Structural, Potentiometric and Thermodynamic Studies of 3-Phenylaminorhodanine-5-azosulfadiazine and Its Metal Complexes

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Abstract— 3-Phenylaminorhodanine-5–azosulfadiazine (H2L) has been synthesized and characterized using different spectroscopic techniques. The energy of HOMO & LUMO, HOMO–LUMO energy gap and additional electronic charge were calculated. In addition, absolute electronegativities, chemical potentials and absolute hardness have been calculated. The proton-ligand dissociation constants of 3-phenylamino rhodanine-5–azosulfadiazine (H2L) and the stability constants of its metal-ligand complexes with (Mn2+, Co2+, Ni2+ and Cu2+) have been determined potentiometrically in 0.1 M (KCl) and 40 % (by volume) ethanol-water mixture and at (298, 308 and 318) K. The order of the stability constants of the formed complexes increases in the sequence Mn2+, Co2+, Ni2+ and Cu2+. The effect of temperature was studied and the corresponding thermodynamic parameters (∆G, ∆H and ∆S) were derived and are discussed. The dissociation process is non-spontaneous, endothermic and entropically unfavourable. The formation of the metal complexes has been found to be spontaneous, endothermic and entropically favourable.

Keywords — Azorhodanine, molecular structure, potentiometry and thermodynamics.

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1 INTRODUCTION

Rhodanine is a five-membered heterocyclic ring with diverse applications particularly in biochemistry, medicinal chemistry, photochemistry, industry and coordination chemistry [1-4]. Sulphadrugs have attracted special attention from their therapeutic importance as they were used against a wide spectrum of bacterial ailments [5]. Some sulphadrugs have been used in the treatment of cancer, malaria, leprosy and tuberculosis [6]. Azo sulphadrug is a subject of current and growing interest and that may have numerous applications e.g. anticancer, antibacterial, antiviral, antifungal and other biological properties [7,8]. Sulphadrug ligands are widespread among coordination compounds and are important components of biological transition metal complexes [9]. Chemically azo sulphadrug containing moieties are of great interest because of their great versatility as ligands [10,11], due to the presence of several potential donor atoms, their flexibility and ability to coordinate in either neutral or deprotonated form [12].

As part of our continuous work reporting on the determination of dissociation and stability constants of some organic compounds and their metal complexes by potentiometric techniques [13-16], we report herein the preparation and characterization of azorhodanine. The geometrical structure of the ligand by HF method with 3-21G basis set was studied. The dissociation constants of the ligand (H2L) and the stability constants of its complexes with Mn2+, Co2+, Ni2+ and Cu2+ at different temperatures were determined potentiometrically. Furthermore, the proton dissociation process is non-spontaneous, endothermic and entropically unfavoured. The formation of the metal complexes was found to be spontaneous, endothermic and entropically favoured.

2 EXPERIMENTAL SECTION

2.1. MATERIALS AND PHYSICAL MEASUREMENTS

The standard chemicals and solvents were purchased from Aldrich chemical company and used as received without further purification. Elemental microanalyses of the separated ligands for C, H, and N were determined on Automatic Ana-

lyzer CHNS Vario ELIII, Germany. The ^{1}H NMR spectrum was obtained by Bruker WP 300 MHz using DMSO-d$_6$ as the solvent and TMS as an internal reference. FT-IR spectra (KBr disks, 4000-400 cm^{-1}) by Jasco-4100 spectrophotometer. The molecular structures of the investigated compounds were optimized by HF method with 3-21G basis set. The temperature was controlled to within ± 0.05 K by circulating thermostated water (JULABO f34-ED) through the outer jacket of the vessel. The pH measurements were performed with a Metrohm 836 Titrando (KF & Potentiometric Titrator) equipped with a combined porolyte electrode. The pH-meter readings in the non-aqueous medium were corrected [17]. The electrode system was calibrated according to the method of Irving et al. [18]. The molecular structure of the investigated ligand was optimized by HF method with 3-21G basis set. The molecule was built with the Perkin Elmer ChemBio Draw and optimized using Perkin Elmer ChemBio3D software [19].

