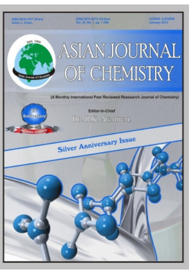
Asian Journal of Chemistry; Vol. 25, No. 4 (2013), 2083-2086

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.13323



Synthesis, Characterization and Biological Activity of Schiff Base Complexes of Sulfa Drug with Transition Metals

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(*Received*: 23 December 2011; *Accepted*: 15 October 2012) AJC-12285

The Schiff base has been prepared by refluxing sulfa pyridine with 2-hydroxynaphthaldehyde in ethanolic media and then complexed with Co(II), Ni(II), Cu(II), Zn(II) and Mn(II) metal ions. The synthesized ligand and complexes were characterized by elemental analysis, molar conductances, magnetic moments, IR, ^{1}H NMR and electronic spectral data. The spectral data of the complexes have revealed bidentate complexing nature of the Schiff base ligand through phenolic oxygen and azomethine nitrogen atoms. The antibacterial and antifungal activity of the Schiff base and its complexes have also been screened. All the metal complexes possess significant to moderate activity and the metal complexes exhibit more activity against various species compared to the Schiff base.

Key Words: Sulfa drug, Schiff base, Metal complexes, Antibacterial, Antifungal.

INTRODUCTION

The sulfa drugs, first effective chemotherapeutic agents are widely used for the cure of bacterial infection in humans. Sulphanilamide is found to be active against several types of bacteria and hence used in the treatment of diseases like pneumonia, gonorrhoea, meningitis, tonsillitis, sinus infections[1] *etc.*

Nowadays Schiff bases are attracting the biochemists as they are known to be biologically important and are used to design medicinal compounds[2]. The azomethine (>C=N-) linkage in Schiff bases play an important role in elucidating the mechanism of transamination and resamination reactions in biological systems[3,4]. The biomedicinal properties of free organic molecules depend upon chelation with suitable metal ions leading to the implementation of metal complexes for several biomedical applications as therapeutically active, possessing analgesic[5], antipyretic[6], antiinflammatory[7], cytotoxic[8], antiviral[9], antitumorous[10] and antitubercular[11] activity besides their applications as antimicrobial agents[12]. The direct use of transition metal salts, as antimicrobial agents cannot be recommended as they are toxic to both the microbes and the host animals. Metal ions play a catalytic role in reactions of Schiff bases. Aromatic Schiff bases and their complexes catalyze reactions of the type oxygenation[13], hydrolysis[14], electroreduction[15] and decomposition[16]. Th(IV) and UO_2(VI) complexes of Schiff base obtained from 2-nitro benzaldehyde and 2-amino pyridine show toxic effects to bacterial and fungal genus[17]. Mn(II), Ni(II), Cu(II) and Zn(II) complexes of the chlorobenzaldehyde Schiff base of S-benzyl esters of the dithiocarbazoic acid are biologically active[18]. Ni(II) and Co(II) complexes of 2-hydroxynaphthylidene-2-aminophenol inhibit the growth of bacterial strains of *Escherichia coli* and *Bacillus substills*[19]. Salicyliden and 2-hydroxynaphthylideneamines have been the subject of particular interest because some of their complexes are found in nature and biological activities have been recorded for the synthesized ones[20]. In view of the importance of coordination compounds in medicinal chemistry[21], the present paper reports the synthesis, characterisation and biological studies on Co(II), Ni(II), Cu(II), Zn(II) and Mn(II) complexes of Schiff base derived from sulfa pyridine and 2-hydroxynaphthaldehyde.

EXPERIMENTAL

All the reagents used were of AR grade (BDH/E. Merck). Solvents were purified and dried according to the standard procedures. Elemental analysis (C, H, N) were performed using elemental analyser. IR spectra of the ligand and its complexes were recorded in KBr pellets with Perkin Elmer IR RXI Spectrometer in the 4000-400 cm^{-1} range. The ^{1}H NMR spectra were recorded on a Bruker 400 MHz FT-PMR spectrometer (DMSO-d_6). Magnetic susceptibilities were determined with a magnetic susceptibility meter (MSB-Auto). Melting points were determined using Elico melting point apparatus. The electronic spectra were recorded in Perkin Elmer Lambda 35 spectrometer in the 190-1100 nm range.Conductivity measurements for the complexes were carried out using Elico conductivity bridge and dip type conductivity cell.

