

Complexes of Co(II) and Zn(II) with Ofloxacin. Crystal Structure of [Co(oflo)₂(MeOH)₂].4MeOH

BENIGNO MACIAS,¹ MARIA V. VILLA,¹ MARIA SASTRE,¹ ALFONSO CASTIÑEIRAS,² JOAQUIN BORRAS³

¹Departamento de Química Inorgánica, Facultad de Farmacia, Universidad de Salamanca, Spain

²Departamento de Química Inorgánica, Facultad de Farmacia, Universidad de Santiago de Compostela, Spain

³Departamento de Química Inorgánica, Facultad de Farmacia, Universidad de Valencia, Spain

Received 4 September 2001; revised 15 April 2002; accepted 22 May 2002

ABSTRACT: Ofloxacin (oflo) is able to interact with Co(II) and Zn(II) salts to form complexes with the general formula [M(oflo)₂].4H₂O, (M = Co, Zn). Bonding takes place through one of the oxygen atoms of the carboxylate group (acting as a monodentate) and the oxygen atom of the ketonic group. The IR bands of the carboxylic and ketonic group at 1713 and 1622 cm⁻¹, respectively, shift to 1615 and 1575 cm⁻¹ in the complexes. After dissolution in methanol, complex [Co(oflo)₂].4H₂O crystallizes as [Co(oflo)₂(MeOH)₂].4MeOH, where Co(II) ion is in an octahedral environment of oxygen atoms. This compound crystallizes in the triclinic system, spatial group P-1, with unit cell dimensions a = 9.3670(12), b = 11.4135(17), c = 11.851(2) Å y α = 71.999(14), β = 73.698(12), γ = 83.528(14)°. Magnetic properties (effective magnetic moment 5.02 BM) and visible spectrum (bands at 490, 510, and 1152 nm) are characteristic of such an octahedral geometry. ¹H- and ¹³C-NMR spectra of the Zn(II) complex indicate only small structural changes in ofloxacin upon coordination to the metallic site. © 2002 Wiley-Liss, Inc. and the American Pharmaceutical Association J Pharm Sci 91:2416–2423, 2002

Keywords: quinolones; ofloxacin; Co(II) complexes; Zn(II) complexes

INTRODUCTION

Interaction of metal ions, mainly those existing in living organisms, with drugs, especially antibiotics, has been the aim of many research studies since several review papers on this subject were published.¹ Quinolones are a group of antibacterial agents currently used in various kinds of infections,² and for some of the members of this family, especially cinoxacin, its interactions with several metal ions has been reported.^{3–7} However, only a few articles have been reported on

the coordination properties of fluorquinolones, some studies have been reported on the compounds formed between ofloxacin and ciprofloxacin with metal cations commonly found in several drugs used as antacids,⁸ and of ofloxacin with Cu(II) and Ni(II).⁹

Ofloxacin ((±)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid), is a nalidixic acid analog with broad spectrum antibacterial activity (Fig. 1) that acts as a specific inhibitor of the bacterial DNA-gyrase, the enzyme responsible for converting double-stranded DNA into a negative superhelical form.²

One of the main objectives when studying the interactions between metal cations and antibiotics is to ascertain the nature of the functional groups responsible for the metal–ligand binding.

Correspondence to: Benigno Macias (Telephone: 34-23-294524; Fax: 34-23-294515; E-mail: bmacias@gugu.usal.es)

Journal of Pharmaceutical Sciences, Vol. 91, 2416–2423 (2002)
© 2002 Wiley-Liss, Inc. and the American Pharmaceutical Association

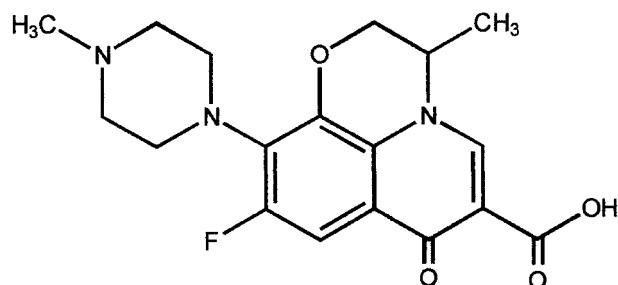


Figure 1. Chemical structure of ofloxacin.

