Journal of Molecular Liquids 221 (2016) 51–60

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Molecular docking, potentiometric and thermodynamic studies of azo rhodanines

A.Z. El-Sonbati [a], I.M. El-Deen [b], M.A. El-Bindary [c,*]

[a] Chemistry Department, Faculty of Science, University of Damietta, Damietta 34517, Egypt
[b] Chemistry Department, Faculty of Science, University of Port Said, Port Said, Egypt
[c] Engineering Chemistry Department, Higher Institute for Engineering and Technology, Damietta, Egypt

ARTICLE INFO

Article history:
Received 3 May 2016
Received in revised form 18 May 2016
Accepted 19 May 2016
Available online 21 May 2016

Keywords:
Azo rhodanine
Molecular docking
Potentiometry
Thermodynamics

ABSTRACT

Molecular docking was used to predict the binding between azo rhodanine derivatives ($\mathbf{HL_n}$) with the receptor prostate cancer 2Q7K hormone. The values of dissociation constant (pK^H) of azo rhodanine derivatives ($\mathbf{HL_n}$) are correlated with Hammett's constant (σ^R). The proton-ligand dissociation constant of azo rhodanine derivatives ($\mathbf{HL_n}$) and metal-ligand stability constants of their complexes with metal ions (Mn^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+}) have been determined potentiometrically in 0.1 M KCl and 40% (by volume) ethanol–water mixture and at 298, 308 and 318 K. The stability constants of the formed complexes increase with the order $Mn^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+}$. The effect of temperature was studied and the corresponding thermodynamic parameters (ΔG, ΔH and ΔS) were derived and discussed. The dissociation process of the ligands is non-spontaneous, endothermic and entropically unfavorable. The formation of the metal complexes has been found to be spontaneous, endothermic and entropically favorable.

1. Introduction

Rhodanine is one of the privileged scaffolds in drug discovery. Biological effects of various rhodanine derivatives have been reviewed by Tomasic and Masic [1,2]. Our research group has studied derivatives of rhodanine as potential antifungal and antimycobacterial agents [3,4]. Efforts have been made to carry out detailed studies to synthesize and elucidate the structural and electronic properties of novel families of complexes with rhodanine derivatives as a novel chelating bidentate azodye models [5]. The high stable potential of rhodanine derivative complexes in different oxidation states increased the application of these compounds in a wide range [6]. Azodyes play an important role in inorganic chemistry and form stable complexes with most transition metal ions [7]. The behavior of azodye complexes has attracted the attention of the bioinorganic chemists, since a number of these complexes are recognized to serve as models for biologically important species [8]. Breast cancer now represents the most common female malignancy in both the developing and developed world, and is the primary cause of death among women globally [9]. Cancer can be described as the uncontrolled growth of abnormal cells [10]. At global level, it accounted for more than 1.6 million new cases in 2010. The incidence or prevalence rate of the breast cancer in India is expected to be more than 90,000 in the coming years and over 50,000 women die each year.

In the present paper, we discuss the binding ability of azo rhodanine derivatives ($\mathbf{HL_n}$) with the receptor prostate cancer 2Q7K hormone. The dissociation constant of azo rhodanine derivatives ($\mathbf{HL_n}$) and the stability constants for their complexes with Mn^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} were obtained by potentiometric studies. Furthermore, the corresponding thermodynamic functions of dissociation and stability constants are derived and discussed.

2. Experimental

2.1. Measurements

Elemental microanalyses of the separated ligands for C, H, and N were determined on Automatic Analyzer CHNS Vario ELIII, Germany. IR spectra (KBr discs, 4000–400 cm^{-1}) by Jasco-4100 spectrophotometer. The pH measurements were carried out using VWR Scientific Instruments Model 8000 pH-meter accurate to ±0.01 units. The pH–meter readings in the non–aqueous medium were corrected [11]. The electrode system was calibrated according to the method of Irving et al. [12]. The temperature was controlled to within ±0.05 K by circulating thermostated water (Neslab 2 RTE 220) through the outer jacket of the vessel. All titrations have been carried out between pH 3.5–12.0 and under nitrogen atmosphere.

* Corresponding author.
E-mail address: m.a_bindary@yahoo.com (M.A. El-Bindary).

http://dx.doi.org/10.1016/j.molliq.2016.05.058
0167-7322/

In the study simulates the actual docking process in which the ligand–protein pair-wise interaction energies are calculated using Docking Server [13]. The MMFF94 Force field was for used energy minimization of ligand molecule using Docking Server. Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged and rotatable bonds were defined. Docking calculations were carried out on 2Q7K hormone protein model. Essential hydrogen atoms, Kollman united atom type charges and solvation parameters were added with the aid of AutoDock tools [14]. Affinity (grid) maps of 20 × 20 × 20 Å grid points and 0.375 Å spacing were generated using the Autogrid program [15]. AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

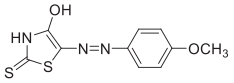
2.2. Materials

All chemicals used in this investigation were chemically pure grade derived from BDH. They include chlorides of Mn^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+}, sodium hydroxide (NaOH) (97%), sodium nitrite ($NaNO_2$) (97%), hydrochloric acid (HCl) (37%); purchased from BDH. The standard chemicals aniline (99%) and 4-alkylanilines (alkyl: OCH_3 (99%) and NO_2 (98%)) purchased from Aldrich, Fluka and Merck and were used without any further purification. Water used was bidistilled water; distillation process was carried out using both of condensation process and ion exchange technique.

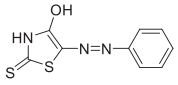
2.3. Preparation of azo rhodanines (*HL₁₋₃*)

The ligands (**HL_{1-3}**) were prepared previously [3,5] by coupling of 2-thioxo-4-thiazolidinone with aniline or its derivatives. 25 cm^3 of distilled water containing 0.01 mol concentrated hydrochloric acid was added to aniline (0.01 mol) or *p*-derivatives (–OCH_3 and –NO_2). To the resulting mixture was cooled to 0 °C, a solution of 0.01 mol of sodium nitrite in 20 ml of water was added dropwise. The formed diazonium chloride was consecutively coupled with an alkaline solution of 0.01 mol 2-thioxo-4-thiazolidinone, in 10 ml of pyridine. The colored precipitate, which formed immediately, was filtered through sintered glass crucible, washed several times with water. The crude products were purified by recrystallization from hot ethanol and then dried in a vacuum desiccator over $CaCl_2$. The purity of the compounds was checked by elemental analyses [3].

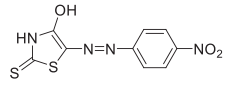
The resulting formed ligands are:



HL_1: 4-hydroxy-5-(4-methoxyphenylazo)thiazole-2(3*H*)-thione.



HL_2: 4-hydroxy-5-(phenylazo)thiazole-2(3*H*)-thione.



HL_3: 4-hydroxy-5-(4-nitrophenylazo)thiazole-2(3*H*)-thione.

