SYNTHESIS, CHARACTERIZATION & ANTIMICROBIAL STUDIES OF COMPLEXES OF TRANSITION METAL CHELATES OF SOME ORGANIC ACIDS WITH CLOXACILLIN

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A number of mixed ligand complexes of transition metal chelates of some organic acids with cloxacillin of the type [ML_n.antb.] 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 five different micro-organism. screened against Interestingly all complexes demonstrated potent in vitro antibacterial/antifungal activity against Gram +ve bacteria Gram -ve bacteria (E.coli) and fungi (S.aureus), (C.albicans).

Key word : Mixed ligand complexes, Transition metal chelates, Cloxacillin, Organic acids, Spectral data & Antimicrobial activity.

7NTRODUCTION

Cloxacillin belongs to quinolines class of antibiotics. It behaves as a monoprotic bidentate ligand coordinating through oxygen atoms of >C=O and -COOH groups of the drug. 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]. The literature survey has indicated that two kinds of mixed ligand fluoroquinolones complexes with transition metal adducts of neutral bidentate ligands have been isolated by several workers. These are of types : [ML_n.antb.] and [M(antb)L_n] where M = Mn(II), Fe(III), Cu(II), Ni(II) etc., L = bidentate neutral ligand, antb. = antibiotics. Recently, we have reported a number of complexes of transition metal chelates of some organic acids with Norfloxacin [6]. In continuation, we have synthesized and characterized several mixed lgand transition metal complexes with well

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known antibiotic cloxacillin 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 (DNP or 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 80°C for nearly one and 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 100°C.

2. Synthesis of mixed ligand complexes of transition metal chelates of some organic acids with Ciprofloxacin : To the suspension of transition metal chelate 2, 4-dinitrophenol or 1-nitroso-2-naphthol in ethanol, cloxacillin 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 80°C 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 100° C

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 30° C at a concentration of 10^{-3} M. The low values (9.6 - 14.5 ohm⁻¹cm²mol⁻¹) of molar conductances, indicate that they are non-electrolyte in nature [7].

| | | Deco | | | % Analysis Found/(Calc.) | | | | |
|-------------------------------|--------------------|----------------------|-------------------|--------------------|--------------------------|----------------|------------------|----------------|----------------|
| Compound | Colour | mp. temp. (°C) | Condu- ctivity | Magnetic moment | С | н | Ν | CI | М |
| [Fe(DNP)2.Norf] | Light brown | 226 | 10.2 | 5.4 | 45.34 (45.21) | 3.24 (3.16) | 13.22 (13.04) | 2.56 (2.47) | 7.56 (7.40) |
| [Ni(DNP)2.Norf] | Dark brown | 285 | 11.5 | 3.1 | 45.18 (45.01) | 3.23 (3.15) | 13.18 (13.05) | 2.55 (2.45) | 7.89 (7.75) |
| [Cu(DNP)2.Norf] | Brown | 230 | 14.1 | 1.9 | 44.89 (44.75) | 3.21 (3.11) | 13.09 (12.80) | 2.54 (2.44) | 8.48 (8.35) |
| [Fe(1N2N)2.Norf] | Brown | 245 | 12.2 | 5.6 | 60.08 (59.95) | 4.17 (4.05) | 9.73 (9.62) | 2.64 (2.55) | 7.79 (7.54) |
| [Ni(1N2N)2.Norf] | Yellowish brown | 290 | 10.5 | 3.2 | 59.85 (59.71) | 4.15 (4.03) | 6.70 (6.52) | 2.63 (2.51) | 8.10 (7.95) |
| [Cu(1N2N) ₂ .Norf] | Golden brown | 235 | 15.0 | 1.8 | 59.46 (59.31) | 4.13 (4.05) | 9.63 (9.51) | 2.61 (2.48) | 8.74 (8.61) |

TABLE -1

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 mixed ligand complexes of Fe(II), Ni(II), Cu(II), bands only appeared in the region 3649 - 3444 cm⁻¹ assignable to O-H(free) stretching. The band $v_{c=0}$ which is present in the ligand at 1600 cm⁻¹ shifted by 25 cm⁻¹ in the complexes indicating the coordination through this group [8]. Presence of -OH group has been supported by a sharp medium bands present in the region 1112 - 1127 cm⁻¹ in the mixed ligand transition metal complexes which indicates M-OH bonding. All the complexes show new medium intensity bands ~586 and ~462 cm⁻¹ may be due to v_{M-N} and v_{M-O} [9-10] respectively.

