

# The synthesis and characterization of new metal complexes from biologically active thiosemicarbazone ligands bound to metal ions

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## ABSTRACT

Transition metal complexes derived from biologically active ligands and selected metal ions have been synthesized. They were characterized by microanalysis, Fourier Transform infrared (FT-IR), proton NMR (<sup>1</sup>HNMR) and Low Resolution Mass Spectrometry (LRMS) techniques. The paramagnetic shift influence observed in some of the complexes is qualitatively discussed.

**Key words:** Transition metal complexes, Microanalysis, FTIR, HNMR, LRMS.

## INTRODUCTION

Intense research involving thiosemicarbazones is currently going on in many laboratories worldwide due to the wide range of biological activities exhibited by the compounds<sup>1-10</sup>. A substantial number of thiosemicarbazones have been found to be biologically active against protozoa, bacteria, viruses and fungi. The list of infections studied, among others, include tuberculosis, leprosy, psoriasis, rheumatism, trypanosomiasis, coccidiosis, leukemia, cancer, Chagas disease, leishmaniasis, Herpes Simplex virus, Neisseria gonorrhoea and Neisseria meningitidis<sup>1-11</sup>. Furthermore, structural activity relationship (SAR) studies have been conducted on a selected range of thiosemicarbazones<sup>1,9</sup>. Our recent studies indicated that a dithio thiosemicarbazone when complexed to certain metal ions produced complexes with high biological activity<sup>10</sup>. In our continued investigations, it was decided to focus our attention in synthesizing the metal complexes utilizing the ligands shown in figure 1 with a view to carrying out biological tests against malarial parasite.

We hereby report the synthesis and characterization of new metal complexes of nickel(II), copper(II), and zinc(II) containing 2-acetylpyridine-4-phenyl-3-thiosemicarbazone and 2-acetylpyridine and 2-formylpyridine thiosemicarbazone.

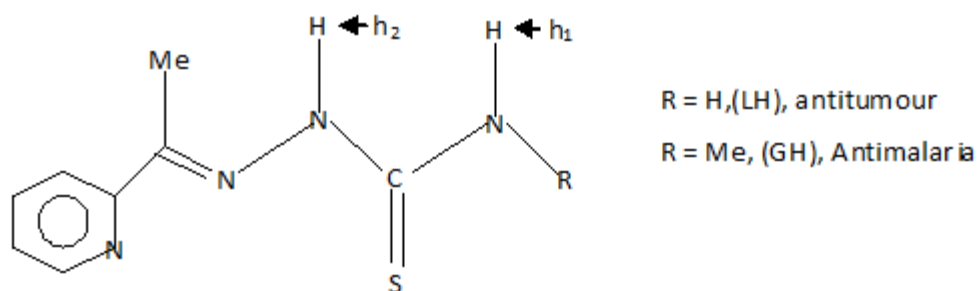
## EXPERIMENTAL

All the chemicals used were purchased from Aldrich and used as received. The spectroscopic measurements FT-IR, <sup>1</sup>HNMR, Microanalyses, and Low Resolution Mass Spectroscopy were done at the University of Cape Town.

### Preparation of the Ligands

#### The synthesis of 2-Acetylpyridine-4-Phenyl-3-thiosemicarbazone (LH)

The thiosemicarbazone ligands were prepared according to a literature method<sup>12</sup> which involved a condensation reaction. The thiosemicarbazone ligands were prepared through a condensation reaction. The reactants were taken in the mole ratio of 1:1. Thus, 2-Acetylpyridine-4-



**Fig. 1: 2-Acetylpyridine thiosemicarbazone, R=H or Me**

Phenyl-3-thiosemicarbazone(LH) was prepared by adding 2-acetylpyridine (2.0 ml) to 4-phenyl 3-thiosemicarbazide (2.982g) in methanol (125ml) followed by acetic acid (equivalent of 1% of the total volume of the mixture) and then refluxing for 3 hours. The reaction mixture was cooled and the thiosemicarbazone precipitated out. It was then filtered off, dried on the pump for 60 minutes and then recrystallized from ethanol. The yield obtained was 1.10 g (36%).