2.4. pH metric titration

The experimental procedure involved the titration of the following solutions (total volume = 50 ml) against a standard CO_2-free (0.002 M) NaOH solution. 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 0.00 l 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 K and 318 K.

The ligands solutions (0.001 M) were prepared by dissolving an accurately weighed amount of the solid in ethanol. Metal ion solutions (0.0001 M) were prepared from analar metal chlorides in bidistilled water and standardized with EDTA [16]. Solutions of 0.001 M HCl and 1 M KCl were also prepared in bidistilled water. A carbonate-free sodium hydroxide solution in 40% (by volume) ethanol–water mixture was used as titrant and standardized against analar oxalic acid [17].

3. Results and discussion

3.1. Molecular docking

Molecular docking aims to achieve an optimized conformation for both the protein and drug with relative orientation between them such that the free energy of the overall system is minimized [18,19]. The data of molecular docking between ligands (**HL_{1-3}**) and receptor prostate cancer 2Q7K hormone showed a possible arrangement between ligands (**HL_{1-3}**) and receptor (2Q7K). On a docking study showing a favorable interaction between ligands (**HL_{1-3}**) and the receptor prostate cancer 2Q7K hormone and the calculated of energy are listed in Table 1 and Fig. 1. 2D plot curves of docking with ligands (**HL_{1-3}**) are shown in Fig. 2. This interaction could activate apoptosis in cancer cells energy of interactions with ligands (**HL_{1-3}**). Binding energies are most widely used mode of measuring binding affinity of ligands. Thus, decrease in binding energy due to mutation will increase the binding affinity of the ligands (**HL_{1-3}**) towards the receptor. The characteristic feature of ligands (**HL_{1-3}**) represent in presence of several active sites available for hydrogen bonding.

3.2. Potentiometric studies

The interaction of a metal with an electron donor atom of ligands (**HL_n**) 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 dissociation constants and

Table 1
Energy values obtained in docking calculations of ligands (**HL_{1-3}**) with the receptor of prostate cancer 2Q7K hormone.

Compound	Est. free energy of binding (kCal/mol)	Est. inhibition constant (K_i) (μM)	vdW + bond + desolv energy (kCal/mol)	Electrostatic energy (kCal/mol)	Total intercooled energy (kCal/mol)	Interact surface
HL_1	−6.90	67.98	−7.67	−0.10	−7.76	490.428
HL_2	−6.33	22.93	−7.25	−0.06	−7.31	479.373
HL_3	−5.69	8.73	−6.72	−0.06	−6.78	445.858

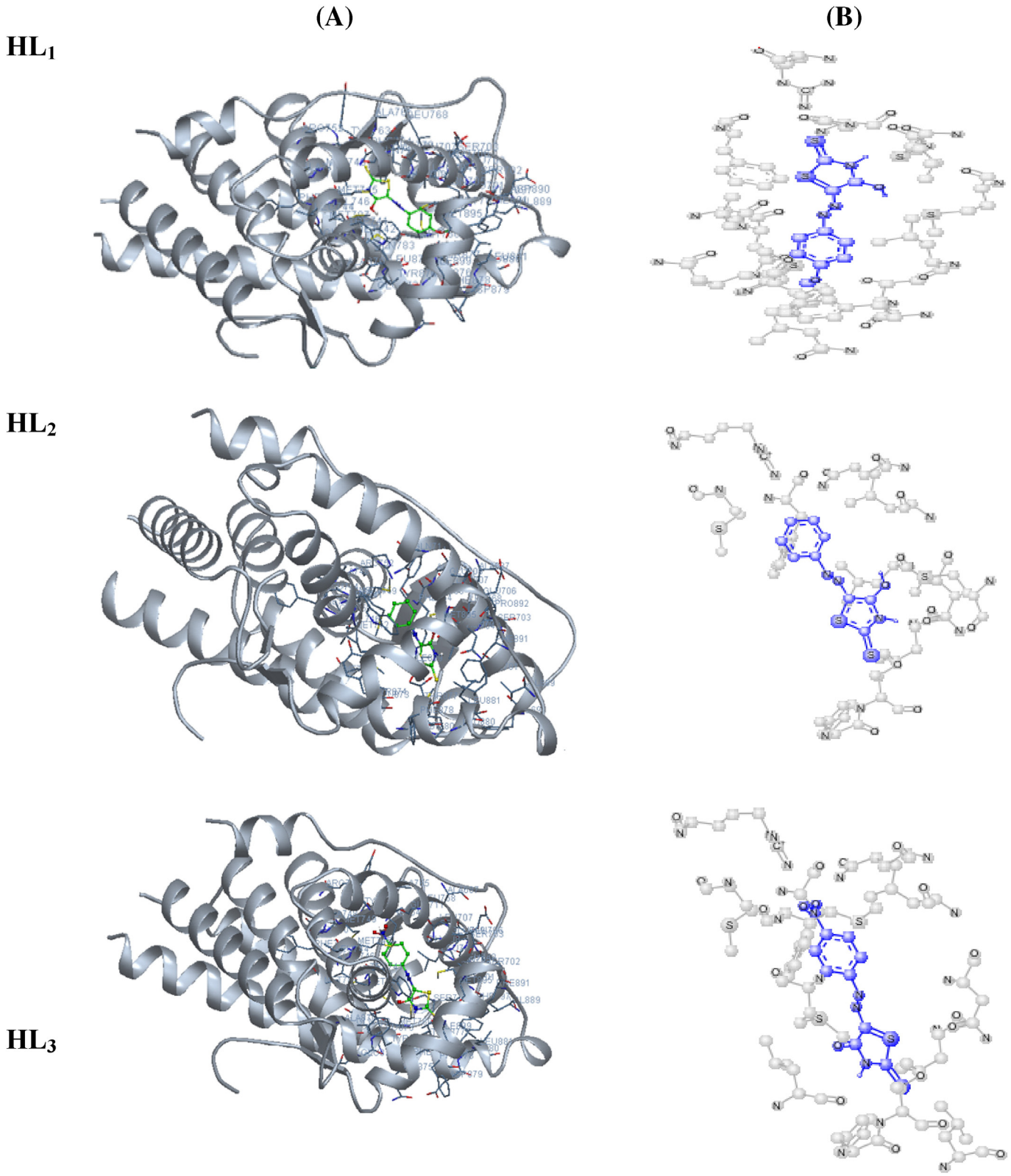
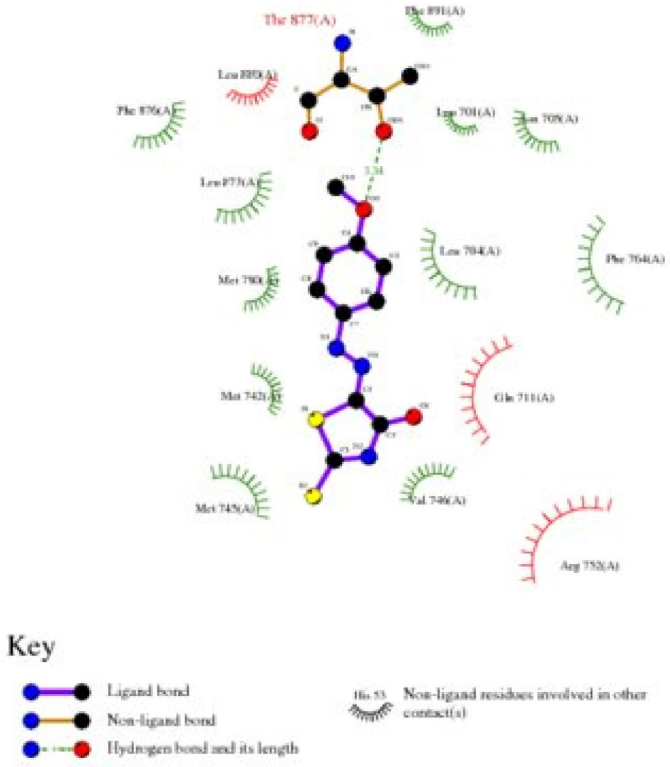


