Novel Lanthanide Complexes of Ciprofloxacin: Synthesis, Characterization, Crystal Structure and *in vitro* Antibacterial Activity Studies

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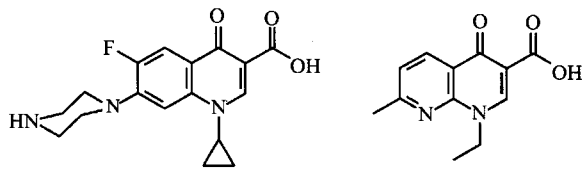
Novel lanthanide coordination compounds with ciprofloxacin (CPFX), including eleven complexes $Ln(CPFX)_2Cl(H_2O)_n$ (Ln = Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb; $n = 7, 8, 9$) and crystalline $[Ce(CPFX)_2(H_2O)_4]Cl\cdot(H_2O)_{3.25}(C_2H_5OH)_{0.25}$, were synthesized. The crystal is of triclinic space group $P\bar{1}$ with $a = 1.3865(2)$ nm, $b = 1.3899(3)$ nm, $c = 1.6505(2)$ nm, $\alpha = 92.73(1)°$, $\beta = 114.39(1)°$, $\gamma = 115.55(1)°$, $Z = 2$ and $R = 0.0449$. FT-IR, electronic spectroscopy and X-ray diffraction were employed to show that the lanthanide ion, which displays an eight-coordinate structure, is chelated by 3-carboxyl and 4-keto oxygen donors of CPFX and two six-membered chelate rings are formed. Test of *in vitro* antibacterial activity against *E. coli*, *P. aeruginosa* and *S. aureus* indicated that the *in vitro* antibacterial activity of the ligand can be improved by complexation with Ce(III).

Keywords Lanthanide complexes, ciprofloxacin, cerium, quinolone, crystal structure, IR, fluorescence enhancement, *in vitro* antibacterial activity

Introduction

It was found in 1962 that nalidixic acid could inhibit the growth of some Gram-negative bacteria,[1] since then, numerous quinolone compounds have been synthesized and many of them are used as antibacterials today.[2] They have antibacterial activity against Gram-negative and Gram-positive bacterial strains such as *Enterbacteriaceae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Neisseria gonorrhoea*, and *Haemophilus influence*.[3] The primary mechanism of antibacterial action is inhibition of topoisomerase II which is responsible for coiling the long DNA molecule into the confined space inside the bacterial cell.[4] Ciprofloxacin (CPFX), 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-quinolone-3-carboxylic acid, is one of the third generation of quinolone antibacterials with a wide spectrum of activity, the *in vitro* antibacterial activity is stronger than that of others of the same generation, while its solubility and bioavailability are relatively poor.[5] The structures of ciprofloxacin (a) and nalidixic acid (b) are showed in Scheme 1.

Scheme 1 Formula of two quinolone antibacterials



(a) ciprofloxacin (b) nalidixic acid

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Received December 12, 2000; revised and accepted March 7, 2001.
Project supported by the National Natural Science Foundation of China (No. 29871020), the Youth Science Foundation of Shanxi Province and the President Foundation of China Pharmaceutical University (No. C9917).

The absorption of quinolone antibacterials can be significantly reduced by magnesium and aluminum antiacids[3] or multi-vitamins containing zinc,[6] other metal complexes containing copper or iron could be involved in the interactions between quinolone antibacterials and DNA molecules.[7] *In vitro* antibacterial tests of norfloxacin complexes with Nd^{3+}/Er^{3+} indicate that the biological activities of the ligand are changed in the presence of lanthanide ions.[8] All of these facts indicate that the coordination chemistry of quinolone antibacterials with metal ions of biological and pharmaceutical significance is of considerable interest.[9]

It is well known that lanthanide compounds have potential application in pharmaceutics,[10,11] and some of them show antibacterial and anti-inflammation activities.[12] Thus the research on complexes of ciprofloxacin with lanthanide ions can not only contribute to a better understanding of the interaction mechanism of quinolone antibacterials with metal ions, but also help us to improve the bioavailability and antibacterial activity of ciprofloxacin by combining it with lanthanide ions in the form of coordination compounds. Different techniques were applied to study the interaction between quinolone antibacterials and metal ions,[13-17] but only a few crystal structures of complexes (Ag^+, Co^{2+}, Cu^{2+}) have been published.[18-22] Rieutord studied the time-resolved fluorescence of the CPFX complexes with terbium.[13] Two solid complexes of norfloxacin with Nd^{3+} and Er^{3+} were synthesized,[8] but up to now, there is no crystal structure reported on any complex between quinolone antibacterials and lanthanide ions.