2.2. Preparation of 3-phenylaminorhodanine-5–azosulfadiazine (H$_2$L)

The organic compound (H$_2$L) was prepared (Fig. 1) by gradual addition of an aqueous solution of 0.01 mole of sodium nitrite to a concentrated hydrochloric acid solution of 0.01 mole of sulphadiazine with stirring and kept for about 20 min. in the ice bath. The formed diazonium chloride solutions were added gradually with vigrous stirring to a 0.01 mole cold solution of 3-phenylaminorhodanine [14] in 50 ml pyridine. After dilution, the compound (H$_2$L) formed was filtered off and washed with water. The crude materials was recrystallized from ethanol and then dried in a vacuum desiccator over anhydrous calcium chloride. Yield 70 %; yellow solid; mp = 170 °C; Anal.: Calcd. for $C_{19}H_{15}N_7O_3S_3$ (485): C, 47.00; H, 3.11; N, 20.19; S, 19.81. Found: C, 47.10; H, 3.07; N, 20.32; S, 19.68. FT-IR spectrum IR (KBr) (v cm^{-1}): 1285 (N-C=S), 1587 (-N=N-), 1625 (C=N), 1600 (C=C), 3184, 3210 (two NH), 3399 (br) (OH) 3399. ^{1}H-NMR spectrum in DMSO-d$_6$, ppm: 11.64 (s, 1H, NH sul-phonamide, D$_2$O exchangable), 10.89 (s, 1H, OH, D$_2$O exchangable), 9.40 (s, 1H, NH) 6.80-8.20 (m, 10H, Ar protons), 8.52 (d, 2H, C$_4$-H, C$_6$-H pyrimidine).
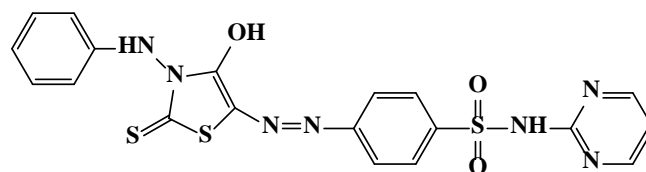

Fig. 1. Structure of 3-Phenylaminorhodanine-5–azosulfadiazine (H$_2$L)

Azorhodanine solution (0.001 M) was prepared by dissolving an accurate weight of the solid in ethanol (Analar). Metal ion solutions (0.0001 M) were prepared from Analar metal chlorides in bidistilled water and standardized with EDTA [20]. Solutions of 0.001 M (HCl) and 1 M (KCl) were also prepared in bidistilled water. A carbonate-free sodium hydroxide solution in a 40 % (by volume) ethanol-water mixture was used as titrant and standardized against oxalic acid (Analar).

The apparatus, general conditions and methods of calculation were the same as in previous work [14-16]. The following mixtures (i)-(iii) were prepared and titrated potentiometrically at 298 K against standard 0.002 M (NaOH) in a 40 % (by volume) ethanol-water mixture:

i) 5 cm^3 0.001 M (HCl) + 5 cm^3 1 M (KCl) + 20 cm^3 ethanol.

ii) 5 cm^3 0.001 M (HCl) + 5 cm^3 1 M (KCl) + 15 cm^3 ethanol + 5 cm^3 0.00l M ligand.

iii) 5 cm^3 0.001 M (HCl) + 5 cm^3 l M (KCl) + 15 cm^3 ethanol + 5 cm^3 0.001 M ligand + 10 cm^3 0.0001 M metal chloride.

For each mixture, the volume was made up to 50 cm^3 with bidistilled water before the titration. These titrations were repeated for temperatures of (308 and 318) K. All titrations

have been carried out between pH 3.0 and 11.0.

