



Physico-Chemical and Biological Analysis of N-4-Disubstituted Thiosemicarbazone Ligand and its Transition Metal Complexes

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Available online at: www.isca.in, www.isca.me

Received 30th August 2015, revised 24th September 2015, accepted 12th November 2015

Abstract

The Cr(III), Mn(II), Fe(II) and Ni(II) transition metal complexes of novel (E)-1-(2-hydroxybenzylidene)-4,4-diethylthiosemicarbazide have been prepared and characterized by micro analysis (elemental), spectral (FTIR, ¹H-NMR), molar conductivity and X-ray diffraction studies. A molar conductivity measurement shows that, Cr (III) and Fe (II) complex of ligand (HBDT) are electrolytic in nature. FTIR studies suggested the attachment of central metal ion to ligand portion through the imine linkage-nitrogen, thioketonic sulphur and phenolic oxygen. According to spectral studies an octahedral geometry may be assigned for all four complexes. The ligand (HBDT) and its transition metal complexes have also been tested for their antibacterial and antifungal activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Aspergillus niger* and *Fusarium oxysporium* species. All complexes and ligand showed considerable activity compared with standard drug ciprofloxacin.

Keywords: N-4-Disubstituted thiosemicarbazone, Biological activity, XRD structure.

Introduction

Coordination compounds such as metal based drugs have recently become a very active area of research. The application of inorganic chemistry to medicine is a rapidly developing area and novel therapeutic and diagnostic metal complexes which are of current clinical use¹⁻⁴. The synthesis and study of stable metal complexes containing Schiff bases with ONS / NNS-donor atoms is interesting field of research in inorganic and bioinorganic chemistry⁵⁻¹⁰. Thiosemicarbazones and their metal complexes showed potent cytotoxic activities against human tumor cells in culture¹¹⁻¹³. Transition metal complexes of (E)-1-(2-hydroxybenzylidene)-4,4-diethylthiosemicarbazide obtained from the condensation reaction of N-4-Diethyl-3-thiosemicarbazide with 2-hydroxybenzaldehyde. The ligand and its metal complexes were tested for antibacterial and antifungal activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Aspergillus niger* and *Fusarium oxysporium*. Thiosemicarbazones are regarded as versatile ligands due to their potential to form stable and biologically active complexes¹⁴⁻¹⁸. Thiosemicarbazones are acts as chelating ligands with metal ion bonding through sulphur and hydrazine nitrogen atom. Certain thiosemicarbazones are comparatively specific inhibitors of ribonucleotide reductase, which is an important metabolic target for the development of chemotherapeutic agents against tumor cells¹⁹. Ni (II) complexes of thiosemicarbazone ligands are found to act as sensor²⁰. Thiosemicarbazones are also used for spectrophotometric analysis of metal ion²¹⁻²². Therefore in the present paper we are describing the synthesis of N-4 disubstituted thiosemicarbazone and their four transition metal complexes.

Materials and Methods

Experimental: (E)-1-(2-hydroxybenzylidene)-4,4-diethylthiosemicarbazide was prepared by adopting and modifying a reported procedure of scovil²³. All chemicals used were of analytical grade and solvents were dried and distilled before use according to standard procedure (vogel, 1989). 2-hydroxybenzaldehyde and all metal salts were purchased from Aldrich and were used as received.

1.1- Synthesis of Schiff base ligand (E)-1-(2-hydroxybenzylidene)-4,4-diethylthiosemicarbazide (HBDT): Schiff base ligand HBDT was prepared by mixing together equimolar amount of ethanolic solution of 2-hydroxybenzaldehyde (0.01M, 1.22 gm) and ethanolic solution of N-4-Diethyl-3-thiosemicarbazide (0.01M, 1.47 gm). The resulting mixture refluxed for 1.5 hours and allowed cooling at room temperature. This reaction mixture was chilled (overnight). Yellow colored shiny crystals were separate out which was filtered, washed with alcohol and ether. It was recrystallised from dichloromethane-ethanol mixture (1:2proportion) and subsequently dried over CaCl₂ in vacuum desiccator. The purity of ligand was checked by TLC, melting point and elemental analysis. The data are given in (Table-1). The ligand was insoluble in alcohol, slightly soluble in acetone, DCM and completely soluble in DMF and DMSO. Yield of ligand: 86% M.P-148^oC. Proposed molecular formula: C₁₂H₁₇N₃OS (Mol.Wt. 251.35). The reaction is a type of condensation reaction which takesplace in between salicylaldehyde and N-4-Diethyl-3-thiosemicarbazide with elimination of water molecule which form thiosemicarbazide.

