Journal of Molecular Liquids 219 (2016) 914–922

Contents lists available at ScienceDirect

Journal of Molecular Liquids

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

Potentiometric, equilibrium studies and thermodynamics of novel thiosemicarbazones and their bivalent transition metal(II) complexes

Abeer Taha Abd El-Karim *, Ahmed A. El-Sherif

Department of Chemistry, Faculty of Science, Cairo University, Cairo, Egypt

ARTICLE INFO

Article history:
Received 13 December 2015
Received in revised form 20 February 2016
Accepted 1 April 2016
Available online 26 April 2016

Keywords:
Thiosemicarbazone
Protonation
Thermodynamics
Copper, potentiometry

ABSTRACT

Protonation constants of novel thiosemicarbazones including 2-(1-(2-phenyl-hydrazono)-propan-2-ylidene) hydrazine-carbothioamide (TPHP) and *N*-methyl-2-(1-(2-phenyl-hydrazono)-propan-2-ylidene)hydrazinecarbothioamide (MTPHP) ligands and their corresponding metal-ligand formation constants with Cu(II), Ni(II), Mn(II) and Co(II) ions were determined at 15 °C, 25 °C and 35 °C in 50% DMSO solution at $I = 0.1$ mol·dm^{-3} $NaNO_3$. The stability order of complexes with reference to the metal ions has been followed this order Cu(II) > Ni(II) > Co(II) > Mn(II) in concord with the Irving-Williams stability order. Also, chemical equilibrium studies indicated that substitution of hydrogen in thiosemicarbazone (TPHP) by methyl group causes lowering of acidity as a result of the electron-releasing effect of the methyl group in the substituted amino group of the thiosemicarbazide moiety. The speciation of different species in solution has been evaluated as a function of pH. Additionally, the effect of temperature on protonation of thiosemicarbazone ligands and formation of their M(II)-thiosemicarbazone complexes was investigated. The thermodynamic parameters (ΔH, ΔS and ΔG) were calculated and discussed. It was found that both log K_1 and $-\Delta H_1$, for M(II)-thiosemicarbazone complexes are somewhat larger than $\log_{10} K_2$ and $-\Delta H_2$, indicating a change in the dentate character of these ligands from tridentate (SNN-donors) in 1:1 chelates to bidentate (SN-donors) in 1:2; M:L chelates. Also, the lower values of $\log_{10} K_2$ and $-\Delta H_2$ than log K_1 and $-\Delta H_1$ may be attributed to steric hindrance produced by the entrance of a second molecule.

1. Introduction

Protonation constants are important physicochemical parameters, which can provide critical information about drug properties such as solubility, lipophilicity, acidity, basicity [1,2], transport behavior, bonding to receptors [2–4], and permeability [5]. Hence, the relationship between the protonation constants and structure in drug design studies is important [2,3,6]. Protonation constants are also important parameters for the selection of the optimum conditions in the development of analytical methods [5,7] and choosing a suitable pH value for carrying out spectrophotometric quantitative analyses. Additionally, knowledge of the protonation constants of some compounds is necessary for the calculation of the concentration of each ionized species at any pH, which is important for the complete understanding of the physiochemical behavior of such molecules [8] and provides also information about the stereochemical and conformational structures of active centers of enzymes [9]. There are various techniques such as potentiometry, conductometry and spectrophotometry that are used in the determination of protonation constants. In this study a potentiometric technique was employed because it has the widest area of applicability and reliability [10–12].

Thiosemicarbazones and their complexes have been extensively studied because they have a wide range of actual or potential medical applications [13–17] which include notably antiparasital [18], antibacterial [19] antitumor activities [20], antiviral [21], fungicidal [22] and antineoplastic [23]. In spite of the large interest always shown in the coordination properties of thiosemicarbazone ligands and the attention paid in recent years to the possible variable biological activities of their metal complexes, studies dealing with protonation and complex formation equilibria of thiosemicarbazones and their complexes are still very rare. These findings stimulated our interest to study the solution equilibria of novel thiosemicarbazones and their metal complexes. In conjunction with our research program [24–33] directed to study ligands of biological significance and their complexes, the present investigation aims to study the solution equilibria of thiosemicarbazone-ligands and their M(II)–complexes in 50% DMSO–water mixture; the effects of temperature, thermodynamics, nature of the central metal ion and structure of the ligands on the protonation of novel thiosemicarbazones and their metal complexes.

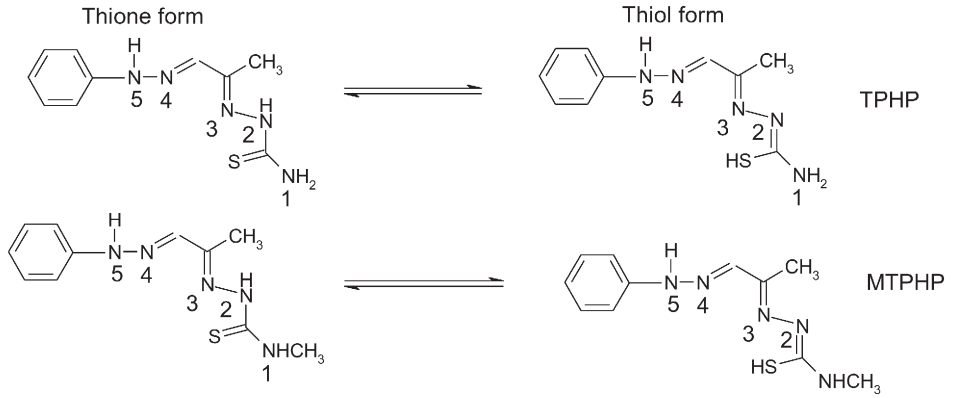
2. Experimental

2.1. Materials and reagents

All chemicals utilized in this investigation were of the analytical reagent grade (AR) quality and used without further purification. They

* Corresponding author.
E-mail address: tabdelkarima@yahoo.com (A.T.A. El-Karim).

http://dx.doi.org/10.1016/j.molliq.2016.04.005
0167-7322/



Scheme 1. Molecular structure of TPHP and MTPHP thiosemicarbazone compounds.

included HCl and KOH provided by BDH. Aniline, ethyl acetoacetate and sodium nitrite were obtained from Sigma. Thiosemicarbazide and 4-(*N*-methyl)-thiosemicarbazide were purchased from Merck. Metal salts including $CuCl_2 \cdot 2H_2O$ (Aldrich, ≥ 99.99%), $CoCl_2 \cdot 6H_2O$ (Sigma-Aldrich, 98%), $NiCl_2 \cdot 6H_2O$ (Aldrich, 99.9%) and $MnCl_2 \cdot 4H_2O$ (Sigma-Aldrich, ≥ 99%). DMSO was provided by Aldrich Chemicals Company.

