

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

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New mixed ligand complexes of transition metal chelates of some organic acids with norfloxacin of the type $[ML_n.antb.]$ have been synthesized. These complexes have been isolated at pH = 5.0 – 6.5. On the basis of various physico-chemical investigation, it has been found that the drug behaves as a monoprotic bidentate ligand coordinating through oxygen atoms of $>C=O$ and $-COOH$ groups of the drug. Antimicrobial efficiency of the compounds has been screened against five different micro-organism. 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*).

Key word : Norfloxacin, 2, 4-Dinitrophenol, 1-Nitroso-2-naphthol, Transition metal chelates, Infrared spectra & Antimicrobial studies.

INTRODUCTION

Norfloxacin belongs to quinolones 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 norfloxacin 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 quinolones complexes with transition metal adducts of neutral bidentate ligands have been isolated by several workers. These are of type $[M(bdl.)antb.]^+$, where M = Fe(II), Cu(II), Ni(II) etc., bdl. = neutral bidentate ligands and antb. = fluoroquinolones antibiotics.

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As coordination through oxygen atom containing ligands have been reported to be more antimicrobial and no neutral bidentate ligand, viz. 1-nitroso-2-naphthol(1N2N), 2,4-dinitrophenol (DNP) have been studied both in terms of stereochemistry and bioactivity being as part of quinolone complex, hence we decided to synthesize quinolone of the type The literature survey has indicated that two kinds of mixed ligand quinolones complexes of the type [MLn.antb.], the antibiotic selected is norfloxacin to study the relative activity of transition metal complexes of the same antibiotics were studied in view of known cell permeability of these metals.

EXPERIMENTAL :

Pure sample of norfloxacin, 2,4-dinitrophenol, 1-nitroso-2-naphthol, Fe(II), Cu(II), Ni(II) acetate and all other chemicals/solvents used were of AnalaR or Merck grade. *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 or 3 : 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, washed with the solvent and dried in an electric oven at 100°C.

Synthesis of mixed ligand complexes of transition metal chelates of some organic acids with norfloxacin : To the suspension of transition metal chelate of 2, 4-dinitrophenol or 1-nitroso-2-naphthol in ethanol, norfloxacin 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. The complexes are found to be coloured. They decomposed at higher temperature without melting. They are sparingly soluble in water and common organic solvents like benzene, ether, chloroform but soluble in methanol, ethanol and DMF. Molar conductance values of the complexes were measured in DMF at 30°C at a concentration of 10⁻³ M. The low values (10.5 - 15.0 ohm⁻¹ cm² mol⁻¹) of molar conductances, indicate that they are non-electrolyte in nature[6].

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 3740 - 3885 cm^{-1} assignable to O-H (free) stretching. The band $\nu_{\text{C=O}}$, which is present in the ligand at 1620 cm^{-1} shifted by 5 -10 cm^{-1} in the complexes indicating the coordination through this group[7]. Presence of -OH group has been supported by a sharp medium bands present in the region 1110 - 1128 cm^{-1} in the mixed ligand transition metal complexes which indicates M-OH bonding. All the complexes show new medium intensity bands in the region 415 - 485 cm^{-1} may be due to $\nu_{\text{M-O}}$ [8,9] involving $\text{H}_2\text{O}/1\text{N}2\text{N}$.

Magnetic and electronic spectra : The electronic spectra of all the complexes of norfloxacin shows broad a broad band at 35587 cm^{-1} which is due to $\pi_2 \rightarrow \pi_4$ transition.

The Fe(II) complex showed band at 23807 cm^{-1} and a broad asymmetric band near 13368 - 17331 cm^{-1} may be assigned to the ${}^6\text{A}_{1\text{g}} \rightarrow {}^4\text{E}_{\text{g(G)}}$, ${}^6\text{A}_{1\text{g}} \rightarrow {}^4\text{T}_{1\text{g(G)}}$ transitions characteristic of octahedral stereochemistry around metal ion. Magnetic moment of Fe(II) complex was found to be 5.6 BM 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 ${}^6\text{A}_{1\text{g}}$) complexes[10].

The Ni(II) complex gave three bands at 1550, 19000 and 25500 cm^{-1} due to transitions : ${}^6\text{A}_{1\text{g(F)}} \rightarrow {}^3\text{T}_{2\text{g(F)}}$, ${}^3\text{A}_{2\text{g}} \rightarrow {}^3\text{T}_{2\text{g(F)}}$ & ${}^3\text{A}_{2\text{g}} \rightarrow {}^3\text{T}_{1\text{g(P)}}$ respectively, indicating an octahedral geometry[10]. The ligand field parameters Dq, B and β values were found to be 1255 cm^{-1} , 456 cm^{-1} & 0.4427 respectively. The magnetic moment of Ni(II) complex is 3.20 BM, also indicates its octahedral geometry, because the range for octahedral Ni(II) complexes is 2.9 - 3.4 BM.

In the electronic spectra of Cu(II) complex, one broad band in the region 12030 – 13650 cm^{-1} has been observed which may be assigned to ${}^2\text{E}_{\text{g}} \rightarrow {}^2\text{T}_{2\text{g}}$ transition in distorted octahedral field. The magnetic moment of Cu(II) complex was found to be 1.80 BM, showing its paramagnetic character.

Microbial studies : Drug (Norfloxacin) and all the synthesized complexes 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[11]. A comparative study of minimum inhibitory concentration(MIC) values shown in (Table - 3). In general, infer that the complexes of Fe(II), Ni(II) & Cu(II) with this drug shows remarkable antibacterial activity against *E.coli*, *Salmonella typhosa*, *Bacillus subtilis* and *Shigella flexneri* bacteria as compared to parent drug. All the complexes show average little or nil activity against *Bacillus pyocyanus* bacteria. The complexes also show good and remarkable antifungal activity against *Trichoderma viride*, *Candida albicans* and *Chrysosporium pannicale* fungus. All the complexes have nil activity against *Aspergillus niger* and *Aspergillus flavus* species.

CONCLUSION

Norfloxacin complexes were isolated at pH = 5.0 – 6.5. On the basis of chemical investigations, it has been found that the drug behaves as a monoprotic bidentate ligand coordinating through oxygen atoms of $>C=O$ and $-COOH$ groups of the drug and DNP/1N2N. The drug shows a much higher antibacterial activity towards Gram +ve cocci and Gram -ve bacteria. The transition metal complexes are found to be more antimicrobial activity than the metal chelates of the drugs. On the basis of analytical and spectral datas, the probable structures of the complexes are shown in Fig. 1.

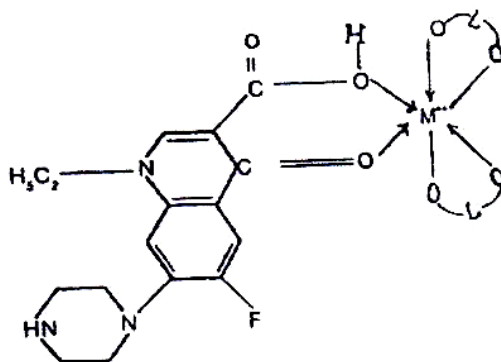


Fig. 1

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