Synthesis of Schiff Base (HNSP): To a hot stirred solution of sulfapyridine (0.0025 mol) in ethanol was added a solution of 2-hydroxy naphthaldehyde (0.0025 mol) in ethanol. The reaction mixture was refluxed for 4 h. The yellow coloured solid mass formed during refluxing was cooled to room temperature, filtered and washed thoroughly with ethanol. The purity of the ligand was checked by TLC. (m.p. 238 ºC; yield 82 %).

General method for preparation of metal complexes: To a hot magnetically stirred dioxane (25 mL) solution of Schiff base (0.002 mol), an aqueous solution of the corresponding metal(II) chloride (0.001 mol) was added. The mixture was refluxed for 4-5 h on a water bath. The precipitates formed during refluxing were cooled in an ice bath and collected by suction filtration, washed with small amount of dioxane and dried. The coloured solids obtained are mostly insoluble in some common organic solvents and soluble in polar solvents like DMF and DMSO. The yield of the ligand and its metal complexes together with colour, analytical data and other physical properties are reported in Table-1.

RESULTS AND DISCUSSION

Analytical data: The analytical data obtained for the ligand and complexes (Table-1) agree very well with the proposed molecular formulae and also indicates the formation of 1:2 (M:L) complexes of general formula of $[M(HNSP)_2Cl_2]$ [M = Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and Mn^{2+}].

Conductance and magnetic susceptibility measurements: The observed molar conductance of all the complexes in 10^{-3} M DMF solutions are found within the range 4.9-13.8 ohm^{-1} cm^{2} mol^{-1} showing their non-electrolytic nature. This in turn suggests that the chloride ions are coordinated with the metal ions and present inside the coordination sphere in all the complexes. The observed magnetic moment around 3.0 BM for the Co(II) and Ni(II) complexes is consistent with octahedral geometry around the metal ion for both the complexes. The magnetic moment value of 1.80 BM measured for the Cu(II) complex lies in the range expected for d^9 system, which contains one unpaired electron with octahedral geometry[22]. The Zn(II) complex is found to be diamagnetic as expected. The observed magnetic moment value of 5.76 BM for the Mn(II) complex suggests octahedral geometry.

IR Spectra: The IR spectral bands of Schiff base and its metal complexes are given in Table-2. The Schiff base contains five potential donor sites (i) the phenolic oxygen (ii) the azomethine nitrogen (iii) the sulphonamide oxygen (iv) the sulphonamide nitrogen and (v) ring nitrogen[23]. In the IR spectrum of the Schiff base ligand, a band is observed at 1618 cm^{-1} that is assigned to the >C=N- stretching mode. This band shifts to lower frequency by 6-26 cm^{-1} after complexation except for Zn(II) complex where the band shifts to higher frequency by 6 cm^{-1}, indicating the coordination of azomethine nitrogen to metal ion. A medium broad band observed at 3428 cm^{-1} in the Schiff base indicates the presence of phenolic oxygen. The shift of this frequency in complexes by 5-33 cm^{-1} indicates coordination through phenolic oxygen. The bands in the ligand due to $\nu_{as}(SO_2)$ and $\nu_s(SO_2)$ appear at 1133 and 1358 cm^{-1}, respectively. These bands almost remain unchanged in the complexes indicating that this $-SO_2$ group is not participating in coordination. This is confirmed by the unchanged ν(S-N) and ν(C-S) modes appearing around 959 and 826 cm^{-1}, respectively. The ring nitrogen (=N-) of the Schiff base does not take part in coordination, supported by unchanged band around 1275 cm^{-1}. The coordination of phenolic oxygen and azomethine nitrogen is further supported by the appearance of two non ligand bands in the region 480-432 and 568-547 cm^{-1} due to ν(M-O) and ν(M-N), respectively in all the complexes[24].

