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Synthesis and Biological Activity of Divalent Metal Chelates of Metronidazole

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The complexing behaviour of metronidazole (1H-imidazole-1-ethanol-2-methyl-5-nitro) towards Co(II), Ni(II), and Cu(II) has been studied. The complexes of the general formula $ML_2X_2 \cdot 2H_2O$ and CuL_4Cl_2 [where M = Co(II) or Ni(II)], L = $C_6H_9N_3O_3$ (drug) as ligand and X = Cl^-] have been prepared and characterised by elemental analysis, molar conductance, magnetic susceptibility measurements, electronic and infrared spectral data. They have also been tested for their antibacterial activities.

INTRODUCTION

Chelation or complexation observe more potent antibacterial effects against some microorganisms than the respective drugs[1, 2]. A detailed investigation has shown that imidazole and its derivatives have a biological interest[3, 4]. Metronidazole has been shown to be an effective agent against protozoal and anaerobic microbial infections[5–8]. The aim of the present work is to study the stereochemistry and change in biological activity of the prepared complexes.

RESULTS AND DISCUSSION

Physical and analytical data of the complexes obtained are listed in Table-1. These complexes are microcrystalline high spin, soluble in DMF and DMSO. Co(II) and Ni(II) complexes have 1 : 2 : : M : L stoichiometry with two chlorine atoms and two water molecules while Cu(II) has 1 : 4 : : M : L stoichiometry with two chlorine atoms has been assigned for elemental analysis. Presence of coordinated chlorine atoms and water molecules was confirmed by IR data.

The molar conductance of 10^{-3} M DMF solution of the complexes of Co(II), Ni(II) and Cu(II) were found to be in the range 14.76, 36.08 and 45.92 ohm^{-1} cm^2 mol^{-1} respectively. The slightly higher values than those expected for non-electrolytes indicate the solvolation of the complexes resulting in the displacement of anion from coordination sphere by strong donor DMF molecules[9]. The complexes may be regarded as non-electrolytes.

The cobalt(II) complex possesses magnetic moment value 3.6 BM which may be due to spin state equilibrium between high-spin and low-spin octahedral species[10]. The electronic spectrum of cobalt(II) complex shows two bands in the region 14705–14084 cm^{-1} and 17391 cm^{-1} which may be due to $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$ transitions respectively[11]. The ligand

field parameters Dq, B and β were calculated and found to be 784 cm^{-1}, 766 cm^{-1} and 0.78 respectively suggesting an octahedral stereochemistry for the cobalt(II) complex.

TABLE-1

Complexes (Colour) (m.w.)	Elemental analysis % Found (Calcd.)				Molar conductance (mhos)*	μ_{eff} BM.	Decomposition temp. (°C)
	M	C	H	N			
$[Co(C_6H_9N_3O_3)_2 \cdot Cl_2 \cdot 2H_2O]$ (Light lilac) (507.9)	11.89 (11.59)	28.86 (28.35)	4.82 (4.33)	16.29 (16.53)	14.76	3.6	320
$[Ni(C_6H_9N_3O_3)_2 \cdot Cl_2 \cdot 2H_2O]$ (Ocean spray) (507.7)	11.86 (11.56)	28.66 (28.36)	4.85 (4.33)	16.75 (16.54)	36.08	2.8	148
$[Cu(C_6H_9N_3O_3)_4 \cdot Cl_2]$ (Pista green) (818.54)	7.96 (7.76)	35.88 (35.18)	4.23 (4.39)	20.35 (20.52)	45.92	1.74	170

*Values are in DMF.

The reflectance spectrum of nickel(II) complex shows bands at 14705 cm^{-1} and 23584 cm^{-1}. These bands are assigned to $^3A_{2g} \rightarrow {}^3T_{1g}(F)(\nu_2)$ and $^3A_{2g}(F) \longrightarrow {}^3T_{1g}(P)(\nu_3)$ transitions respectively, in conformity with an octahedral symmetry[12–14]. Also the room temperature magnetic moment value (2.8 BM) obtained for the Ni(II) complex is indicative of an octahedral stereochemistry for the nickel(II) complex. The values of Racah parameters Dq = 1005 cm^{-1} ν_2/ν_1 (1.43), B = 508 cm^{-1} and β = 0.52 have been calculated low value of ν_2/ν_1 further supports the octahedral nature of the nickel(II) complex.

In the electronic spectra of copper(II) complex one broad asymmetric band in the region 13698–12048 cm^{-1} is assignable to $^2E_g \longrightarrow {}^2T_{2g}$ transition in distorted octahedral geometry. Magnetic moment value of Cu(II) complex (1.74 BM) shows paramagnetic character[15].

