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Ni(II), Pd(II) and Pt(II) complexes with ligand containing thiosemicarbazone and semicarbazone moiety: synthesis, characterization and biological investigation

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Abstract: The synthesis of nickel(II), palladium(II) and platinum(II) complexes with thiosemicarbazone and semicarbazone of *p*-tolualdehyde are reported. All the new compounds were characterized by elemental analysis, molar conductance measurements, magnetic susceptibility measurements, mass, ^{1}H-NMR, IR and electronic spectral studies. Based on the molar conductance measurements in DMSO, the complexes may be formulated as $[Ni(L)_2Cl_2]$ and $[M(L)_2]Cl_2$ (where M = Pd(II) and Pt(II)) due to their non-electrolytic and 1:2 electrolytic nature, respectively. The spectral data are consistent with an octahedral geometry around Ni(II) and a square planar geometry for Pd(II) and Pt(II), in which the ligands act as bidentate chelating agents, coordinated through the nitrogen and sulphur/oxygen atoms. The ligands and their metal complexes were screened *in vitro* against fungal species *Alternaria alternata*, *Aspergillus niger* and *Fusarium odum*, using the food poison technique.

Keywords: thiosemicarbazone; semicarbazone; transition metal complexes; spectral studies; biological screening.

INTRODUCTION

Thiosemicarbazones have aroused considerable interest in the field of chemistry and biology due to their antibacterial, antifungal, antimalarial, antineoplastic and antiviral activities.[1–5] The biological activities of thiosemicarbazones are considered to be related to their ability to form chelates with metals. The biological activities of metal complexes differ from those of either the free ligands or metal ions and increased or decreased activities in relation to the non-complexed thiosemicarbazones have been reported for several transition metal complexes.[6] After the discovery of the chemotherapeutically active platinum complexes of thiosemicarbazide derivatives,[7] most of the thiosemicarbazone compounds showing biological activities were synthesized. Among the metal complexes of

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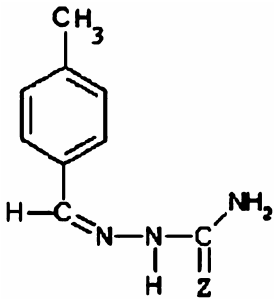
thiosemicarbazones, the palladium(II) chelates have been especially studied regarding their antitumour potentials.[8,9] Moreover, palladium(II) complexes with nitrogen-containing ligands are the subject of intensive biological evaluation in the search for less toxic and more selective anticancer therapies.[10,11] In addition to these, Ni(II) and Pt(II) complexes of thiosemicarbazones have been reported as compounds that present biological activity.[12,13a]

In view of the above discussion, in the present paper the synthesis, spectral and antifungal studies of the bidentate ligands (Fig. 1) with the Ni(II), Pd(II) and Pt(II) metal ions are reported.



Z =S, for L^1
Z =O, for L^2

Fig. 1. Structure of the ligands.

EXPERIMENTAL

All the employed chemicals were of analytical grade and procured from Sigma–Aldrich and Fluka. The metal salts were purchased from Merck and were used as received. All the employed solvents were of standard spectroscopic grade.

Synthesis of the ligands

Ligand L^1. A hot ethanolic solution (20 ml) of thiosemicarbazide (1.82 g, 0.020 mol) and an ethanolic solution (20 ml) of *p*-tolualdehyde (2.18g, 0.020 mol) were mixed slowly with constant stirring. This mixture was refluxed at 70–80 °C for 3 h. On cooling, a white coloured compound precipitated out, which was filtered, washed with cold EtOH and dried under vacuum over P_4O_{10}. Yield 62 %; m.p. 225 °C. Anal. Calcd. (%) for $C_9H_{11}N_3S$ (193): C, 55.95; H, 5.69; N, 21.76. Found: C, 56.01; H, 5.73; N, 22.81.

Ligand L^2. An aqueous solution (20 m.) of semicarbazide hydrochloride (2.22 g, 0.020 mol) and an ethanolic solution (20 ml) of *p*-tolualdehyde (2.18 g, 0.020 mol) were mixed in the presence of sodium acetate (2.72 g, 0.020 mol). The reaction mixture was stirred vigorously for 1 h. On cooling, a white coloured compound precipitated out, which was filtered, washed with cold EtOH and dried under vacuum over P_4O_{10}. Yield 65 %; m.p. 205 °C. Anal. Calcd. (%) for $C_9H_{11}N_3O$ (177): C, 61.02; H, 6.21; N, 23.72. Found C, 61.11; H, 6.18; N, 23.66.