^{1}H NMR spectra: ^{1}H NMR spectra of free ligand and its Co(II) complex were recorded in DMSO-d_6. The ligand showed peak at δ = 8.9 ppm, suggests the presence of -CH=N- linkage. The peaks at δ = 15.3 ppm and 6.53-8.49 ppm indicate hydroxyl proton and aromatic proton. The ^{1}H NMR spectra of complexes apparently provides following two informations, regarding complexation.

TABLE-1
PHYSICAL CHARACTERISTICS AND ANALYTICAL DATA OF SCHIFF BASE AND THE COMPLEXES

Schiff base and complexes	Colour	Elemental analysis (%) found (calcd.) C	H	N	m.p. (ºC)	Yield (%)	Molar conductance (ohm^{-1} cm^{2} mol^{-1})	Magnetic moment (BM)
HNSP	Yellow	65.59 (65.50)	3.74 (4.22)	10.47 (10.42)	238	62	–	–
$[Co(HNSP)_2Cl_2]$	Light yellow	57.05 (56.54)	2.91 (3.43)	8.26 (8.99)	261	78	7.9	3.56
$[Ni(HNSP)_2Cl_2]$	Cream	57.14 (56.55)	3.88 (3.43)	9.85 (9.00)	252	60	11.8	3.13
$[Cu(HNSP)_2Cl_2]$	Green	56.56 (56.26)	3.02 (3.41)	8.41 (8.95)	258	72	13.8	1.80
$[Zn(HNSP)_2Cl_2]$	Orange	56.67 (56.15)	3.55 (3.40)	9.20 (8.93)	268	59	4.9	dia
$[Mn(HNSP)_2Cl_2]$	Cream	56.33 (56.78)	2.90 (3.44)	8.60 (9.03)	245	53	6.9	5.76

TABLE-2
INFRA RED AND ELECTRONIC ABSORPTION SPECTRAL DATA OF SCHIFF BASE AND THE COMPLEXES

Schiff base and complexes	Key, IR bands (cm^{-1}) ν(OH)	ν(>C=N)	ν(M-O)	ν(M-N)	UV-VIS (cm^{-1})
HNSP	3428	1618	–	–	–
$[Co(HNSP)_2Cl_2]$	3433	1592	450	568	21596, 27246
$[Ni(HNSP)_2Cl_2]$	3445	1600	480	547	36274, 35237, 23762, 25643, 26137
$[Cu(HNSP)_2Cl_2]$	3457	1612	458	563	36260, 34509, 26818
$[Zn(HNSP)_2Cl_2]$	3395	1624	432	564	36490,30840, 25922
$[Mn(HNSP)_2Cl_2]$	3439	1605	465	565	32350, 31460, 27268, 25370

TABLE-3
ANTIMICROBIAL ACTIVITY OF SCHIFF BASE AND COMPLEXES

Antimicrobial activity of the ligand and complexes	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Candida albicans*	*Aspergillus niger*
HNSP	++	++	++	++
$[Co(HNSP)_2Cl_2]$	++	++	+++	+++
$[Ni(HNSP)_2Cl_2]$	+++	+++	+++	++
$[Cu(HNSP)_2Cl_2]$	++	+++	+++	++
$[Zn(HNSP)_2Cl_2]$	+++	+++	+++	+++
$[Mn(HNSP)_2Cl_2]$	+++	+++	+++	+++

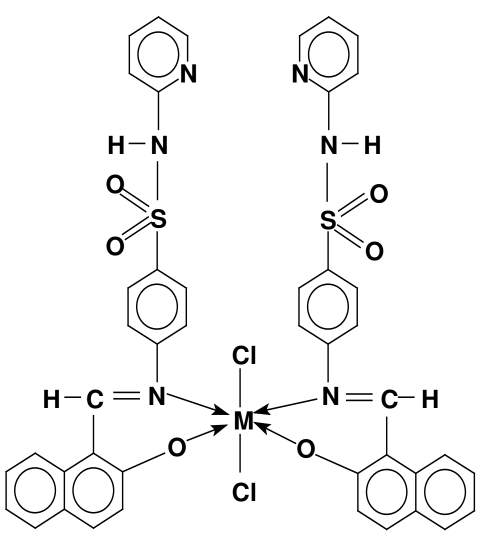
Standard = Ciprofloxacin 5 μg/disc for bacteria; Nystatin = 100 units/disc for fungi. Highly active = +++ (inhibition zone > 15 mm); moderatively active = ++ (inhibition zone >10 mm); slightly active = + (inhibition zone > 5 mm); inactive = - (< 5 mm).