A comparison of the infrared spectra of the ligand and its complexes of Co(II), Ni(II) and Cu(II) indicated that the compound functions as a neutral unidentate ligand coordinating through tertiary nitrogen of imidazole moiety[16–20]. The shifting of OH bands in the complexes to the higher frequency is indicative of extensive hydrogen bonding between hydroxy proton on N-1 and the nitro group of C-5 position. C—N stretching of C—N($CH_2 \cdot CH_2OH$) near 1540, 1350 and 860 cm^{-1} remains almost unchanged, indicating that N-1 is not taking part in metal bonding. The band near 1075 cm^{-1} displayed by C—OH and C—O stretching in the ligand is shifted to higher frequency by 5 to 10 cm^{-1} because of participation of —OH group in hydrogen bonding. The bands due to NO_2, N—O stretching and C—N of C—NO_2 have very slight change in complexes as compared to the ligand, which indicates the non-participation of NO_2 group in chelation. ν(C=N) (imidazole ring) observed at 1565 cm^{-1} in the ligand has been shifted to higher frequency. This shifting clearly indicates the coordination through tertiary nitrogen of imidazole ring and is further supported by the

appearance of a new band in the complexes at 460–450 cm^{-1} due to metal-nitrogen bonding ν(M—N). ν(M—Cl) was observed as medium intensity band in the region 410–400 cm^{-1} in the spectra of Co(II), Ni(II) and Cu(II) complexes.

Biological Activity: Antibacterial screening of metranidazole and metal complexes against *Escherichia coli* (gram −ve) and *Bacillus subtilis* its (gram +ve) microorganisms have been carried out employing filter paper disc diffusion plate method[21].

Table-2 records the inhibition zone of the complexes at 10 mg/mL concentration against the pathogenic bacteria. It has been found that the cobalt complex showed maximum and remarkable antibacterial activity against *Bacillus subtilis* bacteria as compared to the parent drug. In rest of the cases synthesized complex was either equally or lesser inhibitor than the parent compound. The copper complex showed no inhibition zone against *E. coli* bacteria.

TABLE–2
BACTERIOSTATIC EFFECT OF METRONIDAZOLE AND ITS METAL COMPLEXES

Organism	Zone of inhibition* (mm) caused by			
	A	A_1	A_2	A_3
Bacillus subtilis	20	28	12	12
Escherichia coli	8	8	(–)	6

* Average of three readings, concentration of compounds 10 mg/mL. (–) No activity.
A—Metronidazole (Mz); A_1—Co-Mz complex; A_2—Cu-Mz complex; A_3—Ni-Mz complex

Higher bacterocidal activity of certain metal complexes than the pure drug may be due to the fact that complexation with metal imparts some important characteristics to the drug, which are helpful in its biological activity, *e.g.*, low dissociation constant (strong metal bond), special redox-potential, electron distribution and solubilities. It also helps in the natural process of bond formation and bond cleavage and the group transfer reactions[22]. As a result, the metal complex has increased duration of action and posseses enhanced blood concentration, which may probably be due to a comparatively faster diffusion of the metal chelate as a whole through the organism, due to its more liposoluble nature (more covalent metal-to-ligand bond) on being coordinated with the metal ion forming stable chelates.

EXPERIMENTAL

Metranidazole was obtained from Eskayef Limited, Bangalore, in pure form and used as such. All the solvents and reagents used were of AR grade.

All compounds were prepared generally by the same method. To a hot solution of the appropriate metal salt in ethanol, solution of the ligand in the same solvent in ratio 1 : 2 : : M : L were added and the resulting mixture was refluxed on a water bath for 10–12 h. The precipitated complex was filtered, washed with ethanol and dried over anhydrous $CaCl_2$ and then at 110°C for 1 h.

The elemental analysis were carried out on a Carlo Erba analyser at RSIC, CDRI Lucknow. The conductivity measurements were carried out in DMF at a concentration 10^{-3} M using Elico type CM–82T conductivity bridge. Magnetic susceptibility measurements were done at room temperature by Gouy's method using

$Hg[Co(NCS)_4]$ as calibrant. Reflectance spectra were carried out at RSIC, IIT, Bombay in the range 350 to 1100 nm. The infrared spectra (KBr) were recorded on Shimadzu IR–470 infrared spectrophotometer.

Pregrown cultures of the bacteria were inoculated. Sterilized Whatman No. 1 filter paper discs (diameter 5 mm.) were thoroughly moistend with the synthesized complex solution to be tested and were placed on seeded agar plates. Petridishes with the bacteria were incubated at 37°C for 24 h. The zone of inhibition was then measured and compared with that of the standard.

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