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SYNTHESIS AND X-RAY STRUCTURAL CHARACTERIZATION OF AN IRON(III) COMPLEX OF THE FLUOROQUINOLONE ANTIMICROBIAL CIPROFLOXACIN, [Fe(CIP)(NTA)]3·5H_2O (NTA = NITRILOTRIACETATO)

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Abstract—Reaction of the fluoroquinolone antimicrobial ciprofloxacin (cip) with iron(III) in the presence of nitrilotriacetate (nta) results in the isolation of yellow crystals of the complex [Fe(cip)(nta)]3·5H_2O. The X-ray structural studies establish that, in the solid state, coordination of the iron(III) occurs through the keto and the carboxylic acid oxygen of the ciprofloxacin ligand to form a six-membered ring.

The pyridone carboxylic acids nalidixic acid (nal) (**I**), oxolinic acid (oxo) (**II**) and cinoxacin (cnx) (**III**), as well as the fluoroquinolones ciprofloxacin (cip) (**IV**), norfloxacin (nor) (**V**), lomefloxacin (**VI**) and ofloxacin (**VII**) (Fig. 1) are representatives of a class of antimicrobial drugs which have excellent activity against many Gram-positive and Gram-negative bacterial pathogens.[1,2] The primary mechanism of the antibacterial action of these drugs is the inhibition of DNA gyrase (Topoisomerase II), an enzyme responsible for coiling the long DNA molecule into the confined space inside the bacterial cell; inactivation of this enzyme is lethal to the microorganism.[3]

The formation of complexes of the pyridone carboxylic acids with transition and non-transition metal ions has been the subject of a number of literature reports.[4–13] The interest in the interaction of metal ions with these compounds arises from reports of detrimental effects of metal ions on absorption of the drugs,[1,14] and it has been proposed that the reduction in bioavailability of these compounds is a consequence of complex formation in the gastric system,[14] although a recent report suggests that complex formation, with ciprofloxacin at least, does not occur.[15] Recently we showed that copper(II) does interact with ciprofloxacin, the complexes [Cu(cip)(bipy)$(Cl)_{0.7}(NO_3)_{0.3}$](NO_3)·2H_2O and [$Cu(cip)_2$]Cl_2·11H_2O being structurally characterized.[16] In both these complexes chelation of the metal occurred through the 3-carboxylate/4-keto moiety. Our result is in contrast to an earlier report which suggested that in complexes of cop-

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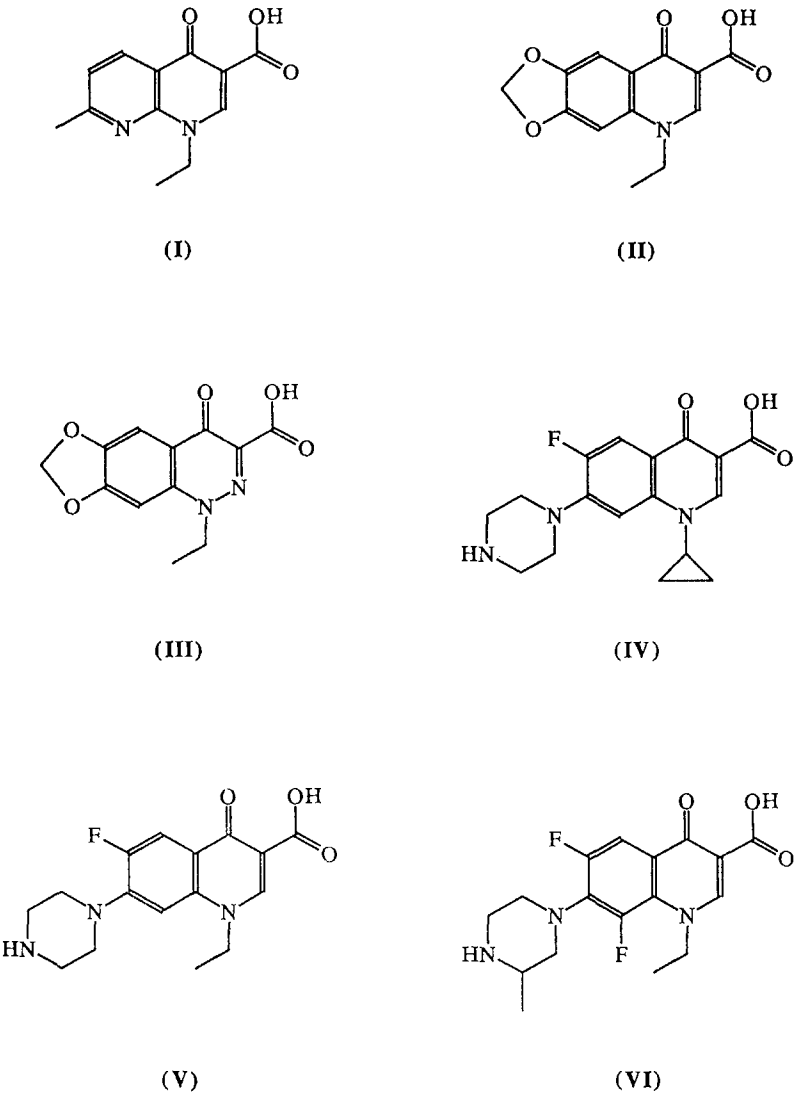

