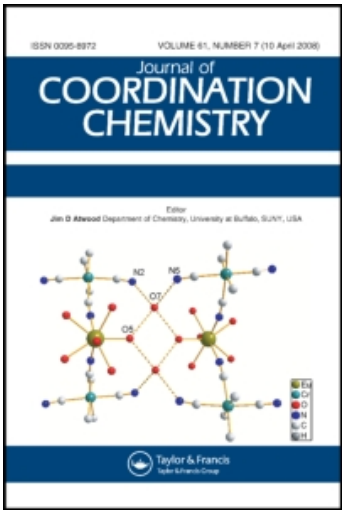

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Iron(II) and Iron(III) Perchlorate Complexes of Ciprofloxacin and Norfloxacin

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Online publication date: 15 September 2010

To cite this Article Al-Mustafa, Jamil and Tashtoush, Bassam(2003) 'Iron(II) and Iron(III) Perchlorate Complexes of Ciprofloxacin and Norfloxacin', Journal of Coordination Chemistry, 56: 2, 113 — 124
To link to this Article: DOI: 10.1080/0095897031000088246
URL: http://dx.doi.org/10.1080/0095897031000088246

J. Coord. Chem., 2003, Vol. 56, No. 2, pp. 113–124

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IRON(II) AND IRON(III) PERCHLORATE COMPLEXES OF CIPROFLOXACIN AND NORFLOXACIN

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(Received 1 May 2002; In final form 24 September 2002)

The reactions of ciprofloxacin (CIP) and norfloxacin (NOR) with iron(II) and iron(III) perchlorate have been investigated. The optical spectra support the formation of four complexes for each oxidation state with 1 : 1, 1 : 2, 1 : 3 and 1 : 4 metal to ligand molar ratios. The electrical conductivity and magnetic susceptibility measurements show that the isolated complexes are high spin and the $Fe(ClO_4)_2$ and $Fe(ClO_4)_3$ complexes behave as 1 : 2 and 1 : 3 electrolytes, respectively. The IR spectra indicate that CIP and NOR bind to the iron ion as bidentate ligands through the carbonyl oxygen atom and one of the oxygen atoms of the carboxylate group.

Keywords: Ciprofloxacin; Norfloxacin; Quinolone antibiotics; Iron(II) perchlorate; Iron perchlorate; Drug–metal ion interactions

INTRODUCTION

Ciprofloxacin (CIP) and norfloxacin (NOR) (Fig. 1) are synthetic fluorinated organic derivatives related to the quinolone nalidixic acid. These compounds are commonly used as broad-spectrum orally administered antibacterial agents to cure a wide range of infections [l,2]. The antibacterial activity of these compounds is attributed to their interference with the bacterial DNA synthesis [2–8].

Understanding of the reactions of CIP, NOR and other quinolone antibiotics with metal ions is extremely important. On one hand, it has been suggested that these reactions are essential for the activity of the quinolone antibiotics and magnesium, copper or iron ions may bridge the binding of the quinolone to the DNA gyrase [3–6] or to the bacterial DNA directly [7,8]. On the other hand, the reactions of the quinolone antibiotics with metal ions present in food and other medications, such as Mg^{2+}, Ca^{2+}, Al^{3+} and Fe^{2+} have a detrimental effect on the absorption of the antibiotics when ingested concurrently [9–15]. In all of these reports, reduction in the absorption of the quinolones was attributed to formation of nonabsorbable metal ion–quinolone complexes [9–15].

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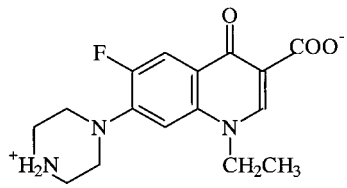
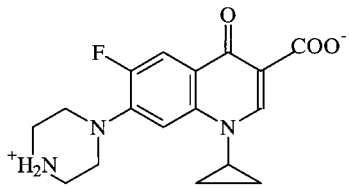
ISSN 0095-8972 print: ISSN 1029-0389 online © 2003 Taylor & Francis Ltd
DOI: 10.1080/0095897031000088246



Norfloxacin



Ciprofloxacin

FIGURE 1 The zwitterionic structure of ciprofloxacin and norfloxacin.

Early studies by Nakano demonstrated the ability of the quinolone nalidixic acid to complex a number of metal ions [16]. The crystal structures and spectroscopic studies of the quinolone complexes [17–32] indicate that quinolone antibiotics can participate in the formation of complexes in a number of ways. Complexes isolated from acidic media usually contain singly or doubly protonated quinolone cations that are incapable of bonding to the metal ion and in these cases only electrostatic interaction was observed between the drug and the metal ions [17–20,32]. In other cases [21–26,30,32] it was found that neutral quinolones in the zwitterionic state are capable of forming simple complexes. In these complexes, the quinolone acts as a bidentate ligand through the carbonyl group at position 4 and through one of the oxygen atoms of the carboxylato group at position 3. Quinolones can also act as a bridging ligand and thus capable of forming polynuclear complexes [30,32].

