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Synthesis, characterization, molecular modeling and biological activity of mixed ligand complexes of Cu(II), Ni(II) and Co(II) based on 1,10-phenanthroline and novel thiosemicarbazone ☆

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ABSTRACT

A combined experimental and computational study of novel mixed ligand Cu(II), Ni(II) and Co(II) ccomplexes of 2-(1-(2-phenyl-hydrazono)-propan-2-ylidene)hydrazine-carbothioamide (TPHP) and 1,10-phenanthroline (1,10-Phen) have been synthesized. The complexes have been characterized by elemental analyses, IR, solid reflectance, magnetic moment, ^{1}HNMR and molar conductance. Spectral data showed that the 1,10-phenanthroline acts as neutral bidentate ligand coordinating to the metal ion through two nitrogen donor atoms and thiosemicarbazone acts as monobasic tridentate coordinating through two imine-N and thiolate sulphur groups. The geometry of the studied M(II) complexes has been fully optimized using parameterized PM3 semiempirical method. It was observed that the M–S bond length is longer than that of M–Cl in the isolated complexes and the M–N bond length is shorter than that of M–Cl. Also, valuable information is obtained from calculations of molecular parameters for all complexes including net dipole moment of the metal complexes, values of binding energy, which proved that the complexes are more stable than the free ligand. The metal chelates have been screened for their antimicrobial activities using the disc diffusion method against different selected types of bacteria (G^{+}: *Bacillus subtillis* RCMB 010067, *Staphylococcus aureus* RCMB 010028); G^{-}: *Pseudomonas aeuroginosa* RCMB 010043, *Escherichia coli* RCMB 010052)) and fungi (*Aspergillus flavus* RCMB 02568, *Pencicillium italicum* RCMB 03924, *Candida albicans* RCMB 05031, *Geotricum candidum* RCMB 05097). Finally, structure–activity relationship studies were investigated with the aim to correlate physico-chemical properties that may be related to the antimicrobial action of the studied compounds. Protonation constant of (TPHP) ligand and stability constants of its M(II) complexes were determined by potentiometric titration method in 70%:30% DMSO–water mixture at 0.1 mol dm^{-3} NaCl.

1. Introduction

In recent years, the number of life-threatening infections diseases caused by multi-drug resistant Gram-positive and Gram-negative pathogen bacteria has reached an alarming level in many countries around the world [1]. More than 50 million people worldwide are infected and up to 110,000 of these die every year. Antibiotics provide the main basis for the therapy of microbial (bacterial and fungal) infections. However, overuse of antibiotics has become the major factor for the emergence and dissemination of multi-drug resistant strains of several groups of microorganisms [2]. Furthermore, the pharmacological drugs available are either too expensive or have undesirable side effects [3]. Thus, in light of the evidence of rapid global spread of resistant clinical isolates, the need to find new antimicrobial agents is of paramount importance. Considerable attention has been focused on thiosemicarbazone compounds due to their wide biological activities [4,5]. Thiosemicarbazones and their complexes have been extensively studied because they have a wide range of actual or potential medical applications [6–10] which include notably antiparasital [11], antibacterial [12] antitumor activities [13], antiviral [14], fungicidal [15] and antineoplastic [16]. In general, thiosemicarbazones are obtained by condensation of the corresponding

Abbreviations: PHP, 1-(phenyl-hydrazono)-propan-2-one; TPHP, 2-(1-(2-phenyl-hydrazono)-propan-2-ylidene) hydrazine-carbothioamide; QM, quantum calculations.

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thiosemicarbazide with aldehydes or ketones. Thiosemicarbazones (TSCNs) exist in the tautomeric thione (A) and thiol (B) forms (Scheme 1). It is well known that some drugs exhibit increased activity when administered as metal complexes [17,18] and several metal chelates have been shown to inhibit tumor growth [19]. 1,10-Phenanthroline (Scheme 2) is the parent of an important class of chelating agents. The choice of phenanthroline is mainly due to two factors. This heteroaromatic moiety can provide a further binding site for metal cations. It is rigid, and provides two aromatic nitrogens whose unshared electron pairs can act co-operatively in binding cations [20]. The π-electron deficiency makes phenanthroline an excellent π-acceptor. Moreover, 1,10-phenanthroline, the ligand moiety of the ternary complexes presented in this work is of considerable interest also according to the biological or pharmacological properties (antifungal, antimycoplasma and antiviral) of some of its metal complexes [21]. In view of the above facts and in continuation of our interest in studying the ligating behavior of such bio-relevant compounds [22–31], herein we carry out synthesis, spectral characterization and biological studies of mixed-ligand complexes involving some transition metal ions, 1,10-phen and TPHP. Also, the structure–activity relationship studies were investigated with the aim to correlate chemical properties and biological activities of studied compounds.

2. Experimental

2.1. Materials

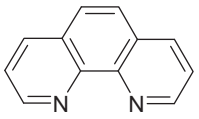
All chemicals used were of analytical reagent grade (AR), and of the highest purity available. They included $CuCl_2.2H_2O$ (Sigma), $CoCl_2{\cdot}6H_2O$ and $NiCl_2{\cdot}6H_2O$ (BDH), C_2H_5OH (Sigma), DMSO (BDH), HCl, KOH (BDH) thiosemicarbazide (Merck); 1,10-phenanthroline (1,10-phen), aniline, ethyl acetoacetate, sodium acetate trihydrate and sodium nitrite (Sigma). Bi-distilled water was used.

2.2. Synthesis

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

It is prepared as reported in the literature [32,33] 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 separatory funnel. The tip of the stem of the separatory 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 °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. Chemical equations for preparation are shown in Scheme 3.



1,10-Phenanthroline
(1,10-Phen)

Scheme 2. Structural formula of 1,10-phenanthroline.

2.2.2. Synthesis of TPHP-thiosemicarbazone

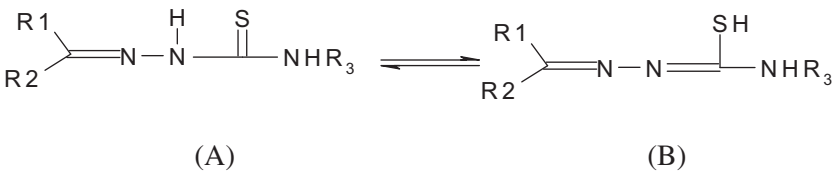
The general route of synthesis (Scheme 4) is shown in the following. Equimolar amounts of (PHP) (0.1620 g, 1 mmol) in 25 ml ethanol with an ethanolic solution (25 ml) of thiosemicarbazide (0.0911 g, 1 mmol) were mixed and then refluxed on a hot plate for 4–5 h. The obtained precipitate was separated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

2.2.2.1. 2-(1-(2-Phenyl-hydrazono)-propan-2-ylidene)hydrazine-carbothioamide (TPHP). Yield, 72%. Colour, Yellow. *Anal.* Calc. for $C_{10}H_{13}N_5S$: C, 51.02; H, 5.53; N, 29.78; S, 13.62. Found: C, 50.98; H, 5.40; N, 29.70; S, 13.60%. IR (KBr, cm^{-1}): 3265, 3384 (NH_2), 1500, 1247, 1095, 750 (Thioamide bands, I, II, III and IV respectively), 3151 (N^2H), 1068 (N–N), 1595 (C=N). ^1H NMR (DMSO): 11.32 (s, 1H, N^2H), 10.31 (s, 2H, NH_2), 2.02 (s, 3H, $-CH_3$), 7.61 (m, 5H, –Ar).