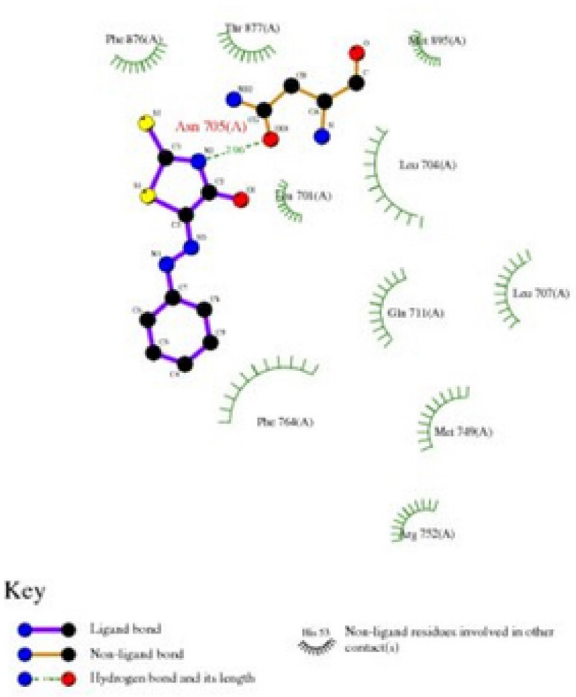
Fig. 1. The ligands (HL_n) (green in (A) and blue in (B)) in interaction with the receptor of prostate cancer 2Q7K hormone. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the stability constants of its complexes from the potentiometric titration. The average number of the protons associated with ligands (**HL_n**) at different pH values, $\bar{n}_A$, was calculated from the titration curves of the acid in the absence and presence of ligands (**HL_n**). Applying Eq. (1):

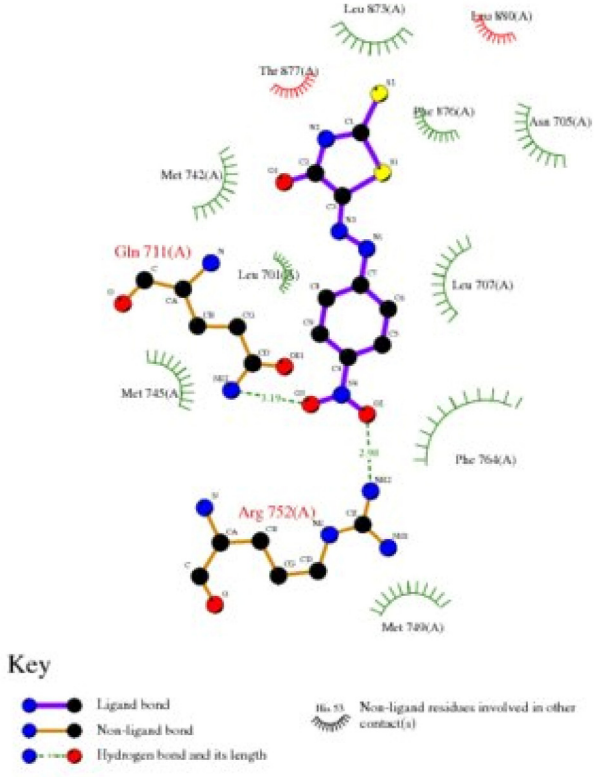
$$\bar{n}_A = Y \pm \frac{(V_1 - V_2)(N^\circ + E^\circ)}{(V^\circ - V_1)TC^\circ_L} \quad (1)$$



HL_1



HL_2



HL_3

Fig. 2. 2D plot of interaction between ligands (**HL_{1-3}**) and the receptor of prostate cancer 2Q7K hormone.

Table 2
Thermodynamic functions for the dissociation of (**HL_{1-3}**) in 40% (by volume) ethanol-water mixture and 0.1 M KCl at different temperatures.

Compound	Temperature (K)	Dissociation constant	Gibbs energy (kJ mol^{-1})	Enthalpy change (kJ mol^{-1})	Entropy change (J mol^{-1} K^{-1})
		pK^H	ΔG	ΔH	−ΔS
HL_1	298	8.36	47.70		77.87
	308	8.22	48.48	24.50	77.86
	318	8.09	49.26		77.87
HL_2	298	8.06	45.99		60.02
	308	7.91	46.65	28.10	60.21
	318	7.75	47.19		60.01
HL_3	298	7.48	42.68		61.02
	308	7.34	43.29	24.50	61.01
	318	7.21	43.90		61.02

Table 3
Stepwise stability constants for complexes of (**HL_{1-3}**) in 40% (by volume) ethanol-water mixtures and 0.1 M KCl at different temperatures.

Compound	M^{n+}	298 K		308 K		318 K	
		$logK_1$	$logK_2$	$logK_1$	$logK_2$	$logK_1$	$logK_2$
HL_1	Mn^{2+}	7.53	5.45	7.68	5.60	7.83	5.75
	Co^{2+}	7.71	5.63	7.86	5.78	8.01	5.93
	Ni^{2+}	7.80	5.73	7.94	5.87	8.10	6.03
	Cu^{2+}	8.07	5.98	8.22	6.12	8.37	6.25
HL_2	Mn^{2+}	7.35	5.22	7.48	5.36	7.63	5.50
	Co^{2+}	7.49	5.39	7.62	5.54	7.76	5.69
	Ni^{2+}	7.60	5.52	7.74	5.66	7.89	5.80
	Cu^{2+}	7.84	5.77	7.99	5.92	8.15	6.08
HL_3	Mn^{2+}	6.93	4.92	7.08	5.06	7.23	5.19
	Co^{2+}	7.10	5.05	7.26	5.21	7.41	5.35
	Ni^{2+}	7.19	5.14	7.34	5.29	7.49	5.43
	Cu^{2+}	7.42	5.38	7.60	5.53	7.75	5.68

Table 4
Thermodynamic functions for ML and ML_2 complexes of (**HL_{1-3}**) in 40% (by volume) ethanol-water mixture and 0.1 M KCl.

