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A Physico-chemical Study of the Interaction of Cobalt(II) Ion with Ciprofloxacin

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Reaction between the quinolone antibacterial agent ciprofloxacin (abbreviation cfH) and Co^{II} in aqueous medium was studied. The ability of ciprofloxacin to form metal complexes is highly dependent on the pH value of the solution. UV spectroscopy and solubility of ciprofloxacin · HCl were used to determine the optimal conditions for complex isolation in the pH region between 5 and 10, where the solubility of quinolones is very low. The isolated complex $[\text{Co}(\text{cf})_2] \cdot 3\text{H}_2\text{O}$ was characterized by elemental analysis, FAB-MS, TG analysis, IR spectroscopy and magnetic measurements. Cobalt K-edge EXAFS was used for the identification of the Co site in the complex.

Key words: quinolone, ciprofloxacin, metal-ion complexation, cobalt.

INTRODUCTION

Derivatives of compounds composed of 3-carboxy-4-oxo-1,4-dihydroquinoline (*i.e.* 4-quinolones) are active against a wide range of gram-negative organisms and gram-positive cocci.¹ The first member of the quinolone carboxylic

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acid family of antimicrobials introduced into clinical practice, nalidixic acid, was used in the treatment of urinary tract infections.² A major advance in activity occurred with the introduction of fluorine atom on position 6 into the quinoline ring to enhance the spectrum and the potency of activity, and with addition of piperazinyl group on position 7 to enhance permeability and potency.³ Ciprofloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid) and norfloxacin (1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid) are currently fluoroquinolones with the widest clinical use. They received Food and Drug Administration approval in 1986 and 1987, respectively. A reduced absorption of ciprofloxacin, when given concomitantly with antacids containing magnesium-aluminium, was described as early as in 1985.⁴ Since this report, numerous investigations have extended this observation to interactions of quinolones with other metal ions.

The synthesis and characterization of new metal complexes with quinolone antibacterial agents are of great importance for understanding the drug-metal ion interaction and for their potential pharmacological use. Low solubility of quinolones and their complexes in pH region 5 to 10 represents a great difficulty in preparing single crystals of quinolone metal complexes. Only a few crystal structures where quinolone is coordinated to the metal ion are known.⁵⁻⁹ On the other side, numerous crystal structures of mixed metal complexes with coordinated quinolones and N-, S- or other O-donors have been reported.¹⁰⁻¹⁶ Similarly, ionic metal-quinolone compounds can be easily prepared.¹⁷⁻²¹

Our aim was to isolate and characterize the Co^{II} complex with ciprofloxacin and to determine the optimum conditions for its isolation. In a few preliminary analytical investigations it was shown that quinolone is coordinated to the metal in the pH range above 7.^{17, 22-23} We were careful to avoid quinolone supersaturation in order to prevent its co-precipitation with the complex. We determined the molar concentrations of saturated quinolone solutions in the low solubility pH region of 5 to 10 using UV spectroscopy. The complex $[\text{Co}(\text{cf})_2] \cdot 3\text{H}_2\text{O}$ was isolated in its pure form only at pH = 8. Elemental analysis, FAB-MS, TG analysis, IR spectroscopy, EXAFS and magnetic measurements were used for its characterization.

EXPERIMENTAL

Materials

All reagents were received from commercial sources. The solutions were prepared with twice-distilled water.

Instrumentation

Spectrometric measurements were performed on a Perkin-Elmer UV-Vis-NIR Lambda 19 instrument, equipped with 10-mm quartz cells.

The pH's of the solutions were determined using a pH 540 GLP WTW (Wissenschaftlich-technische Werkstätten) pH-meter equipped with a WTW Sen Tix pH electrode.

The elemental analysis was carried out on a Perkin-Elmer 2400 CHN microanalyzer.

Infrared spectra (IR) were recorded on a Perkin-Elmer 1720 IR Fourier Transform Spectrophotometer in poly-(chlorotrifluoroethylene) oil mulls between CsI windows, resolution 2 cm^{-1} , 10 scans.

Thermogravimetric (TG) data was recorded on a Mettler TA 3000 system with platinum crucibles at a heating rate of 5 K min^{-1} and dry airflow rate of 20 mL min^{-1} . The mass of the sample was 13.40 mg. Differential thermal analysis (DTA) data were recorded on a Perkin-Elmer DTA 7 instrument in an alumina crucible. The empty alumina crucible was used as reference. The heating rate was 5 K min^{-1} and the sample mass 2.53 mg.

