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Synthesis and Characterization of New Mannich Base of 1-(morpholin-4-ylmethyl) pyrrolidine-2,5-dione (L) with Some Transition Metal Complexes



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ABSTRACT

Mannich bases play an active role in the formation of succinimide derivatives. The Mannich base was prepared by condensation of succinimide, formaldehyde and morpholine. The synthesized base was reacted with Mn(II), Co(II) and Ni(II) metal ions to form complexes. They were characterized by elemental analysis, molar conductance, IR, ^1H & ^{13}C NMR, UV-Vis, mass spectral studies and thermal analysis. The metal complexes isolated are non-electrolytes and paramagnetic in nature. The presence of coordinated water molecules in these complexes was indicated by IR spectra and TG analysis. Thermal data (TG/DTA) of some of the compounds show that the thermal decompositions take place mostly in two steps to produce metal oxides as final residues. The antibacterial and antifungal activities of the ligand and a few complexes were screened by agar well diffusion method. The metal complexes are more active than the organic ligand.

1. INTRODUCTION

Cyclic imides, such as succinimides, maleimides, glutarimides, phthalimides and related compounds possess structural features, which confer on them potential biological activities and pharmaceutical applications. Their molecules contain an imide ring and the general structure - CO-N(R)-CO-, so that they are hydrophobic and neutral, and can therefore diffuse through biological membranes¹. Various classes of cyclic imides have received attention due to their antibacterial, antifungal, analgesic, anxiolytic and antitumor activities and HIV-1 reverse transcriptase inhibitor property²⁻⁷. Succinimide derivatives are important in biology due to their pharmacological properties. They have been evaluated as agricultural fungicides, bactericides, cytotoxic agents, antioxidants, anticonvulsants and as corrosion inhibitors⁸⁻¹¹. In view of the significance of morpholine and succinimide derivatives we report here a systematic study on Mn(II), Co(II) and Ni(II) coordination compounds with 1-(morpholin-4-ylmethyl)pyrrolidine-2,5-dione.

2. EXPERIMENTAL

2.1 MATERIALS AND METHODS

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.HNO₃. 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 ¹H and ¹³C NMR of the ligand were recorded on a Bruker instrument employing TMS as internal reference and DMSO-d₆ 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/N₂ 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.

2.2 Synthesis of the Mannich base ligand (L)

A new Mannich base (L) was synthesized by employing Mannich condensation reaction between morpholine, formaldehyde and succinimide in 1:1:1 mole ratio. It was recrystallized from ethanol (yield: 80 %, melting point: 100.2° C).

2.3. Synthesis of Mannich base metal complexes

Metal complexes of the Mannich base ligand (L) were isolated from alcoholic medium. 1-(morpholin-4-ylmethyl) pyrrolidine-2, 5-dione ligand was dissolved in hot ethanol. Hot ethanolic solution of Mn (II) / Co(II) / Ni(II) sulphate and nitrate was added dropwise 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.

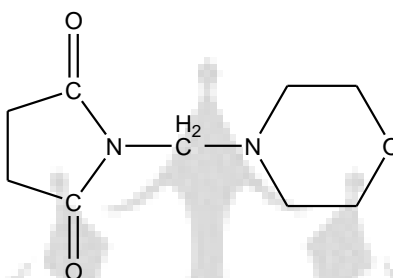
2.4. Antimicrobial Screening

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 *tetracycline* 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 100µg/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.

3. RESULTS AND DISCUSSION

3.1. Structural characterization of 1-(morpholin-4-ylmethyl) pyrrolidine-2, 5-dione (L)

Analysis: Calculated for $C_9H_{14}N_2O_3$: C 54.54, H 7.07, N 14.14%; Found: C 54.10, H 7.06, N 14.13%; Uv (DMF nm): 336, 262; IR (KBr cm^{-1}): 1771,1702 (C=O), 1163, 1150 (CNC); 1H NMR ($CDCl_3$ δ ppm): 2.49 (NCH₂), 2.65 (CH₂ succinimide), 3.38 (O-(CH₂)₂ of morpholine), 4.19 (NCH₂N); ^{13}C NMR ($CDCl_3$ δ ppm): 178.63, 66.05,50.45,29.49,59.24; Mass (m/z): 198 (M⁺ peak). Thus based on the data obtained from various physical and Chemical studies, which is showing below as the molecular structure of L is confirmed.



