanine amino acid

Measuring for the solution equilibria of the studied $M(II)$ -SAH-Phe complexes cannot be investigated in aqueous solution as a result of the nature of the involved compounds and in order to obtain homogenous solution. The 60%-40% DMSO-water solution mixture was selected as a solvent due to the studied hydrazone ligand and its metal complexes are soluble forming stable solutions. This solvent mixture has some features over pure DMSO in potentiometric determination of stability constants due to pure DMSO is very hygroscopic and controlling its water content is very difficult [32] which could affect reproducibility of the results. However, DMSO-water 60%:40% mixture possesses

small hygroscopic character. On the other hand, its compatibility with the standard glass electrode, allows measuring of pH in identical way to that used in a purely aqueous solution. Thus, the usage of pure DMSO is not recommended for potentiometric measurements. Furthermore, the large acidity of the DMSO-water 60:40% mixture ($pK_w = 15.58$) allows the determination of deprotonation equilibria of weak acids which could be hardly investigated in aqueous solution [33,34]. The solution equilibrium studies were also investigated in 60% DMSO-40 % water mixture at different temperatures. In all the systems, the ionic strength was kept constant at 0.1 mol dm^{-3} by addition of NaCl as supporting electrolyte and these constants are given in Table 1. Upon addition of NaOH deprotonation of the investigated ligands occurs and representation of the protonation constants (K_a) in stability study expressed in terms of proton-ligand formation constant or protonation constants was given by Eqs. 3 and 4. The protonation constants of SAH/Phe amino acid given in Table 1 correspond to the following equilibria (3 and 4):



The $\log_{10}K_1$ value is linked to the attachment of proton to the phenolic oxygen in SAH and $\log_{10}K_2$ value is related to the attachment of proton to the phthalazine nitrogen atom in SAH ligand. Also, two protonation constants for the investigated phenylalanine amino acid are calculated according to Eqs 3 and 4. The $\log_{10}K_1$ value is associated to the attachment of proton to the NH_2 -group in phenylalanine and $\log_{10}K_2$ value corresponds to the protonation of α -carboxylate group.

Table 1. Protonation and stability constants of binary and mixed-ligand complexes of hydrazone (SAH) and phenylalanine in 60% DMSO-40 % water at different temperatures and $I = 0.1 \text{ mol dm}^{-3}$ NaCl.

System	$T(^{\circ}C)$	l	p	q	r	$\log_{10}\beta$	S	$\log_{10}K_1^a$	$\log_{10}K_2^b$	$\log_{10}K_1 - \log_{10}K_2$
SAH	15	0	1	0	1	10.61 ± 0.03	$2.1 \text{ E-}8$			
		0	1	0	2	14.56 ± 0.05				
Phe		0	0	1	1	9.63 ± 0.02	$5.8 \text{ E-}8$			
Cu-SAH		1	1	0	0	12.02 ± 0.04	$1.2 \text{ E-}8$	12.02	10.06	1.96
		1	2	0	0	22.08 ± 0.06				
Cu-Phe		1	0	1	0	9.70 ± 0.03	$3.8 \text{ E-}8$	9.70	7.48	2.22
		1	0	2	0	17.18 ± 0.06				
Ni-SAH		1	1	0	0	10.48 ± 0.04	$2.9 \text{ E-}8$	10.48	8.11	2.37
		1	2	0	0	18.59 ± 0.05				
Ni-Phe		1	0	1	0	6.59 ± 0.02	$4.8 \text{ E-}8$	6.59	5.74	0.85
		1	0	2	0	12.33 ± 0.04				
Co-SAH		1	1	0	0	10.05 ± 0.03	$7.2 \text{ E-}8$	10.05	7.44	2.61
	1	2	0	0	17.49 ± 0.04					
Co-Phe	1	0	1	0	5.55 ± 0.03	$3.9 \text{ E-}8$	5.55	4.55	1.0	
	1	0	2	0	10.10 ± 0.05					
Mn-SAH	1	1	0	0	7.98 ± 0.06	$1.2 \text{ E-}8$	7.98	5.94	2.04	
	1	2	0	0	13.92 ± 0.08					