Comp.	M^{n+}	T/K	Gibbs energy (kJ mol^{-1})		Enthalpy change (kJ mol^{-1})		Entropy change (J mol^{-1} K^{-1})	
			$-\Delta G_1$	$-\Delta G_2$	ΔH_1	ΔH_2	ΔS_1	ΔS_2
HL_1	Mn^{2+}	298	42.97	31.10			235.48	195.65
		308	45.29	33.02	27.21	27.21	235.39	195.56
		318	47.68	35.01			235.48	195.65
	Co^{2+}	298	43.99	32.12			238.92	199.10
		308	46.35	34.09	27.21	27.21	238.83	199.01
		318	48.77	36.11			238.93	199.10
	Ni^{2+}	298	44.51	32.69			240.58	200.95
		308	46.82	34.62	27.19	27.19	240.30	200.67
		318	49.32	36.72			240.59	200.95
	Cu^{2+}	298	46.05	34.12			245.82	196.70
		308	48.48	36.09	27.21	24.50	245.73	196.71
		318	50.96	38.05			245.82	196.70
HL_2	Mn^{2+}	298	41.94	29.78			225.88	185.16
		308	44.11	31.61	25.37	25.39	225.60	185.08
		318	46.46	33.49			225.88	185.16
	Co^{2+}	298	42.74	30.75			225.55	194.50
		308	44.94	32.67	24.48	27.21	225.37	194.41
		318	47.25	34.65			225.55	194.50
	Ni^{2+}	298	43.36	31.50			233.74	190.91
		308	45.65	33.38	26.29	25.39	233.56	190.82
		318	48.04	35.31			233.75	190.91
	Cu^{2+}	298	44.73	32.92			244.42	204.79
		308	47.12	34.91	28.10	28.10	244.23	204.60
		318	49.62	37.02			244.43	204.79
HL_3	Mn^{2+}	298	39.54	28.07			223.99	176.41
		308	41.75	29.84	27.21	24.50	223.90	176.42
		318	44.02	31.60			223.99	176.41
	Co^{2+}	298	40.51	28.81			230.32	188.06
		308	42.81	30.73	28.12	27.23	230.32	188.16
		318	45.12	32.58			230.32	188.06
	Ni^{2+}	298	41.03	29.33			228.97	186.71
		308	43.29	31.20	27.21	26.31	228.88	186.71
		318	45.61	33.06			228.97	186.71
	Cu^{2+}	298	42.34	30.70			242.60	194.31
		308	44.82	32.61	29.96	27.21	242.78	194.22
		318	47.19	34.58			242.60	194.31

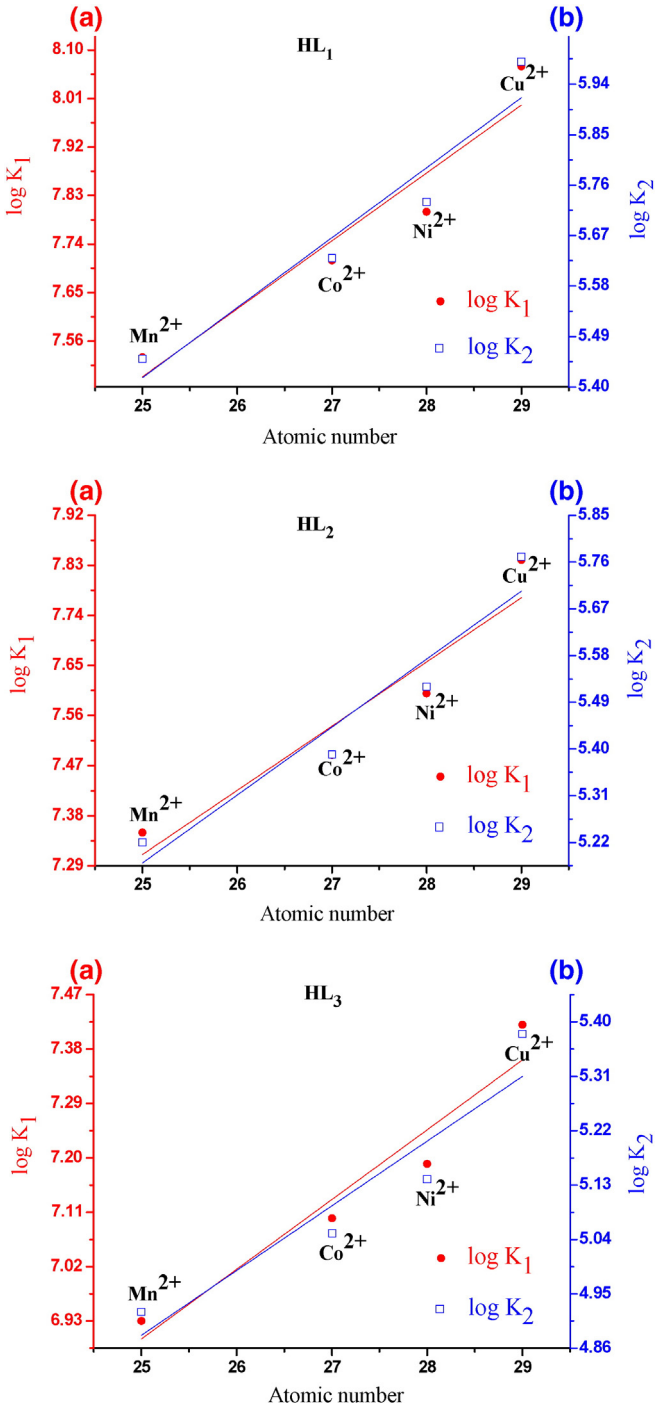


Fig. 3. The relation between stability constants (log K_1 and log K_2) and atomic number of metal complexes at 298 K for ligands ($\mathbf{HL_{1-3}}$).