Formation of insoluble compounds with cations such as Al^{3+} , Mg^{2+} , Fe^{2+} , and Ca^{2+} , has been proposed in some cases to justify a decrease in the amount of quinolone absorbed after its simultaneous oral administration with antacids.⁸

In the present article we study the complexes formed through reaction of ofloxacin and Co(II) or Zn(II) salts, where the nature of the functional groups coordinating on the metal cations has been undoubtedly established.

MATERIALS AND METHODS

Materials

Ofloxacin was provided by Sigma, and all reagents used were of analytical grade. Chemical analyses for carbon, hydrogen, and nitrogen were performed on a 2400 elemental analyzer from Perkin-Elmer. Nickel and copper were determined on a ICP spectrometer (Perkin-Elmer model 2380 Plasma 2).

IR spectra were recorded using KBr mulls and a Perkin-Elmer FT-IR instrument. Electronic spectra were recorded on a Hewlett Packard 8452A diode (200–800 nm) and a Perkin-Elmer Lambda 9 (800–1600 nm) spectrophotometers.

Room-temperature magnetic moment was measured by the Faraday method on a AZTEC DSM8 pendulum-type susceptometer.

Water content in the complexes was determined by thermal analysis, using a Perkin-Elmer TGA-7 thermobalance and a DTA-7 differential thermal analysis apparatus, both operating at a heating rate of $5^\circ\text{C}/\text{min}$ and under oxygen as the reaction atmosphere.

Molecular masses were measured by Servicio de Masas (Universidad Autónoma de Madrid, Spain) by de FAB method with samples held on a nitrobenzyl alcohol (NBA) matrix and L-SIMS

ionization mode, in a VG AUTOSPEC apparatus; the source was maintained at 30°C and 35 keV, and Cs^+ ion were used.

^1H - and ^{13}C -NMR spectra were obtained in methanol- d_4 solution on a Bruker DX400 instrument.

Syntheses of the Complexes

Ofloxacin interacts directly with Co(II) and Zn(II) salts in an aqueous medium at neutral pH, as concluded from the observation that ofloxacin (insoluble in water) is slowly solubilized as salts of these cations are added; total solubilization of ofloxacin is achieved for a metal:ofloxacin molar ratio of 1:2; simultaneously, the color of the Co(II) solution is enhanced and the Zn(II) solution becomes slightly yellow.

Unfortunately, the compounds formed in a neutral pH cannot be well defined from a chemical point of view, as the anion of the original metal salt is usually incorporated to the compounds formed, giving rise to formation of polymers.⁹ To avoid such a polymer formation, the reaction is carried out in a basic medium as follows: 0.092 mmol ofloxacin are dissolved in 10 mL NaOH 0.1 M, and 0.46 mmol of the metal salt dissolved in 5 mL water are added. After a few minutes stirring a pale pink or white precipitate (for cobalt or zinc, respectively) is formed, which is separated by filtration and washed with bidistilled water.

These complexes are not soluble in water, but soluble in different organic solvents, such as dimethylformamide, methanol, or dimethylsulfoxide. Elemental chemical analysis data are in agreement with a general formula $[\text{M}(\text{oflo})_2] \cdot 4\text{H}_2\text{O}$ ($\text{M} = \text{Co(II)}$ or Zn(II)). Data obtained were as follows: $[\text{Co}(\text{oflo})_2] \cdot 4\text{H}_2\text{O}$, Found (%): C = 51.02, H = 5.61, N = 9.79, and Co = 6.80; Calculated (%): C = 50.74, H = 5.42, N = 9.86, and Co = 6.92. For $[\text{Zn}(\text{oflo})_2] \cdot 4\text{H}_2\text{O}$, Found (%): C = 50.39, H = 5.47, N = 9.66, Zn = 7.47; Calculated (%): C = 50.36, H = 5.38, N = 9.79, and Zn = 7.62.

