

Synthesis, Characterization and Biological Studies of a Mannich Base *N*-[Phenyl(pyrrolidin-1-yl)methyl]acetamide and Its VO(IV), Mn(II) and Fe(II) Complexes

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N-[Phenyl(pyrrolidin-1-yl)methyl]acetamide was synthesized using Mannich reaction. The complexes of oxovanadium(IV), manganese(II) and iron(II) with this Mannich base were prepared and characterized by elemental analysis and spectral measurements. The spectral data reveal that the ligand acts as bidentate coordination to the metal ion through the CNC nitrogen and carbonyl oxygen atoms. Based on the UV spectral and magnetic moment data, octahedral geometry is assigned for all the complexes. The antimicrobial screening shows that the complexes are more active than the ligand.

Key Words: VO(IV), Mn(II), Fe(II), Complexes, Mannich base, Disc diffusion, Octahedral geometry, Biological study.

INTRODUCTION

Due to strong basic character¹, the carbonyl group in acetamide is known to form metal complexes. They behave as antimicrobial², antirheumatic³, antipyretic⁴, analgesic and anticancer⁵ drugs. In continuation of our earlier work reported^{6,7} on Mannich base derivatives of acetamide and their transition metal complexes, we are presenting here our extended studies.

EXPERIMENTAL

High purity acetamide(Merk), benzaldehyde(Merk), pyrrolidine(Merk) were used as supplied. All other solvents and metal salts used were of A.R. grade and used as such.

Synthesis of the ligand and complexes: *N*-[Phenyl-(pyrrolidin-1-yl)methyl]acetamide (PBA) was synthesized by employing the Mannich condensation⁸ reaction between acetamide, benzaldehyde and pyrrolidine in 1:1:1 mol ratio. The ethanolic solution of acetamide (5.90 g) was mixed with benzaldehyde (10 mL) and pyrrolidine (7.1 mL) with constant stirring in an ice bath. After 12 days, a pale yellow solid was obtained. It was washed with water and acetone, dried and recrystallized from ethanol. The yield of the compound was 78 %. (m.p: 120-124 °C).

The hot methanolic solution of the metal salts was added slowly with constant stirring to the hot ethanolic solution of the ligand in 2:1 mol ratio. The insoluble complexes formed were filtered, washed with methanol and ethanol to remove the unreacted metal and ligand. They were dried in an air oven at 80 °C.

Antibacterial and antifungal screening: Antibacterial and antifungal activities of the ligand as well as the metal complexes were tested *in vitro* against six bacterial species *viz.* *E. coli*, *P. aeruginosa*, *S. typhi*, *B. subtilis*, *S. pyogenes*, *S. aureus* and the two fungal species *A. niger* and *A. flavus* by disc diffusion method using agar nutrient as medium and gentamycin as control.

RESULTS AND DISCUSSION

Infrared spectrum of PBA shows a sharp band at 3306 cm⁻¹ is assigned to ν(NH) stretching vibration of the secondary amide group⁹. The strong band at 1646 cm⁻¹ may be attributed to the ν(C=O) stretching mode. The medium absorption band appears at 1149 cm⁻¹ may be assigned to the new C-N-C bond formed, due to the formation of Mannich base by the insertion of pyrrolidinobenzyl group on acetamide.

The ¹H NMR spectrum¹⁰ shows a signal at δ 8.42 ppm, which may be assigned to the secondary amide NH proton. The methyl proton shows a singlet at δ 1.89 ppm. The multiplet in the range δ 7.39-7.26 ppm is attributed to the protons of the benzene ring. The protons of N(CH₂)₂ occurs at δ 2.51 and 1.65 ppm for α, α' and β, β' groups of pyrrolidine ring. According to the ¹³C NMR spectrum obtained, the carbonyl carbon shows a signal at δ 169.62 ppm. The signals observed between δ 141.62-127.68 ppm are due to aromatic carbons of phenyl group. The signals observed at δ 49.23 and 23.59 ppm is due to α, α' and β, β' carbons of pyrrolidine ring.

UV-visible spectrum in DMF registers an intense split bands centered at 287 and 226 nm which are presumably due

TABLE-1
ANALYTICAL, CONDUCTANCE AND MAGNETIC MOMENT DATA FOR V(IV), Mn(II) and Fe(II) complexes of PBA

Complex	Elemental analysis (%): Found (calcd.)					Λ_M (ohm ⁻¹ cm ² mol ⁻¹)	Colour (μ_{eff} B.M)
	C	H	N	M	SO ₄		
VOSO ₄ .PBA.H ₂ O	32.08 (31.90)	3.51 (3.68)	5.89 (5.73)	10.65 (10.42)	19.13 (19.63)	06.22	Dark Green (1.73)
MnSO ₄ .PBA.2H ₂ O	32.50 (32.70)	3.41 (3.77)	6.21 (5.87)	11.95 (11.52)	19.80 (20.13)	15.43	Colourless (5.31)
FeSO ₄ .2PBA	44.30 (43.70)	4.72 (5.04)	7.50 (7.84)	8.08 (7.82)	13.28 (13.45)	31.59	Brown (2.50)

to $n \rightarrow \pi^*$ transition of the carbonyl group and $\pi \rightarrow \pi^*$ transition of the carbonyl group and the benzene ring. The mass spectrum was obtained on electron ionization mode¹¹. It shows a very weak molecular ion peak at $m/z = 218$, which confirms the molecular mass to this Mannich base (Fig. 1).

