

SYNTHESIS AND CHARACTERIZATION OF SELECTED METAL COMPLEXES OF NALIDIXIC ACID

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Abstract

Neutral mononuclear transition metal complexes of nalidixic acid with Ni(II) and Co(II) in presence of 1,10-phenanthroline (phen) or 2,2'-bipyridyl (bipy) have been prepared. The prepared complexes were characterized and studied with FT-IR, UV-Visible, XRD, TGA-DTA and elemental analysis. Spectroscopic studies suggest that the nalidixic acid acts as bidentate ligand in all the complexes and bind with the metal ion through the pyridine and one carboxylic oxygen atom.

Keywords: Nalidixic Acid, Metal complexes; Quinolone

1. Introduction

Medicinal inorganic chemistry can explore the unique properties of metal ions for the design of new drugs. In pharmaceutical field the transition metal ions are well known to enhance the drug action and the efficiency of drug enhanced upon the coordination with the metal ion. Metal based drugs with promising pharmacological application offer unique therapeutic opportunities.

Quinolones are such type of bio ligands which are known as synthetic broad spectrum antimicrobial agent. This type of antimicrobial agent contains the basic structure of 4-oxo-3-carboxylic-1, 4-dihydroquinoline skeleton. Quinolones resist normal microbial DNA synthesis and leads to bacterial cell death^[1,2]. Due to this, they are employed as drug in various infectious diseases^[3,4]. Nalidixic acid (nal) (Figure 1) is the first synthesised quinolone^[5] and was used against gram negative bacteria. Later, various

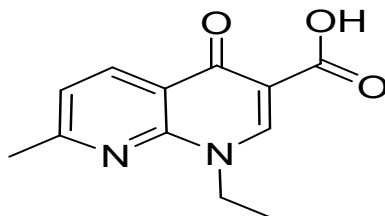


Fig 1. Nalidixic acid



structural modification have been achieved on the basis of structure-activity relationship [6,7]. In order to further improve the bioactivity, the metal complexes of nal were prepared and studied. Due to the ring carbonyl group at position 4 and one of the oxygen atoms of carboxylato group at position 3, the quinolones act as bidentate ligands. It is evident that all the quinolones can bind with metal ions. Only the extent of interaction differs from one quinolone to another [8].

The inspiration acquired by the aforementioned discussion, the present paper is initiated with the preparation, characterization, and biochemical screening of some of the nal complexes of Ni(II) and Co(II) using 1,10-phenanthroline and 2,2'-bipyridyl.

2. Experimental

2.1 Materials

Nal was purchased from Sigma Aldrich. Sodium hydroxide, 1,10-phenanthroline, 2,2'-bipyridyl and the metal salts NiCl₂·4H₂O and CoCl₂·6H₂O were obtained from Merck. All the chemicals used for this work were of analytical grade.

2.2 Synthesis of the complexes

All the complexes of nal were synthesised in presence of N-N heterocyclic compound as ligand with different metal ions in 1:1:1 ratio with the help of hydrothermal vessel as following:

Sodium nalidixate was synthesised prior to the experiment to increase solubility of nal. The complex was synthesised by mixing 5 mL 0.5 mmol of heterocyclic compound and 0.5 mmol of metal salt in 5 ml of double distilled water. The mixture was stirred on a magnetic stirrer for 10 minutes at room temperature. Then the resulting mixture was added to 5 mL aqueous solution containing 0.5 mmol of nalidixic acid and 0.5 mmol of NaOH after adjusting its pH 7.0. Then the overall mixture was heated in a hydrothermal vessel at 100°C for 24 hrs followed by the slow cooling of the vessel for 5 days. Both the heating and cooling was carried out in an oven of programmed temperature.

Table 1. Molecular weight, yield, colour, elemental analysis of the nal complexes.