In addition to these two complexes, it is also possible to isolate the Co(II) complex in a crystalline form, although as a methanol solvated species. For this, the $[\text{Co}(\text{oflo})_2] \cdot 4\text{H}_2\text{O}$ complex is dissolved in methanol (ca. 0.2 g in 50 mL) and after standing at room temperature for 2 or 3 days, reddish crystals are formed. These crystals decompose and turn to blue color when they are removed from the solution where they have been crystallized and completely dried, and so elemental chemical analysis could not be carried out,

Table 1. Crystal Data and Structure Refinement for [Co(olfo)₂(MeOH)₂] · 4MeOH

Empirical formula	CoC ₄₂ H ₆₂ F ₂ N ₆ O ₁₄
Formula weight	971.91
Temperature	208 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1 (No. 2)
Unit cell dimensions:	
a = 9.3670(12) Å	α = 71.999(14)°
b = 11.4135(17) Å	β = 73.698(12)°
c = 11.851(2) Å	γ = 83.528(14)°
Volume	1156.1(3) Å ³
Z	1
Calculated density	1.396 g/cm ³
Absorption coefficient	0.450 mm ⁻¹
F(000)	513
Crystal size	0.15 × 0.15 × 0.15 mm
θ range for data collection	1.87 a 27.45°
Limiting indexes	-11 < h < 12, -13 < k < 14, 0 < l < 15
Reflections collected/unique	5278/5278 [R(int) = 0.0000]
Max. and min. transmission	0.946 and 0.876
Refinement method	Full-matrix least-squares on F ²
Data/restraints/parameters	5278/0/275
Goodness-of-fit on F ²	0.921
Final R indices [I > 2σ(I)]	
R ₁ = 0.0533	wR ₂ = 0.1873
R Indices (all data)	
R ₁ = 0.0580	wR ₂ = 0.2070
Largest diff. peak and hole	1.279 and -0.469 e. Å ⁻³

although from X-ray diffraction results (the crystal was not fully dried when transferred to the capillary tube for X-ray analysis) the formula was established as [Co(olfo)₂(MeOH)₂] · 4MeOH. A similar procedure failed to prepare the analogous Zn(II) complex.

X-Ray Structure Determination of [Co(olfo)₂(MeOH)₂] · 4MeOH

X-ray Data Collection and Reduction

A rose cubic crystal of [Co(olfo)₂(MeOH)₂] · 4MeOH was mounted on a glass fiber and used for data collection. Cell constants and an orientation matrix for data collection were obtained by least-squares refinement of the diffraction data from 25 reflections in the range of 3.668 7 < θ < 9.874° on an Enraf Nonius CAD4 automatic diffractometer.¹⁰ Data were collected at 208 K using [MoKα] radiation (λ = 0.71073 Å) and the omega-scan technique, and corrected for Lorentz and polarization effects.¹¹ A semi-empirical absorption correction (ψ-scans) was made.¹²

Structure Solution and Refinement

The structure was solved by direct methods¹³ and subsequent difference Fourier maps, and refined on F₂ by a full-matrix least-squares procedure using anisotropic displacement parameters.¹⁴ All hydrogen atoms were located in their calculated positions (C-H 0.93–0.97 Å), and were refined using a riding model. Atomic scattering factors from “International Tables for X-ray Crystallography.”¹⁵ Molecular graphics from PLATON.¹⁶ A summary of the crystal data, experimental details and refinement results are listed in Table 1.

RESULTS AND DISCUSSION

Thermal Study and Mass Spectrometry

The presence of four water molecules per complex molecule has been assessed by thermogravimetric (TG) and differential thermal analyses (DTA). So, a 8.4% weight loss in the TG curves is associated to removal of four water molecules. These losses

occur in the same temperature range (95–100°C) as endothermic peaks in the DTA curves, as expected for a dehydration process.

However, the molecular masses of these compounds are recorded in mass spectrometry analysis at $m/z = 780$ and 784 , respectively, for the Co and Zn complexes, i.e., those corresponding to the fully dehydrated compounds, probably as a consequence of fast removal of the water molecules in the ionization chamber, suggesting the bonding of these water molecules to the corresponding complexes should be rather weak.