Several attempts have been made to prepare and characterize quinolone–iron ions complexes. Barba-Behrens [33] and coworkers isolated a complex of the quinolone nalidixic acid with iron(III). In this complex, it was suggested that nalidixic acid acts as a chelating ligand through the two oxygen atoms of the carboxylate group [33]. Gao *et al.* reported [34] the preparation of an iron(III)-NOR complex with the formula $[Fe(NOR)_2(H_2O)_2]Cl_3 \cdot 6H_2O$ that was found to have stronger antibacterial activity than NOR. The authors suggested that the NOR acts as a bidentate ligand through the two oxygen atoms of the carboxylate group. Wallis [26] and coworkers reported the crystal structure of the $[Fe(CIP)(NTA)]_3 \cdot 5H_2O$ (NTA = Nitrilotriacetato) which showed that the binding of CIP to the iron occur through the 4-keto and the 3-carboxylic groups. In another attempt Turel *et al.* reported [17] the synthesis of another iron-enrofloxacin (ENR) adduct with the formula $[FeCl_4](H_2ENR)Cl$. The crystal structure of this adduct showed the enrofloxacin to be doubly protonated and incapable of binding to the iron ion. Several reports described the utilization of the complexes formed from the interaction of CIP and NOR with iron ions in the ferric and the ferrous states as colorimetric agents for the determination of the concentration of the antibiotic or the iron ion [35,36]. In these studies no complexes were isolated.

In this work, we report the results of an investigation of the complexes formed from the interaction of CIP and NOR with iron(II) and iron(III) perchlorate in methanol. We report the isolation and the characterization, by electrochemical and spectroscopic techniques, of a series of novel biologically-relevant complexes that contain the drug and iron ions in different molar ratios.

EXPERIMENTAL

Measurements

The optical spectra of the complexes were measured using a Shimadzu 2401 UV-Vis spectrophotometer. The FTIR spectra were recorded on a Nicolet Avatar spectrophotometer as powders using an ATR sample holder. The differential scanning calorimetry (DSC) and the thermogravimeteric analysis (TGA) were measured using a Shimadzu DSC-50 instrument. The magnetic moments were measured using a Sherwood magnetic susceptibility balance. The C, H and N were analyzed at the Laboratoire d'Analyse Elementaire, Montreal, Quebec, Canada. The percentage of C, H and N used for the determination of the formulas of the complexes were the average of two measurements.

Materials and Methods

The iron(II) perchlorate hydrate and the iron(III) perchlorate hydrate were purchased from Aldrich. Due to the hygroscopic nature of these salts, the percentage of iron in the salt was assayed photometrically using the thioscyanate method [37] on the day of the experiment. HPLC grade methanol was used as a solvent. The number and composition of the complexes formed from the interaction of CIP and NOR with the iron perchlorates in methanol were determined from the variation of absorbance with ligand-to-metal ratio. This was done by preparing a series of solutions containing a fixed concentration of the iron ion (1×10^{-4} M) and a variable concentration of CIP or NOR and recording their spectra.

All of the complexes reported herein were prepared using the same procedure. In a typical experiment, to 0.6 mmol (= 0.2 g) of CIP or NOR suspended in 30 mL of methanol, the required quantity of iron(II) or iron(III) perchlorate dissolved in a minimum amount of methanol was added in dropwise manner. The solution was stirred for 24 h at room temperature. After that, the volume of the reaction mixture was reduced and the precipitated complex was filtered off and dried over $CaCl_2$ at room temperature under reduced pressure. Complexes with composition 1 : 1, 1 : 2, 1 : 3 and 1 : 4 metal to ligand molar ratio were obtained by varying the moles of iron ion mixed relative to the moles of ligand. The isolation of one complex and the purity of the isolated complex were confirmed by thin layer chromatography.