Complexes	mol.weight	yield(%)	colour	(calcd) found		
				% C	%H	%N
nal	232		White			
1. [Ni(nal)(phen)(Cl)]Cl. CH ₃ CH ₂ OH	584.25	73	dark yellow	53.31 (53.45)	4.23 (4.31)	9.62 (9.59)
2. [Co(nal)(phen)(Cl)]. 3H ₂ O	555.86	78	straw yellow	51.78 (51.86)	4.59 (4.53)	9.95 (10.08)
3. [Ni(nal)(bipy)(H ₂ O)]Cl ₂ . H ₂ O	550.19	70	yellow	48.15 (48.03)	4.19 (4.21)	10.27 (10.18)
4. [Co(nal)(bipy)(Cl)] .5H ₂ O	567.88	68	straw yellow	46.61 (46.53)	5.23 (5.15)	9.80 (9.87)

2.3 Physical measurements

Infra-red (FT-IR) spectra were recorded on a spectrometer Perkin Elmer Spectrum BX II in the range of 400-4000 cm⁻¹ by preparing sample pellets with KBr. UV-visible spectra were recorded in DMSO at concentration 10 ppm on a instrument Analytik jena SPECORD 250. C, H and N elemental analysis were performed on a instrument named elementer varioELIII. TGA-DTA measurements were carried out in an N₂ atmosphere from ambient temperature to 900°C using Perkin Elmer Diamond. X-ray diffraction patterns were recorded with a diffractometer, Bruker D8 using Cu K α radiation.

3. Result and discussions

3.1 Infra-red spectroscopy

FT-IR band assignments of the synthesised complexes were compared with those of the free ligand nal for the determination of coordination mode of quinolone. The most characteristic band assignments are given

in Table 2. FT-IR spectra of nal showed carboxylic stretch $\nu(\text{C}=\text{O})_{\text{carb}}$ at 1718 cm^{-1} and pyridine stretch $\nu(\text{C}=\text{O})_{\text{p}}$ at 1617 cm^{-1} . In the FT-IR spectra of the complexes **1-4** $\nu(\text{C}=\text{O})_{\text{carb}}$ has been replaced by two strong characteristic bands in the range of $1558\text{-}1577$ and $1354\text{-}1370\text{ cm}^{-1}$ assigned as $\nu(\text{O}-\text{C}-\text{O})$ asymmetric and symmetric stretching vibrations respectively where $\nu(\text{C}=\text{O})_{\text{p}}$ was shifted from 1617 to 1623 cm^{-1} due to the bonding with metal ions. The difference $\Delta\nu = \nu(\text{O}-\text{C}-\text{O})_{\text{a}} - \nu(\text{O}-\text{C}-\text{O})_{\text{s}}$ is the important criteria for the determination of coordination mode of the ligand^[15]. These criteria are (i) $\Delta\nu \sim 200\text{ cm}^{-1}$ for unidentate mode of carboxylate complexes, (ii) $\Delta\nu < 100\text{ cm}^{-1}$ for bidentate carboxylate complexes (iii) $\Delta\nu \sim 150\text{ cm}^{-1}$ for bridging complexes. In the present case, $\Delta\nu$ values for the synthesised complexes fall in the range of $198\text{-}223\text{ cm}^{-1}$ indicating the monodentate coordination mode of the carboxylic group of the nal. The overall changes in the FT-IR spectra indicate that the nal is coordinated to the metal ion through the pyridine and one carboxylate oxygen atoms^[14].

Table 2. Characteristic FT-IR assignments (cm^{-1}) of the complexes.

Complexes	$\nu(\text{C}=\text{O})_{\text{p}}$	$\nu(\text{O}-\text{C}-\text{O})_{\text{a}}$	$\nu(\text{O}-\text{C}-\text{O})_{\text{s}}$	$\Delta\nu$
Nalidixic acid	1617	1718		
4. $[\text{Fe}(\text{Nal})(\text{phen})(\text{Cl})]\text{Cl} \cdot \text{CH}_3\text{CH}_2\text{OH}$	1623	1558	1355	203
2. $[\text{Mn}(\text{Nal})(\text{Phen})(\text{Cl})] \cdot 3\text{H}_2\text{O}$	1618	1577	1354	223
3. $[\text{Fe}(\text{III})(\text{Nal})(\text{bipy})(\text{H}_2\text{O})]\text{Cl}_2 \cdot \text{H}_2\text{O}$	1623	1577	1358	219
4. $[\text{Mn}(\text{Nal})(\text{bipy})(\text{Cl})] \cdot 5\text{H}_2\text{O}$	1618	1577	1370	207