IR Spectra

The FTIR spectra of ofloxacin and of the three complexes synthesised are shown in Figure 2. The most relevant bands have been labeled. The band due to the free carboxylic group at 1713 cm^{-1} (Fig. 1a), vanishes in the spectra of the complexes, as a carboxylate group, responsible for the bonding to the metallic site, is formed. The band due to the antisymmetric stretching mode of the carboxylate group is recorded at $1619\text{--}1612\text{ cm}^{-1}$, while the symmetric one is recorded at 1475 cm^{-1} (Figs. 2b–2d). The band at 1622 cm^{-1} in the spectrum of ofloxacin, related to the ketonic group, shifts up to $1581\text{--}1570\text{ cm}^{-1}$ for the complexes, as this group also participates in the bonding to the metallic site, thus giving rise to an important shift towards lower wavenumbers from its position in the free, uncoordinated ligand.^{17,18} Another important band is that corresponding to the metal–ligand(oxygen) bond, which is recorded in this case in the $510\text{--}503\text{ cm}^{-1}$ range.

Bands due to vibration bonds not involved in the bonding to the metal (e.g., C–F, eter group) are less affected upon formation of the coordination compounds. The main conclusion we can reach from these spectra is that the structure of all three complexes should be rather similar for all of them, as the number and positions of the bands are similar in all cases. This result is of large importance, because although we could resolve only the crystalline structure of one of the complexes obtained, the IR similarities suggest the coordination is through the same functional groups in all cases.

Crystal Structure of $[\text{Co}(\text{oflo})_2(\text{MeOH})_2] \cdot 4\text{MeOH}$

An ORTEP diagram of the complex, including the atomic numbering scheme, is shown in Figure 3 and selected bond distances and angles are presented in Table 2. Atomic coordinates and

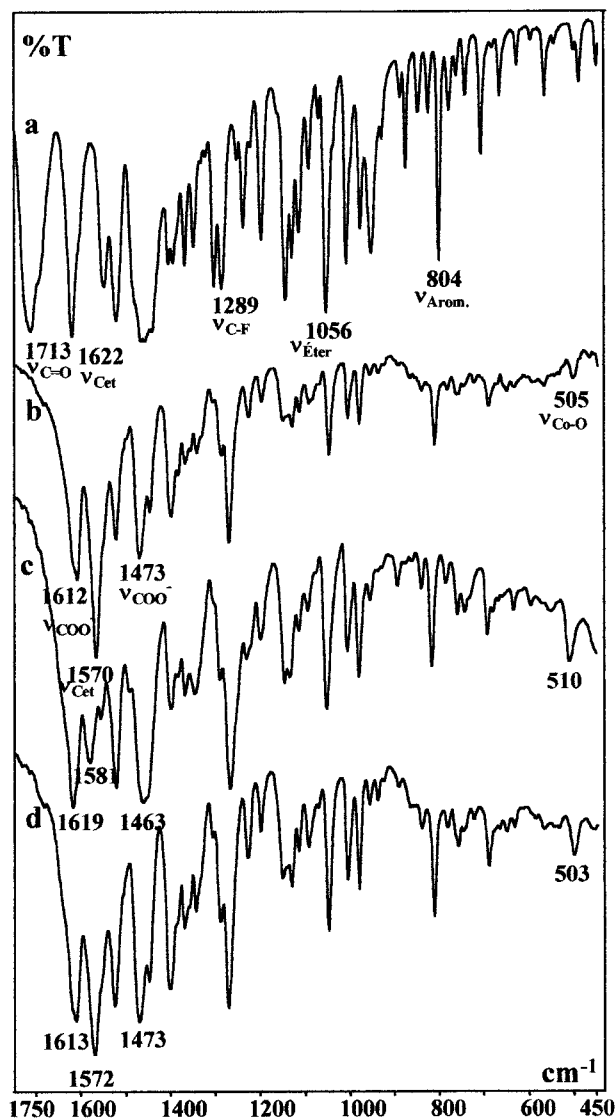


Figure 2. FTIR spectra ($1750\text{--}450\text{ cm}^{-1}$) for the compounds: (a) ofloxacin, (b) $[\text{Co}(\text{oflo})_2] \cdot 4\text{H}_2\text{O}$, (c) $[\text{Co}(\text{oflo})_2(\text{MeOH})_2] \cdot 4\text{MeOH}$, and (d) $[\text{Zn}(\text{oflo})_2] \cdot 4\text{H}_2\text{O}$.

equivalent isotropic displacement coefficients are shown in Table 3.