| Assignments | Norfloxacin | [Fe(DNP) ₂ . Nor] | [Cu(DNP) ₂ . Nor] | [Fe(1N2N) ₂ . Nor] | [Cu(1N2N) ₂ . Nor] | [Ni(1N2N)2. Nor] |
|---|---------------------|---------------------------------|---------------------------------|----------------------------------|----------------------------------|---------------------|
| U _{O-H} | | 3805 | 3885, 3750 | 3800 | 3880, 3750 | 3830, 3740 |
| $\upsilon_{\text{N-H}}$ | 3400 | 3300, 3205 | 3380, 3000 | 3305, 3210 | 3360, 3010 | 3415, 3075 |
| UC=0 | 1620 | 1630 | 1625 | 1625 | 1620 | 1630 |
| UCOO-/COOH | 1470 | 1440 | 1465 | 1445 | 1470 | 1565, 1495, |
| UC=N | 1350 | 1335 | 1338 | 1330 | 1335 | 1340 |
| UC-N(ring vibration) | 1255, 1190, 1130 | 1270, 1190, 1110 | 1260, 1190 | 1265, 1195, 1115 | 1250, 1190, 1110 | 1265, 1190 |
| UC-F | 1375 | 1370 | 1380 | 1365 | 1385 | 1385 |
| υ _{M-OH} (bending) | | 1128 | 1110 | 1130 | 1115 | 1120 |
| Out of plane deformation benzenoid ring | 745, 625 | 750, 620 | 750, 625 | 755, 610 | 760, 535 | 625 |
| C-N-C (bending) | 525 | 515 | 515 | 510 | 522 | 520 |
| U _{M-O} | | 485, 415 | 485 | 480, 420 | 476 | 475 |

TABLE – 2

Magnetic and electronic spectra: The electronic spectra of all the complexes of cloxacillin shows broad a broad band in the region ~40000 cm⁻¹ which is due to $\pi_2 \rightarrow \pi_4$ transition.

The Fe(II) complex showed bands at 13774, 17513 and 23980 cm⁻¹ corresponding to ${}^{6}A_{1g} \rightarrow {}^{4}T_{1g}$, ${}^{6}A_{2g} \rightarrow {}^{4}T_{2g}$ and ${}^{6}A_{1g} \rightarrow {}^{4}E_{g}$ transitions respectively, characteristic of octahedral stereochemistry around metal ion. Magnetic moment of Fe(II) complex was found to be 4.1BM indicating the presence of four unpaired electrons, *i.e.* paramagnetic in nature. This value is well within the range of octahedral Fe(II) (ground state ${}^{6}A_{1g}$) complexes [11]. The ligand field parameters Dq, B and β values were found to be 630.3 cm⁻¹, 573 cm⁻¹ and 0.5645 respectively.

The electronic spectral bands around 12500, 19050 and 25600 cm⁻¹ due to transitions : ${}^{3}A_{2g}(F) \rightarrow {}^{3}T_{2g}(F)$, ${}^{3}A_{2g} \rightarrow {}^{3}T_{1g}(F)$ & ${}^{3}A_{2g} \rightarrow {}^{3}T_{1g}(P)$ respectively indicate that the central Ni(II) ion is present in an octahedral field^[11]. The ligand field parameters Dq, B and β values were found to be 1255 cm⁻¹, 456 cm⁻¹ and 0.4427 respectively. The magnetic moment of Ni(II) complex is 3.10 BM, also indicates its octahedral geometry, because the range for octahedral Ni(II) complexes is 2.9 - 3.4 B.

In the electronic spectra of Cu(II) complex, one broad band in the region 11764 - 13793 cm⁻¹ has been observed which may be assigned to ${}^{2}E_{g} \rightarrow {}^{2}T_{2g}$ transition in distorted octahedral field. The magnetic moment of Cu(II) complex was found to be 1.72 BM, which indicates its paramagnetic nature with a single unpaired electron.

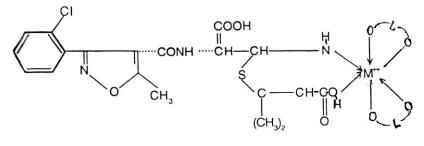
Microbial studies : Drug (Cloxacillin) and all the synthesized complexes were screened for their antimicrobial activity against the bacteria at 35°C for 24h and fungi in suitable nutrient medium at 26°C for 48h by adopting Serial Dilution Method [12]. A comparative study of MIC values shown in (Table - 3). In general, infer that the complexes of Fe(II), Ni(II) and Cu(II) with this drug shows remarkable antibacterial activity against *Bacillus subtillis and Shigella flexneri* bacteria as compared to parent drug. All the complexes show average little or nil activity against *Bacillus pyocyaneus* bacteria. All the complexes also show greater antifungal activity against *Tricoderma viride, Candida albicans* and *Chrysosporium pannicale* fungus as compared to the parent drug. All the complexes have nil activity against *A. flavus species*.

| 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 | | |
|----------------------------|---|--|--|-----------------------------|-----------------|--|-----------------------------|-----------------|
| | | | [Fe (DNP)2.Nor] | [Cu(DNP) ₂ .Nor] | [Ni(1N2N)2.Nor] | [Fe(1N2N) ₂ .Nor] | [Cu(DNP) ₂ .Nor] | [Ni(1N2N)2.Nor] |
| E.coli | + | ++ | ++ | ++ | ++ | ++++ | ++++ | ++++ |
| Salmonella typhosa | + | + | + | + | + | ++ | ++ | ++ |
| Bacillus subtillis | + | + | + | + | + | ++ | ++ | ++ |
| Bacillus pyocyaneus | - | - | - | + | - | - | - | - |
| Candida albicans | + | + | + | + | + | + | + | ++ |
| Chrysosporium pannicale | + | + | + | + | + | + | + | ++ |

TABLE - 3

CONCLUSION

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





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