Synthesis of complexes

A hot ethanolic solution (20 ml) of the required metal salts (0.010 mol) was mixed with a hot ethanolic solution (20 ml) of the required ligand (0.010 mol). This reaction mixture was continuously stirred and refluxed for 4 h at 75 °C. On cooling, a coloured complex separated out, which was filtered, washed with cold ethanol and dried under vacuum over P_4O_{10}.

Physical measurements

Elemental analysis was performed on a Carlo-Erba EA 1106 elemental analyzer and the nitrogen content of the complexes was determined using the Kjeldahl method.[13b] The molar conductivity was measured on a Elico CM82T conductivity bridge. The magnetic moment was measured at room temperature on a Gouy balance using $CuSO_4 \cdot 5H_2O$ as the callibrant. Electronic impact mass spectra were recorded on a JEOL JMS-DX-303 mass spectrometer. The ^{1}H-NMR spectra of the ligands were recorded at room temperature on a Brucker Advance DPX-300 spectrometer using DMSO-d_6 as the solvent. The IR spectra were recorded as KBr pellets on a FTIR spectrum BX-II spectrometer. The electronic spectra were recorded in DMSO on a Shimadzu UV mini-1240 spectrophotometer.

Antifungal screening

The *in vitro* biological screening effects of the investigated compounds were tested against the fungal species *Alternaria alternata*, *Aspergillus niger* and *Fusarium odum* by the food poison method[14] using a potato dextrose agar medium. The stock solutions of compounds were prepared by dissolving the compounds in DMSO. Chlorothalonil was used as a commercial fungicide and DMSO served as the control. Appropriate quantities of the compounds in DMSO were added to obtain a concentration of 250 and 500 ppm of the compound in the medium. The medium was poured into a set of two Petri plates under aseptic conditions in a laminar flow hood. After solidification of the medium in the plates, a mycelial disc of 0.5 cm in diameter, cut from the periphery of a 7-day old culture, was aseptically inoculated upside down in the centre of the Petri plates. These treated Petri plates were incubated at 26±1 °C until fungal growth in the control Petri plates was almost complete.

The mycelial growth of the fungi (mm) in each Petri plates was measured diametrically and the growth inhibition (I, %) was calculated using the formula:

$$I = \frac{d_C - d_T}{d_C} \times 100$$

where d_C and d_T are the diameters of the fungus colony in the control and test plates, respectively.

RESULTS AND DISCUSSION

Based on the elemental analyses, the complexes were assigned the compositions shown in Table I. The molar conductance data of the Ni(II) complexes in DMSO lay in the range 8.0–11 Ω^{-1} cm^2 mol^{-1}, indicating their non-electrolytic nature. However, the Pd(II) and Pt(II) complexes are 1:2 electrolytes with conductance values of 208–217 Ω^{-1} cm^2 mol^{-1}. Thus, these complexes may be formulated as $[Ni(L)_2Cl_2]$ and $[M(L)_2]Cl_2$ (where L = L^1 and L^2, M = Pd(II) and Pt(II)).

The electron-impact mass spectra of the ligands L^1 and L^2 are shown in Figs. 2 and 3, respectively.

The ^{1}H-NMR spectra (Table II) of the free ligands show three singlets at δ 3.41–3.45, 11.90–11.95 and 8.02–8.08 ppm due to the $-NH_2$ proton, −NH proton and azomethine proton (−CH=N−), respectively.

The IR spectra (KBr, cm^{-1}) of the free ligands display two sharp bands at *ca.* 3420 and 3350 cm^{-1}, assignable to the asymmetric and symmetric NH_2 group,

respectively; 1606, 1597 ν(C=N), 765 ν(C=S), 1680 ν(C=O), 440–452 ν(M−N), 304–312 ν(M−S) and 408–418 ν(M−O). The important IR bands are given in Table II.

