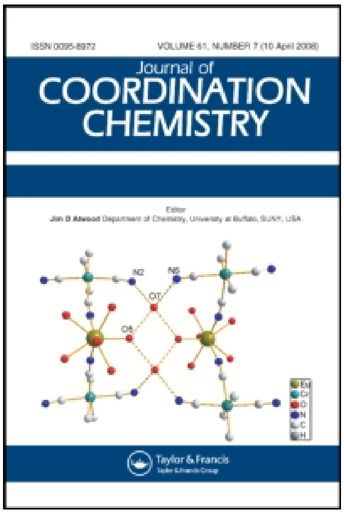

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# Synthesis, spectroscopic and the biological activity studies of thiosemicarbazones containing ferrocene and their copper(II) complexes

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Two Schiff bases, 1-acetylferrocene thiosemicarbazone ($HL^1$) and 1,1′-diacetyl-ferrocene dithiosemicarbazone ($H_2L^2$) and their copper(II) complexes were prepared and characterized by elemental analysis, magnetic susceptibility, conductivity, and spectral (IR, UV–Vis, ESR) measurements The IR spectra showed that $HL^1$ acts as neutral or monobasic bidentate ligand, coordinating to copper(II) through either thiono- or thiolo-sulphur and azomethine-N atoms, whereas $H_2L^2$ is a neutral or dibasic mononucleating or binucleating quadridentate ligand coordinating through the same atoms. Other spectral measurements indicate that complexes $[(L^1)_2Cu]$, $[(L^2)Cu]$ and $[(HL^1)_2Cu]X_2$, $X = Cl$, Br or $ClO_4$ have square-planar geometry around copper(II) while $[(HL^1)CuX_2]$ and $[(H_2L^2)Cu_2X_4]$, $X = Cl$ or Br, have distorted tetrahedral geometry. The biological activity studies of the complexes and the free ligands towards two gram positive and two gram negative bacteria and one fungal species have been studied and the potential is related to the nature and structure of the tested compounds.

*Keywords:* Ferrocene; Thiosemicarbazones; Copper (II) complexes; Spectra; Biological activity

## 1. Introduction

Schiff bases and their metal complexes have aroused considerable research interest for several decades [1–4]. Thiosemicarbazides and their corresponding Schiff bases are biologically active; their antibacterial [5] anticarcinogenic and antifungal [6] properties and their metal complexes showed some degree of cytoxic activity [6]. Ferrocene-containing metal chelates can be regarded as multi-nuclear molecules possessing the features of both organometallic and coordination complexes. Electron transfer between metal sites with different environments and oxidation states may introduce a new type of reactivity towards substrates [4]. Schiff bases of ferrocene derivatives [7, 8] and their metal complexes with lanthanide [9, 10] and transition metal ions were

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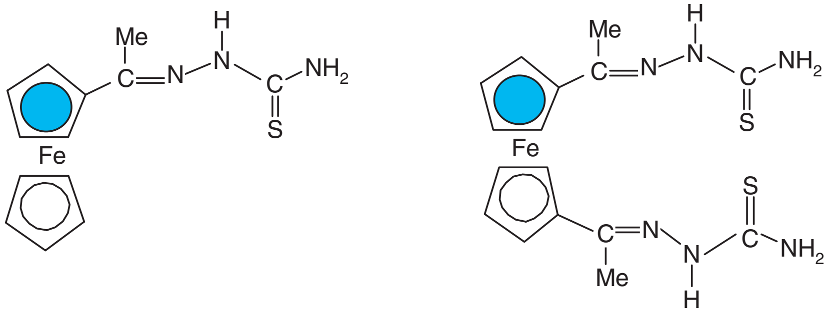


$HL^1$ $H_2L^2$

Figure 1. Structures of ligands $HL^1$ and $H_2L^2$.

synthesized and some of their structures were characterized [11, 12]. In the present work, Schiff bases of thiosemicarbazide with two ferrocene derivatives, acetylferrocene and 1,1′-diacetylferrocene, $HL^1$ and $H_2L^2$, respectively, figure 1, were synthesized and reacted with copper(II) salts. The isolated copper(II) complexes were characterized by elemental analysis, IR, UV–Vis, ESR and magnetic susceptibility methods.