1.2-Synthesis of Metal Complexes: Hot methanolic solution (1mmol) of metal salt was mixed with hot methanolic solution of ligand (2mmol). The reaction mixture was then refluxed for 2-3 hours. The solid precipitate formed was allowed to keep overnight at room temperature then it was filtered, washed and dried in vacuum over anhydrous calcium chloride in desiccators. The complexes obtained are microcrystalline solids which are stable in air and decompose above 300°C. They are insoluble in organic solvents such as acetone and chloroform but soluble in DMF and DMSO. (Yield-75-80%). The relevant data included in the (Table-1).

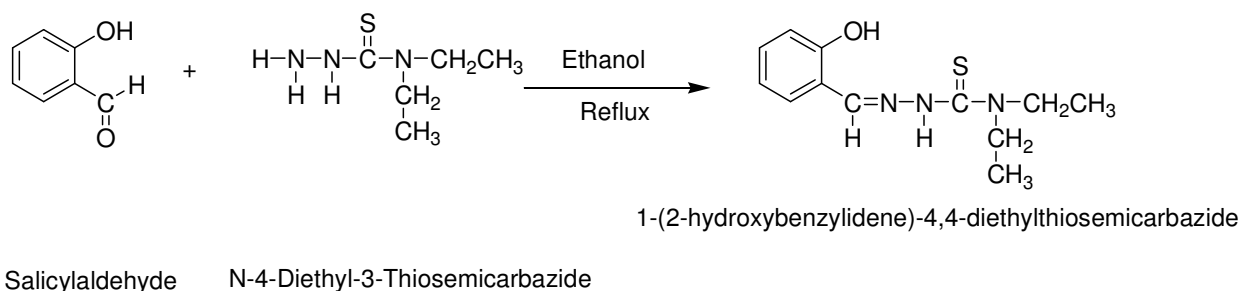
Results and Discussion

Microanalytical data of the ligand and its complexes were given in table-1

¹H-NMR Spectra of Ligand: The ¹H-NMR spectrum of ligand was recorded in DMSO. The spectra of ligand HBDT shows signals at 11.52δ due to phenolic -OH group 10.74δ are of NH group and 8.34δ value is due to H-C=N proton. Aromatic protons show a multiplet at 6.8-7.50δ (m, Ar-H). These assignments are in a concord with the values already reported²⁴.

FTIR Studies: The experimental assignments of the IR spectral

bands to confirm the structural identity of the ligand and its metal complexes are given in Table-2. In order to study the binding mode of ligand to metal in complexes IR spectrum of ligand was compared with IR spectrum of metal complexes. In the solid state the ligand (HBDT) remains in the thione form as ν(S-H) band expected to be at 2570 cm⁻¹ is absent. A sharp ν(N-H) band is observed at 3056cm⁻¹, 2976cm⁻¹ for O-N-S donor ligand. A sharp ν(C=S) band and a low intensity δ(C=S) band are observed in ligand at 1347cm⁻¹, 762cm⁻¹ while in case of metal complexes it is in the range of 1270-1380cm⁻¹ and 700-780cm⁻¹. Ligand (HBDT) shows ν(OH) band at 3220cm⁻¹ due to intramolecular hydrogen bonding and free δ(OH) at 1418cm⁻¹. Band observed at 3400-3460cm⁻¹ in complexes indicating presence of coordinated or lattice water²⁵. Other characteristic absorption bands at 1538cm⁻¹, 1620cm⁻¹ and 1120cm⁻¹ region due to C=N, N-N and C-O Vibration respectively. While in metal complexes of ligand (HBDT) having bands in the range of 1520-1600cm⁻¹ predicts that azomethine nitrogen takes part in coordination²⁶. Shifting of ν(C-O) band at 1120cm⁻¹ to 1200cm⁻¹ confirms the presence of ν(M-O) band also the bands in the range of 530-570cm⁻¹ and 430-490cm⁻¹ shows ν(M-N) and ν(M-S) bond.



