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Preparation, Characterization and Biological Evaluation of Schiff Base Transition Metal Complexes with Cephadrine

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Abstract: Transition metals (Mn (II), Co (II), Ni (II), Cu (II) and Zn (II)), complexes of Schiff base derived from Cephadrine and Salicylaldehyde were prepared and characterized by elemental analysis, conductance, magnetic moments and spectroscopic data. In these complexes an amino group available in the Cephadrine was allowed to react with Salicylaldehyde to obtain Schiff base and which then subsequently reacted with Transition metals. Schiff base was derived from condensation of salicylaldehyde and cephadrine in equimolar quantities (1:1). Ligand chelates through OH and -C=N- functional group of the Schiff base. The complexes were formulated as ML_2 (1:2) type. All the complexes were found to be six-coordinate dihydrates. The geometry of the complexes appears to be simple octahedral. All the compounds under investigation possess somewhat antibacterial activity. The antibacterial activity showed the following trend; Transition metal complexes > Schiff base ligand > Parent drug

Key words: Metal based drugs, Schiff base complexes, transition metal complexes, antibacterial, coordination compounds

INTRODUCTION

Compound containing an azomethine group (-CH=N-) are known as Schiff bases. Schiff bases are generally bi- or tri- dentate ligands capable of forming very stable complexes with transition metals. Schiff base metal complexes with different drugs are relatively less studied. The wide use of antibiotics in man and animals and their extensive use in areas other than the treatment and prophylaxis of disease have resulted in a serious problem of drug resistance. More and more bacterial strains have become resistant to the available drugs. Various strategies have been worked out and tried upon to cope with the resistance problem and enhance the activity, or broaden the spectrum of the drugs^[1]. Preparation of different synthetic derivatives of antibiotics based on structure-activity relationship has been one of the best approaches. A relation between the structure of the complexes and their anti-bacterial activity can be observed^[2]. In the present work we have attempted to widen the scope of derivatization by providing more flexibility through Schiff base formation with the drug substances containing -NH₂ groups and complexation with metal elements. The Schiff base structure provides for a greater choice and flexibility and complexation with a metal element adds to stability and versatility of the molecule. The drug molecule used in

the present study contains -NH₂, -COOH and other donor groups; construction of molecular model indicates that the structure is suitable for chelate formation. Interaction of various metal ions with antibiotic may enhance or suppress their antimicrobial activity but usually in many cases the pharmacological activity of antibiotics after complexation with metals is enhanced as compared to that of the free ligands^[3,4].

Many of the well-known antibiotics, penicillin, streptomycin, tetracycline etc; are chelating agents, their action is improved by the presence of small amounts of metal ions^[5]. The antimicrobial activity of the ligands and their transition metal complexes against different bacteria are also reported. Copper complexes have more antibacterial activity against the bacteria *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Salmonella typhi* etc.^[6]. It is found that the complexes have higher activities than those of the free Schiff bases.

MATERIALS AND METHODS

Materials: All chemicals were of analytical grade and were obtained from E. Merck (Germany) and Sigma Chemical Co. (USA). Cephadrine was obtained in pure form from a local Pharmaceutical company and was used without further purification.

Preparation of Schiff base ligand: Schiff base ligand was prepared by reacting the Cephadrine with salicylaldehyde. The method of preparation was as follows:

The Cephadrine (5 mmol) dissolved in methanol (50 cm³) was mixed with salicylaldehyde dissolved in methanol (50 cm³). To this KOH (0.1% in methanol) was added to adjust the pH of the solution between 7-8 and the mixture was refluxed for 30 min (approx.). A clear colored solution was obtained. The Schiff base ligand was isolated by crystallization after volume reduction by evaporation. The crystalline product was dried under vacuum and kept in a desiccator till further use.

Preparation of Schiff base metal complexes: The Schiff base ligand (2 mmol) dissolved in methanol (25 cm³) was mixed with transition metals, Mn (II), Co (II), Ni (II), Cu (II) and Zn (II), (1 mmol) dissolved in methanol (25 cm³). The reaction mixture was refluxed for 2-3 h. The product was isolated after reduction of volume by evaporation. It was filtered off, washed with methanol and dried under vacuum. The complexes thus obtained are listed in Table 1.

