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Synthesis, characterization and Microbial Study of Complexes of Cu(II) and Ni(II) with thiosemicarbazone

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ABSTRACT

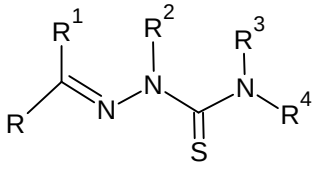
The synthesis of Cu(II) and Ni(II) complexes with thiosemicarbazone(L) ligand have been reported. The ligand was characterized by elemental analysis and spectral (IR and 1H NMR) studies and its complexes were characterized by electronic, UV/VIS, EPR and IR studies. At room-temperature EPR spectrum of Cu(II) complex was recorded, indicated distorted octahedral structure. The electronic spectrum of Ni(II) complex indicated the octahedral geometry around the Ni(II) ion. Their antibacterial activities were evaluated by the diameter of zone of inhibition (mm) against four bacteria such as B. subtilis, S. aureus, E. coli and K. pneumonia. The ligand and the 6-coordinate Ni(II) complex did not inhibit the growth of the test organisms, while the Cu(II) complex showed good antibacterial activity than parent ligand against the same bacteria

Keywords: Spectral studies; *Invitro*-antibacterial; Cu(II) and Ni(II) complexes; thiosemicarbazone.

INTRODUCTION

Thiosemicarbazone ligands, derived from the combination of a thiosemicarbazide and an aldehyde or ketone, a useful ligand type for obtaining coordination spheres with mixed N/S donors. Interest in these ligands has been driven, that they have been studied for a considerable period of time for their biological properties. Traces of interest to the beginning of the 20th century but the first reports on their medical applications began to appear in the Fifties as drugs against tuberculosis and leprosy.[1,2] In the Sixties their antiviral properties were discovered and a huge amount of research was carried out that eventually led to the commercialization of methisazone, Marboran®, to treat smallpox.[3] In this period one of the first antitumor activity results was published.[4] Recently Triapine® (3-aminopyridine-2-carboxaldehyde

thiosemicarbazone) has been developed as an anticancer drug and has reached clinical phase II on several cancer types.[5,6] Presently, the areas in which thiosemicarbazones are receiving more attention can be broadly classified according to their antitumor, antiprotozoal, antibacterial or antiviral activities and in all cases their action has been shown to involve interaction with metal ions.[7,8] However, to date there are no such investigations on metal complex derivatives.



Thiosemicarbazones

(The drawing represents the general formula for thiosemicarbazones. R1, R2, R3 & R4 = H, or any organic substituent.)

Biological activities of metal complexes differ from those of either ligands or the metal ions and increased and/or decreased biological activities have been reported for several transition metal complexes, like Cu(II) and Ni(II).[12-14] The activity of these compounds is strongly dependent upon the nature of the heteroatom ring and the position of attachment of thiosemicarbazone to the ring as well as the form of the thiosemicarbazone moiety.[15] These have been studied extensively due to their flexibility, selectivity and sensitivity towards the central metal atom, structural and similarities with natural biological substances and the presence of imine group (-N=CH-) which imparts the biological activity.[16] (α)-Heterocyclic thiosemicarbazones derived from ketone have shown to present an interesting pharmacological profile and it has been demonstrated that the presence of a bulky group at terminals strongly improves their biological activity,[17] probably due to increase in lipophilicity. In the present work, report is made regarding the synthesis and spectroscopic characterization of Cu(II) and Ni(II) complexes of the ligand and in vitro – antibacterial activity of these compounds that were extensively studied.

EXPERIMENTAL SECTION

Materials and general procedures

All the chemicals were commercially available and used as received. The IR spectra of the compounds were recorded on a Nicolet FT-IR 560 Magna spectrometer using KBr. The Bruker 300 MHz NMR spectrometer was used to obtain the ^{1}H NMR spectrum of the ligand. Elemental analysis was obtained from vario-micro qub elementar analyzer. The electronic spectra of the complexes were recorded on a UV-VIS,UV-2601. EPR spectra were recorded on an EPR spectrometer (JEOL FE - 1X) operating in the X-band frequencies with a modulation frequency of 100 kHz. The magnetic field was scanned from 2200 to 4200 G, with a scan speed of 250Gmin-1. 100mg of powdered metal complex was taken in a quartz tube for EPR measurements. Copper(II) chloride and nickel(II) chloride salts were obtained from Loba AR-grade and were used as such. Thiobarbituric acid (TBA), trichloroacetic acid (TCA), α-tocopherol, butylatehydroxyl toluene (BHT), 1,1-diphenyl-2-picrylhydrazyl (DPPH), 4-phenyl-3-thiosemicarbazide and 2,6-diacetylpyridene were procured from Merck Chemical Company. All the solvents obtained commercially were distilled before use.

