

Characterization and CNS Depressant Studies on Complexes of Mn(II), Co(II) and Ni(II) with 2-(Thiophene-2-Formylimino)Benzimidazole

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Complexes of Mn(II), Co(II) and Ni(II) with 2-(thiophene-2-formylimino)benzimidazole have been synthesized. The characterization have been done on the basis of elemental analysis, conductivity measurements, magnetic studies, IR and electronic spectral studies. Complexes have been found psychopharmacologically more effective in taming, hypnotic activities and possess much higher toxicity as compared to the ligand. Complexes with distorted octahedral geometry with ML_2X_2 stoichiometries have been reported (where $X = Cl^-$, NO_3^- , CH_3COO^- and $C_6H_5COO^-$).

Key Words: Synthesis, Characterization, Mn(II), Co(II) and Ni(II) complexes, 2-(Thiophene-2-formylimino)benzimidazole, Central nervous system.

INTRODUCTION

Central nervous system (CNS) depression activity comprising of a muscular hypotonia initially and culminating in complete muscular flaccidity¹ is indicated by benzimidazole. Anticonvulsant properties² and paralyzing action³ of some benzimidazoles were reported by Domino and his coworkers. The coordination of the azomethine molecule derived from the condensation of 2-aminobenzimidazole and thiophene-2-carboxaldehyde through the thiophene ring sulphur and azomethine nitrogen of the amino group thus hopefully provide a more potent drug for the psychopharmacological disorders.

EXPERIMENTAL

2-Aminobenzimidazole was procured from Sigma Aldrich Chemical Co. (USA) and used as such. Thiophene-2-carboxaldehyde was purchased from Fluka and was used after redistillation. All other chemicals used were of AnalaR grade or were used after recrystallization.

Ligand preparation: 2-Aminobenzimidazole (0.1 mol) and thiophene-2-carboxaldehyde (0.1 mol) each in 100 mL methanol were mixed together. The mixture was refluxed for 8 h on a water bath with anhydrous $CaCl_2$ guard tube at the top of the condenser. The refluxed mass was cooled in a freezing mixture for 2 h. The

crystals separated were filtered in suction and dried in a hot air oven at 60-70 °C. The yield was *ca.* 60 % (w/w) in the form of light yellow crystalline powder (m.p. 188-190 °C).

Preparation of complexes: Saturated solution of the ligand in methanol and saturated solution of corresponding metal salt in methanol were mixed together and refluxed for 4 h on a water bath using anhydrous CaCl₂ guard tube at the top of the condenser. The reaction mixture was cooled up to room temperature and then kept in a refrigerator (5-10 °C) for 2 h. Separated crystals of the complexes were filtered on suction and dried in hot a air oven at 70-80 °C (yield 40-60 %).

Molar conductances of the complexes were measured in solution of the complexes in nitrobenzene on a Sytronix 321 conductivity bridge at room temperature. The IR spectrum of the complexes were recorded on a Perkin-Elmer-577 grating spectrophotometer using KBr pellets in the range 4000-200 cm⁻¹. The electronic spectra of all the complexes have been recorded at ambient temperature on a CZI Specord UV spectrophotometer in the range 200-1100 nm. The magnetic susceptibility of the complexes were measured at room temperature using Johnson Matthey Alfa products magnetic susceptibility balance. The elemental analysis (CHN) was carried out on a VarioEL CHNO/S elemental analyser. The metal content in the complexes were determined by using atomic absorption spectrophotometer 220 FS.

RESULTS AND DISCUSSION

All the synthesized complexes have been found stable in air at room temperature. Fairly soluble in DMSO, DMF and THF but less soluble in methanol and nitrobenzene. Elemental analysis data indicate that in all the metal complexes the metal-ligand stoichiometric ratio is 1:2. Low molar conductivity for all the complexes indicates that the anions have entered into the coordination sphere during the complex formation. The same has been confirmed by the qualitative tests for the anions carried out in aqueous suspensions and ethanolic solution of the complexes. Elemental analysis data, molar conductance data (10⁻³ M nitrobenzene solution), percentage yield and colour of the complexes are shown in Table-1.

