

**CRYSTAL STRUCTURE AND CHARACTERIZATION OF A NEW
COPPER(II)-CIPROFLOXACIN (cf) COMPLEX [Cu(cf)(H₂O)₃]SO₄·2H₂O[#]**

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Abstract

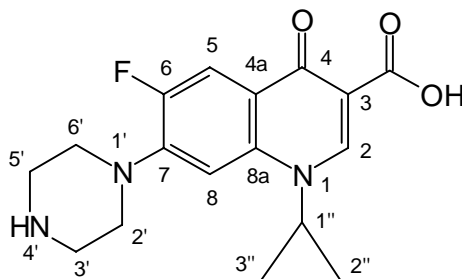
A new copper complex of quinolone ciprofloxacin (cf) with the formula [Cu(cf)(H₂O)₃]SO₄·2H₂O was isolated and its crystal structure was determined by X-ray crystallography. There is a slightly distorted square pyramidal coordination around central copper ion in the structure. Quinolone molecule is bonded to the metal through carbonyl O(3) atom (Cu-O(3) = 1.939(1) X) and carboxylic O(1) atom (Cu-O(1) = 1.915(2) X). Two water molecules are coordinated to copper in the basal plane with distances Cu-O(8) = 1.972(2) X and Cu-O(9) = 1.989(2) X. The apical water molecule is coordinated at a longer distance (Cu-O(10) = 2.174(2)X). This structural pattern is considerably different from the bonding in copper-quinolone complexes reported in the literature so far.

Introduction

Quinolones are a group of synthetic antibacterial agents active against various microorganisms [1]. They have a complex forming ability with several metal cations and

[#]Dedicated to the memory of Prof. Dr. Jože Šiftar

they bond in most cases through carboxyl group at position 3 and ring carbonyl group at position 4. Ciprofloxacin (cf = 1-cyclopropyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid) is a typical member of this family (see Scheme).



The crystal structures of the metal ion-quinolone complexes reported in the literature include several metal ions; copper [2-4], cobalt [5], silver [6], zinc [7] and cadmium [8, 9]. Simple copper complexes of various quinolones are the most frequent [2-4], but the number of copper complexes is higher if we also consider mixed ligand complexes containing additional ligands [10-13]. In all simple copper complexes reported, the copper(II) ion is bonded to two quinolone molecules bidentately through one of the carboxylic oxygens and ring carbonyl oxygen. In contrast it was found that metal ions are not bonded to the quinolone in the highly acidic medium. At such conditions ionic compounds containing protonated quinolones were isolated [14-17].

In our previous studies we have studied the copper(II)-ciprofloxacin system by different physico-chemical methods. The crystal structure of $[\text{Cu}(\text{cf})_2]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ was determined [2]. This system was also studied in the solution. The stability constants were calculated by potentiometric method [18] and the NMR relaxation rates were also determined [19]. From both later techniques the indications were obtained that apart from prevailing $\text{Cu}:\text{cf} = 1:2$ complex also some species with different bonding mode or even different stoichiometric ratio of metal-quinolone could be present in the solution.

The aim of this study was to isolate any new compounds from copper-cf system and to characterize the new products by different physico-chemical techniques.

Experimental

Synthesis

Copper(II) sulphate pentahydrate (0.079 g) was dissolved in 20 mL of distilled water. The solution was stirred and ciprofloxacin (0.100 g) was added. The colour of the solution slightly changed from light blue to green. The green crystals were grown by evaporation on air. Found: C, 35.21; H, 4.70; N, 7.14. $C_{17}H_{28}N_3O_{12}CuFS$ requires C, 35.14; H, 4.82; N, 7.24%.

Analyses and physical measurements

The analyses of carbon, hydrogen and nitrogen were carried out on a Perkin-Elmer 204C microanalyzer.

Infrared spectra were recorded in the solid state on Nujol mulls between CsI windows on a Perkin-Elmer 1720X FT-IR spectrometer. Conditions: range 4000-220 cm^{-1} , resolution 2 cm^{-1} , number of scans 10.

Crystal data, data collection summary and refinement parameters of the title compound are given in Table 1. An automated Enraf-Nonius CAD-4 diffractometer with MoK_{α} was used for the determination of the unit cell and data collection. The following programs were used: for data collection CAD-4 Software [20], cell refinement: X-ray PARAM (local program). Xtal 3.2 [21] was used for data reduction, solving and refining the structure. ORTEP program was used to prepare molecular illustrations [22]. All hydrogen atoms but two were found in the difference map and were not refined.