Experimental

Materials and methods

Ciprofloacin·HCl was kindly provided by Taiyuan Pharmaceutical Corporation and used as received. $CeCl_3 \cdot 7H_2O$ was purchased from Yuelong Chemical Factory in Shanghai and the other lanthanide oxides ($\geqslant 99.99\%$) were obtained from Hunan Rare Earth Institute.

The C, H and N micro-analyses were carried out on a Vario EL elemental analyser, and the lanthanide ions were determined with EDTA titration. IR spectra were recorded on a Perkin-Elmer 1700 Fourier transform infrared spectrometer using KBr pellets. UV-vis spectra were recorded on a Shimadzu UV-365 recording spectrometer over the range 200—900 nm (in Tris-NaCl solution, 10^{-5} mol/L). Fluorescence measurements were made with a Hitachi Model-850 fluorescence spectrometer, and excitation and emission slits were of 5 nm.

Synthesis of complexes

$Ln(CPFX)_2Cl(H_2O)_n$ (Ln = Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb; $n = 7$—9)

Ciprofloxacin·HCl (0.6 g, 1.5 mmol) was dissolved in 15 mL of 1 mol/L HCl and pyridine was added dropwise until the drug was completely dissolved (solution **A**). An appropriate amount of lanthanide oxide (corresponding to a molar ratio of 1:2 with ligand) was dissolved in concentrated HCl and heated near dryness, then dissolved in 4 mL of H_2O (solution **B**). **B** was dropped into **A** and the mixture was stirred for a period of time (varying from 2 h to 5 days). The precipitates were filtered and washed repeatedly with ethanol, and then dried under vacuum at 50—60℃ for 24 h. Elementary analyses results were summarized in Table 1.

$[Ce(CPFX)_2(H_2O)_4]Cl \cdot (H_2O)_{3.25}(C_2H_5OH)_{0.25}$

4 mL of aqueous solution of $CeCl_3 \cdot 7H_2O$ (0.75 mmol) was added to solution **A** and stirred for 7 days, then about 20 mL of ethanol was added. This mixed solution was allowed to stand at room temperature, and yellow crystal was obtained. $C_{34.5}H_{50}CeClF_2N_6O_{13.5}$ requires: C, 42.31; H, 5.11; N, 8.59. Found: C, 42.30; H, 4.74; N, 8.70.

X-ray structure determination

A yellow crystal of dimensions $0.54 \times 0.54 \times 0.54$ mm was sealed in a glass capillary and used for X-ray diffraction data collection on a SIEMENS P4 four-cycle diffractermeuer at 290(2) K with Mo K_α radiation (λ = 0.071073 nm). Calculation was performed with the SHELXTL 5.03 program and the structure was solved by the direct method. Hydrogen atoms, except those of lattice H_2O molecules and aqueous ligands, were introduced in idealized locations. More crystal parameters and refinement results were summarized in Table 2.

Table 1 Elementary analyses results of title complexes/Found % (Calcd. %)

