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Synthesis, Characterization & Antimicrobial Studies of Complexes of Alkali/Transition Metal Chelates of Some Organic Acids With Ciprofloxacin

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Abstract :- New mixed ligand complexes of transition metal chelates of some organic acids with ciprofloxacin of the type [ML_n.antb.] and neutral alkali metal complexes of type [M(antb). $(H_2O)_4$] have been synthesized. These complexes have been characterized by elemental analysis, spectral data, conductance and magnetic moment measurements. Antimicrobial efficiency of the compounds has been screened against five different micro-organism.

Keywords:-Interestingly all Complexes Demonstrated Potent in Vitro Antibacterial/Antifungal Activity Against Gram +ve Bacteria (S.aureus), Gram -ve Bacteria (E.coli) and Fungi *(*C.albicans*).*

I. INTRODUCTION

Ciprofloxacin belongs to fluoroquinolines class of antibiotics. Many drugs possess modified toxicological and pharmacological properties when they are complexed with metals[1-3]. Metal complexes of the quinolone antibacterial agent ciprofloxacin with Mn(II), Fe(III), Co(II) and Ni(II) are reported[4-5]. Recently, we have reported, a number of complexes of alkali/transition metal chelates of some organic acids with Nalidixic acid[6] and Norfloxacin[7]. In continuation, we have synthesized and characterized several mixed lgand alkali/ transition metal complexes with well known antibiotic ciprofloxacin to study the relative bioactivity and stereochemistry of the complexes.

Experimental : 1. Synthesis of Transition Metal Chelates of Organic Acids, Ml_n: 95% Ethanolic solution of organic acid(1N2N) and suspension/solution of metal acetate in 95% ethanol were mixed together in 2 : 1 molar proportion. The mixture was refluxed on magnetic hot plate at 80ºC for nearly one & half hours with continuous stirring. The colour of the contents changed and a clear solution was obtained, on adding ammonia solution, the adduct got separated. It was filtered and washed with the solvent and dried in an electric oven at 100ºC.

2. Synthesis of Mixed Ligand Complexes of Transition Metal Chelates of Some Organic Acids With Ciprofloxacin: To the suspension of transition metal chelate of 1-nitroso-2-naphthol in ethanol, ciprofloxacin was added in 1 : 1 molar proportion till the colour changed/precipitate formed. The mixture was refluxed on magnetic hot plate with constant stirring at 80ºC for 1-2 hours. On cooling the solution, characteristic colour precipitate got separated. It was filtered, washed with absolute ethanol and finally dried in an electric oven at 100ºC

3. Synthesis of Neutral Alkali Metal Complexes of Ciprofloxacin: To hot solution of the antibiotic(ciprofloxacin) in ethanol was added slowly with constant stirring to an ethanolic solution of alkali metal hydroxide in 1 : 1(mole). pH of the solution was so adjusted as to get the indication of complex formation by colour change or by precipitation. All the complexes prepared were obtained in pH range 4.0 to 6.5. After adjusting the pH, the content was refluxed over steam bath for about an hour. Precipitate so obtained was filtered and washed many times with the solvent. It was dried in an electric oven at about 100ºC and stored in a desiccator over anhydrous $CaCl_2$.

II. RESULT & DISCUSSION

Colours, decomposition temperatures, molar conductances, magnetic moment values and analytical data of the prepared complexes are given in Table -1. Molar conductance values of the complexes were measured in DMF at 30ºC at a concentration of 10^{-3} M. The low values (8.3 - 13.5 $ohm^{-1}cm^2mol^{-1}$) of molar conductances, indicate that they are non-electrolyte in nature[8].

A. Infrared spectra

The assignment of the infrared bands in the complexes have been carried out by comparison with the spectrum of pure drug (Table-2). In the infrared spectra of neutral complexes of Na & K bands in the regions : 3760 - 3775, 1560 - 1576 & 880

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- 885 cm^{-1} assignable to O-H stretching, bending and rocking vibrations respectively indicating the presence of coordinated water molecules in the Na and K metal complexes. While in the infrared spectra of mixed ligand complexes of Fe(II), Ni(II), Cu(II), bands only appeared in the region 3695 - 3840 cm^{-1} assignable to O-H(free) stretching. The band $\upsilon_{C=0}$ which is present in the ligand at 1600 cm^{-1} shifted by 25 cm^{-1} in the complexes indicating the coordination through this group[9]. Presence of –OH group has been supported by a sharp medium bands present in the region 1115 – 1125 cm^{-1} in the mixed ligand transition metal complexes which indicates M-OH bonding. All the complexes show mew medium intensity band in the region 415 – 500 cm^{-1} may be due to υ_{M-O}[10-11] involving H_2O/1N2N.