Mass spectrometry was performed on a VG-Analytical AutospecEQ instrument. Ionization was accelerated with Cs^+ ions with energies of 20–30 keV (Fast Atom Bombardment, FAB). *m*-nitrobenzylalcohol (NBA) was used as a matrix.

Powder diffraction analyses were performed on a Guinier Camera 620 with a Guinier Monochromator 615 using Cu-K α radiation. Powder Diffraction File PDF-2 was used for data matching.²⁴

EXAFS (Extended X-ray Absorption Fine Structure) spectra of $[\text{Co}(\text{cf})_2] \cdot 3\text{H}_2\text{O}$ at Co K-edge were measured in transmission mode at the HASYLAB E4 beamline of DESY, Hamburg. The beamline provides a focused beam from an Au-coated mirror and a Si(111) double-crystal monochromator with 1.5 eV resolution at the Co K-edge. Harmonics were effectively eliminated by a plane Au-coated mirror and by slight detuning of the monochromator crystals using the beam stabilization feedback control. The sample in the form of fine powder was prepared on adhesive tape. The standard stepping progression within 1000 eV region of the Co K-edge was adopted. A reference spectrum was measured on empty tapes without the sample.

Room temperature magnetic susceptibility measurements of powdered samples were performed with a Scherwood Scientific MBS-1 balance using $\text{Hg}[\text{Co}(\text{NCS})_4]$ as calibrant. Diamagnetic corrections were applied using Pascal's constants and the effective magnetic moments were calculated from the expression: $\mu_{\text{eff}} = 2.828 (\chi_{\text{M}}T)^{1/2}$.

Spectrophotometric Measurements

Aqueous solutions of ciprofloxacin \cdot HCl ($5.0 \times 10^{-5}\text{ mol L}^{-1}$) were prepared for all integer values of pH from 2 to 11. Only 0.10 mol L^{-1} NaOH, 0.01 mol L^{-1} NaOH, 0.10 mol L^{-1} HCl or 0.01 mol L^{-1} HCl were used for the pH adjustment to avoid interactions with buffer solutions. The UV absorption spectra of the solutions were recorded in the range from 220 to 400 nm.

The solubility of ciprofloxacin \cdot HCl was studied in the pH region 5–10 at pH = 5.0, 6.0, 7.0, 8.0, 9.0 and 10.0 in triplicate measurements. Excess drug was added to twice-distilled water. Solutions were stirred (400 turns/min) for seven days at ambi-

ent temperature ($22\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$). The necessary duration was determined in a preliminary experiment. A supersaturation of the ciprofloxacin \cdot HCl solutions was observed. The drug readily dissolved, but precipitation was observed after 24 h. The precipitated compound was ciprofloxacin as proven by powder diffraction analysis. The pH's of the solutions were adjusted with NaOH and HCl solutions. The pH was measured every 24 hours and adjusted if necessary to ± 0.05 pH. After seven days, the samples were filtered. The concentration of the saturated solutions was determined with UV spectroscopy. In advance, the validity of Beer's law was checked in the concentration range of 5.0×10^{-4} mol L $^{-1}$ to 1.0×10^{-5} mol at each pH. After appropriate dilution into the range, the UV spectrum of each sample was recorded in the wavelength interval from 220 to 400 nm (Figure 1). The concentration of the solution was determined by comparison with the calibration UV spectrum with the same position of absorption maxima.

Preparation of the Compound

The ability of ciprofloxacin to form metal complexes is very sensitive to the pH of the solution. S. C. Wallis *et al.* reported the specification plots of the potentiometric titration of Cu $^{\text{II}}$ /ciprofloxacin solution.¹⁵ The metal ciprofloxacin species (Cu(cf) $_2$) represents the main species in the solution at pH > 8. The low solubility of ciprofloxacin in pH region between 5 and 10 is the main obstacle to the synthesis of metal complexes, leading to a very small yield. Our experiments showed that at higher pH's, where the solubility of ciprofloxacin is considerably higher, the co-precipitation of the metal hydroxide baffles the synthesis of a pure metal complex. We performed the synthesis of the complex at ciprofloxacin / metal mole ratios 1 : 1, 2 : 1 and 3 : 1. Experiments showed that the complex with ciprofloxacin / metal ratio 2 : 1 precipitated in all the three cases. The synthesis of the compound [Co(cf) $_2$] \cdot 3H $_2$ O in the pure form is possible only when it is isolated from saturated solution of ciprofloxacin at pH = 8.