2.2. Synthesis

2.2.1. Synthesis of 1-(phenyl-hydrazono)-propan-2-one (PHP)

It is prepared as reported in the literature [34,35] as follows: in a 4-l beaker equipped with a mechanical stirrer, 65 g (64 ml, 0.5 mol) of ethyl acetoacetate was added to 35 g (0.53 mol) of 85% potassium hydroxide in 1120 ml of water. The mixture is allowed to stand at room temperature for 24 h. Forty-seven grams (48 ml, 0.5 mol) of aniline is dissolved in 200 ml of aqueous HCl (prepared from equal volumes of concentrated acid and water) in a 2-l beaker. The beaker is equipped with a mechanical stirrer and immersed in an ice-salt bath. After the solution has cooled to 0–5 °C, 36 g. (0.52 mol) of sodium nitrite dissolved in 1 l of water is added slowly, with stirring, from a separating funnel. The tip of the stem of the separating funnel dipped well below the surface of the liquid. The rate of addition is adjusted to maintain the temperature between 0 and 5 °C. A drop of the reaction mixture is tested from time to time with starch-iodide paper until nitrous acid persists in the solution during a 5-min interval. The solution of potassium acetoacetate is cooled to 0 °C, and 45 ml of concentrated HCl in 150 ml of ice water is added slowly with stirring. The diazonium salt solution is then added over a period of 20 min, and the mixture is made basic by the addition of 82 g of sodium acetate dissolved in 300 ml of water. The temperature of the reaction mixture is raised slowly to 50 °C and maintained at this temperature for 2 h; the separated solid is collected on a filter and dried. The yield of crude product is 77 g (95%). Purification can be effected by recrystallization from 200 ml of toluene. The purified product weighs 66 g (82%); m.p. 148–150 °C.

2.2.2. Synthesis of TPHP and MTPHP thiosemicarbazone compounds

The general route of synthesis is shown as follow: Equimolar amounts of (PHP) (0.1620 g, 1 mmol) in 25 ml ethanol with an ethanolic solution (25 ml) of thiosemicarbazide (0.0911 g, 1 mmol) and methyl- (0.1051 g, 1 mmol) thiosemicarbazides were mixed and then refluxed on a hot plate for 4–5 h. The obtained precipitates were separated out, filtered off, washed with diethyl ether and dried overnight under silica gel (See Scheme 1).

2.3. Instruments

Potentiometric measurements were made using a Metrohm 686 titroprocessor equipped with a 665 Dosimat (Switzerland-Herisau). A thermostatted glass-cell was used equipped with a magnetic stirring system, a Metrohm glass electrode, a thermometric probe, a microburet delivery tube and a salt bridge connected with the reference cell filled with 0.1 M KCl solution in which saturated calomel electrode was dipped. Temperature was maintained constant inside the cell at 25.0 ± 0.01 °C, by the circulating water by a thermostated bath. All potentiometric measurements in this study were carried out in water-DMSO mixtures containing 50% DMSO because of low solubility of the synthesized thiosemicarbazone compounds and possible hydrolysis in aqueous solution.

2.4. Potentiometric titrations

The protonation constants of the ligands and stability of complex formation were measured potentiometrically using earlier described method [36]. 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 with standard buffer solutions, potassium hydrogen phthalate (pH = 4.008) and a mixture of KH_2PO4 and Na_2HPO_4 (pH = 6.865) at 25.0 °C, prepared according to NBS specifications [37]. The titration reaction was investigated in presence of purified N_2 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 [38]. In order to avoid probable hydrolysis of TPHP and MTPHP ligands in aqueous solution, potentiometric titration was carried out in 50% DMSO-water mixture.

To keep the ionic strength (I) constant during the titration process, supporting electrolyte of sodium nitrate was used i.e., the ionic strength was maintained constant at 0.1 M sodium nitrate with the addition of appropriate amount of 0.8 M $NaNO_3$ solution.

As is known, pH-meters read -log a_{H+} (pH), whereas the potentiometric method we used for the calculation of stability constants requires –log[H^+] (p[H]). Hence, the first step in computations was to convert the pH-meter readings (B) recorded in DMSO-water solutions to hydrogen ion concentration [H^+] [39]. This can be achieved by using the widely used relation given by the Van Uitert and Hass equation, Eq. (1) [40] as shown below,

$$-\log_{10}[H^+] = B + \log_{10} U_H \quad (1)$$

where $\log_{10} U_H$ is the correction factor for the solvent composition and ionic strength for which B is read. Values of pK_w in DMSO-water mixtures

were determined as described previously [41]. For this purpose, various amounts of standard NaOH solution were added to 50% aqueous DMSO solutions containing 0.1 mol·dm^{-3} $NaNO_3$. The [OH^-] was calculated from the amount of base added. The [H^+] was calculated from the pH value. The product of [OH^-] and [H^+] was taken. The mean values obtained in this way for -$\log_{10}$ [H^+][OH^-] ($pK_w = 15.52 \pm 0.2$) are in agreement with the literature values [42].

A carbonate-free sodium hydroxide solution in 50% (by volume) DMSO-water mixture was used as titrant and standardized against potassium hydrogen phthalate (Analar). The apparatus, general conditions, and method of calculations were the same as in previous work [43,44].

The proton association constants of the ligands (TPHP or MTPHP) were determined potentiometrically by titrating (1.25×10^{-3} mol·dm^{-3}) of the ligand solution (40 cm^3). The stability constants of the metal(II) complexes were determined using potentiometric data obtained from (40 cm^3) mixture containing $MCl_2 \cdot nH_2O$ (1.25×10^{-3} mol·dm^{-3}) + (TPHP or MTPHP) (1.25×10^{-3} mol·dm^{-3} / 2.5×10^{-3} mol·dm^{-3}).

The equilibrium constants evaluated from the titration data are defined by Eqs. (1) and (2), where M, L and H stand for the metal(II) ion, thiosemicarbazone ligands (TPHP/MTPHP) and proton, respectively

$$p(M) + q(L) + r(H) \rightleftharpoons \left[M_p(L)_q(H)_r\right] \quad (2)$$

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

Table 1
Protonation constants of TPHP and MTPHP thiosemicarbazones in 50% DMSO-50% H_2O (*v*/*v*) at different temperatures and $I = 0.1$ mol dm^{-3} $NaNO_3$.

System	*T* (°C)	p	q	r	$\log_{10}\beta$	S	log K_{NH}	log K_{SH}
TPHP	15	0	1	1	11.16 ± 0.03	2.1 *E*-8	11.16	7.55
		0	1	2	18.71 ± 0.05			
	25	0	1	1	11.07 ± 0.01	3.7 E-8	11.07	7.41
		0	1	2	18.48 ± 0.04			
	35	0	1	1	10.87 ± 0.05	6.3E-8	10.87	7.34
		0	1	2	18.21 ± 0.07			
MTPHP	15	0	1	1	11.27 ± 0.02	4.3E-8	11.27	8.60
		0	1	2	19.87 ± 0.04			
	25	0	1	1	11.15 ± 0.04	5.1E-8	11.15	8.48
		0	1	2	19.63 ± 0.07			
	35	0	1	1	10.93 ± 0.02	4.9E-8	10.93	8.36
		0	1	2	19.29 ± 0.06			

2.5. Data processing

The calculations were obtained from ca. 100 data points in each titration using the computer program MINIQUAD-75 [45]. The species distribution diagrams were obtained using the program SPECIES [46] under the experimental conditions employed.

3. Results and discussion

3.1. Protonation constants of thiosemicarbazone ligands

The study of protonation equilibria by the studied thiosemicarbazone ligands cannot be carried out in aqueous solution because of the nature of the compounds involved. These compounds are insoluble in water. This solvent has been widely used for potentiometric determination of protonation and formation equilibria as mentioned in literature [47–49]. The mixture DMSO-water 50%:50% was the chosen solvent for our study.