Compounds	C	N	H	Ln
$Yb(CPFX)_2Cl(H_2O)_9$	39.02(39.51)	8.03(8.13)	4.82(5.08)	16.39(16.74)
$Tm(CPFX)_2Cl(H_2O)_8$	40.52(40.38)	8.30(8.31)	4.61(4.99)	16.71(16.70)
$Er(CPFX)_2Cl(H_2O)_8$	40.39(40.44)	8.30(8.33)	4.73(5.00)	16.39(16.57)
$Ho(CPFX)_2Cl(H_2O)_8$	40.74(40.54)	8.40(8.35)	4.65(5.01)	15.94(16.39)
$Dy(CPFX)_2Cl(H_2O)_8$	40.34(40.64)	8.35(8.37)	4.76(5.03)	15.63(16.17)
$Tb(CPFX)_2Cl(H_2O)_8$	40.73(40.78)	8.41(8.40)	4.82(5.04)	15.14(15.87)
$Gd(CPFX)_2Cl(H_2O)_8$	40.54(40.85)	8.35(8.41)	4.79(5.05)	15.37(15.74)
$Eu(CPFX)_2Cl(H_2O)_8$	41.36(41.07)	8.57(8.45)	4.82(5.08)	14.83(15.29)
$Sm(CPFX)_2Cl(H_2O)_8$	40.22(41.13)	8.31(8.47)	4.95(5.09)	14.41(15.15)
$Nd(CPFX)_2Cl(H_2O)_7$	42.48(42.16)	8.80(8.68)	4.57(5.01)	14.94(14.53)
$Pr(CPFX)_2Cl(H_2O)_7$	43.17(42.30)	8.95(8.71)	4.67(5.02)	14.41(14.60)

Table 2 Crystal data and structure refinement summary

Empirical formula	$C_{34.5}H_{50}CeClF_2N_6O_{13.5}$
Formula weight	978.38
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	$a = 1.3865(2)$ nm $\alpha = 92.73(1)°$
	$b = 1.3899(3)$ nm $\beta = 114.39(1)°$
	$c = 1.6505(2)$ nm $\gamma = 115.55(1)°$
Volume, Z	2.5113(7) nm^3, 2
Density (calculated)	1.294 Mg/m^3
Absorption coefficient	1.025 mm^{-1}
$F(000)$	1000
Reflections collected	8941
Independent reflections	8227 ($R_{int} = 0.0098$)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	8227/2/559
Goodness-of-fit on F^2	1.071
Final R indices [$I > \sigma(I)$]	$R_1 = 0.0449$, $wR_2 = 0.1354$
R indices (all data)	$R_1 = 0.0508$, $wR_2 = 0.1391$
Largest diffraction peak and hole	1456 and −473 e/nm^3

Antibacterial activity tests

MIC (minimum inhibitory concentration) of CPFX-Ce, CPFX-Er and ciprofloxacin HCl were determined by using the broth tube dilution method with incula of ~ 6 × 10^5 cfu/mL.[23] The chosen bacterial strains include *E. Coli* and *P. Aeruginosa* which belong to G(−) strains and *S. Aureus* which is a G(+) strain. *E. coli 44148*, *P. Aeruginosa 10102* and *S. Aureus 26001* were obtained from National Institute for the Control of Pharmaceutical and Biological Products. The MIC values were determined as the lowest concentration of the antimicrobial agent that inhibited the visible growth of the test organism after 24 h incubation at 37℃. This test was performed at the Microbiological Laboratory in Shanxi Medical University.

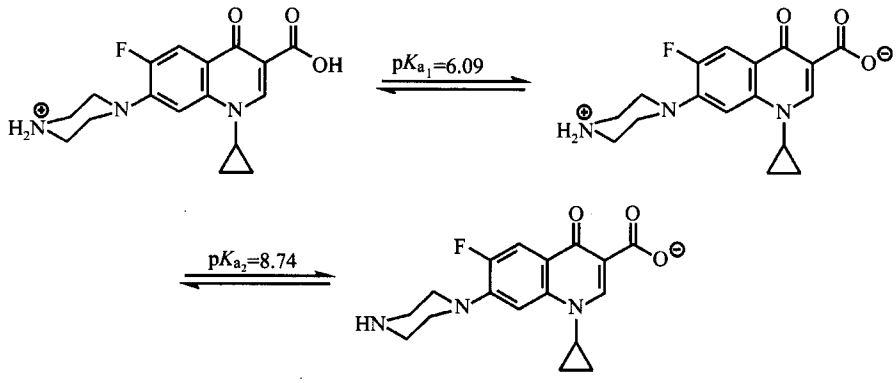
Results and discussion

Preparation

Interaction of lanthanide ions with ciprofloxacin results in the formation of complexes with the general formula $Ln(CPFX)_2Cl(H_2O)_n$. These complexes in powder form are stable in air, while the yellow crystals of $[Ce(CPFX)_2(H_2O)_4]Cl\cdot(H_2O)_{3.25}(C_2H_5OH)_{0.25}$ be-

come opaque slowly. In the case of its zwitterionic structure (see Scheme 2, $pI = 7.42$),[24] CPFX has very low solubility in water (neutral condition) or organic solvents, whereas the solubility of its complexes (esp. Ce-CPFX) appears much better than the ligand itself, both in water and methanol.