2.2.3. Synthesis of complexes

To a solution of TPHP (0.235 g, 1 mmol) in hot ethanol (25 mL) was added sodium acetate trihydrate (0.136 g, 1 mmol) followed by 1,10-phenanthroline (0.180 g, 1 mmol) and finally metal salt (0.170 g, $CuCl_2{\cdot}2H_2O$, 0.2379 g $CoCl_2{\cdot}6H_2O$, 0.2376 g $NiCl_2{\cdot}6H_2O$, 1 mmol). The mixture was heated under reflux for 5–6 h at 80 °C. The precipitated complexes were then filtered off, washed with petroleum ether and dried overnight in a vacuum desiccator.

*2.2.3.1. [Cu(1,10-phen)(TPHP)Cl] (**1**).* Yield, 78%. *Anal.* Calc. for $C_{22}H_{20}N_7SCuCl$ (Mwt, 513.51): C, 51.46; H, 3.93; N, 19.09; S, 6.24; Cl, 6.90. Found: C, 51.39; H, 3.91; N, 19.05; S, 6.20; Cl, 6.86%. IR (KBr, cm^{-1}): 1502, 1249, 1090, 733 (Thioamide bands, I, II, III and IV respectively), 1084 (N–N), 1574 (C=N), 410 (M–N), 330 (M–S), 275 (M–Cl), 1548 (C=N, phen).



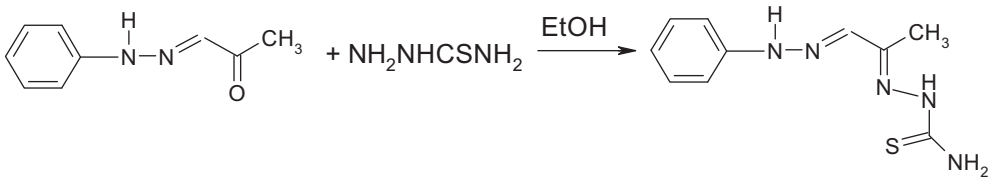
Scheme 1. Thione-thiol tautomers of thiosemicarbazones.

$$CH_3COCH_2CO_2C_2H_5 + KOH \rightarrow CH_3COCH_2CO_2K + C_2H_5OH$$

$$CH_3COCH_2CO_2K + HCl \rightarrow CH_3COCH_2CO_2H + KCl$$

$$CH_3COCH_2CO_2H + C_6H_5N{=}NCl \rightarrow C_6H_5NH\text{-}N{=}CHCOCH_3 + CO_2 + HCl$$

Scheme 3. Chemical reactions involved in the preparation of the PHP ligand.



Scheme 4. Preparation of TPHP-thiosemicarbazone ligand.

*2.2.3.2. [Ni(1,10-phen)(TPHP)Cl] (**2**).* Yield, 75%. *Anal.* Calc. for $C_{22}H_{20}N_7SNiCl$ (Mwt, 508.65): C, 51.95; H, 3.96; N, 19.28; S, 6.30; Cl, 6.97. Found: C, 51.87; H, 3.90; N, 19.23; S, 6.28; Cl, 6.90%. IR (KBr, cm^{-1}): 1496, 1248, 1089, 729 (Thioamide bands, I, II, III and IV respectively), 1081 (N–N), 1571 (C=N), 403 (M–N), 328 (M–S), 270 (M–Cl), 1552 (C=N, phen).

*2.2.3.3. [Co(1,10-phen)(TPHP)Cl]·H_2O (**3**).* Yield, 80%. *Anal.* Calc. for $C_{22}H_{22}N_7OSCoCl$ (Mwt, 526.92): C, 50.15; H, 4.21; N, 18.61; S, 6.07; Cl, 6.73. Found: C, 50.11; H, 4.17; N, 18.56; S, 6.01; Cl, 6.69%. IR (KBr, cm^{-1}): 3573 (OH), 1493, 1251, 1088, 721 (Thioamide bands, I, II, III and IV respectively), 1079 (N–N), 1570 (C=N), 401 (M–N), 328 (M–S), 267 (M–Cl), 1555 (C=N, phen).

2.3. Molecular modeling

An attempt to gain a better insight on the molecular structure of the synthesized thiosemicarbazone complexes, geometric optimization and conformation analysis has performed using semiempirical parameterized PM3 method as implemented in HyperChem 7.5 [34]. A gradient of 1×10^{-2} cal $A^{\circ -1}$ mol^{-1} was set as a convergence criterion in all the molecular mechanics and quantum calculations

2.4. Biological activity

The antimicrobial bioassay was performed according to protocols described previously using a modified Kirby-Bauer disc diffusion method [35–41]. The antimicrobial activities of metal complexes were studied against Gram (+) bacteria as *Bacillus subtillis* RCMB 010067, *Staphylococcus aureus* RCMB 010028); Gram (−) bacteria as (*Pseudomonas aeuroginosa* RCMB 010043, *Escherichia coli* RCMB 010052) and fungi as *Aspergillus flavus* RCMB 02568, *Pencicillium italicum* RCMB 03924, *Candida albicans* RCMB 05031, *Geotricum candidum* RCMB 05097. Standard discs of *Gentamicin* and *Ampicillin* (antibacterial agents), *Amphotericin B* (antifungal agent) served as positive controls for antimicrobial activity but filter discs impregnated with 10 μl of solvent (DMSO) were used as a negative control.

The antibacterial results of the compounds were compared with the standard and % activity index for the complexes was calculated by using the formula as given below:

$$\%\text{Activity index} = \frac{\text{Zone of inhibition by test compound(diameter)}}{\text{Zone of inhibition by standard(diameter)}} \times 100$$

2.5. Instruments

Elemental analyses were carried out at the Department of Chemistry, Faculty of Science, King Abdul-Aziz University, Jeddah21589, KSA. The analyses were performed twice to check the accuracy of the analyses data. Infrared spectra were recorded on an 8001-PC FTIR Shimadzu spectrophotometer using KBr pellets. The solid reflectance spectra were measured on a Schimadzu 3101 pc spectrophotometer. The molar conductance of the complexes was measured for 1.00×10^{-3} M DMSO solutions at 25 ± 1 °C using a systronic conductivity bridge type 305. The room temperature magnetic susceptibility measurements for the complexes were determined by the Gouy balance using $Hg[Co(SCN)_4]$ as a calibrant. The ^1H NMR spectra were recorded using a Bruker ARX-300 instrument. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane using deuterated DMSO as solvent. EPR signals were recorded at room temperature by using a Bruker EMX spectrometer (X-band) product of Bruker, Germany. The operating conditions are, microwave power = 0.201 mW, modulation amplitude = 4.00 Gauss, modulation frequency = 100 kHz, sweep width = 200 Gauss, microwave frequency = 9.775 GHz, time constant = 81.92 ms and sweep time = 20.97 s. The detection limits of EPR technique depends on the type of sample, sample size, detector sensitivity, frequency of the incident microwave radiation.