RESULTS AND DISCUSSION

Determination of the Number of Complexes Formed

Examination of the optical spectra of a series of solutions that contain a fixed concentration (1×10^{-4} M) of iron ion and a variable concentrations of CIP or NOR showed pronounced spectral changes between 400 and 500 nm. Fig. 2 shows the spectral

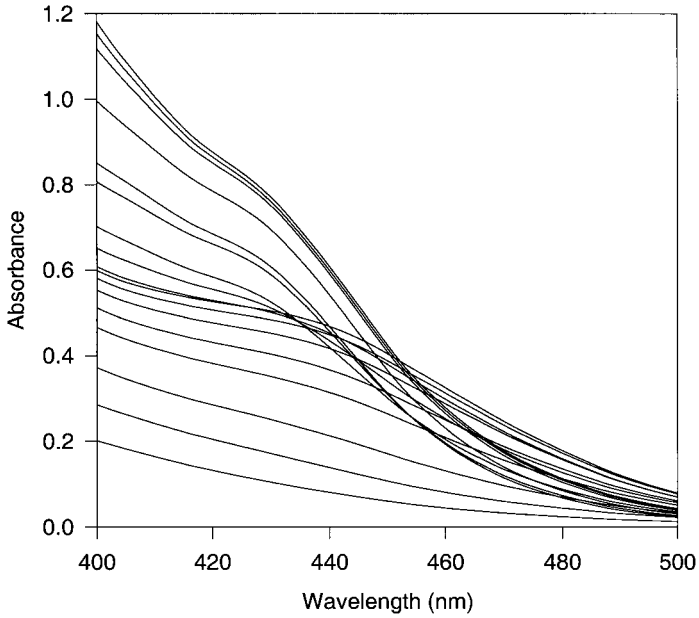


FIGURE 2 The optical spectra of a series of solutions containing a fixed concentration (1×10^{-4} M) of $Fe(C1O_4)_3$ and a variable concentration of NOR. The molar ratio of NOR to Fe^{3+}, in these solutions vary from 0 to 8 folds.

changes caused by the reaction of $Fe(ClO_4)_3$ with NOR. The molar ratio of NOR to Fe^{3+}, in these solutions was varied from zero to eight. Due to the weak absorption of the free NOR in this region, these spectral changes must be attributed to the coordination of NOR to the Fe^{3+} ion [35,36]. Figure 3 shows the changes in absorbance at the wavelengths 435 and 450 nm for the reactions of NOR with $Fe(ClO_4)_3$ as a function of NOR to Fe^{3+} molar ratio. Figure 3 demonstrates that the observed spectral changes are complex and can be interpreted only by assuming the formation of several complexes. At 450 nm, it can be seen that increasing the NOR to Fe^{3+} mole ratio gradually increases the absorbance until the molar ratio of 1 : 1 is reached indicating the formation of a complex with a 1 : 1 iron to NOR mole ratio. After that a dramatic increase in absorbance that peaks at around the mole ratio of 1 : 2 iron to NOR is reached. This behavior is indicative of the formation of a second complex of 1 : 2 iron to NOR molar ratio. The decrease in absorbance at 450 nm and the minimum formed near the mole ratio of 1 : 3 can be attributed to the formation of another complex with 1 : 3 iron to NOR mole ratio. Finally, the increase in absorbance between the mole ratios of 1 : 3 and 1 : 4 and the plateau formed after that demonstrate the formation of a fourth complex with 1 : 4 iron to NOR mole ratio. The absence of spectral changes above the mole ratio of 1 : 4 rules out the formation of complexes with higher composition. The observation of three isosbestic points at 434, 441 and 454 nm in the spectra of the solutions (Fig. 2) also supports the formation of four complexes. Similar conclusions can be reached by examining the spectral changes observed at 435 nm. The observation of the titration end points at 1 : 1, 1 : 2, 1 : 3 and 1 : 4 metal to ligand molar ratios supports the formation of monomeric complexes. The preceding observations clearly demonstrate that the interaction of NOR with $Fe(ClO_4)_3$ leads