The stoichiometric protonation constants of the investigated thiosemicarbazone compounds (TPHP and MTPHP) were determined in 50% DMSO-water mixture at 25 °C and these constants are given in Table 1. The compounds studied here have two protonation constants. The log K_{SH} and log K_{NH} are related to the protonation of thiolate sulfur and hydrazo group, respectively. This is also illustrated in the species distribution of the TPHP ligand in Fig. 1. By rising of pH, the ligand (H_2L) loses its protons from SH group to form HL^-, which is the predominant species in pH range 8.8–9.7. As conditions become more alkaline, the second NH group begins deprotonation to the free ligand L^{2-} anion which is the predominant species at pH > 11. From Table 1, log K_{SH} of (MTPHP) ligand is 8.48 and that of (TPHP) is 7.41 and log K_{NH} of (MTPHP) is 11.15 and that of (TPHP) is 11.07. Substitution by methyl group instead of hydrogen causes a 1.07 unit increase of log K_{SH} and a 0.08 unit increase for log K_{NH}, which means a lowering of acidity. This can be explained by the electron-releasing effect of the methyl group in the substituted amino group. Also, it is observed that, the change in log K_{NH} is smaller than log K_{SH}. This is in accordance with the fact that, the inductive effect decreases as the distance increases. The log K_{NH} values ranges from (10.76–11.27) is similar to that found in literature for the hydrazo moiety (10.98) [50]. Also, the order of basicity of thiosemicarbazone ligands, is as follows; MTPHP > TPHP. The increase in basicity or decrease in the acidity is due to the electron-donating property (+I-effect) of the *N*-substituted moiety of the thiosemicarbazide moiety i.e., Methyl > Hydrogen. This is in accord with the published data in literature for *N*-

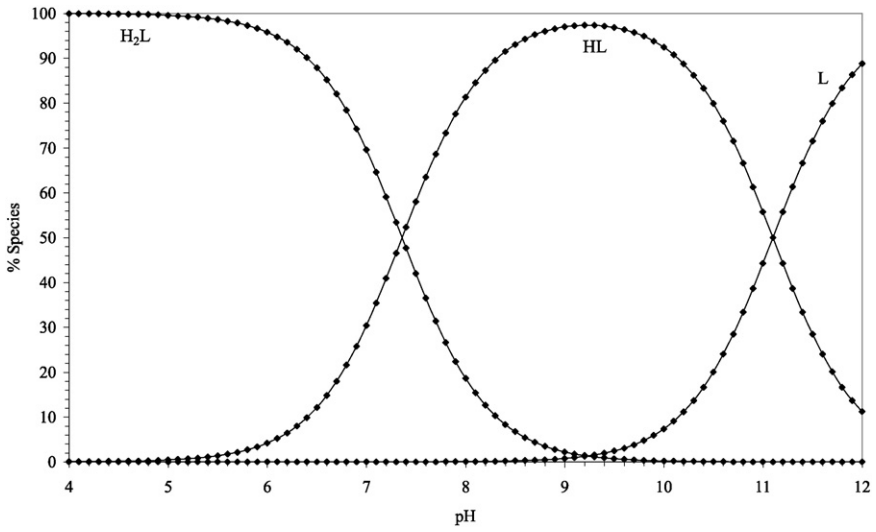


Fig. 1. Concentration distribution of various species as a function of pH in the TPHP system (at concentration of 1.25 mol·dm^{-3} for TPHP) at 25 °C and $I = 0.1$ mol·dm^{-3} $NaNO_3$.

alkyliminobis(methylphosphonic acid) derivatives whereas the pK values of *N*-ethyliminobis(methylphosphonic acid) (12.20, NH) [51], and *N*-methyliminobis(methylphosphonic acid) (11.75,NH) [51] are considerably greater than that of iminobis(methylphosphonic acid) (11.20, NH) [52]. This means that, substitution with an alkyl group has a great influence on the protonation equilibria of the neighboring groups.

3.2. Stability constants of the thiosemicarbazone complexes

The stability constants of ML complexes of thiosemicarbazone ligands with some divalent metal ions in DMSO-water solution were determined by use of the Miniquad-75 computer program. Comparing the titration curve of the free thiosemicarbaazone ligand with those of the complexed ligand shows that addition of the copper ion to the free thiosemicarbazone ligand solution of the complexes shifts the curve to lower pHs. In other words, the curves of the complexes are situated at lower pHs than the free ligand curve as they required more alkali to have the same pH as the free ligand. This can be explained simply as a result of proton release from the coordinated ligand, which implies complex formation. The stoichiometric stability constants of M(II) complexes of the investigated thiosemicarbazone ligands were determined in 50% DMSO-water mixture at different temperatures and these constants are given in Table 2. The data also showed the formation of the metal complexes with stoichiometric coefficients 110, 111 and 120.

The high stability of M(II)-MTPHP complexes than M(II)-TPHP complexes can be attributed to the presence of $-CH_3$ group in the thiosemicarbazide moiety which is in agreement with the basicity of these ligands. This is quite reasonable because the presence of the above $-CH_3$ group (i.e. an electron-donating group) will enhance the electron density by their high positive inductive effect, whereby stronger chelation was formed. This study indicated that alkylation of the N-terminal of thiosemicaarbazone has a highest effect on the stability of the formed complexes. This is in accord with the published data in literature [53].

The pK_a of the protonated complex can be calculated using Eq. (4) [54,55].

$$pK_a = \log\beta_{111} - \log\beta_{110} \quad (4)$$

This value is in fair agreement with pK_a of SH group (7.41) taking into consideration the acidification upon complexation i.e. the lower value (6.25) than that of free TPHP ligand (7.36) indicates acidification upon coordination to Cu(II) as a representative example of protonated metal(II)-thiosemicarbazone complexes by 1.16 pH units (7.41 to 6.25). This may indicate that the NN donors of TPHP are the binding sites in the protonated (CuHL) complex.

In order to investigate change in the concentration of the copper(II) complexes with pH, the species distribution diagram for Cu-TPHP system is examined (Fig. 2) as a representative example of Cu(II) complexes. In the Cu-TPHP distribution diagram, it will be seen that the complex CuHL is formed with maximum percent of 80% at pH 5.0. The deprotonated Cu-TPHP complex is formed with maximum percent of 63% at pH 8.0 forms. $Cu(TPHP)_2$ complex is formed with maximum percent of 18% at pH 8.0. Copper(II) ion was found to combine easily with TPHP-thiosemicarbazone ligand to form deprotonated (CuL), protonated (CuHL) and CuL_2 complexes depending on the pH of the solution.

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 periodic table properties [56] and the stability constants of complexes. In this investigation, it was found that, the formation constants of M^{II}-complexes of some transition

Table 2
Stability constants of M(II)-thiosemicarbazones in 50% DMSO-50% water at different temperatures and $I = 0.1$ mol dm^{-3} $NaNO_3$.