The following method was used for the synthesis. The saturated solution of ciprofloxacin \cdot HCl at pH = 8 was prepared. The pH was adjusted with 0.10 M NaOH. CoCl $_2$ \cdot 6H $_2$ O was added in a mole ratio cfH / Co $^{\text{II}}$ = 2 : 1. The solution was stirred and a pale rose precipitate appeared after one day. The solution was filtered, washed with ethanol and dried at 60 $^{\circ}\text{C}$ for 2 hours. The product was insoluble in water and organic solvents. It decomposed in diluted solutions of all strong acids. All attempts to prepare single crystals failed.

Anal. Calcd. for C $_{34}$ H $_{40}$ N $_6$ F $_2$ O $_9$ Co (M_r = 773.65): C 52.78, H 5.22, N 10.86%; found: C 52.99, H 4.98, N 10.68%.

RESULTS AND DISCUSSION

UV Spectroscopy and Solubility Studies

Figure 1 shows the UV absorption spectra of ciprofloxacin \cdot HCl solution in the wavelength interval from 220 nm to 400 nm at different pH values. Three main maxima are observed in all spectra. The position and height of the maxima are very sensitive to the pH of the solution. At pH = 2, the first maximum appears at 277 nm, the second at 316 nm, and the third at 328

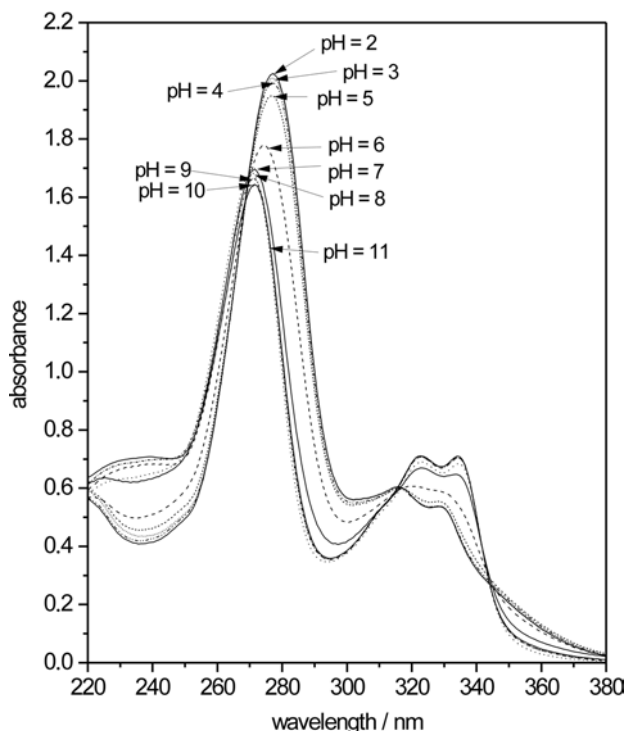


Figure 1. UV spectra of ciprofloxacin · HCl solutions at different pH values.

nm. With increasing pH, the first maximum shifts to a lower value while the second and third maxima shift to higher values. These changes can be attributed to the extent of ionisation of the carboxylic group as a consequence of the removal of a proton.²⁵ At pH = 11, the three maxima appear at 272 nm, 323 nm, and 334 nm, respectively. In this way, we were able to monitor the pH of the diluted solutions via the position of the absorption maxima.

The absorbance of the solution in the wavelength region of the first maximum at about 275 nm was used to determine the concentration of the saturated solutions of quinolone. With increasing pH, the height of the first maximum decreases, while the other two maxima increase. The molar absorptivity of the ciprofloxacin solutions at the first absorption maximum at pH = 2 (the position of the maximum 277 nm) is $40\,500\text{ L mol}^{-1}\text{ cm}^{-1}$, while at pH = 11 (the position of the maximum 272 nm) it is $32\,880\text{ L mol}^{-1}\text{ cm}^{-1}$. To avoid systematic errors, the concentration of each sample was not determined spectrometrically by the standard procedure at a single wavelength, but instead the absorbance of the solution was systematically taken at the position of the first maximum in the spectrum.²⁶

The solubility of ciprofloxacin · HCl in the pH range between 5 and 10 is given in Table I. The solubility has the lowest value at pH = 7. Ross and Riley reported the solubility of ciprofloxacin · HCl at pH = 5, 7 and 9 at 25 °C and 37 °C.²⁷ Their values are slightly higher, but comparable with our results. The differences probably arise from the higher temperature and a shorter preparation time (48 hours) of their saturated solutions.