3. Results and discussion

3.1. Molecular structure

The selected geometrical structure of the investigated ligand is calculated by optimizing their bond lengths and bond angles. The calculated molecular structure for ligand H₂L is shown in Fig. 2. The bond lengths and bond angles are listed in Table 1. Both the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are the main orbital takes part in chemical stability. The HOMO represents the ability to donate an electron, LUMO as an electron acceptor represents the ability to obtain an electron. The HOMO and LUMO for ligand H₂L are shown in Fig. 3. The calculated quantum chemical parameters are given in Table 2. Additional parameters such as ΔE, absolute electronegativities, χ, chemical potentials, Pi, absolute hardness, η, absolute softness, σ, global electrophilicity, ω, global softness, S, and additional electronic charge, ΔN_{max}, have been calculated according to the following equations (1-8) [21,22]:

$$\Delta E = E_{LUMO} - E_{HOMO} \qquad (1)$$

$$\chi = \frac{-(E_{HOMO} + E_{LUMO})}{2} \qquad (2)$$

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2} \qquad (3)$$

$$\sigma = \frac{1}{\eta} \qquad (4)$$

$$Pi = -\chi \qquad (5)$$

$$S = \frac{1}{2\eta} \qquad (6)$$

$$\omega = \frac{Pi^2}{2\eta} \qquad (7)$$

$$\Delta N_{max} = -\frac{Pi}{\eta} \qquad (8)$$

The HOMO–LUMO energy gap, ΔE, which is an im-

portant stability index, is applied to develop theoretical models for explaining the structure and conformation barriers in many molecular systems [22-24].
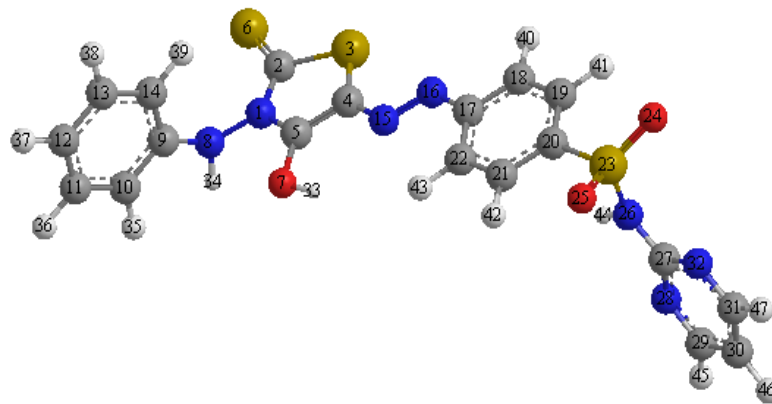

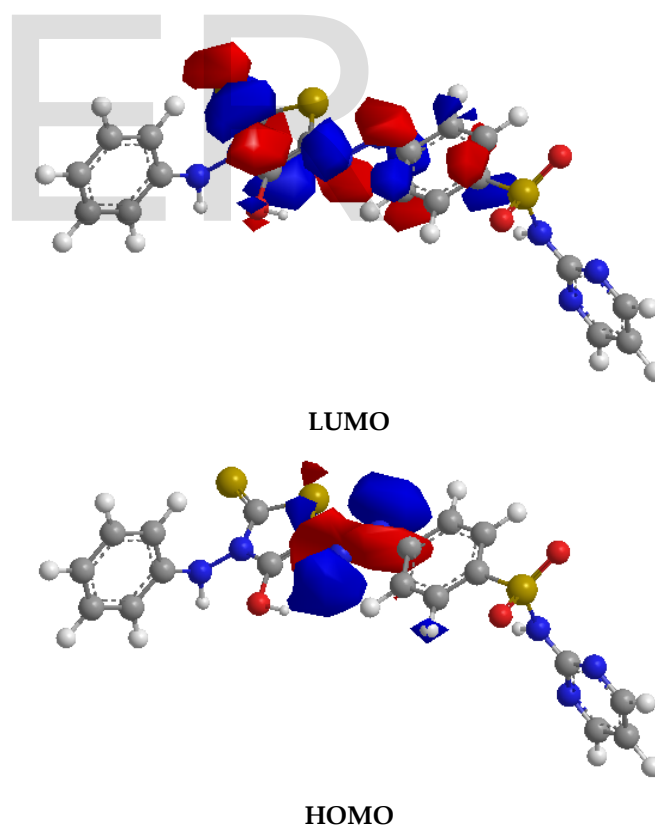**Fig. 2.** Geometry optimized structures of H₂L.