Synthesis of thiosemicarbazone

Thiosemicarbazone (L) was prepared as per the procedure reported in literature.[11] The melting point was reported 152°C and the yield was 65-70%. The characterization of L was carried out by IR and 1H NMR spectroscopy. The 1H NMR (400 Hz, DMSO, δ): 10.654 (s, 1H, -NH-ph), 10.184 (s, 1H, -NH-ph), 8.538 (d, 2H, py-H, ^{3}J = 8 Hz), 7.819 (d, 1H, py-H, ^{3}J = 8 Hz),

7.552 (d, 4H, Ar-H, ^3J = 8 Hz), 7.371 (t, 4H, Ar-H, ^3J = 7.6 Hz), 7.213 (t, 2H, Ar-H, ^3J = 7.2 Hz), 2.484 (s, 6H, -CH3) were obtained. .

Preparation of Cu(II) complex (1)

A hot ethanolic (40 mL) solution of ligand (0.002 M) and a hot ethanolic (40 mL) solution of copper(II) sulphate (0.02M) were mixed together with constant stirring and the resulting mixture was refluxed for 4-5 hours at 60-65°C. On cooling, yellow orange colored complex was formed, which was filtered off, washed with cold ethanol and dried in vacuum. Yield was 40-50%. UV/VIS spectrum (nm) 1256, 1160, 948 and 845 were determined. EPR spectrum with {g} tensor was found to be g_1 = 2.25, g_2 = 2.15, and g_3 = 2.07, and effective magnetic momentum was found to be 1.81-1.87 BM.

Preparation of Ni(II) complex (2)

The ligand (0.50 mmol) was dissolved in absolute ethanol (30mL), then the corresponding nickel(II) sulphate (0.6 mmol) in absolute ethanol was added, and the resultant mixture was refluxed by heating for about 3 hours until the volume is reduced to 20 mL. The precipitate, thus formed was filtered and washed with absolute ethanol twice, and then dried in vacuum. Yield was 50-60%. UV/VIS spectrum (nm) 951, 630-653 and 462.

Antibacterial screening

The antibacterial activities of both ligand (L) and its metal complexes 1 and 2 were studied by usual cup-plateagar diffusionmethod.[12-14] The bacterial species used in the screening were *Klebsiella pneumonia*, *Escherichia coli*, *(gram negative)* and Staphylococcus aureus *Bacillus subtilis* (gram-positive). Stock cultures of the test bacterial species were maintained on *Nutrient Agar media* by sub culturing on petri dishes. The media were prepared by adding the components as per manufacturer's instructions and sterilized in the autoclave at 121°C temperature and 15 lbs pressure for 15 minutes and then cooled to 45-60°C. 20 mL of each medium was poured in a Petri dish and allowed to solidify. After solidification, Petri plates with media were spread with 1.0 mL of bacterial suspension, which is prepared in sterile distilled water. The wells were bored with cork borer and the agar plugs were removed. 100 µl of the compound reconstituted in DMF (Dimethyl formamide) in concentrations of 1.0 mg/mL was added to the agar wells. DMF was used as a negative control and antibiotics such as ampicillin and tetracycline were used as positive control standards. The plates were incubated at 37°C for 24 hours and then the plates were observed for the growth inhibition zones. The presence of clear zones around the wells indicated that the compound is active. The diameter of the zone of inhibition was calculated in millimeters. The well diameter was deducted from the zone diameter to get the actual zone of the inhibition diameter and the values have been tabulated.

RESULTS AND DISCUSSION

The Cu(II) and Ni(II) ions forms the 1:1 (metal : ligand) complexes with ligand has been determined on the basis of Job's continuous variation method.[19]

Electronic and EPR spectra of Cu(II) complex

The powdered X-band EPR spectrum of 1 at room temperature is shown in Fig. 1. The spectrum of Cu(II) complex reveals three sets of resonances at low, mid and Cu(II) and Ni(II) with thiosemicarbazone high fields corresponding to g_1, g_2 and g_3 respectively. From the peak positions g-values evaluated are g, g_1 = 2.26, g_2 = 2.16, and g_3 = 2.07 (Table 1). Hyperfine structure is not resolved. The calculated g values provide valuable information on the electronic ground state of the ion.[20] For g values $g_1 > g_2 > g_3$, the quantity $R = g_2\text{-}g_3/g_1\text{-}g_2$. If R is greater

than unity, then the ground state is $^2A_1$ (dz^2) and if R is less than unity, then the ground state is $^2A_1$(dx^2-y^2). In the present study, the calculated R value is less than unity (R = 0.8) and hence the ground state is $^2A_1$ (dx^2-y^2). The room temperature solid state electronic spectrum of 1 exhibits four absorption bands as shown in Fig. 2, at 1256, 1160, 948 and 845 nm which are attributed to $^2A1(dx^2\text{-}y^2)$ - $^2A_1(dz^2)$, $^2A_1(dx^2\text{-}y^2)$ _ $^2A_2$(dxy), $^2A_1(dx^2\text{-}y^2)$ _ $^2B_1$(dxz) and $^2A_1(dx^2\text{-}y^2)$ _$^2B_2$(dyz), respectively. From the results and analysis of electronic and EPR spectra, the site symmetry of Cu(II) ion in Cu(II) complex is ascertained to be a rhombically distorted octahedron with $^2A_1(dx^2\text{-}y^2)$ as the ground state.[21]

