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STUDIES ON COMPLEXES OF Cu^{II} AND Zn^{II} METAL IONS WITH 2-(THIOPHENE-2-FORMYLIMINO) BENZIMIDAZOLE

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ABSTRACT

Cu^{II} and Zn^{II} complexes with 2-(thiophene-2-formylimino)benzimidazole having ML_2X_2 stoichiometries have been reported (where X = Cl, NO_3, CH_3COO and C_6H_5COO). On the basis of elemental analysis, conductivity measurements, magnetic studies, IR and electronic spectral studies, the complexes were characterized. All the complexes show higher central nervous system (CNS) depressant activity and possess much higher toxicity as compared to the ligand.

Key words: Synthesis, Cu^{II}, Zn^{II}, Complexes, 2-(Thiophene-2-formylimino) benzimidazole, CNS.

INTRODUCTION

An unusual type of central nervous system (CNS) depressant activity is indicated by benzimidazole. Domino and his coworkers reported anticonvulsant properties[1] and the paralyzing action[2] of some benzimidazole. The ligation of the azomethine molecule derived from the condensation of 2-aminobenzimidazole and thiophene-2-carboxaldehyde 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[3,4].

EXPERIMENTAL

Material and methods

Thiophene-2-carboxaldehyde was purchased from 'Merck' 2-Aminobenzimidazole was procured from Sigma Aldrich Chemical Company (U.S.A) and used as such. All other chemicals used were of AnalaR grade or were used after recrystallization.

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Ligand preparation

Thiophene-2-carboxaldehyde (0.1 mol) and 2-aminobenzimidazole (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^oC. The yield was approximately 60% (w/w) in the form of light yellow crystalline powder (m.p.188-190^oC).

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 (5-10^oC) for 2 h. Separated crystals of the complexes were filtered on suction and dried in hot air oven at 70-80^oC (yield 40-60% w/w).

Molar conductances of the complexes were measured in solution of the complexes in nitrobenzene on a Systronics 321 conductivity bridge at room temperature. The IR spectra 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 in ethanol at ambient temperature on a CZl Specord UV spectrophotometer in the range 200-1100 nm. The magnetic susceptibility of the complexes was 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

General and elemental analysis

All the synthesized complexes have been found stable in air at room temperature. These were 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 ehtanolic solution of the complexes. 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.

IR Spectral studies

In the IR spectrum of the ligand, the absorption bands at 3320, 3150 and 1610 cm^{-1} are assignable to $\nu_s(NH_2)$, $\nu_{as}(NH_2)$ and $\delta(NH_2)$ vibrations of the base amino compound 2-aminobenzimidazole were absent[5]. The absorption band at 1710 cm^{-1}, which is assignable to ν(C=O) stretching vibrations corresponding to C=O moiety of the aldehydic group of thiophene-2-carboxaldelyde was also found absent in the spectrum of the ligand; thus, confirming that the C=O moiety of thiophene-2-carboxaldelyde have entered into condensation with the amino group of 2-aminobenzimidazole to form the azomethine. The sharp new band at 1640 cm^{-1} in the spectrum of the ligand is assignable to $\nu_{C=N}$ (azomethine) stretching vibration[6,7]. The imino (NH) group stretching frequency at 3210 cm^{-1} did not suffer any change except a small change in band intensity attributable to the polarization effect of the heterocyclic aldelydic group due to the condensation. A sharp stretching frequency at 890 cm^{-1} corresponds to C-S-C moiety[8].

Comparing the IR spectra of the ligand and complexes, the azomethine $\nu_{C=N}$ of the ligand found shifted to negative side by 30-35 cm^{-1} in all the complexes confirming the participation of azomethine nitrogen in cordination[9]. The thiophene ring sulphur $\nu_{C=S}$ shifted to negative side by30-40 cm^{-1} confirming the coordination to metal ion through thiophene ring sulphur[10]. The ν(C=N) and ν(N-H) of imidazole ring at 1570 and 3210 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-CI stretching vibrations,[11-13] respectively.

In the IR of nitrato complexes, additional sharp bands at ca. 1015-10, ca. 1280-70 and ca. 1435-30 cm^{-1} are assignable to ν_2, ν_1 and ν_4 modes of coordination 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 unindentate manner is confirmed[14, 15].