Mn-Phe		1	0	1	0	4.66±0.04	3.5 E-8	4.66	3.75	0.91
		1	0	2	0	8.41±0.07				
Cu-SAH-Phe		1	1	1	0	23.17±0.08	1.7 E-7			
Ni-SAH-Phe		1	1	1	0	18.68±0.08	2.6 E-7			
Co-SAH-Phe		1	1	1	0	16.88±0.09	1.3 E-7			
Mn-SAH-Phe		1	1	1	0	13.98±0.09	7.1 E-7			
SAH	25	0	1	0	1	10.47±0.02	4.9 E-8			
		0	1	0	2	14.37±0.04				
Phe		0	0	1	1	9.50±0.03	3.3 E-8			
Cu-SAH		1	1	0	0	11.84±0.05	6.2 E-8	11.84	9.94	1.9
		1	2	0	0	21.78±0.06				
Cu-Phe		1	0	1	0	9.56±0.02	5.6 E-8	9.56	7.40	2.16
		1	0	2	0	16.96±0.06				
Ni-SAH		1	1	0	0	10.33±0.03	3.8 E-8	10.33	8.03	2.30
		1	2	0	0	18.36±0.07				
Ni-Phe		1	0	1	0	6.50±0.01	4.7 E-8	6.50	5.66	0.84
		1	0	2	0	12.16±0.03				
Co-SAH		1	1	0	0	9.91±0.05	6.8 E-8	9.91	7.34	2.57
		1	2	0	0	17.25±0.05				
Co-Phe		1	0	1	0	5.47±0.02	4.1 E-8	5.47	4.50	0.97
		1	0	2	0	9.97±0.04				
Mn-SAH		1	1	0	0	7.88±0.05	3.7 E-8	7.88	5.86	2.02
		1	2	0	0	13.74±0.07				
Mn-Phe		1	0	1	0	4.59±0.06	2.9 E-8	4.59	3.69	0.90
		1	0	2	0	8.28±0.08				
Cu-SAH-Phe		1	1	1	0	22.95±0.07	3.2 E-7			
Ni-SAH-Phe		1	1	1	0	18.51±0.09	2.9 E-7			
Co-SAH-Phe		1	1	1	0	16.71±0.08	4.9 E-7			
Mn-SAH-Phe		1	1	1	0	13.85±0.08	6.4 E-7			
SAH	35	0	1	0	1	10.32±0.04	3.5 E-8			
		0	1	0	2	14.18±0.08				
Phe		0	0	1	1	9.36±0.04	2.7 E-8			
Cu-SAH		1	1	0	0	11.72±0.05	4.5 E-8	11.72	9.81	1.91
		1	2	0	0	21.53±0.07				
Cu-Phe		1	0	1	0	9.45±0.03	5.2 E-8	9.45	7.29	2.16
		1	0	2	0	16.74±0.04				
Ni-SAH		1	1	0	0	10.22±0.05	6.2 E-8	10.22	7.90	2.32
		1	2	0	0	18.12±0.06				
Ni-Phe		1	0	1	0	6.43±0.02	7.8 E-8	6.43	5.60	0.83
		1	0	2	0	12.03±0.04				
Co-SAH		1	1	0	0	9.80±0.03	6.9 E-8	9.80	7.25	2.55
		1	2	0	0	17.05±0.06				
Co-Phe		1	0	1	0	5.40±0.02	5.8 E-8	5.40	4.43	0.97
		1	0	2	0	9.83±0.05				
Mn-SAH		1	1	0	0	7.76±0.03	6.9 E-8	7.76	5.78	1.98
		1	2	0	0	13.54±0.06				

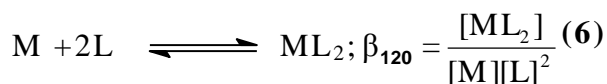
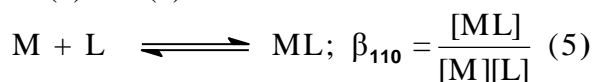
Mn-Phe	1	0	1	0	4.53±0.02	5.8 E-8	4.53	3.64	0.89
	1	0	2	0	8.17±0.05				
Cu-SAH-Phe	1	1	1	0	22.76±0.06	6.2 E-7			
Ni-SAH-Phe	1	1	1	0	18.34±0.08	7.3 E-7			
Co-SAH-Phe	1	1	1	0	16.57±0.09	5.5 E-7			
Mn-SAH-Phe	1	1	1	0	13.72±0.09	8.9 E-7			

^alogK₁: Corresponds to the first association constant of the ligand or formation of 1:1 ML complex.

^blogK₂: Corresponds to the second association constant of the ligand or formation of 1:2 ML₂ complex.

3.1.2. Metal-ligand binary systems

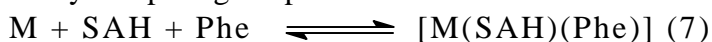
Analysis of potentiometric titrations indicated that binary complex formation curves are shifted to lower pH values than the free ligand solution curves. This indicated that formation of complexes through release of hydrogen ion upon complex formation. Calculation of the stability constants of all binary complexes with SAH and amino acids taking into account all the possible species (H₂L, HL, L, M(II), ML and ML₂). Table 1 shows the logarithm of the formation constants for all types of complexes, which have been identified using Potentiometric titration as given by the following equilibria (5) and (6)



Stability constants that have been obtained in this study is consistent with the values reported in literature, but the little difference in values between them is due to the difference in the practical conditions of the experiments (I = 0.1 mol dm⁻³ NaCl and 60 % DMSO-40% water mixture). The difference between the stability constants for the complexes formed in the molar ratios 1: 1 and 1: 2 is usually positive, ranging between 0.82-2.61

3.1.3. Metal-ligand ternary systems

According to the difference between the complexation ability of both to SAH-hydrazone and the amino acid, the ternary complex formation may proceeds through either a simultaneous or stepwise mechanism. The formation constants of the binary metal (II) complexes with SAH and the phenylalanine were found approximately to be of the same order. Accordingly, the coordination of SAH-hydrazone and phenylalanine will occur simultaneously according to Eq. 7. This hypothesis is confirmed by comparing the potentiometric data with the theoretically calculated values.