**The synthesis of 2-Pyridine Carboxaldehyde -4-Phenyl -3- thiosemicarbazone (2-formylpyridine-4-phenyl-3-thiosemicarbazone GH)**

The formylthiosemicarbazone ligand (GH) was prepared by dissolving of 4-phenyl 3-thiosemicarbazide (3.516g) in methanol (150ml) and adding 2-Pyridine carboxaldehyde (2.0 ml) then refluxing the mixture for 20 minutes after adding acetic acid as in the previous case. Upon cooling the precipitate formed was filtered off, dried at the water pump for 45minutes. The ligand was not recrystallised due to its insolubility in most solvents. The yield was 4.25 g(79%).

**Preparation of Thiosemicarbazone Complexes Preparation of the Copper complex, CuLCI**

$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (0.3g) was dissolved in distilled water (25 ml) while the ligand (0.414g) was dissolved in ethanol (130 ml). The two solutions were mixed by adding slowly the cupric solution to the ligand solution with continuous stirring.

A green precipitate which formed was allowed to settle. It was then filtered off, washed with

water, ethanol and ether and then allowed to dry at the pump for 30 minutes. The complex was recrystallized from acetone. The yield was 0.56 g(86%).

**Preparation of the Zinc complex, ZnL(LH)Ac**

$(\text{CH}_3\text{-COO})_2\text{Zn} \cdot 2\text{H}_2\text{O}$  (0.3g) were dissolved in distilled water (20 ml) and the ligand (0.423g) was dissolved in ethanol (200 ml). Upon mixing the two solutions a yellow precipitate formed. It was then filtered off, washed with water, ethanol and ether, and then allowed to dry at the water pump for 30 minutes. The complex formed was not recrystallised due to the lack of a suitable solvent. The yield was 0.22 g(24%).

**Preparation of the Nickel complex, NiL<sub>2</sub>**

Two solutions prepared by dissolving  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (0.3g) and the ligand (0.681g) in distilled water (15 ml) and in ethanol (140 ml) respectively were mixed. Upon adding the metal solution to the ligand solution a fine brown precipitate was produced. A little excess of  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  was added to complete the precipitation.

The precipitate was filtered off, washed with water, ethanol and ether. It was then air-dried at the water pump for 30 minutes. The complex was also found to be insoluble in the common solvents tried. The yield obtained was 0.70 g(93%).

**Preparation of 2-formylpyridine-4-phenyl-3-thiosemicarbazone, (GH) Complexes Preparation of the Copper complex, CuGCI**

Two solutions were prepared by dissolving

of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (0.3g) in distilled water (25ml) and the ligand (0.451g) in Dimethyl Sulphoxide (DMSO) (70 ml). The metal solution was then attached to the ligand solution with stirring. A dark green precipitate was immediately formed. It was then filtered off, washed with water, ethanol and then ether and allowed to dry at the water pump for 45 minutes. The complex was also found to be insoluble in the common solvents used. Its yield was 0.30 g(48%).

The preparation of the Zinc complex,  $\text{ZnG}(\text{GH})\text{Ac}$  Two solutions were prepared by dissolving  $(\text{CH}_3\text{-COO})_2\text{Zn} \cdot 2\text{H}_2\text{O}$  (0.30 g) in distilled water (30 ml), while the ligand (0.351g) was dissolved in DMSO (60ml). The metal solution was slowly added to the ligand solution with stirring. The bright yellow precipitate which was formed was filtered off, washed with water, ethanol and ether. It was then dried at the water pump for 45 minutes. The complex was also found to be insoluble in the common solvents. The yield obtained is 0.11 g(13%).

## RESULTS AND DISCUSSION

The metal complexes of nickel(II), copper(II), and zinc(II) containing 2-acetylpyridine-4-phenyl-3-thiosemicarbazone and 2-acetylpyridine and 2-formylpyridine thiosemicarbazone were characterized by microanalysis, Low Resolution Mass Spectrometry(LRMS), proton NMR and Fourier Transform IR techniques. The results are

presented in Tables 1-6 and Figures 4-8. These results are consistent with the formation of the ligands LH and GH as well as  $\text{NiL}_2$ ,  $\text{ZnL}(\text{LH})\text{Cl}$ ,  $\text{CuLCl}$ ,  $\text{ZnG}(\text{GH})\text{Cl}$ , and  $\text{CuGCl}$  complexes.