In acetato and benzoato complexes, the coordination of anions with metal have been confirmed by comparing the spectra of metal acetates and benzoate salts with the spectra of respective complexes. Frequencies at ca.1560-50 cm^{-1} and ca. 1425-10 cm^{-1} assignable to ν_{as}

and ν_s carboxylic mode[16] 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 large 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[17].

Magnetic studies and electronic spectra

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. This suggests a tetragonally distorted D_h symmetry for these complexes[18]. 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 BM is in fair agreement with the reported values for the spin free complexes with tetragonally distorted octahedral environment around Cu^{II} ions[19, 20].

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 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 carried out[21,22], 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.[23] and Witkin et al.[24] The compounds were administered orally and the ED_{50}, PD_{50} and LD_{50} values are shown in Table 2.

The ligands and their metal complexes were screened for their antibacterial and antifungal activity *in vitro* against *Staph*. *Aureus* 209p, *E. Coli* ESS 2231, *Aspergillus fumigatus, Candida albicans, Candida albicans* ATCC10231, *Candida Krusei* GO 3 and *Candida glabrata* HO5, using standard agar well diffusion assay method[25]. The Cu^{II} complexes showed good antifungal and moderate antibacterial activity. It is interesting to note that Zn^{II} complexes are moderately active against *Candida Spp*.

Table 1: Elemental and analytical data of complexes of divalent copper and zinc

M.F. (Colour)	Molar conductivity (ohm^{-1} cm^{2} mol^{-1})*	Yield (%)	% Analysis. Found (Calcd.)					
			C	H	N	S	Cl	Metal
$C_{12}H_9N_3S$(L) (Dark buff)	3.2	60	63.33 (63.42)	3.97 (3.99)	18.42 (18.49)	14.01 (14.11)	-	-
CuL_2Cl_2 (Greenish Blue)	5.0	48	48.82 (48.94)	3.10 (3.08)	14.30 (14.27)	10.84 (10.89)	12.11 (12.04)	10.86 (10.79)
$CuL_2(NO_3)_2$ (Green Blue)	5.4	46	44.68 (44.89)	2.84 (2.83)	17.48 (17.45)	9.92 (9.96)	-	9.95 (9.90)
$CuL_2(CH_3COO)_2$ (Light Greenish Blue)	5.0	50	52.72 (52.86)	3.81 (3.80)	13.25 (13.21)	10.11 (10.08)	-	10.15 (9.99)
$CuL_2C_6H_5COO)_2$ (Whitish pink)	4.4	50	59.87 (60.03)	3.70 (3.71)	10.99 (11.05)	8.49 (8.43)	-	8.40 (8.36)
ZnL_2Cl_2 (White)	6.2	40	48.65 (48.79)	3.06 (3.07)	14.18 (14.22)	10.80 (10.85)	12.06 (12.00)	11.13 (11.06)
$ZnL_2(NO_3)_2$ (White)	5.9	45	44.62 (44.77)	2.83 (2.82)	17.32 (17.40)	10.02 (9.96)	-	10.09 (10.15)
$ZnL_2(CH_3COO)_2$ (Off white)	5.5	45	52.60 (52.71)	3.80 (3.79)	13.11 (13.17)	10.01 (10.05)	-	10.29 (10.25)
$ZnL_2(C_6H_5COO)_2$ (White)	6.1	40	59.75 (59.89)	3.69 (3.70)	10.97 (11.03)	8.44 (8.41)	-	8.55 (8.58)

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

Table 2: CNS depressant activity, Effect of the treatment of 2-aminobenzimidazole, 2-(thiophene-2-formylimino)benzimidazole and the complexes on the mice (Muscles 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)	60	200	1200
4.	CuL_2Cl_2	20	40	120
5.	$CuL_2(C_6H_5COO)_2$	30	70	200
6.	Zn L_2Cl_2	25	60	150
7.	$ZnL_2(C_6H_5COO)_2$	40	85	240

*The values for 2-aminobenzothiazole (4-methyl) were taken from the article of Domino et al.[1, 2]

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 does, 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 affected mice were not able to recover to complete normal state even after 12 h)

CONCLUSION

Thus, the evidences obtained from IR, electronic spectra and magnetic measurements suggest spin free complexes with tetragonally distorted octahedral environment around Cu^{II} ions. On the basis of the analogy, octahedral symmetry is proposed for all the zinc complexes. The four 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. The ligands are not effective against the microbes, but their metal complexes seem to have developed a fairly good antimicrobial activity. Such enhanced antimicrobial activity in the metal complexes were also reported earlier[26].

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