The stability constants for ternary complexes giving the best fit of the pH-metric titration curves are given in Table 1. The stability constants of the ternary systems in terms of metal ions obeyed this order log₁₀K_[Cu(SAH)(Phe)] = 22.95 > log₁₀K_[Ni(SAH)(Phe)] = 18.51 > log₁₀K_[Co(SAH)(Phe)] = 16.71 > log₁₀K_[Mn(SAH)(Phe)] = 13.85.

3.2. Speciation diagrams

Determination of equilibrium concentrations of metallic complexes in terms of pH gives the true picture of the coordination of the metal ion in the solution. The species distribution curve for Co(SAH)Phe complex as a representative example of the metal ligand complexes is given in Fig. 2. Co-SAH complex starts to form at pH ~ 3 reaching its maximum concentration of 77 % at pH ~ 5.2. The mixed ligand complex Co-(SAH)-Phe starts to form at pH 4.8 reaching its maximum concentration of 95 % at pH ~ 9.2.

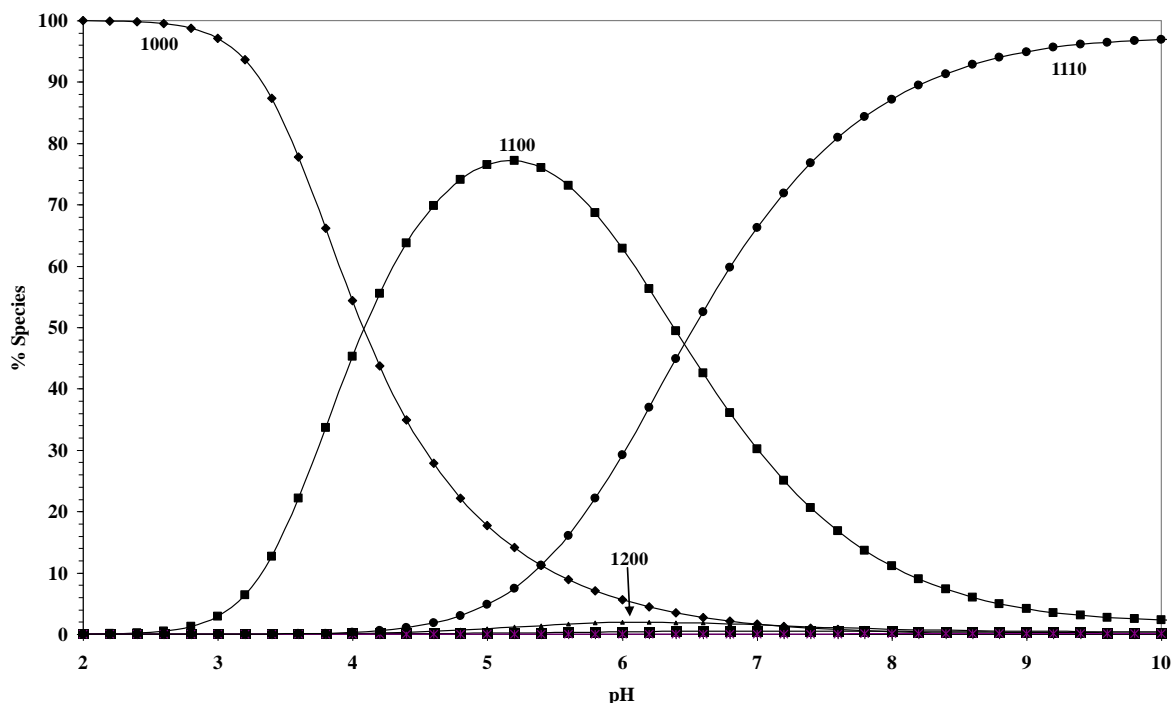


Figure 2. Concentration distribution curve of various species as a function of pH in the Co-SAH-Phenylalanine system (Species less than 5% are neglected).

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

In order to explain why a given ligand prefers binding to one metal instead of another metal, it is important to link the relationship between the stability constants of metal complexes and properties of the metal ions, such as the atomic number, ionic radius, ionization potential and electronegativity. Here, we have discussed the relationship between the properties of metal ions given in Table 2 [35] and the stability constants of complexes. In this investigation, it was found that, the formation constants of M^{II} -complexes of some transition metal ions with SAH obeyed this arrangement: $Mn^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+}$ which is consistent with Irving-Williams' order [36].