### Paramagnetic shift influence

We recently discerned paramagnetic shift influence in the ferrocene-based thiosemicarbazone copper(II) complexes<sup>13</sup>. The <sup>1</sup>HNMR spectral data of the ligand LH ( $\text{H}_1$ ) and the zinc complex  $\text{ZnL}(\text{LH})\text{Ac}$  ( $\text{H}_3$ ) are given in Table 2. For LH( $\text{CDCl}_3$  solvent), the signals at  $\delta$  values 2.446 and 2.477 ppm can tentatively be

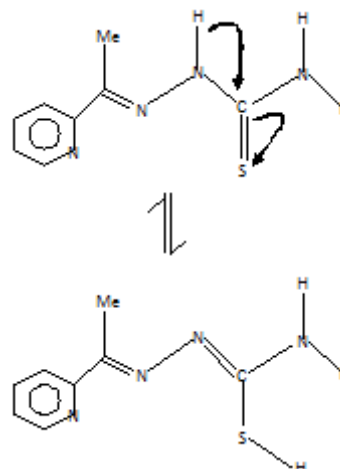


Fig. 2: 2-Acetylpyridine thiosemicarbazone, tautomerism

Table 1: Analytical data and low resolution mass spectrometry molar mass (LRMS) of the ligands and their complexes

Comp.	Analytical data		Calculated(cal.)		%found		(Fd)%		MM	LRMS
	C		H		N		S			
	Cal	Fd	Cal.	Fd	Cal	Fd	Cal.	Fd	MM	LRMS -MM
$\text{H}_1$	62.22	61.12	5.19	5.08	20.74	20.25	11.85	10.86	270.00	270.90
$\text{H}_2$	56.31	54.98	4.36	4.36	18.77	17.88	10.73	9.82	596.70	597.30
$\text{H}_3$	54.27	53.09	4.52	4.28	16.88	17.11	9.65	9.21	663.40	663.70
$\text{H}_4$	45.66	43.18	3.53	3.36	15.22	13.93	8.70	7.42	367.97	332.50
$\text{H}_5$	60.94	60.21	4.69	4.57	21.88	20.96	12.50	11.60	256.00	257.10
$\text{H}_6$	52.88	51.53	3.93	3.87	17.63	17.91	10.07	11.11	-	-
$\text{H}_7$	44.07	43.70	3.11	3.06	15.82	15.02	9.04	8.21	353.95	353.10

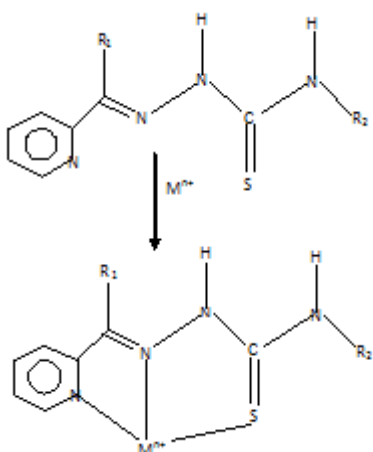
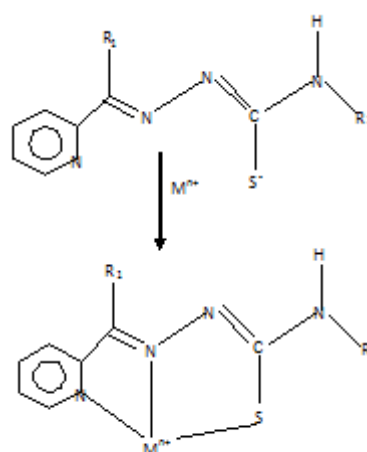
$\text{H}_1$  = 2-acetylpyridine -4-phenyl-3-thiosemicarbazone (LH),  $\text{H}_2$  =  $\text{NiL}_2$ ,  
 $\text{H}_3$  =  $\text{ZnL}(\text{LH})\text{Ac}$ ,  $\text{Ac} = \text{CH}_3\text{COO}^-$ ,  $\text{H}_4$  =  $\text{CuLCl}$ ,  $\text{H}_5$  = 2-formylpyridinethiosemicarbazone (GH),  
 $\text{H}_6$  =  $\text{ZnG}(\text{GH})\text{Ac}$ ,  $\text{H}_7$  =  $\text{CuGCl}$