In the IR spectrum of the ligand, the stretching and bending vibrations at 3320, 3150 and 1610 cm⁻¹ are assignable to $\nu_s(\text{NH}_2)$, $\nu_{as}(\text{NH}_2)$ and $\delta(\text{NH}_2)$ vibrations of the base amino compound 2-aminobenzimidazole were absent⁴. The frequency $\nu(\text{C}=\text{O})$ corresponding to the aldehydic C=O moiety of the thiophene-2-carboxaldehyde at 1710 cm⁻¹ was also absent in the spectrum of the ligand. A new sharp band at 1640 cm⁻¹ was found in the spectrum of the ligand assignable to $\nu(\text{C}=\text{N})$ azomethine stretching vibrations^{5,6}. The imino (NH) group stretching frequency at 3210 cm⁻¹ of the base compound did not suffer any change except a small change in the band intensity attributable to the polarizing effect of the heterocyclic aldehydic group due to the condensation. A sharp stretching band at 890 cm⁻¹ corresponds to C-S-C moiety of the thiophene ring.

TABLE -1
ELEMENTAL AND ANALYTICAL DATA OF COMPLEXES OF DIVALENT
MANGANESE, COBALT AND NICKEL

m.f. (Colour)	Molar cond. (ohm ⁻¹ cm ² mol ⁻¹)*	Yield (%)	% Analysis, found (Calcd.)					
			C	H	N	S	Metal	Cl
C ₁₂ H ₉ N ₃ S(L) (Light yellow)	3.2	60	63.33 (63.42)	3.97 (3.99)	18.42 (18.49)	14.01 (14.11)	–	–
MnL ₂ Cl ₂ (White)	4.7	40	46.63 (46.67)	3.15 (3.13)	14.51 (14.48)	10.95 (11.05)	9.50 (9.47)	12.17 (12.22)
MnL ₂ (NO ₃) ₂ (Pinky grey)	6.8	50	45.42 (45.50)	2.88 (2.86)	17.56 (17.69)	10.08 (10.12)	8.63 (8.67)	–
MnL ₂ (CH ₃ COO) ₂ (Light buff)	4.9	40	53.53 (53.59)	3.86 (3.85)	13.34 (13.39)	10.25 (10.22)	8.80 (8.75)	–
MnL ₂ (C ₆ H ₅ COO) ₂ (Whitish pink)	3.8	40	60.58 (60.71)	3.77 (3.75)	11.09 (11.18)	8.49 (8.53)	7.28 (7.31)	–
CoL ₂ Cl ₂ (Light reddish blue)	5.1	46	49.46 (49.36)	3.12 (3.10)	14.34 (14.38)	10.92 (10.97)	10.11 (10.08)	12.15 (12.13)
CoL ₂ (NO ₃) ₂ (Light pink)	5.3	46	45.14 (45.22)	2.86 (2.85)	17.62 (17.58)	10.10 (10.06)	9.27 (9.24)	–
CoL ₂ (CH ₃ COO) ₂ (Light pink)	4.3	50	53.12 (53.25)	3.81 (3.83)	13.40 (13.31)	10.11 (10.15)	9.29 (9.33)	–
CoL ₂ (C ₆ H ₅ COO) ₂ (Light pink)	5.7	48	60.46 (60.39)	3.74 (3.73)	11.15 (11.12)	8.43 (8.48)	7.85 (7.80)	–
NiL ₂ Cl ₂ (Light green)	4.9	55	49.26 (49.35)	3.12 (3.11)	14.42 (14.39)	10.92 (10.98)	10.11 (10.05)	12.20 (12.14)
NiL ₂ (NO ₃) ₂ (Light green)	5.7	40	49.18 (45.23)	2.84 (2.85)	17.52 (17.58)	10.01 (10.06)	9.26 (9.21)	–
NiL ₂ (CH ₃ COO) ₂ (Light green)	4.7	60	53.12 (53.27)	3.82 (3.83)	13.36 (13.31)	10.12 (10.16)	9.25 (9.30)	–
NiL ₂ (C ₆ H ₅ COO) ₂ (Light green)	5.9	55	60.23 (60.41)	3.73 (3.74)	11.08 (11.12)	8.54 (8.49)	7.81 (7.77)	–

L = 2-(Thiophene-2-formylimino)benzimidazole; *In 10⁻³ M nitrobenzene solution.

