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Synthesis, characterization and screening of antimicrobial activity of metal complexes derived from the mannich base, N-(piperidinomethyl)phthalimide

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ABSTRACT

A new Mannich base, N-(Piperidinomethyl)phthalimide (L), formed by the condensation of piperidine, formaldehyde and phthalimide, and its Cu(II) complexes have been synthesized. Their structures have been elucidated on the basis of elemental analysis, molar conductance, IR, UV-visible, mass, ^{1}H NMR and ^{13}C NMR, EPR, magnetic and thermal studies. All the complexes exhibit octahedral geometry. Infrared spectral data show that the organic ligand is bidentate, binding through one of the two carbonyl oxygen atoms of the phthalimide moiety and the piperidine ring nitrogen and also the existence of coordinated water molecules. The X band EPR spectra of Cu(II) complexes in DMSO at room temperature were recorded and their salient features are reported. Thermal data of some of the compounds show that the thermal decompositions take place mostly in two steps to produce metal oxides as final residues. Antimicrobial activities of the newly synthesized compounds were also investigated.

Keywords: Mannich base, thermal analysis, electrochemical behaviour, biological studies.

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INTRODUCTION

Mannich base ligands and their metal complexes have attracted great interest in chemistry and biology due to their facile synthesis and wide applications[1-3]. Considerable attention has been focused on the syntheses of new copper(II) complexes of ligands containing bulky groups because of their role in the development of coordination chemistry, and in inorganic biochemistry, catalysis, optical materials, antibacterial, antifungal, analgesic, anxiolytic, antitumor[4-8] activities and so on. Metal complexes of Mannich bases have been studied[9-10] extensively in recent years due to their selectivity and sensitivity towards various metal ions. A search through the literature reveals that no work has been done on the Mannich base of piperidine and phthalimide. It is well known from the literature that phthalimide compounds containing the imido 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-(Piperidinomethyl) phthalimide and its coordination chemistry.

MATERIALS AND METHOD

All the reagents used for synthesizing the ligand and its complexes were of A.R. grade. The solvents used were commercial products of the highest available purity and were further purified by distillation. Micro elemental data were obtained with Carlo Erba 1108 elemental analyzer. Metal contents were estimated by usual procedure14, after digesting the complexes with con.HNO_3. Conductance data were obtained in ~10-3 M DMF solution of the complexes using digital conductivity meter. IR spectra were recorded using Perkin Elmer FT-IR spectrometer by using KBr pellets. Absorbance in UV-Visible region was recorded in DMF solution using UV-Visible spectrometer. The ^{1}H and ^{13}C NMR of the ligand were recorded on a Bruker instrument employing TMS as internal reference and DMSO-d_6 as solvent. The FAB mass for the ligand was carried out using Mass spectrometer. The room temperature magnetic susceptibility measurements of the complexes were made by using a Gouy Magnetic Balance. Thermal studies were carried out on a Perkin Elmer Diamond TG/DTA thermal analyzer in an atmosphere of air/N_2 at a linear heating rate of 10˚ C/min from ambient to 900˚ C using alumina as the reference material. The TG was derivatized to get DTG by the software associated with the instrument. The antimicrobial activity was determined the agar well diffusion method.

Synthesis of the Mannich base ligand (L)

A new Mannich base N-(Piperidinomethyl)phthalimide (L) was synthesized by employing Mannich condensation reaction[11] between piperidine, formaldehyde and phthalimide in 1:1:1 mole ratio. It was recrystallized from ethanol (yield: 82 %., melting point: 115˚ C).

Synthesis of Mannich base metal complexes

Metal complexes of the Mannich base ligand (L) were isolated from alcoholic medium. N-(Piperidinomethyl)phthalimide ligand was dissolved in hot ethanol. Hot ethanolic solution of Cu (II) salt was added drop wise to the ligand solution with constant stirring. The insoluble complex precipitated in each case was filtered, washed repeatedly with ethanol and with minimum quantity of acetone, and then dried in a vacuum desiccator.

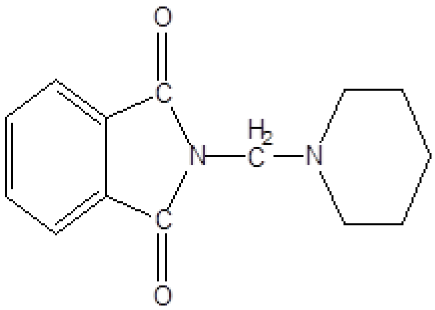
Antimicrobial Screening

Antibacterial and antifungal activities of the organic ligand and its selected few metal complexes were screened *in vitro* against the bacterial strains viz. *E.coli* and *S.aureus* and the fungal species *C.albicans* and *A.niger* employing agar well diffusion technique. Nutrient agar medium was used for culturing bacteria and Rose Bengal Chloramphenicol agar medium was used for culturing fungal species. *Kanamycin* and *tetracyclin* were used as standard antibacterial drugs and *amphotericin* and *nystatin* were used as the standard antifungal agents. Wells were made on the previously seeded agar plate with a metallic borer and various concentrations of the test solutions in DMF were transferred into the wells. The concentrations tested were 25, 50, 75 and 100 µg/mL. The nutrient agar plates inoculated with the bacterial organisms under test were incubated at 35 - 37°C for 24 h, but the plates streaked with fungal species were incubated at 35 - 37°C for 48 h and then the diameters of inhibition zones (in mm) were measured.

