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Synthesis, characterization and antibacterial activity of Pyrrolidine based Mannich base ligand and its metal (II) complexes

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Abstract : Mannich base, N-(1-pyrrolidinobenzyl)semicarbazide (PBS), formed by the condensation of pyrrolidine, semicarbazide and benzaldehyde, and its Cu(II), Ni(II), Co(II) and Zn(II) complexes have been synthesized. Their structures have been elucidated on the basis of analytical, magnetic, electrical conductivity, spectral study as well as elemental analyses. The X-band ESR spectra of Cu(II) complex in DMSO at 300 and 77 K were recorded and their salient features are reported.

Keywords. : Mannich base; transition metal (II) complexes; spectral study; antimicrobial activity.

Introduction

Studies of Mannich base complexes have grown over the years due to the selectivity and sensitivity of the ligands to various metal ions. From the survey of existing literature[1-5], it appears that metal complexes of Mannich bases have played a vital role in the development of coordination chemistry. 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. Earlier work reported that some drugs showed increased activity when administered as metal chelates rather than as organic compounds. It is well known from the literature that semicarbazide compounds[5] containing the amide moiety have a strong ability to form metal complexes. Therefore, it was thought worthwhile to synthesise some metal complexes of this type of Mannich base and investigate its bonding characteristics. We herein report a new Mannich base, N-(1-pyrrolidinobenzyl)semicarbazide formed by the three component condensation, containing active hydrogen on nitrogen (pyrrolidine), benzaldehyde and semicarbazide. In this ligand system, dicoordination takes place via the N and O of semicarbazide. The proposed structure of the synthesised Mannich base complexes are given in the following scheme 1.

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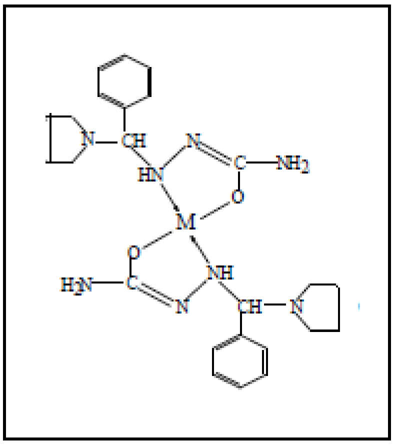

Scheme 1: proposed structure of Mannich base complexes

Experimental

All the reagents used for the preparation of the ligand and the complexes were Merck products. The carbon, hydrogen and nitrogen contents in each samples were done at the Regional Sophisticated Instrumentation Centre, Central Drug Research Institute, Lucknow. ^{1}H-NMR spectra of the samples were measured in DMSO-d_6 at Madurai Kamaraj University, Madurai. The IR spectra were recorded as KBr pellets using a Perkin–Elmer 783 spectrophotometer. UV-Vis spectra of the complexes were recorded on a Shimadzu UV-1601 spectrophotometer. The X-band ESR spectra of the copper was recorded in DMSO at 300 and 77 K on a Varian 112 ESR spectrophotometer using tetracyanoethylene (TCNE) as the internal standard at the Regional Sophisticated Instrumentation Centre, Indian Institute of Technology, Mumbai. Magnetic susceptibility measurements of the complexes were done using a Gouy balance. Copper sulphate was used as the calibrant. Molar conductivity was measured on a Systronic conductivity bridge with a dip-type cell, using 10^{-3} M solution of complexes in DMSO. FAB-mass spectrum of the complex was recorded on a JEOL SX 102/DA-6000 mass spectrometer/ data system using Argon/Xenon (6 kV, 10 mA) as the FAB gas. Accelerating voltage was 10 kV and spectra were recorded at room temperature.

Synthesis of Mannich base *:* Benzaldehyde (1.06 ml, 10 mmol) was added to Semicarbazide hydrochloride (1.1g, 10 mmol) in 20 ml of ethanol was neutralized with ammonia. To this solution pyrrolidine (0.9 ml, 10 mmol) was added dropwise with constant stirring under the same condition. Then and the reaction mixture kept at room temperature for 3 days and colourless solid was obtained. The solid formed was filtered and recrystallised from ethanol. Yield : 66 % ; m.p : 184 ^{0}C.