## 2. Experimental

1-Acetylferrocene, 1,1′-diacetylferrocene, thiosemicarbazide (Aldrich) and all solvents and other reagents were analytical grade and were used without further purification.

### 2.1. *Schiff bases $HL^1$ and $H_2L^2$*

The ligands were prepared according to the general method: (a) $HL^1$ was prepared as follows. A solution of thiosemicarbazide (0.91 g, 0.01 mol) in anhydrous EtOH (30 $cm^3$) was added to a solution of 1-acetylferrocene (2.28 g, 0.01 mol) in anhydrous EtOH (30 $cm^3$). The mixture was refluxed for 2 h and upon cooling to room temperature, a reddish-yellow crystalline solid separated. The product was recrystallized from EtOH, filtered, washed several times with cold EtOH and dried under vacuum over $P_4O_{10}$ (m.p. $145 \pm 1°C$).

$H_2L^2$ was prepared similarly using double the amount (1.82 g, 0.02 mol) of thiosemicarbazide and the same amount (2.70 g, 0.01 mol) of the corresponding 1,1′-diacetylferrocene. Reddish-brown crystals were isolated (m.p. $155 \pm 1°C$).

The purity of the prepared compounds was tested by TLC, sharp melting points and microanalyses (table 1).

### 2.2. *Copper(II) complexes*

The copper(II) complexes of $HL^1$ and $H_2L^2$ were prepared according to the following general procedure. A hot solution of the metal salt, (0.01 mol) in EtOH (30 $cm^3$) was added dropwise with stirring to solutions of the ligands $HL^1$ (6.0 g, 0.02 mol) and $H_2L^2$ (4.2 g, 0.01 mol) in EtOH (50 and 30 $cm^3$, respectively). The reaction mixture was heated under reflux for 30–60 min. The precipitate was separated by filtration,

Table 1. Elemental analyses of $HL^1$ and $H_2L^2$ and their copper(II) complexes.

| | Found (Calcd) (%) | | | |
|---|---|---|---|---|
| Compound | C | H | N | S |
| $HL^1$ | 51.5(51.8) | 4.5(4.9) | 13.6(13.9) | 10.7(10.6) |
| $[(L^1)_2Cu]$ | 46.3(46.8) | 4.0(4.2) | 12.3(12.6) | 10.0(9.6) |
| $[(HL^1)CuCl_2]$ | 35.3(35.8) | 3.1(3.4) | 9.7(9.6) | 7.5(7.3) |
| $[(HL^1)CuBr_2]$ | 29.5(29.6) | 2.9(2.8) | 7.9(7.9) | 6.2(6.0) |
| $[(HL^1)_2Cu](ClO_4)_2$ | 36.0(36.1) | 3.3(3.5) | 9.8(9.7) | 7.2(7.4) |
| $[(HL^1)_2Cu]Cl_2$ | 46.8(47.0) | 4.0(4.2) | 12.6(12.6) | 9.4(9.6) |
| $[(HL^1)_2Cu]Br_2$ | 41.1(41.4) | 3.4(3.7) | 11.3(11.5) | 8.7(8.8) |
| $H_2L^2$ | 46.1(46.1) | 4.4(4.8) | 20.3(20.1) | 15.2(15.3) |
| $[(L^2)Cu]$ | 40.0(40.2) | 4.2(3.8) | 17.7(17.6) | 13.6(13.4) |
| $[(H_2L^2)Cu_2Cl_4]$ | 27.8(28.1) | 3.3(2.9) | 12.4(12.3) | 9.2(9.4) |
| $[(H_2L^2)Cu_2Br_4]$ | 22.5(22.2) | 2.6(2.3) | 10.0(9.7) | 7.1(7.4) |

washed several times with hot EtOH, $Et_2O$ and dried under vacuum over $P_4O_{10}$. The isolated complexes were brownish and decompose at temperatures above 300°C. The analytical data are listed in table 1.