Fig. 1. Pyridone carboxylic acids.

per(II) with nalidixic acid, in the absence of added ligands, chelation occurred through the 3-carboxylate group, whilst in the presence of ligands such as phenanthroline chelation was through the 3-carboxylate and the 4-keto groups.[13]

Our interest is now directed toward the complexation properties of ciprofloxacin with Fe^{III}. It has been suggested recently that whilst ofloxacin coordinates with Fe^{II} through the carboxylate moiety, ciprofloxacin containing the same 3-carboxylate/4-keto moiety does not react with Fe^{II}.[15] We have chosen to focus on iron(III), rather than iron(II) because it has been shown that Fe^{II} is rapidly oxidized to Fe^{III} *in vitro* in pH conditions similar to those found in the small intestine.[17,18] Complexes of the type $[Fe(nal)_3]\cdot 2H_2O$ and $[Fe(nal)_2OH]$ have been proposed, with chelation occurring through the chelating carboxylate.[10,19] The characterization of these complexes was based on microanalytical and spectroscopic data.[10] Further, the complex $[Fe(cip)_3]$ was proposed although no structural details were reported.[20] Issopolous suggested that at pH 3 in aqueous solution the iron(III) complex with norfloxacin was of the form $[Fe(nor)_2(H_2O)_2]^-$ with chelation to the metal ion occurring through the 3-carboxylate/4-keto moiety.[21] The ubiquitous nature of the carboxylate ligand in biology[22] means that the establishment of the bonding mode of the fluoroquinolone antimicrobials is of considerable importance. In addition, and as an added incentive, there are few reported examples of chelating bidentate coordination of carboxylate ligands to iron(III). The complex $[Fe_3O(O_2CCH_3)_6([9]aneN_3)]$[23] displays a terminal bidentate acetate ligand and, more interestingly, recent results suggest that the native form

of ribonucleotide reductase, which has a (μ-oxo) diiron(III) core, has a chelating carboxylate as well as a bidentate bridging and two monodentate carboxylates.[24,25]

We now report the results of a study undertaken to gain a further insight into the nature of the interaction of ciprofloxacin with Fe^{III}.

EXPERIMENTAL

IR spectra were recorded with a Perkin–Elmer FT-1600 spectrophotometer using KBr disks. Ciprofloxacin · HCl was obtained from Sigma Chemical Co. (St Louis, Mo, U.S.A.) and used as received.

Synthesis

[Fe(cip)(nta)]3 · $5H_2O$. Ciprofloxacin · HCl (0.0594 g; 1.5×10^{-4} mol) was dissolved in water (30 cm^3) and the pH of the solution adjusted to 7 with dilute ammonia solution. An aqueous solution (20 cm^3) of $Fe(NO_3)_3 \cdot 9H_2O$ (0.0605 g; 1.5×10^{-4} mol) was added to an aqueous solution of $ntaHNa_2$ (0.0348 g; 1.5×10^{-4} mol). The light yellow iron(III)–nta solution was stirred for 3 min, then added to the solution of ciprofloxacin, resulting in a deep golden coloured solution. The solution was stirred for 48 h, filtered and stored at 0°C. The golden orange precipitate which formed was isolated by filtration and dried in a desiccator. Recrystallization from hot water resulted in yellow needle-like crystals. Found: C, 43.6; H, 4.8; N, 8.8. Calc. for $Fe(C_{17}H_{18}FN_3O_3)(C_6H_6NO_6)3.5H_2O$: C, 43.3; H, 4.9; N, 8.8%.