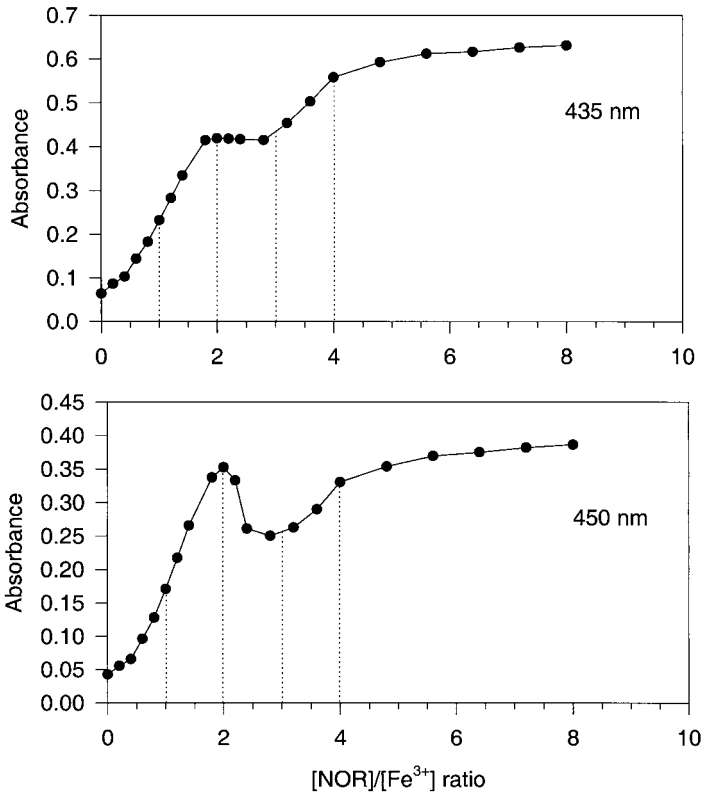


FIGURE 3 The changes in absorbance observed at 435 nm (upper) and 450 nm (lower) for the reaction of NOR with Fe^{3+} as function of [NOR]/[Fe^{3+}] ratio. The experimental conditions are as in Fig. 2.

to the formation of four complexes with 1 : 1, 1 : 2, 1 : 3 and 1 : 4 metal to ligand molar ratios. Similar plots were obtained for the reactions of NOR with ferrous perchlorate and for the reaction of CEP with $Fe(ClO_4)_3$ and $Fe(ClO_4)_2$.

Characterization of the Isolated Complexes

The colors of the solid complexes isolated from the reactions of CIP and NOR with $Fe(ClO_4)_3$ and $Fe(ClO_4)_2$ vary from dark amber or brown (1 : 1 complexes) to orange (1 : 2 complexes) to yellow (1 : 3 complexes) and finally to pale yellow for the 1 : 4 iron to quinolone complexes. This indicates that the composition of the product formed is dependent on the metal to ligand ratio used. The C, H and N elemental analysis data shown in Table I is in good agreement with the proposed formulas. The complexes are soluble in DMSO and DMF, slightly soluble in methanol, ethanol and water and practically insoluble in dichloromethane and chloroform. The electrical conductivities are in the range of 1 : 2 and 1 : 3 electrolytes for complexes of iron(II) and iron(III) perchlorate, respectively. The magnetic moments of the complexes indicate that all of the complexes are high spin with 4 ($\mu_{eff} = 5$–5.6 BM) and 5 ($\mu_{eff} = 5.7$–6 BM) unpaired electrons for the iron(II) and iron(III) complexes, respectively. The IR spectra of all of the complexes show a strong band near 630 cm^{-1} that can

TABLE 1 Elemental analysis of the isolated complexes and the predicted formulas

Compound	*Carbon (%)*		*Hydrogen (%)*		*Nitrogen (%)*	
	Calc.	*Found*	*Calc.*	*Found*	*Calc.*	*Found*
$[Fe(CIP)(H_2O)4](ClO_4)_2 \cdot H_2O$	30.20	29.84	4.17	4.06	6.22	6.08
$[Fe(CIP)_2(H_2O)_2](ClO_4)_2 \cdot 3H_2O$	40.54	40.76	4.60	4.470	8.34	8.28
$[Fe(CIP)_3(H_2O)](ClO_4)_2 \cdot 5H_2O$	45.15	45.03	4.90	4.71	9.29	9.19
$[Fe(CIP)_4](ClO_4)_2 \cdot 7H_2O$	47.87	48.12	5.08	4.87	9.85	9.79
$[Fe(CIP)(H_2O)_4](ClO_4)_3 \cdot 6H_2O$	23.69	23.70	4.40	4.35	4.88	4.79
$[Fe(CIP)_2(H2O)_2](ClO_4)_3 \cdot 7H_2O$	34.64	34.8	4.62	4.45	7.13	7.12
$[Fe(CIP)_3(H_2O)](ClO_4)_3 \cdot 6H_2O$	41.55	41.65	4.65	4.37	8.55	8.53
$[Fe(CIP)_4](ClO_4)_3 \cdot 7H_2O$	45.23	45.26	4.80	4.52	9.31	9.26
$[Fe(NOR)(H_2O)_4](ClO_4)_2 \cdot 5H_2O$	26.04	26.04	4.94	4.76	5.69	5.63
$[Fe(NOR)_2(H_2O)_2](ClO_4)_2 \cdot 6H2O$	37.05	36.76	5.05	5.12	8.10	8.00
$[Fe(NOR)_3(H_2O)](ClO_4)_2 \cdot 8H_2O$	41.94	42.21	5.28	5.11	9.17	9.08
$[Fe(NOR)_4](ClO_4)_2 \cdot 10H_2O$	44.90	44.78	5.42	5.26	9.82	9.71
$[Fe(NOR)(H_2O)_4](ClO_4)_3 \cdot 6H_2O$	22.61	22.60	4.46	4.38	4.93	4.81
$[Fe(NOR)_2(H_2O)_2](ClO_4)_3 \cdot 5H_2O$	34.35	34.26	4.50	4.35	7.51	7.43
$[Fe(NOR)_3(H_2O)](ClO_4)_3 \cdot 6H_2O$	40.09	39.92	4.77	4.46	8.77	8.68
$[Fe(NOR)_4](ClO_4)_3 \cdot 10H_2O$	42.43	42.24	5.12	4.81	9.28	9.18