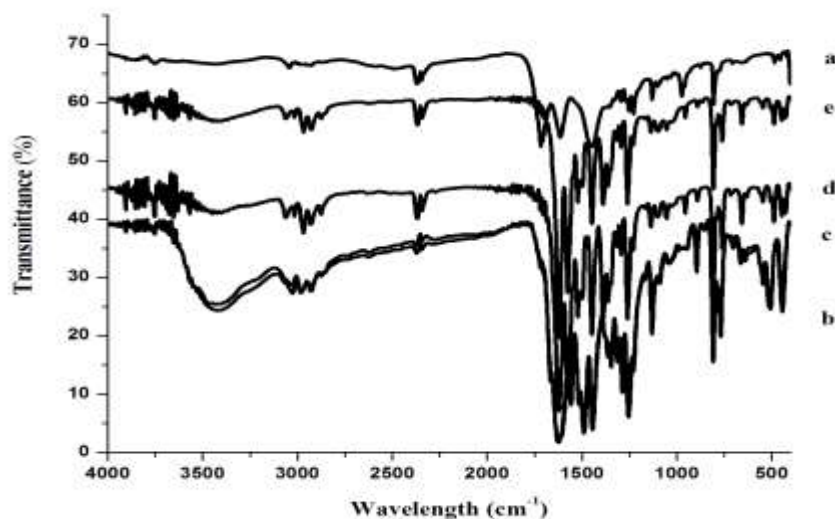


Fig. 2 FT-IR spectra of a) nal b) $[\text{Fe}(\text{nal})(\text{phen})(\text{Cl})]\text{Cl}\cdot\text{CH}_3\text{CH}_2\text{OH}$, c) $[\text{Mn}(\text{nal})(\text{Phen})(\text{Cl})]\cdot 3\text{H}_2\text{O}$ d) $[\text{Fe}(\text{nal})(\text{bipy})(\text{H}_2\text{O})]\text{Cl}_2\cdot\text{H}_2\text{O}$, e) $[\text{Mn}(\text{nal})(\text{bipy})(\text{Cl})]\cdot 5\text{H}_2\text{O}$

3.2 UV-visible spectroscopy

Formation of metal complex is also supported by UV-visible spectrum which is shown in Figure 3. UV-visible spectra of the complexes were recorded in the range of 255-900 nm. Free nal shows two characteristic band at 282 nm attributed to $\pi\text{-}\pi^*$ transition due to heterocyclic and phenyl moiety and another band at 340 attributed to the $\text{n-}\pi^*$ transition. In the UV-Visible spectra of the synthesised complexes this two bands are similar to the ligand^[14] but hypochromically or hyperchromically affected indicating nal coordinate to metal ions through the pyridine and one carboxylate oxygen atoms which is in agreement with the result of the FT-IR spectra. UV-visible spectra of all synthesised complexes are identical with that of the nal and differences due to the presence of nitrogen containing ligand (phen, bipy) are not easily determined.

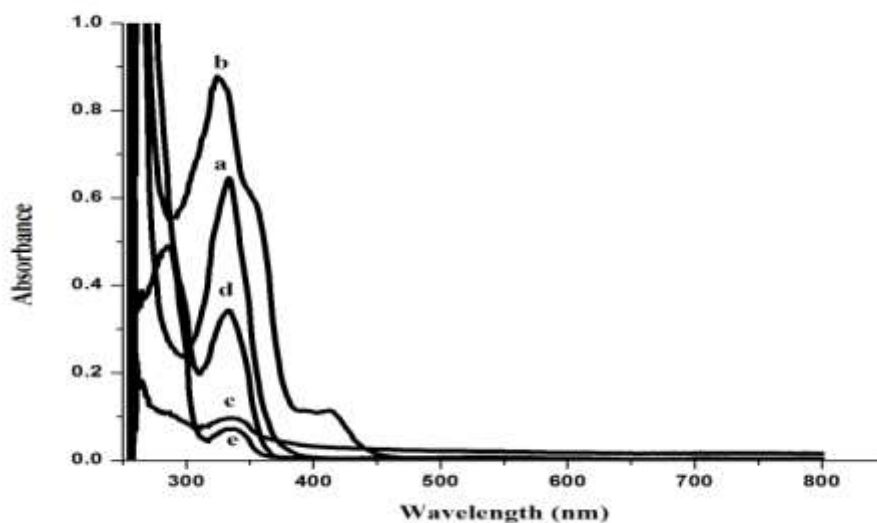


Fig. 3 UV-visible spectra of a) nal b) $[\text{Fe}(\text{nal})(\text{phen})(\text{Cl})]\text{Cl} \cdot \text{CH}_3\text{CH}_2\text{OH}$,
c) $[\text{Mn}(\text{nal})(\text{Phen})(\text{Cl})] \cdot 3\text{H}_2\text{O}$ d) $[\text{Fe}(\text{nal})(\text{bipy})(\text{H}_2\text{O})]\text{Cl}_2 \cdot \text{H}_2\text{O}$, e)
 $[\text{Mn}(\text{nal})(\text{bipy})(\text{Cl})] \cdot 5\text{H}_2\text{O}$