**Table 2: Colour, melting point and the yield of the ligands and the complexes**

Comound	Colour	m.p. (°C)	Yield
H <sub>1</sub> (LH)	Pale yellow	190-192	36
H <sub>2</sub> (NiL <sub>2</sub> )	Brown	248-252	93
H <sub>3</sub> [ZnL(LH)Ac]	Yellow	262-264	24
H <sub>4</sub> (CuLCl)	Green	308-310	86
H <sub>5</sub> (HG)	Pale yellow cotton like	212-214	79
H <sub>6</sub> (ZnG(GH)Ac)	Yellow	290-292	13
H <sub>7</sub> (CuGCl)	Green	250-252	48

**Table 3: <sup>1</sup>HNMR of H<sub>1</sub> (CDCl<sub>3</sub>) and H<sub>3</sub> (DMSO), (δ-values, ppm)**

H <sub>1</sub> (CDCl <sub>3</sub> )	Tentative Assignment	H <sub>3</sub> (DMSO)	Tentative Assignment
2.446	Me	2.503	DMSO
2.477	Me	2.708	Me
7.20-7.50 (m)		3.280	S-H/Ac
[7.381,7.385,7.409]	Ph		
7.60-8.00 (m)	Py	7.80-8.00 (m)	
		[7.855,7.881,7.905,7.913]	Ph
8.60-8.90 (t)	h <sub>1</sub>	9.220	h <sub>1</sub>
9.40-9.60 (d)	h <sub>2</sub>		

**Fig. 3(a): Mode of bonding of protonated ligand****Fig. 3(a): Mode of bonding of deprotonated ligand**

assigned to the methyl fragments  $\text{CH}_3$ . The signal at  $\delta$  value of 2.446 could be attributed to  $\text{CH}_3$  of the ligand fragments and the signal at  $\delta$  value of 2.477 could be attributed to the Me fragment from the acetate ion,  $\text{CH}_3\text{COO}^-$  and S-H tautomer (see figure 2).

The clustered NMR signals centered around 7.20-7.5.0 and 7.60-8.00 ppm ranges may be assigned to the phenyl and pyridine hydrogens respectively. The pyridine hydrogens NMR peaks have been observed to appear at higher  $\delta$  values

**Table 4:  $^1\text{HNMR}$  of  $\text{H}_5$  ( $\text{D}_2\text{O}$ )  $\text{H}_5$  ( $\text{CDCl}_3$ )**

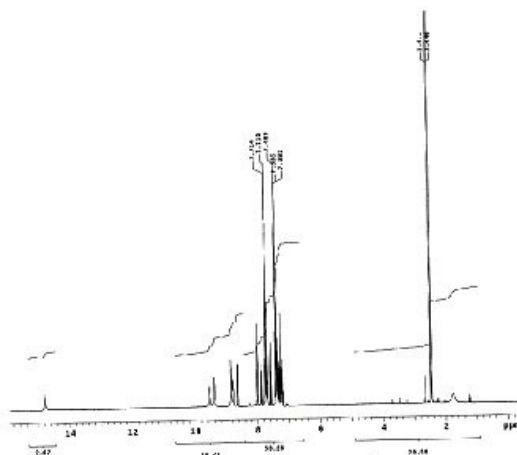
1.806	Me	1.30	Me
2.433	Ac	1.56	Ac
4.647	$\text{D}_2\text{O}$		
7.60			
7.90	Ph, Py		
8.10	$\text{h}_1$		