2.6. Potentiometric titrations

The potentiometric cell was calibrated before each experiment to convert the pH meter readings into hydrogen ion concentration as reported in literature [42]. The ionic products ($K_w = [H^+][OH^-]$) were calculated at a constant ionic strength of 0.10 mol-dm^{-3} with NaCl in 70% aqueous DMSO solutions based on measurements of $[OH^-]$ and pH in several series of experiments. We calculated the reproducible values of pK_w for the examined 70% aqueous dimethyl sulfoxide solution. The pK_w value obtained is 15.75 ± 0.2 in this medium [43]. Potentiometric titrations were carried out at constant temperature and in an inert atmosphere of nitrogen with CO_2-free standardized 0.05 mol-dm^{-3} NaOH as titrant in a 40.0 ml solution at constant ionic strength 0.1 mol dm^{-3}, (adjusted with NaCl). The proton association constants of the ligands (TPHP) were determined potentiometrically by titrating (1.25×10^{-3} - mol dm^{-3}) of the ligand solution (40 cm^3). The stability constants of the M(II) complexes were determined using potentiometric data obtained from (40 cm^3) mixture containing M(II) (1.25×10^{-3} - mol dm^{-3}) + (TPHP) (1.25×10^{-3} mol dm^{-3}).

All titrations were performed in a purified N_2 atmosphere at $I = 0.1$ mol dm^{-3} NaCl and $T = 25$ °C. The potentiometric cell was calibrated before each experiment so as to measure the hydrogen ion concentration rather than its activity. The pH-meter readings (B) recorded in DMSO–water solutions were converted to hydrogen ion concentration [H^+] by using the widely used relation given by Van Uitert and Hass Eq. (1) [44] as shown below.

$$-\log[H^+] = B + \log U_H \quad (1)$$

where log U_H is the correction factor for the solvent composition and ionic strength for which B is read.

2.7. Data processing

The calculations were obtained from ca. 100 data points in each titration using the computer program MINIQUAD-75 [45]. The protonation constants of the isolated compounds were determined at 70% DMSO-30% H_2O by trying various possible composition models. The model selected gave the best statistical fit and was chemically consistent with the titration data without giving any systematic drifts in the magnitudes of various residuals, as described elsewhere [45]. The fitted model was tested by comparing the experimental titration data points and the theoretical curve calculated from the values of the acid dissociation constant of the compounds. The species distribution diagrams were obtained using the program SPECIES [46] under the experimental conditions employed.

3. Results and discussion

3.1. Elemental analysis

The analytical data of the complexes show the formation of 1:1:1 [M:1,10-phen:TPHP] ratio, where M represents Cu(II), Ni(II) and Co(II) ions, TPHP, represents the deprotonated thiosemicarbazone while 1,10-phen represents the neutral bidentate 1,10-phenanthroline. The isolated solid complexes are stable in air and are insoluble in water and common organic solvents but soluble in DMF and DMSO. The molar conductance indicates that all the complexes are nonelectrolytic in nature. Elemental analyses data were in a good agreement with the suggested formula of the isolated metal chelates. Attempts to obtain single crystal suitable for X-ray determination were unsuccessful, thus molecular modeling for these complexes were investigated.

3.2. IR Spectra and mode of bonding

As known, the TPHP ligand has different potential coordinating sites. In the absence of more powerful techniques such as X-ray, the IR has proven to be, in this particular case, a suitable technique to give enough information to elucidate the way of bonding of TPHP. Thus a detailed interpretation of IR spectra of TPHP and the effect of binding of Cu(II), Ni(II) and Co(II) ions on the vibration frequencies of the free TPHP ligand is discussed in this paper. The IR spectra of the free ligand and its metal complexes are carried out in the 4000–200 cm^{-1} range. All of the thiomamide bands in the free TPHP ligand are shifted to some degree upon complexation but the most significant change is that observed in the thioamide IV band, which contain the largest proportion of ν(CS) activity, i.e. the C=S on coordination gains C–S character. The negative shift of the ν(C=S) band in the complexes confirm the coordination via the thiolate sulfur [47-49]. The spectra of the free (TPHP) show two bands at 3265 and 3384 cm^{-1}, due to ν_{sym} and ν_{asym} of the NH_2 group. These absorptions remain unaltered in the metal complexes confirming the non-involvement of this terminal NH_2 group upon coordination. In the ligands spectra, the strong band observed at 1595 cm^{-1} is assigned to ν(C=N) stretching vibration [49]. In the spectra of complexes, this band was not observed at the same frequencies and the same intensities. They shifted after coordination to lower energies by ca. 21–25 cm^{-1}, indicating coordination via azomethine nitrogen [50]. The ν(N–N) of the thiosemicarbazone ligand is found at 1068 cm^{-1}. The increase in frequency of this band in the spectra of complexes is an evidence for the enethiolization of the ligand and the coordination via the azomethine nitrogen. A band which appeared at 3151 cm^{-1} due to N–H in the TPHP-ligand disappeared on complexation which acts as further evidence for the enethiolization of the ligand. Also, the possibility of α-nitrogen (N^2H) coordination is ruled out because of considerable strain [51]. The IR spectrum of the free 1,10-phen ligand shows a very stronger bands at ~1570 cm^{-1} due to stretching frequency of C=N present in 1,10-phenanthroline moiety. This band was shifted to lower frequencies in the complexes ~15–22 cm^{-1}, which clearly indicate that the coordination of the two nitrogen atoms of the neutral 1,10-phen ligand to M(II) ion upon complexation. The bands observed at 3573–3566 cm^{-1} are due to ν(O–H). As reported in literature, coordinated water should exhibit frequencies at 825, 575 and 500 cm^{-1} [22,52,53]. The absence of spectral bands in these regions in the spectra of complexes indicates that the water molecules in these complexes are not coordinated but are present as lattice water. The coordination positions of the thiosemicarbazones in the M(II) complexes are confirmed by assigning the strong bands observed in the far IR spectra of the complexes. The bands observed at (410–401) and (330–328) cm^{-1} are assigned to ν(M–N) [54] and ν(M–S) [55] respectively. The values of ν(M–N) and ν(M–S) follow the order Cu > Ni > Co in parallel with the crystal field stabilization energies [55,56]. In the literature, the bands appearing between 160 and 300 cm^{-1} are allotted to the vibration of the M–X bonds where M = metal and X=Cl or Br [50,56]. In our case the ν(M–Cl) frequencies appearing between 275–267 cm^{-1} are in good agreement with the reported values in the literature. Based on the above spectral evidences, it is confirmed that the ligand is coordinated to the M(II) ion as a tridentate anion, coordinating via the two azomethine nitrogen atoms and the thiolate sulfur atom after deprotonation.

3.3. ^1H NMR spectra

The ^1H NMR spectra of the TPHP-thiosemicarbazone compound in DMSO-d_6 don't show any resonance at ca. 4.0 ppm attributable to –SH proton resonance, while the appearance of a peak at 11.32 ppm (field of appearance of the signal of NH group next to C=S) confirms that even in a polar solvent such as DMSO they remain in the thione form. The methyl protons appear at 2.02 ppm region. The multiplet at 7.61 ppm has been assigned to the aromatic ring protons of the thiosemicarbazone ligand. The spectra of TPHP compound showed signals at δ 10.31 ppm assigned to the NH_2 protons.

3.4. Magnetic moment and electronic spectra

The electronic spectral data along with magnetic susceptibility measurements gave adequate support in establishing the geometry of the metal complexes. The solid reflectance spectra of metal complexes show different bands at different wavelengths, each one is corresponding to certain transition which suggests the geometry of the complex compounds. The magnetic moments of the complexes were measured at room temperature. These data along with the tentative assignments of spectral bands and the magnetic moment values are presented in Table 1.

Table 1
Molar conductance, magnetic moment, electronic spectral data and ESR parameters of the complexes.