TABLE I. Molar conductance and elemental analysis data of the complexes

Complex	Molar conductance Ω^{-1} cm^2 mol^{-1}	Colour	M.p. °C	Yield %	Elemental analysis Found (Calcd.), %			
					M	C	H	N
$[Ni(L^1)_2Cl_2]$	8	Green	250	68	11.39	41.53	4.20	16.31
$NiC_{18}H_{22}N_6S_2Cl_2$					(11.43)	(41.86)	(4.26)	(16.28)
$[Ni(L^2)_2Cl_2]$	11	Green	262	65	12.28	44.56	4.49	17.40
$NiC_{18}H_{22}N_6O_2Cl_2$					(12.19)	(44.62)	(4.55)	(17.36)
$[Pd(L^1)_2]Cl_2$	212	Brown	270	60	18.78	38.30	3.88	14.88
$PdC_{18}H_{22}N_6S_2Cl_2$					(18.82)	(38.36)	(3.91)	(14.92)
$[Pd(L^2)_2]Cl_2$	208	Grey	257	62	20.02	40.62	4.09	15.89
$PdC_{18}H_{22}N_6O_2Cl_2$					(19.96)	(40.68)	(4.14)	(15.81)
$[Pt(L^1)_2]Cl_2$	214	Yellow	280	60	29.88	33.20	3.42	12.82
$PtC_{18}H_{22}N_6S_2Cl_2$					(29.91)	(33.13)	(3.37)	(12.88)
$[Pt(L^2)_2]Cl_2$	217	Yellow	272	63	31.52	34.79	3.62	13.59
$PtC_{18}H_{22}N_6O_2Cl_2$					(31.45)	(34.84)	(3.55)	(13.55)

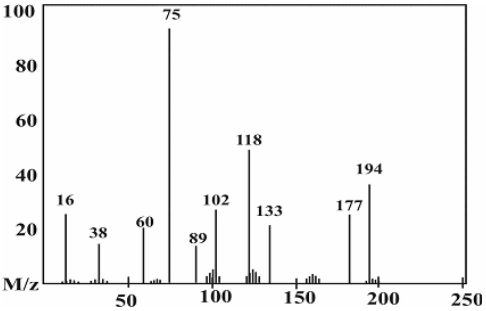


Fig. 2. Electron-impact mass spectrum of ligand L^1.

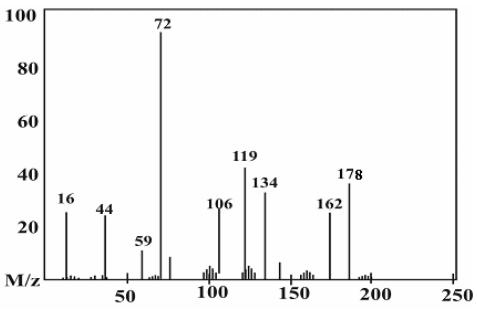


Fig. 3. Electron-impact mass spectrum of ligand L^2.

TABLE II. ^{1}H-NMR and IR spectral data of the ligands and their complexes

Compound	^{1}H-NMR (δ, ppm)			IR (cm^{-1})					
	–NH_2	–NH	HC=N	ν(C=N)	ν(C=S)	ν(C=O)	ν(M–S)	ν(M–O)	ν(M–N)
L^1	3.42	11.92	8.06	1606	765	–	–	–	–
L^2	3.45	11.90	8.02	1597	–	1680	–	–	–
$[Ni(L^1)_2Cl_2]$	3.43	11.93	8.20	1620	752	–	308	411	452
$[Ni(L^2)_2Cl_2]$	3.41	11.95	8.28	1609	–	1665	305	408	445
$[Pd(L^1)_2]Cl_2$	3.44	11.90	8.32	1625	740	–	312	410	448
$[Pd(L^2)_2]Cl_2$	3.42	11.94	8.26	1612	–	1652	310	413	440
$[Pt(L^1)_2]Cl_2$	3.43	11.90	8.18	1622	745	–	304	415	443
$[Pt(L^2)_2]Cl_2$	3.44	11.91	8.30	1615	–	1662	307	418	450

The magnetic moment of Ni(II) complexes lies in the range 2.95–2.98 μ_B, corresponding to two unpaired electrons. These values are in tune with a high spin configuration and show the presence of an octahedral environment around the Ni(II) ion. However, all the Pd(II) and Pt(II) complexes (Table III) show diamagnetic behaviour.