TABLE I
Solubility (s) of ciprofloxacin · HCl at different pH values^a

pH	10 ⁴ s / mol L ⁻¹	
	Mean ^b	SD ^c
5	98.8	13.4
6	3.31	0.295
7	1.98	0.140
8	2.04	0.109
9	5.46	0.412
10	27.3	1.73

^aAt 22 °C. ^bThe sample mean. ^cStandard deviation of the results.

Thermal Analysis

The TG and DTA curves of the complex are presented in Figure 2. The dehydration process of the compound takes place in a single step. The DTA curve indicates an endothermic process that ends at 135 °C. The observed mass change (7.14%) is in good agreement with the calculated value of 6.97%, corresponding to the loss of three water molecules per molecule of the substance. The single step of dehydration indicates that only lattice water is included in the structure of the compound. Pyrolysis starts at 260 °C and ends at 460 °C and forms two sharp peaks in the DTA curve, indicating an exothermic process. Co₃O₄ is determined as a residue of the thermal decomposition.²⁴ The 7.16% content of cobalt in the original sample is in good agreement with the calculated value (7.62%).

IR Spectroscopy

Only the most informative region in the IR spectra of [Co(cf)₂] · 3H₂O and cfH · HCl · H₂O (1800–1300 cm⁻¹) is selected and assigned in Figure 3. In contrast to the spectrum of cfH · HCl · H₂O (curve a), the [Co(cf)₂] · 3H₂O spectrum (curve b) shows no absorption band at 1706 cm⁻¹, characteristic of the ν(C=O)

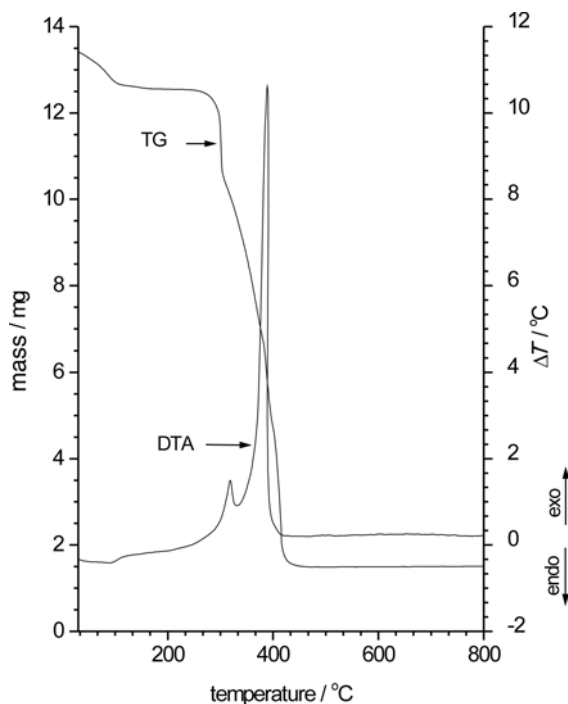


Figure 2. TG and DTA curves of $[\text{Co}(\text{cf})_2] \cdot 3\text{H}_2\text{O}$.

vibration of the carboxylic group. This is characteristic of ionic carboxylates. In addition, ionic carboxylates have two absorption bands in the ranges $1650\text{--}1510\text{ cm}^{-1}$ and $1400\text{--}1280\text{ cm}^{-1}$, which could be assigned to $\nu(\text{O}\text{--}\text{C}\text{--}\text{O})$ asymmetric and symmetric stretching vibrations, respectively.²⁸ Comparison of $\text{cfH} \cdot \text{HCl} \cdot \text{H}_2\text{O}$ and $[\text{Co}(\text{cf})_2] \cdot 3\text{H}_2\text{O}$ spectra shows that in the case of $[\text{Co}(\text{cf})_2] \cdot 3\text{H}_2\text{O}$ complex, three new absorption bands emerge at 1582 , 1559 and 1534 cm^{-1} and additional weak absorption bands appear in the range of $1400\text{--}1280\text{ cm}^{-1}$. In the spectrum of $\text{cfH} \cdot \text{HCl} \cdot \text{H}_2\text{O}$, the absorption bands spread around 1490 cm^{-1} , corresponding to the stretching vibrations of $\text{C}\text{--}\text{C}$ and $\text{C}\text{--}\text{N}$ bonds in quinolone ring; in the $[\text{Co}(\text{cf})_2] \cdot 3\text{H}_2\text{O}$ spectrum, they are shifted to around 1480 cm^{-1} . A similar IR spectrum was found for $[\text{Cu}(\text{cf})_2]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ where copper ion is coordinated by four oxygens from two quinolone molecules (one oxygen from pyridone and one from the carboxylic group of each molecule).⁷

