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Synthesis, Characterization and Antibacterial study of some metal complexes derived from bis(5-(benzylthio)-1,3,4-thiadiazol-2-yl)methane

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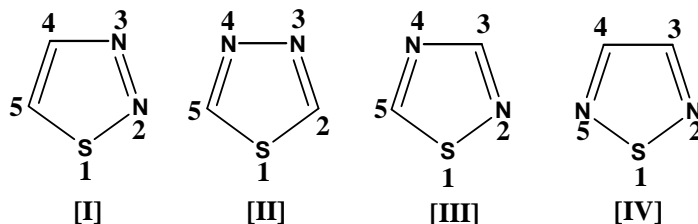
ABSTRACT

This work involves the chemical synthesis of new complexes derived from bis(5-(benzylthio)-1,3,4-thiadiazol-2-yl)methane, and characterized by C.H.N.M. elemental analysis, FTIR spectroscopy, Electronic spectra (Uv-visible), in addition to molar conductance (Ω_m) of complexes solution in DMF solvent, and evaluation the magnetic moments (M_{eff}) via Gouy's method. The antibacterial activity for the ligand and their metal complexes were studied against three selected micro-organisms *Staphylococcus aureus*, *Pseudomonas*, and *Klebsiella*. The antibiotic Gentamycin has been chosen to compare with the ligand and complexes.

Keywords: Antibacterial activity, Gentamycin, molar conductance.

INTRODUCTON

Thiadiazoles, are five-membered rings associated with diverse biological and pharmacological properties [1]. There are four isomeric types: 1,2,3-thiadiazole (I); 1,3,4-thiadiazole (II); 1,2,4-thiadiazole (III) and 1,2,5-thiadiazole (IV).



Thiadiazole nucleus constitutes the active part of several biologically active compounds, including antibacterial, [2–5] antimycotic, [6,7] antiviral, [8,9] carbonic anhydrase inhibitor, [10–12] and anti-inflammatory, [13,14] activities. Substituted thiadiazoles have been reported to display diverse applications as oxidation inhibitor, cyanic dyes and metal complexing agents [15–17]. Metal complexes of 1,3,4-thiadiazole moiety applications.

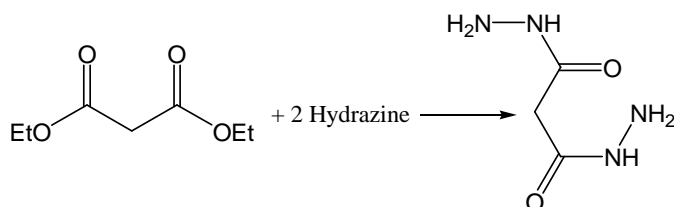
The wide range of application of the ligand and its metal complexes aroused our interest to prepare a new series of some of those metal complexes.

EXPERIMENTAL SECTION

All chemicals used were of reagent grade (supplied by either Merck or Fluka) and used as supplied. The FTIR spectra in the range (4000–600 cm⁻¹ in general) were recorded as cesium iodide disc on FTIR 8300 Shimadzu Spectrophotometer. Proton NMR spectra were recorded on a Bruker -DPX 300 MHz spectrometer with TMS as internal standard in Jordan University. The UV-Visible spectra were measured in ethanol using Shimadzu UV-Vis. 160 A spectrophotometer in the range (200–1000) nm. Magnetic susceptibility measurement for complexes were obtained at room temperature a using (Magnetic susceptibility Balance Model MSB-MKI). Flame atomic absorption of elemental analyzer, Shimadzu AA-670 was used for metal determination. Elemental micro analysis was carried out using C.H.N elemental analyzer model 5500-Carlo Erba instrument. Gallen Kamp M.F.B.600.010 F. Melting point apparatus was used to measure the melting point of all the prepared compounds.

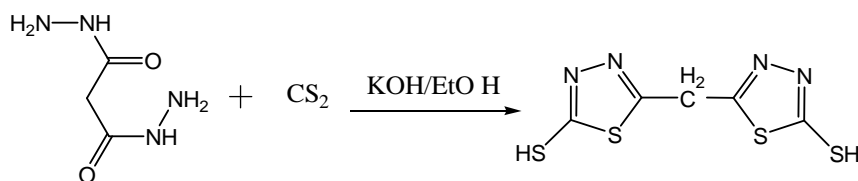
Synthesis of malonyldihydrazide: Malonyldihydrazide was prepared by reacting the diethylmalonate (1 mole) with hydrazine hydrate (2 moles) according to a previous method. [18].