Table 2. Periodic table properties of metal ions^a

Metal ion	Mn ²⁺	Co ²⁺	Ni ²⁺	Cu ²⁺
Atomic number	25	27	28	29
Ionic radius(pm)	81	79	71	74
Electronegativity	1.55	1.88	1.91	2.00
Second ionization energy (kJ/mol)	1509	1646	1753	1958

^a Values were taken from Ref. [35].

The relation between the $\log_{10}K_{ML}$ and the reciprocal ionic radii ($1/r$) of the studied transition metal ions represents nearly a linear relationship. Additionally, a linear relation has been noticed between $\log_{10}K_{ML}$ and the electronegativities of the metal ions under investigation (Fig. 3). This is consistent with the fact that the increase in the electronegativity of metals ($Mn^{2+}(1.55) < Co^{2+}(1.88) < Ni^{2+}(1.91) < Cu^{2+}(2.00)$) will reduce the difference in electronegativity between the metal atom and the donor atom of the ligand. Therefore, the metal-ligand bond should have more covalent character, leading to increase the degree of stability of complexes.

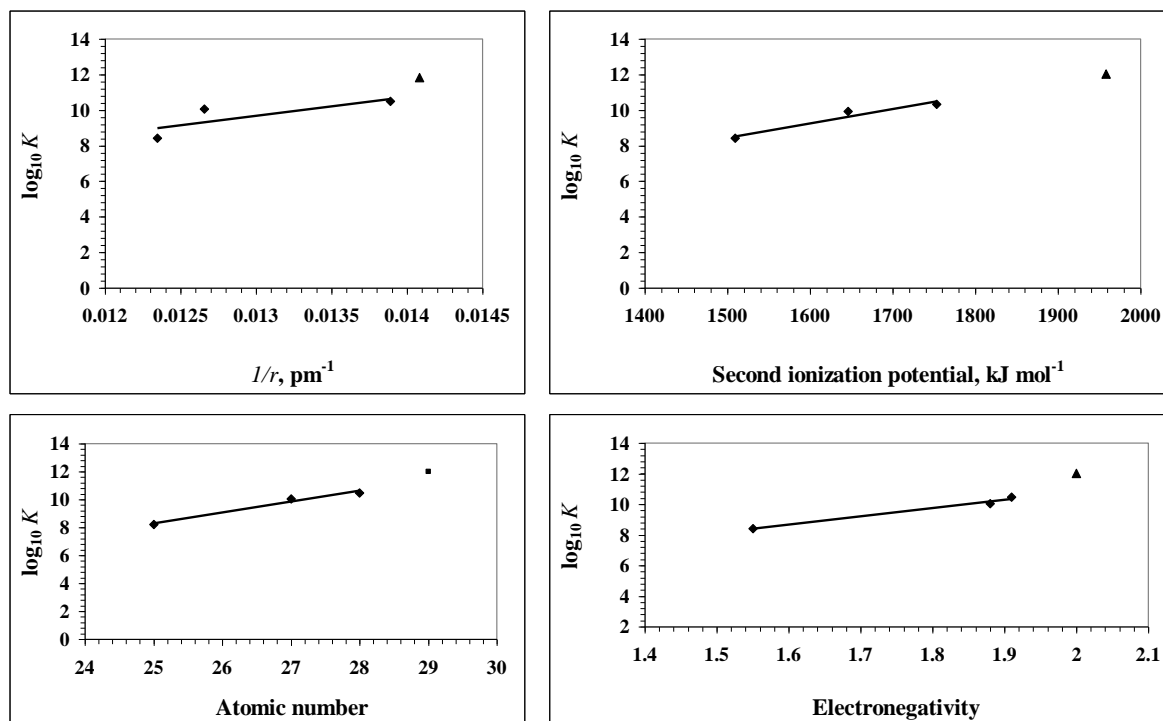


Figure 3. Variation of the stability constants at 25 °C for the M(II)-SAH complexes with properties of the metal(II) ions

A good linear correlation has been obtained between the stability constants of metal complexes and the second ionization potential of the metal ions under investigation. Generally, it is observed that the stability constant of the Cu²⁺ complex is larger in comparison to the other metals. The ligand field

had given Cu^{2+} further stability as a result of tetragonal distortion of the octahedral symmetry [37]. Therefore, if the relationship between the stability constants of metal chelates is plotted versus properties of the metal ions, the $\log_{10}K$ value for the Cu(II)-complex will deviate significantly as shown in Fig. 3.

3.4. Effect of temperature and thermodynamics

The values of thermodynamic parameters that are related to the protonation of both SAH, Phe and their metal(II) complexes have been calculated from the temperature dependent data given in Table 1. Values of ΔH° and ΔS° were obtained by drawing the relationship between the values of equilibrium constants ($\ln K$) versus reciprocal of temperature ($1/T$) ($\ln K = -\Delta H^\circ/RT + \Delta S^\circ/R$) leading to an intercept $\Delta S^\circ/R$ and a slope $-\Delta H^\circ/R$ (Fig. 4 and 5). Main conclusions from the data can be summarized as follows:

(I) The protonation reaction of the N-site of SAH/Phe is exothermic with a net negative ΔG° (Table 3).