LUMO

HOMO

Fig. 3. HOMO and LUMO molecular orbital of H₂L.

Table 1. Bond lengths and bond angles of the ligand (H₂L).

Bond lengths (Å)			
C(31)-H(47)	1.102	S(23)-O(24)	1.457
C(30)-H(46)	1.101	C(20)-S(23)	1.801
C(29)-H(45)	1.102	N(16)-C(17)	1.268
N(26)-H(44)	1.051	N(15)-N(16)	1.252
C(22)-H(43)	1.103	C(4)-N(15)	1.268
C(21)-H(42)	1.103	N(8)-C(9)	1.272
C(19)-H(41)	1.103	N(1)-N(8)	1.356
C(18)-H(40)	1.105	C(5)-O(7)	1.365
C(14)-H(39)	1.103	C(2)-S(6)	1.574
C(13)-H(38)	1.103	C(9)-C(10)	1.345
C(12)-H(37)	1.103	C(2)-S(3)	1.789
C(11)-H(36)	1.103	C(4)-S(3)	1.483
C(10)-H(35)	1.104	C(5)-C(4)	1.356
N(8)-H(34)	1.051	N(1)-C(5)	1.277
O(7)-H(33)	0.972	C(2)-N(1)	1.267
C(31)-N(32)	1.264	N(26)-C(27)	1.274
C(27)-N(32)	1.271	S(23)-N(26)	1.702
N(28)-C(27)	1.272	S(23)-O(25)	1.457
C(29)-N(28)	1.265		
C(30)-C(29)	1.339		
C(31)-C(30)	1.339		
C(17)-C(22)	1.347		
C(21)-C(22)	1.343		
C(20)-C(21)	1.344		
C(19)-C(20)	1.343		
C(18)-C(19)	1.342		
C(17)-C(18)	1.347		
C(9)-C(14)	1.346		
C(13)-C(14)	1.342		
C(12)-C(13)	1.341		
C(11)-C(12)	1.341		
C(10)-C(11)	1.342		

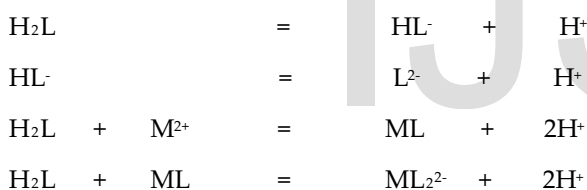|			
N(28)-C(27)-N(26)	116.784	H(35)-C(10)-C(11)	118.648
H(44)-N(26)-C(27)	115.153	H(35)-C(10)-C(9)	120.715
H(44)-N(26)-S(23)	118.907	C(11)-C(10)-C(9)	120.636
C(27)-N(26)-S(23)	124.844	C(14)-C(9)-C(10)	118.923
N(26)-S(23)-O(25)	110.498	C(14)-C(9)-N(8)	122.988
N(26)-S(23)-O(24)	110.257	C(10)-C(9)-N(8)	118.089
N(26)-S(23)-C(20)	82.578	N(16)-N(15)-C(4)	119.251
O(25)-S(23)-O(24)	123.739	C(2)-S(3)-C(4)	93.396
O(25)-S(23)-C(20)	110.701	H(33)-O(7)-C(5)	110.078
O(24)-S(23)-C(20)	111.525	S(3)-C(4)-C(5)	110.774
H(42)-C(21)-C(22)	118.637	S(3)-C(4)-N(15)	131.766
H(42)-C(21)-C(20)	120.433	C(5)-C(4)-N(15)	117.46
C(22)-C(21)-C(20)	120.929	H(34)-N(8)-C(9)	115.193
C(21)-C(20)-C(19)	118.328	H(34)-N(8)-N(1)	116.676
C(21)-C(20)-S(23)	120.705	C(9)-N(8)-N(1)	123.549
C(19)-C(20)-S(23)	120.96	C(4)-C(5)-N(1)	116.146
H(41)-C(19)-C(20)	120.743	C(4)-C(5)-O(7)	123.107
H(41)-C(19)-C(18)	118.697	N(1)-C(5)-O(7)	120.747
C(20)-C(19)-C(18)	120.559	C(5)-N(1)-C(2)	114.001
H(43)-C(22)-C(17)	121.794	C(5)-N(1)-N(8)	122.378
H(43)-C(22)-C(21)	117.041	C(2)-N(1)-N(8)	123.477
C(17)-C(22)-C(21)	121.165	S(3)-C(2)-N(1)	105.683
H(40)-C(18)-C(19)	118.205	S(3)-C(2)-S(6)	125.063
H(40)-C(18)-C(17)	120.205	N(1)-C(2)-S(6)	129.253
C(19)-C(18)-C(17)	121.59		
C(22)-C(17)-C(18)	117.428		
C(22)-C(17)-N(16)	125.784		
C(18)-C(17)-N(16)	116.788		