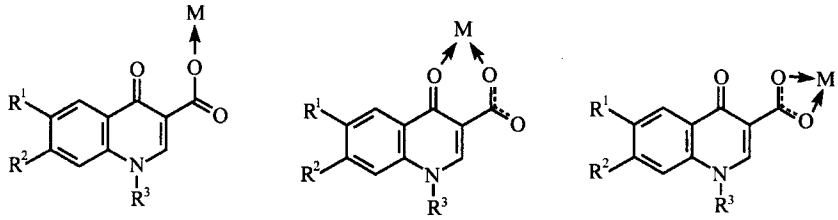
Scheme 2 Zwitterionic structures of ciprofloxacin



IR *spectrum studies*

The IR spectra of quinolone antibacterials are quite complex, and there are still controversies on the assignment to some bands in their metal complexes. All of the coordination modes proposed in previous studies are listed in Scheme 3.

Scheme 3 Possible coordination modes of quinolone metal complexes proposed in previous studies



In the IR spectrum of CPFX · HCl the carbonyl stretching mode of 3-carboxyl (ν_{COOH}) is observed as a band at 1709 cm^{-1}. The band at 1626 cm^{-1} can be ascribed to carbonyl stretch of 4-keto ($\nu_{C=O}$).

IR spectra of all title complexes appeared to have very similar characteristic bands. The band at 1709 cm^{-1} (ν_{COOH}) in the spectra of ligand disappeared in the case of the conversion from COOH to COO^-, while two new bands at 1631—1633 cm^{-1} and 1562—1576 cm^{-1} appeared in the spectra of complexes. Some authors proposed that the band at 1631—1633 cm^{-1} could be assigned to carbonyl stretch of 4-keto,[15,20] but if it is true, $\nu_{C=O}$ of 4-keto would be violet-shifted from 1626 cm^{-1} to 1633 cm^{-1}. This inference cannot explain the participation of the 4-keto group in coordination (according to the following result of crystal structure measurement), so from our point of view, the band at 1631—1633 cm^{-1} should be assigned to asymmetrical carbonyl stretch of 3-carboxyl (ν_{as,COO^-}) and $\nu_{C=O}$ of 4-keto is red-shifted to 1562—1576 cm^{-1}. The assignment of selected IR bands for CPFX·HCl and some of the title complexes is shown in Table 3.

There are three possible binding modes of 3-carboxyl to metal ions proposed in previous studies: monodentate **i**, monodentate **ii** and bidentate **iii** (see Scheme 3). Because the value of Δ (see the footnote of Table

Table 3 Selected IR bands for CPFX·HCl and its lanthanide complexes (cm^{-1})

	ν_{C-F}	$\nu_{C=C}$ (aromatic ring)	$\nu_{C=O}$	ν_{COOH}	$\nu_{as,\ COO^-}$	$\nu_{as,\ COO^-}$	Δ^*
CPFX·HCl	1273	1613, 1495, 1450	1626	1709	—	—	—
CPFX·Ce	1271	1617, 1486, 1456	1567	—	1631	1304	327
CPFX·Pr	1271	1617, 1487, 1455	1562	—	1632	1304	328
CPFX·Er	1272	1617, 1487, 1455	1570	—	1632	1307	325

* $\Delta = \nu_{as,COO^-} - \nu_{s,COO^-}$

3) is much greater than 144 cm^{-1}, the coordination mode of the 3-carboxyl group with Ln^{3+} ought to be monodentate.[25] Furthermore, considering red-shift of $\nu_{C=O}$ (4-keto) from 1626 cm^{-1} to 1562—1576 cm^{-1}, we think that 3-carboxyl and 4-keto participate in coordination via a six-membered ring with Ln^{3+} (mode **ii**).