Single-crystal X-ray structure determination

Crystal data. Formula $[Fe(C_{17}H_{18}FN_3O_3)(C_6H_6NO_6)]3.5H_2O$, $M = 638.38$, monoclinic, space group $P2_1/c$, $a = 9.134(3)$, $b = 29.586(4)$, $c = 9.878(1)$ Å; $\beta = 103.01(2)°$, $V = 2600.8(9)$ $Å^3$, D_c ($Z = 4$) = 1.600 g cm^{-3}, μ(Cu-K_α) = 52.34 cm^{-1}, $\lambda = 1.5418$ Å, $F(000) = 1304$. Specimen: yellow needle, $0.30 \times 0.02 \times 0.03$ mm, $T_{max,min} = 0.940, 0.927$, $N = 4235$, $N_o = 2029$, $R = 0.079$, $R_\omega = 0.081$, $\omega = 1/(\sigma^2(F_o))$ [$R = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$, $R_\omega = (\Sigma\omega(|F_o| - |F_c|)^2/\Sigma\omega F_o^2)^{1/2}$].

Solution analysis and refinement. For diffractometry the crystal was mounted on a glass fibre with cyanoacrylate resin. Lattice parameters at 21°C were determined by least-squares fits to the setting parameters of 25 independent reflections, measured and refined on an AFC-7 four-circle diffractometer employing graphite monochromated Cu-K_α radiation. Intensity data were collected in the range $1 < \theta < 60°$. Data reduction and application of Lorentz, polarization, absorption and decomposition corrections were carried out using the teXsan system.[26]

The structure was solved by direct methods using SHELXS-86[27] and the solution was extended by difference Fourier methods. Hydrogen atoms were included at calculated sites with fixed isotropic thermal parameters. All other atoms with the exception of a disordered water molecule were refined anisotropically. Full-matrix least-squares methods were used to refine an overall scale factor, positional and thermal parameters. Neutral atom scattering factors were taken from Cromer and Waber.[28] Anomalous dispersion effects were included in F_c;[29] the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[30] The values for the mass attenuation coefficients are those of Creagh and Hubbel.[31] All calculations were performed using the teXsan[26] crystallographic software package of Molecular Structure Corporation and plots were drawn using ORTEP.[32] The high R value obtained was a consequence of the small crystal employed in the analysis. The atom numbering scheme is given in Fig. 2. Listings of bond lengths and angles are given in Tables 1 and 2. Final atomic coordinates, observed and calculated structure factors, non-hydrogen atom thermal parameters and hydrogen atom coordinates and thermal parameters and a crystal packing diagram (Fig. S1) are available from the Cambridge Crystallographic Data Centre.

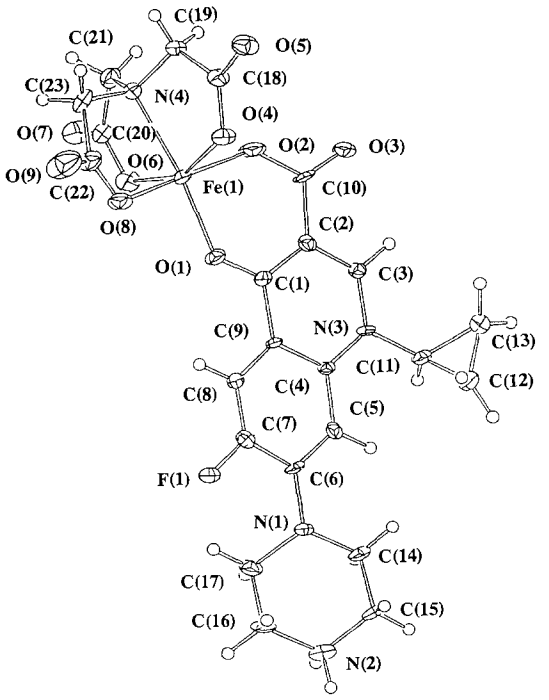

Fig. 2. ORTEP plot of [Fe(cip)(nta)].

