Research Paper

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Synthesis, Characterisation and Antimicrobial Activity Study of (Morpholino (Thiophen-2-Yl) Methyl) Nicotino Hydrazide and its Metal(II) Complexes

Chemistry

KEYWORDS : N-(morpholino (thiophen-2-yl)methyl) nicotinohydrazide(MTN),Mixed-ligand complexes, Antimicrobial activities, Cu(II), Ni(II) and Zn(II).

M. Syed Ali Padusha — Post Graduate and Research Department of Chemistry Jamal Mohamed College(Autonomous), Tiruchirappalli – 620 020, Tamil Nadu South India

S. Farook Basha — Post Graduate and Research Department of Chemistry Jamal Mohamed College(Autonomous), Tiruchirappalli – 620 020, Tamil Nadu South India

ABSTRACT

A new Mannich base, namely N-(Morpholino(thiophen-2-yl)methyl)nicotino hydrazide(MTN) was synthesized through Mannich condensation by reacting thiophene-2-carboxaldehyde, morpholine and benzohydrazide as substrate. The structure of the formed compound was characterised by IR, 1HNMR and mass spectroscopy and CHN analyses. Using the above compound as ligand, metal complexes were prepared and their structures were established by elemental analyses, IR , UV-visible spectra, molar conductivity and magnetic moment studies. The results of these study indicate the square planar geometry for all the complexes. Further, the ligand and the metal complexes were tested for antimicrobial activity. Antimicrobial studies revealed that metal complexes possess higher activity than those of the metal salts and ligands.

INTRODUCTION

Mannich reaction is a three component condensation reaction consisting of an aldehyde, an amine and a compound containing an active hydrogen atom. Many researchers have studied the numerous applications of Mannich reactions [1, 2]. In the development of coordination chemistry, the metal complexes of Mannich bases play a major role. Mannich bases are of interest in various areas of application [3-7]. Recently much interest has been paid on the synthesis and characterisation of transition metal complexes containing a Mannich base due to their wide pharmaceutical properties [8-12]. Many metal ions are known to play very important roles in biological processes in the human body [13, 14]. Metal ions like zinc(II) and copper(II) ions are the most abundant transition metals in human body, found either at the active sites or as structural components of a number of enzymes [15, 16]. These metals and some of their complexes have been found to exhibit antimicrobial activities [17-19]. Metal complexes depends on the metal ions and the ligand. In some metal complexes, the drug action has been noticed very high, when compared with the ligand[20, 21]. Hydrazone derivatives are found to possess antimicrobial, antitubercular and anti-inflammatory activities. Particularly, the antibacterial, antifungal and anticancer activities of hydrazones and their complexes with some transition metal ions were studied and reported by R.N.Patel et al.

Following all these observations and as a part of our research on the coordination chemistry of multidendate ligands, We report here, the synthesis, characterization and antimicrobial activities the new copper(II), nickel(II) and zinc(II) mixed-ligand complexes of N-(morpholino(thiophen-2-yl)methyl) nicotinohydrazide(MTN).

EXPERIMENTAL

Materials

All reagents were commercially available and used without further purification. Solvents were distilled using appropriate drying agents subsequently prior to use. The bacterial cultures such as Staphylococcus aureus, Bacilus subtilis, Escherchia coli, Pseudomonas aeruginosa, Aspergillus niger, Rhizoctonia bataicola obtained from Eumic Analytical Laboratory and Research Institute, Tiruchirappalli.

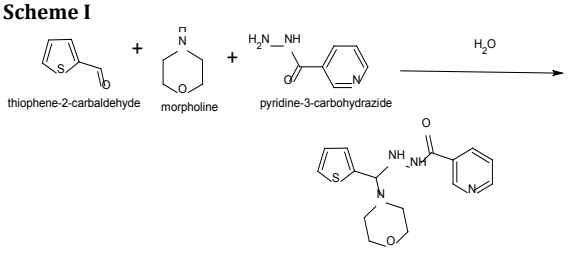
Physical measurements

Melting point was determined using open capillary tube and are uncorrected. The purity of the compound was checked by thin layer chromatography on glass plates using silica gel G as absorbent and solvent system. 1HNMR spectrum was recorded on a Bruker Ultra Shield(300 MHZ) spectrometer using DMSO as a solvent and TMS as internal standard. Molar conductivity was determined using systronic conductivity bridge with a dip type cell using 10-3 M solution of complexes in DMSO using Perkin Elmer spectrophotometer, UV-visible spectra of complexes were recorded using 10-3 M solution of complexes in DMSO for the range 4000-400 cm^{-1}.