**Table 5: FT-IR of  $\text{H}_1$  and  $\text{H}_2$  ( $\text{Cm}^{-1}$ )**

$\text{H}_1=\text{HL}$	$\text{H}_1=\text{NiL}_2$	$\text{H}_3=\text{ZnL}$ (LH)Ac
3367 m <sup>*</sup>	N-H	3415 w
3333 m	N-H	3325 w
3065 m	CH-ar <sup>*</sup>	3020 w
3019 s <sup>*</sup>	CH-ar	
2986 vs	CH-al <sup>*</sup>	2928 m
2856 w	CH-al	856 w <sup>*</sup>
1698 s	C=N	1698 m
1596 vs		1592 m
1523 vs		1532 m
1466 vs	Ring	1496 m
1446 s	nodes	1484 m
1419 m		1411 s
1361 m		1318 m
1304 m		1415 m
1252 m		1318 w
1179 vs		1226 s, cluster
1152 m	C-H	1178 m
1125 m	bend	1149 m
1107 m		1098 w
		1075 w

\*ar=aromatic rings, Ph and Py, al-aliphatic  
m=medium, s=strong, w=weak

in the NMR spectra<sup>14</sup>. The broad triplet signal centered at 8.60-8.90 value range may be attributed to the  $\text{h}_1$  hydrogen. The splitting is likely due to the coupling with  $^{14}\text{N}$  ( $I = 1$ ,  $M_I = 1, 0, -1$ ) nitrogen. The doublet signal at  $\delta$  values of 9.40 and 9.60 ppm may be assigned to  $\text{h}_2$  hydrogen. Unlike the  $\text{h}_1$  hydrogen, the signal has not been resolved into



**Fig. 4: Proton NMR of  $\text{H}_1(\text{LH})$**

**Table 6: FT-IR of  $\text{H}_6$  and  $\text{H}_7$  ( $\text{cm}^{-1}$ )**

$\text{H}_6 = \text{ZnG}(\text{GH})\text{Ac}$	$\text{H}_7 = \text{CuGCl}$
3416 w	3400 w
3007 s	3013 w
2928 vs	2928 m
2855 s	2855 w
2100 w, br	
1697 m	
1620 m	1681 w
1601 s	1594 m
1525 m	1542 m
1498 s	1492 w
1448 m	1456 w
1404 vs	1425 m
1354 m	
1313 m	
1292 w	
1219 m, cluster	1226 vs, cluster
1181 m	
1153 w	
1131 m	1131 w
1100 w	
1050 m	

triplets. The proton NMR spectrum of  $ZnL(LH)Ac$  using DMSO as a solvent is also shown in Table 2. The signal at 2.503 ppm can be assigned to DMSO. The peak at 2.708 ppm is assigned to Me fragment of the ligands. The signal at 3.280 may be assigned to the Me fragment of the  $CH_3COO^-$  and S-H hydrogen arising from the tautomerism of the ligand in solution. A similar signal which may be assigned to S-H tautomerism (see figure 2) is also found in the proton NMR of 2-formylpyridine thiosemicarbazone (DMSO solvent) which has no methyl fragment. The multiplet peaks in the  $\delta$  range 6.90-7.40 ppm may be assigned to the Ph fragment while the one with an absorption in the  $\delta$  value range of 7.80-8.00 can be assigned to the pyridine ring (Py). The last peak at  $\delta$  value of 9.220 ppm may be assigned to the  $h_1$  hydrogen. The Zn(II) ion has a  $d^{10}$  configuration, and hence there are no unpaired electrons. In this case the complex will not show paramagnetic shift influence.

The proton NMR spectrum of  $CuLCl(H_4)$  complex in  $CDCl_3$  showed one broad large signal at  $\delta$  value of 1.56 ppm and a smaller peak at 1.30 ppm. These could be due to the Me fragments of the ligand stereoisomers arising from the presence C=N fragment in the molecule. The signals due to Ph and Py fragments were very much obscured due to paramagnetic shift influence of Cu(II) ion ( $d^9$ ) which has one unpaired electron. However, when  $D_2O$  was used as a solvent, weak broadened peaks were observed at  $\delta$  values of 1.806, 2.433, 4.647( $D_2O$ ), 7.60, 7.90, 8.10 and 8.50 (see Table 4). The first two peaks may be assigned to the Me stereoisomers, while the last four may be assigned to Ph and Py fragments. The N-H ( $h_1$ ) hydrogen signal was completely submerged. Thus, it appears that paramagnetic shift influence is also influenced by the nature of the solvent used. Finally, by comparing the  $^1H$ NMR of  $H_1(LH)$  and  $H_3[ZnL(LH)Ac]$  Figures 4 and 5 respectively, it is quite clear that the peaks in the zinc complex have a better resolution possibly due to ligand coordination despite the absence of paramagnetic shift influence in the complex.