Table 1. Bond lengths (Å) for [Fe(cip)(nta)]3·5H_2O

Fe(1)—O(1)	1.942(8)	Fe(1)—O(2)	1.97(1)
Fe(1)—O(4)	2.037(9)	Fe(1)—O(6)	1.969(9)
Fe(1)—O(8)	1.983(9)	Fe(1)—N(4)	2.21(1)
F(1)—C(7)	1.36(1)	O(1)—C(1)	1.30(1)
O(2)—C(10)	1.33(2)	O(3)—C(10)	1.18(2)
O(4)—C(18)	1.32(1)	O(5)—C(18)	1.24(1)
O(6)—C(20)	1.33(2)	O(7)—C(20)	1.19(2)
O(8)—C(22)	1.24(2)	O(9)—C(22)	1.22(2)
N(1)—C(6)	1.40(1)	N(1)—C(14)	1.45(2)
N(1)—C(17)	1.46(2)	N(2)—C(15)	1.48(2)
N(2)—C(16)	1.50(2)	N(3)—C(3)	1.34(1)
N(3)—C(4)	1.37(2)	N(3)—C(11)	1.50(2)
N(4)—C(19)	1.45(1)	N(4)—C(21)	1.52(2)
N(4)—C(23)	1.48(2)	C(1)—C(2)	1.41(2)
C(1)—C(9)	1.44(1)	C(2)—C(3)	1.37(2)
C(2)—C(10)	1.51(2)	C(4)—C(5)	1.40(1)
C(4)—C(9)	1.42(2)	C(5)—C(6)	1.36(2)
C(6)—C(7)	1.44(2)	C(7)—C(8)	1.33(2)
C(8)—C(9)	1.37(2)	C(11)—C(12)	1.50(2)
C(11)—C(13)	1.50(2)	C(12)—C(13)	1.51(2)
C(14)—C(15)	1.51(2)	C(16)—C(17)	1.54(2)
C(18)—C(19)	1.51(2)	C(20)—C(21)	1.50(2)
C(22)—C(23)	1.55(2)		

RESULTS AND DISCUSSION

While the tris(bidentate)iron(III) complex with nal has been reported,[10] our interest in the structural characterization was centred on the mode of bonding (3-carboxylate vs 3-carboxylate/4-keto) of the fluoroquinolone ciprofloxacin (cip). The synthetic methodology employed in this work uses nta (nitrilotriacetato) as a quadridentate ligand in order to simplify the structural complexity of the final complex, as complexation of nta with Fe^{III} would be expected to result in a species in solution which has two coordination sites available for reaction with the fluoroquinolone. Thus, reaction of $Fe(NO_3)_3 \cdot 9H_2O$, cip and $ntaHNa_2$ in aqueous solution resulted in the isolation of yellow crystals of a product subsequently identified as [Fe(cip)(nta)]3·5H_2O. Crystals suitable for X-ray structural analysis were isolated from dilute aqueous solution.

The structure consists of the neutral [Fe(cip)(nta)] complex and 3.5 water molecules. The iron(III) atom is coordinated to the keto and the carboxylic acid oxygen of the cip ligand to form a six-membered ring. The remaining four coordination sites are occupied by the nta ligand. The piperazinyl ring of the cip ligand is protonated on the external nitrogen.