Comparing the IR spectra of the ligand and complexes the azomethine $\nu(\text{C}=\text{N})$ of the ligand found shifted to negative side by 30-35 cm⁻¹ in all the complexes confirming the participation of azomethine nitrogen in coordination⁷. The thiophene ring sulphur $\nu(\text{C}=\text{S})$ shifted to negative side by 30-40 cm⁻¹ confirming the coordination to metal ion through thiophene ring sulphur⁸. The $\nu(\text{C}=\text{N})$, $\nu(\text{N}-\text{H})$ of imidazole ring at 3210-1570 cm⁻¹ do not show any appreciable shift indicating that these groups do not participate in the coordination. Fairly appreciable metal ligand overlapping is also confirmed by the "B" values for the complexes.

In the chloro complexes, medium intensity bands observed in the far IR at 580-520, 440-350 and 330-270 cm⁻¹ are assignable to (M-O), (M-N), (M-Cl) stretching vibrations⁹⁻¹¹, respectively confirmed the coordination of ligand through the thiophene ring sulphur and azomethine nitrogen and the coordination of anions to the central metal ion.

In the IR of nitrate complexes, additional sharp bands at *ca.* 1015-1010, *ca.* 1280-1270 and *ca.* 1435-1430 cm^{-1} observed are assignable to ν_2 , ν_1 and ν_4 modes of coordinating nitrates ions. The magnitude of separation between ν_4 and ν_1 band is *ca.* 165-160 cm^{-1} . Hence coordination of nitrate ion in a unidentate manner is confirmed^{12,13}.

In acetate and benzoate complexes, the coordination of these anions with metal ion has been confirmed by comparing the spectra of metal acetates and benzoate salts with the spectra of respective complexes. Frequencies at *ca.* 1560-1550 and *ca.* 1425-1410 cm^{-1} assignable to ν_{as} and ν_{s} carboxylic mode¹⁴ of the acetate and benzoate ions (in metal salts) have been found to be shifted to the opposite sides upon complex formation, *i.e.*, ν_{as} shifted to higher side (30-20 cm^{-1}) and ν_{s} shifted to lower side (30-15 cm^{-1}). This larger difference between the asymmetric and symmetric frequencies in comparison to the uncoordinated acetate and benzoate ion thus confirms the coordination of these ions as unidentate anions through the C-O moiety of their respective carboxylic groups¹⁵.

In the electronic spectra of manganese complexes 4 bands were observed in the region 17460-17800, 22450-23350, 24290-24650 and 26650-27300 cm^{-1} which are tentatively assignable to ${}^4\text{T}_{1\text{g}}(\text{G}) \rightarrow {}^6\text{A}_{1\text{g}}$, ${}^4\text{T}_{2\text{g}}(\text{G}) \rightarrow {}^6\text{A}_{1\text{g}}$ and ${}^4\text{E}_{\text{g}}(\text{G}) \rightarrow {}^6\text{A}_{1\text{g}}$ and ${}^4\text{T}_{2\text{g}}(\text{G}) \rightarrow {}^6\text{A}_{1\text{g}}$ transitions¹⁶.

In the electronic spectra of cobalt complexes bands in the regions of 8480-8660, 17770-18100, 19360-19600 and 27500-28000 cm^{-1} were assignable to ${}^4\text{T}_{2\text{g}}(\text{F}) \rightarrow {}^4\text{T}_{1\text{g}}(\text{F})$, ${}^4\text{A}_{2\text{g}} \rightarrow {}^4\text{T}_{1\text{g}}(\text{F})$, ${}^4\text{T}_{1\text{g}}(\text{P}) \rightarrow {}^4\text{T}_{1\text{g}}(\text{F})$ and charge-transfer, respectively^{17,18}.

In the nickel complexes the bands at 8600-8900, 18820-19800, 25100-25300 cm^{-1} were assignable to ${}^3\text{T}_{2\text{g}}(\text{F}) \rightarrow {}^3\text{A}_{2\text{g}}$, ${}^3\text{T}_{1\text{g}}(\text{F}) \rightarrow {}^3\text{A}_{2\text{g}}$ and ${}^3\text{T}_{1\text{g}}(\text{P}) \rightarrow {}^3\text{A}_{2\text{g}}$ transitions, respectively¹⁹ for spin free complexes. 10Dq, "B" values calculated using the Figgis equation and ν_2/ν_1 ratio are shown in Table-2. All the complexes suggest sufficient metal ligand overlapping and distorted octahedral geometry.