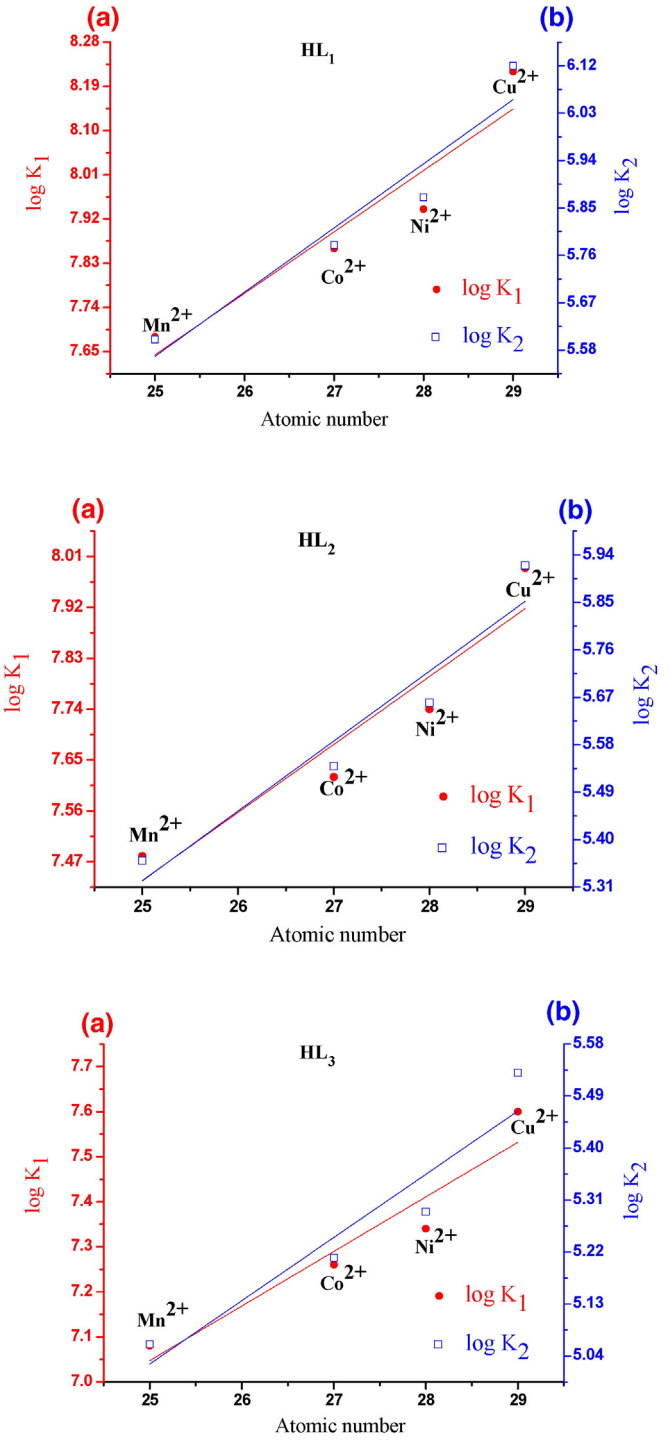


Fig. 4. The relation between stability constants (log K_1 and log K_2) and atomic number of metal complexes at 308 K for ligands ($\mathbf{HL_{1-3}}$).

where Y is the number of available protons in ligands ($\mathbf{HL_n}$) (Y = 1) 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° is the normality of sodium hydroxide solution and E° is the initial concentration of the free acid. Thus, the formation curves ($\bar{n}_A$ *vs.* pH) for the proton-ligand systems were constructed and found to extend between 0 and 1 in the $\bar{n}_A$ scale. This means that ligands ($\mathbf{HL_n}$) have ionizable proton (the enolized hydrogen ion of –OH group of the rhodanine moiety, pK^H). Different computational methods were applied to evaluate the dissociation constant [20]. Three replicate titrations were performed; the average values obtained are listed in Table 2. The completely protonated form of the ligands ($\mathbf{HL_n}$) has dissociable proton, that dissociates in the measurable pH range. The deprotonation of the *o*-hydroxy group most probably results in the formation of stable intramolecular H–bonding with the nitrogen of the azo group. Such an interaction decreases the dissociation process of ligands ($\mathbf{HL_n}$), i.e. increases the pK^H value [21,22].

The formation curves for the metal complexes were obtained by plotting the average number of ligands attached per metal ion ($\bar{n}_A$) *vs.* the free ligands exponent (pL), according to Irving and Rossotti [23].

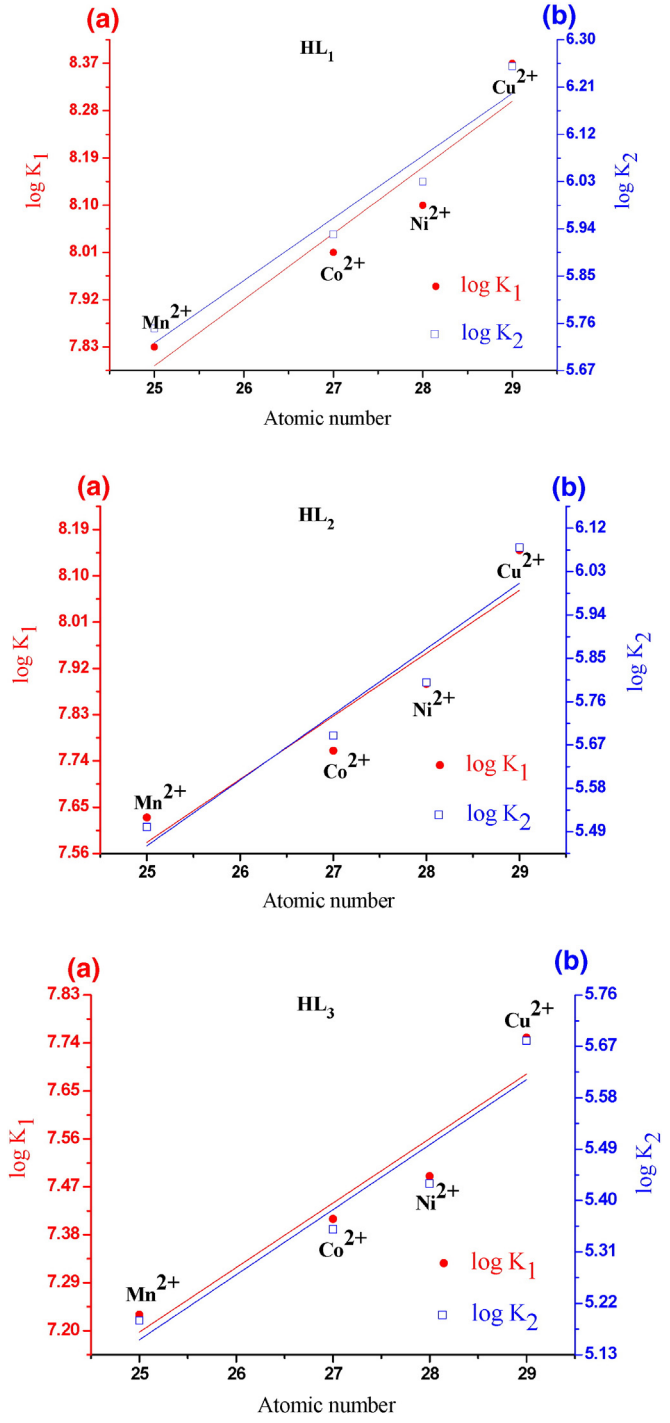


Fig. 5. The relation between stability constants (log K_1 and log K_2) and atomic number of metal complexes at 318 K for ligands (**HL_{1-3}**).