(II) Often, the color of the solution after formation of the complex differs from the color associated with the free ligand at the same pH.

(III) - Formation constants of metal complexes at different temperatures have been calculated and discussed as follows:

-These values decrease with rising of temperatures increase, proposing that the process of complex formation is favored at low temperature.

-As it is known that divalent metal ions exist in solution in the form of octahedral hydrated species [38]. So it can be considered that the values of entropy and enthalpy, which was obtained as the sum of the contributions of both liberation of water molecules and formation of bonds between the metal and ligand. From these results the following conclusions can be derived:

1- The positives values of differences between the stability constants $\log_{10}K_1$ and $\log_{10}K_2$ is attributed to the more freely available sites on the metal for coordination of the first ligand than the second one.

2- The study showed increase of stability constants of metal chelates for the same ligand at constant temperature in this arrangement $\text{Cu}^{2+} > \text{Ni}^{2+} > \text{Co}^{2+} > \text{Mn}^{2+}$ [36]. This order of stability indicated that the changes in the heat of complex formation across this series results from a combination of the influence of both the polarizing ability of the metal ion³⁸ and the stabilization energy of crystal field [39].

3- All negative values of the Gibb's free energy associated with the process of formation of complexes illustrate the spontaneity of the chelation process.

4- The negative values of the heat content (ΔH°) showed that the process of formation of complexes is exothermic demonstrating that the process of chelation is preferable at low temperatures. Moreover, the formation of the coordinate bond between the metal ion and the ligand often increases the charge density on the metal. So, its affinity for the next ligand molecule causing an increase of ΔG° and ΔH° of the complexes.

5- Generally, it has been observed that $-\Delta G_1^\circ > -\Delta G_2^\circ$ and $-\Delta H_1^\circ > -\Delta H_2^\circ$ (Table 3) is due to the steric hindrance as a result of entering the second molecule.

Table 3. Thermodynamics for the association of SAH, Phe and ternary complex formation equilibria of M-SAH-Phe complexes in 60% DMSO-40% H₂O(v/v).

Equilibrium	ΔH° (kJmol ⁻¹)	ΔS° (JK ⁻¹ mol ⁻¹)	ΔG° (kJmol ⁻¹)
Phe			
$L^\pm + H^+ \rightleftharpoons LH^+$	-44.40	30.34	-53.29
SAH			
$L^- + H^+ \rightleftharpoons LH$	-47.69	37.68	-58.73
$HL + H^+ \rightleftharpoons H_2L^+$	-14.80	24.12	-21.87
M(II)-Phe			
$Cu^{2+} + L^\pm \rightleftharpoons CuL^+$	-41.15	42.69	-53.66
$CuL^+ + L^\pm \rightleftharpoons CuL_2$	-31.22	34.84	-41.43
$Ni^{2+} + L^\pm \rightleftharpoons NiL^+$	-26.33	34.65	-36.48
$NiL^+ + L^\pm \rightleftharpoons NiL_2$	-23.03	29.86	-31.79
$Co^{2+} + L^\pm \rightleftharpoons CoL^+$	-24.68	20.58	-30.71
$CoL^+ + L^\pm \rightleftharpoons CoL_2$	-19.72	18.74	-25.21
$Mn^{2+} + L^\pm \rightleftharpoons MnL^+$	-21.39	14.96	-25.77
$MnL^+ + L^\pm \rightleftharpoons MnL_2$	-19.72	8.94	-20.72
M(II)-SAH			
$Cu^{2+} + L^- \rightleftharpoons CuL^+$	-49.4	58.39	-66.52
$CuL^+ + L^- \rightleftharpoons CuL_2$	-41.11	49.97	-55.75
$Ni^{2+} + L^- \rightleftharpoons NiL^+$	-42.80	52.01	-58.04
$NiL^+ + L^- \rightleftharpoons NiL_2$	-34.49	35.72	-44.96
$Co^{2+} + L^- \rightleftharpoons CoL^+$	-41.15	49.39	-55.62
$CoL^+ + L^- \rightleftharpoons CoL_2$	-31.26	33.89	-41.19
$Mn^{2+} + L^\pm \rightleftharpoons MnL^+$	-36.17	27.18	-44.13
$MnL^+ + L^\pm \rightleftharpoons MnL_2$	-26.32	22.40	-32.88
M(II)-SAH-Phe			
$Cu^{2+} + SAH + Phe \rightleftharpoons [Cu(SAH)(Phe)]$	-67.46	209.27	-128.81
$Ni^{2+} + SAH + Phe \rightleftharpoons [Ni(SAH)(Phe)]$	-55.92	163.50	-103.85
$Co^{2+} + SAH + Phe \rightleftharpoons [Co(SAH)(Phe)]$	-51.02	136.71	-91.09
$Mn^{2+} + SAH + Phe \rightleftharpoons [Mn(SAH)(Phe)]$	-42.77	119.1	-77.67

