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Synthesis, characterization and antimicrobial activity of 2-(dimethylamino-methyl)isoindoline-1,3-dione and its cobalt(II) and nickel(II) complexes

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ABSTRACT

In the present study a new Mannich base 2-(dimethylaminomethyl)isoindoline-1,3-dione and its metal complexes with cobalt(II) and nickel(II) ions have been synthesized and characterized. Their structures have been established on the basis of analytical, magnetic, conductance and spectral data. 2-(Dimethylaminomethyl)-isoindoline-1,3-dione is found to act as a neutral bidentate ligand coordinating to the metal ion through a carbonyl oxygen and tertiary amino nitrogen atoms. The non-electrolytic natures of the complexes are evidenced by their molar conductance values. On the basis of magnetic moments and electronic spectral data, the Co^{II}, Ni^{II} *complexes are assigned a tetrahedral stereochemistry and the* Ni^{II} *complexes are assigned / octahedral geometry. The antimicrobial activity of the ligand and its complexes has been studied by agar-well diffusion method. Both the organic ligand and the complexes possess significant antimicrobial activity comparable to that of the standard drugs.*

Keywords: Mannich base, metal complexes, magnetic moment, stereochemistry, antimicrobial activity.

INTRODUCTION

Phthalimides possess a structural features –CO-N(R)-CO- and an imide ring which help them to be biologically active and pharmaceutically useful[1]. Phthalimides have received attention due to their antibacterial, antifungal, analgesic [2], antitumour [3, 4], anxiolytic [5] and anti HIV-1 activities. When phthalimide is subjected to Mannich condensation, it may yield Mannich bases [6] which may display more potent biological activities. Metal complexes of Mannich bases have been studied extensively in the recent years due to the selectivity and sensitivity of the ligands towards biologically important metal ions. Recently Mannich bases of succinimide and phthalimide and their metal complexes have been synthesized, characterized and screened for their biological activities [7-9]. In view of these facts, we report herein the synthesis, characterization and anti-microbial screening of the new Mannich base 2-(dimethylaminomethyl)isoindoline-1,3-dione and its cobalt(II) and nickel(II) complexes.

MATERIALS AND METHODS

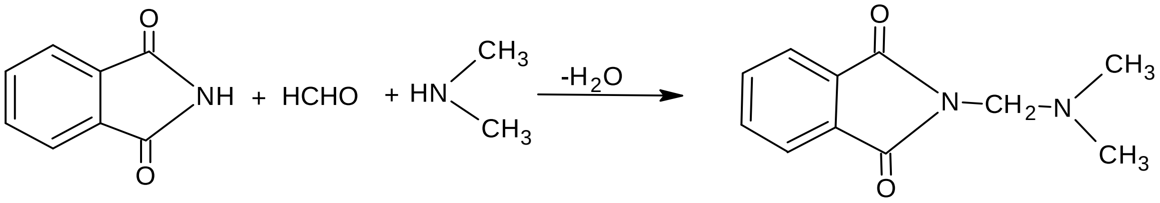
All the reagents and solvents were of Analar grade (Merck) and were used as such without further purification. Elemental analyses were performed using Carlo Erba 1108 CH analyzer and Coleman N analyzer. The molar conductivities of the metal complexes were measured in ~10^{-3}M DMF solutions at room temperature using Systronics Direct Reading Conductivity Meter 304. Infrared spectra were recorded on a Perkin Elmer 337 FT-IR spectrophotometer using KBr pellets. The UV-visible absorption spectra of the compounds were recorded on a Perkin Elmer EZ 301 spectrophotometer. Both ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL GSX-400 spectrometer employing TMS as internal reference and DMSO-d_6 as solvent at ambient temperature. The mass spectral study of the ligand was carried out using JEOL D-300 (EI) mass spectrometer. Magnetic susceptibility measurements were carried out using a Gouy magnetic balance at room temperature. $Hg[Co(SCN)_4]$ was used as a standard and diamagnetic corrections were made with Pascal's constants[10]. Wet chemical analyses for metal ions and anions (chloride and sulphate) were performed using standard methods [11]. Antimicrobial screening of the test compounds was carried out using Agar-well diffusion method.