Compounds	Λ_M[a]	μ_{eff} (B.M.)	λ_{max} (cm^{-1})	Assignment	Geometry	$g_{\|\|}$	$g_{\perp}$	g_{avg}	G
[Cu(1,10-phen)(TPHP)Cl] (**1**)	11.5	1.89	16286	$^2B_{1g} \rightarrow {}^2B_{2g}$	Octahedral	2.131	2.030	2.097	4.64
[Ni(1,10-phen)(TPHP)Cl] (**2**)	10.2	2.88	10100	$^3A_{2g} \rightarrow {}^3T_{2g}(F)$	Octahedral	–	–	–	–
			16900	$^3A_{2g} \rightarrow {}^3T_{1g}(F)$					
			23800	$^3A_{2g} \rightarrow {}^3T_{1g}(P)$					
[Co(1,10-phen)(TPHP)Cl]·H_2O (**3**)	9.6	5.02	9950	$^4T_{1g} \rightarrow {}^4T_{2g}(F)$	Octahedral	–	–	–	–
			17400	$^4T_{1g} \rightarrow {}^4A_{2g}(F)$					
			19800	$^4T_{1g} \rightarrow {}^4T_{1g}(P)$					

[a] Molar conductance measured for 10^{-3} M DMSO solution, Ω^{-1} cm^2 mol^{-1}.

3.4.1. Magnetic moment

The magnetic susceptibility measurements in the solid state show that the present complexes are paramagnetic at room temperature. For the [Cu(1,10-phen)(TPHP)Cl] complex; the magnetic moment is equal to 1.89 B.M. (Table 1) which assigned to octahedral geometry. Ni(II) complex gave a magnetic moment of 2.88 B.M and hence assigned as octahedral, because of the square planar complexes of Ni(II) are a diamagnetic while tetrahedral complexes have magnetic moments in the range 3.20–4.10 B.M. [57]. The Co(II) octahedral complexes generally show magnetic moments (μ_{eff}) between 4.7 and 5.2 B.M. because of the orbital contribution [57]. Since the orbital contribution of tetrahedral Co(II) complexes have generally lower magnetic moments (~3.87 B.M.), as compared to that of octahedral complexes (~4.7–5.2 B.M.) [58]. Co(II) complex showed a magnetic moment of 5.02 B.M. at room temperature suggesting consistency with its octahedral environment.

3.4.2. Electronic spectra

Electronic spectra of six coordinate copper(II) complexes have either D_{4h} or C_{4v} symmetry, and the e_g and t_{2g} levels of the ^2D free ion term will split into B_{1g}, A_{1g}, B_{2g} and E_g levels, respectively. Thus the three spin allowed transitions are expected in the visible and near IR regions. These bands may be assigned to following transitions: $^2B_{1g} \rightarrow {}^2A_{1g}$ ($d_{x^2-y^2} \rightarrow d_{z^2}$), $^2B_{1g} \rightarrow {}^2B_{2g}$ ($d_{x^2-y^2} \rightarrow d_{xy}$) and $^2B_{1g} \rightarrow {}^2E_g$ ($d_{x^2-y^2} \rightarrow d_{xz}$, d_{yz}) in order of increasing energy. The energy level sequence will depend on the amount of distortion due to ligand field and Jahn–Teller effect [59]. But only few complexes are known in which such bands are resolved either by Gaussian analysis or single crystal polarization studies. The electronic spectra of copper (II) complex showed one band at 16286 cm^{-1} (614 nm) corresponding to $^2B_{1g} \rightarrow {}^2B_{2g}$ transition (Fig. 1) and this is consistent with an octahedral configuration [60]. The solid reflectance spectrum of the Ni(II) complex shows three bands in the near IR–visible region at ν_1 = 10100 cm^{-1} (990 nm) [$^3A_{2g} \rightarrow {}^3T_{2g}(F)$], ν_2 = 16900 cm^{-1} (592 nm) [$^3A_{2g} \rightarrow {}^3T_{1g}(F)$] and ν_3 = 23800 cm^{-1} (420 nm) [$^3A_{2g} \rightarrow {}^3T_{1g}(P)$] (Table 1). These frequencies are well within the range expected for octahedral Ni(II) complexes [59,60]. The Co(II) complexes generally give rise to three absorption bands in the visible region under the influence of the octahedral field by the excitation of the electron from the ground state $^4T_{1g}$ (F) to the excited states $^4T_{2g}(F)$, $^4A_{2g}(F)$ and $^4T_{1g}(P)$. In the [Co(1,10-phen)(TPHP)Cl]·H_2O complex, three bands are observed at 9950 cm^{-1} (1005 nm) [$^4T_{1g}$ (F) → $^4T_{2g}$ (F)] (υ_1), 17400 cm^{-1} (575 nm) [$^4T_{1g}$ (F) → $^4A_{2g}$ (F)] (υ_2) and 20200 cm^{-1} (495 nm) [$^4T_{1g}$ (F) → $^4T_{1g}$ (P)] (υ_3) as reported in many octahedral cobalt(II) complexes.

3.5. Ligand field parameters

The ligand field splitting energy (10 Dq), interelectronic repulsion parameter (B), ratio ν_2/ν_1 and covalency factor (nephelauxetic ratio) (β) for the Co(II) and Ni(II) complexes were calculated using the secular equations given by König [61] (Table 2). The value of β lies in the range 0.673–0.782. These values indicate that the appreciable covalent character of metal ligand bond.

3.6. ESR spectrum of [Cu(1,10-phen)(TPHP)Cl] complex

ESR spectroscopy is a direct measurement of electron spin when there are unpaired electrons within a chemical structure and thus provides a way to investigate the electronic spin state and oxidation state of the coordinated metal ion. Also, the ESR spectra of the complexes provide information about hyperfine and superhyperfine structures that are important in studying the metal ion environment in the complexes, such as geometry, nature of ligation sites from the ligand to the metal, and the degree of covalence of the metal–ligand bonds. To obtain further information about the stereochemistry and the site of the metal ligand bonding and to determine the magnetic interaction in the metal complexes, ESR spectra of the complexes were recorded in the solid state. The room temperature powder ESR spectrum of [Cu(1,10-phen)(TPHP)Cl] exhibits an axial signal with two g values ($g_{\|}$ = 2.131, $g^{\perp}$ = 2.030). In axially elongated octahedral and square planar complexes, the unpaired electron occupies the $d_{x^2-y^2}$ orbital with $^2B_{1g}$ ground state resulting in $g_{\|} > g_{\perp}$. However, in a compressed octahedron the unpaired electron occupies the d_{z2} orbital with $^2A_{1g}$ ground state having $g_{\perp} > g_{\|}$. The observed "g" values suggest that the unpaired electron lies predominantly in the $d_{x^2-y^2}$ orbital. Therefore the trend $g_{\|} > g_{\perp} > g_e$ (2.0023) observed for this complex indicating that $d_{x^2-y^2}$ is the ground state with the d^9 [Cu^{2+}] octahedral geometry around the copper(II) ion [62] in the complex. Kivelson and Neiman [63] have reported that $g_{\|} < 2.3$ and $g_{\|} > 2.3$ is characteristic for covalent and ionic characters, respectively. By applying this criterion, the Cu(II)-complex under study has mainly covalent metal–ligand bonding. In axial symmetry, the g-values are related by the expression, $G = (g_{\|} - 2)/(g_{\perp} - 2)$, where G is the exchange interaction parameter and, according to Hathaway [62], if the value of G is greater than 4, the exchange interaction between copper(II) centers in the solid state is negligible, whereas when G is less than 4, a considerable exchange interaction is indicated in the solid complex. For [Cu(1,10-phen)(TPHP)Cl], the calculated G value for Cu(II)-complex is 4.64, suggesting that the local tetragonal axes are only slightly misaligned and the exchange interactions between Cu(II) ions are negligible [64].