## 2.3. *Measurements*

Infrared spectra were recorded as KBr discs with a Perkin-Elmer 2000 FT-IR spectrophotometer. Electronic spectra were recorded on a Cary Varian 5 UV/Vis/NIR spectrophotometer. The $^1$H NMR spectra were recorded in d$^6$-DMSO or $CDCl_3$ as solvents using tetramethylsilane (TMS) as internal standard in absence and presence of $D_2O$ with a Bruker DPX Avance 400 MHz spectrometer. The X-band ESR spectra were recorded on a polycrystalline sample and as $CH_2Cl_2$ solution in the presence of DPPH as a standard utilizing a ECS 106 spectrometer. Magnetic susceptibilities were measured by employing the Faraday balance technique. Diamagnetic corrections were made using Pascal's constants. Molar conductances in DMF ($10^{-3}$ M solution) were measured at 25°C on a Systronics model 303 conductivity meter. Microanalyses of C, H and N were conducted with elemental analyzer LECO CHNS-932. All the measurements were done by the help of the Analab, Kuwait University.

## 2.4. *Biological activity studies*

The *in vitro* biological activity investigations were screened against two gram positive bacteria: *Bacillus subtilis* (I), *Staphylococcus* (II), two gram negative bacteria: *Escherichia coli* (III), *Salmonella typhi* (IV) and one fungal species: *Candida albicans* (V), following the flat bed counting method [13, 14]. The bacteria were grown at 37°C in a culture media prepared by mixing NaCl (5 g), beef extracts (5 g), protein extracts (10 g) and $H_2O$ (1000 g). The concentration in DMSO in the tests were 50 ppm for the ligands and their copper(II) complexes. The inhibitory ratios were calculated from the death ratios compared with those in DMSO.

The two fungal species were bred in subouraud media at 37°C. Nystatin, the clinically useful therapeutic agent, was used as the reference. The concentrations of the ligands and their copper(II) complexes were 100 and 200 ppm.

## 3. Results and discussion

### 3.1. *Characterization of the ligands*

The reactions of 1-acetylferrocene and 1,1′-diacetylferrocene with thiosemicarbazide in ethanol yielded the corresponding thiosemicarbazones; 1-acetylferrocene thiosemicarbazone ($HL^1$) and 1,1′-diacetylferrocene dithiosemicarbazone ($H_2L^2$). The $^1H$ NMR spectrum of the ligand $HL^1$ as a $CDCl_3$ solution at room temperature showed chemical shifts at $\delta$ 2.15 ppm (3H; $CH_3$, s), 4.10 ppm (5H; protons of the unsubstituted cyclopentadienyl ring, s), closely spaced signals at $\delta$ 4.35, 4.48 and 4.68 ppm with integrations corresponding to 2H ($H^2$ and $H^5$), 1H ( $H^3$) and 1H ($H^4$) of the substituted cyclopentadienyl ring. The two weak broad signals at $\delta$ 6.85 and 7.18 ppm (each corresponding to one H, s) are characteristic of $NH_2$ protons. These two signals diappeared in the presence of $D_2O$. The hydrazonic proton of C=N–NH– appeared as two weak resolved signals at $\delta$ 8.70 and 8.93 ppm and disappeared in presence of $D_2O$. The appearance of two signals for each of $NH_2$ and the hydrazonic NH are due to the E and Z-forms of this ligand [15].

The $d^6$-DMSO solution of $H_2L^2$ showed a $^1H$ NMR spectrum similar to that obtained for $HL^1$. The spectrum exhibits two broad and weak signals at $\delta$ 7.55 (2H), 7.85 ppm (2H) (disappeared in the presence of $D_2O$) attributable to –$NH_2$. The C=NNH– proton appeared as two signals at $\delta$ 9.72 and 9.95 ppm (disappeared in the presence of $D_2O$). The appearance of two signals for each the terminal $NH_2$ and the hydrazonic protons indicates the E and Z forms in DMSO. Furthermore the low field position of both indicate involvement in hydrogen bonding. The two cyclopentadienyl protons showed three signals at $\delta$ at 4.1 with integration corresponding to four protons ($2H^2$ and $2H^5$, s), 4.2 ppm corresponding to four protons ($2H^1$ and $2H^3$, s) and 4.70 ppm equivalent to two protons ($2H^4$, s), indicating the symmetrical nature of the two ferrocene rings. The singlet at $\delta$ 2.05 ppm with integration corresponding to 6H is attributed to the two methyl groups.