Synthesis and characterization of 2-(dimethylaminomethyl)isoindoline-1,3-dione (L)

2-(Dimethylaminomethyl)isoindoline-1,3-dione is commonly known as N-(dimethylamino-methyl)phthalimide. It was characterized by the Mannich condensation reaction. Phthalimide (14.71g, 0.1mol) was mixed with 37% aqueous formaldehyde (7.5mL, 0.1mol) and then with dimethylamine (12.8mL, 0.1mol) with constant stirring at room temperature. The oily solution obtained was kept aside for two hours. The colourless solid product formed was suction filtered, washed with distilled water several times and finally with a small amount of acetone. It was dried at 60°C and recrystallized from ethanol (yield 86%). It melts at 77°C. The synthetic route of synthesized compound L is shown in **Scheme-1**.

The analytical and spectral data obtained for the ligand are summarized below:

Analysis: calculated for $\mathbf{C_{11}H_{12}N_2O_2}$: C 64.70, H 5.88, N 13.72 %, Found: C 64.60, H 5.96 , N 13.59 %, **FT-IR** (KBr, cm^{-1}): 2943, 2837(C-H), 1768, 1713 (C=O), 1393, 1313 (C-N), 1158, 1089 (C-N-C); ^{1}**H NMR** (DMSO-d_6, δppm): 2.20 (s, 6H, $N(CH_3)_2$), 4.39 (s, 2H, N-CH_2-N), 7.89-7.40 (m, 4H, aromatic); ^{13}**C NMR** (DMSO-d_6, δppm): 42.37 - 39.21(m, 2C, $N(CH_3)_2$), 59.89 (s, 1C, N-CH_2-N), 123.12 (m, 4C, aromatic), 134.48 -131.48 (m, 2C, aromatic bridgehead), 168.86 (s, 2C, C=O); **Mass** (m/z): 203.98 (M^+ peak).



Scheme-1

Synthesis of Metal Complexes

Ethanolic solution of the Mannich base ligand L (0.01mol) was added to a hot ethanolic solution of the metal salt (0.01mol) taken in a 100ml beaker with constant stirring. The content of the beaker was digested on a water bath for an hour. The solid product thrown out was filtered, washed with ethanol and dried under vacuum in a desiccator. The metal complexes thus obtained were subjected to chemical and physical measurements.

RESULTS AND DISCUSSION

Based on analytical and spectral data, the structure of the ligand confirmed. The fragmentation pattern of the molecular ion also confirms the structure of the Mannich base ligand (L).

The analytical and molar conductance data of the cobalt(II) and nickel(II) complexes of L provided in **Table 1**. The analytical and conductance data indicate that all the metal complexes synthesized are non-electrolytes. The non-electrolytic nature of the metal complexes suggests that the anions of the salts have coordinated to the metal ions. The cobalt (II) complexes have 1:1 stoichiometry while those of nickel(II) have either 1:1, 2:1 or 1:2 stoichiometry.
The characteristic IR absorption bands of the Co^{II} and Ni^{II} complexes have been compared with the free ligand L (**Table 2**) in order to get meaningful information regarding the bonding sites. The ligand exhibits absorption bands at 1768 and 1713cm^{-1} which are assigned to ν_{CO} of phthalimide moiety [12, 13]. But in the IR spectra of metal complexes the band at1713cm^{-1} has split into two bands one at a higher position and another at a lower position indicating the coordination of one of the two carbonyl oxygens to the metal ion. Based on such observations in the study of imidato complexes, Adams *et al* [12] and Fairlamb *et al* [13] have also proposed the bonding of only one carbonyl oxygen to the metal centre. The binding of carbonyl oxygen to the metal ion has also been confirmed by the appearance of bands due to ν_{MO} in the far IR region at 566 – 523cm^{-1}.