Scheme-1
Synthesis of Ligand (HBDT)

Table-1
Elemental analysis of ligand and its metal complexes-

Ligand/Metal Complex	Mol. Wt..	Molar Cond. (Ω ⁻¹ cm ² mol ⁻¹)	Color	Yield	Elemental Analysis (%), Found (Calculated)				
					C	H	N	S	M
HBDT	251.3	—	Yellow	86%	57.28 (57.3)	6.80 (6.82)	15.95 (16.7)	12.71 (12.76)	-
[Cr(C ₂₄ H ₃₄ N ₆ O ₂ S ₂)]	554.6	127	Brown	75%	51.80 (51.9)	6.13 (6.12)	15.12 (15.1)	11.50 (11.53)	9.77 (9.53)
[Mn(C ₂₄ H ₃₄ N ₆ O ₂ S ₂)]	557.6	45	Brown	76%	51.50 (51.6)	5.99 (6.09)	15.02 (15.0)	11.46 (11.47)	10.29 (10.0)
[Fe(C ₂₄ H ₃₄ N ₆ O ₂ S ₂)]	558.5	103	Dark Brown	76%	51.60 (51.5)	6.01 (6.08)	15.0 (15.0)	11.30 (11.45)	10.41 (10.1)
[Ni(C ₂₄ H ₃₄ N ₆ O ₂ S ₂)]	561.3	20	Yellow	80%	51.21 (51.3)	6.00 (6.05)	15.10 (14.9)	11.70 (11.40)	10.59 (10.5)

Table-2
FTIR spectral data of the ligand and its metal complexes (in cm⁻¹)

Ligand / Metal Complexes	$\nu(\text{C-O})$	$\nu(\text{O-H})$	$\delta(\text{O-H})$	$\nu(\text{N-H})$	$\nu(\text{C=N})$	$\nu(\text{N-N})$	$\nu\delta(\text{C=S})$
HBDT	1186	3220	1418	2976	1538	1620	1276, 753
[Cr(C ₂₄ H ₃₄ N ₆ O ₂ S ₂)]	1150	3409	1437	2983	1581	1602	1347, 762
[Mn(C ₂₄ H ₃₄ N ₆ O ₂ S ₂)]	1152	—	1473	2976	1554	1596	1358, 762
[Fe(C ₂₄ H ₃₄ N ₆ O ₂ S ₂)]	1145	3410	1433	2981	1570	1599	1355, 757
[Ni(C ₂₄ H ₃₄ N ₆ O ₂ S ₂)]	1151	3443	1441	2978	1527	1580	1275, 754

X-Ray Diffraction Study: X-ray diffraction was performed to obtain further assertion related to the structure of the complexes. The diffractogram obtained for the Cr (III) complex were given in Figure-2 and the xrd patterns betokened crystalline nature for the Cr (III) complex. The X-ray diffractogram of complexes were recorded in the range of 0 to 80° 2 θ value and wavelength of 1.540598Å. The major reflexes were measured and related 'd' values were calculated using Bragg's equation. The independent indexing of major reflexes were carried out by using least square method. All the reflections have been indexed for h, k, l values using reported methods in the literature²⁷. The 2 θ value of each peak, relative intensity and diffractogram associated data revealed the interplanar spacing and lattice constants a, b and c for each unit cell parameter as shown in Table-3. Cr (III) complex having triclinic crystal system, Mn(II) and Fe(II) complex having monoclinic crystal system while Ni(II) complex orthorhombic crystal system. Unit cell volume for each system is determined by respective equation.

Antibacterial and antifungal screening: Thiosemicarbazone ligand and its metal complexes having a good variety of biological activity^{28,29}. Complexes of thiosemicarbazone ligand are important because of their antibacterial, antifungal³⁰, antimalarial, antiviral and antitumor³¹ activities. The antibacterial and antifungal activity of the newly prepared ligand (HBDT) and their transition metal complexes were carried out successively. Results of these studies are given in Table-4 the studies were carried out on *Aspergillus niger*, *Fusarium oxasporum* species and *Staphylococcus aureus*, *Bacillus subtilis* species using paper disc method on appropriate medium³². The susceptibilities of certain strains of bacteria and fungus to the ligand (HBDT) and its transition metal complexes were determined by measuring the size of bacteriostatic diameter. The results show that the ligand as well as its metal complexes is highly active against the bacteria and fungi and having high antimicrobial and antifungal activity which is comparatively almost equal to the activity of standard ciprofloxacin.