### 3.2. *Characterization of the complexes*

The two compounds $HL^1$ and $H_2L^2$ reacted with copper(II) salts, $CuX_2$ where X = Cl, Br, OAc or $ClO_4$, in absolute ethanol under refluxing conditions in molar ratios 1 : 1 and 1 : 2 (metal : ligand) in case of $HL^1$ and 1 : 2 only in case of $H_2L^2$, forming the series of metal complexes listed in table 1. The dark brown complexes are stable for long times, insoluble in water and most organic solvents but are freely soluble in DMF and DMSO. The molar conductance values of $10^{-3}$ M solutions of the complexes in DMF showed that complexes $[(HL^1)_2Cu]X_2$, X = Cl, Br or $ClO_4$ are 1 : 2 electrolytes ($\Lambda_M = 151–158\ \Omega^{-1}\,cm^2\,mol^{-1}$), but the rest of the complexes are non-electrolytes ($\Lambda_M = 2.9–4.7\ \Omega^{-1}\,cm^2\,mol^{-1}$) [13].

### 3.3. *Infrared spectra*

The main IR absorption bands of both ligands $HL^1$ and $H_2L^2$ and their copper(II) complexes, along with their tentative assignments are given in table 2. The spectra of the ligands $HL^1$ and $H_2L^2$ displayed absorption bands at 3100–3420, 1588/1625 ($HL^1/H_2L^2$), 824/813 $cm^{-1}$, assigned to the different vibrational modes of N–H and $NH_2$ groups, $\nu$(C=N) and thioamide IV, which is mainly $\nu$(C=S) mode,

Table 2. Main IR spectral bands ($\tilde{\nu}$, cm$^{-1}$) for $HL^1$ and $H_2L^2$ and their copper(II) complexes.

| Compound | $\nu$(NH) | $\nu$(C=N) | $\nu$(CS) | $\nu$(N–N) | $\nu$(M–N) | $\nu$(M–S) | $\nu$(M–X) |
|---|---|---|---|---|---|---|---|
| $HL^1$ | 3125m<br>3260m<br>3450m | 1585vs | 813m | 992m | | | |
| $[(L^1)_2Cu]$ | 3448m | 1625s | 728m | 1016m | 359m | 282w | |
| $[(HL^1)CuCl_2]$ | 3220m<br>3405m | 1622s | 793m | 1017m | 360m | 265w | 328w |
| $[(HL^1)CuBr_2]$ | 3241m<br>3440m | 1620s | 790m | 1022m | 358m | 268w | 232w |
| $[(HL^1)_2Cu](ClO_4)_2$ | 3212m<br>3450m | 1622s | 776m | 1022m | 356m | 272w | |
| $[(HL^1)_2Cu]Cl_2$ | 3210m<br>3260m<br>3438m | 1616s | 786m | 1019m | 352m | 265w | 336m |
| $[(HL^1)_2Cu]Br_2$ | 3190m<br>3300m<br>3445m | 1615s | 784m | 1019m | 352m | 267w | 242w |
| $H_2L^2$ | 3100m<br>3269m<br>3420m | 1588vs | 824m | 996m | | | |
| $[(L^2)Cu]$ | 3418m | 1618s | 724m | 1022m | 355m | 269w | |
| $[(H_2L^2)Cu_2Cl_4]$ | 3346b | 1615s | 780m | 1022m | 356m | 270w | 342m |
| $[(H_2L^2)Cu_2Br_4]$ | 3365b | 1615s | 780m | 1022m | 360m | 266w | 226w |