TABLE III. Magnetic moments and electronic spectral data of the complexes

Complexes	μ_{eff} / μ_B	λ_{max} / nm	Assignments
$[Ni(L^1)_2Cl_2]$	2.95	982	$^3A_{2g}$ (F) → $^3T_{2g}$(F) (ν_1)
		697	$^3A_{2g}$ (F) → $^3T_{1g}$(F) (ν_2)
		395	$^3A_{2g}$ (F) → $^3T_{1g}$(P) (ν_3)
$[Ni(L^2)_2Cl_2]$	2.98	973	$^3A_{2g}$ (F) → $^3T_{2g}$(F) (ν_1)
		702	$^3A_{2g}$ (F) → $^3T_{1g}$(F) (ν_2)
		405	$^3A_{2g}$ (F) → $^3T_{1g}$(P) (ν_3)
$[Pd(L^1)_2]Cl_2$	Diamagnetic	480	$^1A_{1g}$→ $^1A_{2g}$(ν_1)
		452	$^1A_{1g}$→ $^1B_{1g}$(ν_2)
		390	$^1A_{1g}$→ ^1E_g(ν_3)
$[Pd(L^2)_2]Cl_2$	Diamagnetic	472	$^1A_{1g}$→ $^1A_{2g}$(ν_1)
		443	$^1A_{1g}$→ $^1B_{1g}$(ν_2)
		397	$^1A_{1g}$→ ^1E_g(ν_3)
$[Pt(L^1)_2]Cl_2$	Diamagnetic	530	$^1A_{1g}$→ $^1A_{2g}$(ν_1)
		416	$^1A_{1g}$→ $^1B_{1g}$(ν_2)
		362	$^1A_{1g}$→ ^1E_g(ν_3)
$[Pt(L^2)_2]Cl_2$	Diamagnetic	520	$^1A_{1g}$→ $^1A_{2g}$(ν_1)
		410	$^1A_{1g}$→ $^1B_{1g}$(ν_2)
		345	$^1A_{1g}$→ ^1E_g(ν_3)

The electronic spectra of the Ni(II) complexes display three absorption bands in the ranges of 973–982 nm, 697–702 nm and 395–405 nm. These bands may be assigned to three spin-allowed transitions: $^3A_{2g}$ (F) → $^3T_{2g}$ (F) (ν_1), $^3A_{2g}$ (F) → → $^3T_{1g}$ (F) (ν_2) and $^3A_{2g}$ (F) → $^3T_{1g}$ (P) (ν_3), respectively. The positions of these bands indicate that the complexes have an octahedral environment.[15–18]

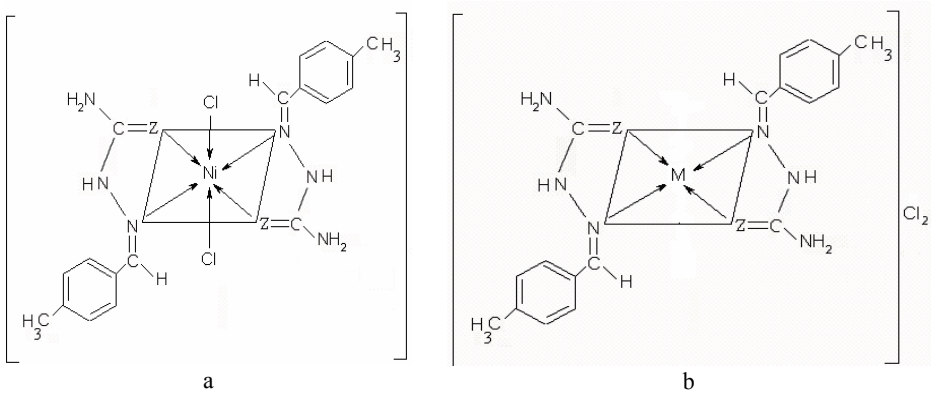


Fig. 4. Suggested structure of the complexes (M = Pd(II) and Pt(II); Z = S/O).

