Asian Journal of Chemistry Vol. 14, Nos. 3–4 (2002), 1551–1555

Synthesis, Characterization and Antibacterial Activity of Metal Complexes of N-(1-piperidinobenzyl)nicotinamide

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Solid complexes of a new Mannich base N-(1-piperidino benzyl)nicotinamide (PBN) with Cu(II),Co (II), Ni(II) and Zn(II) complexes have been synthesised and characterised by spectral studies, molar conductance, magnetic susceptibility and elemental analyses. The antibacterial activity of the complexes has also been studied.

Key Words: Synthesis, Characterization, Antibacterial, Metal, Complexes, N-(1-Piperidinobenzyl)nicotinamide.

INTRODUCTION

It is well known from the literature that the compounds containing amide moiety have a strong ability to form metal complexes and exhibit a wide range of biological activities[1–4]. We have synthesised a new Mannich base, N-(1-piperidinobenzyl)nicotinamide which also contains amide moiety. In continuation of our earlier work[5, 6], we herein report the synthesis of N-(1-piperidinobenzyl)nicotinamide and its complexation characteristics with Co(II), Ni(II), Cu(II) and Zn(II) salts and their antibacterial activity.

EXPERIMENTAL

All the chemicals were of AR grade. IR spectra were recorded on a Perkin-Elmer 783 spectrophotometer. KBr disc method was used for recording the IR spectra. UV spectra were recorded on Shimadzu 160 UV-Visible spectrophoto meter. Analysis of the metal contents in the complexes was performed by standard methods[7]. Carbon, hydrogen and nitrogen contents were determined at the Regional Sophisticated Instrumentation Centre, Central Drug Research Institute, Lucknow. Magnetic susceptibility measurements were carried out using the Gouy method. Mercury(II) tetrathiocyanatocobaltate(II) was used as calibrant The molar conductivity of the complexes was measured using dimethyl sulphoxide as solvent. Mueller-Hinton agar was used for testing the susceptibility of micro organisms to antibacterial agents using the well-diffusion technique.

General procedure for preparation of N-(1-piperidinobenzyl)nicotinamide (PBN)

The PBN ligand has been prepared by the reaction of appropriate aldehyde with the mixtue of nictoninamide and piperidine in 1 : 1 : 1 mole ratio as per our earlier work[5].

Synthesis of metal complexes using PBN

Ni(II), Cu(II), Co(II) and Zn(II) complexes have been synthesised using PBN as ligand. PBN was dissolved in chloroform and mixed with an ethanolic solution of the metal salt in 1 : 1 mole ratio. The reaction mixture was gently warmed on a water-bath for 1/2 h. The resulting solid complex formed was washed with petroleum ether and dried.

RESULTS AND DISCUSSION

All the coloured complexes are stable at room temperature. They are insoluble in water but soluble in $CHCl_3$, DMF and DMSO. The analytical data of the ligand and its complexes along with some physical properties are summarised in Table-1. An examination of the elemental analysis of the products listed in Table-1 reveals the formation of 1 : 1 (metal : ligand) complexes. Molar conductance values of the complexes reveal their non-electrolytic nature[8]. The magnetic susceptibility measurement values show tetrahedral structures for cobalt, nickel and zinc and octahedral for copper complex.

TABLE-1

ANYLYTICAL DATA OF THE COMPLEXES

Complex (colour)	% Analysis, Found (calcd)				Yield (%)	μ_{eff} (B.M.)	λm (mho cm^{-2} mol^{-1})
	M	C	H	N			
$[CuCl_2\cdot PBN\cdot(H_2O)_2]$	13.1	45.9	5.2	8.8	53	1.9	15.4
(green)	(13.6)	(46.4)	(5.3)	(9.0)			
$[COCl_2\cdot PBN](H_2O)_2$	13.2	48.0	4.9	9.2	58	3.1	12.1
(pink)	(13.3)	(48.8)	(5.2)	(9.5)			
$[NiCl_2\cdot PBN](H_2O)_2$	12.5	47.9	5.1	9.4	61	—	10.6
(green)	(13.2)	(48.8)	(5.2)	(9.5)			
$[ZnCl_2\cdot PBN](H_2O)_2$	13.7	47.4	4.8	9.1	62	—	14.2
(yellow)	(13.9)	(48.1)	(5.1)	(9.3)			

In PBN, the bands observed at 3300, 1640 and 1100 cm^{-1} have been assigned to ν(NH), amide ν(C=O) and ν(C—N—C) of piperidine group respectively[9]. In the IR spectra of all the complexes, the ν(NH) band remained at the same position as in the free ligand, indicating that the secondary nitrogen is not coordinated. In all the complexes, the amide ν(C=O) and ν(C—N—C) of piperidine bands displayed substantial negative shifts with fairly low intensity indicating coordination through the oxygen of amide moiety and nitrogen of piperidine entity present in the ligand. The Cu(II) complex showed a hump at 3450–3000 cm^{-1} followed by sharp peaks at 850–820 cm^{-1} attributed to stretching and rocking modes respectively of coordinated water molecules[10]. According to elemental analysis, the Co(II), Ni(II) and Zn(II) complexes contain water molecule. However, a band around 880 cm^{-1}, characteristic of coordinated water, is not observed in the IR spectrum of those complexes. It may thus be assumed that the water molecule is lattice held. Some new bonds were found around 540–530, 450–440 cm^{-1} of M—O, M—N bonds respectively[11, 12] which further confirm that the ligands are bidentate in nature. In all the complexes, an additional medium band found at 325 cm^{-1} is assigned to M—Cl stretching vibration[13, 14].