The Fe—O and Fe—N bond lengths in the Fe(nta) portion of the molecule [Fe—O_{av} 1.996(9) Å; Fe—N 2.21(1) Å] are similar to those observed previously in similar Fe(nta) complexes (Ba[{Fe(nta)(H_2O)}$_2$O]4H_2O, Fe—O_{av} 2.01(1) Å, Fe—N 2.23(1) Å; $[Fe(nta)(DBC)]^{2-}$ (DBC is 3,5-di-*tert*-butylcatecholato), Fe—O_{av} 2.025(3) Å, Fe—N 2.224(3) Å) although shorter than those observed for $Na_3[Fe(nta)_2] \cdot 5H_2O$ [Fe—O_{av} 2.049(2) Å, Fe—N 2.291(3) and 2.314(3) Å].[33-35] In the iron–ciprofloxacin portion of the molecule, the iron(III) atom is coordinated through the oxygen atoms of the keto and carboxylic acid resulting in a six-membered ring. The Fe^{III}—O distances [1.942(8) (keto), 1.97(1) Å (acid)] are within the range of those reported for $[Fe(hfac)_2(hfptH_2)]^-$ (hfac = hexafluoroacetylacetone; $hfptH_2$ = 1,1,1,5,5,5,-hexafluoropentane-2,2,4,4-tetraol dianion) [1.905(4)–2.096(5) Å][36] but shorter than those for $[Fe(acac)_3]$ (acac = acetylacetone) [1.987(6)–1.993(6) Å][37] and $[Fe(mal)]^{3-}$ (mal = malonato) [1.962(1)–2.022(1) Å],[38] complexes with a similar six-membered ring structure. The piperazinyl and cyclopropyl rings are non-coplanar with the quinolone ring [C(12)—C(11)—N(3)—C(4) 71.85°, C(12)—C(11)—N(3)—C(3) −109.33°; C(17)—N(1)—C(6)—C(7) −50.93°, C(14)—N(1)—C(6)—C(5) −2.59°], the piperazinyl group adopting a chair conformation.

Previous studies of the nature of the complex formed between Fe^{III} and nal proposed that complexation occurs through the carboxylate resulting in a four-membered ring.[10] The structural analysis was based on that employed most successfully in the case of metal complexes of simple acetates where the frequency difference ($\Delta\nu$) between the intense antisymmetric and symmetric carboxylate stretching vibrations [$\nu(OCO)_{as}$-$\nu(OCO)_s$] has been related to the mode of coordination.[39-41] As well, the position of the $\nu(OCO)_s$ band was considered, as it has been suggested that simultaneous examination of the position of the symmetrical carboxylate stretching vibration together with the $\Delta\nu$ separation may represent a more accurate assessment of the bonding mode in structurally elaborate carboxylate molecules.[10,42,43] Mendoza-Diaz *et al.* suggested that in cases where the carboxylate group acts as a chelate, $\nu(OCO)_s$ is in the region 1483–1495 cm^{-1}.[10] Battaglia *et al.* suggested that for compounds of carboxylates and amino acids which do not contain complicating donor side chains, monodentate coordination is indicated by values for $\nu(OCO)_s$ in the ~1400–1414 cm^{-1} spectral region, whilst values lower than 1400 cm^{-1} are suggestive of bidentate coordination.[42] The IR spectrum of the complex [Fe(cip)(nta)] shows bands at 1633, 1626, 1515, 1490, 1469, 1383 and 1278 cm^{-1}, the presence of the nta complicating assignment of the $\nu(OCO)_{as}$