3.3 Thermal analysis

Thermal studies of the metal complexes of nal were also investigated. The heating rate was controlled at $10^\circ\text{C min}^{-1}$. Weight loss was studied from ambient temperature to 900°C under a oxygen atmosphere. The temperature ranges and percentage weight loss of every decomposition are listed in Table 3. All the complexes show (Figure 4) three to five stages of weight loss. First weight loss is due to the formation of corresponding anhydrous compound. Second, third fourth and five stages are due to the decomposition of counter ion and different part of the coordinated ligands.

Table 3. Thermal data of nalidixic acid and the complexes

Entry	Steps	Temp. range (°C)	Weight loss (%) Found Calc	M.P (°C)	Eliminated moiety
a	1 st	203 - 354	92.44 97.34	232	CH ₂ CH ₃ +N ₂ +8CH ₂ +CO ₂
b	1 st 2 nd 3 rd 4 th 5 th	6 - 138 138 - 325 325 - 431 431- 724 724 - 915	9.8 8.8 15.36 13.98 32.4 28.14 21.34 19.22 3.4 5.91	343	CH ₃ 2C ₂ H ₂ Cl ₂ +2H ₂ +N ₂ +O ₂ CO+CO ₂ +N ₂ .5O ₂
c	1 st 2 nd	17 - 349 349 - 489	80.52 77.12 12.5 13.45	385	6C ₂ H ₂ +3H ₂ O+Cl ₂ +CO+NO+O ₂ N ₂
d	1 st 2 nd 3 rd	7- 107 107- 408 408 - 963	8.0 6.8 65.54 62.33 4.40 6.29	342	CH ₃ +H ₂ O 6C ₂ H ₂ +bipy+Cl ₂ +CO ₂ +.5N ₂ .5O ₂
e	1 st 2 nd 3 rd	15 - 274 274 - 471 471 - 962	26.32 26.53 39.47 41.94 13.42 15.32	365	5H ₂ O C ₂ H ₅ +.5Cl ₂ +Bipy+7C ₂ H ₅ +N ₂ +O ₂ CO+N ₂

