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Synthesis and Characterization of Psychopharmacologically Active Complexes of Copper(II) and Zinc(II) with 2-(Furan-2-formylimino)benzimidazole

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Synthesis of Cu(II) and Zn(II) complexes with 2-(furan-2-formylimino)-benzimidazole having ML_2X_2 stoichiometries have been reported (where $X = Cl^-$, NO_3^-, CH_3COO^- and $C_6H_5COO^-$). Characterizations have been done on the basis of elemental analysis, conductivity, magnetic, IR and electronic spectral studies. Complexes have been found psychopharmocologically more effective in taming and hypnotic activities and possess much higher toxicity as compared to the ligand.

Key Words: Synthesis, Cu(II) and Zn(II) complexes, Benzimidazole derivative.

INTRODUCTION

Benzimidazole indicated an unusual type of central nervous system (CNS) depression activity comprising of a muscular hypotonia initially and culminating in complete muscular flaccidity, the neck area and diaphragm being the least affected parts[1]. Domino and his coworkers reported anticonvulsant properties[2] and the paralysing action[3] of some benzimidazoles. Little work on the complexes of psychopharamacologically active benzimidazoles and no systematic study on the effect of coordination on their psycho-therapeutical activity has been reported so far. The coordination of the azomethine molecule, derived from the condensation of 2-aminobenzimidazole and furan-2-carboxaldehyde (furfural), through the furan ring oxygen and the azomethine nitrogen of the amino group, thus hopefully provide 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 Homeopathic therapies for the treatment of psychopharmacological, cardiovascular and various other disorders[4, 5].

EXPERIMENTAL

2-Amino benzimidazole was procured from Sigma Aldrich Chemical Company (U.S.A.) and used as such. Furan-2-carboxaldehyde (furfural) was purchased from Fluka and was used after redistillation. All other chemicals used were of AnalaR grade or were used after recrystallization.

Preparation of the ligand

2-Aminobenzimidazole (0.1 mol) and furan-2-carboxaldehyde (0.1 mol) each

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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 on suction and dried in a hot air oven at 60–70°C. The yield was approximately 55% (w/w) in the form of brown crystalline powder (m.p. 152–156°C).

Preparation of complexes

Saturated solution of the ligand in methanol and saturated solution of metal salt in methanol were mixed together and refluxed for 4 h on a water bath using anhydrous $CaCl_2$ guard tube at the top of the condenser. The reaction mixture was cooled up to room temperature and then kept in a refrigerator in the bottom shelf (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% w/w).

Elemental analysis data, molar conductance data (10^{-3} M nitrobenzene solution), percentage yield, colour of the complexes and magnetic moment values are shown in Table-1.

TABLE-1
ELEMENTAL AND ANALYTICAL DATA OF
COMPLEXES OF DIVALENT COPPER AND ZINC

S. No.	m.f. (Colour)	Molar conductivity (ohm^{-1} cm^2 mol^{-1})‡	Yield (%)	% Analysis, Found (Calcd.)				
				C	H	N	Cl	Metal
1.	$C_{12}H_9N_3O$(L) (Dark buff)	3.6	55	68.41 (68.24)	4.3 (4.29)	19.95 (19.89)	—	—
2.	CuL_2Cl_2 (Light green)	5.2	62	51.63 (51.76)	3.24 (3.26)	15.14 (15.09)	12.68 (12.75)	11.367 (11.41)
3.	$Cu_2L_2(NO_3)_2$ Greenish grey)	5.8	65	47.07 (47.26)	3.02 (2.97)	18.42 (18.31)	—	10.37 (10.42)
4.	$Cu_2L_2(CH_3COO)_2$ (Light bluish greem)	5.0	55	55.53 (55.67)	3.97 (4.00)	13.85 (13.91)	—	10.48 (10.52)
5.	$Cu_2L_2(C_6H_5COO)_2$ (Bluish green)	4.8	45	62.79 (62.68)	3.91 (3.88)	11.48 (11.54)	—	8.78 (8.73)
6.	ZnL_2Cl_2 (White)	7.2	50	51.46 (51.59)	3.26 (3.25)	15.10 (15.04)	12.16 (12.69)	11.74 (11.70)
7.	$ZnL_2(NO_3)_2$ (Dirty white)	6.4	50	47.07 (47.26)	3.0 (2.97)	18.24 (18.31)	—	10.62 (10.68)
8.	$ZnL_2(CH_3COO)_2$ (Off white)	6.0	45	55.53 (55.67)	4.01 (3.99)	13.82 (13.87)	—	10.74 (10.79)
9.	$ZnL_2(C_6H_5COO)_2$ (White)	4.7	45	62.41 (62.52)	3.85 (3.87)	11.54 (11.51)	—	8.90 (8.95)

L = 2-(Furan formylimino)benzimidazole; ‡In 10^{-3} M nitrobenzene solution.