The Reaction:



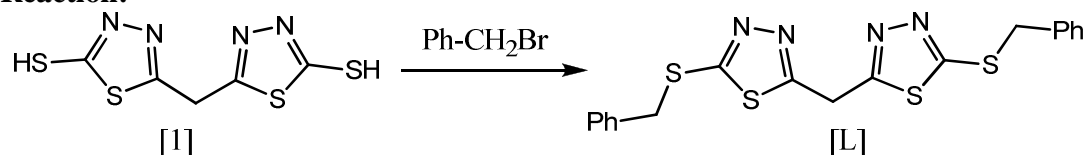
Synthesis of 5,5'-methylenebis(1,3,4-thiadiazole-2-thiol): Potassium hydroxide (18.2 g, 0.32 mole) was dissolved in absolute ethanol (40 ml) and carbon disulfide (36.6 g, 0.48 mole) was added to the solution. After the addition of carbon disulfide (CS₂), malonohydrazide (13.5g, 0.45 mol) in absolute ethanol (80 ml) was added and the mixture was stirred for 15 minutes then refluxed for 6hr. Most of the solvent was removed under reduced pressure and the residue was dissolved in water (100 ml) and carefully acidified with hydrochloric acid (15ml). The resulting solid residue was crystallized from ethanol [19].

The Reaction:



Synthesis of the ligand bis(5-(benzylthio)-1,3,4-thiadiazol-2-yl)methane: To a solution of potassium hydroxide (10 mmole) in absolute ethanol (50 ml) 5,5'-methylenebis(1,3,4-thiadiazole-2-thiol) (5mmole) was added with stirring. A solution of benzyl bromide (10mmole) in (20ml) ethanol was added [20]. The reaction mixture was heated under reflux for 2hrs. After cooling, water (100ml) was added which lead to a precipitate formation the resulting solid residue was crystallized from ethanol. ¹HNMR (3.2 s(4H) for CH₂, 2.8 s(2H) for CH₂, m. 7.2(1H) for CH Aromatic).

The Reaction:



Synthesis of complexes: The salts [MnCl₂.4H₂O, CoCl₂.6H₂O, NiCl₂.6H₂O, CuCl₂.2H₂O and ZnCl₂] were dissolved in ethanol, and added to an ethanolic solution of ligand (L) in (2:1) mole ratio ligand to metal respectively, (except for Zn (II) complex in 1:1 ratio) with stirring. The mixture was heated under reflux for three hours, during this period, the precipitation was completed from, and collected by filtration, then washed with ethanol, and dried under vacuum for 4 hours. All these complexes were analyzed by using different available techniques, the physical proportion of the ligand (L) and its metal complexes are listed in table (1).

Study of complexes formation in solution: Complexes of ligand (L) with metal ions were studied in solution using ethanol (or DMF) as solvents, in order to determine (M:L) ratio in the complex following molar ratio method [21, 22]. A series of solution were prepared having a constant concentration 10⁻³ M of metal ion and ligand (L). The [M:L] ratio was determined from relationship between absorption of the absorbed light and mole ratio of [M:L]. The results of complexes formation in ethanol were listed in table (1).

Study of biological activity for ligand (L) and C₁-C₅ complexes: The biological activity of the prepared new ligand and their metal complexes were studied against selected types of bacteria which included *Klebsiella*, and *Pseudomonas aersginosa* as gram negative and *Staphylococcus aureus*, as gram positive tope cultivated in brain hart broth agar media, which is used DMF as a solvent and as a control for the disc sensitivity test [23]. This method involves the exposure of the zone of inhibition toward the diffusion of micro-organism on agar plate. The plates were incubated for (24hr), at 37°C, the zone of inhibition of bacteria growth around the disc was observed.