Bond angles (°)			
H(47)-C(31)-N(32)	117.362	C(17)-N(16)-N(15)	119.577
H(47)-C(31)-C(30)	120.943	H(38)-C(13)-C(14)	120.014
N(32)-C(31)-C(30)	121.694	H(38)-C(13)-C(12)	119.846
H(46)-C(30)-C(29)	122.58	C(14)-C(13)-C(12)	120.14
H(46)-C(30)-C(31)	122.577	H(37)-C(12)-C(13)	120.16
C(29)-C(30)-C(31)	114.843	H(37)-C(12)-C(11)	120.152
H(45)-C(29)-N(28)	117.313	C(13)-C(12)-C(11)	119.688
H(45)-C(29)-C(30)	120.855	H(36)-C(11)-C(12)	119.89
N(28)-C(29)-C(30)	121.831	H(36)-C(11)-C(10)	120.043
C(31)-N(32)-C(27)	120.055	C(12)-C(11)-C(10)	120.067
C(27)-N(28)-C(29)	119.883	H(39)-C(14)-C(9)	121.134
N(32)-C(27)-N(28)	121.694	H(39)-C(14)-C(13)	118.321
N(32)-C(27)-N(26)	121.522	C(9)-C(14)-C(13)	120.545

Table 2. The calculated quantum chemical parameters of the ligand (H₂L).

Parameter	
HOMO (a.u.)	-0.08272
LUMO (a.u.)	-0.07794
ΔE (a.u.)	0.00478
χ (a.u.)	0.08033
η (a.u.)	0.00239
σ (a.u.)⁻¹	418.410
Pi (a.u.)	-0.08033

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S (a.u.)$^{-1}$	209.205
ω (a.u.)	1.349
ΔN_{max}	33.611

3.2. Potentiometric studies

The interaction of a metal with an electron donor atom of a ligand is usually followed by the release of H$^+$. Alkaline potentiometric titrations are based on the detection of the protons released upon complexation. The main advantage of this technique, compared to other methods is that from the titration curves it is possible to follow complexation continuously as a function of pH and to detect exactly at which pH complexation takes place. Furthermore, it is possible to calculate the pK$_a$ values, the dissociation constants and the stability constants [25]. The following equilibria were used for the determination of the pK$_a$ values and the stability constants:

$$H_2L \qquad = \qquad HL^- \quad + \quad H^+$$
$$HL^- \qquad = \qquad L^{2-} \quad + \quad H^+$$
$$H_2L \quad + \quad M^{2+} \quad = \quad ML \quad + \quad 2H^+$$
$$H_2L \quad + \quad ML \quad = \quad ML_2^{2-} \quad + \quad 2H^+$$

H$_2$L represents an azorhodanine molecule, which bears two dissociable H$^+$, while M^{2+} are divalent metal ions.