3.7. Conductivity measurements

The chelates were dissolved in DMSO and the molar conductivities of 10^{-3} M of their solutions at 25 ± 1 °C were measured. As seen from Table 1, the molar conductivity values for M(II)-chelates are 9.6–11.5 Ω^{-1} cm^2 mol^{-1} indicating nonelectrolytic nature of the complexes. On the other hand, copper(II) complexes are more conductive than cobalt(II) and nickel(II) complexes. These results may be due to from higher stability constants of the copper(II)

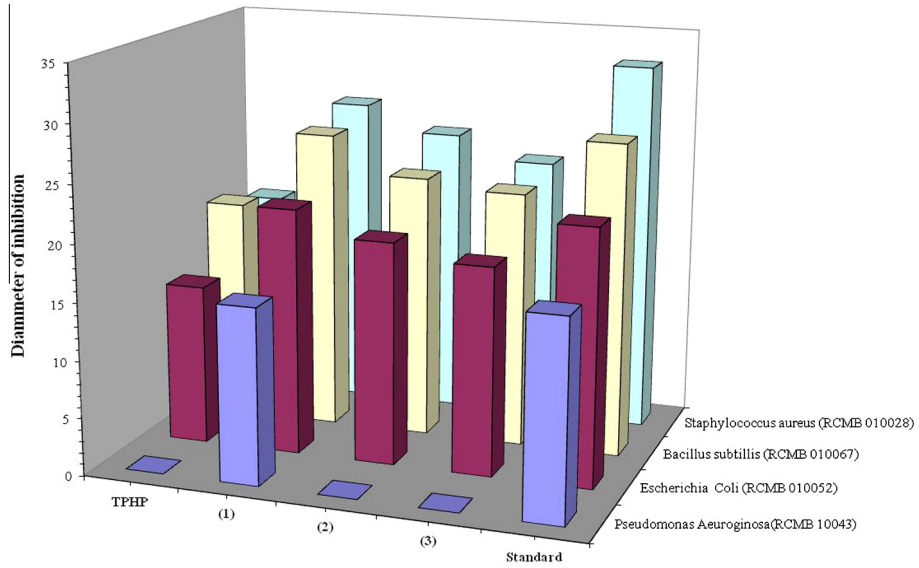


Fig. 1. Antibacterial activity of mixed-ligand complexes (The antibacterial standard agents used were *Gentamicin* for G^- and *Ampicillin* for G^+).

Table 2
Electronic parameters of the Co(II) and Ni(II) complexes.[a]

Complex	Observed bands/cm^{-1}			ν_2/ν_1	B	β	β_o	10 Dq
	ν_1	ν_2	ν_3					
[Ni(1,10-phen)(TPHP)Cl] (**2**)	10100	16900	23800	1.67	693	0.673	32.68	10100
[Co(1,10-phen)(TPHP)Cl]·H_2O (**3**)	9950	17400	20200	1.74	762	0.785	21.44	11141

[a] The ligand field splitting energy (10 Dq), interelectronic repulsion parameter (B) and covalency factor nephelauxetic ratio) (β) for the Co(II) and Ni(II) complexes were calculated using the secular equations given by König [63].

complexes than both the nickel(II) and cobalt(II) complexes [65]. Hence, the conductivity measurements of the metal(II)-chelates confirm the proposed general formulae of those chelates as suggested depending upon the results of elemental analyses, UV–Vis, ESR and IR spectra.

3.8. Antimicrobial activity

The question about the involvement of the metal complexes in medical treatment is of special interest, as it is known that the bacteria can achieve resistance to antibiotics through biochemical and morphological modifications [66]. Therefore, researching new compounds of antimicrobial activity is of paramount importance [67–70]. It seems therefore to be of considerable interest to assess the biological potential of the novel thiosemicarbazone ligand its mixed-ligand complexes against different species of bacteria. The organisms used in the present investigations included two Gram positive (*S. pyogones* and *B. subtillis*) and two Gram negative (*P. aereuginosa* and *E. coli*). The diffusion agar technique was used to evaluate the antibacterial activity of the synthesized mixed ligand complexes [66–73]. The medium used for growing the culture was nutrient agar. The results of antimicrobial assessment, Table 3, exhibit that TPHP has a high antibacterial activity against *B. subtillis* (RCMB 010067) with 19.4 mm inhibition zone. The TPHP ligand and its complexes did not exhibit antibacterial activity against *P. euroginosa* (RCMB 010043) except Cu(II)-complex has a comparable zone of inhibition (15.4 mm) to the standard antibacterial agent (17.3 mm). Cu(II), Ni(II) and Co(II) complexes have high antimicrobial activity against *S. aureus* (RCMB 010028), the inhibitions zones are 27.5, 24.9 and 23.7 mm, respectively. It is worth noting that the comparison of antibacterial activity (Table 3) of the compounds against the selected types of bacteria (Fig. 2) indicates that $Cu^{II} > Ni^{II} > Co^{II}$ [74]. The synthesized thiosemicarbazone compound and its complexes are inactive against *Candida* (Table 4). Cu(II), Ni(II) and Co(II) complexes have high antifungal activity against *Geotricum candidum* (RCMB 05097), the inhibitions zones are 24.7, 21.3 and 20.9 mm, respectively. The highest activity index for Cu(II)-complex is 98.6 vs. *E. coli* (RCMB 010052) and 91.9 vs. *A. flavus* (RCMB 02568). The increased activity of the metal chelate can be explained on the basis of chelation theory. It is known that chelation tends to make the ligand act as more powerful and potent bactericidal agent, killing more of the bacteria than the ligand. It is observed that in a complex, the positive charge of the metal is partially shared with the donor atoms present in the ligands and there may be π-electron delocalization over the whole chelation. This increases the lipophilic character of the metal chelate and favors its permeation through the lipoid layer of the bacterial membranes.

3.9. Molecular modeling

In the absence of a crystal structure, to obtain the molecular conformation of a compound, energy minimization studies were carried out on the basis of the semi-empirical PM3 level provided by HyperChem 7.5 software. The calculated dipole moment, total energy, binding energy, HOMO, and LUMO energies after geometrical optimization of the structures of complexes were given in Table 5.

3.9.1. Bond length and bond angle calculations

The bond lengths and bond angles of [Ni(1,10-phen)(TPHP)Cl] complex as a representative example of M(II) compounds are given

Table 3
Antibacterial activity of M(II) complexes.