Synthesis of complexes *:* An ethanolic solution of Mannich base (1.25 g, 5 mM) was mixed with metal(II) chloride (5 mM) in ethanol and chloroform (1:6) mixture (40 mL) solution was then warmed for *ca.* 3 h on a water bath till the complex precipitated out. The solid complex obtained was removed by filtration, successively washed with water, dried at room temperature and recrystallised from ethanol.

Results and Discussion

All the metal complexes are stable at room temperature. They are insoluble in water but soluble in MeCN, DMF and DMSO. The ligand L, on interaction with Cu(II), Co(II), Ni(II) and Zn(II) chlorides, yields complexes corresponding to the general formula [ML_2]. This stoichiometric assignment is supported by the microanalytical data (Table 1). The low molar conductance values of the complexes (2.6-5.8 mhocm^{2}mol^{-1}) support their neutral nature[6].

Table 1. Analytical, molar conductance and magnetic susceptibility data of ligand and its complexes.

Compound/ complex	Colour	Found (calculated) (%) M	C	H	N	λm (mho cm^{2} mol^{-1})	Mol. wt.	M.p. (°C)	$\mu_{eff.}$ (BM)
[$C_{12}H_{18}N_4O$]	Colourless	–	56·24 (56·58)	6·84 (6·28)	20·58 (21·28)	–	218	184	–
[$C_{24}H_{34}N_8O_2Cu$]	Green	10·62 (10·30)	50·60 (51·28)	6·72 (6·10)	19·42 (19·94)	4.2	530	212	1·8
[$C_{24}H_{34}N_8O_2Co$]	Pink	10·73 (10·57)	50·91 (51·70)	6·01 (6·15)	19·87 (20·10)	2.6	524	198	4·8
[$C_{24}H_{34}N_8O_2Ni$]	Pale green	10·93 (10·53)	50·12 (51·72)	6·01 (6·15)	19·58 (20·11)	4.8	526	214	–
[$C_{24}H_{34}N_8O_2Zn$]	Colourless	9·02 (11·59)	51·01 (51·11)	5·69 (6·08)	19·11 (19·87)	5.8	532	208	–

FAB mass spectra

The FAB mass spectra of the Mannich base ligand and its copper complex are used to compare their stoichiometric composition. The Mannich base ligand shows a molecular ion peak M+ at m/z = 218. The molecular ion peak for Cu complex was observed at m/z = 530, which confirms the stoichiometry of metal chelates as [ML_2] type.

Electronic absorption spectra

The UV-Vis spectrum of copper complex in DMSO solution displays a broad band at 10658 cm^{-1} and a well-defined shoulder around 21800 cm^{-1}, attributable to $^{2}B_{1g} \rightarrow {}^{2}A_{1g}$ and $^{2}B_{1g} \rightarrow {}^{2}B_{2g}$ transitions which strongly favor square-planar geometry around the central metal ion[7–9] . The broadness of the band can be taken as an indication of distortion from perfect planar symmetry. This is further supported by the magnetic susceptibility value (1.8 BM). The nickel complex is diamagnetic suggesting square-planar geometry. The electronic absorption spectrum of the nickel complex shows a *d–d* band at 22246 cm^{-1} as-signed as $^{1}A_{1g} \rightarrow {}^{1}B_{1g}$ transition,[10] which also indicates the square planar geometry. Absence of any band below 10,000 cm^{-1} rules out the possibility of tetrahedral structure for this nickel chelate. The cobalt complex shows a *d–d* band at 16216 cm^{-1} as-signed to $^{1}A_{1g} \rightarrow {}^{1}B_{1g}$ transition, which confirms square planar geometry. This is further confirmed by its magnetic susceptibility value (4.8 BM). . The Zn(II) complex is found to be diamagnetic as expected for d^{10} configuration.

