

Synthesis, characterization and biological studies of nalidixic acid Na^+ , K^+ , Fe^{2+} and Cu^{2+} metal complex

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ABSTRACT

Nalidixin acid complexes of alkali and transition metals have been prepared and studied. The compounds have been characterized on the basis of elemental analysis, molar conductance, magnetic measurements, electronic absorption and infrared spectral data. All the prepared metal complexes with antibiotic drug nalidixic acid are screened for their antibacterial and antifungal activities.

Key words: Metal complex, Nalidixic acid, biological activity.

INTRODUCTION

Alkali and transition metals play a vital role in biological systems¹⁻⁵. It is well known that some of metal ions (e.g. Na^+ , K^+ , Fe^{2+} , Cu^{2+}) are very important for the life processes of animals and plants. A slight change in concentration brings about enormous changes of animals various diseases. This is mainly due to the impairment of biological activities. Concentration of metal ions in the body can be controlled by administration of drugs. In this process the drug forms complex with the metal ions essential for life processes. The metal also helps in the storage and transport of the drug in the body system through, enzyme or amino acids. The process of formation of complexes with drugs and metal ions essential for life processes have drawn attention of a large number of chemists⁶⁻¹¹. It has been reported that complexes of metallic salts are more potent and less toxic in many cases as compared to the parent drug¹².

The present work is to investigate the structure of the complexes of antibiotic drug Nalidixin acid with life essential metal ions like. Na^+ , K^+ , Mg^{2+} , Ca^{2+} and also determining the change in the activities of drugs due to complexation.

EXPERIMENTAL

Preparation of the Complexes

Nalidixic acid was obtained in pure and was used as such. Metallic salts and other chemicals used were of AnalaR or E. Merck grade.

The complexes were prepared by refluxing the mixture of concentrated solution of nalidixin acid in chloroform and metal salt in 1:1 or 1:2 (mole) for one hour at pH 4.0 – 5.5. The refluxed mixture was kept at 5 – 15°C over night, when characteristic colour precipitate was obtained. The precipitated complex was filtered, washed several times with the solvent, dried in an electric oven at 100°C and stored in a desiccator over anhydrous CaCl_2 .

RESULTS AND DISCUSSION

Some physical properties of the ligand and metal complexes are listed in Table-1. All the complexes are coloured crystalline solid, stable at room temperature. They are soluble in methanol, DMF etc. but insoluble in water and most of organic solvents namely chloroform, n-hexane, benzene etc. All complexes undergo decomposition at temperature higher than the melting point of the ligand, indicating thereby greater thermal stability.

The molar conductance (in $\text{ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$) of the complexes were measured on Systronics digital direct reading conductivity meter-304 at 30°C in 10^{-3}M solution in DMF (Table-1). The complexes show low values ($15 - 20 \text{ ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$) of molar conductivity, indicating that they are non-electrolytes.

The electronic absorption spectra of the complexes in methanol were recorded on Shimadzu

UV-210A spectrophotometer in the range of 200 to 800 nm. The electronic spectra of all the complexes of nalidixic acid show broad band in the region 236-278 cm^{-1} which indicate the $\pi-\pi^*$ transition. On electronic spectra of the complexes show charge transfer bands in region 329-390 nm. The shift in position $\pi-\pi^*$ and charge transfer bands of the complexes show that there is a π -interaction between metal and nalidixic acid orbital.

Table 1

Compound	Colour	Decomp. Temp. ($^\circ\text{C}$)	% Analysis Found (Calcd.)			
			C	H	N	M
$[\text{Na}(\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3)(\text{OH})(\text{H}_2\text{O})_3]$	Dark violet	301	46.90 (44.58)	5.27 (4.95)	9.17 (8.66)	4.00 (4.47)
$[\text{K}(\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3)(\text{OH})(\text{H}_2\text{O})_3]$	White	295	40.01 (39.17)	4.04 (4.46)	4.00 (4.47)	18.16 (18.37)
$[\text{Fe}(\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3)_2(\text{H}_2\text{O})_2]$	Dark brown	315	50.15 (50.36)	4.04 (4.19)	9.52 (9.79)	9.92 (9.76)
$[\text{Cu}(\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3)_2(\text{H}_2\text{O})_2]$	Light blue	300	40.15 (39.36)	5.12 (4.92)	8.95 (7.65)	16.99 (17.37)

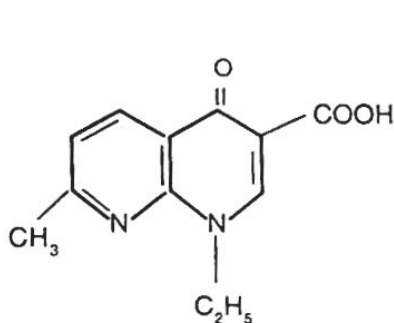


Fig. 1.