Electronic spectrum studies

UV spectra of the title complexes have almost the same bands in the range 250—350 nm. Two distinctive bands were observed at 270 nm ($n\rightarrow\pi^*$) and 325 nm ($n\rightarrow\pi^*$). Fluorescence studies show an apparent decrease of fluorescence intensity at 425 nm as compared with the ligand, but the peak is not shifted. The aqueous ions of Tb^{3+} and Eu^{3+} emit very weak fluorescence, but the fluorescence is dramatically enhanced when they are coordinated with CPFX, and the corresponding peak positions are as follows: $Tb(CPFX)_2Cl(H_2O)_8$, 487, 545, 585, 620 nm, which can be assigned to $^5D_4\rightarrow{}^7F_n$ ($n = 6,5,4,3$) respectively; $Eu(CPFX)_2Cl(H_2O)_8$, 578, 593, 614, 643, 700 nm which can be assigned to $^5D_0\rightarrow{}^7F_n$ ($n = 0, 1, 2, 3, 4$) respectively. This is the result of intramolecular energy transfer from the ligand to the central lanthanide ions, namely LMCT. According to the dramatically large extent of fluorescence enhancement (see Fig. 1), some planar or near planar chelate ring should be formed,[26] so it can be inferred that Ln^{3+} could be coordinated with 3-carboxyl and 4-keto in the form of a six-membered chelate ring[13] (mode **ii** in Scheme 3).

Crystal structure analysis

Selected bond distances and bond angles of the complex $[Ce(CPFX)_2(H_2O)_4]Cl\cdot(H_2O)_{3.25}(C_2H_5OH)_{0.25}$ are given in Table 4, the ORTEP view of the title complex with atomic labeling is given in Fig. 2.

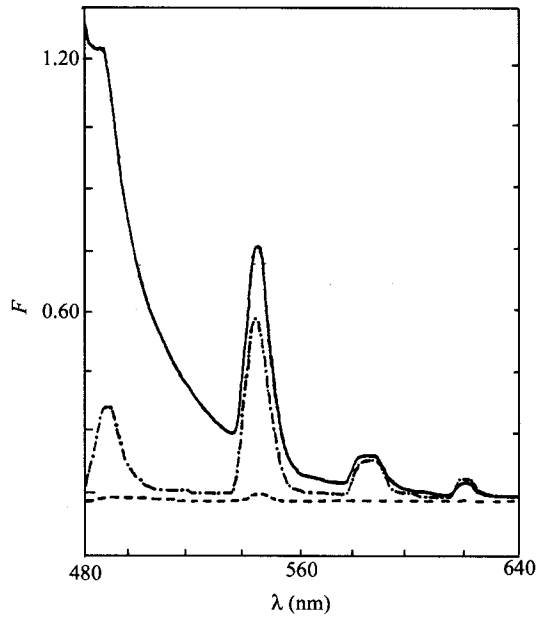


Fig. 1 Fluorescence spectra of $Tb(CPFX)_2Cl(H_2O)_8$ with excitation at 275 nm. — $Tb(CPFX)_2Cl(H_2O)_8$, 10^{-5} mol/L; – · – $TbCl_3$, 10^{-2} mol/L; ····· $TbCl_3$, 10^{-5} mol/L.

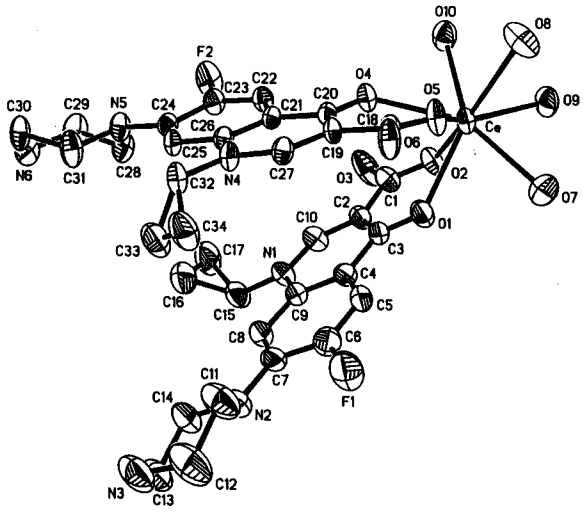


Fig. 2 ORTEP view of $[Ce(CPFX)_2(H_2O)_4]Cl\cdot(H_2O)_{3.25}(C_2H_5OH)_{0.25}$.