respectively [16, 17]. Several significant changes have been observed in the spectra of copper(II) complexes. The bands of NH and $NH_2$ were replaced by a single band at ~3400 cm$^{-1}$ and the thioamide IV is shifted to lower wavenumber by ~100 cm$^{-1}$ in the neutral complexes containing the deprotonated ligands $(L)^{1-}$ and $(L)^{2-}$. These observations are consistent with the disappearance of the NH group(s) as a consequence of the formation of the thiol form, SH, group which is involved in complexation after deprotonation. This causes a decrease in the bond order of thioamide IV which becomes mainly $\nu$(C–S). In complexes containing the neutral form of $HL^1$ and $H_2L^2$, the vibrational modes of NH and $NH_2$ groups are not greatly affected by complex formation, wheares the $\nu$(C=S) mode is red shifted by ca. 30 cm$^{-1}$, suggesting bonding to copper(II) ion through thione-S-atom. In all isolated complexes, the $\nu$(N–N) absorption is shifted towards higher wavenumber by 24–30 cm$^{-1}$, compared with that of the free ligands, indicating the participation of one of the two azomethine-N in bonding to copper(II) ion. Furthermore, bonding of the azomethine group(s) to the copper(II) ion and the formation of –C=N–N=C–, in some complexes is expected to reduce the electron density in the –C=N–N=C– moiety, causing a reduction in its vibrational frequency. However, such an absorption appears to be shifted to higher frequency in all isolated complexes, presumably due to constraints of ring formation upon complexation on the –C=N–N=C– vibration. These conclusions are further supported by the appearance of absorption bands at 445–420, 352–360 and 282–296 cm$^{-1}$, which are not observed in the spectra of $HL^1$ and $H_2L^2$. These bands are assigned to $\nu$(Cu–N), $\nu$(Cu–S)(thiol) and $\nu$(Cu–S)(thione), respectively [18]. The absorption bands recorded at 1455, the ligand spectra are characteristic of the ferrocene moiety and are not greatly affected by complexation. From the above IR data, $HL^1$ acts as a neutral or monobasic bidentate ligand and coordinates to copper(II) ion via the azomethine-N and thione or thiol S atoms. On the other hand, $H_2L^2$ acts as a neutral or dibasic mononucleating or binucleating quadridentate ligand through the same coordination centers as with $HL^1$. The chloro and bromo complexes, table 2, display absorption bands characteristic of terminally coordinated chloride and bromide ions, and the spectra of the perchlorate complexes show very intense absorption bands at 1080–1095 cm$^{-1}$ characteristic of ionic perchlorate groups [18].

### 3.4. *Magnetic moments and electronic spectra*

The room temperature magnetic moments of the copper(II) complexes are listed in table 3. For bischelate complexes $[(HL^1)_2Cu]X_2$, $X = Cl$, Br or $ClO_4$ and, $[L^2Cu]$ and $[(L^1)_2Cu]$, values are in the 1.75–1.79 B.M. range whereas for monochelate complexes $[(HL^1)CuX_2]$ and binuclear $[(H_2L^2)CuX_4]$ values are in the 1.98–2.10 B.M. These values are characteristic of magnetically dilute copper(II) complexes with one unpaired electron in the copper(II) ion. The over-excess spin-only magnetic moment (1.73 B.M. per Cu(II)) is due to spin-orbit coupling. These magnetic moment data suggest that: (i) iron is in oxidation state of (II) in the complexes, (ii) the alignment of the two cyclopentadienyl rings around the iron atom does not interfere with the complex formation, and thus, (iii) no magnetic interaction occurs between copper(II) and the diamagnetic iron of the ferrocene.

The UV-Vis absorption data of both ligands and their copper(II) complexes are listed in table 3 the spectra of all the complexes are similar, but different from the free ligands. The *K* bands (band 2), $\pi$–$\pi^*$ transition, of the ligands are observed at 300 and 292 nm for $HL^1$ and $H_2L^2$, respectively. These bands are red shifted by ca. 28–24 and 24–18 nm in copper(II) complexes containing deprotonated and neutral ligands, respectively. This bathochromic shift can be attributed to overlap of the copper(II)-d-orbital with the p-orbital of the donor atom, which causes an increase in conjugation in the ligand and thus lowers the $\pi$–$\pi^*$ energy [19, 20]. The absorption peaks at 266 and 270 nm are assigned to the B band (band 1) of cyclopentadienyl rings in the two ligands [21]. These bands suffer a hypsochromic shift by ca. 12–4 nm in the copper(II) complexes. The broad absorption bands (band 4) appearing at 412 and 416 nm in the spectra of