Structural data indicate that Co(II) ions are in an octahedral local geometry, surrounded by six oxygen atoms; those in equatorial positions belonging to the two coordinating ofloxacin molecules, and the axial (*trans*) positions occupied by the methanol molecules. The Co–O(ax) length is slightly longer than the Co–O(eq) lengths (2.113 versus 2.024 and 2.033 Å), thus indicating a tetragonal distortion along the z-axis, as expected from the Jahn-Teller effect for this d^7 configuration in a high spin octahedral environment.¹⁹

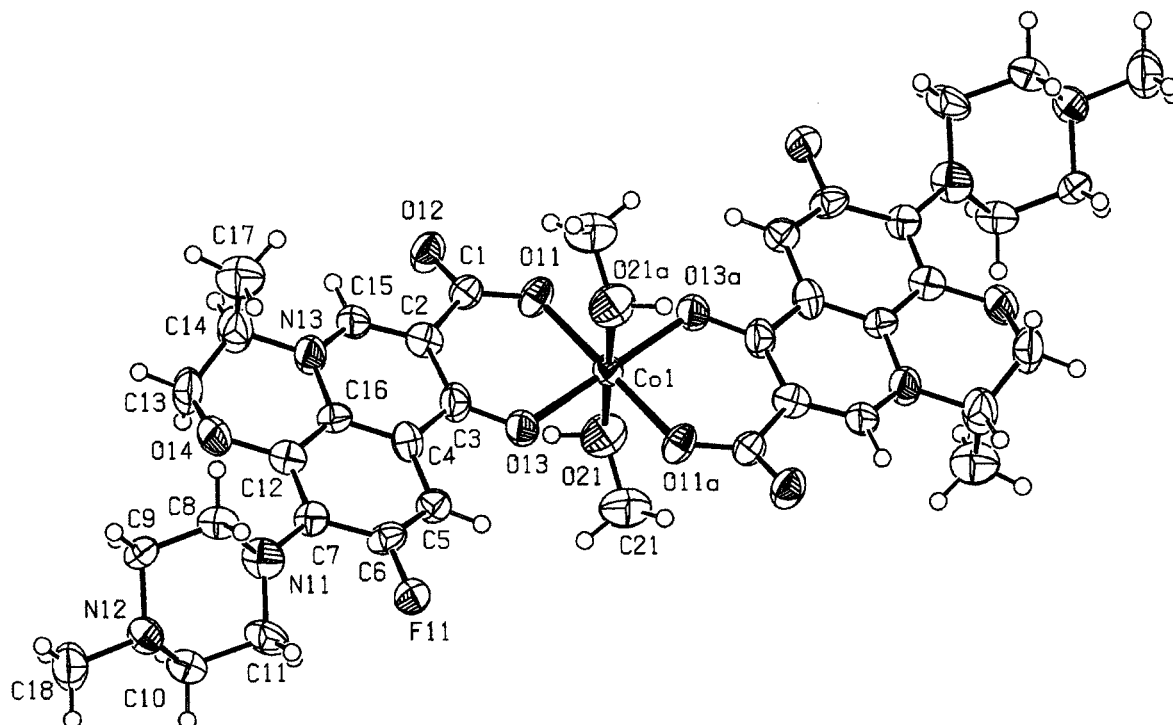


Figure 3. ORTEP diagram for $[\text{Co}(\text{olfo})_2(\text{MeOH})_2] \cdot 4\text{MeOH}$ with the atom-labeling scheme.

The coordinating oxygen atoms from the ofloxacin molecule are chemically different: that labeled as O13 in Figure 3 belongs to the ketonic group, whereas that labeled as O11 belongs to the

Table 2. Selected Bond Lengths (Å) and Angles (°) for $[\text{Co}(\text{olfo})_2(\text{MeOH})_2] \cdot 4\text{MeOH}$