The electronic spectra of the Pd(II) and Pt(II) complexes show three d–d spin-allowed transitions. These correspond to the transitions from the three lower lying d levels to the empty $d_{x^2-y^2}$ orbital. The ground state is $^1A_{1g}$. The three d–d transitions were observed in the regions 472–530, 410–452 and 345–397 nm. These bands are attributed to $^1A_{1g} \rightarrow {}^1A_{2g}$ (ν_1), $^1A_{1g} \rightarrow {}^1B_{1g}$ (ν_2) and $^1A_{1g} \rightarrow {}^1E_g$ (ν_3) transitions, respectively. The electronic spectra of these complexes indicate square planar geometry around the Pd(II) and Pt(II) ion.[19,20]

Based on the above spectral studies, the structures shown in Fig. 4 may be suggested for the complexes.

The results of fungicidal screening (Fig. 5) show that the metal complexes have a higher antimicrobial activity than the free ligands. The increased activity of the metal chelates can be explained based on the chelation theory.[21] On chelation, the polarity of the metal ion is reduced largely due to the overlap of the ligand orbital and the partial sharing of the positive charge of the metal ion with the donor groups. Furthermore, it increases the delocalization of the π-electrons over the whole chelating ring and enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms. There are other factors which also increase the activity, such as solubility, conductivity and bond length between the metal and the ligand.

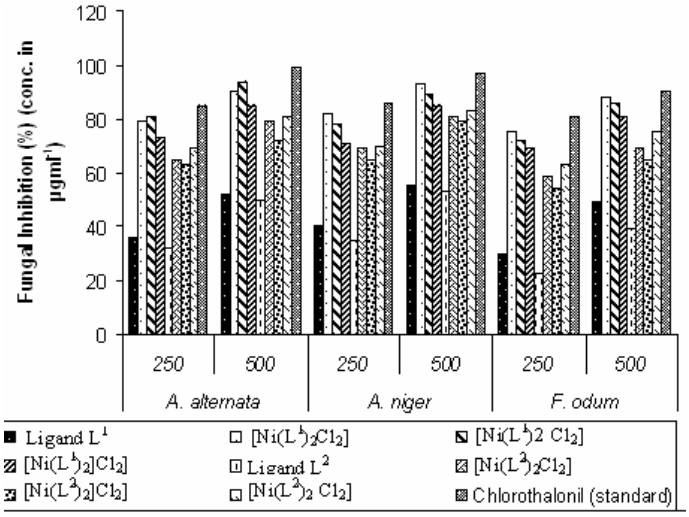


Fig. 5. Biological activity of the compounds.

CONCLUSIONS

The present study revealed octahedral geometry around the Ni(II) and square planar geometry around the Pd(II) and Pt(II) complexes, in which the ligands act as bidentate chelating agents coordinating through the nitrogen and sulphur/ /oxygen atoms.

The determined antimicrobial activities indicate that the metal chelates show a greater inhibitory effect than the parent ligands. It is also proposed that concentration plays a vital role in increasing the degree of inhibition; as the concentration increases, the activity increases. It is also interesting to note that the sulphur bonded ligands and their complexes are more active than the oxygen bonded ligands and their complexes.

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И З В О Д

Ni(II), Pd(II) И Pt(II) КОМПЛЕКСИ СА ЛИГАНДИМА КОЈИ САДРЖЕ ТИОСЕМИКАРБАЗОНСКУ И КАРБАЗОНСКУ ГРУПУ: СИНТЕЗА, КАРАКТЕРИЗАЦИЈА И БИОЛОШКА ИСТРАЖИВАЊА

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Приказана је синтеза никал(II), паладијум(II) и платина(II) комплекса са тиосемикарбазоном и семикарбазоном *p*-толуалдехида. Нова једињења су окарактерисана елементалном анализом, мерењем молске проводљивости и магнетне сусцептибилности, као и ^{1}H-NMR, IR и електронском спектроскопијом. На основу молске проводљивости у DMSO, могуће формуле комплекса су $[Ni(L)_2Cl_2]$ и $[M(L)_2]Cl_2$ (M = Pd(II) and Pt(II)) због њихове неелектролитске и 1:2 електролитске природе, респективно. Спектрални подаци су у складу са октаедарском геометријом око Ni (II) и квадратно-планарном геометријом око Pd(II) and Pt(II), у којима су лиганди бидентатни хелатни агенси, везани преко азотовог и сумпоровог/кисеониковог атома. Биолошка активност лиганада и њихових металних комплекса испитивана је *in vitro* према гљивичним врстама *Alternaria alternata*, *Aspergillus niger* и *Fusarium odum* помоћу технике тровања храном.

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