#### Infrared spectra

The FT-IR spectra of  $H_1(LH)$ ,  $H_2(NiL_2)$ ,  $H_3[ZnL(LH)Ac]$ ,  $H_6[ZnG(GH)Ac]$ , and  $H_7(CuGCl)$  are

given in Tables 4 and 5 and representative spectra shown in Figs 6-8. The spectra show peaks mainly characteristic of the functional groups C-H (alkyl), C-H (aromatic), C=N, C=S, C-N and NH

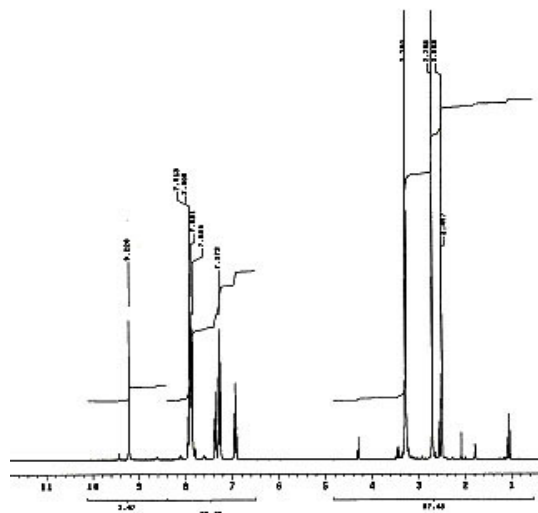
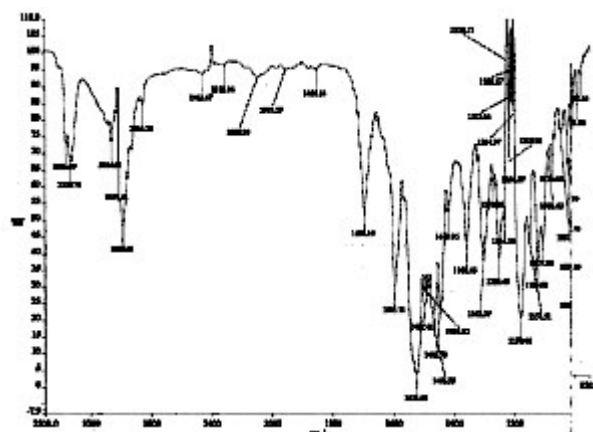


Fig. 5: Proton NMR of  $H_3[ZnL(Lh)Ac]$

functional groups. The peaks for  $LH(H_1)$  can tentatively be assigned<sup>14-15</sup> as follows, N-H (3367, 3333  $cm^{-1}$ ), C-H (3064, 3019, 2986, 2850), C=N (1698), benzene and pyridine rings (1596-1419), C-H (1466, 1446), and C-H bends (1179-1107). In  $NiL_2(H_2)$  complex, the loss of one of the N-H hydrogens gives rise to the decreased intensity and a small weak peak at 3415  $cm^{-1}$ . In the case of the zinc complex  $[ZnL(LH)Ac](H_3)$ , both  $L^-$  and LH have N-H hydrogens which exhibit weak peaks at 3417 and 3321  $cm^{-1}$ . The zinc(II) complex,  $[ZnG(GH)Ac](H_6)$  has a medium peak at 3416  $cm^{-1}$  due to N-H. Finally, the copper(II),  $CuGCl(H_7)$  complex shows a weak peak around 3400  $cm^{-1}$  due to the N-H fragment.