Table 3. Magnetic and spectral data of copper(II) complexes of $HL^1$ and $H_2L^2$.

| Compound | $\mu_{eff}$[a] | UV–Vis absorption bands ($\lambda_{nm}$/nm)[b] | ESR data $g_\parallel$ | $g_\perp$ | $G$ | $A_\parallel$ (cm$^{-1}$) |
|---|---|---|---|---|---|---|
| $[(L^1)_2Cu]$ | 1.79 | 520, 630 | 2.26 | 2.06 | 4.33 | 188 |
| $[(HL^1)CuCl_2]$ | 2.10 | 600, 715, 790, 995 | 2.28 | 2.06 | 4.67 | 92 |
| $[(HL^1)CuBr_2]$ | 1.98 | 620, 710, 780, 980 | 2.27 | 2.05 | 5.40 | |
| $[(HL^1)_2Cu](ClO_4)_2$ | 1.78 | 525, 635 | 2.26 | 2.05 | 5.20 | 193 |
| $[(HL^1)_2Cu]Cl_2$ | 1.76 | 510, 630 | 2.25 | 2.05 | 5.00 | |
| $[(HL^1)_2Cu]Br_2$ | 1.75 | 510, 625 | 2.28 | 2.06 | 4.70 | |
| $[(L^2)Cu]$ | 1.79 | 515, 620 | 2.30 | 2.06 | 5.00 | 186 |
| $[(H_2L^2)Cu_2Cl_4]$ | 2.01 | 615, 700, 775, 975 | 2.28 | 2.05 | 5.60 | 85 |
| $[(H_2L^2)Cu_2Br_4]$ | 2.07 | 625, 720, 785, 990 | 2.26 | 2.05 | 5.20 | |

[a] Effective magnetic moment values (B.M. per Cu atom) at room temperature.
[b] Nujol mull technique.

$H_2L^2$ and $HL^1$ ligands, respectively, are assigned to charge transfer from the iron to either the non-bonding or antibonding orbitals of the cyclopentadienyl rings. These absorption bands became weaker with no appreciable shift in position in the spectra of their copper(II) complexes [20, 22]. The broad absorption band (band 3) appearing at 334–340 nm in copper(II) complexes bearing deprotonated ligands may result from extended conjugation in the ligand forced by the chelated copper(II) ion. The visible spectra of copper(II) complexes $[(L^1)_2Cu]$, $[(HL^1)_2Cu](ClO_4)_2$, $[(HL^1)_2Cu]X_2$, X = Cl or Br and $[(L^2)Cu]$, have the same features and display a broad band at 600–635 nm, suggesting a square-planar ligand field around copper(II) [20]. This band can be assigned to the $^2B_{1g} \rightarrow {}^2A_{1g}$ transition. The band due to $^2B_{1g} \rightarrow {}^2E_g$ transition may be obscured by the high intensity absorption of iron(II) at 510–525 nm [23]. However, the spectra of $[(HL^1)CuX_2]$ and $[(H_2L^2)Cu_2X_4]$; X = Cl or Br, gave bands at 620–625, 700–720, 775–790 and 975–990 nm which are not consistent with a square-planar ligand field but rather with a distorted tetrahedral ligand field around copper(II) [23, 24]. According to the energy level correlation of tetrahedral ligand field, the energy level sequence is $d_{xz} > d_{x^2-y^2} > d_{yz} > d_{z^2} > d_{xy}$. Thus, the two bands at 700–720 and 975–990 nm can be assigned to $A_2(d_{xy}) \rightarrow B_1(d_{xz})$ and $B_2(d_{yz}) \rightarrow B_1(d_{xz})$ transitions in $C_{2V}$ symmetry group, respectively. Since the two orbitals $d_{x^2-y^2}$ and $d_{z^2}$ belong to $a_1$ irreducible representation of the point group $C_{2v}$, the two transitions at 600–625 and 775–790 nm are due to transition from the mixed orbitals $C_1 d_{x^2-y^2} + C_2 d_{z^2}$, with different percentages [23], to the $d_{xz}$ orbital.