B. Magnetic And Electronic Spectra

The electronic spectra of all the complexes of ciprofloxacin shows broad band in the region ~35971 cm^{-1} which is due to $\pi_2 \rightarrow \pi_4$ transition. The sodium complex exhibits a weak and broad band near 14044 - 19305 cm^{-1} which could be attributed to $^6A_{1g} \rightarrow {}^4T_{1g}(4G)$ transition. This value is well within the range of octahedral complex.

The magnetic moments of sodium and potassium complexes were found to be negligible(~0) indicating the presence of paired electrons, i.e. diamagnetic in nature.

The Fe(II) complex showed bands ~23923 cm^{-1} and a broad and asymmetric band near 17421 cm^{-1} may be assigned to the $^6A_{1g} \rightarrow {}^4E_g(G)$, $^6A_{1g} \rightarrow {}^4T_{1g}(G)$ transitions characteristic of octahedral stereochemistry around metal ion. Magnetic moment of Fe(II) complex was found to be 5.6BM indicating the presence of five unpaired electrons, i.e. paramagnetic in nature. This value is well within the range of octahedral Fe(II) (ground state $^6A_{1g}$) complexes[12].

The Ni(II) complex gave three bands at 12531, 18867 and 25445 cm^{-1} due to transitions: $^6A_{1g}(F) \rightarrow {}^3T_{2g}(F)$, $^3A_{2g} \rightarrow {}^3T_{2g}(F)$ & $^3A_{2g} \rightarrow {}^3T_{1g}(P)$ indicating an octahedral geometry[12].

The ligand field parameters Dq, B and β values were found to be 1253 cm^{-1}, 447 cm^{-1} & 0.4339 respectively. 3.20 BM magnetic moment of Ni(II) complex also indicates its octahedral geometry, because the range for octahedral Ni(II) complexes is 2.9 - 3.4 BM, indicating the presence of two unpaired electrons.

The magnetic moment of Cu(II) complex was found to be 1.62 BM, showing paramagnetic character. In the electronic spectra of Cu(II) complex one broad band in the region 12150 - 13703 cm^{-1} has been observed which may be assigned to $^2E_g \rightarrow {}^2T_{2g}$ transition in distorted octahedral field.

C. Microbial Studies

Drug(Ciprofloxacin) and all the synthesized compounds were screened for their antimicrobial activity against the bacteria at 37°C for 24h and fungi in suitable nutrient medium at 28°C for 48h by adopting Serial Dilution Method[13]. A comparative study of MIC values shown in (Table - 3). In general, infer that the complexes of Fe(II), Ni(II), Cu(II), Na & K with this drug shows remarkable antibacterial activity against E.coli and Shigella flexneri bacteria as compared to parent drug. All the complexes show nil activity against Bacillus pyocyaneus bacteria. These metals complexes also show good and remarkable antifungal activity against Tricoderma viride, Candida albicans and Chrysosporium pannicale fungus. All the complexes show average little activity against Aspergillus niger and Aspergillus flavus species.

III. CONCLUSION

On the basis of analytical and spectral datas, the probable structures of the complexes are shown in Fig. 1 & 2. The drug shows a much higher antibacterial activity towards Gram –ve bacteria and Gram +ve cocci. Mixed ligand transition metal complexes of the drugs are found to be more antimicrobial activity than the metal chelates of the drugs.

