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Complexing Behaviour of 7-Bromo-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide with Mn(II), Co(II) and Ni(II) and The Effect of Coordination on their Drug Potential

N.H. ZEINUL HUKUMAN
Department of Chemistry, Sir Syed College
Taliparamba-670 142, India
E-mail: zeinulhukuman@yahoo.com

Synthesis of psychopharmacologically active complexes of divalent Mn, Ni and Co with 7-bromo-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide having ML_4X_2 stoichiometries have been reported (where $X = Cl^-$, NO_3^- and CH_3COO^-). Characterizations have been done on the basis of elemental analysis, conductivity, magnetic, IR and electronic spectral studies. Complexes have been found as neuropharmacologically more effective in taming and hypnotic activities and possess much higher toxicity as compared to the ligand.

Key Words: Mn(II), Co(II), Ni(II), Complexes, 7-Bromo-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide, Drugs.

INTRODUCTION

Coordination compounds of a large number of N-oxides with various metals in different stoichiometries have been reported in literature[1–3]. Studies on the complexes of benzodiazepines are comparatively recent and a number of benzodiazepine complexes with different metals and stoichiometries have also been reported in literature[4–8].

7-Bromo-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide possesses effective neuropharmacological activity. Presence of N-oxide group at position 4 in the diazepine ring of this compound makes it a heterocyclic N-oxide donor ligand and since the N-oxide group is not responsible for the drug activity of the compound, the coordination of the group may not affect its pharmacological activity[9]. On the contrary, coordination of more than one such molecule with a metal may concentrate more activity in the newly synthesized complex molecules, thus hopefully providing a more potent drug in the interest of mankind. Since coordination of biologically active compounds with metals often results in a compound with enhanced activity[10], coordination of the above ligand with divalent Mn, Co and Ni has been reported. Mn, Co and Ni are the metals which do not posses any reported psycho-pharmacological activity. The study of their coordination with the above ligand is done because many of the newly synthesized compounds show an activity or change leading to the discovery of any useful compound of these metals in the psycho-medicinal field.

EXPERIMENTAL

All the chemicals used in synthetic and analytical work were either of AnalaR grade or were used after recrystalization.

Preparation of the ligand: The ligand 7-bromo-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide was prepared by following the method of Sternbach and Reeder in principle[11]. 50 g of 2-amino-5-bromobenzophenone was converted into its oxime and was subjected to chloroacetylation using chloroacetic acid. The acetylated product was further treated with methylamine. The crystals of the ligand were washed with 50% ethanol (chilled) and dried in an electric oven at 75–80°C (yield *ca.* 24 g).

Preparation of complexes: Saturated solution of the ligand in ethanol was respectively mixed with the saturated ethanolic solutions of chlorides, acetates and nitrates of Mn(II), Co(II) and Ni(II), metal ions in 4 : 1 (6 : 1 in nitrates) molar ratio. The mixtures of solutions were refluxed for 2 h each using $CaCl_2$ guard tube at the top of the condenser.

After refluxing, the mixtures were concentrated (10%) on a water bath and were allowed to cool overnight. The crystals separated were filtered and recrystallised from ethanol. The filtered solid was redissolved in just sufficient amount of ethanol at *ca.* 70°C and readily filtered hot on suction. The solutions were slightly concentrated and allowed to cool overnight in a refrigerator. The separated out fine crystals were filtered and dried in an eletric oven at 75–80°C. Elemental analysis data, molar conductance data (in 0.001 M nitrobenzene solution) and colour of the complexes are shown in Table-1.