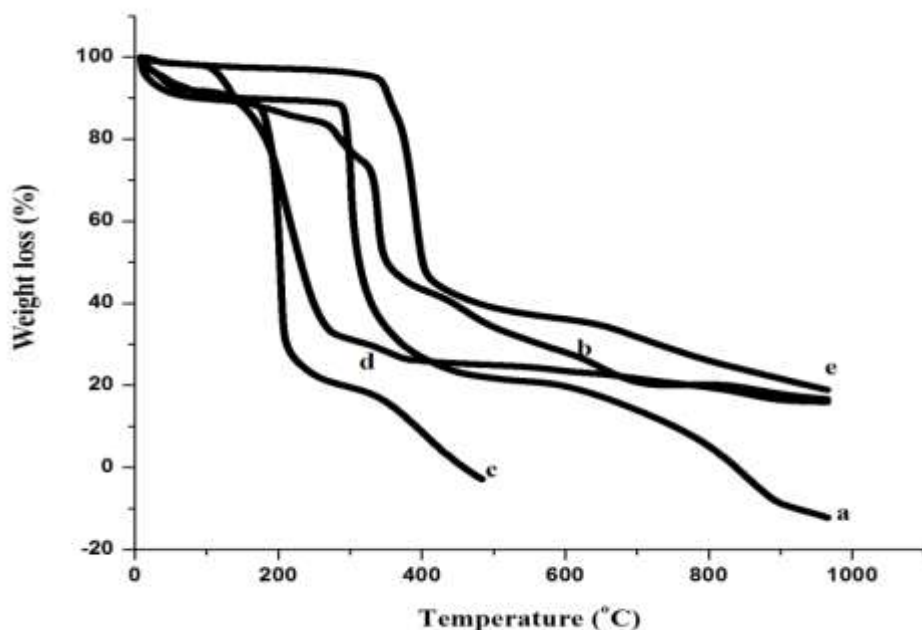


Figure 4. TGA of a)nal b) $[\text{Fe}(\text{nal})(\text{phen})(\text{Cl})]\text{Cl}\cdot\text{CH}_3\text{CH}_2\text{OH}$, c) $[\text{Mn}(\text{nal})(\text{Phen})(\text{Cl})]\cdot 3\text{H}_2\text{O}$ d) $[\text{Fe}(\text{nal})(\text{bipy})(\text{H}_2\text{O})]\text{Cl}_2\cdot\text{H}_2\text{O}$, e) $[\text{Mn}(\text{nal})(\text{bipy})(\text{Cl})]\cdot 5\text{H}_2\text{O}$

3.4 Powder X-ray diffraction

XRD patterns of all the synthesised complexes are recorded in the range of $2\theta=2-90$. It has been found that all the complexes are amorphous in nature because there is no clear well separated sharp peaks. We are trying for the preparation of single crystal.

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References

- Kampranis, S.C; and Maxwell, A.; (1998). Conformational changes in DNA gyrase revealed by limited proteolysis. *J Biol Chem.*, 273, 22606–22614.
- Marlans, K.J; and Hiasa, H. (1997). Mechanism of quinolone action-a drug-induced structural perturbation of the DNA precedes strand cleavage by topoisomerase IV. *J Biol Chem.*, 272, 9401–9409.
- Chu, D. T. W.; and Fernandes, P. B. (1991) Recent developments of the field of quinolone antibacterial agents. *J. Adv. Drug Res. Test.*, 21, 42–144.
- Neu, H. C. *Am. J. Med.* 1987, 82, 395-404.
- Leshner, Y. E.; Froelich, J. M.; Gruett, D. J.; Bailey, H.; and Brundage, P. R. (1962). 1,8- Naphthyridine Derivatives. A New Class of Chemotherapeutic Agents *J. Med.Chem.*, 5, 1063-1065.
- Chu, D.T.W.; (1991). Fernandes, P.B. Recent developments in the field of quinolone antibacterial agents; *Advances in Drug Research*: London,.
- Reynolds, J.E.F. *Martindale, Synthesis, crystal structure, and characterization of metal-quinolone compounds*: London, 1993.
- R.E. Polk, (1989) Drug-drug interactions with ciprofloxacin and other fluoroquinolones. *Am. J. Med.*, 87, 576-581.
- Anacona, J.R.; Mundaray, M.; and Bastardo, E.; (2001). Synthesis and antibacterial studies of some metal complexes containing clavulanic or nalidixic acid.2001, *J. Coord. Chem.*, 53, 281-288.
- Sekhon, B.S.; and Gandhi,L; (2001) synthesis and characterization of metal complexes of some antibacterial drugs. *int. j. chemtech res.* , 2, 286-288.



- Bivian-Castro, E.Y.; Lopez, G. M.; Pedraza-Reyes, M.; Bernes, S.; and Mendoza-Diaz, (2009). G. Synthesis, Characterization and Biological Activity Studies of Copper(II) Mixed Ligand Compound with Histamine and nalidixic acid. *Bioinorg. Chem. Appl.*, 1-8.
- Guillermo, M-D.; Luz, M.R.; M-A.; and Raul, P-A. (1987). Synthesis and Characterization of Mixed Ligand Complexes of Copper with Nalidixic Acid and (N-N) Donors. Crystal Structure of [Cu(Phen)(Nal)(H₂O)]NO₃.3H₂O. *Inorg. Chim. Acta.*, 13, 41-47.
- Lee, S. S.; Jung, O-S.; Lee, C. O.; Choi, S. U.; Jun, M-J; and Sohn, Y. S; (1995). Cationic diamineplatinum (II) complexes of nalidixic acid. *Inorg. Chim. Acta.*, 239, 133-138.
- Mendoza-Díaz; and Ireta-Moreno, (1994) G. J. synthesis and characterization of zinc mixed complexes with nalidixate anion and (N-N) doners, *J. Inorg. Biochem.*, 54, 235-246.
- Deacon, G. B.; and Phillips, (1980). R. J. Relationships between the carbon-oxygen stretching frequencies of carboxylato complexes and the type of carboxylate coordination. *Coord. Chem. Rev.*, 33, 227-250.