be assigned to an iron–ligand bond. The IR spectra (Figs. 4, 5) of all of the isolated complexes show three strong bands near 1100 cm^{-1}. These bands are absent in the spectrum of the free NOR and CIP and occur in the region were the ν_3 band of the ClO_4^- ion is expected [38]. The IR spectra of the complexes of NOR and CIP with iron(II) and iron(III) perchlorate show broad bands near 3400, 2840, 2484 and 2030 cm^{-1}. These bands can be assigned to the N–H vibrations of the quaternized nitrogen of the piperazinyl group [40] which indicate that the zwitterionic ionic form of NOR and CIP is involved in coordination to the metal ions investigated. The appearance of these bands and the known weak coordinating properties of the perchlorate anion confirm that the counter anion in these complexes is the perchlorate ion. The conductivity data and the preparation of the complexes from neutral methanol solutions rules out the possibility of formation of hydroxo-, mixed hydroxo-drug-complexes or complexes that contain doubly-protonated quinolones as counter cation.

Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) have been used to investigate the thermal properties of the isolated complex. The results indicate that most of the complexes isolated lose more than 80% of their weight in a single explosive decomposition step at about 190–200°C. The only exception is $Fe(CIP)(ClO_4)_3(H_2O)6$ which decomposes at 140°C. The complexes $Fe(CIP)_2(ClO_4)_2(H_2O)_5$ and $Fe(NOR)_4(ClO_4)_2(H_2O)_{10}$ show two step decomposition at about 200 and 300°C. These decomposition patterns are characteristic of quinolone complexes [41]. The TGA data reveal that all of the complexes contain mainly lattice water and the number of coordinated water molecules is as shown in Table I.

Interaction of CIP and NOR with iron perchlorate

Figures 4 and 5 show the FTIR spectra of norfloxacin, ciprofloxacin and the complexes isolated from their reactions with $Fe(ClO_4)_3$. The assignments of selected IR bands are given in Table II. For the free NOR (Fig. 4), the νCOOH and the νCO absorptions can be seen at 1730 and 1617 cm^{-1}, respectively. These bands have been observed