Mass Spectrometry

In the mass spectra of the compound a strong mass peak appears at m/z 720, corresponding to $[\text{Co}(\text{cf})(\text{cfH}_2)]^+$ ion, while the mass peak for molecular

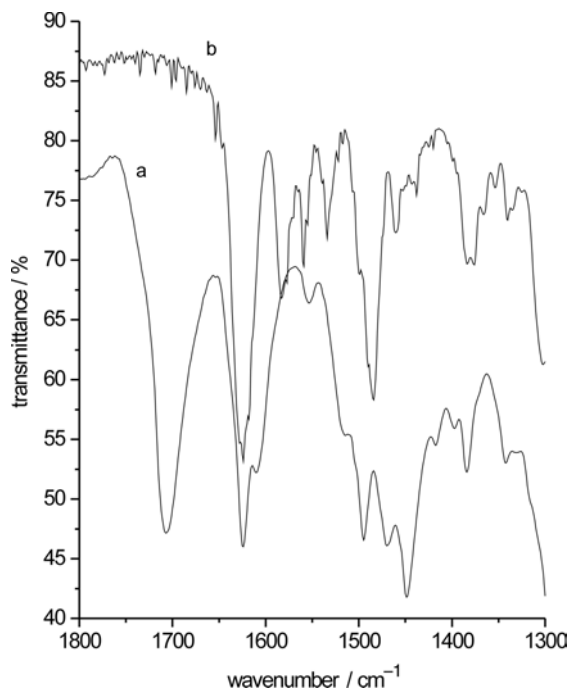


Figure 3. IR spectra of $\text{cfH} \cdot \text{HCl} \cdot \text{H}_2\text{O}$ (a) and $[\text{Co}(\text{cf})_2] \cdot 3\text{H}_2\text{O}$ (b).

ion is not observed. There are also two strong mass peaks at m/z 332 and m/z 663, corresponding to $[\text{cfH}_2]^+$ and $[(\text{cfH})(\text{cfH}_2)]^+$ ions. In a previous study we showed that, in the FAB mass spectra of ionic compounds, there were no mass peaks of $[\text{M}(\text{cf})(\text{cfH}_2)]^+$ ions, but only strong mass peaks of $[\text{cfH}_2]^+$ and $[(\text{cfH})(\text{cfH}_2)]^+$ ions.²³ However, a mass peak of $[\text{M}(\text{cf})(\text{cfH}_2)]^+$ ion was observed in the mass spectra of coordination compounds.²³

EXAFS

Information on the local coordination of Co in the compound is obtained from the Co K-edge EXAFS spectrum. EXAFS analysis is performed with the University of Washington programs using FEFF6 code for *ab initio* calculation of scattering paths.^{29–30} Contribution of three distinct shells of Co neighbours is found in the k^2 weighted Fourier transform of the EXAFS spectrum (Figure 4). A very good fit of the first shell in the R range of 1.4–2.0 Å is found with 4 oxygen atoms located at a distance of 2.06 (± 0.01) Å from Co atom, with a Debye-Waller factor of 0.006 (± 0.001) Å².

Two more distant peaks in the spectrum can be ascribed to more distant shells of Co neighbours, *i.e.* carbon and oxygen atoms of the two ciprofloxacin

molecules surrounding the Co ion. However, due to a high correlation of the fit parameters, a precise distribution of Co neighbours in the R range beyond 3.0 Å cannot be determined.