### 3.5. *Electron spin resonance spectra*

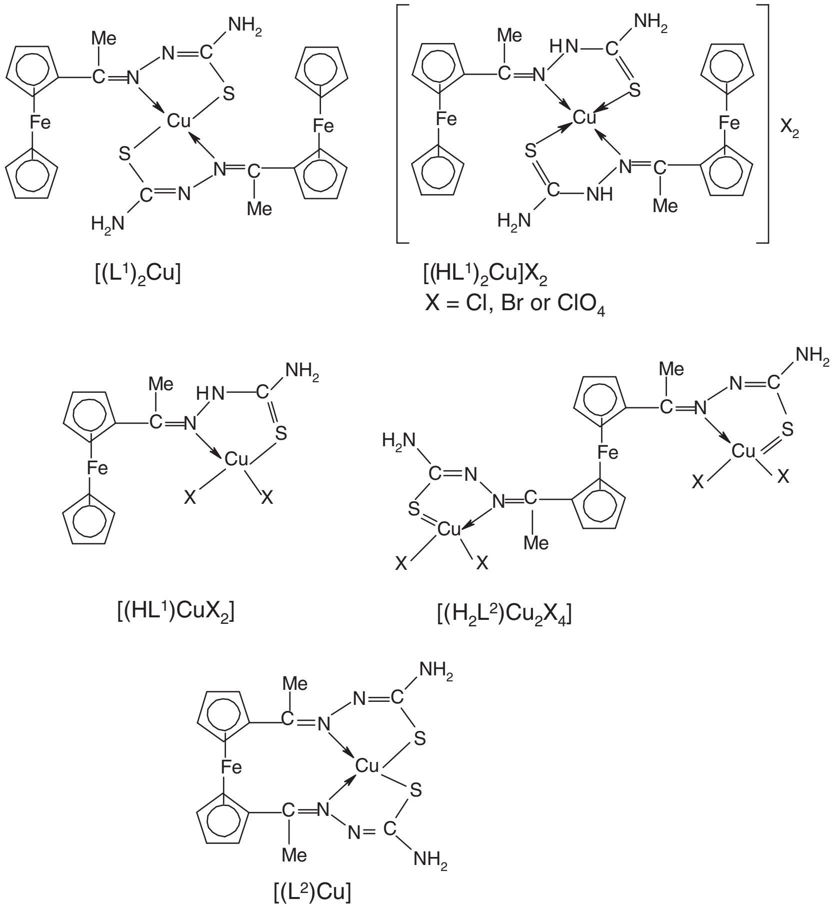
The room temperature X-band ESR spectra of the polycrystalline samples of the copper(II) complexes, exhibit an axial pattern with two *g*-values, table 3. The fact that $g_{\parallel} > g_{\perp} > 2.00$ suggests tetragonal copper(II) complexes and that the unpaired electron is mainly in the $d_{x^2-y^2}$ orbital, with possibly some $d_{z^2}$ character due to the low symmetry [25–27]. The *G*-parameter, $G = (g_{\parallel} - 2)/(g_{\perp} - 2)$ is $> 4.00$ suggesting the absence of an interaction between copper(II) centers in the solid state and that all the local tetragonal axes are aligned parallel or slightly misaligned. The anisotropic hyperfine line coupling is estimated for some of these complexes and found to be 92 and 85 $cm^{-1}$ in $[(HL^1)CuCl_2]$ and $[(H_2L^2)Cu_2Cl_4]$, respectively, similar to the data reported for pesudo tetrahedral copper(II) complexes containing sulphur ligands [28].

Based on the foregoing observations from elemental analysis, conductivity, magnetic moment and spectral studies, the following tentative structures, figure 2, are proposed for the isolated copper(II) complexes of the two ligands.

### 3.6. *Biological activity*

The antimicrobial activity of the free ligands and their copper(II) complexes clearly illustrate that the free ligands are less active than their complexes against all the studied bacteria and fungi. This could be taken as evidence that the introduction of copper(II) to the thiosemicarbazones increase their biological activities. The data are summarized in table 4. The data indicate that:

(i) The inhibition effect of $HL^1$ is lower than that of $H_2L^2$ which could be attributed to the presence of two thiosemicarbazones in $H_2L^2$.