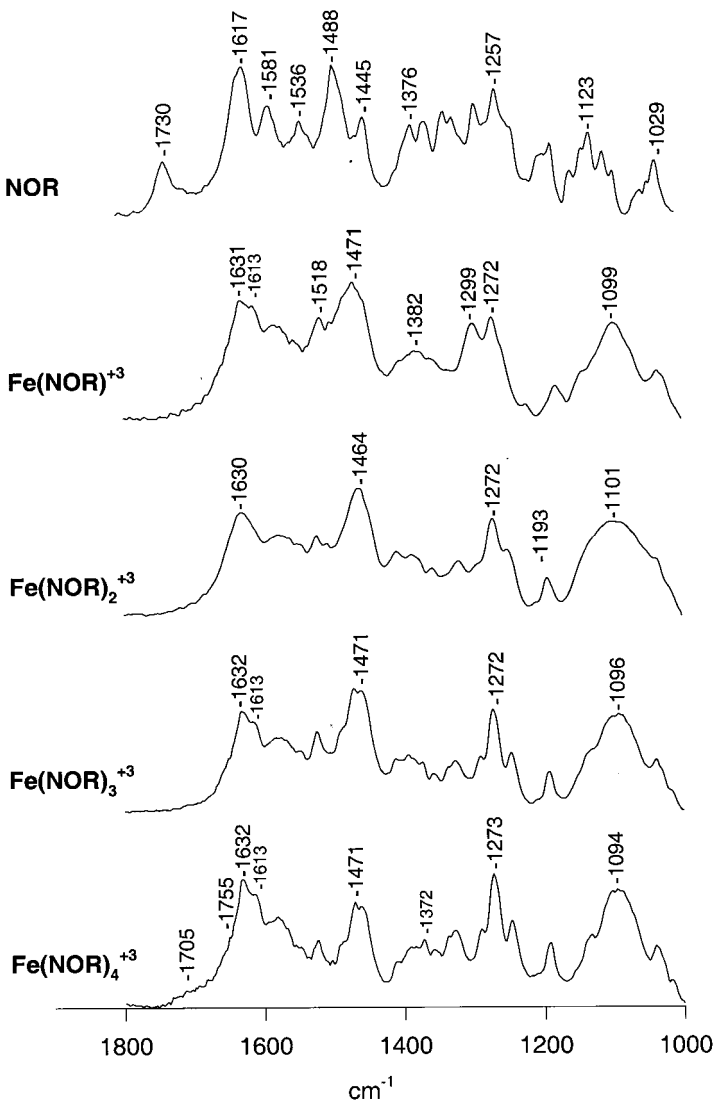


FIGURE 4 The absorption FTIR spectra of norfloxacin and the complexes isolated from its reaction with iron(III) perchlorate.

and assigned previously [18,32]. Upon complexation, The νCO exhibits 3–5 cm^{-1} shift to lower energy for the various complexes. This shift can be considered indicative of the CO involvement in coordination. In the FTIR spectra of the isolated complexes, the νCOOH of the free NOR vanishes completely and appears to be replaced by two strong peaks near 1630 and 1470 cm^{-1}, assigned to the asymmetric and the symmetric stretch of the coordinated COO^- group [32]. The carboxylato group can act as a unidentate, bidentate or bridging ligand. Distinction between these binding states can be made from the frequency separation ($\Delta\nu = \nu_a COO - \nu_a COOO$) between the symmetric and the asymmetric stretching of this group. Deacon and Phillips observed the following correlation in the carboxylato complexes. (i) unidentate carboxylato

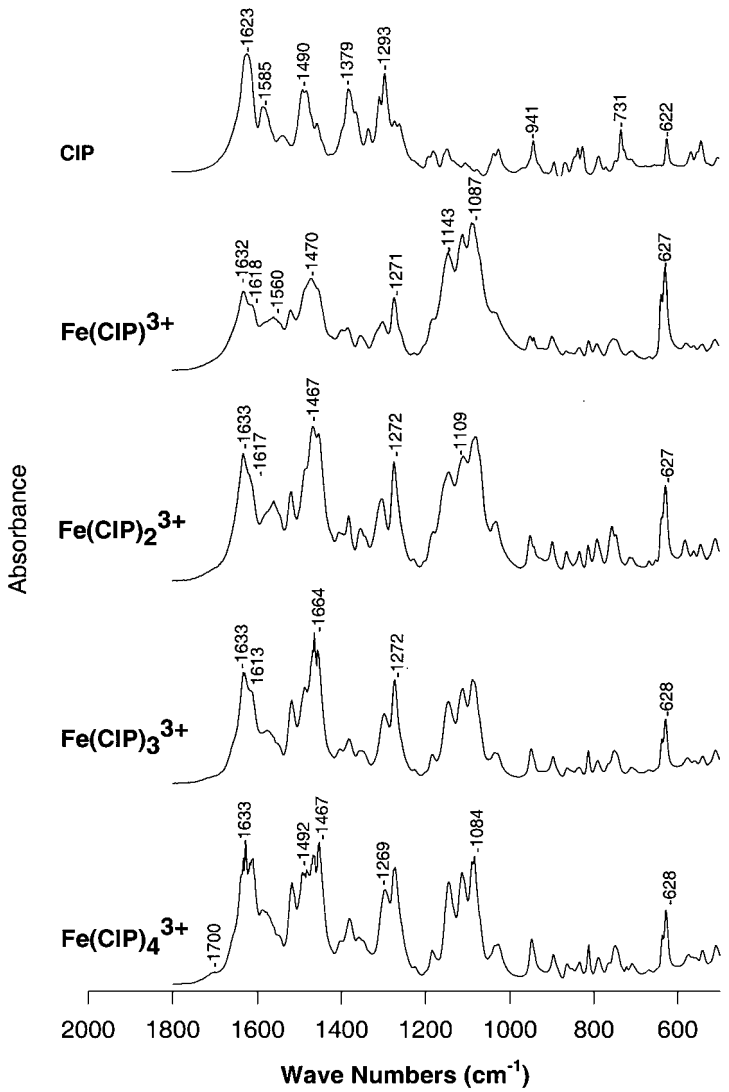


FIGURE 5 The absorption FTIR spectra of ciprofloxacin and the complexes isolated from its reaction with iron(III) perchlorate.