The ^1H NMR spectra of PBN displayed the expected signals. PBN exhibits a multiplet signal at 6.5–7.5 δ (m, Ar–H and pyridine H), 8.0–8.1 δ (d, CH), 8.2–8.6 δ (pyridine H), 5.8–5.9 δ (d, sec. amide, NH). 2.5–2.6 δ (piperidine N—CH_2), 2.4 δ (s, CH_3) and 1.5 δ (piperidine CH_2). In Zn(II) complex, the doublet of N—H proton shifted slightly downfield to 5.9–6.1 δ which reveals the coordination of carbonyl oxygen to Zn(II) ion. The slight downfield shift of amide proton is due to less shielding of the proton since the electron pair on nitrogen is shifted towards the carbonyl group upon oxygen coordination. The signal due to piperidine (N—CH_2) protons also shifted slightly downfield and appeared at 2.7 δ in the complex. This is an indication of the coordination of piperidine nitrogen. There is no appreciable change in all of the other signals of this complex. Thus ^1H NMR and IR results confirm the bidentate nature of PBN ligand.

The electronic absorption spectra of the ligand and its copper(II), cobalt(II), nickel(II) and zinc(II) complexes were recorded in DMSO solution.

The green Cu(II) complex showed a broad band at 14048 cm^{-1} which is assigned to $^2E_g \rightarrow {}^2T_{2g}$ transition indicating octahedral structure[15] of the complex. The Co(II) complex exhibits a band at 16720 cm^{-1} which is assigned to $^4A_2 \rightarrow {}^4T_1$ for tetrahedral geometry[16]. The Ni(II) complex showed a band at 15128 cm^{-1} which is assigned to $^3E_g \rightarrow {}^3A_{1g}$ confirming a tetrahedral geometry for the complex.

The magnetic moment value for Cu(II) complex (1.90 B.M.) indicates the octahedral arrangement of the ligand around the central metal ion. The four coordinated Co(II) complex shows μ_{eff} value of 3.1 B.M. which supports the tetrahedral geometry for the complex.

Antibacterial Study

The ligand PBN and its copper(II), cobalt(II), nickel(II) and zinc(II) complexes were tested for antibacterial activity. Mueller-Hinton agar was used for testing the susceptibility of microorganisms to antibacterial agents by well diffusion method[17], using DMF as solvent, at a concentration of 100 μg/10 μL against Gram positive (*Staphylococcus aureus*) and Gram negative (*Escherichia coli*) bacteria. The minimum inhibitory concentrations (MIC) values were determined at the end of an incubation period of 24 h at 37°C. The zone of inhibition against the growth of microorganisms is presented in Table-2. The ligand and its complexes are more active towards *Escherichia coli* than *Staphylococcus aureus*. The order of activity towards *Staphylococcus aureus* is Cu > Co > Ni > Zn and towards *Escherichia* coli is Cu > Zn > Co > Ni. A comparative study of the ligand and its complexes at the minimum inhibitory concentration indicates that the metal complexes are more active than the free ligand. The increase in antibacterial activity is due to faster diffusion of metal complexes as a whole through the cell membrane or due to the combined activity effect of the metal and ligand[18]. Such increased activity of the metal chelates can be explained on the basis of Overtone's concept[19] and the Tweedy's chelation theory[20, 21]. According to Overtone's concept of cell permeability, the ligand membrane that surrounds the cell favours the passage of only lipid-soluble materials due to which liposolubility is an important factor which controls the antimicrobial activity. On chelation, the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalisation of π-electrons over the whole chelate ring and enhances the lipophilicity of the complexes. This increased lipophilicity enhances the penetration of the complexes into lipid membrane and blocking of the metal binding sites in the enzymes of microorganisms.

TABLE-2
ANTIBACTERIAL ACTIVITY OF METAL COMPLEXES OF PBN

No.	Compound (Colour)	Inhibition zone (mm) at concentration (100 μg/10 μL)	
		S. aureus	*E. coli*
1.	PBN	12	14
2.	$[CuCl_2{\cdot}PBN{\cdot}(H_2O)_2]$	20	22
3.	$[CoCl_2{\cdot}PBN](H_2O)_2$	19	19
4.	$[NiCl_2{\cdot}PBN](H_2O)_2$	17	19
5.	$[ZnCl_2{\cdot}PBN](H_2O)_2$	16	20

ACKNOWLEDGEMENTS

The authors express their sincere thanks to the Principal and Managing Board of VHNSN College, Virudhunagar for providing research facilities. They are also thankful to Prof. S. Subramanian and Prof. A. Shunmugasundaram for their encouragement.

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(*Received*: 13 March 2002; *Accepted*: 21 May 2002) AJC–2725