Asian Journal of Chemistry Vol. 17, No. 2 (2005), 1135–1139

Neuropharmacologically Active Complexes of Cu(II) and Zn(II) with Substituted 1,4-Benzodiazepine-4-oxides

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Synthesis of Cu(II) and Zn(II) complexes with 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one-4-oxide having ML_4X_2 stoichiometries has 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: Cu(II), Zn(II), 1,4-Benzodiazepine-4-oxides, Neuropharmacologically active complexes.

INTRODUCTION

Studies of the benzodiazepine complexes are comparatively less and a few benzodiazepine complexes have been reported in literature[1–3].

7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one-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, therefore the coordination of this group may not affect its pharmacological activity[4]. 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. Copper and zinc metals and their compounds have been reported to possess effective drug potential and are frequently used in Indian Ayurvedic and Homoeopathic therapies for the treatment of psychopharmacological, cardiovascular and other various disorders[5, 6]. Since coordination of bologicially active compounds with metals often results into the compound with enhanced activity[7], therefore coordination of the above ligand with Cu(II) and Zn(II) has been reported.

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EXPERIMENTAL

All the chemicals used are either of AnalaR grade or are used after recrystallization. The ligand 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one-4-oxide was prepared by following the method of Sternbach and Reeder in principle[8]. 20 g of chlorodiazepoxide was acetylated by the treatment of acetic anhydride in pyridine. Crystals of acetylated chlorodiazepoxide were washed with ethanol (ice-cold). Mild hydrolysis of acetylated product was done in presence of dilute hydrochloric acid (0.01 M). After hydrolysis pH was raised to 7.5–8 by adding dilute ammonia solution. Separated crystals of the ligand were washed with 50% ethanol (ice-cold) and dried in an electric oven at 75–80°C (yield 10.4 g).

Saturated solution of the ligand in ethanol was respectively mixed with the saturated ethanolic solutions of chlorides, acetates and nitrates of Zn(II) and Cu(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. Crystals separated were filtered and recrystallized from ethanol. The filtered solids were redissolved in just sufficient amounts 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 electric 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	Elemental analysis %: Found (Calcd.)			Molar conductance (ohm^{-1} cm^2 mol^{-1})†	Colour
	N	Cl	M		
Ligand	9.68 (9.77)*	12.30 (12.36)	—	—	Ceramic white
CuL_4Cl_2	8.72 (8.75)	16.58 (16.60)	4.93 (4.96)	3.12	Bluish white
ZnL_4Cl_2	8.69 (8.73)	16.58 (16.57)	4.99 (5.09)	3.32	White
$CuL_4(CH_3COO)_2$	8.44 (3.44)	10.68 (10.67)	4.77 (4.78)	2.84	Bluish white
$ZnL_4(CH_3COO)_2$	8.43 (8.43)	10.65 (10.66)	4.92 (4.92)	2.96	Off white
$CuL_4(NO_3)_2$	10.39 (10.50)	10.57 (10.62)	4.69 (4.76)	3.02	Bluish white
$ZnL_4(NO_3)_2$	10.47 (10.48)	10.59 (10.61)	4.81 (4.89)	3.14	Off white

* Calculated values are in parentheses. † In nitrobenzene (0.001 M solution).

L = 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one-4-oxide.

RESULTS AND DISCUSSION

The complexes have been found stable at room temperature and are sparingly soluble in ethanol, however, 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 N—O stretching [ν(N–O)] frequency[9], corresponding to the N-oxide group at position 4 on the diazepine ring of the ligand (at 1300 cm^{-1}), has invariably been found to be shifted 50–30 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[10].

N—O bending [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[11].

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 far 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 M–Cl stretching [ν(M–Cl)] vibrations[12]. 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 M–O stretching[13], one corresponding to the coordination of N-oxide group of the ligand to the metal[14], while the other corresponding to the 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 region 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 unidentate ion is confirmed[15].

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[15]. Obviously the ν_{asym} frequency (which is assignable to C═O moiety of the acetate ion) in all the complexes has invariably been shifted 50–40 cm^{-1} towards higher side and ν_1 frequency (which is assignable to COO^- moiety of the acetate ion) has been found invariably shifted 46–36 cm^{-1} towards 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[15].