During the refinement of the structure a difference map showed some additional maxima around sulfur with a reasonable S-O distance. These peaks correspond to another position of sulfate group O4', O5', O6' and O7' with the same position of a sulfur atom (Figure 1). The refinement was continued with constrained population parameters of O4, O5, O6, O7 and O4', O5', O6', O7' to sum 1.0. The average angle between these two orientations is 48° .

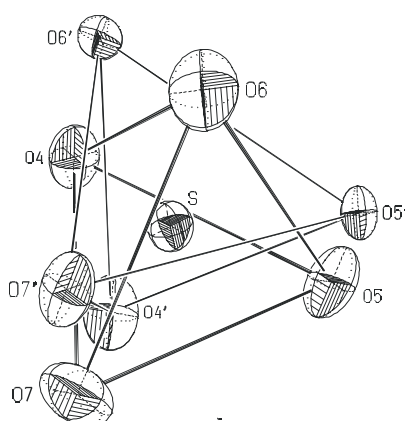


Figure 1: Disordered position of a sulfate ion.

Table 1. Crystal Data and Structure Refinement for $[\text{Cu}(\text{cf})(\text{H}_2\text{O})_3]\text{SO}_4 \cdot 2\text{H}_2\text{O}$.

Empirical formula	$\text{C}_{17}\text{H}_{28}\text{CuFN}_3\text{O}_{12}\text{S}$
Formula weight	580.5
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	$\text{P}2_1/\text{c}$
Unit cell dimensions	$a = 14.816(1)$ Å $b = 14.965(2)$ Å $\beta = 93.02(1)^\circ$ $c = 10.517(1)$ Å
Volume	$2328.6(4)$ Å ³
Z	4
Density (calculated)	1.657 g/cm ³
Absorption coefficient	1.097 mm ⁻¹
$F(000)$	1204
Crystal size	irregular form (0.30 x 0.38 x 0.38 mm)
Theta range for data collection	$1\text{--}28^\circ$
Index ranges	$-19 \leq h \leq 19$, $0 \leq k \leq 19$, $-13 \leq l \leq 13$
Reflections collected	11667
Independent reflections	5591 [R(int) = 0.036]
Refinement method	Full-matrix least-squares on F
Data / restraints / parameters	3654 / 7 / 353
Goodness-of-fit on F	0.936
Final R indices [I > 2.5 (I)]	R1 = 0.032, wR2 = 0.031
R indices (all data)	R1 = 0.069, wR2 = 0.058
Largest diff. peak and hole	0.6 and -1.3 e.Å ⁻³