Table1: Analytical and molar conductance data for L and its metal complexes

Compound	% Analysis found (Calculated)					Λ_M ohm^{-1} cm^2 mol^{-1}
	C	H	N	M	Anion	
L ($C_{11}H_{12}N_2O_2$)	64.60 (64.70)	5.96 (5.88)	13.59 (13.72)	-	-	-
$CoCl_2$.L	39.56 (39.52)	3.61 (3.59)	8.33 (8.38)	17.61 (17.65)	21.29 (21.26)	37
$Co(NO_3)_2$.L	34.13 (34.11)	3.07 (3.10)	14.45 (14.47)	15.28 (15.23)	-- (32.05)	26
$CoSO_4$.L	36.80 (36.77)	3.36 (3.34)	7.06 (7.01)	16.38 (16.42)	26.73 (26.75)	19
$NiCl_2$.2L	50.08 (50.03)	4.59 (4.55)	10.57 (10.61)	11.14 (11.12)	13.42 (13.45)	31
$Ni(NO_3)_2$.L	34.17 (34.13)	3.08 (3.10)	7.28 (7.24)	15.22 (15.18)	-- (32.06)	43
$2NiSO_4$.L	25.74 (25.71)	2.36 (2.34)	5.49 (5.45)	22.89 (22.86)	37.43 (37.40)	46

The ligand L exhibits vibrational absorption bands at 1158 and 1089cm^{-1} which are assigned to ν_{CNC} [14,15]of the dimethylamino moiety. These bands have shifted to lower region (1145 and 1021cm^{-1}) in the complexes indicating the coordination of the tertiary amino nitrogen atom to the metal ion. The appearance of bands due to ν_{MN} in the far IR region 453-421cm^{-1} is also indication of metal-nitrogen bonding in the metal complexes. Though the coordination of aliphatic tertiary amino nitrogen is not sterically favoured, the high electron densities available on tertiary amino nitrogen favour its coordination to a metal ion where there is a possibility for chelation [9, 16, 17].

The metal nitrato complexes have shown IR absorptions in the three regions at about 1460(ν_5), 1380(ν_1) and 1040cm^{-1}(ν_2) suggesting unidentate nitrato coordination. But the metal sulphato complexes absorb at ~1145, 1096, 1050cm^{-1}(ν_3) and at ~715, 665, 565cm^{-1}(ν_4) suggesting chelating bidentate coordination. In the case of metal chloro complexes, observation of absorptions at 360-340cm^{-1} points to the binding of chloro group to the metal ion.

Table 2: Infrared spectral data of L and its complexes with Co(II) and Ni(II) ions

Compounds	$\nu_{C=O}$	$\nu_{C=N}$	$\nu_{C\text{-}N\text{-}C}$	$\nu_{M\text{-}O}$	$\nu_{M\text{-}N}$	$\nu_{M\text{-}X}$
L ($C_{11}H_{12}N_2O_2$)	1768, 1713	1393,1313	1158,1089	--	--	--
$CoCl_2$.L	1750,1691,1595	1350	1144,1057	534	453	362
$Co(NO_3)_2$.L	1769,1715,1623	1379	1139,1105	536	438	--
$CoSO_4$.L	1630	1385	1145,1021	566	421	--
$NiCl_2$.2L	1594	1384	1143,1058	552	447	336
$Ni(NO_3)_2$.L	1724,1619	1385	1091,1044	523	451	--
$2NiSO_4$.L	1745,1628,1601	1383	1096,1050	540	446	--

Electronic spectrum

The colours, magnetic moments and electronic spectral data of the Co^{II} and Ni^{II} complexes are summarized in **Table 3**. The electronic spectra of Co^{II} complexes display absorption bands in the regions 4000-3800, 6900-6700, 15200-14800 and ~ 28000cm^{-1}, which may be assigned to $^4A_2(F) \rightarrow {}^4T_2$ (F), $^4A_2(F) \rightarrow {}^4T_1$ (F), $^4A_2$ (F) $\rightarrow {}^4T_1$(P) and charge transfer transitions respectively. These spectral features [18-24] indicate tetrahedral stereochemistry of Co^{II} in its complexes and it is further supported by the observed magnetic moment values [24,25] in the range 4.28 - 4.06BM.