N-(Morpholinomethyl)succinimide (L)

3.2. 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 sphere¹²

Table 1 Analytical and physical data of the Mannich base (L) and its metal complexes

Compound	Analytical (%) found (calculated)					Λ_M ($\Omega^{-1} cm^2 mol^{-1}$)
	C	H	N	M	A	
$MnSO_4 \cdot L \cdot 2H_2O$	27.64 (28.06)	4.02 (4.68)	6.56 (7.27)	14.89 (14.27)	24.21 (24.94)	18.21
$Co(NO_3)_2 \cdot L$	27.81 (28.35)	4.08 (3.67)	13.26 (14.70)	15.86 (15.47)	- (32.55)	22.45
$CoSO_4 \cdot L \cdot 2H_2O$	27.56 (28.35)	3.90 (4.73)	6.98 (7.35)	14.93 (15.47)	25.86 (25.20)	12.55
$Ni(NO_3)_2 \cdot L \cdot 2H_2O$	25.10 (25.92)	3.96 (4.32)	12.56 (13.44)	13.68 (14.09)	- (29.76)	13.30
$NiSO_4 \cdot L \cdot H_2O$	29.81 (29.13)	3.90 (4.32)	6.58 (7.55)	15.02 (15.84)	25.10 (25.89)	28.73

Table 2 Important IR spectral data (cm⁻¹) of ligand and its complexes

Compound	$\nu_{C=O}$	ν_{CNC}	ν_{M-O}	ν_{M-N}	ν_{M-X}	ν_{OH}
L(C ₉ H ₁₄ N ₂ O ₃)	1702	1150	-	-	-	-
MnSO ₄ .L.2H ₂ O	1605	1103	483	-	-	3399
Co(NO ₃) ₂ .L	1658	1105	540	438	-	-
CoSO ₄ .L.2H ₂ O	1661	1114	535	490	-	3418
Ni(NO ₃) ₂ .L.2H ₂ O	1658	1102	-	477	-	3399
NiSO ₄ .L.H ₂ O	1579	1099	-	467	-	3410

Analytical and conductance data (Table 1) indicate the stoichiometry of the complexes as MnSO₄.L.2H₂O, Co(NO₃)₂.L, CoSO₄.L.2H₂O, Ni(NO₃)₂.L.2H₂O and NiSO₄.L.H₂O. The IR spectrum of the complexes registered lower frequency values for the C=O by about 97, 44, 41 44 and 123 cm⁻¹ respectively. The CNC of the ligand shifted to lower frequency of 47, 45, 36, 48 and 51 cm⁻¹ respectively, which suggests bidentate coordination of the ligand (Table 2).

Table 3 Colour, Electronic Spectral Bands, Transition Assignments, Metal Environment and Magnetic Moment Values of Mn^{II}, Co^{II} and Ni^{II} Complexes of L

Complex	Colour (μeff. B.M)	Environment	Absorption maxima(cm ⁻¹)	Transition Assignment
MnSO ₄ .L.2H ₂ O	Brown 5.42	N, 5O	18712 22779 25810	⁶ A _{1g} → ⁴ T _{1g} (G) ⁶ A _{1g} → ⁴ T _{2g} (G) ⁶ A _{1g} → ⁴ A _{1g} + ⁴ E _g (G)
Co(NO ₃) ₂ .L	Pink 5.19	N, 5O	7218 15527 18960 29328	⁴ T _{1g} (F) → ⁴ T _{2g} (F) ⁴ T _{1g} (F) → ⁴ A _{2g} (F) ⁴ T _{1g} (F) → ⁴ T _{1g} (P) CT
CoSO ₄ .L.2H ₂ O	Pale brown 5.28	N, 5O	7210 14858 18692 33720	⁴ T _{1g} (F) → ⁴ T _{2g} (F) ⁴ T _{1g} (F) → ⁴ A _{2g} (F) ⁴ T _{1g} (F) → ⁴ T _{1g} (P) CT
Ni(NO ₃) ₂ .L.2H ₂ O	Green 3.62	N, 5O	9843 14895 25685 35420	³ A _{2g} (F) → ³ T _{2g} (F) ³ A _{2g} (F) → ³ T _{1g} (F) ³ A _{2g} (F) → ³ T _{1g} (P) CT
NiSO ₄ .L.H ₂ O	Light green 3.39	N, 3O	3845 8571 15432 26850	³ T _{1g} (F) → ³ T _{2g} (F) ³ T _{1g} (F) → ³ A _{2g} (F) ³ T _{1g} (F) → ³ T _{2g} (P) CT