TABLE-1

Complex/Ligand	Analysis (%): Found (Calcd.)			Molar conductance (ohm^{-1} cm^{-2} mol^{-1})	Colour
	N	Br	M		
Ligand	12.11 (12.21)	23.20 (23.25)	–	–	–
MnL_4Cl_2	11.09 (11.09)	5.30 (5.33)	3.65 (3.65)	3.20	Buff white
CoL_4Cl_2	11.08 (11.16)	5.20 (5.31)	3.89 (3.91)	3.00	Pinkish white
NiL_4Cl_2	11.11 (11.16)	5.28 (5.31)	3.80 (3.90)	3.00	Green white
$MnL_4(CH_3COO)_2$	10.72 (10.85)	5.16 (5.16)	3.54 (3.54)	4.22	Pinkish white
$CoL_4(CH_3COO)_2$	10.72 (10.82)	5.14 (5.14)	3.78 (3.79)	3.82	Pinkish white
$NiL_4(CH_3COO)_2$	10.70 (10.82)	5.14 (5.14)	3.78 (3.78)	3.84	Pale greenish white
$MnL_4(NO_3)_2$	12.59 (12.60)	5.10 (5.14)	3.50 (3.53)	3.40	Buff white
$CoL_4(NO_3)_2$	12.56 (12.57)	5.10 (5.12)	3.68 (3.78)	3.00	Pinkish white
$NiL_4(NO_3)_2$	12.56 (12.58)	5.09 (5.13)	3.68 (3.76)	2.80	Pale greenish white

RESULTS AND DISCUSSION

Reported complexes have been found stable at room temperature during the course of investigation. The complexes are sparingly soluble in ethanol and are comparatively more soluble in THF, DMSO and DMF. Molar conductance data (in 0.001 M nitrobenzene solution) and qualitative tests for anions in ethanol indicate that all the complexes are non-ionic in nature.

In the IR spectra ν(N—O) stretching frequency[12] corresponding to the N-oxide group at position 4 on the diazepine ring of the ligand (at 1310cm^{-1}) has invariably been found to be shifted 30–50 cm^{-1} towards the lower side in all the complexes. This shift confirms the coordination of the ligand to the metals, in all the complexes, through the oxygen of the N-oxide group of the ligand[13].

The δ(N—O) vibration, which has been observed at 940 cm^{-1} in the spectra of the ligand, has also shown a negative shift, invariably in all the complexes. This is in fair agreement with the earlier reported views[14]. Complexation of the ligand to the metal through the oxygen of the N-oxide group of the former has further been confirmed by the appearance of a new medium intensity band in the IR region between 550–520 cm^{-1} in all the complexes. Another new medium intensity absorption band observed in the chloro complexes between 340–320 cm^{-1} is assignable to ν(M—Cl) stretching vibrations[15]. This confirms the coordination of the chloride ions to the metal ions. The above observations and molar conductance data confirm that in all the reported complexes anions are coordinated to the metal ions.

In acetato and nitrato complexes coordination of the ligand to metal is confirmed by the appearance of a doublet in the far IR region between 540–490 cm^{-1}. This doublet is assignable to the two ν(M—O) stretchings[16], one corresponding to the coordination of N-oxide group of the ligand to the metal[17] while the other corresponding to the ν(M—O) stretching arising due to the coordination of anion.

Three new bands have been observed in the IR spectra of all the nitrato complexes in the regions 1430–1420, 1320–1310 and 1210–1200 cm^{-1}. These are assigned to ν_5, ν_1 and ν_2 frequencies of the coordinated nitrate group. Since the separation between the two highest frequencies ν_5 and ν_1 is 120–110 cm^{-1}, therefore the coordination of NO_3^- ion as a unidentate ion is confirmed[18].

Two new bands observed invariably, in the IR spectra of all the acetato complexes in the region 1370–1360 and 1620–1600 cm^{-1}, are assignable respectively to ν_{sym} and ν_{asym} (carboxylic) stretching vibrations. ν_{sym} and ν_{asym} vibrations of the free acetate ion (non-coordinated) are normally reported as at *ca.* 1420 and 1560 cm^{-1}, respectively[18]. Obviously the ν_{asym} frequency (which is assignable to C=O moiety of the acetate ion) in all the complexes has invariably been shifted 40–50 cm^{-1} towards the higher side and ν_1 frequency (which is assignable to COO$^-$ moiety of the acetate ion) has been found invariably shifted 36–46 cm^{-1} towards the lower side. This shows a large separation between the two frequencies upon coordination. This opposite side shift in these two frequencies confirms that acetate ions are coordinated as unidentate ions through the oxygen of COO$^-$ moiety of the carboxylic group of the acetate ion[18].