Co(1)–O(13)	2.024(3)
Co(1)–O(13a)	2.024(3)
Co(1)–O(11)	2.033(3)
Co(1)–O(11a)	2.033(3)
Co(1)–O(21)	2.113(4)
Co(1)–O(21a)	2.114(4)
O(13)–Co(1)–O(13a)	179.998(2)
O(13)–Co(1)–O(11)	90.32(13)
O(13a)–Co(1)–O(11)	89.68(13)
O(13)–Co(1)–O(11a)	89.68(13)
O(13a)–Co(1)–O(11a)	90.32(13)
O(11)–Co(1)–O(11a)	180.0
O(13)–Co(1)–O(21)	90.59(17)
O(13a)–Co(1)–O(21)	89.41(17)
O(11)–Co(1)–O(21)	89.29(14)
O(11a)–Co(1)–O(21)	90.71(14)
O(13)–Co(1)–O(21a)	89.40(17)
O(13a)–Co(1)–O(21a)	90.59(17)
O(11)–Co(1)–O(21a)	90.70(14)
O(11a)–Co(1)–O(21a)	89.30(14)
O(21)–Co(1)–O(21a)	179.999(1)

carboxylate group, which acts as a monodentate ligand. The distance Co–O13 is slightly shorter than the Co–O11 distance, 2.024 and 2.033 Å, respectively, these values being very similar to those previously reported for similar cobalt complexes with cinoxacin, with a distorted octahedral structure.²⁰ It should be stressed, however, the high regularity of the angle bonds, with 180° for the *trans* oxygen atoms, and 90° for the *cis* ones.

The unit cell contains four methanol molecules (not shown in Fig. 3), which increase the stability of the crystal by hydrogen bonding. Removal of these methanol molecules, which are weakly bonded, lead to the losing of the three-dimensional network, making opaque the substance.

Crystalline determination studies further confirm coordination takes place through the carboxylate and the ketonic group, in a similar fashion to other complexes with quinoline, above cited.

NMR SPECTRA

Only broad, ill defined, bands were recorded in the spectra of the Co complexes, due to their paramagnetic character. However, the ¹H- and ¹³C-NMR spectra of the pure ofloxacin and of the

Table 3. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{Å}^2 \times 10^3$) for $[\text{Co}(\text{oflo})_2(\text{MeOH})_2] \cdot 4\text{MeOH}$

	x	y	z	U(eq) ^a
Co(1)	10000	5000	0	32(1)
F(11)	3376(3)	4583(3)	4355(3)	49(1)
O(11)	10645(4)	6777(3)	-577(3)	42(1)
O(12)	10391(4)	8802(3)	-886(3)	51(1)
O(13)	7990(3)	5491(3)	955(3)	48(1)
O(14)	4231(4)	8723(4)	3884(4)	57(1)
O(21)	9198(5)	5346(4)	-1574(4)	64(1)
N(11)	2419(5)	6734(5)	5020(4)	52(1)
N(12)	-328(4)	7389(4)	6430(4)	46(1)
N(13)	6903(4)	8592(3)	2099(4)	51(1)
C(1)	9982(5)	7732(4)	-319(4)	37(1)
C(2)	8550(5)	7591(3)	740(4)	39(1)
C(3)	7700(5)	6505(4)	1273(4)	45(1)
C(4)	6371(5)	6549(4)	2228(4)	40(1)
C(5)	5435(5)	5502(4)	2815(4)	39(1)
C(6)	4233(5)	5591(4)	3743(4)	42(1)
C(7)	3747(5)	6655(4)	4132(3)	37(1)
C(8)	2352(5)	7156(5)	6085(4)	42(1)
C(9)	1044(5)	8013(4)	6326(4)	38(1)
C(10)	-213(5)	7048(5)	5347(5)	48(1)
C(11)	1104(5)	6145(6)	5113(5)	56(1)
C(12)	4656(5)	7642(4)	3557(4)	40(1)
C(13)	4911(6)	9800(5)	2984(6)	58(2)
C(14)	6491(6)	9657(5)	2573(7)	68(2)
C(15)	8070(4)	8563(4)	1173(5)	44(1)
C(16)	5974(4)	7604(4)	2631(4)	35(1)
C(17)	7182(9)	9404(7)	3720(6)	66(2)
C(18)	-1632(7)	8212(5)	6653(7)	68(2)
C(21)	8230(10)	4653(9)	-1765(8)	76(3)
O(31)	6179(7)	2727(6)	1742(6)	87(1)
C(31)	5404(13)	3151(11)	951(11)	90(3)
O(41)	1308(9)	9491(8)	2120(7)	82(2)
C(41)	1988(11)	8673(9)	1654(9)	70(2)

^aU(eq) is defined as one-third of the trace of the orthogonalized Uij tensor.