System	T (°C)	p	q	r	$\log_{10}\beta$	S
Cu-TPHP	15	1	1	0	11.84 ± 0.04	3.8E−7
		1	1	1	18.17 ± 0.06	
		1	2	0	22.62 ± 0.07	
	25	1	1	0	11.70 ± 0.05	4.2E−7
		1	1	1	17.93 ± 0.06	
		1	2	0	22.32 ± 0.05	
	35	1	1	0	11.53 ± 0.04	5.1E−7
		1	1	1	17.67 ± 0.08	
		1	2	0	22.02 ± 0.07	
Cu-MTPHP	15	1	1	0	12.30 ± 0.05	5.6E−7
		1	1	1	18.80 ± 0.06	
		1	2	0	23.64 ± 0.06	
	25	1	1	0	12.14 ± 0.06	6.2E−7
		1	1	1	18.53 ± 0.07	
		1	2	0	23.31 ± 0.04	
	35	1	1	0	11.98 ± 0.05	6.8E−7
		1	1	1	18.29 ± 0.08	
		1	2	0	23.02 ± 0.07	
Ni-TPHP	15	1	1	0	11.08 ± 0.06	7.5E−8
		1	1	1	16.94 ± 0.09	
		1	2	0	21.20 ± 0.05	
	25	1	1	0	10.64 ± 0.05	6.3E−8
		1	1	1	16.72 ± 0.07	
		1	2	0	20.93 ± 0.07	
	35	1	1	0	10.49 ± 0.04	7.7E−8
		1	1	1	16.48 ± 0.08	
		1	2	0	20.63 ± 0.06	
Ni-MTPHP	15	1	1	0	11.21 ± 0.03	4.8E−8
		1	1	1	17.40 ± 0.06	
		1	2	0	21.40 ± 0.08	
	25	1	1	0	11.02 ± 0.04	5.2E−8
		1	1	1	17.14 ± 0.06	
		1	2	0	21.12 ± 0.09	
	35	1	1	0	10.91 ± 0.03	4.8E−8
		1	1	1	16.91 ± 0.06	
		1	2	0	20.82 ± 0.08	
Co-TPHP	15	1	1	0	10.18 ± 0.04	3.4E−8
		1	2	0	19.95 ± 0.06	
	25	1	1	0	10.02 ± 0.03	5.9E−8
		1	2	0	19.66 ± 0.07	
	35	1	1	0	9.90 ± 0.05	4.2E−8
		1	2	0	19.40 ± 0.06	
Co-MTPHP	15	1	1	0	10.59 ± 0.05	3.9E−8
		1	2	0	20.21 ± 0.07	
	25	1	1	0	10.47 ± 0.04	3.5E−8
		1	2	0	19.96 ± 0.08	
	35	1	1	0	10.30 ± 0.06	4.6E−8
		1	2	0	19.65 ± 0.06	
Mn-TPHP	15	1	1	0	9.87 ± 0.04	5.1E−8
		1	2	0	19.18 ± 0.08	
	25	1	1	0	9.72 ± 0.06	4.9E−8
		1	2	0	18.92 ± 0.09	
	35	1	1	0	9.60 ± 0.05	7.2E−8
		1	2	0	18.65 ± 0.08	
Mn-MTPHP	15	1	1	0	10.05 ± 0.06	8.1E−8
		1	2	0	19.45 ± 0.09	
	25	1	1	0	9.91 ± 0.07	3.4E−8
		1	2	0	19.20 ± 0.08	
	35	1	1	0	9.77 ± 0.08	9.5E−8
		1	2	0	18.90 ± 0.09	

Definitions of stability constants.
$K_{ML} = [ML]/[M][L]$.
$K_{MHL} = [MHL]/[ML][H]$.
(L = thiosemicarbazone ligands); (Charges are omitted for simplicity).

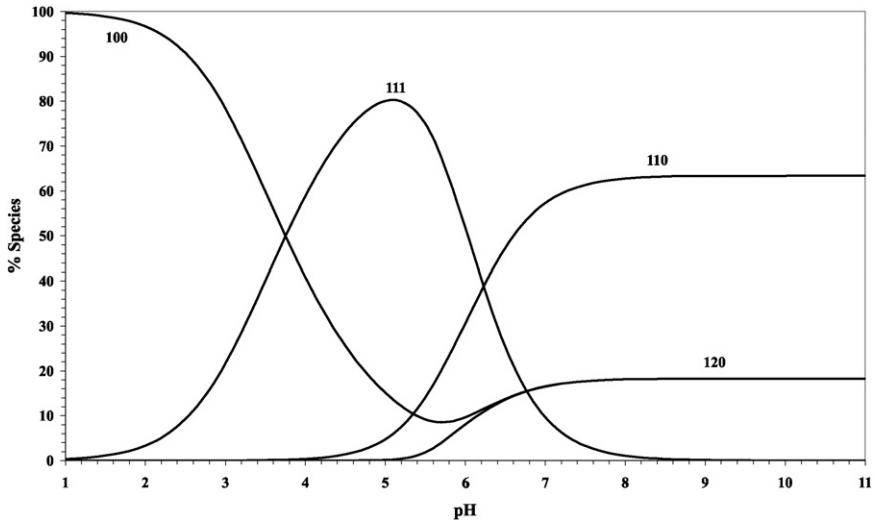


Fig. 2. Concentration distribution of various species as a function of pH in the Cu-TPHP system (at concentrations of 1.25 mol·dm^{-3} for Cu(II) and 1.25 mol·dm^{-3} for TPHP) at 25 °C and $I = 0.1$ mol·dm^{-3} $NaNO_3$.

metal ions with thiosemicarbazones obeyed this arrangement: Mn(II) < Co^{2+} < Ni^{2+} < Cu^{2+} which is consistent with Irving-Williams' order [57].

The relation between the $\log_{10}K_{ML}$ and reciprocal of the 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(II) (1.55) < Co^{2+}(1.88) < Ni^{2+} (1.91) < Cu^{2+} (2.0)) 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.

A good linear correlation has been obtained between the stability constants of metal complexes and the second ionization potential of the metal ions (Fig. 3) under investigation. Generally, it is observed that the stability constant of the Cu^{2+} 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 [58].

3.4. Effect of temperature and thermodynamics

The values of thermodynamic parameters that are related to the protonation of thiosemicarbazones and their metal(II) complexes have been calculated from the temperature dependent data given in Tables 3 and 4. Values of ΔH and ΔS were obtained by drawing the relationship between the values of equilibrium constants (logK) versus reciprocal of temperature (1/T) (logK = − ΔH/RT + ΔS/R) leading to an intercept ΔS/R and a slope −ΔH/R (Figs. 4 and 5). Main conclusions from the data can be summarized as follows:

(I) The protonation reaction of the thiosemicarbazones is exothermic with a net negative ΔG (Table 5).
(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:
[1] These values decrease with rising of temperatures, proposing that the process of complex formation is favored at low temperature.