Magnetic moments and electronic spectral studies

In the electronic spectra of all copper complexes a broad weak band observed in the region 12420–12400 cm^{-1} which is assignable to $^2T_{2g} \leftarrow {}^2E_g$ transition only corresponding to a distorted octahedral field around Cu(II) ions[16]. The values of the above transition directly correspond to the 10 Dq values for these complexes[16]. Other parameters in these complexes could not be calculated because of the absence of second band. However, the observed magnetic moment values (between 1.80–1.92 BM) are in fair agreement with the reported values for the spinfree complexes with tetragonally distorted octahedral environment around the Cu(II) ions[16, 17].

Zn(II) complexes were found to be diamagnetic in character and in the electronic spectra of these complexes the observed strong absorption band around 29500 cm^{-1} may possibly be due to the charge transfer transitions only.

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 reported method in literature[18].

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 although the ligand possesses the muscle relaxant activity similar to chlorodiazepoxide but the complexes show much higher taming and muscle relaxant activity. Complexes have shown powerful hypnotic effect. Lethal dose for the complexes has 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-CHLORO-1,3-DIHYDRO-5-PHENYL-2H-1,4-BENZODIAZEPIN-2-ONE-4-OXIDE COMPLEXES OF METAL(II) CHLORIDES, ON MICE

Complex	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.
Ligand	100	40	1700	1950
[CuL_4Cl_2]	50	25	1000	1200
[ZnL_4Cl_2]	50	30	800	1200

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

REFERENCES

1. J.A. Real and J. Borras, *Synth. React. Inorg. Met-org. Chem.*, **14,** 843 (1983).
2. A. Alvarez. M. Julve and M. Verdaguer, *Inorg. Chem.*, **29,** 4500 (1990).
3. Suresh, B.K. Prabhakar and V.H. Kulkarni, *Asian J. Chem.*, **4**, 210 (1992).
4. B.A. Kocchilin and L.D. Arconte, *Anal. Biochem.*, **5,** 195 (1963).
5. C.R. Bhandari, Vananshadhi Chandrodaya (An Encyclopedia of Indian Botanics and Herbs), Chaukamba Sanskrit Sansthan, Varanasi, Part V, pp. 10–15 (1985).
6. W. Borrik, Homoeopathic Materia Medica.
7. J.R.J. Sorenson, L.W. Oberley, V. Kishore, S.W.C. Leuthauser and A. Pezeshk, 1st International Conference on Biochemistry, Florence (1983).
8. L.H. Sternbach and E. Reeder, *J. Org. Chem.*, **26,** 4936 (1961).
9. G. Piptay, K. Burger, E. Papp-Molnar, Sz. Szebni and F. Ruff, *J. Inorg. Nucl. Chem.*, **31,** 2359 (1969).
10. R.G. Garvey, J.H. Nelson and R.O. Ragsdale, *Coord. Chem. Rev.*, **3,** 375 (1968).
11. C.P. Prabhakaran and C.C. Patel, *J. Inorg. Nucl. Chem.*, **34,** 3485 (1972).
12. R.J.H. Clark and C.S. Williamns, *Inorg. Chem.*, **4,** 350 (1965).
13. C. Natrajan, *Indian J. Chem.*, **29A,** 572 (1990).
14. N.M. Karayannis, S.D. Sousino, C.M. Milkulski, *Inorg. Chim. Acta,* **4,** 141 (1970).
15. K. Nakamoto, Infrared and Raman Spectra of Inorganic and Coordination Compounds, John Wiley, pp. 232, 349 (1978).
16. B.N. Figgis, Introduction to Ligand Fields, Wiley Eastern, p. 218, 279 (1976).
17. D.K. Rastogi and K.C. Sharma, *J. Inorg. Nucl. Chem.*, **36,** 22 (1974).
18. R.E.T. Tedesche, D.H. Tedesche, A. Mucha, L. Cook, P.A. Mattia and E.J. Fellows, *J. Pharmacol. Exptl. Therap.*, **125,** 28 (1959).

(*Received*: 24 July 2004; *Accepted*: 3 January 2005) AJC-4058