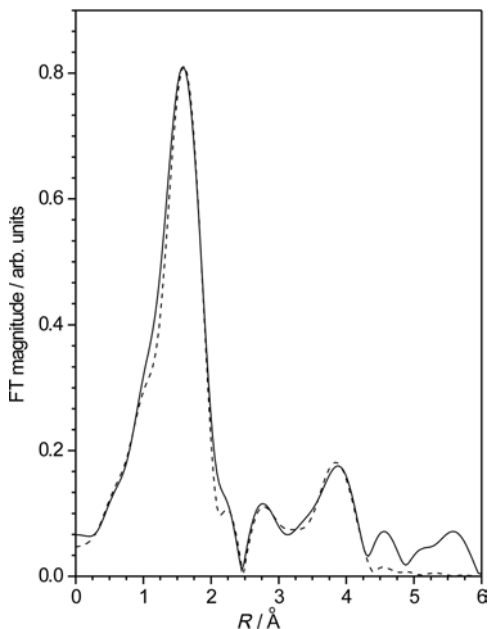


Figure 4. The k^2 weighted Fourier transform of the Co K-edge EXAFS spectrum of the $[\text{Co}(\text{cf})_2] \cdot 3\text{H}_2\text{O}$ compound calculated in the k range of 4–11 Å⁻¹; solid line – experiment, dotted line – fit.

Magnetic Measurements

From the measurement of the magnetic susceptibility of Co in the compound, additional information about the local coordination of Co is obtained. Magnetic moment of 5.19 μ_{B} indicates three unpaired electrons per Co atom. In case of a fourfold coordination of cobalt, this result indicates the tetrahedral symmetry of the ligands.

CONCLUSION

The synthesis of the compound $[\text{Co}(\text{cf})_2] \cdot 3\text{H}_2\text{O}$ in the pure form is possible only when it is isolated from saturated solution of ciprofloxacin at pH = 8. Mass spectrometry of the compound indicates bonding of Co^{II} ion to quinolone, forming $[\text{Co}(\text{cf})_2]$ molecules. Co K-edge EXAFS and magnetic suscepti-

bility measurements show that the cobalt ion in the compound is tetrahedrally coordinated by four oxygens. IR spectrum of the compound is similar to the spectrum of $[\text{Cu}(\text{cfH})_2]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$, where the copper ion is coordinated to the two pyridone and two carboxylic oxygen atoms of two quinolone molecules.⁷ Therefore we propose the same bonding of quinolone molecules to cobalt ion in our compound. The proposed structure of the $[\text{Co}(\text{cf})_2]$ molecule is illustrated in Figure 5. Thermal analysis indicates that water molecules are included as lattice water in the crystal structure of $[\text{Co}(\text{cf})_2] \cdot 3\text{H}_2\text{O}$.

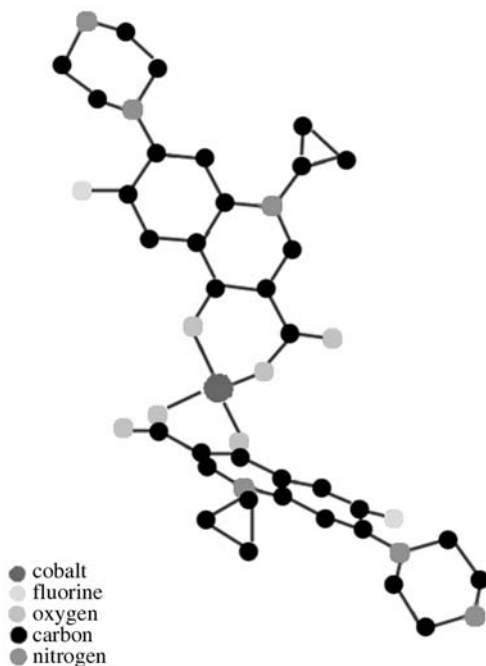


Figure 5. The proposed structure of the $[\text{Co}(\text{cf})_2]$ molecule.

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SAŽETAK**Fizikalno-kemijsko proučavanje interakcije iona kobalta(II) s ciprofloksacinom**

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Proučavana je reakcija kinolonskog antibakterijskog agensa ciprofloksacina i iona Co^{II} u vodenom mediju. Sposobnost ciprofloksacina za tvorbu metalnih kompleksa, vrlo je ovisna o pH-vrijednosti otopine. Primjenjena je UV spektroskopija i podatci o topljivosti ciprofloksacin \cdot HCl da bi se odredili optimalni uvjeti za izolaciju kompleksa u području $5 < \text{pH} < 10$, gdje je topljivost kinolona vrlo malena. Izolirani kompleks $[\text{Co}(\text{cf})_2] \cdot 3\text{H}_2\text{O}$ okarakteriziran je elementnom analizom, FAB-MS, TG analizom, IR spektroskopijom i magnetskim mjerenjima. Da bi se odredio položaj Co u kompleksu primijenjena je tehnika »K-edge EXAFS« s kobaltom.