International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.4, No.3, pp 918-924, July-Sept 2012

Synthesis, Characterization and Antimicrobial Studies on Bivalent Copper, Nickel and Cobalt Complexes of Thiosemicarbazone

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Abstract: A series of metal complexes of Cu(II), Ni(II) and Co(II) having the general composition $[M(L)_2]Cl_2$ [where L= m-nitrobenzaldehyde-4-(4'-sulphoamidephenyl)-3-thiosemicarbazone; M = Cu(II), Ni(II) and Co(II)] have been prepared and characterized by elemental analysis, spectral (IR and ^{1}H NMR) studies, molar conductance, magnetic susceptibility measurements and thermogravimetric analysis. The spectral data suggests the involvement of thione sulphur and azomethine nitrogen in coordination to the central metal ion. On the basis of above studies, a distorted square-planar geometry and square-planar geometry has been assigned for Cu(II) and Ni(II) complexes respectively, while cobalt(II) complex is tetrahedral in nature. The free ligand and its metal complexes have been tested in vitro against a number of microorganisms. The tested compounds exhibited significant activity.
Key words: Thiosemicarbazone, Copper(II), Nickel(II), Cobalt(II), Antimicrobial Activity.

Introduction

The synthesis and structural investigations of thiosemicarbazone and their metal complexes are of considerable centre of attention because of their potentially beneficial pharmacological properties and a wide variation in their modes of bonding and stereochemistry.[1–3] Interest in metal complexes with thiosemicarbazone and semicarbazone ligands has been stimulated because biological activities are often enhanced on complexation. Thiosemicarbazones and their metal complexes have received considerable attention because of their antibacterial, antifungal, antitumor, antiamoebic, antimalarial, antiviral, radioprotective, trypanocidal and anti-inflammatory activities.[4–14] The biological activity is considered to involve three kinds of mechanisms: (a) inhibition of enzyme ribonucleoside diphosphate reductase (essential for DNA synthesis); (b) creation of lesions in DNA strand by oxidative rupture; (c) binding to the nitrogen bases of DNA or RNA, hindering or blocking base replication.[15] In addition of this, they have been screened for their medical properties because they possess some cytotoxic effect. They also stabilize uncommon oxidation states, generate a different coordination number in transition metal complexes in order to participate in various redox reactions.[16,17] Much attention has been drawn towards the chemistry of transition metals[18,19] in

different coordination spheres. With the growing interest of thiosemicarbazones,[20–23] the present work was undertaken in order to investigate the ligational behaviour of the thiosemicarbazone towards metal ions, Cu(II), Ni(II) and Co(II) as well as their biological activity in inhibiting the growth of some pathogenic bacteria and fungi.

Experimental

Material

All the chemicals used were of Anala R grade and procured from Sigma-Aldrich and Fluka. $CuCl_2.2H_2O$, $NiCl_2.6H_2O$ and $CoCl_2.6H_2O$ were purchased from E. Merck and used as received.

Synthesis of m-nitrobenzaldehyde-4-(4'-sulpho amidephenyl)-3-thiosemicarbazone (L):

(a)Preparation of 4-(4'-Sulphoamidephenyl)-3-thiosemicarbazide

Sulphanilamide (0.01 mol), ethanol (30 mL) and ammonium hydroxide (20 mL) were mixed together and cooled below 20°C. Carbon disulphide (8 mL) was then added with constant stirring for 15 minutes. It was then allowed to stand for one hour. Then, sodium 2-chloroacetate (4 mL) and hydrazine hydrate (14 mL, 50%) were added and the volume was reduced to half by heating. It was then allowed to stand for overnight. The product was crystallized out from DMF-water, yield 78 %, m.p. 116°C. IR (ν, cm^{-1}) (KBr): 3150 (N-H), 1260 (C=S), 1050 (N-N), 1280-1310 (S=O), 900-920 (N-SO_2); ^{1}H NMR (DMSO): δ 6.74-7.68 (m, 4H, ArH), 2.4 (s, 2H, -SO_2NH_2), 9.2 (s, 1H, Ar-NH-CS-), 9.6 (s, 1H, >NH), 4.8 (s, 2H, -NH_2). Anal. Calcd for $C_7H_{10}N_4O_2S_2$: C, 34.13, H, 4.09, N, 22.75%. Found C, 34.02, H, 4.13, N, 23.93%.