Table (1): Physical data of the ligand (L) and their metal complexes

No.	Color	Crystallization solvent	M.p C°	Yield %	M:L ratio	Suggested formula	Elemental analysis calc.(found)	
							Metal %	N %
L	Yellow	Ethanol	190-192	90	-	C ₁₉ H ₁₆ N ₄ S ₄	-	13.07(11.6)
C ₁	Brown	DMF	215 ^d	70	1:2	[MnL ₂] Cl ₂	5.59 (5.11)	11.91(10.89)
C ₂	Olive	DMF/H ₂ O	240 ^d	80	1:2	[CoL ₂] Cl ₂	5.97 (5.0)	11.35(10.06)
C ₃	Orange	Hot ethanol	260	95	1:2	[NiL ₂] Cl ₂	4.15 (3.88)	11.87(10.11)
C ₄	Greenish blue	DMF/H ₂ O	270	92	1:2	[CuL ₂] Cl ₂	6.41 (5.31)	11.30(10.0)
C ₅	White yellow	DMF	293/	80	1:1	ZnL Cl ₂	11.58 (10.01)	9.92(8.6)

Table (2) : The FT-IR bands of (L) and their metal complexes

No.	ν C-S	ν C=N	ν N-N	ν M-N	ν M-CL
[1]	980/2300(W)(S-H)	1605	1455	-	-
L	975(m),3050(C-H)A, 2972(C-H ₂)	1608(s)	1458	-	-
C ₁	962	1590(s)	1440	450-470(m)	-
C ₂	975(m)	1580(s)	1443	425(m)	392.280(w)
C ₃	965(m)	1585	1447	465(m)	-
C ₄	970(m)	1595(s)	1450(m)	515(m)	280-315(w)
C ₅	965(m)	1592(s)	1448(m)	403(m)	270(m)

Table (3): Electronic spectral data, molar conductance, magnetic moments and suggested geometries of the prepared complexes

Comp.	Uv.vis λ max(nm)		Ω_m MCml ⁻¹	μ_{eff} (B.M)	K_s ml ⁻¹ .lit.	Suggested geometry
	λ max	Assignment				
Ligand	220 315	$\pi \rightarrow \pi^+$ $\pi \rightarrow \pi^*$	-	-	-	-
C ₁	246 360	$\pi \rightarrow \pi^+$ C.T Mn ⁺² \rightarrow CL ⁻	180	5.30	3*10 ⁵	Tetrahedral
C ₂	225 295 400 800	$\pi \rightarrow \pi^+$ n $\rightarrow \pi^+$ T _{1g} ⁴ \rightarrow A _{2g} ⁴ T _{1g} ⁴ \rightarrow T _{1g} (p)	40	3.50	2*10 ⁶	Octahedral
C ₃	270 515	n $\rightarrow \pi^+$ A _{2y} ¹ \rightarrow A _{1g} ²	175	0.0	4*10 ⁶	Square planar
C ₄	250 362 505	n $\rightarrow \pi^*$ C.T CL ⁻ \rightarrow Cu ⁺² E _g ² \rightarrow T _y ²	35	1.40	6*10 ⁶	Octahedral
C ₅	215 310 350	$\pi \rightarrow \pi^+$ n $\rightarrow \pi^*$ C.T(Zn ⁺² \rightarrow CL ⁻)	25	0.0	1.5*10 ⁵	Tetrahedral

RESULTS AND DISCUSSION

Elemental analyses: The physical and analytical data of the ligand and its metal complexes are given in table (1). The results obtained from elemental analysis are in satisfactory agreement with the calculated values. The suggested molecular formula was also supported by spectral measurements as well as magnetic moments.

Infrared spectroscopic study: The spectrum of the ligand and the spectra of the complexes with their assignment are shown in the table (2). Ligand exhibited the diagnosis (ν C=N) at 1605cm⁻¹, (ν N-N) at 1455cm⁻¹, and (C-S) at 980 cm⁻¹ vibrations. Most of the following changes were noticed in spectra of complexes. The band due to (ν C=N) were shifted to lower frequencies around 1585cm⁻¹. The inspection of the bands due to (N-N) stretching frequencies showed small relative changes in the position accompanied by reduction in the intensity especially for the band (C-S) frequencies, for all complexes, which rule out the coordination through donor nitrogen atoms of thiadiazole rings. The bands attributed to (M-N) and (M-Cl) were observed in the region (403-515) and (270-392) cm⁻¹ respectively in all complexes [24, 26].

Electronic spectroscopic study: The Uv-visible data of metal complexes in DMF solution in the range (200-1000) nm.

C₁: For C₁ complex the measured magnetic moment was 5.30 BM this show the manganese is in its brownish complex to be paramagnetic with d-configuration. The spectrum of this complex shows tow bands at 246 and 360 nm, can be assigned to charge transfer of Mn⁺²→Cl⁻¹, this indicates tetrahedral environmental around Mn (II). The conductivity measurement showed that the complex was electrolyte in 1:2 ratio [27].