There are infrared spectral evidences for the binding of anions to the metal centre. In the Co(II) nitrate complex spectrum ν_1 , ν_2 , ν_5 and ν_6 bands due to nitrate groups appear at 1317, 1183, 1591 and 865 cm^{-1} respectively. A large difference (274 cm^{-1}) between ν_5 and ν_1 suggests bidentate coordination of nitrate groups. But in Ni(II) nitrate complex the ν_1 , ν_2 , ν_5 and ν_6 absorption bands of the coordinated nitrate groups appear at 1379, 1102, 1511 and 867 cm^{-1} respectively. The separation between ν_5 and ν_1 (132 cm^{-1}) is much less than 200 cm^{-1} suggesting monodentate coordination.

The absorption bands observed at 1140, 1044 and 921 (ν_3); 805 (ν_1); 794 and 631 (ν_4) and 483 cm^{-1} (ν_2) in the case of Mn(II) sulphate complex and bands seen at 1144, 1114 and 939 (ν_3); 775, 752 and 672 (ν_4); 858 (ν_1) and 442 cm^{-1} (ν_2) in the case of Co(II) sulphate complex are consistent with bidentate coordination of sulphate group. But in Ni(II) sulphate complex the vibrations observed at 1099 (ν_3), 795 and 616 (ν_4), 898 (ν_1) and 468 (ν_2) indicate monodentate sulphate group.

The UV spectrum of the Mannich base ligand exhibits absorption bands at 336 and 262 nm which are due to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions respectively of the carbonyl group. These bands have shifted to lower values in the spectra of metal complexes suggesting coordination of carbonyl oxygen to the metal ion. The Mn (II) sulphate complex exhibit electronic absorption bands (Table 3) at 25810 cm^{-1} due to ${}^6A_{1g} \rightarrow {}^4T_{1g}(G)$ (ν_1); 22799 cm^{-1} due to ${}^6A_{1g} \rightarrow {}^4T_{2g}(G)$ (ν_2) and at 18712 cm^{-1} due to ${}^6A_{1g} \rightarrow {}^4A_{1g} + {}^4E_g(G)$ (ν_3) suggesting octahedral environment around the metal ion. Also the magnetic moments measured at 5.42 B.M indicate octahedral geometry of Mn(II) in its complexes.

The nitrate and sulphate complexes of Co(II) exhibit absorption bands at 7210-7218, 15527-14858, 18960-18692 and $29328-33720\text{ cm}^{-1}$ which are attributed to ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ (ν_1); ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ (ν_2); ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ (ν_3) and charge transfer transitions respectively. The ν_2/ν_1 ratio for these nitrate and sulphate complexes are at 2.59-2.62 indicating octahedral stereochemistry of Co(II) complexes. These nitrate and sulphate complexes measure magnetic moments at 5.19-5.28 B.M which are expected for high spin octahedral Co(II) species¹³.

The Ni(II) nitrate complex exhibits bands at 9843, 14895, 25685 and 35420 cm^{-1} which are due to ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ (ν_1); ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ (ν_2) and ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ (ν_3) ligand field transitions and charge transfer transition respectively. The ν_2/ν_1 ratio of 1.51 and the magnetic moment at 3.62 B.M. for the nitrate complex indicate an octahedral geometry of Ni(II).

The Ni(II) sulphate complex exhibit absorption band at 3845, 8571, 15432 and 26850 cm^{-1} which are assigned to ${}^3T_{1g}(F) \rightarrow {}^3T_{2g}(F)$ (ν_1); ${}^3T_{1g}(F) \rightarrow {}^3A_{2g}(F)$ (ν_2); ${}^3T_{1g}(F) \rightarrow {}^3T_{2g}(P)$ (ν_3) ligand field transitions and charge transfer transition respectively. The ν_2/ν_1 ratio for these complexes is 2.23. The μ_{eff} values for the Ni(II) sulphate complex is 3.39 B.M. These spectral features and magnetic data indicate tetrahedral environment around Ni(II).