(b) Synthesis of m-nitrobenzaldehyde-4-(4'-sulphoamidephenyl)-3-thiosemicarbazone(L)

4-(4'-Sulphoamidephenyl)-3-thiosemi carbazide (0.01mol) and m-nitro benzaldehyde (0.01 mol) in ethanol (50 mL) were mixed and refluxed for 2 hours. The reaction mixture was kept overnight at room temperature and the resulting mixture was poured in crushed ice whereby precipitate was obtained. It was filtered off, washed several times with water, recrystallized from DMF-water and finally dried in vacuum desiccator over $CaCl_2$. Yield 82 %, m.p.168°C. IR (ν, cm^{-1}) (KBr): 3150-2950 (>NH stretching), 1610 (C=N), 820 (C=S), 1020 (N-N), 1280-1310 (S=O), 900-920 (N-SO_2), 1530 (N=O); ^{1}H NMR (DMSO): δ 6.72-7.68 (m, 8H, Ar-H), 8.03 (s, 1H, >CH-), 2.0 (s, 2H, -SO_2NH_2), 4.0 (s, 1H, Ar-NH-CS-), 11.57 (s, 1H, >NH). Elemental chemical data is shown in **Table I.**

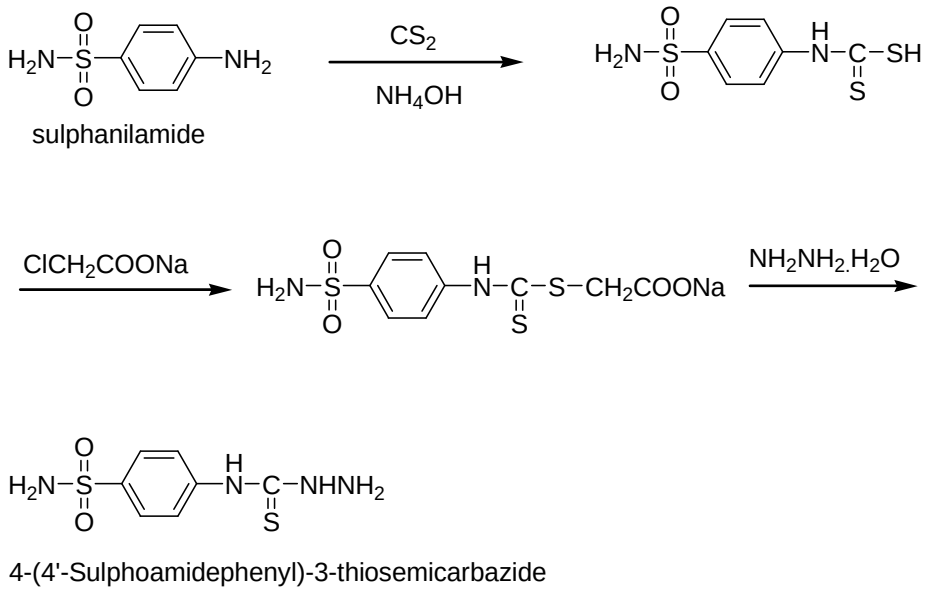

Figure 1. Synthesis and structure of 4-(4'-Sulphoamidephenyl)-3-thiosemicarbazide

Table I. Analytical data for the ligand and its complexes

Compounds	Colour	Yield (%)	Elemental Analysis found (Calcd) %				Molar conductance ($\Omega^{-1}cm^2mol^{-1}$)
			C	H	N	M	
Ligand (L)	Brown	82	44.02 (44.33)	3.15 (3.43)	18.29 (18.47)	-	-
$[Cu(L)_2]Cl_2$	Brown	72	37.32 (37.65)	2.82 (2.91)	15.56 (15.69)	6.93 (7.11)	132
$[Ni(L)_2]Cl_2$	Red-brown	68	37.68 (37.85)	2.74 (2.93)	15.67 (15.77)	6.48 (6.61)	138
$[Co(L)_2]Cl_2$	Black	75	37.59 (37.84)	2.66 (2.93)	15.48 (15.77)	6.45 (6.63)	124

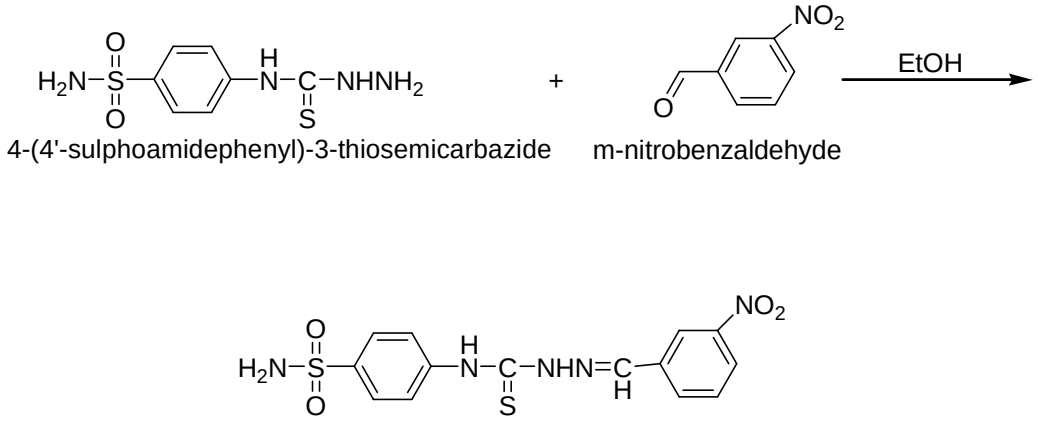

Figure 2. Synthesis and structure of Ligand(L)