The average number of the reagent molecules attached per metal ion, $\bar{n}_A$, and free ligands exponent, pL, can be calculated using Eqs. (2) and (3):

$$\bar{n} = \frac{(V_3 - V_2)(N^\circ + E^\circ)}{(V^\circ - V_2)\cdot \bar{n}_A \cdot TC^\circ_M} \tag{2}$$

and

$$pL = \log_{10} \frac{\sum_{n=0}^{n=J} \beta_n^H \left(\frac{1}{[H^+]}\right)^n}{TC^\circ_L - \bar{n}\cdot TC^\circ_M} \cdot \frac{V^\circ + V_3}{V^\circ} \tag{3}$$

where TC°_M is the total concentration of the metal ion present in the solution, β_n^H 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 metal-ligand stability constants were determined using different computational methods [24,25]. The values of the stability constants (log K_1 and log K_2) are given in Table 3. The following general remarks can be pointed out:

(i) The maximum value of $\bar{n}_A$ was ~2 indicating the formation of 1:1 and 1:2 (metal:ligand) complexes [3].
(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 [26,27].
(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 [28].
(iv) For the same ligand at constant temperature, the stability of the chelates increases in the order: $Mn^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+}$ [29]. This order largely reflects that the stability of Cu^{2+} complexes is considerably larger than those of other metals of the 3d series. Under the influence of both the polarizing ability of the metal ion and the ligand field [30,31] 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 produced by the well known *Jahn–Teller* effect [32].

3.3. Effect of temperature

Stepwise dissociation constants for the ligand (HL) and the stepwise stability constants of their complexes with Mn^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} have been calculated at 298, 308 and 318 K. The corresponding thermodynamic parameters (ΔG, ΔH and ΔS) were evaluated. The dissociation constant (pK^H) for ligands (**HL_n**) as well as the stability constants of their complexes with Mn^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} have been evaluated at 298, 308 and 318 K, and given in Tables 2 and 4, respectively. The enthalpy (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 representation of *van't Hoff* Eqs. (4) and (5):

$$\Delta G = -2.303\,RT\log K = \Delta H - T\Delta S \tag{4}$$

or

$$\log K = (-\Delta H/2.303\,R)(1/T) + (\Delta S/2.303\,R) \tag{5}$$

where R is the gas constant = 8.314 J mol^{-1} K^{-1}, K is the dissociation constant for the ligand stability and T is the temperature (K). From the values of free energy change (ΔG) and enthalpy (ΔH), can deduce the entropy ΔS using the well known Eqs. 4 and 6:

$$\Delta S = (\Delta H - G)/T \tag{6}$$

All thermodynamic parameters of the dissociation process of ligands (**HL_n**) are recorded in Table 2. 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 increases.
(ii) A positive value of ΔH indicates that the process is endothermic.
(iii) A large positive value of ΔG indicates that the dissociation process is not spontaneous [33].

(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 of the ligands are recorded in Table 4. It is known that the divalent metal ions exist in solution as octahedral hydrated species [25] 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 stability constants (log K_1 and log K_2) for **HL_n** complexes increase with increasing temperature, i.e. its stability constants increase with increasing temperature [4].

(ii) The stability constants (log K_1 and log K_2) of Mn^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} complexes were increased with increasing atomic number in the order $Cu^{2+} > Ni^{2+} > Co^{2+} > Mn^{2+}$ at different temperatures (298, 308 and 318 K) as shown in Figs. 3–5.

(iii) The negative value of ΔG for the complexation process suggests the spontaneous nature of such processes.

(iv) The values of free energy change (ΔG_1 and ΔG_2) of formed complexes were increased with increasing atomic number at different temperatures (298, 308 and 318 K) as shown in Figs. 6–8.

(v) The ΔH values are positive, meaning that these processes are endothermic and favorable at higher temperature.

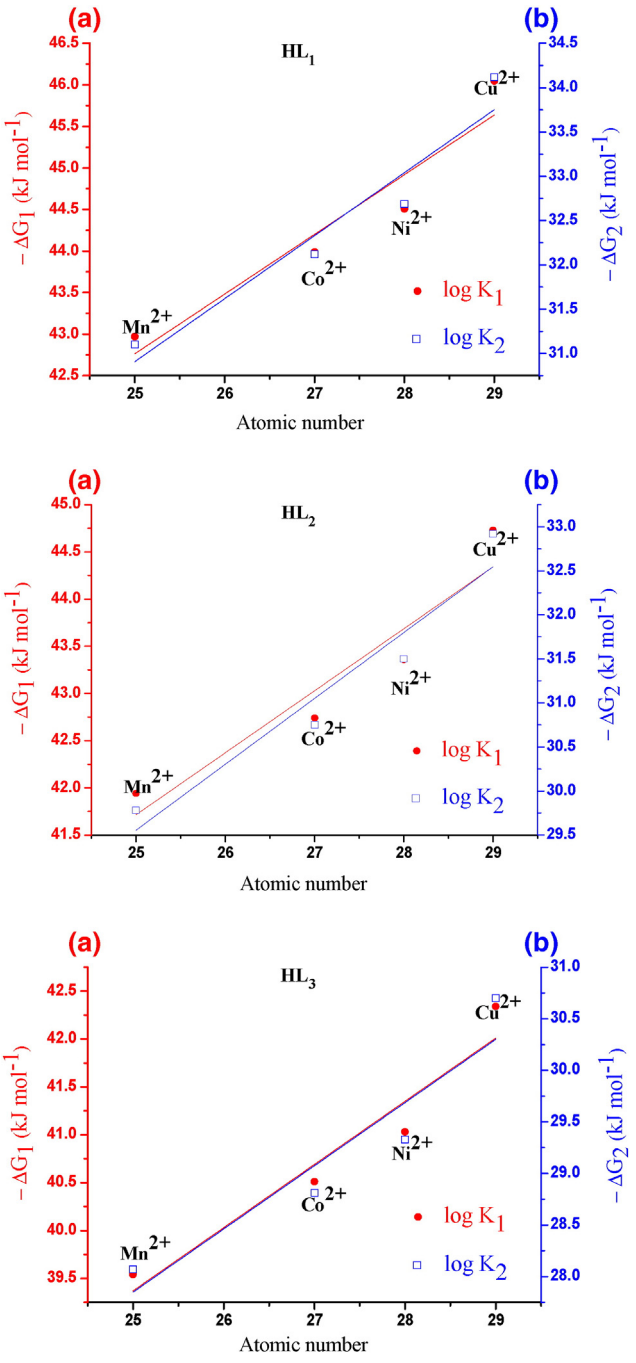


Fig. 6. The relation between free energy change (ΔG_1 and ΔG_2) and atomic number of metal complexes at 298 K for ligands (**HL_{1-3}**).