Table 4 Selected bond distances (nm) and bond angles (°) of $[Ce(CPFX)_2(H_2O)_4]Cl\cdot(H_2O)_{3.25}(C_2H_5OH)_{0.25}$

Ce—O(2)	0.2449(3)	Ce—O(1)	0.2457(3)
Ce—O(5)	0.2420(3)	Ce—O(4)	0.2439(3)
Ce—O(7)	0.2504(4)	Ce—O(9)	0.2511(3)
Ce—O(8)	0.2519(4)	Ce—O(10)	0.2536(3)
F(1)—C(6)	0.1332(6)	O(1)—C(3)	0.1273(6)
O(3)—C(1)	0.1247(6)	N(1)—C(10)	0.1343(6)
N(1)—C(15)	0.1462(6)	C(1)—C(2)	0.1492(7)
C(2)—C(3)	0.1420(7)	C(15)—C(17)	0.1482(8)
N(1)—C(9)	0.1386(6)	O(2)—C(1)	0.1274(6)
N(2)—C(11)	0.1469(7)	N(2)—C(7)	0.1399(6)
O(5)-Ce-O(4)	69.7(1)	O(2)-Ce-O(1)	68.8(1)
O(7)-Ce-O(9)	72.8(1)	O(8)-Ce-O(10)	77.6(1)
O(4)-Ce-O(8)	107.1(1)	O(2)-Ce-O(7)	102.2(1)
O(5)-Ce-O(9)	140.9(1)	O(1)-Ce-O(8)	140.2(1)
C(1)-O(2)-Ce	128.8(3)	C(3)-O(1)-Ce	129.9(3)
C(20)-O(4)-Ce	131.8(3)	C(18)-O(5)-Ce	137.9(3)
O(3)-C(1)-O(2)	122.1(4)	O(2)-C(1)-C(2)	119.7(4)
C(3)-C(2)-C(1)	124.1(4)	O(1)-C(3)-C(2)	124.8(4)
O(3)-C(1)-C(2)	118.2(4)	C(10)-N(1)-C(9)	119.7(4)
C(10)-N(1)-C(15)	120.0(4)	C(9)-N(1)-C(15)	120.2(4)
N(1)-C(15)-C(17)	118.8(5)	N(1)-C(15)-C(16)	118.0(5)
C(15)-C(17)-C(16)	60.1(4)	C(15)-C(16)-C(17)	59.6(4)
C(8)-C(7)-N(2)	122.2(5)	N(2)-C(7)-C(6)	121.4(5)
C(7)-N(2)-C(14)	115.3(5)	C(7)-N(2)-C(11)	118.2(4)
N(2)-C(14)-C(13)	111.9(5)	C(14)-N(2)-C(11)	111.1(5)
C(12)-N(3)-C(13)	110.3(5)	N(3)-C(12)-C(11)	108.9(6)
(1)-C(6)-C(7)	118.8(4)	F(1)-C(6)-C(5)	118.2(5)