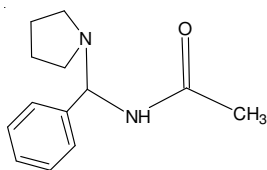


Fig. 1. N-[Phenyl(pyrrrolidin-1-yl)methyl]acetamide (PBA)

To find out the stoichiometry of the complexes, the percentage of the metal ions, anions and CHN were determined. The molar conductance values confirm that all the complexes are non-electrolytes (Table-1). In the IR spectra of all the PBA complexes, the stretching frequencies of C=O and C-N-C bonds are lowered. This indicates that both carbonyl oxygen and CNC nitrogen atoms are coordinated to the metal ions. The bands at the ranges of 1150, 1000 and 900 cm⁻¹ are due to 'SO' stretching mode; the 'OSO' bending mode splits up into 650, 600 and 580 cm⁻¹ in the complexes. The frequencies 750(ν_1) and 500(ν_2) cm⁻¹ observed are due to coordinated sulphato group associated with bidentate chelation¹². The bands around 3500-3300, 1630-1600, 880-820, 705-620 and 540-520 cm⁻¹ found only in the spectra of VO and Mn(II) sulphato complexes indicates the presence of coordinated water molecule.

The UV-visible spectrum of oxovanadium(IV) sulphato complex shows a broad band at 17915 cm⁻¹ due to the ${}^2B_2 \rightarrow {}^2B_1$ transition and the one at 23184 cm⁻¹ is ascribed to the ${}^2B_2 \rightarrow {}^2A_1$ transition. The bands at 31976 and 39245 cm⁻¹ are due to charge transfer from ligand to metal. The EPR spectrum¹³ of this complex do not show any resolution at g_{\parallel} region, so it can be assumed that g_x and g_y are same or nearly the same. The G value of 1.9704 indicates strong interaction between the ligand and the metal ion. The magnetic moment value is 1.73 B.M., which suggests a hexa coordinate geometry (Fig. 2).

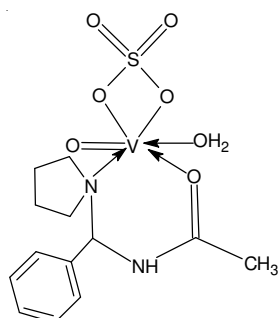


Fig. 2. VOSO₄.PBA.H₂O

The electronic spectrum of Mn(II) shows the three absorption bands at 18021, 24967 and 28305 cm⁻¹ are attributable to the three spin allowed transitions *viz.*, ${}^6A_{1g} \rightarrow {}^4T_{1g}$, ${}^6A_{1g} \rightarrow {}^4E_g + {}^4A_{1g}$ and ${}^6A_{1g} \rightarrow {}^4T_{2g}$. The magnetic moment value was found to be 5.31 B.M., suggest a hexa coordinate environment around Mn(II) ion (Fig. 3).

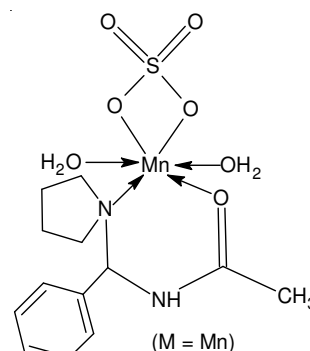


Fig. 3. MnSO₄.PBA.2H₂O

The UV-visible spectrum of Fe(II) registers highly intense CT band at 39942 cm⁻¹, which obscures the other very low intensity *d-d* absorption bands. The μ_{eff} value of 2.50 B.M. points to a low spin octahedral structure for the complex (Fig. 4).

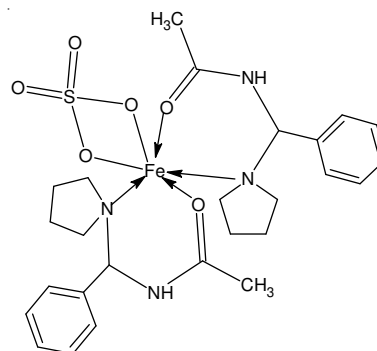


Fig. 4. FeSO₄.2PBA

Antibacterial screening: Among the various complexes, the VO(IV) sulphato complex was found to be the most active against all the species. This pronounced activity may be explained as follows. The lipids and polysaccharides are important constituents of the cell wall and membrane, which are very much preferred for the metal ion interaction. The cell also contains many aminophosphates and carbonyl and cysteinyl ligands, which maintain the integrity of the membrane by acting as a diffusion barrier and also provide suitable sites for binding. Since the VO(IV) sulphato complex has one labile water molecule and coordinately unsaturated, the metal center in this complex can exchange water molecules for biological binding sites¹⁴. As a result of chelation, the polarity of the

metal ion is reduced and the increased lipophilic character favours the interaction of metal complexes of the cell, resulting in interference with the normal cell processes.

Antifungal screening: It is interesting to note that the fungitoxicity of free ligand is less severe than that of metal chelates. Among the complexes screened, the order of activity was found to be VO(IV) complex > Fe(II) complex > Mn(II) complex > PBA. A possible mechanism of toxicity may be speculated in the light of chelation theory¹⁵. Chelation considerably reduces the polarity of the metal ion mainly due to partial sharing of its positive charge with donor groups and possible π -delocalization over the chelate ring. This increases the lipophilic character of the neutral chelate, which favours its permeation through lipid layers of fungus membranes¹⁶. Furthermore, the mechanism of action of the compounds may involve the formation of a hydrogen bond through the uncoordinated O, S and N heteroatoms with the active centers of the cell constituents, resulting in interference with the normal cell process. The presence of lipophilic and polar substituents like C=O, C=S, SH and NH are expected to enhance the fungitoxicity.

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