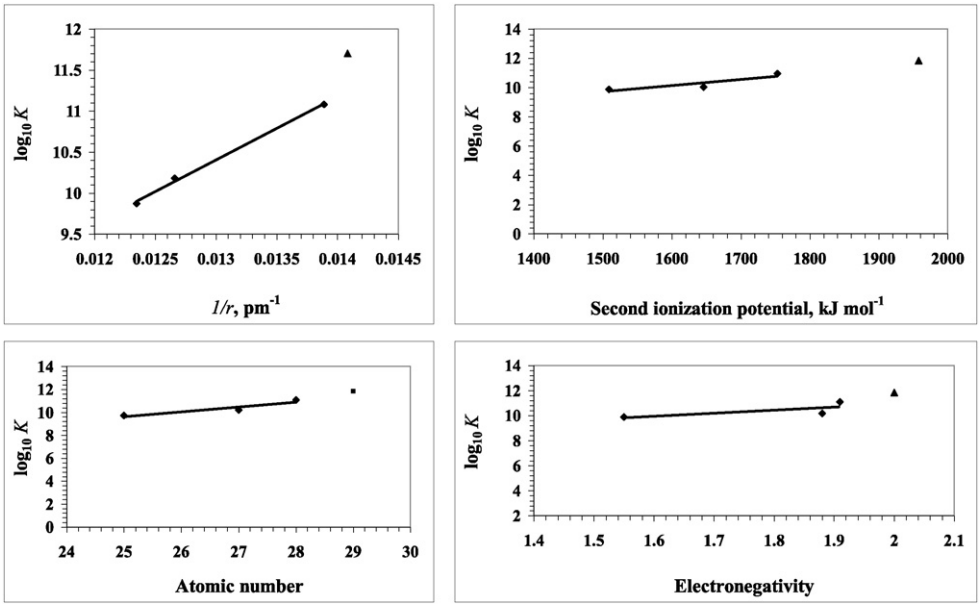


Fig. 3. Variation of the stability constants for the M(II)-TPHP complexes with properties of the metal(II) ions.

Table 3
Stepwise stability constants for ML and ML_2 complexes of TPHP-thiosemicarbazone ligands in 50% (*v*/*v*) DMSO-water mixtures and 0.1 mol·dm^{-3} $NaNO_3$ at different temperatures.

M^{n+}	15 °C		25 °C		35 °C	
	$logK_1$	$logK_2$	$logK_1$	$logK_2$	$logK_1$	$logK_2$
Mn^{2+}	9.87	9.31	9.72	9.21	9.60	9.05
Co^{2+}	10.18	9.77	10.02	9.64	9.90	9.50
Ni^{2+}	11.08	10.12	10.94	9.99	10.79	9.84
Cu^{2+}	11.84	10.78	11.70	10.62	11.53	10.49

Table 4
Stepwise stability constants for ML and ML_2 complexes of MTPHP-thiosemicarbazone ligands in 50% (*v*/*v*) DMSO-water mixtures and 0.1 mol.dm^{-3} $NaNO_3$ at different temperatures.

M^{n+}	15 °C			25 °C	35 °C	
	$logK_1$	$logK_2$	$logK_1$	$logK_2$	$logK_1$	$logK_2$
Mn^{2+}	10.05	9.40	9.91	9.29	9.77	9.13
Co^{2+}	10.59	9.62	10.47	9.49	10.30	9.35
Ni^{2+}	11.21	10.19	11.03	10.09	10.91	9.91
Cu^{2+}	12.30	11.14	12.14	11.04	11.98	10.84

] It is known that divalent metal ions exist in solution in the form of octahedral hydrated species [59]. 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:

[3] Of the data (Tables 3 and 4) reveals that $logK_1$ for TPHP and MTPHP complexes is somewhat larger than $logK_2$·This is due to the fact that the interaction of a second bulky ligand molecule is usually weaker than the first ligand, i.e., the ML_2 (1:2) species is not formed until complete formation of the ML(1:1) species. This can be ascribed to: (i) The increase in the Lewis acidity of the free metal ion (M^{+n}) as compared to the 1:1 chelated ion ($ML^{+\,n-1}$) and (ii) The steric hindrance caused by the addition of a second bulky ligand molecule on the $ML^{+\,n-1}$ chelated ion.

[4] For the same ligand at constant temperature, the stability of the chelates increases in the order $Cu^{2+} > Ni^{2+} > Co^{2+} > Mn^{2+}$ [60–62]. 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 [63] and the ligand field [64], 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 [64].

[5] All negative values of the Gibb's free energy associated with the process of formation of complexes illustrate the spontaneous nature of the complex formation reactions.

[6] 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.

[7] The values (ΔS) for the ligand complexes are positive, confirming that the complex formation is entropically favourable [65] and the mechanism of complexation is based on hydrogen ion (H^+) liberation and the release of water molecules [66]. During formation of metal chelates, water molecules from the primary hydration sphere of the metal ion are displaced by the chelating ligand. Thus there is an increase in the number of particles in the system i.e., randomness of the system increases as shown in the following equation

$$\left[M(H_2O)_n\right]^{+2}{}_{(aq)} + L^-{}_{(aq)} \rightleftharpoons ML^+{}_{(aq)} + nH_2O. \quad (5)$$

[8] The negative values of both ΔG and ΔH of the complexation process indicate that the complexation process proceeds spontaneously and exothermically, respectively, i.e., the complex formation is enthalpically favourable.

In general, the abnormal higher positive values of ΔS for all the complex systems are consistent with the hypothesis that a large number of water molecules are released upon complexation with probability of change for the coordination number [67]. This was supported by the values of ΔH, where it was found that $-\Delta H_1 > -\Delta H_2$ for the TPHP and PTPHP-thiosemicarbazone complexes (Tables 6 and 7). The lower negative values of ΔH_2 were taken as good evidence for a change in the dentate character of the TPHP and PTPHP ligands from tridentate (SNN-donors) in the 1:1 complexes to bidentate (SN-donors) in the 1:2, M:L, complexes, whereby the steric hindrance in the 1:2 species is relieved. Similar observations were obtained by Evans et al. [68]. The higher values of the thermodynamic functions for the Cu(II)-complexes is attributed to the $3d^9$-configuration of Cu(II) which undergoes Jahn-Teller distortion. On the other

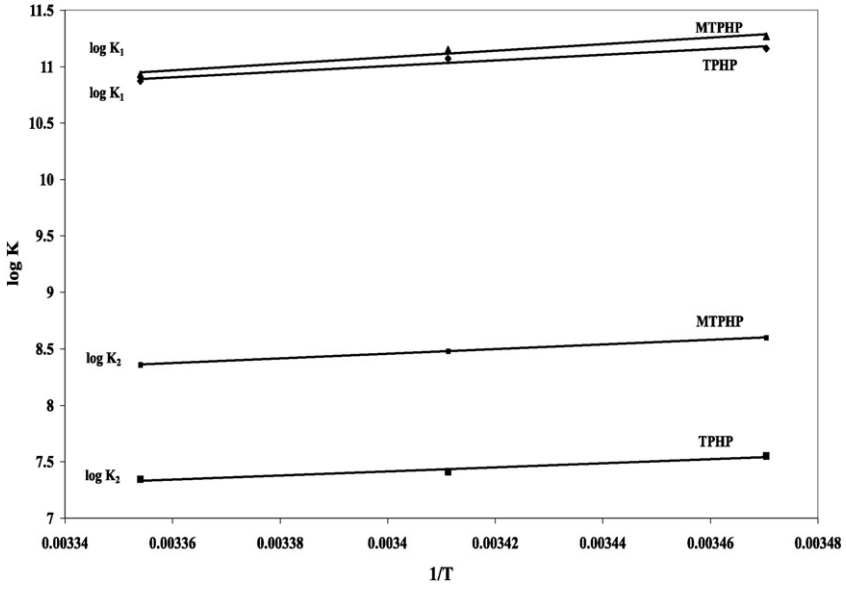


Fig. 4. Effect of temperature on the protonation constant of TPHP and MTPHP .