Table-3
Lattice constant, Unit cell volume, Crystal system of metal complexes

Unit cell of Compound	Lattice constant			Crystal System	hkl	Unit cell Volume	Inter axial angle	2 θ	D value (Å)
	a (Å)	b (Å)	c (Å)			V (Å ³)			
Cr(III)	8.23	10.9	15.3	Triclinic	0, -1, 2	110.66	$\alpha \neq \beta \neq \gamma \neq 90$	11.9	7.41
Mn(II)	11.0	14.0	15.8	Monoclinic	-1, 0, 1	214.87	$\alpha = \beta = 90 \neq \gamma$	8.20	10.77
Fe(II)	11.8	13.0	7.02	Monoclinic	-1, 1, 0	106.58	$\alpha = \beta = 90 \neq \gamma$	10.1	8.68
Ni(II)	14.0	18.5	15.4	Orthorhombic	0, 0, 2	561.49	$\alpha = \beta = \gamma = 90$	8.19	10.78

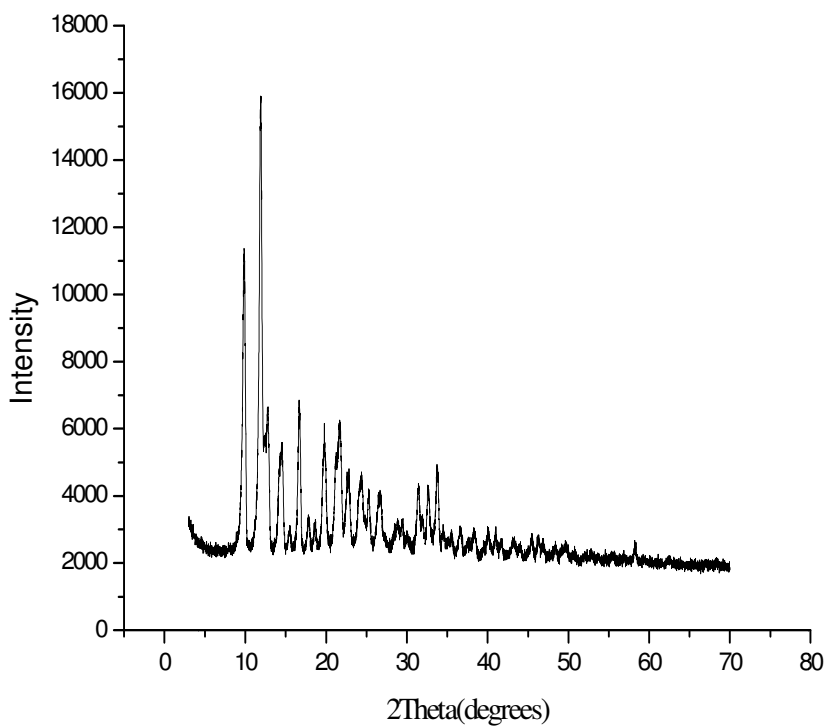


Figure-1
 XRD spectrum of Cr (III) complex [X-ray diffraction plot]