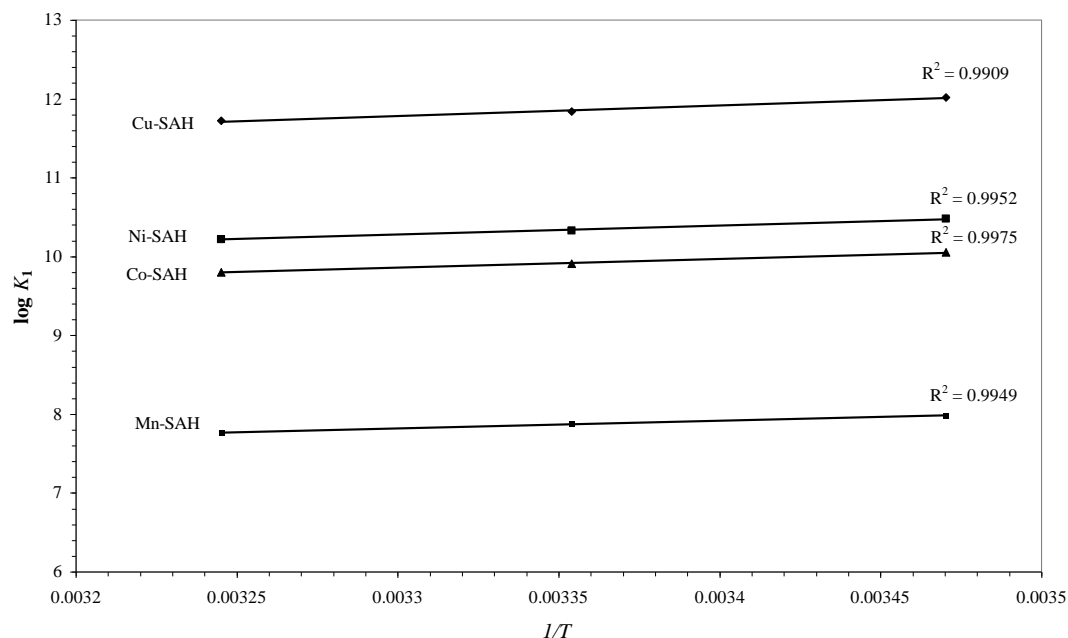


Figure 4. Van't Hoff plot of $\log_{10} K$ of M(II)-SAH binary complexes versus $1/T$.

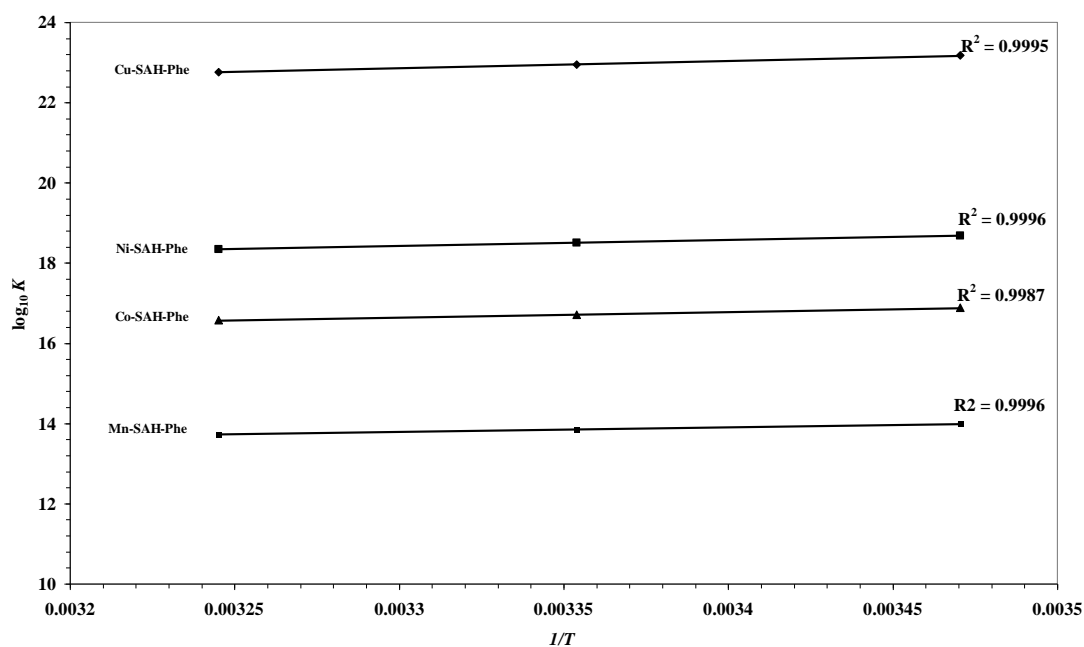


Figure 5. Van't Hoff plot of $\log_{10} K$ of M-SAH-Phe complexes versus $1/T$.