RESULTS AND DISCUSSION

Synthesis and Characterization of the Mannich base ligand (L)

Analysis: Calculated for $C_{14}H_{16}N_2O_2$: C 68.85, H 6.55, N 11.48%; Found: C 68.23, H 6.87, N 11.22%; Uv (DMF nm): 292, 272; IR (KBr cm^{-1}): 1763,1718 (C=O), 1256,1174 (CNC); ^{1}HNMR ($CDCl_3$ δppm): 7.85(aromatic H), 2.47(NCH_2), 1.45 (CH_2 piperidine), 4.43 (NCH_2N); ^{13}CNMR ($CDCl_3$ δppm): 168.76, 134.44, 131.4, 123.06, 52.14, 51.19, 25.38, 23.25, 59.85; Mass (m/z): 244 (M^+ peak). Thus based on the data obtained from various physical and chemical studies, the molecular structure of L is confirmed as shown below.



2-(piperidin-4-ylmethyl)isoindoline-1,3-dione (L)

Characterization of metal complexes

The analytical data and the stoichiometries of the metal complexes are shown in Table 1. The molar conductivity values of the metal complexes establish the fact that they are non-ionic due to the inclusion of anions within the coordination sphere[12]

Analytical and conductance data (Table 1) indicate the stoichiometry of the complexes as $Cu(NO_3)_2.L.2H_2O$ and $CuSO_4.L.2H_2O$. The IR spectrum of the complexes registered lower frequency values for the C=O by about 51 and 46 cm^{-1} respectively. The CNC of the ligand shifted to lower frequency of 37 and 64 cm^{-1} respectively, which suggests bidentate coordination of the ligand (Table 2). Thus the Mannich base ligand (L) in all the complexes studied behaves as a chelating or bridging bidentate one and the binding sites are one carbonyl oxygen atom and the piperidine ring nitrogen atom. The nitrato and sulphato complexes of Cu(II) also exhibits bands at 3485-3335 (ν_{OH}) due to the presence of coordinated water in the aqua complexes. This fact is also supported by the thermal data.

Table 1 Analytical and physical data of the metal complexes of L.

Compound	Colour	Analytical (%) found (calculated)					Λ_M (Ω^{-1} cm^{2}mol^{-1})
		C	H	N	M	A	
$Cu(NO_3)_2.L.2H_2O$	bluish green	35.21 (35.93)	4.78 (4.28)	11.68 (11.98)	13.20 (13.59)	- (26.52)	9.45
$CuSO_4.L.2H_2O$	pale green	38.68 (38.22)	4.18 (4.55)	6.56 (6.37)	14.39 (14.46)	21.30 (21.84)	22.49

Table 2 IR spectral assignments of the ligand L and its complexes

Compound	$\nu_{C=O}$	ν_{CNC}	ν_{M-O}	ν_{M-N}	ν_{M-X}	ν_{OH}
L ($C_{14}H_{16}N_2O_2$)	1644	1174	-	-	-	-
$Cu(NO_3)_2.L.2H_2O$	1593	1137	533	-	-	3435
$CuSO_4.L.2H_2O$	1598	1110	490	420	-	3485

Table 3: Magnetic and electronic spectral data of the metal complexes

Complex	Magnetic moment (B.M)	Coordination Environment	Absorption maxima	Transition Assignment
$Cu(NO_3)_2.L.2H_2O$	1.40	N, 5O	9814	$^2B_{1g} \rightarrow {}^2A_{1g}$
			11242	$^2B_{1g} \rightarrow {}^2B_{2g}$
			13123	$^2E_g \rightarrow {}^2T_{2g}$ (F)
			25365	CT
$CuSO_4.L.2H_2O$	1.22	N, 5O	9403	$^2B_{1g} \rightarrow {}^2A_{1g}$
			11448	$^2B_{1g} \rightarrow {}^2B_{2g}$
			13532	$^2E_g \rightarrow {}^2T_{2g}$ (F)
			26110	CT