Synthesis of N-(morpholino(thiophen-2-yl)methyl) nicotinohydrazide(MTN)

Thiophene-2-carboxaldehyde, nicotinic acid hydrazide and morpholine were taken in 1:1:1 ratio and were reacted as shown in the scheme I. Nicotinic acid hydrazide (13.7 g, 0.1 mol) was taken in a round bottom flask and 5 ml of water was added. To this solution, morpholine(8.7 mL, 0.1 mol) was added and stirred well for 15 min, by keeping the reaction mixture on a magnetic stirrer in an ice cold condition. After 2 h, the solid formed was filtered and washed with ethanol. The crude solid thus obtained was dried and recrystallised using ethanol and dried over vacuum.

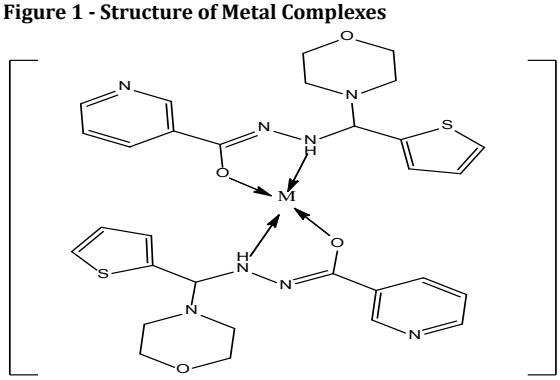
Scheme I



Synthesis of Metal(II) complexes

To the 10 mL methanolic solution of MTN(0.85g, 0.1 mol), each of metal Cu(II), Ni(II) and Zn(II) (0.1) chloride dissolved in a mixture of methanol and Chloroform 1:1(v/v) was added slowly. This mixture was kept on a magnetic stirrer and stirring was continued for an hour. The solid separated out was washed, filtered and dried over vacuum.

Figure 1 - Structure of Metal Complexes



M = Cu(II), Ni(II) and Zn(II)

Antimicrobial tests

Invitro antimicrobial activities of the ligand, complexes and free metal ions were evaluated by the disc diffusion method against the microorganisms such as Staphylococcus aureus, Bacilus subtilis, Escherchia coli, Pseudomonas aeruginosa, Aspergillus niger, Rhizoctonia bataicola. Ampicillin and Amphotericin B were used as standard for bacteria and fungi. The microbial isolates were maintained on agar slant at 4˚C. The strains were sub cultured on fresh appropriate agar plate in an incubator for 18 h prior to any microbial test.

The nutrient agar medium was prepared and sterilized by autoclaving at 121˚C, 15 lbs pressure for 15 min and then aseptically poured the medium into the sterile petri plates and allowed to solidify the bacterial broth culture and these are swabbed on each petri plates by sterile buds. Then wells were made by well cutter.

The Kirby Bauer Agar(KBA) medium was used for the diffusion assays determination and Nutrient broth was used as microbial growth medium. This procedure was repeated for each petri plate, then the petri plates were incubated at 37˚C for about 24h. After incubation, the plates were observed for the zone of inhibition. The effect produced by the sample was compared with the effect produced by the positive control. Nutrient agar(NA) was used for the activation of Bacillus species, while NA alone was used for the other bacteria.

Result and discussion

The results of the elemental analyses present in the Table indicate the stoichiometry of the metal complex is 1:2(M:L), $Cu(MTN)_2Cl_2.H_2O$ whose complex ion is similar to $Ni(MTN)_2Cl_2.H_2O$ and $Zn(MTN)_2Cl_2.H_2O$. The complexes are very stable in air whereas the starting metal salts are hygroscopic in nature. The melting point of MTN was found to be 198˚C. The complexes are different in colour from the starting metal salts from which they are derived. The colour of the complexes are presented in table 1. The low conductance of the chelates supports the non-electrolytic nature of the metal complexes.

Table 1. Physical characterization, analytical and molar conductance data of the ligand(MTN) and its metal(II) complexes

No	Molecular Formula	Colour	Mol. Wt.	Melting point (˚C)	Yield %	Found%(Calcd %)						Molar Conductance ($\Omega^{-1}mol^{-1}cm^2$)
						C	H	N	O	S	Cl	
01	MTN $C_{15}H_{18}N_4O_2S$	White	318.4	198	70	55.68 (55.05)	8.07 (8.12)	29.51 (29.41)	6.74 (6.53)	8.02 (8.14)	--	--
02	$Cu(MTN)_2Cl_2$	Blue	645.1	226	74	54.53 (54.02)	7.63 (7.53)	31.79 (31.87)	6.05 (6.34)	7.88 (7.92)	16.42 (16.85)	29
03	$Ni(MTN)_2Cl_2$	Green	640.2	274	78	63.77 (63.04)	6.36 (6.44)	13.94 (13.23)	15.93 (15.88)	11.52 (11.50)	18.02 (18.68)	21
04	$Zn(MTN)_2Cl_2$	Creamy White	646.9	256	80	66.88 (66.32)	7.37 (7.21)	16.62 (16.41)	11.44 (11.12)	11.53 (11.55)	17.98 (18.34)	34