Results and Discussion

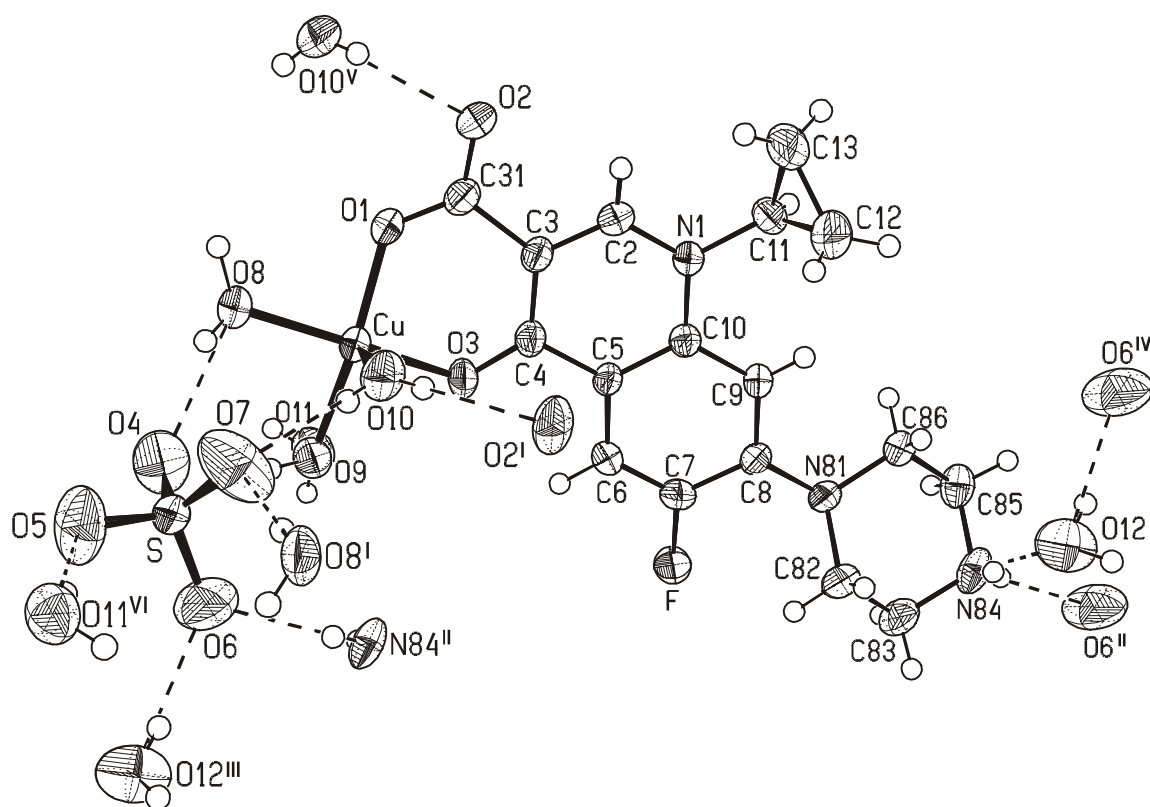
Description of the Crystal Structure

There is a distorted square pyramidal coordination around copper ion in the crystal structure of $[\text{Cu}(\text{cf})(\text{H}_2\text{O})_3]\text{SO}_4 \cdot 2\text{H}_2\text{O}$. A view of the complex with atomic labelling is given in Figure 2 and Figure 3 shows the stereoscopic view of the title compound unit cell. Final relevant atomic positions are given in Table 2.

Table 2. Fractional nonhydrogen atomic coordinates, equivalent isotropic displacement (\AA^2) and population parameters.

	$U_{\text{eq}} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*a_i \cdot a_j$				
	x	y	z	U_{eq}	p
Cu	0.80393(2)	0.60057(2)	0.47467(2)	0.02677(7)	
S	1.02749(4)	0.68421(4)	0.23672(5)	0.0305(2)	
F	0.47828(9)	0.3958(1)	0.1047(1)	0.0462(5)	
O(1)	0.7510(1)	0.6554(1)	0.6174(1)	0.0350(5)	
O(2)	0.6469(1)	0.7365(1)	0.7048(2)	0.0450(6)	
O(3)	0.6904(1)	0.5480(1)	0.4124(2)	0.0329(5)	
O(4)	1.0263(2)	0.6242(2)	0.3448(3)	0.0511(9)	0.794(6)
O(5)	1.1158(2)	0.7288(3)	0.2332(4)	0.056(1)	0.794(6)
O(6)	1.0082(2)	0.6377(2)	0.1184(3)	0.066(1)	0.794(6)
O(7)	0.9599(3)	0.7562(2)	0.2522(4)	0.064(1)	0.794(6)
O(4')	1.0346(8)	0.712(1)	0.3668(9)	0.064(4)	0.206(6)
O(5')	1.1077(7)	0.7010(7)	0.168(1)	0.042(3)	0.206(6)
O(6')	1.0185(7)	0.5788(6)	0.248(1)	0.059(4)	0.206(6)
O(7')	0.9403(5)	0.7108(8)	0.180(1)	0.042(3)	0.206(6)
O(8)	0.9235(1)	0.6292(1)	0.5558(2)	0.0447(6)	
O(9)	0.8655(1)	0.5243(1)	0.3509(2)	0.0354(5)	
O(10)	0.7967(1)	0.7187(1)	0.3542(2)	0.0406(5)	
O(11)	0.8491(1)	0.3604(1)	0.4405(2)	0.0496(6)	
O(12)	0.1062(2)	0.6161(2)	-0.0883(2)	0.0668(8)	
N(1)	0.4407(1)	0.6558(1)	0.4671(2)	0.0267(5)	
N(81)	0.3060(1)	0.4698(1)	0.1291(2)	0.0287(5)	
N(84)	0.1500(1)	0.4410(1)	-0.0358(2)	0.0382(6)	
C(2)	0.5133(1)	0.6801(1)	0.5405(2)	0.0283(6)	
C(3)	0.5988(1)	0.6478(1)	0.5287(2)	0.0268(6)	
C(31)	0.6703(1)	0.6829(2)	0.6234(2)	0.0295(6)	
C(4)	0.6145(1)	0.5829(1)	0.4339(2)	0.0253(6)	
C(5)	0.5354(1)	0.5543(1)	0.3566(2)	0.0239(5)	
C(6)	0.5424(1)	0.4883(2)	0.2621(2)	0.0277(6)	
C(7)	0.4683(1)	0.4625(2)	0.1898(2)	0.0291(6)	