Characterization: Microanalysis was performed by the usual techniques. Mn (II), Co (II), Ni (II), Cu (II) and Zn (II) were estimated by atomic absorption spectrometry. Molecular masses were determined mass-spectrometrically. Conductivity measurements were made with the Orion Model 160-conductivity meter using DMF as solvent at room temperature. The magnetic moments of the metal complexes were determined by Gouy's technique using Hg (II)-tetrathiocyanatocobaltate as calibrant; diamagnetic corrections were calculated from Pascal's constants^[7]. Infrared spectra were recorded with an FT-IR (Midac) spectrophotometer using KBr disc

and Nujol mull techniques. Electronic absorption spectra were obtained with a Hitachi Model 121-0032 spectrophotometer using methanol (for the ligands) and DMF (for the complexes) as solvents. To evaluate the changes in microbial activity of Cephadrine after complexation, antibacterial studies were carried out by observing the changes in MIC^[8] (Minimum Inhibitory Concentration) of the complexes and compared with the parent drug by measuring the zone of inhibition of complexes against both Gram positive and Gram negative bacteria.

RESULTS AND DISCUSSION

The complexes under investigation were isolated by refluxing the Mn (II), Co (II), Ni (II), Cu (II) and Zn (II)^[9] hydrated salt with Schiff base ligand in methanol separately. The isolated complexes were fairly soluble in DMF and DMSO and insoluble in other common organic solvents. The complexes were found to be hygroscopic. Microanalytical data (Table 1) confirmed the ML₂ composition of the complexes, in which M is Mn (II), Co (II), Ni (II), Cu (II), Zn (II) and L the Schiff base ligand. The complexes decomposed between 190 to 330°C and did not show sharp melting points. Karl-Fischer titration indicated the presence of water molecules in the complexes.

The molecular masses determined mass-spectrometrically also confirmed the ML₂ composition. The bonding of the ligand to metal elements was investigated by comparing the FT-IR spectra of the complexes with those of the free ligands. The FT-IR spectra of the complexes contained all the absorption bands from the ligand and some new absorption bands indicative of coordination of the ligands with metal ions

Table I: Physical and microanalytical data of the Schiff base ligand and their metal complexes

Compound	Yield (%)	Colour	Decomposition point, (°C)	Elemental analysis found % (Calculated %)			
				C	H	N	M
Salicylidenecephradine	51	Light yellow	190	61.44 (60.91)	5.42 (5.11)	9.73 (9.26)	-
Salicylidenecephradine-Mn (II).2H ₂ O	49	orange	280	55.23 (55.47)	4.75 (4.85)	8.29 (8.43)	5.42 (5.51)
Salicylidenecephradine-Co (II).2H ₂ O	52	Dark orange	330	55.61 (55.25)	4.57 (4.83)	8.05 (8.40)	5.56 (5.89)
Salicylidenecephradine-Ni (II).2H ₂ O	48	Dark brown	290	55.91 (55.26)	4.91 (4.84)	8.22 (8.41)	5.33 (5.87)
Salicylidenecephradine -Cu (II).2H ₂ O	51	Dark yellow	265	54.42 (54.99)	4.03 (4.81)	8.96 (8.36)	6.77 (6.33)
Salicylidenecephradine -Zn (II).2H ₂ O	53	Yellow	280	54.29 (54.89)	4.62 (4.80)	8.66 (8.35)	6.02 (6.49)

Table 2: Observed IR (cm⁻¹), Electronic Spectral data, Conductance and Magnetic moments of the Ligand/Complexes

Compound	ν (OH)	ν (C=N)	π (CO)	ν (MN)	ν (MO)	λ_{max} (cm ⁻¹)	Conduc. (μ S cm ⁻¹)	Magnetic moment (BM)
Salicylidenecephradine	3520	1650	545	-	-	20790, 16840, 5037	15.5	-
Salicylidenecephradine-Mn (II).2H ₂ O	3390	1635	530	-	-	16435, 7320, 1630	13.5	4.70
Salicylidenecephradine-Co (II).2H ₂ O	3450	1625	545	-	-	17834, 6543, 1578	10.8	3.40
Salicylidenecephradine-Ni (II).2H ₂ O	3480	1640	535	480	415	7261, 6215, 1436	12.6	2.60
Salicylidenecephradine -Cu (II).2H ₂ O	3440	1655	540	465	380	7837, 6473, 1478	9.7	2.10
Salicylidenecephradine -Zn (II).2H ₂ O	3460	1610	565	440	375	7284, 6317	11.4	Diamagnetic