The ligand field parameters for the cobalt (II) complexes have been computed and presented in **Table 4**. The observed ν_2/ν_1 ratios (1.748-1.722) are much lower than 1.80 indicating the tetrahedral geometry of Co^{II}. The order of Dq values (397, 390, 386cm^{-1}) among the tetrahedral Co^{II} complexes is found to be $CoCl_2$.L> $Co(NO_3)_2$.L>$CoSO_4$.L. This trend is in accordance with the position of anions in the spectrochemical series. From the calculated β% values (32.90–30.00) covalent character of the Co^{II} complexes has been established.

The Ni^{II} chloro complex exhibits absorption bands at 7312, 12345, 19607 and 29660cm^{-1} which are assigned to $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ and charge transfer transition respectively, which indicate octahedral geometry of Ni^{II}. The observed magnetic moment at 2.95BM also supports the octahedral stereochemistry of Ni^{II} in $NiCl_2.2L$. the Ni^{II} nitrato and sulphato complexes exhibit bands in the regions 4000-3900, 8800-8600, 15400-15100 and ~28000cm^{-1}, which may be assigned to $^3T_1(F) \rightarrow {}^3T_2(F)$, $^3T_1(F) \rightarrow {}^3A_2(F)$, $^3T_1(F) \rightarrow {}^3T_1(P)$ and charge transfer transition respectively suggesting tetrahedral geometry around Ni^{II}. This is further supported by the magnetic moment values observed in the range 4.23-4.14BM.

Table 3: Colours, Electronic Spectral Bands, Transition Assignments and Magnetic Moment Values of Complexes

Compound	Colour	Magnetic moment B.M	Absorption maxima	Transition Assignment
$CoCl_2.L$	Blue	4.13	3965, 6830, 14847, 28850	$^4A_2(F) \rightarrow {}^4T_2(F)$, $^4A_2(F) \rightarrow {}^4T_1(F)$, $^4A_2(F) \rightarrow {}^4T_1(P)$, CT
$Co(NO_3)_2.L$	Greyish blue	4.28	3905, 6746, 15162, 29360	$^4A_2(F) \rightarrow {}^4T_2(F)$, $^4A_2(F) \rightarrow {}^4T_1(F)$, $^4A_2(F) \rightarrow {}^4T_1(P)$, CT
$CoSO_4.L$	Blue	4.06	3862, 6752, 15036, 32467	$^4A_2(F) \rightarrow {}^4T_2(F)$, $^4A_2(F) \rightarrow {}^4T_1(F)$, $^4A_2(F) \rightarrow {}^4T_1(P)$, CT
$NiCl_2.2L$	Green	2.95	7312, 12345, 19607, 29660	$^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$, CT
$Ni(NO_3)_2.L$	Light green	4.23	3988, 8712, 15207, 28490	$^3T_1(F) \rightarrow {}^3T_2(F)$, $^3T_1(F) \rightarrow {}^3A_2(F)$ $^3T_1(F) \rightarrow {}^3T_1(P)$, CT
$2NiSO_4.L$	Apple green	4.14	3920, 8681, 15106, 28780	$^3T_1(F) \rightarrow {}^3T_2(F)$, $^3T_1(F) \rightarrow {}^3A_2(F)$ $^3T_1(F) \rightarrow {}^3T_1(P)$, CT

The calculated ligand field parameters of Ni^{II} complexes also support the proposed structures. The ν_2/ν_1 ratio for the chloro complex is 1.688 indicating octahedral geometry. But in the nitrato and sulphato complexes the ν_2/ν_1 ratios are 2.185 and 2.214 respectively suggesting tetrahedral stereochemistry of Ni^{II}. The order of Dq values among the tetrahedral complexes is $Ni(NO_3)_2.L > 2NiSO_4.L$. The percentage covalency is found in the order $NiCl_2.2L > Ni(NO_3)_2.L > 2NiSO_4.L$. Based on the above discussion the following structures are tentatively proposed. In the case of $2NiSO_4.L$, a Ni-Ni bonding is proposed in order to account for tetrahedral stereochemistry around Ni^{II} atom. The metal-metal bonding is possible as the organic ligand acts as a bridging bidentate one.