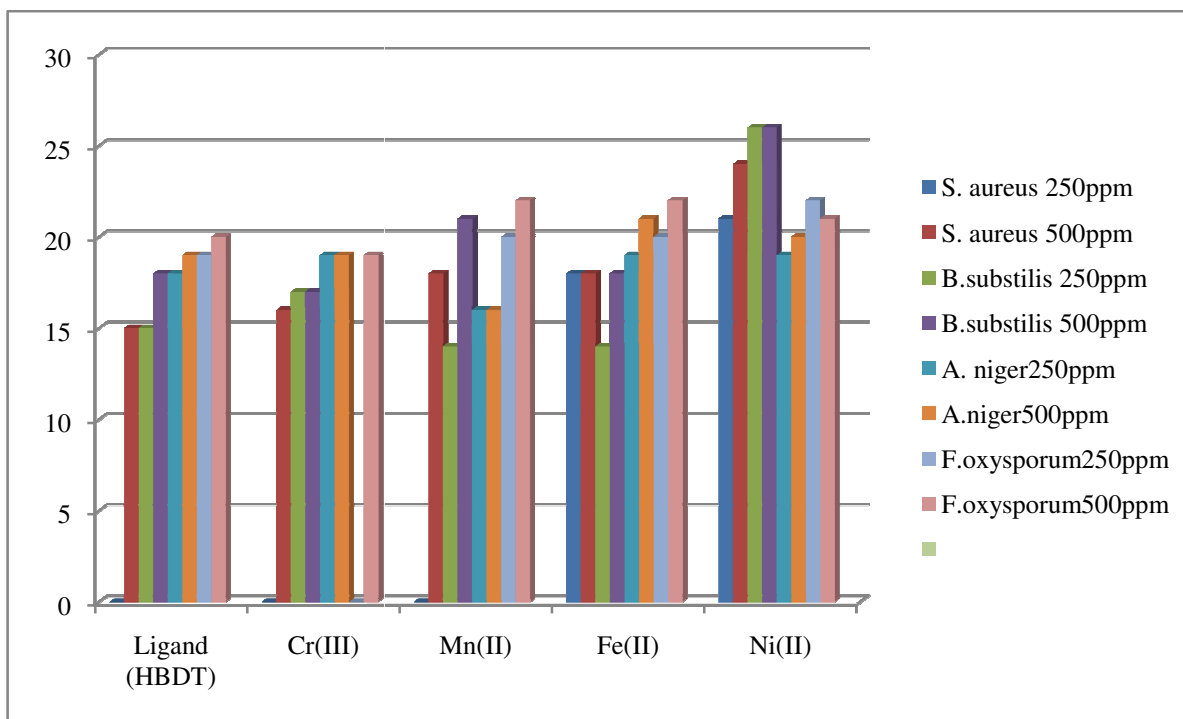


Figure-2
 Comparative study of antimicrobial and antifungal activity of ligand and its metal complexes

Table-4

Antibacterial and Antifungal activity of ligand and their transition metal complexes. [Diameter of inhibition zone in (mm)]

Ligand / Metal Complex	Antibacterial activity				Antifungal activity			
	<i>Staphylococcus Aureus</i>		<i>Bacillus subtilis</i>		<i>Aspergillus Niger</i>		<i>Fusarium Oxysporium</i>	
	250 ppm	500 Ppm	250 ppm	500 ppm	250 ppm	500 Ppm	250 ppm	500 ppm
Ligand (HBDT)	00	15	15	18	18	19	19	20
[Cr(C ₃₂ H ₃₄ N ₆ O ₂ S ₂)]	00	16	17	17	19	19	00	19
[Mn(C ₃₂ H ₃₄ N ₆ O ₂ S ₂)]	00	18	14	21	16	16	20	22
[Fe(C ₃₂ H ₃₄ N ₆ O ₂ S ₂)]	18	18	14	18	19	21	20	22
[Ni(C ₃₂ H ₃₄ N ₆ O ₂ S ₂)]	21	24	26	26	19	20	32	35
Ciprofloxacin	34	36	43	45	22	24	31	38

Conclusion

Synthesis of the Schiff base ligand (E)-1-(2-hydroxybenzylidene)-4,4-diethylthiosemicarbazide (HBDT) and their transition metal complexes is carried out. The X-ray diffraction studies shows Cr (III) complex having triclinic crystal system with Z =1, Ni (II) having orthorhombic crystal system with Z =2 and Fe (II), Mn(II) complex having monoclinic crystal system with Z=1 and Z =2 respectively. The analytical and spectral data concluded that the synthesized complexes are stable at room temperature. Ligand (HBDT) and its metal complexes also shows good antimicrobial and antifungal activity In accordance with the foregoing discussions, the high melting points and insolubility in common organic solvents, also reveals that the three common coordinate sites are phenolic oxygen, azomethine nitrogen and thiol sulphur. It is observed that Cr (III), Fe (II) and Ni (II) complexes of ligand (HBDT) contains two coordinated water molecules and possesses octahedral geometry.

Acknowledgements

The authors are grateful to the Head, department of chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad for providing laboratory facility and financial assistance bys UGC (SAP), DIST-FIST.

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