Compounds	Diameter of inhibition zone (in mm)[a]							
	(G^-)				(G^+)			
	Pseudomonas euroginosa (RCMB 010043)		*Escherichia coli* (RCMB 010052)		*Bacillus subtillis* (RCMB 010067)		*Staphylococcus aureus* (RCMB 010028)	
Conc. (mg/ml)	1 mg/ml	Activity index	1 mg/ml	Activity index	1 mg/ml	Activity index	1 mg/ml	Activity index
TPHP	NA	–	14.0 ± 0.64	62.78	19.4 ± 0.64	70.80	18.1 ± 0.35	55.86
(**1**)	15.4 ± 0.29	89.01	21.6 ± 0.29	96.86	26.3 ± 0.41	95.98	27.5 ± 0.25	84.87
(**2**)	NA	–	19.5 ± 0.37	82.95	23.1 ± 0.39	84.30	24.9 ± 0.37	76.85
(**3**)	NA	–	18.2 ± 0.24	81.61	22.4 ± 0.26	81.75	23.7 ± 0.41	73.14
Standard[b]	17.3 ± 0.15		22.3 ± 0.18		27.4 ± 0.18		32.4 ± 0.10	

[a] Mean zone of inhibition in mm ± standard deviation beyond well diameter (6 mm) produced on a range of environmental and clinically pathogenic microorganisms using (1 mg/ml) concentration of tested samples.
[b] The standard antibacterial agents used are *Gentamicin* for G^- and *Ampicillin* for G^+.

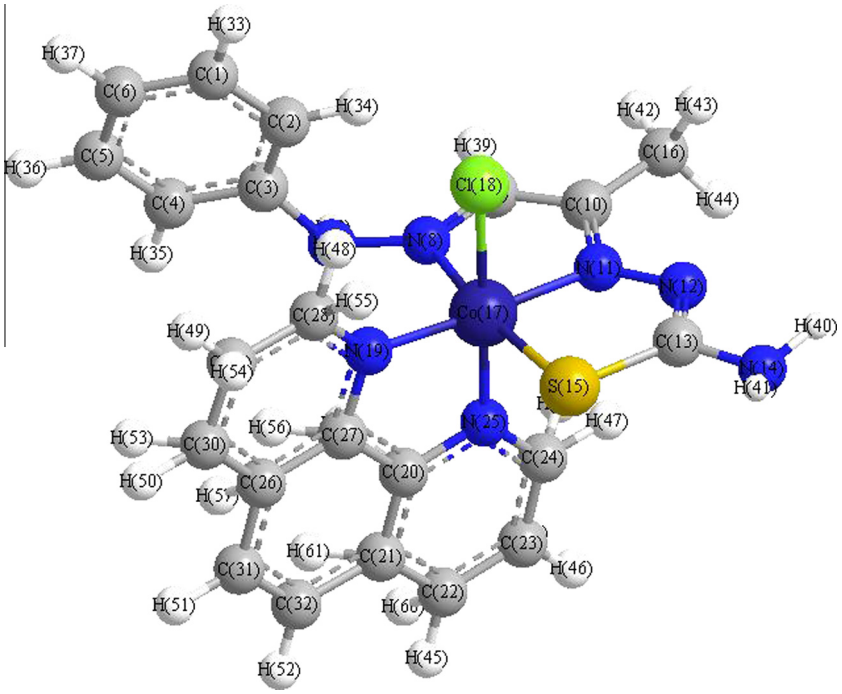


Fig. 2. Octahedral structure of Co(II) complex and numbering system adopted in the present work.

Table 4
Antifungal activity of M(II) complexes.

Compounds	Diameter of inhibition zone (in mm)[a]							
	Aspergillus flavus (RCMB 02568)		*Pencicillium italicum* (RCMB 03924)		*Candida albicans* (RCMB 05031)		*Geotricum candidum* (RCMB 05097)	
Conc. (mg \ml)	1 mg\ml	Activity index	1 mg \ml	Activity index	1 mg \ml	Activity index	1 mg \ml	Activity index
TPHP	15.6 ± 0.58	65.82	14.7 ± 0.44	67.12	NA	–	18.7 ± 0.64	65.15
(**1**)	21.8 ± 0.47	91.98	19.6 ± 0.44	89.4 9	NA	–	24.7 ± 0.15	86.06
(**2**)	17.9 ± 0.51	75.55	16.8 ± 0.57	74.88	NA	–	21.3 ± 0.23	74.21
(**3**)	17.1 ± 0.28	72.15	15.9 ± 0.62	72.60	NA	–	20.9 ± 0.19	72.82
Amphotericin (B)	23.7 ± 0.10		21.9 ± 0.12		19.8 ± 0.20		28.7 ± 0.22	

[a] Mean zone of inhibition in mm ± standard deviation beyond well diameter (6 mm) produced on a range of environmental and clinically pathogenic microorganisms using (1 mg/ml) concentration of tested samples.

in Supplementary data. A drawing of Co(II) and Ni(II) complexes with the atomic numbering scheme is shown in Figs. 2 and 3 while selected bond lengths and angles for M(II) complexes are given in Supplementary data. The coordination results in the changes of bond lengths and angles of the thiosemicarbazone moiety, as expected, thus when the bond lengths in the coordinated thiosemicarbazone ligand are compared with those in the free thiosemicarbazone ligand, it is seen that coordination elongates the thiosemicarbazone moiety's C–S bond from 1.631 Å to 1.750–1.77 Å and contracts adjacent N–C(S) bond from 1.437 Å to 1.314–1.397 Å in , which is consistent with the C–S acquiring a partial single bond and N–C(S) a partial double bond character. These changes in bond lengths are attributable to stabilization of the iminothiolate form of the thiosemicarbazone ligand upon

Table 5
Some energetic properties of the M(II) complexes calculated by PM3 method.

Complex	Total energy (kcal/mol)	Binding energy (kcal/mol)	Electronic energy (kcal/mol)	Dipole moment	HOMO	LUMO
(**1**)	−132306.25	−5695.23	−1158161.10	8.16	−4.01	−1.37
(**2**)	−129041.72	−5840.45	−1190387.68	10.03	−7.03	−1.90
(**3**)	−123331.73	−5995.91	−1150944.83	10.12	−3.65	−1.85

complexation via loss of the hydrazinic proton [75]. This means that, C–S distances which are in the range of single bond character being some of the largest found for thiosemicarbazone complexes (typical bond lengths being C(sp^2)–S 1.706 Å in $(MeS)_2C{=}C(SMe)_2$ and C=S 1.630 Å in naphthylphenylthioketone) [76,77]. This also confirms the IR and spectral data which assumed that the C=S on coordination gains C–S character. Similar structural features are known for other metal complexes of such ligands that have the same coordination sites [75,78]. The other bond lengths and angles also suffer some changes, but not significantly. Moreover, the bond length data shows that the M–N and M–S distances are comparable with those reported for other thiosemicarbazone copper (II) complex (e.g. Cu–N_{iminic} = 1.98 and Cu–S = 2.26 Å in 3-ethoxy-2-oxo butyraldehyde bis(thiosemicarbazonato) copper(II), [79]. In general, the M–S bond length is longer than that of M–Cl for the all M(II) complexes and the M–N bond length is shorter than M–Cl bond length showing that the bond length obeyed this