C(8)	0.3809(1)	0.5001(1)	0.2022(2)	0.0251(5)
C(9)	0.3743(1)	0.5644(1)	0.2964(2)	0.0252(5)
C(10)	0.4498(1)	0.5913(1)	0.3731(2)	0.0237(5)
C(11)	0.3516(1)	0.6921(2)	0.4875(2)	0.0320(6)
C(12)	0.3148(2)	0.7624(2)	0.3980(3)	0.0489(9)
C(13)	0.3426(2)	0.7861(2)	0.5328(3)	0.0490(9)
C(82)	0.3124(2)	0.4663(2)	-0.0098(2)	0.0349(7)
C(83)	0.2393(2)	0.4074(2)	-0.0697(2)	0.0405(7)
C(85)	0.1426(2)	0.4441(2)	0.1047(2)	0.0347(7)
C(86)	0.2172(1)	0.5019(2)	0.1646(2)	0.0285(6)



Symm.oper.: I $x, 1.5-y, z-0.5$; II $1-x, 1-y, -z$; III $1+x, y, z$; IV $x-1, y, z$; V $x, 1.5-y, 0.5+z$; VI $2-x, 0.5+y, 0.5-z$;

Figure 2: View of the title compound. Note that the crystallographic numbering scheme is different as a conventional numbering scheme.

Table 3 lists selected values of bond distances and angles. The copper atom is coordinated in the plane by four oxygen atoms. Ciprofloxacin molecule is bonded to the metal through carbonyl O(3) atom (Cu-O(3) = 1.939(1) Å) and carboxylic O(1) atom

(Cu-O(1) =1.915(2) X). Two water molecules are coordinated to copper in the basal plane with distances (Cu-O(8) =1.972(2) X) and (Cu-O(9) =1.989(2) X). The apical water molecule is coordinated at a longer distance (Cu-O(10) =2.174(2)X). As far to our knowledge this is the first example of the metal-quinolone complex with such bonding where the molar ratio of metal:quinolone is 1:1 (normally 1:2 ratio was observed). The Cu-O(1) and Cu-O(3) lengths are comparable to corresponding distances in the reported copper-quinolone complexes where two quinolones are bidentately bonded to the copper [2-4]. The charge of the $[\text{Cu}(\text{cf})(\text{H}_2\text{O})_3]^{2+}$ cation is compensated by a sulphate anion. It is interesting that the terminal nitrogen atom of piperazine ring system of ciprofloxacin is protonated whereas the carboxylic group is deprotonated. The molecule of ciprofloxacin thus exists in the form of zwitter ion also in this compound.

Table 3: Selected Bond Distances (X) and Angles (°).

Cu-O(1)	1.915(2)	O(1)-Cu-O(3)	93.15(7)
Cu-O(3)	1.939(1)	O(1)-Cu-O(8)	87.90(7)
Cu-O(8)	1.972(2)	O(1)-Cu-O(10)	95.65(7)
Cu-O(9)	1.989(2)	O(3)-Cu-O(8)	167.76(8)
Cu-O(10)	2.174(2)	O(3)-Cu-O(9)	88.03(7)
S-O(4')	1.43(1)	O(3)-Cu-O(10)	96.77(7)
S-O(6)	1.441(3)	O(8)-Cu-O(9)	88.58(7)
S-O(5')	1.44(1)	O(8)-Cu-O(10)	95.26(8)
S-O(4)	1.449(3)	O(9)-Cu-O(10)	95.49(7)
S-O(7')	1.451(8)	O(4')-S-O(5')	113.8(7)
S-O(5)	1.471(3)	O(4')-S-O(7')	109.5(7)
S-O(7)	1.485(4)	O(6)-S-O(4)	111.6(2)
S-O(6')	1.59(1)	O(6)-S-O(5)	109.5(2)
O(1)-C(31)	1.270(3)	O(6)-S-O(7)	109.9(2)
O(2)-C(31)	1.236(3)	O(5')-S-O(7')	119.1(7)
O(3)-C(4)	1.272(2)	O(5')-S-O(6')	106.5(6)
		O(4)-S-O(5)	110.4(2)
		O(4)-S-O(7)	109.1(2)
		O(7')-S-O(6')	103.0(6)
		O(5)-S-O(7)	106.2(2)
		O(4')-S-O(6')	103.1(8)

The quinolone molecule is more or less planar with the exception of the cyclopropyl group that is sticking out of the plane, and the piperazine ring system that is

in the normal chair conformation. All the distances and angles between the atoms are comparable to those found in $[\text{Cu}(\text{cf})_2]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ [2].