TABLE-2
MAGNETIC MOMENT AND LIGAND FIELD PARAMETERS OF THE COMPLEXES OF
DIVALENT MANGANESE, COBALT AND NICKEL

Complexes	μ_{eff} (BM)	10 Dq	B	ν_2/ν_1
MnL_2Cl_2	4.57	8002.50	727.50 (960.00)*	1.30
$\text{MnL}_2(\text{NO}_3)_2$	4.68	8158.33	741.68 (960.00)	1.32
$\text{MnL}_2(\text{CH}_3\text{COO})_2$	5.75	8103.33	736.66 (960.00)	1.30
$\text{MnL}_2(\text{C}_6\text{H}_5\text{COO})_2$	5.90	8096.45	736.04 (960.00)	1.27
CoL_2Cl_2	4.85	10091.17	1051.21 (1120.00)	2.06
$\text{CoL}_2(\text{NO}_3)_2$	4.90	10138.53	1050.09 (1120.00)	2.08
$\text{CoL}_2(\text{CH}_3\text{COO})_2$	5.10	9927.80	1034.14 (1120.00)	2.13
$\text{CoL}_2(\text{C}_6\text{H}_5\text{COO})_2$	4.96	9951.11	1036.58 (1120.00)	2.09
NiL_2Cl_2	3.52	8750.00	892.85 (1040.00)	2.19
$\text{NiL}_2(\text{NO}_3)_2$	3.60	8600.00	877.55 (1040.00)	2.18
$\text{NiL}_2(\text{CH}_3\text{COO})_2$	3.70	8850.00	903.06 (1040.00)	2.18
$\text{NiL}_2(\text{C}_6\text{H}_5\text{COO})_2$	3.64	8900.00	908.16 (1040.00)	2.22

L = 2-(Thiophene-2-formylimino)benzimidazole, *Free ion values are given in the parenthesis.

Effect of coordination on the drug potential of the ligand: The studies on the central nervous system depressant activity have been done by the procedure^{20,21}, to test the drug potential of the newly synthesized compounds. The study of the complexes in comparison with the ligand and 2-aminobenzimidazole was done on mice by the method of Goodsell *et al.*²² and Witkin *et al.*²³. The compounds were administered orally and the ED₅₀, PD₅₀ and LD₅₀ values are shown in Table-3.

TABLE -3
CNS DEPRESSANT ACTIVITY, EFFECT OF THE TREATMENT OF
2-AMINOBENZIMIDAZOLE, 2-(THIOPHENE-2-FORMYLIMINO)BENZIMIDAZOLE
AND THE COMPLEXES ON THE MICE (MUSCLE RELAXANT
ACTIVITY-ORAL ADMINISTRATION ONLY)

Compound	ED ₅₀ (Dose mg/kg body weight)	PD ₅₀ (Dose mg/kg body weight)	LD ₅₀ (Dose mg/kg body weight)
2-Aminobenzothiazole (4-methyl)	30*	60*	600*
2-Aminobenzimidazole	40	100	900
2-(Thiophene formylimino)- benzimidazole ligand (L)	60	200	1200
MnL ₂ Cl ₂	15	30	100
MnL ₂ (C ₆ H ₅ COO) ₂	20	40	120
CoL ₂ Cl ₂	15	30	100
CoL ₂ (C ₆ H ₅ COO) ₂	20	40	120
NiL ₂ Cl ₂	15	30	100
NiL ₂ (C ₆ H ₅ COO) ₂	20	40	110

*The values for 2-aminobenzothiazole (4-methyl) were taken from the article of Domino *et al.*^{2,3}. ED₅₀ = Effective dose which induces sleep or unconsciousness in 50 % of the mice. (The mice recovered to normal state in 4 h after administration). PD₅₀ = Paralyzing does which paralyzed 50 % of the mice. (The mice recovered to normal state after 10-12 h of administration. LD₅₀ = A dose which is lethal for 50 % of the mice. (The effected mice were not able to recover to complete normal state even after 12 h).

Conclusion

Thus the evidences obtained from infrared, electronic spectra and magnetic measurements suggest high spin distorted octahedral complexes for Mn(II), Co(II) and Ni(II) complexes with 2-(thiophene-2-formylimino)benzimidazole as ligand. The 4 coordination positions are satisfied by two bidentate ligands and the other two positions by two univalent anions. Drug potential studies show that the complexes show higher central nervous system (CNS) depressant activity and they are more toxic as compared to the ligand.

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