Table 2. Bond angles (°) for [Fe(cip)(nta)]3 · $5H_2O$

O(1)—Fe(1)—O(2)	89.3(4)	O(1)—Fe(1)—O(4)	103.9(3)
O(1)—Fe(1)—O(6)	100.3(4)	O(1)—Fe(1)—O(8)	89.7(4)
O(1)—Fe(1)—N(4)	171.9(4)	O(2)—Fe(1)—O(4)	86.7(4)
O(2)—Fe(1)—O(6)	92.8(4)	O(2)—Fe(1)—O(8)	170.6(5)
O(2)—Fe(1)—N(4)	98.7(4)	O(4)—Fe(1)—O(6)	155.8(4)
O(4)—Fe(1)—O(8)	84.4(4)	O(4)—Fe(1)—N(4)	77.6(3)
O(6)—Fe(1)—O(8)	96.6(4)	O(6)—Fe(1)—N(4)	78.6(4)
O(8)—Fe(1)—N(4)	82.5(4)	Fe(1)—O(1)—C(1)	130.3(8)
Fe(1)—O(2)—C(10)	133.9(9)	Fe(1)—O(4)—C(18)	116.9(7)
Fe(1)—O(6)—C(20)	121.7(8)	Fe(1)—O(8)—C(22)	115.6(9)
C(6)—N(1)—C(14)	118(1)	C(6)—N(1)—C(17)	119(1)
C(14)—N(1)—C(17)	111.3(9)	C(15)—N(2)—C(16)	112.2(9)
C(3)—N(3)—C(4)	122(1)	C(3)—N(3)—C(11)	120(1)
C(4)—N(3)—C(11)	118.2(9)	Fe(1)—N(4)—C(19)	105.8(7)
Fe(1)—N(4)—C(21)	105.7(7)	Fe(1)—N(4)—C(23)	106.3(8)
C(19)—N(4)—C(21)	114.6(9)	C(19)—N(4)—C(23)	110(1)
C(21)—N(4)—C(23)	113.2(9)	O(1)—C(1)—C(2)	124(1)
O(1)—C(1)—C(9)	118(1)	C(2)—C(1)—C(9)	118(1)
C(1)—C(2)—C(3)	120(1)	C(1)—C(2)—C(10)	126(1)
C(3)—C(2)—C(10)	114(1)	N(3)—C(3)—C(2)	122(1)
N(3)—C(4)—C(5)	121(1)	N(3)—C(4)—C(9)	118.9(9)
C(5)—C(4)—C(9)	120(1)	C(4)—C(5)—C(6)	122(1)
N(1)—C(6)—C(5)	123(1)	N(1)—C(6)—C(7)	120(1)
C(5)—C(6)—C(7)	116(1)	F(1)—C(7)—C(6)	118(1)
F(1)—C(7)—C(8)	119(1)	C(6)—C(7)—C(8)	123(1)
C(7)—C(8)—C(9)	121(1)	C(1)—C(9)—C(4)	119(1)
C(1)—C(9)—C(8)	122(1)	C(4)—C(9)—C(8)	118(1)
O(2)—C(10)—O(3)	122(1)	O(2)—C(10)—C(2)	116(1)
O(3)—C(10)—C(2)	122(1)	N(3)—C(11)—C(12)	116(1)
N(3)—C(11)—C(13)	117.5(9)	C(12)—C(11)—C(13)	60.4(9)
C(11)—C(12)—C(13)	59.7(9)	C(11)—C(13)—C(12)	59.9(9)
N(1)—C(14)—C(15)	110(1)	N(2)—C(15)—C(14)	111(1)
N(2)—C(16)—C(17)	109(1)	N(1)—C(17)—C(16)	109(1)
O(4)—C(18)—O(5)	125(1)	O(4)—C(18)—C(19)	116(1)
O(5)—C(18)—C(19)	119(1)	N(4)—C(19)—C(18)	111(1)
O(6)—C(20)—O(7)	125(1)	O(6)—C(20)—C(21)	114(1)
O(7)—C(20)—C(21)	121(1)	N(4)—C(21)—C(20)	113(1)
O(8)—C(22)—O(9)	124(1)	O(8)—C(22)—C(23)	120(1)
O(9)—C(22)—C(23)	116(1)	N(4)—C(23)—C(22)	111(1)

and $\nu(OCO)_s$ frequencies.[33] Although assignment of $\nu(OCO)_{as}$ arising from the cip in [Fe(cip)(nta)] may be made either to the band at 1633 or 1626 cm^{-1}, assignment of the $\nu(OCO)_s$ frequency is less obvious, with the candidates including bands at 1490, 1469 or 1383 cm^{-1}, the band at 1278 cm^{-1} being associated with the ketone deformation. The unidentate mode of coordination exhibited by the carboxylate suggests that the $\Delta\nu$ value should be greater than that exhibited by the analogous ionic compound.[10,39–41] Comparison of the IR spectra of cip · HCl and Na(cip) permits assignment of $\nu(OCO)_{as}$ and $\nu(OCO)_s$ to bands at 1576 and 1381 cm^{-1}, respectively ($\Delta\nu = 195\,cm^{-1}$), consistent with assignments reported for Na(nal).[10] This suggests that for [Fe(cip)(nta)] $\Delta\nu$ should be >195 cm^{-1}, and that $\nu(OCO)_s$ be assigned to 1383 cm^{-1}. However, this assignment would differ from the previous criteria for the position of $\nu(OCO)_s$ and its relation to the bonding mode.[10,39–41] Except for the case of simple acetate ligands, it would appear that structural analysis based on IR studies alone is not able to establish unambiguously the bonding mode of more complex ligands containing the carboxylato moiety.

The results presented in this paper suggest that for the iron(III) complex of ciprofloxacin, in the solid state, the coordination of the fluoroquinolone is through the 3-carboxylate/4-keto moiety. The present result does not exclude other modes of coor-

dination *in vivo*, or even carboxylate linkage isomerization which has been suggested to be important in biological systems.[44,45]

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