Zn complex could be recorded; the data and their assignments²¹ are summarized in Table 4. Both spectra are rather similar, indicating that coordination to the Zn(II) cation does not heavily modify the conformation of the ofloxacin molecule.

Magnetic Susceptibility and Electronic Spectra

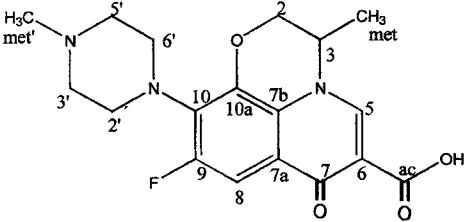
The effective magnetic moment of the $[\text{Co}(\text{oflo})_2] \cdot 4\text{H}_2\text{O}$ complex at room temperature was 5.01 BM, in the range expected for high spin octahedral Co(II) complexes, 4.7–5.2 BM.²² As expected for a d^{10} configuration, the Zn complex is diamagnetic.

The electronic spectra are also in agreement with this structure concluded from X-ray diffraction. Three low intense bands are recorded in the

visible range at 490, 510, and 1192 nm, which, according to the literature,^{22,23} should correspond to transits from the fundamental state, ${}^4\text{T}_{1g}$, to excited states ${}^4\text{T}_{1g}(\text{P})$, ${}^4\text{A}_{2g}$, and ${}^4\text{T}_{2g}$, respectively. In addition, both the Co(II) and the Zn(II) complexes also show four intense bands ($\epsilon > 15,000 \text{ M}^{-1} \text{ cm}^{-1}$) in the ultraviolet region at 228, 256, 290, and 332 nm, due to transitions within the ofloxacin molecule.

ACKNOWLEDGMENTS

The authors thank CICYT (grant PM97-0105-C02-02) for financial support. Critical reading of the manuscript by Prof. V. Rives is also acknowledged.

Table 4. Chemical Shifts (ppm) from ^1H - and ^{13}C -NMR Spectra of Ofloxacin and Zinc Complex


		Ofloxacin		Zn (OFLO) ₂	
		^1H	^{13}C	^1H	^{13}C
ac		—	174.64	—	174.66
met		1.39	19.97	1.33	20.27
met'		2.36	47.43	2.91	46.29
2	2-<'>	4.53	70.90	4.61	71.58
	2-<''>	4.25		4.23	
2'	AX	2.61	52.19	3.48	50.57
	EQ	2.61		3.48	
3'	3	4.40		4.43	58.60
	AX	3.19	57.04	3.21	57.19
5'	EQ	3.19		3.48	
	5	7.19	147.63	7.21	150.39
6'	AX	3.19	57.04	3.21	57.19
	EQ	3.19		3.48	
7	6	—	118.26	—	115.29
	AX	2.61	52.19	3.48	50.54
7a	EQ	2.61		3.48	
	7	—	177.72	—	179.20
7b	7a	—	125.38	—	125.71
	7b	—	126.91	—	127.41
8	8	8.36	106.32	8.65	106.81
	9	—	159.09	—	159.96
10	10	—	156.64	—	157.51
	10a	—	132.71	—	132.61
	10a	—	142.46	—	143.37