Synthesis of Complexes

Hot ethanolic solution (20 mL) of ligand (0.02mol) and hot ethanolic solution (20 mL) of the corresponding metal salt (0.01mol) were mixed together with constant stirring. The mixture was refluxed for 3-4 hours at 70–80°C. On cooling, colored complexes were precipitated out. They were filtered, washed with 50% ethanol and dried in vacuum desiccator. The obtained solid metal complexes and their colour are shown in Table I. The complexes are stable solid and decomposed above 250-300°C without melting.

Physical measurements and analysis

The C, H and N were analyzed on Perkin-Elmer CHNS-2400. Metal ions were determined complexometrically. Molar conductivity of ligand and metal complexes were recorded using 1×10^{-3} M solution of DMF on Equip-tronics Conductivity meter EQ 660A. IR spectra were recorded (KBr) on a Shimadzu 8400S FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DRX 300 MHz FT NMR using TMS as internal standard. Magnetic susceptibilities of the complexes were measured by the Gouy's method at room temperature using $Hg[Co(SCN)_4]$ as standard. The effective magnetic moments were calculated using the relation ($\mu_{eff} = 2.828\ (\chi_m\ T\ )^{1/2}$ B.M. where χ_m is the molar susceptibility corrected using Pascal's constants for diamagnetism of all atoms in the compounds. The TG-DTA measurements were carried out on a Shimadzu thermo gravimetric analyzer.

The synthesized compounds were screened for their antibacterial activity against gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli)* and antifungal activity against *Candida albicans* at a concentration of 40 µg/mL in DMF by cup-plate method.[24,25] Standard antibacterial and antifungal drug, gentamycin and

miconazole respectively were also tested under similar conditions for comparison. The Zone of inhibition measured in mm of synthesized compounds and standard drugs.

Results and Discussion

All the complexes are insoluble in common organic solvents. However, they are soluble in DMSO and DMF. They are amorphous powder and stable at room temperature. The complexes were synthesized by reacting ligand with the metal ions in 2:1 molar ratio in an ethanolic medium. The IR spectral data suggests the involvement of thione sulphur and azomethine nitrogen in coordination to the central metal ion (Figure 3). Elemental analysis of complexes corresponds to the composition as shown in Table I. The molar conductance measurements of the complexes in DMF lies in the range of 124–138 $\Omega^{-1}cm^2mol^{-1}$ (Table I) indicating their 1:2 electrolytic behavior. Thus, the complexes may be formulated as $[M(L)_2]Cl_2$ [where L = m-nitrobenzaldehyde-4-(4'-sulphoamidephenyl)-3-thiosemicarbazone; M = Cu(II), Ni(II) and Co(II)].

Infrared spectra.

The binding mode of the ligand to metal ions was further elucidated by analysis of the IR spectra (Table II) of the ligand and its metal complexes. A study and comparison of infrared spectra of free ligand and its metal complexes, imply that the ligand behaves as bidentate and the metal ion is coordinated through the azomethine nitrogen and the thione sulphur.

A band at 1610 cm^{-1} in the IR spectra of the ligand L is due to ν(C=N) group[26]. Coordination of azomethine nitrogen in complexes is suggested by the shift of ν(C=N) band to lower frequencies.

The intensity of the medium band at 1020 cm^{-1} assigned for ν(N-N) in spectrum of the ligand L is remains unchanged in all the spectra of the complexes, however, it shifted to the higher frequency.[27,28] The strong band observed at 820 cm^{-1} assigned for ν(C=S) in spectrum of the ligand L is shifted towards lower frequency and occurred at 795-775 cm^{-1} in the corresponding spectra of the metal complexes indicating the coordination of the thione sulphur to metal atom[28]. The bands at 3150-2950 cm^{-1} is assigned to the νNH_2 modes which did not undergo any perceptible shifts suggesting that there is no interaction between NH_2 group and metal ion.