IR spectra

In order to study the binding mode of the Mannich base to the metal ion in the complexes, the IR spectrum of the free ligand (Mannich base) was com-pared with the spectra of the complexes. The IR spectrum of the ligand shows bands in the regions 3240 and 1610 cm^{-1}, which are assigned to $\nu_{(N–H)}$ and $\nu_{(C=O)}$ of semicarbazone respectively. The bands due to $\nu_{(C–O)}$ and $\nu_{(C=N)}$ are located in the regions 1150 and 1660 cm^{-1} respectively.[11,12] In the spectra of semicarbazone complexes, the $\nu_{(C=O)}$ mode of the free ligand is not observed indicating the enolisation of C=O followed by deprotonation and complexa-tion with metal ions. The $\nu_{(C=N)}$ mode of ligand is found to shift to lower wave numbers suggesting the coordination of the azomethine nitrogen to the central metal ion. The band at 3240 cm^{-1} observed in the ligand is absent in the complexes, suggesting deprotonation of –NH of the ligand prior to the co-ordination to the metal. This is further confirmed on the basis of ^{1}H-NMR studies. On the basis of this evidence, it is concluded that the ligand acts as a monobasic bidentate manner in all the complexes. In all the complexes bands around 530–470 and 460–420 cm^{-1} which are assignable to $\nu_{(M–O)}$ and $\nu_{(M–N)}$ modes respectively.

^{1}H-NMR spectra

^{1}H-NMR spectra of the ligand and its zinc and nickel complexes were recorded in DMSO-d_6 solution. The ligand shows a multiplet between 7·06 and 7·88 δ, which is due to aromatic protons. It shows the signal at 6·7

δ assigned to the –CH group. A broad absorption around 6·2 δ is due to the NH proton; pyrrolidine –N–CH_2 at 2·2 δ. The singlet corresponding to one proton at 10·8 δ is assigned to –N=C–OH group. In the complexes, the multiplet observed in 7·20–7·24 and 7·92–8·2 δ is due to aromatic protons. Shifting of –CH and –NH protons to the downfield confirms the involvement of azomethine nitrogen in coordination to the metal ion. The peak observed at 10.8 δ in the ligand was absent in the complexes suggesting that the ligand is in enol form followed by coordination of carbonyl oxygen to the metal ion *via* deprotonation.

EPR spectra

The EPR spectrum of copper complex provides informations which are important in studying the metal ion environment [12]. The EPR spectra of the Cu(II) complex were recorded in DMSO at LNT and at RT. The spectrum of the copper complex at RT shows one intense absorption band in the high field and is isotropic due to the tumbling motion of the molecules. The G value of 3.92 indicates negligible exchange interaction of Cu-Cu in the complex[13].

Antimicrobial activities

The *in vitro* antimicrobial activities of the investigated compounds were tested against the bacterial species[14]. One day prior to the experiment, the bacterial cultures were inoculated in broth (inoculation medium) and incubated overnight at 37 °C. Inoculation medium containing 24 hr grown culture was added to the nutrient medium and mixed thoroughly to get the uniform distribution. This solution was poured (25 mL in each dish) into petri dishes and then allowed to attain room temperature. Wells (6 mm in diameter) were cut in the agar plates using proper sterile tubes. Then, wells were filled up to the surface of agar with 0.1 mL of the test compounds dissolved in DMSO (100µM/mL). The plates were allowed to stand for an hour in order to facilitate the diffusion of the drug solution. Then the plates were incubated at 37 °C for 24 hr for bacteria and the diameter of the inhibition zones were read. During this period, the test solution diffused and the growth of the inoculated microorganisms was affected. Minimum inhibitory concentrations (MICs) were determined by using serial dilution method. The concentration of DMSO in the medium did not affect the growth of any of the microorganisms tested. Ampicillin was used as the standard for comparing the results (Table 2). From the result it has been observed that metal complexes have higher antibacterial activities than the free ligand and the standard Ampicillin.

Table 2. Antibacterial activities of metal (II) complexes.

Compound	*B.Subtilis*		*P. aeruginosa*	*S. aureus*	*E. coli*	
Ampicillin	14		15	12	14	
PBS	10		11	11	12	
Cu(II) complex	20		18	17	18	
Co(II) complex	16		19	16	17	
Ni(II) complex	18		18	19	16	
Zn(II) complex	21		19	18	18	

Conclusion

The synthesized Mannich base compound and its complexes of Cobalt (II), Nickel (II), Copper (II) and Zinc (II) were characterized. The structural data established on the basis of ^{1}H NMR, mass, IR, UV, elemental analysis (C,H,N), and magnetic susceptibility analysis of complexes were recorded and discussed.

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