The average number of the protons associated with the reagent molecule, $\bar{n}_A$, was determined at different pH values applying the following eq. 9:

$$\bar{n}_A \;=\; Y \;+\; \frac{(V_1 - V_2)\,(N^\circ + E^\circ)}{(V^\circ + V_1)\,TC^\circ_L} \tag{9}$$

where Y is the number of available protons in azorhodanine ($Y=2$) and V_1 and V_2 are the volumes of alkali required to reach the same pH on the titration curve of hydrochloric acid and reagent, respectively, V° is the initial volume (50 cm^3) of the mixture, TC°_L is the total concentration of the reagent, N$^\circ$

is the normality of the sodium hydroxide solution and E$^\circ$ is the initial concentration of the free acid. The titration curves ($\bar{n}_{A\,vs}$ pH) for the proton-ligand systems were constructed and found to extend between 0 and 2 on the $\bar{n}_A$ scale. This means that H$_2$L has two dissociable protons (the enolized hydrogen ion of the sulfonamide group, pK$_1^H$ and the carbonyl oxygen in the rhodanine moiety, pK$_2^H$). Different computional methods [26] were applied to evaluate the dissociation constants. Three replicate titrations were performed; the average values obtained are listed in Table 3.

Table 3. Thermodynamic functions for the dissociation of H$_2$L in 40 % (by volume) ethanol-water mixture in the presence of 0.1 M KCl at different temperatures.

Temp. K	Dissociation constant		Free energy change kJ mol^{-1}		Enthalpy change kJ mol^{-1}		Entropy change J mol^{-1} K^{-1}	
	pK$_1^H$	pK$_2^H$	ΔG_1	ΔG_2	ΔH_1	ΔH_2	$-\Delta S_1$	$-\Delta S_2$
298	6.15	8.87	35.09	50.61			17.62	69.31
308	5.99	8.69	35.56	51.25	29.84	29.96	18.58	69.12
318	5.72	8.54	35.44	52.00			17.60	69.31

The formation curves for the metal complexes were obtained by plotting the average number of ligands attached per metal ions ($\bar{n}$) versus the free ligand exponent (pL), according to Irving and Rossotti [27]. The average number of the reagent molecules attached per metal ion, $\bar{n}$, and free ligand exponent, pL, can be calculated using the eqs. 10 and 11:

$$\bar{n} \;=\; \frac{(V_3 - V_2)\,(N^\circ + E^\circ)}{(V^\circ + V_2)\,\bar{n}_A\,TC^\circ_M} \tag{10}$$

and

$$pL = \log_{10} \frac{\sum_{n=0}^{n=J} \beta_n^H \left[\frac{1}{\text{anti log pH}}\right]^n}{TC_L^o - \bar{n}TC_M^o} \cdot \frac{V^o + V_3}{V^o} \qquad (11)$$

where TC^o_M is the total concentration of the metal ion present in the solution, β^H_n is the overall proton-reagent stability constant. V_1, V_2 and V_3 are the volumes of alkali required to reach the same pH on the titration curves of hydrochloric acid, organic ligand and complex, respectively. These curves were analyzed and the successive stability constants were determined using different computional methods [28,29]. The values of the stability constants (log K_1 and log K_2) are given in Table 4. The following general remarks can be made:

i) The maximum value of $\bar{n}$ was ~ 2 indicating the formation of 1:1 and 1:2 (metal:ligand) complexes only [30].

ii) The metal ion solution used in the present study was very dilute (2×10^{-5} M), hence there was no possibility of formation of polynuclear complexes [31,32].

iii) The metal titration curves were displaced to the right-hand side of the ligand titration curves along the volume axis, indicating proton release upon complex formation of the metal ion with the ligand. The large decrease in pH for the metal titration curves relative to ligand titration curves point to the formation of strong metal complexes [33,34].

iv) For the same ligand at constant temperature, the stability of the chelates increases in the order Mn^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} [35-37]. This order largely reflects that the stability of Cu^{2+} complexes are considerably larger as compared to other metals of the 3d series. Under the influence of both the polarizing ability of the metal ion [38] and the ligand field,[26] Cu^{2+} will receive some extra stabilization due to tetragonal distortion of octahedral symmetry in its complexes. The greater stability of Cu^{2+} complexes is pro-duced by the well known *Jahn–Teller* effect [39].