Thermal decomposition studies

The thermoanalytical data obtained for the Mannich base ligand (L) and its Co(II) nitrate and Ni(II) chloro complexes are provided in Table. 4. The TG/DTA and TG/DTG patterns are shown in Fig. 1 & 3 and 2 & 4 respectively. 1-(morpholin-4-ylmethyl) pyrrolidine-2,5-dione exhibits an endothermic DTA peak at 100.2°C indicating its melting. Rapid decomposition and weight loss (75%) occur in the range 181-275°C. The DTG peak centered at 231.5°C and exothermic DTA peak at 226.8°C are supportive of the oxidative decomposition of the ligand in air. The intermediate compound having ~15% weight may be a polymer of formaldehyde. In the range of 455-475°C the polymer undergoes complete oxidative decomposition as identified by an exothermic DTA peak at 470°C and DTG peak at 466°C.

The Co (II) nitrate complex undergoes rapid decomposition in the temperature range 241 - 283°C. Elimination of the ligand (L) and simultaneous decomposition of $\text{Co}(\text{NO}_3)_2$ occur to form the residue of CoO. The oxidative decomposition is evidenced by an exothermic DTA peak at 274°C and DTG peak at 255°C

Table 4 Thermal decomposition data for the Mannich base and its metal complexes.

Compound	Stable up to (°C)	Decomposition Temperature range			Probable change / intermediate	DTA Peak (°C) and its	DTG Peak (°C)
		Stage	Initial	Final			
L	181.5				Melting	100.2 endo	-
		I	181	275	Decomposition of L to form polymer of formaldehyde	229 exo	231.5
		II	455	475	Complete decomposition of the polymer of formaldehyde	470 exo	466.3
Co(NO ₃) ₂ .L	240.9	I	240.9	283	Elimination of L and simultaneous decomposition of Co(NO ₃) ₂ to form CoO.	274.1 exo	255