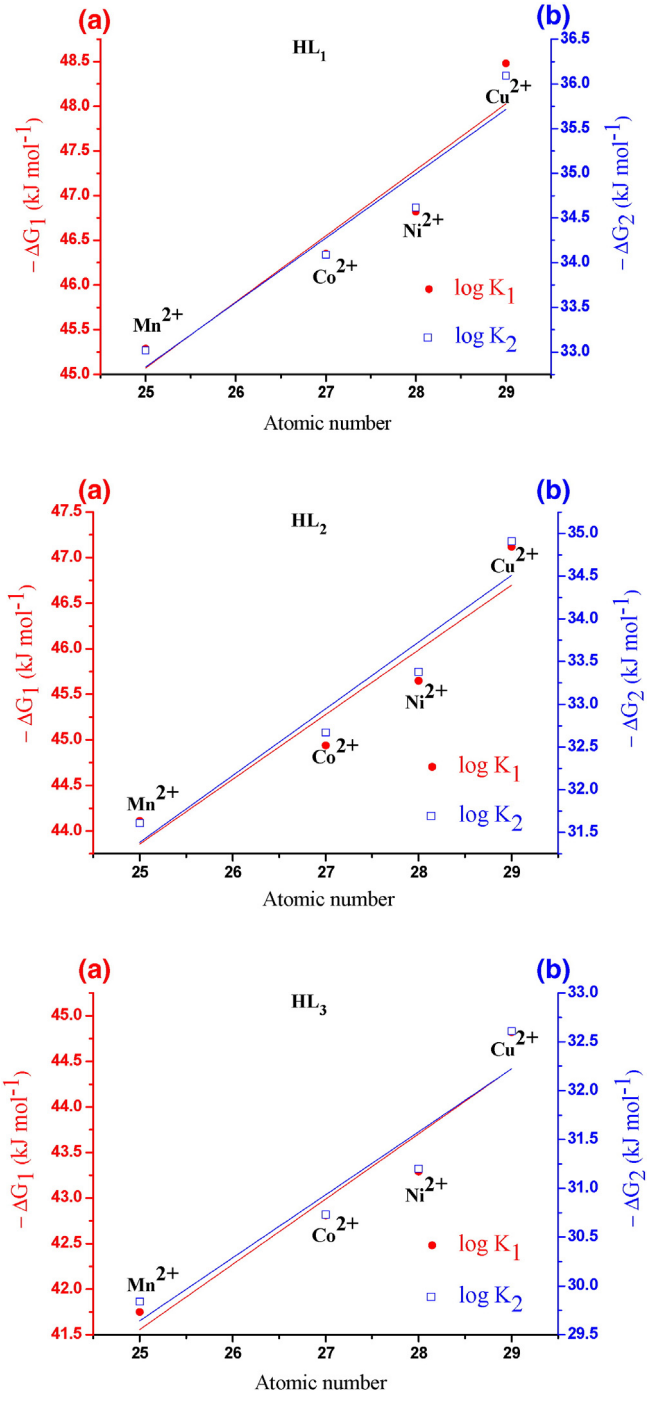


Fig. 7. The relation between free energy change (ΔG_1 and ΔG_2) and atomic number of metal complexes at 308 K for ligands (**HL_{1-3}**).

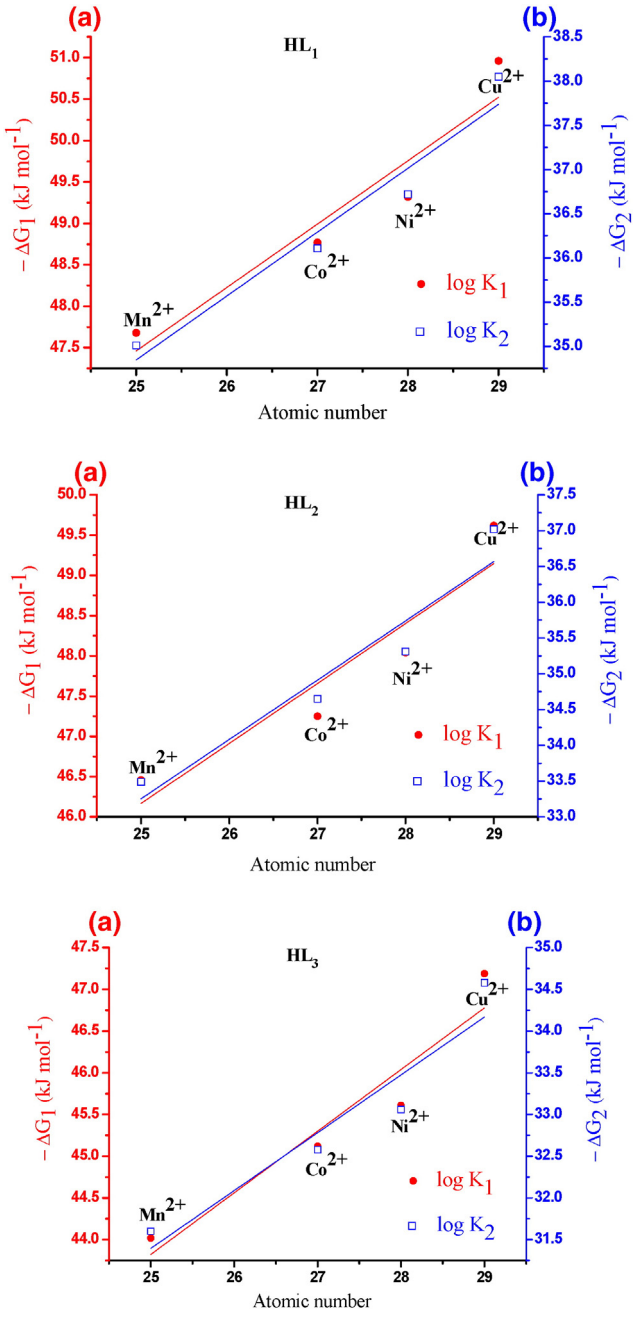


Fig. 8. The relation between free energy change (ΔG_1 and ΔG_2) and atomic number of metal complexes at 318 K for ligands (**HL_{1-3}**).

(vi) The ΔS values for the ligand complexes are positive, confirming that the complex formation is entropically favorable.

An inspection of the results in Table 2 reveals that the pK^H values of (**HL_2**) and its substituted derivatives are influenced by the inductive or mesomeric effect of the substituents. The *p*-OCH_3 derivatives (**HL_1**) have a lower acidic character (higher pK^H values) than the *p*-NO_2 (**HL_3**). This is quite reasonable because the presence of *p*-OCH_3 group (i.e. an electron-donating effect) will enhance the electron density by their high positive inductive or mesomeric effect, whereby a stronger O—H bond is formed. The presence of *p*-NO_2 group (i.e. an electron-withdrawing effect) will lead to the opposite effect. The results are also in accordance with Hammett's *para* substituent constant values (σ^R) as shown in Fig. 9. Straight lines are obtained on plotting pK^H values at different temperature versus σ^R. The para substituents in the phenyl moiety have a direct influence on the pK^H values of the investigated compounds affording a maximum resonance via delocalization of its π-system.