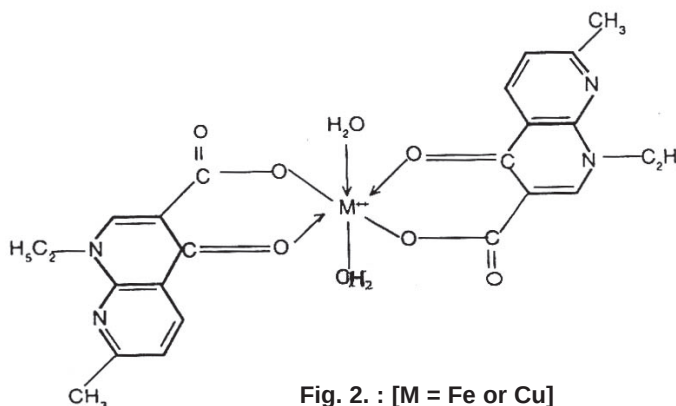


Fig. 2. : [M = Fe or Cu]

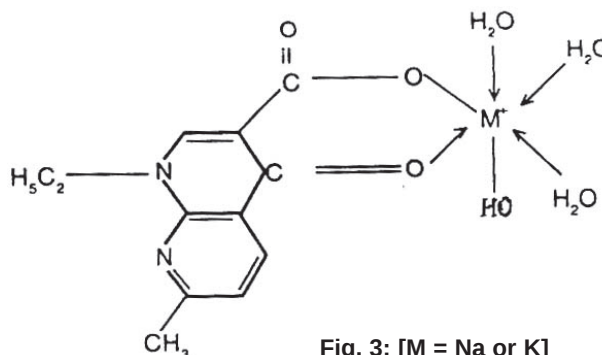


Fig. 3: [M = Na or K]

Table 2: Major IR bands (in cm^{-1}) of the ligand (Nalidixic acid) and its complexes

Assignments	Nalidixic acid		Band Positions		
	$(\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3)$	$[\text{Na}(\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3)(\text{OH})(\text{H}_2\text{O})_3]$	$[\text{K}(\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3)(\text{OH})(\text{H}_2\text{O})_3]$	$[\text{Fe}(\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3)_2(\text{H}_2\text{O})_2]$	$[\text{Cu}(\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3)_2(\text{H}_2\text{O})_2]$
ν_{OH}	—	3690w, 3650w	3690w, 3675w	3685w, 3650w	3689w, 3645w
$\nu_{\text{C=O}}$	1620sp	1625m	1624m	1620sp	1618m
Coordinated H_2O (bending)	1550m	1560mw.	1576m	1540sp	1555mw
$\nu_{\text{CH}_3\text{COO-}}$	1440m	1490m	1475mw	1440mw	1450mw
$\nu_{\text{C-N}}$	1320s	1318w	1315w	1332mw	1338sp
$\nu_{\text{C-N}}$ (ring vibration)	1230s	1265s, 1230mw	1260mw, 1230sp	1225w, 1220br	1255msp, 1219w
$\nu_{\text{N-OH}}$ (bending)	—	1115mbr	1131mw	—	—
Coordinated H_2O (rocking)	888mw, 810w	875w, 856m, 810s	890ms, 875w, 805sp	880br, 846sp	870mw, 840sp
Out of plane deformation	770w	785sp, 675m, 616sp	790w, 775w, 635mw	770w, 704mw	780mw, 695w
benzenoid ring					
C-C (bending)	540mw	550m	545w	540mw	535w
$\nu_{\text{M-O}}$	—	465w	445mw	450w	448w

The infrared spectra of ligand and complexes were recorded in KBr phase between 4000-400 cm^{-1} with the help of Shimadzu IR-470 spectrophotometer. Selected absorption bands are shown in Table -2. In the infrared spectra of alkali and transition metal complexes, broad band $\sim 3600 \text{ cm}^{-1}$ followed by appearance of sharp peaks at ~ 1610 and $\sim 850 \text{ cm}^{-1}$ assignable to O-H stretching, bending and rocking vibrations respectively, indicating the presence of coordinated water molecules in the complexes. The band in the region 1620 cm^{-1} observed due to $\nu_{\text{C=O}}$ in the ligand and in the complexes is shifted by 10 cm^{-1} , indicating the coordination through these group. Presence of -OH group has been supported by sharp medium bands present in the region $1113\text{-}1132 \text{ cm}^{-1}$ which indicates M-OH bending. All the complexes show new medium intensity band $\sim 450 \text{ cm}^{-1}$ may be due to $\nu_{\text{M-O}^{\cdot}}$.

CONCLUSION

On the basis of various physico-chemical investigations, it has been found that the antibiotic drug nalidixic acid behaves as monoprotonic bidentate ligand coordinating through oxygen of $> \text{C=O}$ and COO- groups. The stoichiometric ratio of the metal ion and the ligand has been found to be 1:1 for alkali metals and 1:2 for transition metal complexes. One/two coordination positions are occupied by water molecules. In case of alkali metal complexes three coordination positions are occupied by water molecules and another by -OH group. Presence of

coordinated water molecules and -OH group has been confirmed by infrared spectra and elemental analysis. Probable structures of the complexes are shown in Fig. 1 to 3.

Biological Studies

Measurement of activity

Sterilized Whatman No. 1 filter paper discs (5 mm diameter) were thoroughly moistened with the synthesized complex solution to be tested were placed on the seeded agar plates. Petri dishes with the bacteria were incubated at 37°C for 24 hours, whereas the plates with fungi were kept at room temperature for 48 hours. The zone of inhibition was then measured and compared with that of the standard.

The zone of inhibition of the complexes against a number of gram positive and gram negative pathogens bacteria and fungus was recorded for 24 and 48 hours at a concentration of 0.5 mg/ml and 1 mg/ml at 37°C for bacteria and 30°C for fungi. The inhibition zone of drug and complexes were recorded in Table-3.

All the complexes of nalidixic acid were screened for three antimicrobial studies (Table-4). These complexes show remarkable antibacterial activity against *Escherichia coli*, *Bacillus subtilis* at room temp. These complexes also show remarkable antifungal activity against *Tricoderma viride*, *Chrysosporium pannicale* and *Candida albicans* species as compared to parent drug.

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