Table 4. Stepwise stability constants for ML and ML_2 complexes of H_2L in 40 % (by volume) ethanol-water mixture and 0.1 M KCl at different temperatures.

M^{n+}	298 K		308 K		318 K	
	log K_1	log K_2	log K_1	log K_2	log K_1	log K_2
Mn^{2+}	7.55	5.30	7.70	5.45	7.84	5.59
Co^{2+}	7.64	5.39	7.79	5.53	7.93	5.67
Ni^{2+}	7.70	5.45	7.86	5.60	7.99	5.75
Cu^{2+}	7.85	5.59	7.98	5.86	8.13	5.91

The dissociation constant (pK^H) for H_2L as well as the stability constants of its complexes with Mn^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} have been evaluated at (298, 308 and 318) K, and are given in Tables 3 and 5. The enthalpy change (ΔH) for the dissociation and complexation process was calculated from the slope of the plot pK^H or log K vs. $^1/_T$ using the graphical reperesentation of the van't Hoff eqs. 12 and 13:

$$\Delta G = -2.303 \, RT \log K = \Delta H - T \, \Delta S \qquad (12)$$

or

$$\log K = (-\Delta H / 2.303 \, R)(1/T) + (\Delta S / 2.303 \, R) \qquad (13)$$

From the ΔG and ΔH values one can deduce the ΔS using the well known relationships 12 and 14:

$$\Delta S = (\Delta H - \Delta G) / T \qquad (14)$$

where R = 8.314 J K^{-1} mol^{-1} is the gas constant, K is the dissociation constant for the ligand or the stability constant of the complex, and T is absolute temperature.

All thermodynamic parameters of the dissociation process of azorhodanine are recorded in Table 3. From these results the following conclusions can be made:

i) The pK^H values decrease with increasing temperature, i.e., the acidity of the ligand increase.

ii) A positive value of ΔH indicates that the process is endo-

thermic.

iii) A large positive value of ΔG indicates that the dissociation process is not spontaneous [40].

iv) A negative value of ΔS is obtained due to the increased order as a result of the solvation process.

All the thermodynamic parameters of the stepwise stability constants of complexes are recorded in Table 5. It is known that the divalent metal ions exist in solution as octahedrally hydrated species [29] and the obtained values of ΔH and ΔS can then be considered as the sum of two contributions: (a) release of H_2O molecules, and (b) metal-ligand bond formation. Examination of these values shows that:

i) The stepwise stability constants (log K_1 and log K_2) for ligand complexes increases with increasing temperature, i.e., the stability constants increase with increasing temperature [41].

ii) The negative value of ΔG for the complexation process suggests the spontaneous nature of such processes [42].

iii) The ΔH values are positive, meaning that these processes are endothermic and favourable at higher temperature.

iv) The ΔS values for the ligand complexes are positive, confirming that the complex formation is entropically favourable [19].

Table 5. Thermodynamic functions for ML and ML$_2$ complexes of H$_2$L in 40 % (by volume) ethanol-water mixture and 0.1 M KCl.

M^{n+}	T/K	Gibbs energy / kJ mol^{-1}		Enthalpy / kJ mol^{-1}		Entropy / J mol^{-1} K^{-1}	
		$-\Delta G_1$	$-\Delta G_2$	$-\Delta H_1$	$-\Delta H_2$	ΔS_1	ΔS_2
Mn^{2+}	298	43.08	30.24	26.31	25.39	232.85	186.69
	308	45.41	32.08			232.86	186.61
	318	47.73	33.97			232.85	186.69
Co^{2+}	298	43.59	30.75	26.31	25.39	234.57	188.42
	308	45.94	32.61			234.58	188.33
	318	48.28	34.52			234.57	188.42
Ni^{2+}	298	43.94	31.10	26.33	27.21	235.79	195.65
	308	46.35	33.02			235.98	195.56
	318	48.65	35.01			235.78	195.65
Cu^{2+}	298	44.79	31.90	25.37	29.14	235.45	204.81
	308	47.06	34.56			235.18	206.81
	318	49.50	35.98			235.46	204.79

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