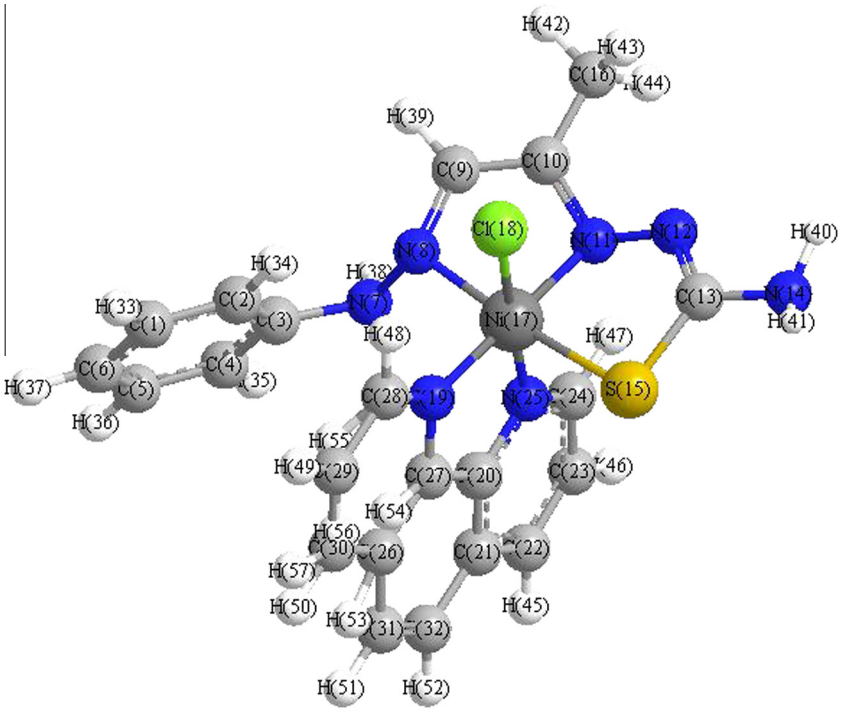


Fig. 3. Octahedral structure of Ni(II) complex and numbering system adopted in the present work.

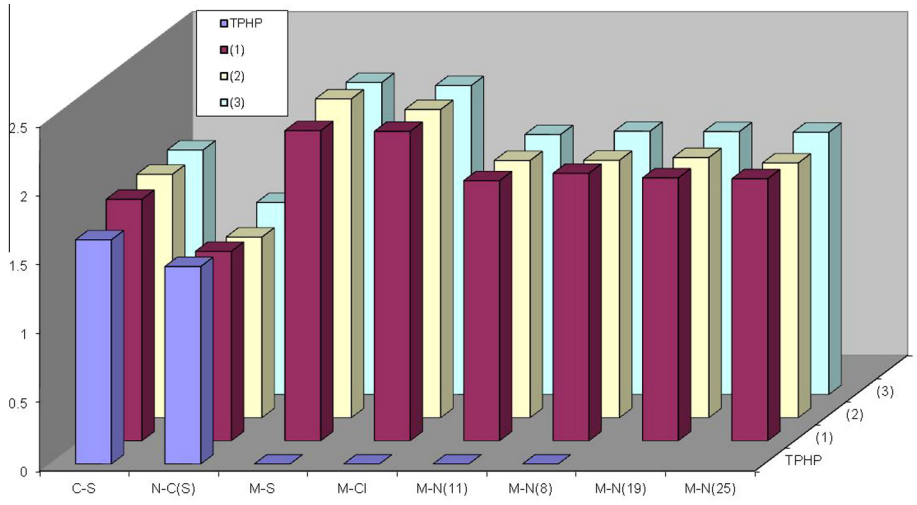


Fig. 4. Calculated bond lengths before and after complexation for TPHP and M(II) complexes.

order M–S > M–Cl > M–N (Fig. 4). The bond angles around the M(II) center (~90) prove that the geometric is octahedral as proposed by the different tools of analysis mentioned previously. Finally, from the interpretation of elemental and thermal analyses, spectral data (infrared, electronic, ^{1}H NMR and ESR) as well as magnetic susceptibility measurements at room temperature, conductivity measurements and QM calculations, it is possible to draw up the tentative octahedral structures of the metal complexes.

3.9.2. Molecular parameters

Quantum chemical parameters of organic compounds are obtained from calculations, such as the energy of the highest occupied molecular orbital, E_{HOMO}, energy of the lowest unoccupied molecular orbital, E_{LUMO}. Additional parameters, such as separation energies (ΔE), absolute electronegativities (χ), chemical potentials (Pi), absolute hardness (η), absolute softness (σ), global electrophilicity (ω) [79–83], global softness (S) and additional electronic charge (ΔN_{max}) have been calculated according to the given equations in literature [84]. The concepts of the parameters v and Pi are related to each other. The inverse of the global hardness is designated as the softness σ [85]. From the obtained data (Table 6) we can deduced that:

(a) The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are very popular quantum chemical parameters. These molecular orbitals are also called the frontier molecular orbitals (FMOs) and determine the way of interaction for the molecule with other species. The FMOs are important in molecular reactivity. The HOMO is the orbital that could act as an electron donor, since it is the highest energy orbital containing electrons. The LUMO is the orbital that could act as the electron accepter, since it is the lowest energy orbital that can accept electrons. The energies of the HOMO (−8.66) and LUMO (−1.05) are negative, which indicate the title molecule is stable [86].
(b) Lower HOMO energy values show that the molecule donating electron ability is weaker. On contrary, a higher HOMO energy implies that the molecule is a good electron donor. The LUMO energy presents the ability of a molecule receiving an electron.
(c) From the calculations of the binding energy we notice that there is an increase of the value of the calculated binding energy of complexes compared to that of the ligand which indicates that the stability of the formed metal complexes is higher than that of TPHP-ligand (−2900.72 kcal/mol).

3.10. Molecular modeling and biological activity

Theoretical calculations were performed in order to investigate physico-chemical properties that may be related to the antimicrobial action of the studied compounds. A property of interest in this study was the dipole moments, which may give some insight on the degree of hydrophobicity/hydrophilicity of the compounds. SAR studies suggested that there is an inverse correlation between the dipole moment and the activity of the isolated M(II)-complexes towards the studied bacterial and fungal species. As dipole moment decreases the polarity decreases and in turn the lipophilic nature of the compound increases, which favors its permeation more efficiently through the lipid layer of the microorganism [87], thus destroying them more aggressively. From the data given in Table 5, [Cu(1,10-phen)(TPHP)Cl] has a lower dipole moment (μ = 8.16), thus, it is suggested that, its lipophilic nature is large in comparison to the other complexes which in turn deactivates enzymes responsible for respiration processes of the tested micro-organisms more than the other complexes i.e. the formation of a lipophilic complex could enhance its penetration through the cytoplasmic membrane, and consequently increase the cellular uptake of metal ions by bacterial cells. The same finding was obtained for tin complexes with thiosemicarbazones [88]. Consequently, the biological activity of the tested complexes obeyed this order Cu > Ni ≈ Co. The dipole moment of both Ni(II) and Co(II) complexes are approximately the same and hence a little difference in the biological activity of both complexes was observed.

Table 6
The calculated quantum chemical parameters of the ligand and its metal complexes.

Compound	χ	η	σ	Pi	ΔE	ω	ΔN_{max}
Cu(II)	2.69	1.32	0.76	−2.69	2.64	2.74	2.04
Ni(II)	4.47	2.57	0.39	−4.47	5.13	3.89	1.74
Co(II)	2.55	1.10	0.91	−2.55	2.20	2.96	2.32

3.11. Structure of the complexes

Single crystals of the complexes could not be isolated; thus, no definitive structure can be described. However, it is concluded that from elemental analysis, IR, ESR and ^{1}H NMR spectra, the thiosemicarbazone ligand (TPHP) behaves as a monobasic tridentate ligand coordinated to the metal ions Cu(II), Ni(II) and Co(II) through the thiolate group and the azomethine-N atoms (NNS) while 1,10-phen acts as a neutral bidentate ligand coordinated through the pyridine nitrogen atoms. On the basis of the elemental analysis and spectral data octahedral geometry is suggested for all investigated complexes.