Magnetic moments of the metal complexes

The observed magnetic moments for Cu(II) complex with ligand was 1.41 B. M. indicate distorted square-planar geometry.[29] The nickel complex was found to be diamagnetic, which suggest a square-planar 4-coordinate structure which may also deduced from their red-brown colour. Octahedral, tetrahedral and square-planar cobalt (II) complexes show magnetic moment between 4.7-5.2, 4.2-4.8 and 2.2-2.9 B.M., respectively.[21,23] The μ_{eff} value measured for the present Co(II) complex with ligand L was 4.59 B.M., which indicate that Co(II) ion is present in tetrahedral geometry.

Table II. Significant infrared spectral bands (cm^{-1}) of ligand and its metal complexes

Compounds	ν(C=N)	ν(N-N)	ν(N=O)	ν(C=S)	ν(M-N)	ν(M-S)	-NH stretching
Ligand (L)	1610	1020	1530	820	-	-	3150-2950
$[Cu(L)_2]Cl_2$	1562	1020	1530	775	450	365	3150-2950
$[Ni(L)_2]Cl_2$	1550	1020	1530	792	455	380	3150-2950
$[Co(L)_2]Cl_2$	1574	1020	1530	786	440	385	3150-2950

Thermogravimetric analysis

Generally, there is less known about the thermal properties of transition metal complexes of thiosemicarbazones.[30] The thermogram of solid complexes shows that there is no weight loss up to 200°C indicating the absence of lattice as well as coordinated water molecules in complexes. A gradual increase in temperature above 200°C has been accompanied by loss in weight up to 300°C. It indicate partial decomposition of ligand moiety. The remaining part of the ligand break at 300-600°C. The horizontal curve has been observed after 600°C. The total weight loss up to 550°C is nearly 80-85% and equal to two moles of ligand indicating 1:2 composition of the complex. This constant weight region corresponds to metal oxides, the final pyrolysis product.

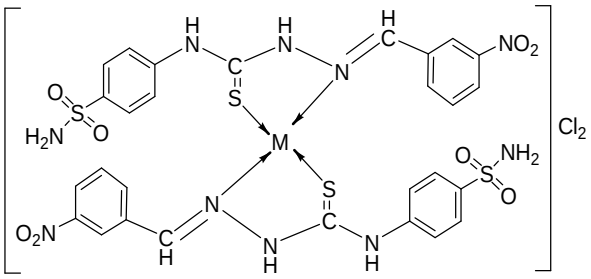

Figure 3: Suggested structure of complexes, where M = Cu(II), Ni(II) and Co(II)

Antimicrobial Studies

The antimicrobial screening data shows that the ligand exhibits antimicrobial properties and it is important to note that the metal chelates exhibit more inhibitory effect than the parent ligand. From Table III, it is clear that the zone of inhibition is much larger for metal chelates against gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli)* pathogenic bacteria. The increased activity of metal chelates can be explained on the basis of chelation theory. It is known that the chelation tends to make the ligand act as a more powerful and potent bactericidal agent, thus 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 ligand and there may be π-electron delocalization over the whole chelating system.[31] This increases the lipophilic character of the metal chelate and favors its permeation through the lipoid layer of the bacterial membranes. There are also other factors which increase the activity, namely solubility, conductivity and bond length between the metal and the ligand.

The result of fungicidal screening (Table III) shows that complexes were more active than the free ligand against pathogenic fungi, *Candida albicans.* The mode of action may involve the formation of a hydrogen bond through the azomethine nitrogen atom with the active centers of the cell constituents, resulting in interference with the normal cell process.[32]

Conclusion

The thiosemicarbazone ligand and its metal complexes were characterized by elemental analysis, spectral studies, molar conductance, magnetic susceptibility measurements and thermogravimetric analysis. On the basis of above data the thisemicarbazone appear to behave as bidentate ligand coordinating through the azomethine nitrogen and the thione sulphur atom. The results of the above studies suggest that copper(II) and nickel(II) complexes probably posses a distorted square-planar geometry and square-planar geometry respectively, while cobalt(II) complex is tetrahedral in nature. The antimicrobial properties of ligand and its complexes were studied. The obtained results of the complexes show enhanced activity compared to the ligand, which indicate that the coordinated metal have an influence on the antimicrobial effects. The complex with Ni(II) was the most active against all the tested bacteria and fungi.

Table III. Antimicrobial activity of the Ligand and its metal complexes

Compounds	*S. aureus*	*E. coli*	*C. albicans*
Ligand (L)	12.8	13.1	09
$[Cu(L)_2]Cl_2$	15.6	14.4	11.5
$[Ni(L)_2]Cl_2$	17.2	17.4	12.6
$[Co(L)_2]Cl_2$	15.9	14.3	9.8
Gentamycin	18.2	16.5	-
Miconazole	-	-	20

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