REFERENCES

- Wolfson JS, Hooper DC, Swarz MN. 1989. Mechanism of action and resistance to quinolone antimicrobial agents. In: Wolfson JS, Hooper DC, editors. *Quinolone antimicrobial agents*. Washington, DC: American Society for Microbiology.
- Sigel H. 1985. *Antibiotics and their complexes*. In: *Metal ions in biological systems*, vol. 19. New York: Marcel Dekker.
- Ruiz M, Ortiz R, Perelló L. 1993. Ni(II) and Zn(II) complexes with cinoxacin. Synthesis and characterization of $\text{M}(\text{Cx})_2(\text{DMSO})_n(\text{H}_2\text{O})_m$ ($n = 0, 2$; $m = 2, 4$). Crystal structures of $[\text{M}(\text{Cx})_2(\text{DMSO})_2] \cdot 4\text{H}_2\text{O}$ ($\text{M} = \text{Ni(II), Zn(II)}$). *Inorg Chim Acta* 211:133–139.
- Ruiz M, Ortiz R, Perelló L, García-Granda S, Díaz MR. 1994. Synthesis and characterization of Cd(II) complexes of cinoxacin. Crystal structure of a dicadmium complex containing two monoatomic-bridging carboxylate oxygen atoms. *Inorg Chim Acta* 217:149–154.
- Ruiz M, Perelló L, Ortiz R, Castiñeiras A, Maichle-Mössmer C, Cantón E. 1995. Synthesis, characterization, and crystal structure of $[\text{Cu}(\text{cinoxacin})_2] \cdot 2\text{H}_2\text{O}$ complex: A square-planar CuO_4 Chromophore. Antibacterial studies. *J Inorg Biochem* 59:801–810.
- Ruiz M, Ortiz R, Perelló L, Latorre J, Server-Carrió J. 1997. Potentiometric and spectroscopic studies of transition-metal ions. Complexes with a quinolone derivative (cinoxacin). Crystal structures of new Cu(II) and Ni(II) cinoxacin complexes. *J Inorg Biochem* 65:87–96.
- Ruiz M, Perelló L, Server-Carrió J, Ortiz R, García-Granda S, Díaz MR, Cantón E. 1988. Cinoxacin complexes with divalent metal ions. Spectroscopic characterization. Crystal structure of a new dinuclear Cd(II) complex having two chelate-bridging carboxylate groups. Antibacterial studies. *J Inorg Biochem* 69:231–239.
- Macías B, Martínez M, Sánchez A, Domínguez-Gil A. 1994. A physico-chemical study of the interaction of ciprofloxacin and ofloxacin with polyvalent cations. *Int J Pharm* 106:229–235.
- Macías B, Villa MV, Rubio I, Castiñeiras A, Borrás J. 2001. Complexes of Ni(II) and Cu(II) with ofloxacin. Crystal structure of a new Cu(II) ofloxacin complex. *J Inorg Biochem* 84:163–170.
- Nonius BV. 1994. CAD4-express software, Ver. 5.1/1.2. Delft, The Netherlands: Enraf Nonius.
- Kretschmar M. 1997. GENHKL: Program for the reduction of CAD4 Diffractometer data. Germany: University of Tuebingen.
- North ACT, Phillips DC, Mathews FS. 1968. A semi-empirical method of absorption correction. *Acta Crystallogr.* A24:351–359.
- Sheldrick GM. 1990. Phase annealing in SHELX-90: Direct method for larger structures. *Acta Crystallogr.* A46:467–473.
- Sheldrick GM. 1997. SHELXL-97. Program for the refinement of crystal structures. Germany: University of Goettingen.
- International tables for X-ray crystallography. 1995. Vol. C. Dordrecht, The Netherlands: Kluwer Academic Publishers.
- Spek AL. 2000. PLATON. A multipurpose crystallographic tool. Utrecht, The Netherlands: Utrecht University.
- Nakamoto K. 1997. *Infrared and Raman spectra of inorganic and coordination compounds*. Part B: Applications in coordination, organometallic and bioinorganic chemistry, 5th ed. New York: Wiley.

18. Bellamy LJ. 1975. *The infrared spectra of complex molecules*, 3rd ed. London: Chapman and Hall.
19. Huheey JE, Keiter EA, Keiter RL. 1993. *Inorganic chemistry: Principles of structure and reactivity*, 4th ed. New York: HarperCollins, pp 449–455.
20. Chulvi C, Muñoz MC, Perelló L, Ortiz R, Arriortua MI, Via J, Urtiaga K, Amigó JM, Ochando LE. 1991. Coordination behaviour of cinoxacin: Synthesis and crystal structure of tris(cinoxacinate)cobaltate(II) of sodium hexahydrate. *J Inorg Biochem* 42:133–138.
21. Pretsch E, Clerc T, Seibl J, Simon W. 1990. *Tabellen zur strukturaufklärung organischer verbindungen mit spektroskopischen metoden*, 3rd ed. Berlin: Springer Verlag.
22. Greenwood NN, Earnshaw A. 1984. *Chemistry of the elements*. Oxford: Pergamon Press, pp 1313–1315.
23. Lever ABP. 1984. *Inorganic electronic spectroscopy*, 2nd ed. Amsterdam: Elsevier, pp 480–489.