[(L$^1$)$_2$Cu]

[(HL$^1$)$_2$Cu]X$_2$
X = Cl, Br or ClO$_4$

[(HL$^1$)CuX$_2$]

[(H$_2$L$^2$)Cu$_2$X$_4$]

[(L$^2$)Cu]

Figure 2. Proposed structures of HL$^1$ and H$_2$L$^2$ copper(II) complexes.

Table 4. Antimicrobial activities[a] of the free ligands and their complexes.

| | 1[b] | | 2[b] | | 3[b] | | 4[b] | | 5[b] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Compound | LN | DR | LN | DR | LN | DR | LN | DR | 100[c] | 200[c] |
| HL$^1$ | 16 | 87 | 28 | 78 | 38 | 69 | 40 | 66 | 79 | 83 |
| [(L$^1$)$_2$Cu | 13 | 89 | 22 | 85 | 32 | 76 | 36 | 71 | 81 | 84 |
| [(HL$^1$)CuCl$_2$] | 7 | 96 | 9 | 94 | 16 | 91 | 16 | 92 | 88 | 89 |
| [(HL$^1$)CuBr$_2$] | 9 | 93 | 11 | 91 | 19 | 88 | 20 | 86 | 81 | 82 |
| [(HL)$_2$Cu]Cl$_2$ | 12 | 91 | 16 | 87 | 24 | 80 | 28 | 80 | 79 | 80 |
| [(HL)$_2$Cu]Br$_2$ | 12 | 90 | 16 | 87 | 23 | 81 | 29 | 76 | 74 | 74 |
| [(HL)$_2$Cu](ClO$_4$)$_2$ | 14 | 89 | 17 | 87 | 24 | 81 | 30 | 74 | 79 | 82 |
| H$_2$L$^2$ | 12 | 90 | 22 | 86 | 26 | 80 | 28 | 74 | 94 | 95 |
| [L$^2$Cu] | 11 | 93 | 20 | 89 | 22 | 83 | 23 | 80 | 96 | 97 |
| [(H$_2$L$^2$)Cu$_2$Cl$_4$] | 5 | 99 | 8 | 97 | 11 | 97 | 11 | 94 | 96 | 98 |
| [(H$_2$L$^2$)Cu$_2$Br$_4$] | 7 | 96 | 8 | 97 | 14 | 96 | 13 | 91 | 94 | 95 |
| Nystatin | | | | | | | | | 97.8 | 98.9 |

[a] LN = live number, DR = death rate (%),
[b] Types of bacteria and fungal species as given in the experimental section.
[c] mg.

(ii) The monochelates exhibit higher inhibition effects relative to the bischelates, in agreement with our earlier observations [13] and that reported by West *et al*. [29].

(iii) All chloride-containing complexes in the series $[(HL^1)CuX_2]$ and $[(H_2L^2)Cu_2X_4$ have significant increase in the potential compared to bromide.

(iv) The complexes $[(H_2L^2)Cu_2CuX_4]$ exhibit significant effects against all the micro-organisms compared to $[(HL^1)CuX_2]$. This could be attributed to the tetrahedral structure of the former series and two copper ions per a molecule while the latter complexes are associated with a square-planar structure with one copper ion per molecule.

(v) The free ligands and their copper(II) complexes are almost as effective as nystatin especially at higher concentration (200 ppm).

## 4. Conclusion

This work describes the synthesis, characterization and biological activity studies of thiosemicarbazones of 1-acetyl- and 1,1′-diacetylferrocene, $HL^1$ and $H_2L^2$, respectively, and their copper(II) complexes. The different spectral data showed that $HL^1$ acts as monobasic or neutral bidentate ligand forming monochelate copper(II) complexes with tetrahedral structure and bischelates having square-planar structure. $H_2L^2$ acts as a neutral or dibasic mononucleating or binucleating ligand giving a mononuclear square planar $[L^2Cu]$ and dinuclear tetrahedral $[(H_2L^2)Cu_2X_4]$. The magnetic data indicate that all complexes are paramagnetic with one unpaired electron per copper ion and there is no electron exchange between Cu and Fe or between Cu and Cu centers. All compounds are biologically active against some bacteria and fungal species.

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