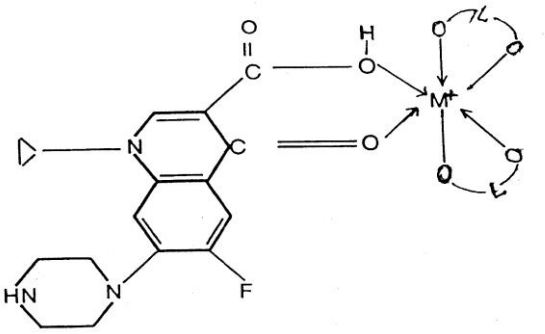

Fig. 1

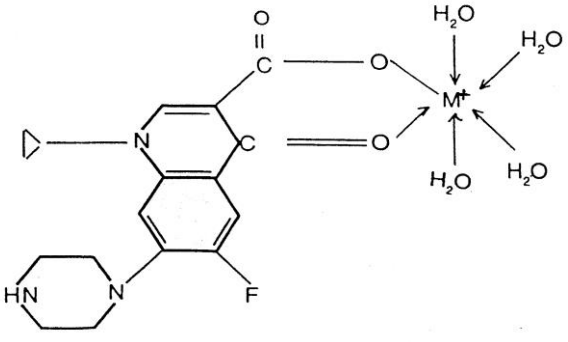

Fig. 2

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Compound	Colour	Decomp. temp.(^{0}C)	Conductivity	Magnetic moment	% Analysis Found/(Calc.)				
					C	H	N	F	M
[Fe(1N2N)$_2$.HCipro]	Dark brown	286		5.60	60.78 (60.86)	3.89 (3.97)	9.45 (9.59)	2.44 (2.60)	7.54 (7.65)
[Ni(1N2N)$_2$.HCipro]	Light green	300	8.3	3.20	60.44 (60.51)	3.95 (4.09)	9.54 (9.64)	2.45 (2.59)	7.88 (8.00)
[Cu(1N2N)$_2$.HCipro]	Green	259	10.5	1.62	60.05 (60.12)	3.98 (4.06)	9.36 (9.48)	2.46 (2.57)	8.45 (8.60)
[Na(Cipro)(H$_2$O)$_4$]	White	285	12.5	Diamag.	48.02 (48.11)	5.83 (5.89)	9.82 (9.90)	4.12 (4.24)	5.32 (5.42)
[K(Cipro)(H$_2$O)$_4$]	White	305	13.5	Diamag.	46.30 (46.36)	5.61 (5.68)	9.45 (9.54)	3.91 (4.09)	8.71 (8.86)

TABLE -1

Assignments	Ciprofloxacin	Na complex	K complex	Fe(II) complex	Cu(II) complex	Ni(II) complex
υ_{O-H}	----	3760	3775	3810, 3750	3840, 3790, 3695	3805, 3710
υ_{N-H}	3450	3375, 3260	3340	3785	3685, 3300	3315
$\upsilon_{C=O}$	1600	1625	1626	1623	1624	1625
$\upsilon_{COO-/COOH}$	1580	1575	1580, 1445	1585	1580	1575, 1450
υ_{C-N}	1330	1303	1305	1306	1308	1305
υ_{C-N}(ring vibration)	1260, 1120	1260, 1185	1290, 1265	1225, 1220	1260, 1185	1255, 1185
υ_{C-F}	1380	1385	1380	1375	1385	1390
υ_{M-OH}(bending)	----	----	----	1120	1125	1115
Coordinated H$_2$O (bending)	----	1560	1576	----	----	----
Coordinated H$_2$O (rocking)	----	885	880	----	----	----
Out of plane deformation benzeniod ring	775, 725	750	745	785, 725	790, 755	785
C-N-C(bending)	550	510	515	545	550	545
υ_{M-O}	----	480	470	500	415	425

TABLE – 2

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Organism	Inhibition zone(mm of Drug 0.5 mg/ml	Inhibition zone(mm) of Drug 1.0 mg/ml	Inhibition zone(mm) of complex 0.5 mg/ml					Inhibition zone(mm) of complex 1.0 mg/ml				
			Na-comp	K-comp	Fe-comp	Cu-comp	Ni-comp	Na-comp	K-comp	Fe-comp	Cu-comp	Ni-comp.
E. coli	+	++	+	+	++	+	+	++	++	++	++	++
Shigella flexneri	+	+	+	+	+	+	+	++	++	++	+	++
Tricoder-ma viride	+	+	++	++	+	++	++	+++	+++	++	+++	+++
Chrysosp-orium pannicle	-	+	+	+	+	++	+	++	++	++	+++	++
Candida albicans	+	+	++	++	+	++	++	+++	++	++++	+++	+++
Aspergill-us niger	+	+	+	-	+	-	+	+	-	+	+	-
Aspergill-us flavus	-	+	-	+	+	-	-	-	+	-	+	-

TABLE - 3

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