This complex displays an eight-coordinating structure, *i.e.* four atoms coordinated with Ce^{3+} are oxygen atoms from the 3-carboxyl and 4-keto of two CPFX molecules, and the other four coordinated sites are occupied by oxygen atoms of water molecules. The 3-carboxyl and 4-keto groups chelate Ce^{3+} giving two six-membered rings, so it is easy to understand the dramatic enhancement effect of fluorescence in Eu and Tb complexes. The average bond length of four C—O bonds (C_3—O_1, C_1—O_2, C_{20}—O_4, C_{18}—O_5) adjacent to Ce—O is 0.1269 nm, while that of other C—O bond of 3-carboxyl (C_1—O_3, C_{18}—O_6), which do not participate coordination, is 0.1250 nm. The bond lengths of C_1—C_2 and C_{18}—C_{19} adjacent to the quinolone ring are 0.1492 nm and 0.1491 nm which are in the range of single C—C bond length, thus no large conjugated structure is expected between the quinolone ring and 4-carboxyl group. The cyclopropyl ring is approximately perpendicular to the plane of the quinolone (N_4-C_{32}-C_{33}-C_{34}, 108.93°; N_1-C_{15}-C_{16}-C_{17}, −107.66°). In the ORTEP view we found an interesting phenomenon that two ciprofloxacin molecules seem to be arranged at *cis* conformation while the two oxygen (keto) donors are at *trans* position. It is possibly due to the similar intermolecular interaction of two CPFX molecules, they have the tendency to be close with each other and thereby adopt a *cis* conformation. Furthermore, in order to "conceal" the two cyclopropyl rings inside them, two keto oxygen donors must be arranged in *trans* position.

The distance between the chlorine and cerium atoms is 0.4930 nm, indicating that Cl^- does not participate in coordination with Ce^{3+}, and there is the cation-anion interaction between $[Ce(CPFX)_2(H_2O)_4]^+$ and Cl^-. Because pyridine was used as the solvent in the synthesis, CPFX does not acquire the zwitterion structure and thereby just one Cl^- ion exists in the complex

molecule. In addition, some strong intermolecular hydrogen bonds have been found: O_6—H···N_6 (0.2744 nm), O_9—H ··· O_3 (0.2706 nm), O_8—H ··· O_6 (0.2802 nm), O_{10}—H···O_2 (0.2809 nm).

Biological activity studies

The MICs (minimum inhibitory concentrations, μmol/L) of two new complexes (CPFX-Ce and CPFX-Er) in comparison with the MIC of CPFX are listed in Table 5. We can find that the antibacterial activity of the complex, CPFX-Ce, is 2.5, 2.5, 1.25 fold higher than that of CPFX for *E. coli*, *P. aeruginosa* and *S. aureus* respectively, while CPFX-Er is 2.5, 1.25 fold higher and 3.0 fold lower for corresponding bacterial strains. According to these comparisons, we can recognize that: (1) The formation of the lanthanide complexes has an influence on the CPFX's antibacterial activities. How does it work? As CPFX has the zwitterionic structure (see Scheme 2), it almost can not be dissolved in water and organic solvents. However, the formation of complexes improves its solubility in both water and methanol, so that complexation may improve the hydrophilic and lipophilic properties of CPFX and thereby give better bioavailability and antibacterial activity. Liposome has been used as biomembrane model to study the absorption of quinolone antibacterial in the presence of metal ions. It has been found that Cu^{2+}, Ni^{2+}, Zn^{2+}, Mn^{2+} and Fe^{3+} can increase the absorption of norfloxacin.[27] Further biological and pharmacological experiments are needed to probe and clarify the mechanism. (2) *In vitro* antibacterial activity of the complex (CPFX-Ce) is better than its ligand, indicating that it has potential application in pharmaceutics. As we know, cerium nitrate was adopted by British Pharmacopoeia as the drug against skin burn in 1982. It has also been reported that some cerium compounds can function as antibacterial and anti-inflammation agents.[11] Therefore, studies on coordination of cerium ion with drug molecules may be conducive to our search for new chemotherapeutic drugs. The further pharmacological studies on anti-inflammation model are under way.

Table 5 MIC values of two new complexes compared with those of CPFX (μmol/L)

	E. coli	*P. aeruginosa*	*S. aureus.*
Ciprofloxacin·HCl	1.01	1.01	1.01
CPFX-Ce	0.21	0.21	0.40
CPFX-Er	0.20	0.39	1.56

Acknowledgements

Special acknowledgements are due to Dr. Tian, Yan-Ni for her generous help in performing X-ray structure determination and manuscript preparation. We are grateful to Prof. LIU, Dian-Sheng (Chemistry Department, Shanxi University), Prof. ZHANG, Ze-Ying (Chemistry Department, Peking University) for their help in crystal structure analysis and Dr. WANG, Gui-Qing (Microbiological Laboratory, Shanxi Medical University) for assistance in antibacterial tests.