complexes exhibit $\Delta\nu$ values which are much larger than those of the ionic salts ($\Delta\nu > 200\,cm^{-1}$). (ii) bidentate or chelating carboxylato complexes exhibit $\Delta\nu$ significantly smaller than ionic values ($\Delta\nu < 100\,cm^{-1}$). Finally, (iii) bridging complexes show $\Delta\nu$ comparable to the ionic values ($\Delta\nu = 150\,cm^{-1}$). Table II shows that the observed $\Delta\nu$ for the various complexes are in the range 149–171 cm^{-1}. These values are comparable to the $\Delta\nu$ observed for the ionic acetate salts [42, 43] ($\Delta\nu = 164\,cm^{-1}$) and may be interpreted as bridging carboxylato ligations. However, this is inconsistent with the observed shift of the carbonyl group, which indicates its involvement in the coordination. It is also inconsistent with the known coordinating properties of NOR and other quinolone complexes established by X-ray crystallography which

TABLE 2 Selected IR frequencies and the values of $\Delta\nu$ for the ligands and the isolated complexes

Compound	νCO	$\nu_{as}COO^-$	$\nu_s COO^-$	$\Delta\nu$
Ciprofloxacin	1623	1585	1379	206
$[Fe(CIP)(H_2O)_4](ClO_4)_2 \cdot H_2O$	1612	1632	1482	150
$[Fe(CIP)_2(H_2O)_2](ClO_4)_2 \cdot 3H_2O$	1612	1629	1480	149
$[Fe(CIP)_3(H_2O)](ClO_4)_2 \cdot 5H_2O$	1612	1632	1472	160
$[Fe(CIP)_4](ClO_4)_2 \cdot 7H_2O$	1612	1632	1469	163
$[Fe(CIP)(H2O)_4](ClO_4)_3 \cdot 6H2O$	1618	1632	1470	162
$[Fe(CIP)_2(H_2O)_2](ClO_4)_3 \cdot 7H_2O$	1617	1633	1467	166
$[Fe(CIP)3(H_2O)](ClO_4)_3 \cdot 6H_2O$	1617	1633	1464	169
$[Fe(CIP)_4](ClO4)_3 \cdot 7H_2O$	1613	1633	1467	166
Norfloxacin	1617	$\nu COOH = 1730$		
$[Fe(NOR)(H_2O)_4](ClO_4)_2 \cdot 5H_2O$	1612	1633	1472	161
$[Fe(NOR)_2(H_2O)_2](ClO_4)_2 \cdot 6H_2O$	1612	1630	1471	159
$[Fe(NOR)_3(H_2O)](ClO_4)_2 \cdot 8H_2O$	1612	1630	1471	159
$[Fe(NOR)_4](ClO_4)_2 \cdot 10H_2O$	1612	1630	1471	159
$[Fe(NOR)(H_2O)_4](C1O_4)_3 \cdot 6H_2O$	1613	1631	1471	160
$[Fe(NOR)_2(H_2O)_2](C1O_4)_3 \cdot 5H_2O$	1613	1630	1464	166
$[Fe(NOR)_3(H_2O)](ClO_4)_3 \cdot 6H_2O$	1613	1632	1461	171
$[Fe(NOR)_4](C1O_4)_3 \cdot 10H_2O$	1613	1632	1461	171

indicates that these ligands act as a bidentate ligand through the carbonyl oxygen atom and one of the oxygen atoms of the carboxylate group [21–26,30,32]. We believe that NOR acts as a bidentate ligand through the oxygen atom of the carbonyl and one of the oxygen atoms of the carboxylato group. The observed low $\Delta\nu$ values can be attributed to hydrogen bonding of the noncoordinated oxygen atom of the carboxylate group to another species such as water giving rise to the so-called "pseudo-bridging" arrangement and thus reducing the value of the $\Delta\nu$. This arrangement has been observed in several carboxylato complexes. In addition, most of the crystal structures of quinolone complexes show the noncoordinated oxygen atom of the carboxyl group to be hydrogen bonded to a water molecule and causing a similar reduction in the $\Delta\nu$ value [21–25,30,32]. Gao *et al*. [34] prepared the complex $[Fe(NOR)_2(H_2O)_2]Cl_3 \cdot 7H_2O$ which is similar to one of the complexes isolated in this work and proposed that NOR acts as a bidentate ligand through the two oxygen atoms of the carboxylate group. We believe that the interaction proposed by Gao is unlikely because the observed $\Delta\nu$ value is larger than expected for chelating carboxylato complexes and this mode of binding has never been observed in the large number of crystal structures of quinolone complexes that have been determined.