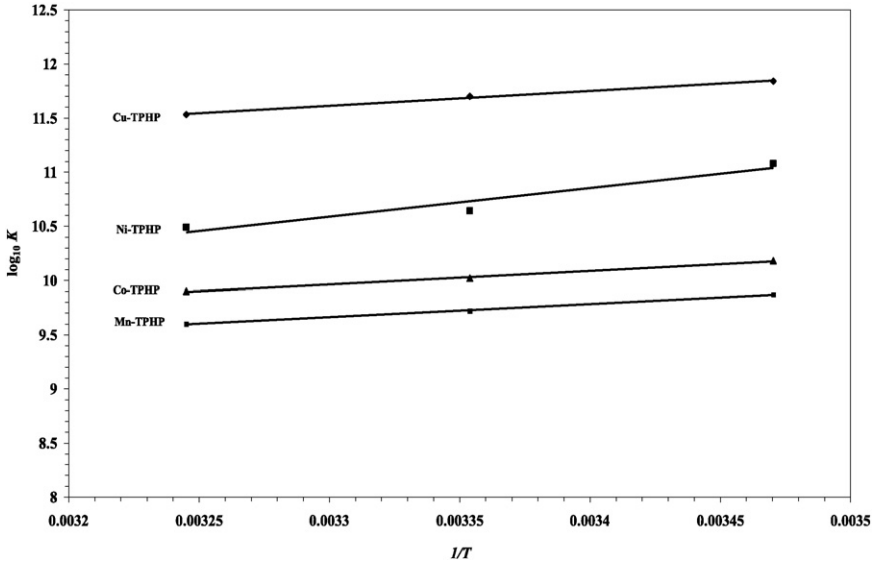


Fig. 5. Effect of temperature on the formation constant of *M*-TPHP complexes.

Table 5
Thermodynamics for the association of TPHP, MTPHP and PTPHP thiosemicarbazones in 50% DMSO-50% H_2O(*v*/*v*).

System	ΔH° (kJmol^{-1})	ΔS° (JK^{-1} mol^{-1})	ΔG° (kJmol^{-1})
TPHP			
$L^- + H^+ \rightleftharpoons LH$	−47.60	48.82	−61.97
$HL + H^+ \rightleftharpoons H_2L^+$	−34.61	24.12	−41.67
MTPHP			
$L^- + H^+ \rightleftharpoons LH$	−55.83	22.21	−62.34
$HL + H^+ \rightleftharpoons H_2L^+$	−39.48	27.57	−47.55

hand, the lower values for the Mn(II)-complexes may be attributed to the $3d^5$– configuration of Mn(II) which probably exists as tetrahedral $[Mn(OH_2)_4]^{2+}$ in aqueous solutions [69].

3.5. Effect of ionic strength on the protonation constants of thiosemicarbazone compounds

The ionic strength of the medium (μ) is given by Eq. (6)

$$\mu = 1/2\Sigma Z_i{}^2 m_i \quad (6)$$

Table 6
Thermodynamic functions for ML and ML_2 complexes of TPHP, thiosemicarbazones in 50% (by volume) DMSO-water mixture and 0.1 mol·dm^{-3} $NaNO_3$.

M^{n+}	T/K	Gibbs energy/kJ·mol^{-1}		Enthalpy/kJ·mol^{-1}		Entropy/J·mol^{-1}·K^{-1}	
		ΔG_1	ΔG_2	ΔH_1	ΔH_2	ΔS_1	ΔS_2
Mn^{2+}	288	−54.46	−51.37	−44.48	−42.77	34.46	30.06
	298	−54.50	−51.53				
	308	−54.80	−51.60				
Co^{2+}	288	−56.17	−53.90	−46.07	−44.42	34.84	32.93
	298	−56.24	−54.11				
	308	−56.52	−54.23				
Ni^{2+}	288	−61.13	−55.83	−47.69	−46.04	46.52	34.08
	298	−61.41	−56.07				
	308	−61.60	−56.17				
Cu^{2+}	288	−65.32	−59.48	−50.96	−47.73	49.97	40.59
	298	−65.67	−59.61				
	308	−65.82	−59.88				

Table 7
Thermodynamic functions for ML and ML_2 complexes of MTPHP, thiosemicarbazones in 50% (by volume) DMSO-water mixture and 0.1 mol·dm^{-3} $NaNO_3$.

M^{n+}	T/K	Gibbs energy/kJ·mol^{-1}		Enthalpy/kJ·mol^{-1}		Entropy/J·mol^{-}·K^{-1}	
		ΔG_1	ΔG_2	ΔH_1	ΔH_2	ΔS_1	ΔS_2
Mn^{2+}	288	−55.45	−51.86	−46.05	−44.34	32.55	26.04
	298	−55.62	−52.09				
	308	−55.77	−52.12				
Co^{2+}	288	−58.43	−56.22	−47.65	−44.40	37.53	30.06
	298	−58.77	−56.42				
	308	−58.80	−56.57				
Ni^{2+}	288	−61.85	−61.46	−49.40	−46.04	43.08	35.42
	298	−61.96	−61.97				
	308	−62.28	−61.88				
Cu^{2+}	288	−67.86	−62.57	−52.63	−49.38	52.85	45.57
	298	−68.14	−62.70				
	308	−68.39	−63.02				

where m_i is the molar concentrations of the ions and Z_i are their charges. This is related to the activity coefficients of the ions in solution by the following Eq. (7)

$$\log\gamma_{\pm} = -\alpha Z_+|Z_-|\mu 1/2 \quad (7)$$

where $\gamma_{\pm}$ is the activity coefficient of cations and anions, α is the degree of dissociation, and $Z_+|Z_-|$ is the positive product of the ionic charges. When the concentration of free ions in solution is very low, $\gamma_{\pm}$ becomes close to unity and the ions are not affected by each other. At higher concentrations, $\gamma_{\pm}$ is not close to unity and the ions of opposite charges attract each other [70]. Therefore, the effect of variation of ionic strength

Table 8
Proton-ligand association constants of TPHP at different ionic strengths at 25 °C.

System	Ionic strength	log K_{NH}[a]	log K_{SH}
TPHP	0.05	11.21 ± 0.05	7.54 ± 0.08
TPHP	0.10	11.07 ± 0.01	7.41 ± 0.04
TPHP	0.15	10.97 ± 0.06	7.29 ± 0.06
TPHP	0.20	10.88 ± 0.01	7.18 ± 0.05
TPHP	0.25	10.79 ± 0.03	7.09 ± 0.08

[a] Protonation constants ± standard deviations.