RESULTS AND DISCUSSION

All the synthesized complexes have been found stable in air at room temperature. Fairly souble in DMSO, DMF and THF but less soluble in methanol and nitrobenzene. Elemental analysis data indicate that in all the 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 solutions of the complexes.

In the IR spectra of the ligand, the stretching and bending vibrations at 3320, 3150 and 1610 cm^{-1} are assignable to $\nu_{sym}(NH_2)$, $\nu_{asym}(NH_2)$ and $\delta(NH_2)$ vibrations of the base amino compound 2-aminobenzimidazole were absent[7]. The frequency ν(C=O) corresponding to the aldehydic C=O moeity of the furan-2-carboxaldehyde at 1720 cm^{-1} was also absent in the spectra of the ligand. A new sharp band at 1630 cm^{-1} was found in the spectra of the ligand assignable to ν(C=N) azomethine stretching vibrations[8, 9]. The imino (NH) group stretching frequency at 3210 cm^{-1} of the base compound did not suffer any change except a small change in band intensity attributable to the polarizing effect of the heterocyclic aldehydic group due to the condensation.

Comparing the IR spectra of the ligand with its complexes the stretching frequencies corresponding to furan ring oxygen and the azomethine groups have been shifted to negative side ranging from 30 to 35 cm^{-1} clearly indicating the participation of furyl oxygen[10] and the azomethine nitrogen in coordination[12]. The ν(C=N), ν(N—H) of imidazole ring at 1580 and 3120 cm^{-1} do not show any appreciable shift indicating that these groups do not participate in the coordination.

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 vibrations[12–14], respectively.

In the IR of nitrato complexes, additional sharp bands at *ca.* 1015–10, *ca.* 1280–70 and *ca.* 1435–30 cm^{-1} observed are assignable to ν_2, ν_1 and ν_4 modes of coordinating nitrate ions. The magnitude of separation between ν_4 and ν_1 band is *ca.* 165–160 cm^{-1}; therefore coordination of nitrate ion in a unindentate manner is confirmed[15, 16].

In acetato and benzoato complexes, the coordination of X anions with X metal has been confirmed by comparing the spectra of metal acetates and benzoate salts with the spectra of respective complexes. Frequencies at *ca.* 1560–50 and *ca.* 1425–10 cm^{-1} assignable to ν_{asym} and ν_{sym} carboxylic mode[17] 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_{asym} shifted to higher side 30–20 cm^{-1} and ν_{sym} 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 groups[18].

Magnetic moment and electronic spectral studies

In the electronic spectra of all the copper complexes a broad asymmetric band appears in the region of 13200 cm^{-1} assignable to $^2T_{2g} \leftarrow {}^2E_g$ transition openly. This suggests a tetragonally distorted D_h symmetry for these complexes[19]. 10 Dq values taken directly from $^2T_{2g} \leftarrow {}^2E_g$ suggest sufficient metal-ligand overlap in the complex.

The magnetic moment value ranging between 1.68–2.00 B.M. is in fair agreement with the reported values for the spin free complexes with tetragonally distorted octahedral environment around Cu(II) ions[20, 21].

All the zinc(II) complexes were found diamagnetic. Transition 30000–28000 cm^{-1} may be attributed to charge-transfer only. On the basis of the analogy of zinc complexes in the elemental analysis, conductivity and IR data with other complexes octahedral symmetry is proposed for all the zinc complexes.

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[22, 23], to test the drug potentiality 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.*[24] and Witkin *et al.*[25] The compounds were administered orally and the ED_{50}, PD_{50} and LD_{50} values are shown in Table-2.

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

S. No.	Compound	ED_{50} (Dose mg/kg body weight)	PD_{50} (Dose mg/kg body weight)	LD_{50} (Dose mg/kg body weight)
1.	2-Aminobenzothiazole (4-methyl)	30*	60*	600*
2.	2-Aminobenzimidazole	40	100	900
3.	Azomethine ligand (L)	100	300	1500
4.	CuL_2Cl_2	30	50	300
5.	$CuL_2(C_6H_5COO)_2$	50	80	600
6.	ZnL_2Cl_2	40	70	300
7.	$ZnL_2(C_6H_5COO)_2$	60	100	700

*The values for 2-aminobenzothiazole (4-methyl) were taken from the article of Domino *et al.*[27]

ED_{50} = Effective dose which induces sleep or unconsciousness in 50% of the mice. (The mice recovered to normal state in 4 h after administration.)

PD_{50} = Paralysing dose which paralysed 50% of the mice. (The mice recovered to normal state after 10–12 h of administration.

LD_{50} = 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.)

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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