There are additionally two water molecules in the structure that are involved in the complex hydrogen bonding network.

The infrared spectra of the title compound and $[\text{Cu}(\text{cf})_2]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ [2] are very similar due to the same atoms of quinolone involved in the bonding to the metal. The main difference represent the typical strong bands that could be assigned to free sulfate ion [23] vibrations and were found at 1142, 1085 and 632 cm^{-1} in the spectrum of the title compound.

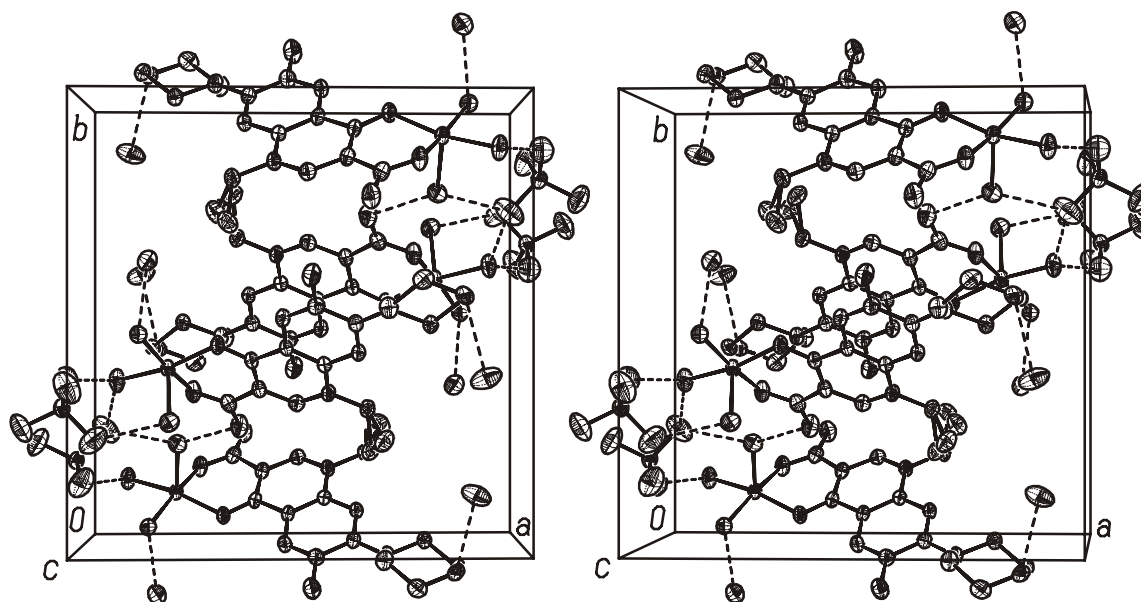


Figure 3: Stereoscopic view of the title compound.

Supplementary Material: anisotropic thermal displacement parameters, hydrogen position parameters with isotropic displacement parameters, additional bond lengths and angles, are available on request from the authors.

Acknowledgements

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Povzetek

Sintetizirali smo nov bakrov kompleks kinolona ciprofloksacina s formulo $[\text{Cu}(\text{cf})(\text{H}_2\text{O})_3]\text{SO}_4 \cdot 2\text{H}_2\text{O}$ in določili njegovo kristalno strukturo. Koordinacijo okrog bakrovega iona v spojini lahko opišemo kot rahlo popačeno kvadratno piramido. Kinolon je vezan na kovino preko karbonilnega O(3) atoma ($\text{Cu}-\text{O}(3) = 1.939(1) \text{ \AA}$) in karboksilnega O(1) atoma ($\text{Cu}-\text{O}(1) = 1.915(2) \text{ \AA}$). Na baker sta v bazalni ravnini koordinirani še dve molekuli vode ($\text{Cu}-\text{O}(8) = 1.972(2) \text{ \AA}$), ($\text{Cu}-\text{O}(9) = 1.989(2) \text{ \AA}$). Vrh piramide zaseda molekula vode na razdalji, ki je nekoliko daljša ($\text{Cu}-\text{O}(10) = 2.174(2) \text{ \AA}$). Način vezave je bistveno drugačen kot v bakrovih kompleksih kinolonov opisanih v literaturi.