The nitrato and sulphato complexes of Cu(II) exhibit electronic absorption bands at 9814 and 9403 cm^{-1} respectively due to $^2B_{1g}\rightarrow{}^2A_{1g}$ transition and at 11242 and 11448 cm^{-1} respectively due to $^2B_{1g}\rightarrow{}^2B_{2g}$ transitions, while these same complexes exhibit bands at 13123 and 13532 cm^{-1} respectively due to $^2E_g\rightarrow{}^2T_{2g}$(F) transitions. The bands observed at 25365 and 26110 cm^{-1} may be due to respective charge transfer transitions (Table 3). The band positions suggest a tetragonally distorted octahedral geometry for these complexes. The effective magnetic moments of 6-coordinated Cu(II) nitrato and sulphato complexes are measured at 1.40 and 1.22 B.M. which are much less than the spin only value indicating the interaction between unpaired spins in the solid state.

EPR spectrum of Cu(II) complex

The X band EPR spectra of polycrystalline nitrato and sulphato complexes of Cu(II) (Figure 5) with L recorded at room temperature (Table 4) using DPPH as a reference standard. The g values of sulphato complex of Cu(II) ion are in the order $g_{\|} > g_{\perp} > g_e$ signifying that the unpaired electron lies predominantly in the $d_{x^2-y^2}$ orbital. The EPR spectrum of the sulphato complex of Cu(II) ion shows axial symmetry which indicates that the geometry around the Cu(II) ion is distorted octahedral. The $g_{\|}$ value of sulphato complex of Cu(II) ion is greater than 2.3 indicating that in the Cu(II) complex, the metal-ligand bonding is slightly ionic in nature[13]. The axial symmetry parameter G is less than 4 in the sulphato complex of Cu(II) due to the presence of considerable interaction between the two Cu(II) ions in the solid state. The EPR spectra of nitrato complex of Cu^{II} ion show only a single line ie. g is isotropic, which indicate that the symmetry of Cu(II) complexes are cubic.

Table 4: EPR Spectral Parameters for Cu(II) Complexes at Room Temperature

Complex	g_{iso}	$g_{\perp}$	g_{II}	G	g_{av}
$Cu(NO_3)_2.L.2H_2O$	2.2749	-	-	-	-
$CuSO_4.L.2H_2O$	-	2.1061	2.3442	3.3229	2.1855

Thermal decomposition studies

The experimental thermal data obtained for the Mannich base ligand (L) and its Cu(II) sulphato complex are provided in Table. 5. The TG/DTA and TG/DTG patterns are shown in Figure 1-4. The TG/DTG curves of the (L) show that it is thermally stable up to 174.55°C. It melts at 113.92°C as shown by a sharp endotherm at 113.92°C. Rapid decomposition and weight loss occur in the temperature range 174.55-310°C. The rapid oxidative decomposition of the organic compound in the presence of air is supported by the existence of an exothermic DTA peak at 304.92°C. There is a rapid decomposition of the residue in the range of 484-540°C as indicated by the endotherm at 524.20°C and by the DTG peak centered at 522.43°C. The presence of 10% weight as the final residue in the temperature range 530-706°C may indicate the formation of some stable polymeric product of formaldehyde, the composition of which is not known.

Table 5 Thermal decomposition data for the Mannich base L and its Cu(II) sulphato complex.

Compound	**Stable up to (°C)**	**Decomposition Temperatur range (°C)**			**Probable change Intermediate**	**DTA Peak (°C) and its nature**	**DTG Peak (°C)**
		Stage	**Initial**	**Final**			
L($C_{14}H_{16}N_2O_2$)	174.5				Melting	113.9	
		I	174.5	310	Oxidative degradation polymer of HCHO.	304.9 exo	251.3
		II	484	540	Decomposition of polymer of HCHO to form more stable higher polymer	524.2 exo	522.43
$CuSO_4$.L.$2H_2O$	70	I	70	78	Elimination of water to give anhydrous complex	75.4 endo	73.6
		II	173	227	Elimination of ½ mol of PMP to form $2CuSO_4$.L	219 endo	217.2
		III	600	700	Elimination of ½ L to form $CuSO_4$	690 endo	664.9

The Cu(II) sulphato complex experiences loss of water from 70°C onwards. The dehydration process is indicated by the DTG peak centered at 73.64°C. At about the same temperature there is an endotherm signaling the loss of water. The anhydrous complex $CuSO_4$.PMP decomposes to give an intermediate complex $2CuSO_4$.L in the temperature range 173-227°C as indicated by the DTG peak centered at 217.17°C. This decomposition is also substantiated by the endothermic peak found at 218.98°C. The intermediate complex rapidly decomposes at a rate of 0.119 mg/min in the temperature range 600-700°C to give anhydrous $CuSO_4$ as final residue.