Table 3: Antibacterial activity data (MIC $\mu\text{g mL}^{-1}$) of the Ligand/Complexes

Ligand/Complex	<i>E. coli</i>	<i>S. aureus</i>	<i>K. pneumoniae</i>
Salicylidenecephradine	65.0	12.0	60.0
Salicylidenecephradine-Mn (II).2H ₂ O	16.5	8.5	17.4
Salicylidenecephradine-Co (II).2H ₂ O	15.8	9.0	15.0
Salicylidenecephradine-Ni (II).2H ₂ O	16.8	10.4	12.0
Salicylidenecephradine-Cu (II).2H ₂ O	9.2	7.2	9.5
Salicylidenecephradine-Zn (II).2H ₂ O	11.0	9.5	13.2

through N and O. Some important absorption bands and their assignments are listed in Table 2. The spectra of these complexes exhibited a broad band around 3390-3520 cm^{-1} which is assigned to water molecules, ν (OH), associated with the complexes^[10]. FT-IR spectra of all the ligands contained a band at 1620-1650 cm^{-1} , ν (C=N), which shifted slightly to a higher value in all the complexes suggesting that the ligand is coordinated to the metal ion through -C=N.^[11] The absorption due to carboxylic group did not change in the spectra of complexes indicating that the carboxylic groups are not involved in coordination with the metal ion. New absorption bands, ν (MN) and ν (MO), appeared at 440-480 cm^{-1} and 380-415 cm^{-1} , respectively, in the spectra of the complexes indicating coordination of the ligand through N and O. In the electronic absorption spectra of the complexes (Table 2) there is an intense band at 20790-6548 cm^{-1} which is assigned to a π - π^* transition originating in the phenyl ring. Lower molar conductance values (9.7-15.5 $\mu\text{S cm}^{-1}$) for the complexes (Table 2) indicate the non-electrolytic nature of the complexes. The Mn (II), Co (II), Ni (II), Cu (II) and Zn (II) complexes had normal values of the magnetic moments, i.e. 2.10-4.70 BM (Table 2), indicating their mononuclear nature. Based on the experimental evidence thus obtained the complexes were characterized as six-coordinates with the two positions occupied by two water molecules (Table 3).

The suggested structure of the complexes under investigation, on the basis of the above experimental evidence, is shown in Fig. 1.

Antibacterial activity: Direct metal complexes of cephradine are known to show antibacterial activity^[12,13]. Schiff base metal complexes of cephradine have also shown enhanced antibacterial activity. A cursory view of the data indicates the following trend in activity of the substances under investigation against *E. coli*, *S. aureus* and *K. pneumoniae*. Mn (II), Co (II), Ni (II), Cu (II) and Zn (II) > Schiff base ligand > Parent drug

All the Schiff base ligand under study was more active than the parent drug against *E. coli*, *S. aureus* and *K. pneumoniae*.

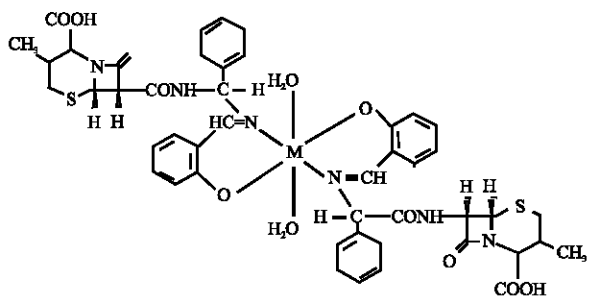


Fig. 1: Suggested structure of metal complexes of salicylidenecephradine.

M: Mn (II), Co (II), Ni (II), Cu (II) and Zn (II)

These results show that the anti-bacterial activity and toxicity of the drugs under investigation is improved after derivatization. These observations, in line with other studies, suggest that the metal-based drugs possess a great potential as therapeutics.

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