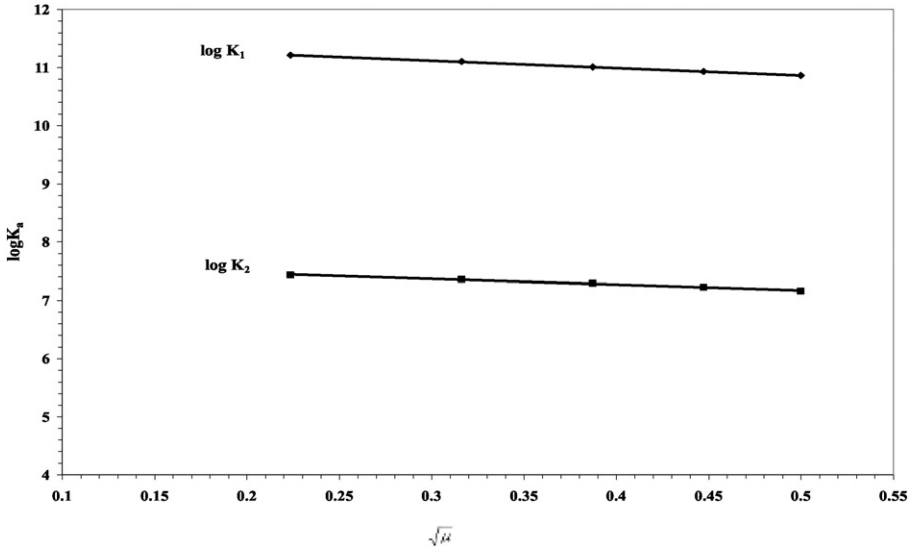


Fig. 6. Plot of log K vs $\sqrt{\mu}$ at 25 °C (the values of correlation coefficients are 0.991–0.993).

on the protonation constants of the TPHP as a representative example of thiosemicarbazone compounds has been investigated. For this purpose, the proton ligand protonation constants of the TPHP ligand have been evaluated at five different ionic strengths (0.05, 0.10, 0.15, 0.20 and 0.25 M) using sodium nitrate as a supporting electrolyte at constant temperature (298 K). It was observed that the protonation constants of the TPHP thiosemicarbazone decrease with increase in the ionic strength of the medium (Table 8) which is in good agreement with the Debye-Hückel equation [71]. $\log K_{Protonation}$ values were plotted vs. square root of μ as per the Debye-Huckel equation (Fig. 6). The plots of log K vs $\sqrt{\mu}$ for all systems were found to be linear with correlation coefficient ranges from 0.98–0.99.

4. Conclusions

Complex formation equilibria of M(II), with thiosemicarbazones were investigated in 50% DMSO-H_2O mixture. Chemical equilibrium studies indicated that substitution of hydrogen in thiosemicarbazone (TPHP) by methyl group causes lowering of acidity as a result of the electron-releasing effect of the methyl group in the substituted amino group. The protonation constants of the TPHP thiosemicarbazone compound decrease with increase in the ionic strength of the medium. M(II)-MTPHP complexes is more stable than M(II)-TPHP complexes as a result of electron-releasing effect of *N*-methyl group complexes. It is hoped that the obtained data will be a significant contribution to workers carrying out mechanistic studies in biological media. For the TPHP and MTPHP complexes, log K_1 > log K_2 indicating that the vacant sites of the metal ions are more freely available for binding of the first ligand than for the second one. The complexation (chelation) process is spontaneous, exothermic and entropically favourable. More stable complexes will be formed with: i) Hard-hard or soft-soft interactions of the metal ions and the ligands; ii) Small sizes of the metal ions; iii) Higher basicity of the ligands and iv) Lower temperatures which is consistent with exothermic complexation.

Abbreviations

PHP	1-(phenyl-hydrazono)-propan-2-one
TPHP	2-(1-(2-phenyl-hydrazono)-propan-2-ylidene) hydrazine-carbothioamide
MTPHP	*N*-methyl-2-(1-(2-phenyl-hydrazono)-propan-2-ylidene)hydrazinecarbo-thioamide

References

[1] M. Meloun, S. Bordovská, A. Vrána, Anal. Chim. Acta 584 (2) (2007) 419–432.
[2] G. Roda, C. Dallanoce, G. Grazioso, V. Liberti, M. deAmici, Anal. Sci. 26 (1) (2010) 51–54.
[3] M. Sanchooli, J. Chemistry vol.2013 (2013), 989362 8 pp.
[4] A.E. Pütün, G. Bereket, E. Keskin, J. Chem. Eng. Data 40 (1) (1995) 221–224.
[5] I. Narin, S. Sarioglan, B. Anilanmert, H. Sari, J. Solut. Chem. 39 (10) (2010) 1582–1588.
[6] S.Ş. Anli, Y. Altun, N. Sanli, G. Alsancak, J.L. Beltran, J. Chemical and Engineering Data, 54 (11) (2009) 3014–3021.
[7] O. Hakli, K. Ertekin, M.S. Ozer, S. Aycan, J. Anal. Chem. 63 (11) (2008) 1051–1056.
[8] H. Sigel, R.B. Martin, Chem. Rev. 82 (1982) 385–426.
[9] C. Öğretir, S. Yarligan, S. Demirayak, T. Arslan, J. Mol. Struct. (THEOCHEM) 666-667 (2003) 609–615.
[10] F.C. Rossotti, H. Rossotti, The Determination of Stability Constants, McGraw-Hill Inc., New York, 1961.
[11] A.A. El-Sherif, M.R. Shehata, M.M. Shoukry, N. Mahmoud, J. Solution Chem. 45 (2016) 410–430.
[12] A.E. Martell, M. Calvin, Chemistry of Metal Chelate Compounds, Prentice-Hall Inc., New York, 1952.
[13] K.J. Duffy, A.N. Shaw, E. Delorme, S.B. Dillon, C. Erickson-Miller, L. Giampa, Y. Huang, R.M. Keenan, P. Lamb, N. Liu, S.G. Miller, A.T. Price, J. Rosen, H. Smith, K.J. Wiggall, L. Zhang, J.I. Luengo, J. Med. Chem. 45 (2002) 3573.
[14] J.R. Dilworth, R. Hueting, Inorg. Chim. Acta 389 (2012) 3.
[15] J.A. Lessa, I.C. Mendes, P.R.O. da Silva, M.A. Soares, R.G. dos Santos, N.L. Spezialic, N.C. Romeiro, E.J. Barreiro, H. Beraldo, Eur. J. Med. Chem. 45 (2010) 5671.
[16] A. Karakucuk-Iyidogăn, D. Tasdemir, E.E. Oruc-Emre, J. Balzarini, Eur. J. Med. Chem. 46 (2011) 5616.
[17] R.J. Glisoni, M.L. Cuestas, V.L. Mathet, J.R. Oubina, A.G. Moglioni, A. Sosnik, Eur. J. Pharm. Sci. 47 (2012) 596.
[18] X. Du, C. Guo, E. Hansel, P.S. Doyle, C.R. Caffrey, T.P. Holler, J.H. McKerrow, F.E. Cohen, J. Med. Chem. 45 (2002) 2695.
[19] D. Kovala-Demertzi, M.A. Demertzis, E. Filiou, A.A. Pantazaki, P.N. Yadav, J.R. Miller, Y. Zheng, D.A. Kyriakidis, Biometals 16 (2003) 411.
[20] J.P. Scovill, D.L. Klayman, D.G. Franchino, J. Med. Chem. 25 (1982) 1261.
[21] L. Klayman, J.P. Scovill, J.F. Bartosevich, J. Bruce, J. Med. Chem. 26 (1983) 35.
[22] D.K. Demertzi, M.A. Demertzis, J.R. Miller, C. Papadopoulou, C. Dodorou, G. Filousis, J. Inorg. Biochem. 86 (2001) 555.
[23] P.K. Singh, D.N. Kumar, Spectrochim. Acta A 64 (2006) 853.
[24] A.A. El-Sherif, J. Solut. Chem. 41 (2010) 249–260.
[25] A.A. El-Sherif, J. Coord. Chem. 64 (12) (2011) 2035–2055.
[25] A.A. El-Sherif, J. Coord. Chem. 264 (7) (2011) 1240–1253.
[26] A.A. El-Sherif, J. Solut. Chem. 39 (2010) 131–150.
[27] A.A. El-Sherif, M.M. Shoukry, J. Main Group Metal Chem. 29 (4) (2006) 189–200.
[28] A.A. El-Sherif, M.M. Shoukry, Spectrochim. Acta A 66 (2007) 691–700.
[29] A.A. El-Sherif, M.M. Shoukry, J. Coord. Chem. 59 (14) (2006) 1541–1556.
[30] A.A. El-Sherif, M.M. Shoukry, J. Coord. Chem. 58 (16) (2005) 1401–1415.
[31] N.A. Al-Awadi, N.M. Shuaib, A.A. El-Sherif, A. El-Dissouky, E. Al-Saleh, Bioinorg. Chem. Appl., 2008, Art. No. 479897.
[32] A.A. El-Sherif, J. Solut. Chem. 39 (2010) 1562–1581.
[33] A.A. El-Sherif, M.M. Shoukry, J. Progress in Reaction Kinetics and Mechanism 36 (2011) 215–226.
[34] N. Rabjohn, Organic Synthesis, Collective Volume 4, John Wiley and Sons Inc., 1963
[35] A.A. El-Sherif, Inorg. Chim. Acta 362 (2009) 4991–5000.