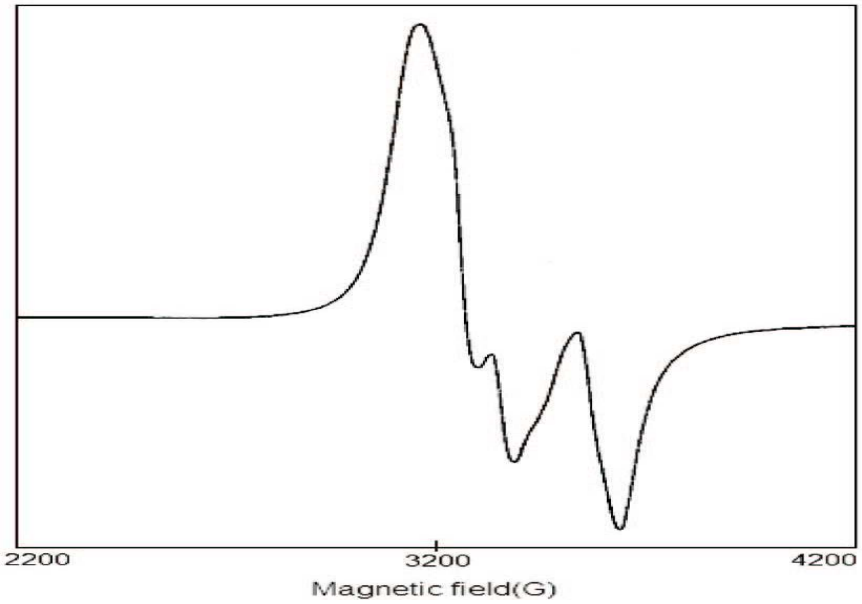


Fig.1. Powder X-band EPR spectrum of complex 1 at room temperature

Table 1. Experimental EPR parameters

Compound	Temperature	g_1	g_2	g_3	g_{ave}	μ_{eff} (BM)
1	27° C	2.26	2.16	2.07	2.15	1.81-1.87

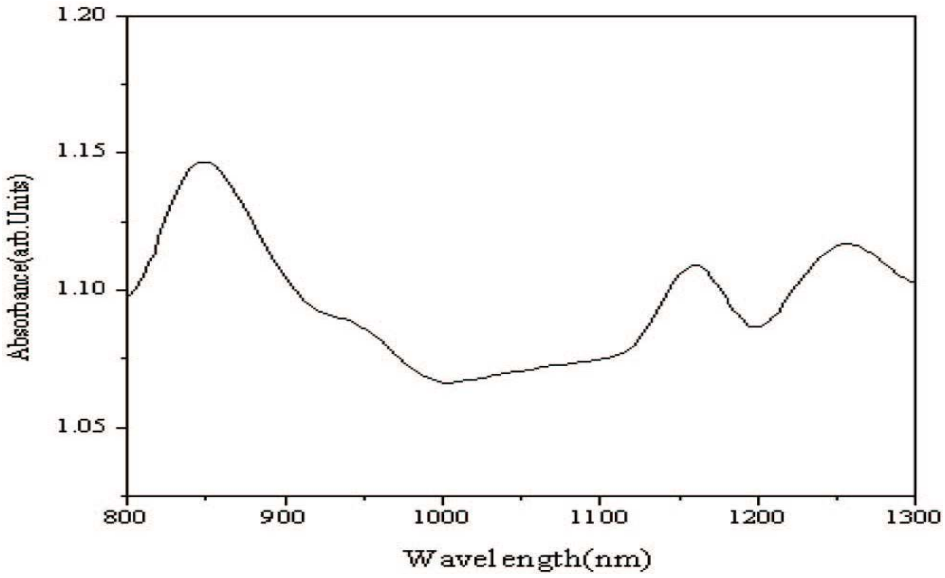


Fig. 2. Solid state electronic spectrum of complex 1

Electronic spectrum of Ni(II) complex

The solid state electronic spectrum of 2 exhibits three bands as shown in Fig. 3, at 951, 625-655 and 462 nm characteristic of an octahedral geometry around the Ni(II) ion in the complex.[22] Thus, these bands can be assigned to the three spin-allowed transitions $^3A_{2g}(F)$ _ $^3T_{2g}(F)$, $^3A_{2g}(F)$ _ $^3T_{1g}(F)$ and $^3A_{2g}(F)$_ $^3T_{1g}(P)$, respectively.