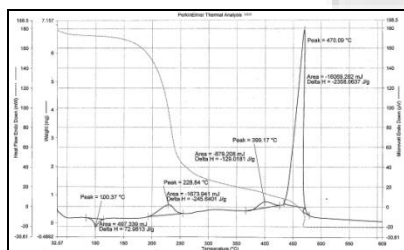


Fig. 1 TG /DTA Pattern of 1-(morpholin-4-ylmethyl)pyrrolidine-2,5-dione

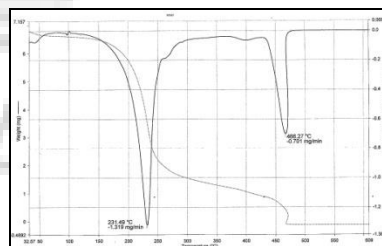


Fig. 2 TG /DTG Pattern of 1-(morpholin-4-ylmethyl)pyrrolidine-2,5-dione

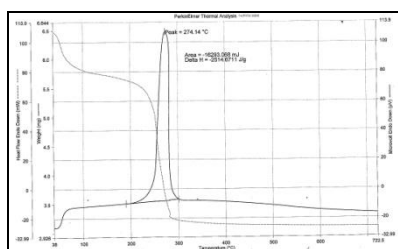


Fig. 3 TG /DTA Pattern of Co(NO₃)₂.L

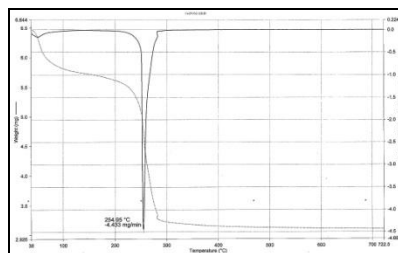


Fig. 4 TG /DTG Pattern of Co(NO₃)₂.L

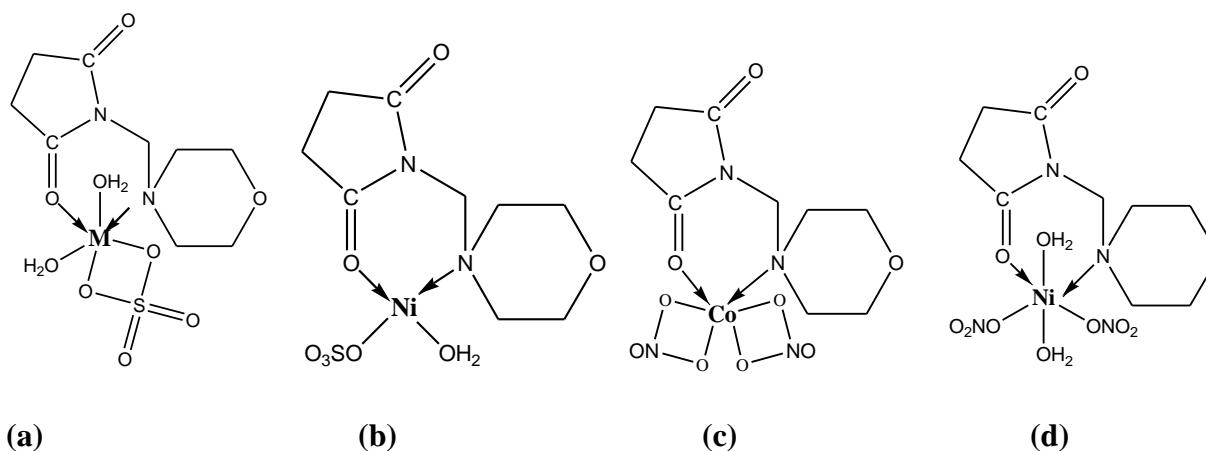


Figure 5 Structures of (a) $M.SO_4.L.2H_2O$ where $M= Mn(II)$ and $Co(II)$, (b) $NiSO_4.L.H_2O$ (c) $Co(NO_3)_2.L$ and (d) $Ni(NO_3)_2.L.2H_2O$

Evaluation of antimicrobial activities

The antibacterial and antifungal activities of the ligand (L) and its $Co(II)$ and $Ni(II)$ complexes studied *in vitro* are provided in Tables 5 and 6 respectively.

Table 5 Antibacterial activity of L and its metal complexes

Compound	Zone of inhibition (mm)							
	<i>A. niger</i>				<i>C. albicans</i>			
	Conc. of compound ($\mu g/mL$)				Conc. of compound ($\mu g/mL$)			
	25	50	75	100	25	50	75	100
L	2	4	5	6	3	4	5	7
$CoSO_4.L.2H_2O$	19	21	24	27	20	23	25	27
$NiSO_4.L.2H_2O$	15	18	21	23	15	18	21	24
Amphotericine	12	-	-	-	-	-	-	-
Nystatin	-	-	-	-	14	-	-	-

Table 6 Antifungal activity of L and its metal complexes

Compound	Zone of inhibition (mm)							
	<i>A. niger</i>				<i>C. albicans</i>			
	Conc. of compound ($\mu\text{g/mL}$)				Conc. of compound ($\mu\text{g/mL}$)			
	25	50	75	100	25	50	75	100
L	2	4	5	6	3	4	5	7
CoSO ₄ .L.2H ₂ O	19	21	24	27	20	23	25	27
NiSO ₄ .L.2H ₂ O	15	18	21	23	15	18	21	24
Amphotericin	12	-	-	-	-	-	-	-
Nystatin	-	-	-	-	14	-	-	-

The metal complexes are more active than the Mannich base ligand. Activity increases with increases in concentration of test compounds. The Co(II) complexes are more toxic than Ni(II) complexes against both bacterial and fungal strains tested. The higher activities of the metal complexes are ascribed to the increase in the lipophilic nature of the complexes arising from chelation (Selwin Joseyphus, 2010). Chelation reduces the polarity of the metal atom and increases its lipophilic nature favouring the permeation through the lipid layer of cell membrane.

4. CONCLUSION

The new Mannich base 1-(morpholin-4-ylmethyl) pyrrolidine-2,5-dione imide (L) and its metal complexes with Mn(II), Co(II) and Ni(II) ions have been synthesized and characterized. The infrared spectral results demonstrate clearly that the Mannich base ligand is bidentate, binding through one of the two carbonyl oxygen and the morpholine ring nitrogen. The metal complexes studied display either octahedral or tetrahedral geometry. The thermal data obtained for L show that the first stage involves decomposition of L to form a polymer of formaldehyde which then decomposes completely at higher temperatures. The Co(II) nitrate complex undergoes simultaneous elimination of L and decomposition of Co(NO₃)₂ to give CoO finally. 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 Co(II) complexes are more potent than the Ni(II) complexes. The enhanced antimicrobial activity of the metal complexes is explained on the basis of chelation theory.

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