3.5. Comparison of the stability constants of the ternary complexes with those of the binary complexes

The formation of binary and ternary complexes from a mixture of M(II) ion, SAH hydrazone ligand and phenylalanine amino acid (Phe) can be shown as the equilibria given in Fig. 6. In general, the following parameters were used for explaining the change in the stability of the mixed complexes with reference to the binary ones namely:

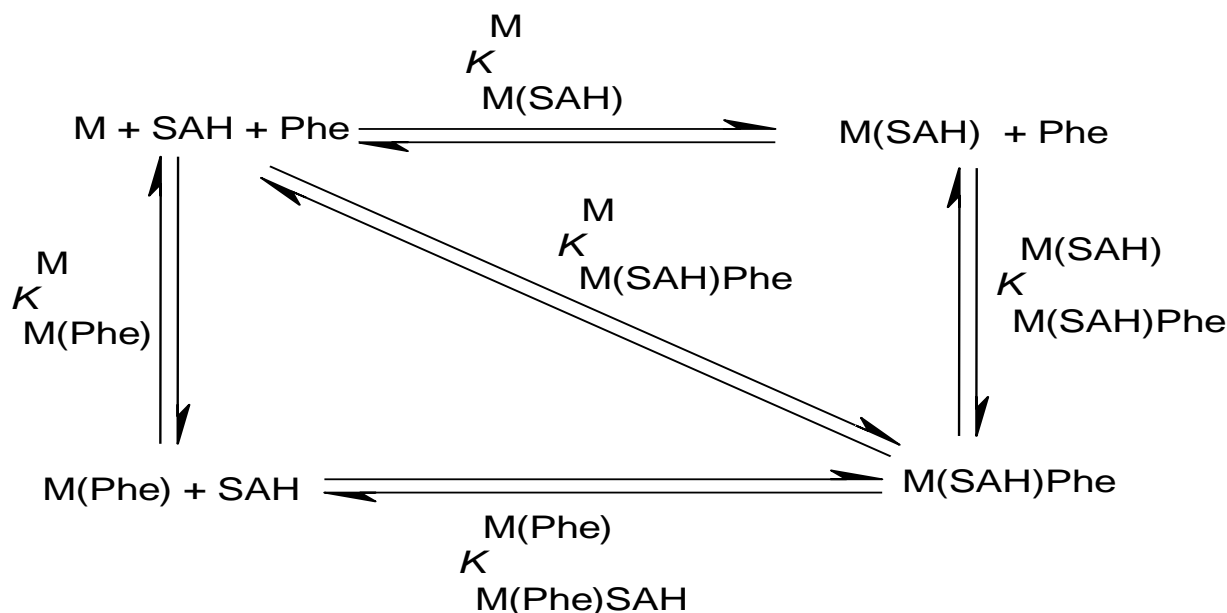
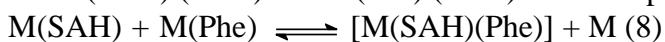


Figure 6. Binary and ternary complexes.

3.5.1. $\Delta \log K$ parameter

$\Delta \log_{10}K$ parameter represents the difference between the stabilities of the binary and mixed ligand complexes. This parameter also reflects the effect of the coordinated primary ligand towards the coming secondary ligand. The characteristics of using $\Delta \log_{10}K$ parameter in comparing stabilities of ternary and binary complexes were reviewed and accepted [37]. As a result of more available coordination sites for binding of ligand in the binary than in the ternary complexes, it was expected that, negative values for $\Delta \log_{10}K$ should be obtained. Depending on the scientific fact that the values of $\Delta \log_{10}K$ depend on the coordination number of metal ion, the values of $\Delta \log_{10}K$ coefficient for a regular and distorted octahedral geometries are -0.4 and -0.9 respectively [40]. According to Sigel [40], the relative stability of the ternary $M(SAH)(Phe)$ (1110) complexes in comparison to its binary complexes $M(SAH)$ (1100) and $M(Phe)$ (1010) can be expressed by the following equations:



$$\Delta \log K_{[M(SAH)(Phe)]} = \log \beta_{[M(SAH)(Phe)]} - (\log \beta_{M(SAH)} - \log \beta_{M(Phe)}) \quad (9)$$

In this study, the amino acid is coordinated with great ease with the free metal ion than with the complexed metal ion $[M(SAH)]^+$ in which the Lewis-acidity of metal(II) ion is depressed. Therefore, the value of $\Delta \log_{10}K$ must be negative. According to the $\Delta \log_{10}K$ values that have been obtained in this study and given in Table 4, the positive values of $\Delta \log_{10}K$ can be considered as strong evidence for the occurrence of promoted stability of the formed complexes involving π -back donation from the -vely charged amino acid to the π -system of the SAH. The enhanced stability of ternary complexes in comparison to the binary complexes can also be explained by suggestion of inter-ligand interaction that exists between Phe amino acid ligand and SAH hydrazone ligand

Table 4. Evaluated values of $\log_{10}\beta$; $\Delta\log_{10}K$; $\Delta\log_{10}\beta$ and $\log_{10}X$ for the formation of $[M(\text{SAH})(\text{AA})]$ complexes in 60 %-40 % DMSO-water mixture at $I = 0.1 \text{ mol dm}^{-3}$ NaCl and $T = 25 \text{ }^\circ\text{C}$.