C₂: The electronic spectrum of this complex showed abroad band consists of these spin forbidden transition at 400, 600 and 800 nm, assignable to T¹g₄→A²g₄, T¹g₄ → T²g₄ ,and T¹g₄ (P) →T¹g₄ (F) respectively which supports the Octahedral Geometry[28].

C₃: The reddish solution of Ni(II) complex in DMF shows weak intensity band at 515nm, which is attributed to A¹g₁ → A²g₂ of square planar complexes. The diamagnetic property of this complex (μff=0. BM) is agree with the proposed structure.

C₄: The broad band at 505nm due to Eg₂ → T²g₂ for Cu(II) complex investigates the distorted Octahedral of d₉, configuration. Also the effective magnetic moment of this complex was to be (1.50BM), this value referred to octahedral suggestion structure [29]. The conductivity measurement showed that the complex was non-ionic, Table(3).

C₅: The prepared white-yellow Zn(II) complex exhibited three main absorption band , which can be assigned to π→π*, n→π*, and C.T (Zn⁺²→Cl⁻¹) respectively, so from there data, was made for the tetrahedral geometry of there complex.

Biological Activity: As a result from the study of antimicrobial of prepared ligand and their metal complexes (Table 4-6), the following point were concluded:

- The results of antibacterial activity study for the bis(5-(benzylthio)-1,3,4-thiadiazol-2-yl)methane indicated that the new ligand exhibited antibacterial activity against the studied bacteria at low and high concentration [30].
- The result reflected that the starting material 5,5'-methylenebis(1,3,4-thiadiazole-2-thiol) (1) exhibition more inhibition than the prepared new doner, base toward *Staphylococcus aureus*, at higher and lower concentration.
- The study of antibacterial activity revealed that (L) exhibited a greater activity against the studied bacteria *Pseudomonas*, and *Klebsiella*.
- Generally ,the result of prepared complexes exhibited antibacterial activity toward *Pseudomonas bacteria* and *Klebsiella* was more than the complexes inhibition on *Staphylococcus aureus*.
- It may be suggested that these complexes deactivate various cellular enzymes, which play a vital role in various metabolic pathways of these microorganisms. It has also been proposed that the ultimate action of the toxicant is the denaturation of one or more proteins of the cell, which as a result, impairs normal cellular processes. There are other factors which also increase the activity, which are solubility, conductivity and bond length between the metal and the ligand [31].

Table (4): The effect of *Pseudomonas eruginosa* toward ligand & complexes (C₁-C₅)

Compound	Radius (cm)	Concentration mM
L	0.2, 0.4, 0.9,1.4	5,10,15,20
C ₁	0.4, 0.7, 0.8,1.4	5,10,15,20
C ₂	0.6, 0.8, 1.2,1.7	5,10,15,20
C ₃	0.2, 0.6, 0.8,1.0	5,10,15,20
C ₄	0.1, 0.3,1.2,1.60	5,10,15,20
C ₅	0.2,0.55 ,0.88,1.8	5,10,15,20
Gen.	0.4,0.8,1.40, 2.10	5,10,15,20

Table (5): The effect of *Klebsiella* toward ligand & complexes (C₁-C₅)

Compound	Radius (cm)	Concentration mM
L	0.2,0.6,0.9,1.7	5,10,15,20
C ₁	0.4,0.7,1.1,1.7	5,10,15,20
C ₂	0.3,0.8,1.2,1.7	5,10,15,20
C ₃	0.4,0.7,0.8,1.5	5,10,15,20
C ₄	0.2,0.4,1.2,1.40	5,10,15,20
C ₅	0.5,0.8,1.2,1.9	5,10,15,20
Gen.	0.4,0.8,1.40,2.0	5,10,15,20

Table (6): the effect of *Staphylococcus aureus* bacteria toward ligand and complexes (C₁-C₆)

Compound	Radius (cm)	Concentration mM
L	0.40,0.50,0.6,0.80	5,10,15,20
C ₁	0.20,0.61,0.75,0.92	5,10,15,20
C ₂	0.31,0.40,1.00,1.40	5,10,15,20
C ₃	0.26,0.44,0.75,1.00	5,10,15,20
C ₄	0.24,0.50,1.00,1.70	5,10,15,20
C ₅	0.41,0.6,0.8,1.90	5,10,15,20
Gen.	0.60,0.95,1.40,2.00	5,10,15,20

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