#### Bonding and possible molecular geometries of the complexes

Nearly all the 2-acetylpyridine thiosemicarbazones and 2-formylpyridine thiosemicarbazone complexes known so far and whose structures have been determined by x-ray analysis, the ligands have been found to exhibit a tridentate mode of coordination. This is shown in figures 3a and 3b. The geometry of  $NiL_2$  is probably a distorted octahedral as was recently found for the



A=N-H B=C-H aromatic C=C-H aliphatic D=C=N

Fig. 6: IR spectrum of H<sub>1</sub>(LH)

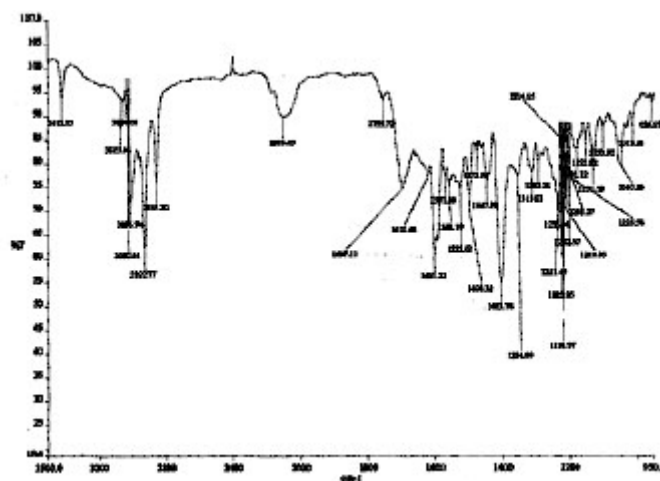


Fig. 7: IR spectrum of H<sub>6</sub> [ZnG(GH)Ac] complex

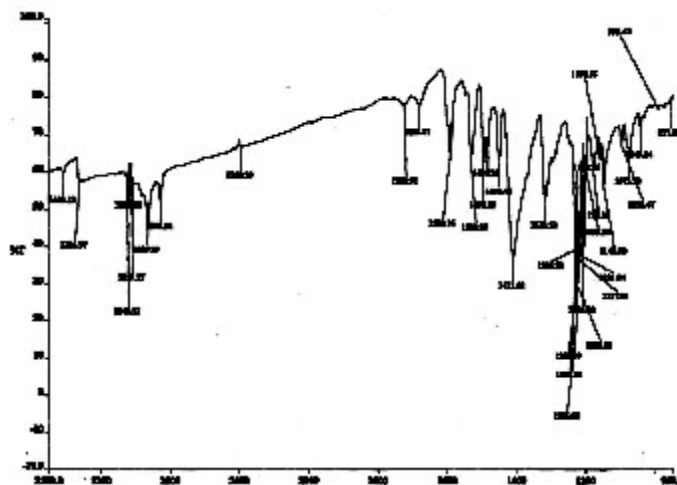


Fig. 8: IR spectrum of H<sub>2</sub> (NiL<sub>2</sub>) complex

cadmium complex<sup>16</sup>, CdL<sup>0</sup><sub>2</sub>. As already stated, the deprotonated ligand L<sup>-</sup> or G<sup>-</sup> normally bonds to a metal in a tridentate fashion<sup>17-18</sup>. In the case of ZnL(LH)Ac complex, both the L<sup>-</sup> and LH ligand may act as a tridentate while Ac<sup>-</sup> acting as a counter ion, or the complex may comprise of L<sup>-</sup> acting as a tridentate and LH as a bidentate and Ac<sup>-</sup> as a monodentate. The same argument applies for the possible geometry of ZnG(GH)Ac. In the case of the CuLCl or CuGCl complex, the plausible geometry adopted is probably a distorted tetrahedral one with L<sup>-</sup> or G<sup>-</sup> acting as a tridentate ligand and the fourth coordination site being occupied by Cl<sup>-</sup>. Further work is in progress to elucidate the geometries of the complexes by x-ray analysis and to determine whether or not the complexes possess biological activity.

## Conclusion

New metal complexes containing formylpyridine-4-phenyl-3-thiosemicarbazone(GH) and 2-acetylpyridine-4-phenyl-3-thiosemicarbazone (LH) ligands have been synthesized.

The complexes are CuLCl, ZnL(HL)Ac, NiL<sub>2</sub>, CuGCl and ZnG(GH)Ac. They were characterized by elemental analysis, FT-IR, Low Resolution Mass Spectrometry and <sup>1</sup>HNMR.

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