Complex	$\log_{10}\beta_{1110}$ (Experimentally)	$\Delta\log_{10}K^a$	$\log_{10}X^b$	$\log_{10}\beta_{\text{stat}}^c$	$\Delta\log_{10}\beta^d$
Cu-SAH-Phe	22.95	1.55	7.16	19.67	3.28
Ni-SAH-Phe	18.51	1.68	6.5	17.27	1.24
Co-SAH-Phe	16.71	1.33	6.2	16.18	0.53
Mn-SAH-Phe	13.85	1.38	5.68	13.62	0.23

$$^a\Delta\log_{10}K = \log_{10}\beta_{1110} - \log_{10}\beta_{1100} - \log_{10}\beta_{1010}$$

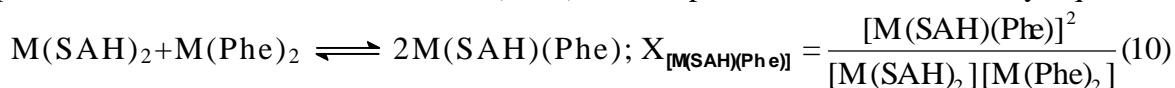
$$^b\log_{10}X = (2\log_{10}\beta_{1110} - \log_{10}\beta_{1020} - \log_{10}\beta_{1200})$$

$$^c\log_{10}\beta_{\text{stat}} = \log_{10}2 + 1/2 \log_{10}\beta_{1020} + 1/2 \log_{10}\beta_{1200}$$

$$^d\Delta\log_{10}\beta = \log_{10}\beta_{1110} - \log_{10}\beta_{\text{stat}}$$

3.5.2. Disproportionation constant

The quantitative stability of mixed-ligand complexes can be expressed in terms of disproportionation constant. The values of $M(\text{SAH})\text{Phe}$ complexes can be calculated by Eqs 10 and 11.



$$\log X_{[M(\text{SAH})(\text{Phe})]} = 2 \log \beta_{[M(\text{SAH})(\text{Phe})]} - (\log \beta_{M(\text{SAH})_2} + \log \beta_{M(\text{Phe})_2}) \quad (11)$$

The value of $\log_{10}X$ on the statistical basis equal is +0.6 for all geometries [41]. The more positive $\log_{10}X$ values than the statistical illustrates remarkable degree of stability of the ternary complexes. Large positive values of $\log_{10}X$ as given in Table 4 assume the obvious stability of the ternary complexes than those in the corresponding binary compounds. Similar results have been published in the scientific literature with 2-picolylamine, bipyridyl and imidazole-4-acetic acid [42-47].

3.5.3. Stabilization constant

The stability of the ternary complexes can be calculated on the basis of statistical using Eq.12. The stabilization constant resulting from the difference between the measured stability constant values for the ternary complexes and those calculated on statistical basis can be calculated using Eq. 13.

$$\log_{10}\beta_{\text{stat}} = \log_{10}2 + 1/2\log_{10}\beta_{1020} + 1/2\log_{10}\beta_{1200} \quad (12)$$

$$\Delta\log_{10}\beta = \log_{10}\beta_{\text{meas.}} - \log_{10}\beta_{\text{Calc.}} \quad (13)$$

The large difference between the measured values of the ternary complexes and the calculated statistical values indicated that mixed-ligand complexes are more stable than the corresponding binary $M(\text{SAH})_2$ and $M(\text{Phe})_2$ complexes. This stability enhancement is referred to as a ‘‘ligand effect’’ which is related to the electrostatic factors arise from charge neutralization, since in the formation of $M(\text{SAH})\text{Phe}$, one positive charge of $M(\text{SAH})^+$ is neutralized by the deprotonated phenylalanine amino acid, this leads to increased σ covalence.

4. CONCLUSION

Complex formation equilibria of M(II), with SAH and phenyl alanine was investigated 60 % DMSO-40 % H₂O mixture was studied. It is hoped that the obtained data from protonation of the investigated SAH-hydrazone and Phe and their complex formation equilibria in 60% DMSO-40% H₂O mixture will be a significant contribution to workers carrying out mechanistic studies in biological media. Less negative $\Delta \log_{10}K$ and more positive $\log_{10}X$ values indicated the remarked stabilities of the mixed ligand complexes in comparison to the binary complexes. The positive values of ΔS values confirming that the complex formation is entropically favourable.

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ABBREVIATIONS:

SAH: (2-((2-phthalazin-1-yl)hydrazono)methyl)phenol)

Phe: Phenylalanine

DMSO: Dimethyl sulphoxide

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