Table 2: IR spectral data(cm-1) of MTN and its metal(II) complexes

Compounds	ν (NH)	ν(NH)	ν(C=N)	ν(CNC)	ν(CH)	ν(M-N)	ν(M-O)
MTN	3421	1625	1670	1290	2926	--	--
$Cu(MTN)_2Cl_2$	3398	1610	1654	1288	2925	480	505
$Ni(MTN)_2Cl_2$	3200	1585	1625	1290	2930	440	512
$Zn(MTN)_2Cl_2$	3275	1598	1625	1290	2925	470	530

Infra Red spectra

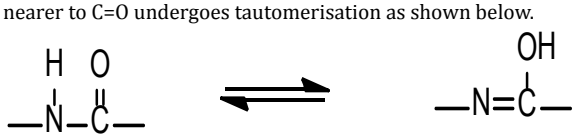
The infrared spectral data of the ligand and its complexes are given in Table 2. In order to study the binding mode of the ligand in the metal complexes, the IR spectrum of the ligand was compared with those of the corresponding metal complexes. In the infrared spectra of the complex, the band due to NH at 3421 cm-1 in the spectrum of the ligand has been found shifted to 20-30 cm-1 in the spectrum of the complexes indicating the coordination of N atom of NH with metal ion. The participation of the nitrogen atom in coordination with the metal ion is further supported by the appearance of new band which is attributed to ν(M-N) [22, 23].

For the ligand, the bands due to νC-O and νC=N appeared in the regions 1647 and 1155 cm-1 respectively. In the spectra of the complexes, the νC=O of the free ligand is not observed indicating the enolisation of C=O followed by deprotonation and complexation with metal ions. The ν(C=N) mode of the ligand has been found shifted to higher frequency in the spectra of the complexes supporting the coordination of oxygen atom of the carbonyl in binding with metal ions.

1HNMR spectra

1HNMR spectrum of the ligand showed a multiplet between δ 6.9 to 7.2 is assigned to aromatic protons. A triplet at δ 2.5 and δ 3.4 are attributed N-CH2 and O-CH2 of morpholine. A broad singlet appeared at δ 3.8 is assigned to NH proton adjacent to CH and a singlet at δ 6.2 is due to the methine proton adjacent to NH. These results indicate that there is no interaction between NH and CH protons. This might be due to nuclear quadrapole effect.

This spectrum is compared with the 1HNMR spectrum of the Zn(II) Chloro complex of MTN. It has been observed that a peak appeared at δ 9.8 in the spectrum of the ligand was found absent in the spectrum of the complex, suggesting the participation of oxygen atom after deprotoration. This arises due to –NH proton nearer to C=O undergoes tautomerisation as shown below.



UV-Vis Spectra

The UV-visible spectrum of copper complex in DMSO solution displayed a broad band at 11232 cm-1 and an another band at 23735 cm-1 are attributed to 2B1g →2A1g and 2B1g →2B2g transitions. These transitions are favour to square planar geometry around the central metal ion. Distortion from perfect planar symmetry is supported by the existence of broad band which is further supported by the magnetic moment value(1.85 BM).

The electronic spectrum of nickel complex exhibited a band at 24547 cm-1 is assigned to 1A1g →1B1g transition which corroborates the Square planar geometry. The possibility of tetrahedral is ruled out from the absence of any band below 10,000 cm-1 for nickel complexes.

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Antimicrobial Studies

The results of the antimicrobial activity of the MTN and its complexes are presented in Table 3. From the table, it is observed that the ligand and the metal complexes are more active than the free ligand and their standards. The increase in antimicrobial activity is due to faster diffusion of metal complexes as a whole through the combined activity of the metal and the ligand.

Table 3 Antibacterial Activities of Metal(II) complexes

Complex	Inhibition zone(mm)			
	Staphylococcus aureus	Escherichia Coli	Pseudomonas aeruginosa	Bacilus subtilis
MTN	11	12	12	10
Cu(II)	15	16	14	15
Ni(II)	14	16	15	13
Zn(II)	19	22	18	20
$CuCl_2$	12	12	10	11
$NiCl_2$	10	11	11	10
$ZnCl_2$	13	13	12	12
Ampicillin	11	11	11	10
DMSO	--	--	--	--
Metal Salt	13	15	14	11

Table 4 Antifungal Activities of Metal(II) complexes

Complex	Inhibition zone(mm)	
	Aspergillus niger	Rhizoctonia bataicola
MTN	12	14
Cu(II)	15	16
Ni(II)	16	16
Zn(II)	21	23
Nutrient Agar	10	11

Conclusion

The ligand, MTN and its metal complexes have been synthesized and characterized by elemental analysis, IR, 1HNMR, UV and magnetic measurements. The results of UV spectral studies and magnetic susceptibility studies confirms square planar geometry of the metal complexes. Antimicrobial screening of ligand and the metal complexes showed their excellent activity. The zone of inhibition of metal complexes are comparably high than the free ligand. The therapeutic promise of the investigated metal(II) complexes were found to exhibit higher antimicrobial activity than the ligand.

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