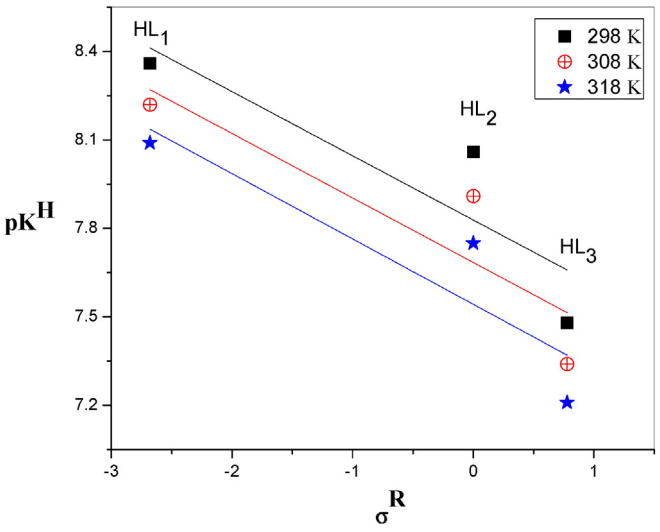


Fig. 9. Correlation of pK^H with Hammett's substituent constant values (σ^R) at 298, 308 and 318 K for ligands (**HL_{1-3}**).

4. Conclusion

Molecular docking was used to predict the binding between azo rhodanine ligands with the receptor of prostate cancer 2Q7K hormone. The proton-ligand dissociation constant of **HL_n** and metal-ligand stability constants of its complexes with metal ions (Mn^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+}) at different temperatures were determined. The stability constants of the formed complexes are increases in the order of $Cu^{2+} > Ni^{2+} > Co^{2+} > Mn^{2+}$. The dissociation process is non-spontaneous, endothermic and entropically unfavorable. The formation of the metal complexes has been found to be spontaneous, endothermic and entropically favorable.

References

[1] T. Tomasic, L.P. Masic, Curr. Med. Chem. 16 (2009) 1596–1629.
[2] T. Tomasic, L. Peterlin Masic, Expert Opin. Drug Discovery 7 (2012) 549–560.
[3] A.Z. El-Sonbati, M.A. Diab, A.A. El-Bindary, G.G. Mohamed, Sh.M. Morgan, Inorg. Chim. Acta 430 (2015) 96–107.
[4] A.Z. El-Sonbati, M.A. Diab, A.F. Shoair, A.A. El-Bindary, A.M. Barakat, J. Mol. Liq. 216 (2016) 821–829.
[5] A.Z. El-Sonbati, M.A. Diab, A.A. El-Bindary, M.M. Ghoneim, M.T. Mohesien, M.K. Abd El-Kader, J. Mol. Liq. 215 (2016) 711–739.
[6] A.Z. El-Sonbati, A.F. Shoair, A.A. El-Bindary, A.S. Mohamed, J. Mol. Liq. 209 (2015) 635–647.
[7] S. De Sousa, S. Lyu, L. Ducasse, T. Toupance, C. Olivier, J. Mater. Chem. B 3 (2015) 18256–18264.
[8] A.A. El-Bindary, A.Z. El-Sonbati, M.A. Diab, Sh.M. Morgan, J. Mol. Liq. 201 (2015) 36–42.
[9] J.R. Benson, I. Jatoi, Future Oncol. 8 (2012) 697–702.
[10] A.A. El-Bindary, A.F. Shoair, A.Z. El-Sonbati, M.A. Diab, E.E. Abdo, J. Mol. Liq. 212 (2015) 576–584.
[11] R.G. Bates, M. Paabo, R.A. Robinson, J. Phys. Chem. 67 (1963) 1833–1838.
[12] H.M. Irving, M.G. Miles, L.D. Pettit, Anal. Chim. Acta 38 (1967) 475–488.
[13] Z. Bikadi, E. Hazai, J. Chem. Inf. 11 (2009) 1–15.
[14] T.A. Halgren, J. Comput. Chem. 17 (1998) 490–519.
[15] G.M. Morris, D.S. Goodsell, R.S. Halliday, R. Huey, W.E. Hart, R.K. Belew, A.J. Olson, J. Comput. Chem. 19 (1998) 1639–1662.
[16] G.H. Jeffery, J. Bassett, J. Mendham, R.C. Deney, Vogel's Textbook of Quantitative Chemical Analysis, fifth ed. Longman, London, 1989.
[17] A.F. Shoair, A.A. El-Bindary, A.Z. El-Sonbati, N.M. Beshry, J. Mol. Liq. 215 (2016) 740–748 (740–748).
[18] M.M. Islam, V.K. Sonu, P.M. Gashnga, N.S. Moyon, S. Mitra, Spectrochim. Acta A 152 (2016) 23–33.

[19] B. Koohshekan, A. Divsalar, M. Saiedifar, A.A. Saboury, B. Ghalandari, A. Gholamian, A. Seyedarabi, J. Mol. Liq. 216 (2016) 8–15.
[20] H. Irving, H.S. Rossotti, J. Chem. Soc. 76 (1954) 2904–2910.
[21] E. Farkas, H. Csoka, J. Inorg. Biochem. 89 (2002) 219–226.
[22] M.M. Omar, G.G. Mohamed, Spectrochim. Acta A 61 (2005) 929–936.
[23] H. Irving, H.S. Rossotti, J. Chem. Soc. 74 (1953) 3397–3405.
[24] F.J.C. Rossotti, H.S. Rossotti, Acta Chem. Scand. 9 (1955) 1166–1176.
[25] M.T. Beck, I. Nagybal, Chemistry of Complex Equilibrium, Wiley, New York, 1990.
[26] P. Sanyal, G.P. Sengupta, J. Indian Chem. Soc. 67 (1990) 342–344.
[27] S. Sridhar, P. Kulanthaip, P. Thillaiarasu, V. Thanikachalam, G.J. Manikandan, World J. Chem. 4 (2009) 133–140.
[28] V.D. Athawale, S.S. Nerkar, Monatsh. Chem. 131 (2000) 267–276.
[29] W.U. Malik, G.D. Tuli, R.D. Madan, Selected Topics in Inorganic Chemistry, third ed. Chand S. & Company Ltd., New Delhi, 1984.
[30] G.G. Mohamed, M.M. Omar, A. Ibrahim, Eur. J. Med. Chem. 44 (2009) 4801–4812.
[31] F.R. Harlly, R.M. Burgess, R.M. Alcock, Solution Equilibria, Ellis Harwood, Chichester, 1980 257.
[32] L.E. Orgel, An Introduction to Transition Metal Chemistry Ligand Field Theory, Methuen, London, 1966 55.
[33] A. Bebot-Bringaud, C. Dange, N. Fauconnier, C. Gerard, J. Inorg. Biochem. 75 (1999) 71–78.