Figure 5 shows the FTIR spectra of CIP and the complexes isolated from its reaction with iron(III) perchlorate. The behavior of the νCO stretching vibration of the CIP complexes is similar to that observed for the complexes of NOR. It can be seen that νCOOH observed at $1730\,cm^{-1}$ for NOR is missing in the spectrum of the free CIP and replaced by two strong bands at 1585 and $1379\,cm^{-1}$ which are assigned to the asymmetric and the symmetric stretching vibrations of the COO^- group, respectively [44]. This behavior was attributed to the existence of CIP in a zwitterionic structure in which the COO^- group is deprotonated and the piperazinyl group is proptonted [44]. The $\Delta\nu$ value ($206\,cm^{-1}$) observed for free CIP is larger than that of the ionic acetate ($\Delta\nu = 164\,cm^{-1}$) and comparable to the expected values for unidentate carboxylato complexes, consistent with the crystal structure of ciprofloxacin, which shows that the two C–O moieties of the COO^- group have slightly different bond lengths [44]. In the

spectra of the CIP complexes, the asymmetric and the symmetric vibrations of the coordinated COO^- occur at similar frequencies to those of the complexes of NOR as shown in Table II. We also propose that CIP acts as a bidentate ligand in these complexes through the carbonyl oxygen atom and one of the oxygen atoms of the COO^- group. That interaction is similar to that observed by Wallis *et al.* [26] in the complex $[Fe(CIP)(NTA)]_3 \cdot 5H_2O$ by X-ray analysis.

Although the spectra of $Fe(CIP)_4^{3+}$ and $Fe(NOR)_4^{3+}$ show all of the features mentioned, they show two additional weak bands at 1705 and 1730 cm^{-1}, respectively. These bands were not observed in the spectra of the complexes having lower ligand to metal ratios and can be considered indicative of the presence of a singly- or doubly-protonated quinolonels [18,19].

In view of the structural evidence presented herein and from the known coordination properties of the quinolone complexes established by X-ray crystallography, we propose the structures shown in Fig. 6 for 1 : 1, 1 : 2 and 1 : 3 iron to quinolone complexes. Several quinolone complexes with similar stoichiometry have been shown by X-ray to have structures similar to those in Fig. 5 [22–24]. The structures of the 1 : 4 complexes,

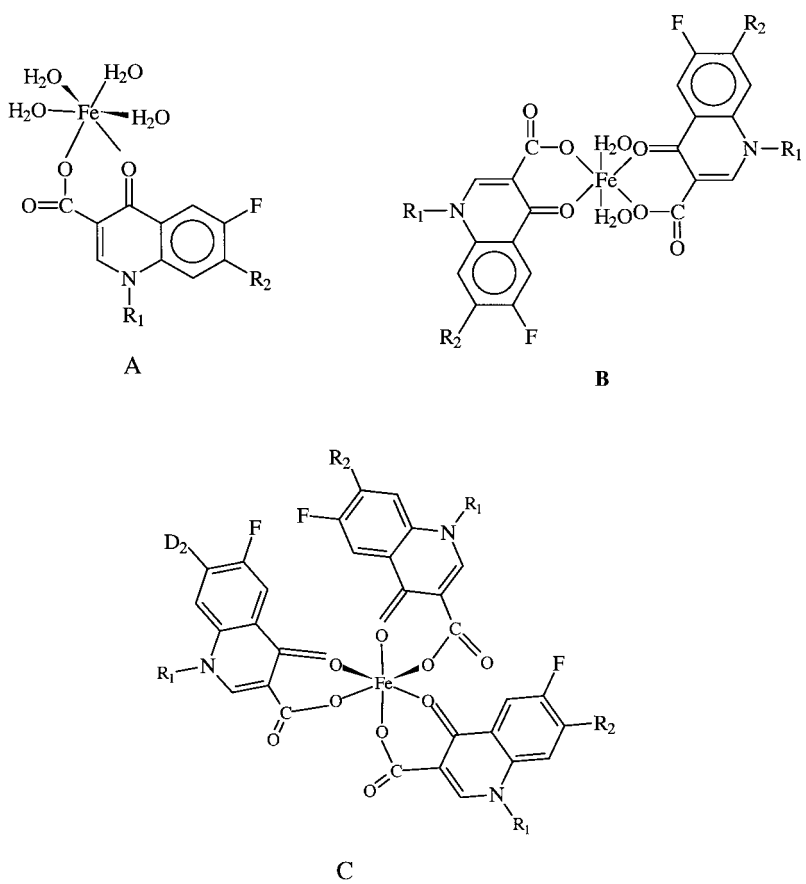


FIGURE 6 Proposed structures for the 1 : 1, 1 : 2 and 1 : 3 iron to quinolone complexes.

which appear to contain two types of interaction, are difficult to predict on the basis of IR spectra and appear to have similar structures to those reported by Chen *et al*. [32].

Acknowledgments

We thank the Deanship of Scientific Research at Jordan University of Science and Technology for the financial support.

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