Magnetic moment values for Mn(II) complexes (5.52–5.98 B.M.) suggest the formation of high spin octahedral complexes around the metal ion with d^5 electronic configuration[19, 20].

In the electronic spectra of Mn(II) complexes, strong bands were observed in the regions 17890–17520, 23200–22360, 24700–24360 and 27350–26610 cm^{-1} which are tentatively assigned to $^4T_{1g}(G) \leftarrow {}^1A_{1g}$, $^4T_{2g}(G) \leftarrow {}^4T_{1g}(G)$, $^4E_g(G) \leftarrow {}^6A_{1g}$ and $^4T_{2g}(D) \leftarrow {}^6A_{1g}$ transitions, respectively[21].

Three broad bands observed in the region 7850–7100, 15380–14360 and 19530–17610 cm^{-1} in the case of all reported Co(II) complexes are tentatively assigned to $^4T_{2g}(F) \leftarrow {}^4T_{1g}$, $^4A_{2g}(F) \leftarrow {}^4T_{1g}$ and $^4T_{1g}(F) \leftarrow {}^4T_{1g}$ transitions respectively.[21] Effective magnetic moment values as observed in the case of all reported complexes are in the region 4.88–5.30 BM. These values are in fair agreement with the earlier reported values for the high spin octahedral complexes. In nickel complexes also, the observed magnetic moment values 3.02–3.35 B.M suggest the spin-free octahedral geometry for the complexes[21].

In the electronic spectra Ni(II) complexes, two strong absorption bands are observed in the region 12600–11740 and 19530–18950 cm^{-1} which are tentatively assigned to $^3T_{2g}(F) \leftarrow {}^3A_{2g}$ and $^3T_{1g}(P) \leftarrow {}^3A_{2g}$ transitions respectively[21]. These band assignments together with the observed magnetic values suggest octahedral stereochemistry for the reported Ni(II) complexes. 10 Dq and the reduced B values in comparison to the free ion values calculated using Figgis equation suggest sufficient metal-ligand overlap.

Effect of coordination on the drug potential of the ligand: The studies of muscle relaxant, taming, hypnotic and lethal effects of the ligand and complexes have been done by the method already reported in literature [22]. Pairs of mice were stimulated by electrical shock applied through a grid to their feet to develop a marked irritability and fighting episodes in them. The results of the study of the ligand and its chloro complexes have been reported in Table-2. Studies have shown that the complexes show much higher taming and muscle relaxant activity. Complexes have also shown powerful hypnotic effect. Lethal doses for the complexes have been found to be very low as compared to the ligand, which shows that the complexes are much high in toxicity values as compared to the ligand.

TABLE-2

MUSCLE RELAXANT, TAMING, HYPNOTIC AND LETHAL EFFECTS OF 7-BROMO-2-METHYLAMINO 5-PHENYL-3H-1,4-BENZODIAZEPINE-4-OXIDE COMPLEXES OF METAL (II)CHLORIDES ON MICE

Complex/Ligand	Inclined screen ED_{50} (mg/kg) P.O.	Fighting ED_{50} (mg/kg) P.O.	Hypnotic effect HD_{50} (mg/kg) P.O.	Toxicity LD_{50} (mg/kg) P.O.
The ligand	80	40	400	480
$[MnL_4Cl_2]$	10	5	15	25
$[CoL_4Cl_2]$	20	10	30	40
$[NiL_4Cl_2]$	20	10	30	40

ED_{50} = Effective dose for 50% of mice; HD_{50} = Hypnotic dose for 50% of mice;
LD_{50} = Lethal dose for 50% of mice.

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