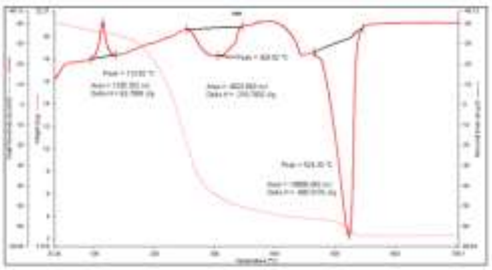


Figure 1 TG /DTA Pattern of (L)

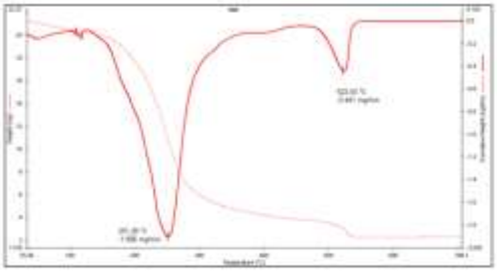


Figure 2 TG /DTG Pattern of (L)

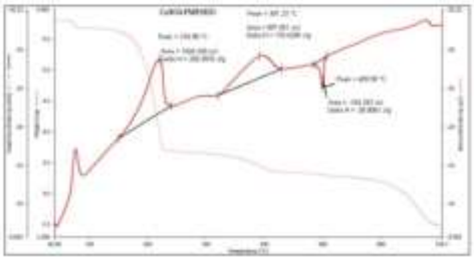


Figure 3 TG /DTA Pattern of $CuSO_4$.L.H_2O

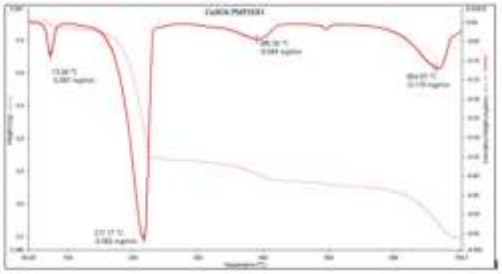
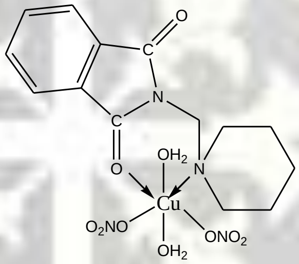
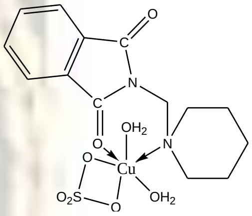


Figure 4 TG /DTG Pattern of $CuSO_4$.L.H_2O

Figure 5 EPR Spectrum of CuSO4.L.2H2O



Cu$(NO_3)_2$.L.$2H_2O$



$CuSO_4$. L.$2H_2O$

Evaluation of antimicrobial activities

The antibacterial and antifungal activities of the (L) and its Cu(II) complexes studied in vitro are provided in Table 6. The metal complexes are more active than the Mannich base ligand. The Cu(II) nitro complex is more toxic than Cu(II) sulphato complex against both bacterial and fungal strains tested. The higher activity of the metal complexes is ascribed to the increase in the lipophilic nature of the complexes arising from chelation. The mode of action of the complexes may also involve formation of hydrogen bonds with the imidato carbonyl groups by the active sites leading to interference in the process of cell wall synthesis

Table 6 Antibacterial and Antifungal activities of the ligand L and its metal complexes

Compound	**Antibacterial activity(Zone of Inhibition in mm)**						**Antifungal Activity (Zone of Inhibition in mm)**					
	E.coli **Conc. of Compound (µg/mL)**			***S.aureus*** **Conc. of Compound (µg/mL)**			***A. niger*** **Conc. of Compound (µg/mL)**			***C. albicans*** **Conc. of Compound (µg/mL)**		
	50	75	100	50	75	100	50	75	100	50	75	10
L ($C_{14}H_{16}N_2O_2$)	6	8	10	6	8	10	4	6	7	6	7	8
$Cu(NO_3)_2.L.2H_2O$	12	14	15	12	12	14	13	14	15	12	14	16
$CuSO_4.L.2H_2O$	11	13	14	10	12	13	11	12	14	11	13	15
Kanamycin	15	-	-	-	-	-						
Tetracyclin	-	-	-	13	-	-						
Amphotericin							12	-	-	-	-	-
Nystatin							-	-	-	14	-	-

CONCLUSION

The new Mannich base (L) and its metal complexes with Cu(II) have been synthesized and characterized. The Mannich base ligand is bidentate, binding through one of the two carbonyl oxygens and the piperidine ring nitrogen. The metal complexes studied display octahedral geometry. The results on antibacterial and antifungal screening of the ligand and its complexes indicate that the metal complexes are more active than the free L and that the Cu(II) nitro complex is more potent than the Cu(II) sulphato complex. The enhanced antimicrobial activity of the metal complexes is explained on the basis of chelation theory.

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