The disappearance of peak at $\delta = 15.3$ ppm indicates the deprotonation of hydroxyl proton due to co-ordination of oxygen to the metal[25].

The coordination of the azomethine nitrogen is inferred by the upfield shifting of the -CH=N proton signal from 8.9 ppm in the ligand to 8.25-8.45 ppm in the complexes.

Electronic spectra: The electronic spectra of the Schiff base and its metal complexes were recorded in DMSO and given in Table-2. The Co(II) complexes exhibited high energy band at 21596 cm^{-1} which is assigned to the transition $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ for a high spin octahedral geometry. A band at 27246 cm^{-1} is assigned to $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ transition. The Ni(II) complex exhibited five absorption bands at 36274, 35237, 23762, 25643 and 26137 cm^{-1}. The two bands at 36274 and 35237 cm^{-1} may be attributed to L → M charge-transfer transitions. The bands in the region around 25000 cm^{-1} can be assigned to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ d-d transition. This suggests octahedral geometry around Ni(II) ion. The Cu(II) complex exhibited three bands at 36260, 34509 and 26818 cm^{-1}. The band at 26818 cm^{-1} is due to $^2E_g \rightarrow {}^2T_{2g}$ transition. The bands at 36260 and 34509 cm^{-1} are due to L → M charge transfer transitions. The Zn(II) complex exhibited three absorption bands at 36490, 30840 and 25922 cm^{-1}, due to L → M charge transfer transitions. The Mn(II) complex had bands at 25370 and 27268 cm^{-1} which may be due to $^6A_{1g} \rightarrow {}^4E_g$ and $^6A_{1g} \rightarrow {}^4T_{2g}(D)$ transitions, respectively whereas the bands at 32350 and 31460 cm^{-1} may be due to M → L charge transfer transitions.

On the basis of foregoing evidences, the structure proposed for the complex is as follows.



Antibacterial activity: The synthesized Schiff base and its metal(II) complexes were screened *in vitro* for antibacterial activity against gram positive (*Staphylococcus aureus*) and gram negative (*Pseudomonas aeruginosa*) bacterial strains using the disc diffusion technique. The test was carried out in DMSO solution at a concentration of 100 ppm using Muller Hinton agar media. Ciprofloxacin was used as the standard drug. $[Ni(HNSP)_2Cl_2]$, $[Zn(HNSP)_2Cl_2]$ and $[Mn(HNSP)_2Cl_2]$ exhibit significant activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, $[Cu(HNSP)_2Cl_2]$ exhibit significant activity against *Pseudomonas aeruginosa* and moderate activity against *Staphylococcus aureus*. (HNSP) and $[Co(HNSP)_2Cl_2]$ show moderate activity against both *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Table-3).

Antifungal activity: Antifungal activity of Schiff base and metal complexes were studied against two fungal cultures *Candida albicans* and *Aspergillus niger* species at concentration of 100 ppm using Sabouraud dextrose agar media disc diffusion technique[22]. Nystatin was used as the standard drug. $[Co(HNSP)_2Cl_2]$, $[Zn(HNSP)_2Cl_2]$ and $[Mn(HNSP)_2Cl_2]$ show significant activity against *Candida albicans* and *Aspergillus niger*. $[Cu(HNSP)_2Cl_2]$ and $[Ni(HNSP)_2Cl_2]$ show significant activity against *Candida albicans* and moderate activity against *Aspergillus niger*. The Schiff base HNSP exhibit moderate activity against both *Candida albicans* and *Aspergillus niger*. Here it is evident that overall potency of uncoordinated compound is enhanced on coordination with metal ions[22]. However the Zn(II) and Mn(II) complexes were observed to be the most active against various species (Table-3).

ACKNOWLEDGEMENTS

The authors are thankful to University Grants Commission, Hyderabad, India, for the financial support.

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