3.12. Equilibrium studies

The study of complex formation equilibria for the investigated 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. The mixture DMSO–water 70%:30% was the chosen solvent for our study. In such a medium, the studied thiosemicarbazones are soluble giving stable solutions. The use of this mixed solvent has some advantages over pure DMSO. Thus, pure DMSO is very hygroscopic and controlling its water content is difficult [43,89]. This fact would affect reproducibility of our experiment. However, DMSO–water 70%:30% mixture has only small hygroscopic character. A further advantage is its compatibility with the standard glass electrode, so that the pH measurements may be carried out in a similar way to that employed in a purely aqueous solution. In contrast, the use of pure DMSO is not recommended for potentiometry. Another advantage of the DMSO–water 70:30% mixture is its large acidity range (pK_w = 15.75 ± 0.2) [43] which allows the investigation of deprotonation equilibria of weak acids which could be hardly studied in water [43,89]. Trials were carried out for studying the complex-formation equilibria for both binary and mixed-ligand complexes. Binary complex formation equilibria was only studied due to the precipitation occurs by addition of 1,10-phen does not permit the determination of their formation constants of the corresponding complexes.

It is known that, protonation constants are important in preparative chemistry. Therefore, if the protonation constants of a certain substance are known, it is possible to isolate it with a maximum yield by finding the pH range where the compounds show minimum ionization. Also, the data related to the protonation constants of bio-relevant compounds will be valuable in further understanding of their chemistry in biological systems. Additionally, analytical chemists are supposed to know the related constants of the species present in the medium to determine the

accuracy and most suitable medium for their analysis. The major reasons for the determination of protonation constants can be summarized as follows:

(1) One can calculate the pH and the ratio of different forms of a certain substance by the use of its protonation constants.
(2) Protonation of a newly synthesized compound can also give supportive information about its structure. If theoretically calculated protonation constants are in good accordance with the experimental values, it is possible that the proposed structure could be correct.
(3) Due to the fact that different forms of different substances have different UV spectra, by choosing a suitable pH value one can carry out spectrophotometric quantitative analyses. The choice of the pH values requires knowledge of protonation constants.
(4) It is necessary that the protonation constants be known in order to prepare buffer solutions at different pH values [90].
(5) In addition, for the calculations of stability constants of the complex formation of bio-active compounds with metal ions, their protonation constants are used [43,91].
(6) Knowledge of the equilibrium 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 [43,91]. Therefore, this study was therefore determining the protonation constants of the newly synthesized compounds.

The overall stability constants (β_{pqr}) of the studied complexes can be defined by Eqs. (2) and (3):

$$pM + qL + rH \leftrightarrow M_pL_qH_r \quad (2)$$

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

where M denotes the metal ion, L the thiosemicarbazone ligand, H the proton and p, q and r are the respective stoichiometric coefficients. The stoichiometric stability constants of M(II) complexes of the investigated TPHP-thiosemicarbazone ligand were determined in 70% DMSO–water mixture at 25 °C and these constants are tabulated in Table 7. The data also show the formation of the binary complexes with stoichiometric coefficients 110 and 111 for both Cu(II) and Ni(II) complexes and 110 species for Co(II) complex. The pK_a of the protonated complex can be calculated using Eq. (4) [92].

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

Table 7
Logarithms of the protonation of TPHP-thiosemicarbazone ligand and stability constants of M(II)–TPHP complexes of in 70% DMSO–water mixture (I = 0.1 mol dm^{-3} NaCl, T = 25.0 ± 0.01 °C).

Compound	p	q	r[a]	log β[b]	S[c]
TPHP	0	1	1	11.25 ± 0.03	3.2E-8
	0	1	2	18.72 ± 0.05	
Cu-TTPHP	1	1	0	11.95 ± 0.07	1.2E-7
	1	1	1	18.30 ± 0.08	
Ni-TTPHP	1	1	0	10.89 ± 0.06	5.7E-7
	1	1	1	17.97 ± 0.08	
Co-TTPHP	1	1	0	10.22 ± 0.03	6.3E-7

[a] p, q, r are the stoichiometric coefficient corresponding to M(II), TPHP and H$^+$ respectively.
[b] Standard deviations.
[c] Sum of squares of residuals.

This value is in fair agreement with pK_a of SH group (7.36) taking into consideration the acidification upon complexation i.e. the lower pK_a values 6.35 and 7.08 for Cu-TPHP and Ni-TPHP complexes respectively than that of free TPHP ligand (7.36) indicates acidification upon coordination to M(II) ion.

The stability constants listed in Table 7 clearly show that the stability order of the M(II)–TPHP binary systems in terms of metal ions is Cu(II) > Ni(II) > Co(II) and copper(II) has the highest stability of all the studied complexes. This behavior is in line with stability order of the binary complexes and Irving–Williams order [93]. In general, it is noted that the stability constant of the Cu^{2+} complex is quite large compared to the other metals ($\log K_{[Cu(TPHP)]} = 11.95 > \log K_{[Ni(TPHP)]} = 10.69 > \log K_{[Co(TPHP)]} = 10.22$). The sharp maximum of the Cu(II) complex is due to the Jahn–Teller which will give Cu^{II} extra stabilization due to tetragonal distortion of the octahedral symmetry [94,95].

4. Conclusions

The present paper reports on the synthesis, characterization and biological activity of [M(1,10-phen)(TPHP)Cl].nH_2O complexes. The synthetic procedure in this work resulted in the formation of complexes in the molar ratio (1:1:1) (M:1,10-phen : TPHP) respectively. From the molar conductance data, it was found that all the M(II) chelates are considered as nonelectrolytes. On the basis of the analytical, conductivity, magnetic data, infrared, molecular modeling and electronic spectral data octahedral geometry is suggested for all investigated complexes. In the absence of X-ray single crystal data of the current synthesized complexes and based on the physicochemical studies and geometrical optimization, a tentative structure could be proposed as shown for Co(II) and Ni(II) complexes in Figs. 2 and 3. Geometry optimization and conformational analysis have been performed and the perfect agreement with the spectral studies allow for suggesting the exact structures of all the studied complexes. The antimicrobial study reveals that some of the synthesized complexes show better activity or comparable activity to the standard drug antibiotic. The metal complexes were more active against Gram-positive than Gram-negative bacteria. It may be concluded that antibacterial activity of the compounds is related to cell wall structure of the bacteria. It is possible because the cell wall is essential to the survival of many bacteria and some antibiotics are able to kill bacteria by inhibiting a step in the synthesis of peptidoglycan. SAR studies suggested that there is an inverse correlation between the dipole moment and the activity of the complexes against the studied bacterial and fungal species. In summary, compounds discussed in this article, represent a good model for comparison to establish a good correlation of structure and activity. The relationship between structural and biological properties has been explored which could be helpful in designing more potent antibacterial agents.

Appendix A. Supplementary material

The antifungal activity curve of the isolated chelates against the selected types of fungi and the visible electronic spectra of [Cu(TPHP)(1,10-Phen)Cl] complex were given in supplementary data. Additionally Tables of bond distances (Å) and angles (°) or [Ni(1,10-phen)(TPHP)Cl] complex and Comparison of Bond length (Å) and angles (°) for free TPHP-thiosemicarbazone ligand and its M(II)-complexes were also given in supplementary data. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ica.2013.06.040.

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