References

1 Albrecht, R. *Prog. Res.* **1977**, *9*, 21.
2 Chu, D. T. V.; Fernandes, P. B. *Adv. Drug Res.* **1991**, *21*, 42.
3 Wolfson, J. S.; Hooper, D. C. *Clin. Microbiol. Rev.* **1989**, *2*, 378.
4 Hooper, D. C.; Wolfson, J. S.; Ng, E. Y.; Swartz, M. N. *Am. J. Med.* (Suppl. 4A) **1987**, *82*, 12.
5 Dai, Z. Y. *Practical Antibacterial Pharmacology*, Shanghai Science and Technology Press, Shanghai, **1992**, p.271.
6 Polk, R. E.; Healy, D. P.; Sahai, J.; Drwal, L.; Racht, E. *Antimicrob. Agents Chemother.* **1989**, *33*, 1841.
7 Shen, L. L.; Pernet, A. G. *Proc. Natl. Acad. Sci. U. S. A.* **1985**, *82*, 307.
8 Yang, P.; Zhang, Z. G.; Du, L.Y. *Wuji Huaxue*, **1992**, *8*, 455 (in Chinese).
9 Castillo-Blum, S. E.; Barba-Behrens, N. *Coord. Chem. Rev.* **2000**, *196*, 3.
10 Evans, C. H. *Biochemistry of the Lanthanides*, Plenum Press, New York, **1990**, p.391.
11 Ni, J. Z. *Bioinorganic Chemistry of Rare Earth Elements*, Science Press, Beijing, **1995**, p.38.
12 Chen, Z. N.; Deng, R. W.; Wu, J. G. *J. Inorg. Biochem.* **1992**, *47*, 81.
13 Rieutord, A.; Vazquez, L.; Soursac, M.; Prognon, P.; Blais, J.; Bourget, P.; Mahuzier, G. *Anal. Chim. Acta* **1994**, *290*, 215.
14 Turel, I.; Bukovec, N. *Polyhydron* **1996**, *15*, 269.
15 Gao, F.; Yang, P.; Xie, J.; Wang, H. F. *J. Inorg. Biochem.* **1995**, *60*, 61.
16 Sanchez, B. M.; Cabarga, M. M.; Navarro, A. S.;

Hurle, A. D. *Int. J. Pharm.* **1994**, *106*, 229.
17 Alkaysi, H. N.; Abolel-Hay, M. H.; Salem, M. S.; Gharaibeh, A. M.; Na'was, T. E. *Int. J. Pharm.* **1992**, *87*, 73.
18 Baenzinger, N.C.; Fox, C.L.; Modak, S.L. *Acta Crystallogr.* **1986**, *C42*, 1505.
19 Chulvi, C.; Munoz, M. C.; Perello, L.; Ortiz, R.; Arriortua, M. I.; Via, J.; Urtiaga, K.; Amigo, J. M.; Ochando, L. E. *J. Inorg. Biochem.* **1991**, *42*, 133.
20 Turel, I.; Leban, I.; Bukovec, N. *J. Inorg. Biochem.* **1994**, *56*, 273.
21 Wallis, S. C.; Gahan, L. R.; Charles, B. G.; Hambley, T. W.; Duckworth, P. A. *J. Inorg. Biochem.* **1996**, *62*, 1.
22 Turel, I.; Golic, L.; Ramirez, O.; Leonel, R. *Acta Chim. Slov.* **1999**, *46*, 203.
23 Cheng, Y. B. *Experiments of Microbiology*, Chinese Medical and Pharmaceutical Science and Technology Press, Beijing, **1994**, p.142.
24 Ross, D.L.; Riley, C.M. *Int. J. Pharm.* **1990**, *63*, 242.
25 Nakamoto, K. *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, 3rd ed., Chemical Industry Press, Beijing, **1986**, p.237.
26 Diamandis, E. P. *Analyst* **1992**, *117*, 1879.
27 Luo, Y. J.; Shen, H. X.; Liu, H. T.; Kong, D. M. *Chem. J. Chin. Univ.* **1998**, *19*, 1730(in Chinese).

(E200012269 JIANG, X.H.; LING, J.)