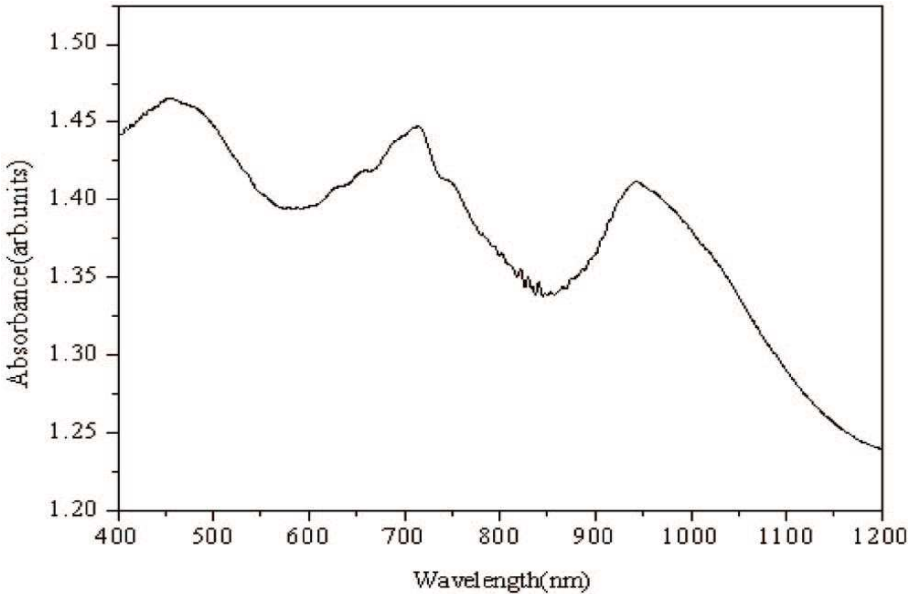


Fig. 3. Solid state electronic spectrum of complex 2

IR studies

The main vibrational bands of free ligand and of its complexes are shown in Table 2. The high frequency bands of the uncomplexed ligand centered at 3369 and 3300 cm-1, 680 are attributed to ν(N-H) stretching vibrations. The disappearance of the latter one absorption upon complexation is a consequence of the double deprotonation of the ligand. Significant changes in the ligand bands upon complexation include variation in the ν(C=N, C=C) vibration energies and systematic shifts of the ν(C-S) absorption bands to lower frequencies shown in Table 2. These data indicate coordination through the azomethine nitrogen, the pyridine nitrogen and the sulfur atoms.[23]

Table 2. The main IR (cm^{-1}) of the ligand and its complexes

Compounds	ν (NH)	ν (C=N, C=C)	ν (C-S) + ν (C-N)	ν (C-S)
Ligand	3369, 3300	1596, 1485, 1540	1355, 1321	820
1	3403	1598, 1500, 1443	1317, 1254	694
2	3297	1596, 1529, 1493,1493	1317, 1253	753

Antibacterial activity

The results of antibacterial activity show that the ligand (L) and Ni(II) themselves do not exhibit antibacterial activities. However it is important to note that Cu(II) complex exhibits antimicrobial activities. The Cu(II) complex shows more activity than the Ni(II) complex. This may be due to the higher stability of Cu(II) complex than the Ni(II) complex. It is interesting to note that 6-coordinate paramagnetic Ni(II) complex does not exhibit antibacterial activities.[24] Data has been demonstrated in Table 3.

Table 3. Antibacterial screening data of ligand (L) and its Cu(II) and Ni(II) complexes at the concentration of 1 mg/mL

Compound	K. *pnuemoniae*	E. *coli*	B. *subtilis*	S. *aureus*
Ligand (L)	-	-	-	-
1	9	12	11	10
2	-	-	-	-
Ampicillin	43	40	43	42
Tetracycline	32	33	30	32

CONCLUSION

The Cu(II) and Ni(II) complexes with thiosemicarbazone have been synthesized . The EPR, magnetic and electronic spectral studies suggested that the Cu(II) complex has a rhombically distorted octahedron with $^2A_1(dx^2\text{-}y^2)$ as the ground state. Whereas in the Ni(II) complex the Ni(II) ion has a octahedral geometry. The Cu(II) complex showed good antibacterial activity against four bacteria (B. *subtilis*, S. *aureus*, E. *coli* and K. *pnuemoniae*) as comparable with parent ligand and Ni(II) complex.

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