Antimicrobial activity

The Mannich base ligand (L) and its cobalt(II) and nickel(II) complexes were screened for their *in vitro* antibacterial activity against *S.aureus* and *E.coli* and for antifungal activity against *C.albicans* and *A.niger* [26,27] at four different concentrations of 25, 50,75 and 100µg/mL in DMF by agar-well diffusion method. Standard drugs Kanamycin, tetracycline, amphotericin and nystatin were screened against *S.aureus*, *E.coli*, *C.albicans* and *A.niger* respectively under identical conditions for comparison. The zones of inhibition produced by the test compounds are presented in **Tables 5** and **6**. It is seen that antimicrobial activity of the test samples increases with increase of their concentrations. Its is observed that the test compounds exhibit activity comparable to standard drugs and that the metal complexes are more active than the free organic ligand. The increased activity of the metal complexes may be explained on the basis of chelation theory. Chelation reduces the polarity of the metal ion and enhances the lipophilic or hydrophobic character of the metal chelate which favours the permeation through microbial cell wall.

Table.4: Ligand Field Parameters of Co^{II} and Ni^{II} complexes

Compound	ν_2/ν_1	B cm^{-1}	Dq	β	β%
$CoCl_2$.L	1.722	652	396.5	0.671	32.90
$Co(NO_3)_2$.L	1.727	679	390.5	0.699	30.10
$CoSO_4$.L	1.748	680	386.2	0.700	30.00
$NiCl_2$.2L	1.588	668	731.2	0.641	35.91
$Ni(NO_3)_2$.L	1.745	797	472.4	0.766	23.40
$2NiSO_4$.L	1.740	802	476.1	0.770	23.10

Table 5: Antibacterial activity of L and its metal complexes

Compound	Zone of Inhibition (mm)							
	S.aureus				*E.coli*			
	Conc. of Compound (µg/mL)				Conc. of Compound (µg/mL)			
	25	50	75	100	25	50	75	100
$L(C_{11}H_{12}N_2O_2)$	10	12	14	14	12	13	15	17
$CoCl_2$.L	11	13	15	19	11	13	17	19
$CoSO_4$.L	12	15	18	20	11	13	17	21
$NiCl_2$.2L	10	12	15	18	11	12	14	18
$2NiSO_4$.L	10	12	15	19	11	14	17	21
Kanamycin	**9**	-	-	-	-	-	-	-
Tetracyclin	-	-	-	-	**10**	-	-	-

Table 6: Antifungal activity of L and its metal complexes

Compound	Zone of Inhibition (mm)							
	A.niger				*C.albicans*			
	Conc. of Compound (µg/mL)				Conc. of Compound (µg/mL)			
	25	50	75	100	25	50	75	100
$L(C_{11}H_{12}N_2O_2)$	7	9	12	13	8	9	12	13
$CoCl_2$.L	12	15	18	21	11	14	17	20
$CoSO_4$.L	11	14	17	19	11	13	15	19
$NiCl_2$.2L	10	12	15	18	10	12	14	18
$2NiSO_4$.L	12	15	18	21	11	14	17	20
Amphotericin	**10**	-	-	-	-	-	-	-
Nystatin	-	-	-	-	**9**	-	-	-

CONCLUSION

The Mannich base ligand(L) and its metal complexes have been newly synthesized and characterized by elemental analysis, IR, NMR, electronic and mass spectra, conductivity and magnetic measurements. The IR and far IR studies indicate that the ligand(L) involves in bidentate coordination through the dimethylamino nitrogen atom and one of the two carbonyl oxygen atoms. On the basis of electronic and magnetic data, tetrahedral geometry is assigned to all the cobalt (II) complexes and to the nitrato and sulphato complexes of nickel (II). Octahedral geometry is proposed to the chloro complex of nickel (II). The ligand and its metal complexes show significant antimicrobial activity. The complexes are found to more effective than the free ligand. The antimicrobial activity of the test compounds are comparable to that of the standard drugs used.

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