[36] A.A. El-Sherif, J. Solut. Chem. 39 (2010) 131–151.
[37] R.G. Bates, Determination of pH, Theory and Practice, 2nd edn. John Wiley and Sons, New York, 1975.
[38] F.J. Welcher, The Analytical Uses of Ethylenediamine Tetraacetic Acid, Princeton, Van Nostand, 1965.
[39] M. Woolley, D.G. Hurkot, L.G. Hepler, J. Phys. Chem. 74 (1970) 3908–3913.
[40] G.L. Van Uitert, C.G. Hass, J American Chemical Society 75 (1971) 451.
[41] E.P. Serjeant, Potentiometry and Potentiometric Titrations, Wiley, New York, 1984.
[42] A. Golcu, M. Tumer, H. Demirelli, R.A. Wheatley, Inorg. Chim. Acta 358 (2005) 1785–1797.
[43] A.E. Martell, R.J. Motekaitis, The Determination and Use of Stability Constants, VCH, Weinheim, 1988.
[44] M. Meloun, J. Havel, J.H. Högfelt, Computation of Solution Equilibria, Wiley, N. Y, 1988.
[45] P. Gans, A. Sabatini, A. Vacca, Inorg. Chim. Acta 18 (1976) 237–239.
[46] L. Pettit, University of Leeds Personal Communication.
[47] A.A. El-Sherif, M.M. Shoukry, M.M.A. Abd-Elgawad, J. Solut. Chem. 42 (2013) 412–427.
[48] A.A. El-Sherif, M.R. Shehata, M.M. Shoukry, M.H. Barakat, Spectrochimica. Acta (A) 96 (2012) 889–897.
[49] D. Martin, H.G. Hauthal, Dimethylsulphoxide, Van Nostrand Reinhold, Wokingham, 1975.
[50] E. Labisbal, K.D. Haslow, A. Sousa-Pedrares, J. Valdes-Martinez, S. Hernandez-Ortega, D.X. West, Polyhedron 22 (2002) 2831–2843.
[51] B. Kurzak, A. Kamecka, K. Kurzak, J. Jezierska, P. Kafarski, Polyhedron 19 (2000) 2083.
[52] M. Aljahdali, C. Foti, A.A. El-Sherif, M.M.A. Mohamed, A.A. Soliman, O.S. Al Ruqi, Monatsh. Chem. 144 (2013) (2013) 1467–1480.
[53] É.A. Enyedy, M.F. Primik, C.R. Kowol, V.B. Arion, T. Kiss, B.K. Keppler, Dalton Trans. 40 (22) (2011) 5895–5905.
[54] M. Aljahdali, A.A. El-Sherif, M.M. Shoukry, S.E. Mohamed, J. Solut. Chem. 42 (2013) 1028–1050.
[55] M.S. Aljahdali, A.T. Abdelkarim, A.A. El-Sherif, J. Solut. Chem. 42 (2013) 2240–2266.
[56] J.E. Huheey, Inorganic Chemistry-Principles of Structure and Reactivity, Harper SI Edn, New York, 1983.
[57] H.M. Irving, H.S. Rossotti, J. Chem. Soc. 2904 (1954).
[58] F.A. Cotton, G. Wilkinson, Advanced Inorganic Chemistry, Wiley, London, 1962.
[59] H.M.N.H. Irving, R.J.P. Williams, The stability of transition-metal complexes, J. Chem. Soc. (1952) 3192–3210.
[60] A.A. El-Sherif, M.R. Shehata, M.M. Shoukry, M.H. Barakat, Bioinorg. Chem. Appl. Volume 2012, Article ID 984291, 10 pp. http://dx.doi.org/10.1155/2012/984291.
[61] W.U. Malik, G.D. Tuli, R.D. Madan, Selected Topics in Inorganic Chemistry, third ed. S. Chand & Company LTD, New Delhi, 1984.
[62] G.A. Ibañez, G.M. Escandar, Polyhedron 17 (25–26) (1998) 4433–4441.
[63] F.R. Harlly, R.M. Burgess, R.M. Alcock, Solution Equilibria, Ellis Harwood, Chichester, UK, 1980.
[64] L.E. Orgel, An Introduction to Transition Metal Chemistry Ligand Field Theory, Methuen, London, 1966.
[65] A.A. El-Sherif, T.M.A. Eldebss, J. Spectrochimica Acta (A) 79 (2011) 1803–1814.
[66] B. Jeragh, D. El-Wahaib, A.A. El-Sherif, A. El-Dissouky, J. Chem. Eng. Data 52 (5) (2007) 1609–1614.
[67] A. McAuley, G.H. Nancollas, K. Torrance, Inorg. Chem. 6 (1967) 136.
[68] A.G. Evans, J.C. Evans, B.A. El-Shetary, C.C. Rowlands, P.H. Morgan, J. Coord. Chem. 19 (1979) 19–29.
[69] P. George, D.S. McClure, Progress in Inorganic Chemistry, Vol. IInterscience, NewYork, 1959.
[70] K. Denbigh, Principles of Chemical Equilibrium, Cambridge Univ. Press, London, 1955.
[71] J. Bjerrum, Metal-Amine Formation in Aqueous Solution, Haase, Copenhagen, 1941.