CRYSTAL STRUCTURE OF TWO HYDRATE PHASES

OF CIPROFLOXACINDI-UM TETRACHLORIDOCOBALTATE(II)

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New $(C_{17}H_{20}FN_3O_3)_2[CoCl_4]_2\cdot 3H_2O$ (**I**) and $C_{17}H_{20}FN_3O_3[CoCl_4]\cdot H_2O$ (**II**) compounds, where $C_{17}H_{18}FN_3O_3$ is ciprofloxacin (CfH), are synthesized and their crystal structures are determined. Crystallographic data for **I**: $a = 18.441(5)$ Å, $b = 9.030(3)$ Å, $c = 27.551(8)$ Å, $V = 4588(4)$ Å^3, space group $Pca2_1$, $Z = 4$; for **II**: $a = 9.305(3)$ Å, $b = 9.885(3)$ Å, $c = 12.999(4)$ Å, $\alpha = 82.782(4)°$, $\beta = 72.954(4)°$, $\gamma = 89.736(4)°$, $V = 1133(1)$ Å^3, P–1 space group, $Z = 2$. Both structures contain CfH_3^{2+} ion pairs bonded by the π–π interaction. Additionally, in the crystal of **I** there is a stacking interaction between the π clouds of aromatic rings and hydrogen atoms of the cyclopropyl group linking the pairs of molecules with each other. The structure of the centrosymmetric crystal of triclinic phase **II** is also formed from CfH_3^{2+} ion pairs bonded by the π–π interaction, which, in this case, are not independent because they are related by the symmetry center. Hydrogen bonds form a branched three-dimensional network linking the CfH_3^{2+} and $CoCl_4^{2-}$ ions and water molecules.

DOI: 10.1134/S0022476613030219

Keywords: ciprofloxacindi-um tetrachloridocobaltate(II), crystal structure, hydrogen bonds, π–π interaction.

Fluoroquinolones are one of the widely used classes of synthetic antimicrobial agents. Ciprofloxacin (CfH) $C_{17}H_{18}FN_3O_3$ — 4-oxo-7-(1-piperazinyl)-6-fluoro-1-cyclopropyl-1,4-dihydroquinoline-3-carboxylic acid [1] has found the most extensive use in medical practice and, therefore, has been comprehensively studied. A significant role in the antimicrobial activity of CfH can be played by supramolecular interactions, the most important of which are hydrogen bonds and intermolecular π–π interactions [2], which can lead to the formation of channels containing neutral and charged hydrophilic particles in the structure. There is a view [3] that this is important for the manifestation of the observed antimicrobial activity. Therefore, the study of features of the supramolecular arrangement in ciprofloxacin compounds is not only of scientific, but also of practical interest. The most suitable objects for the investigation are the ionic compounds of ciprofloxacin because they usually form good crystals suitable for the X-ray diffraction analysis of their structure.

For a systematic study of the supramolecular arrangement law in ciprofloxacin compounds we have synthesized two new compounds: $(C_{17}H_{20}FN_3O_3)_2[CoCl_4]_2\cdot 3H_2O$ bis-(ciprofloxacindi-um tetrachloridocobaltate) trihydrate (**I**) and of $C_{17}H_{20}FN_3O_3[CoCl_4]\cdot H_2O$ (**II**) ciprofloxacindi-um tetrachloridocobaltate(II) monohydrate. Their crystal structures were solved by single crystal X-ray diffraction and their supramolecular arrangement was analyzed.

EXPERIMENTAL

Ciprofloxacindi-um chloride CfH·HCl·H₂O monohydrate (Ranbaxia, India), HCl (chemically pure), and CoCl₂·6H₂O (chemically pure) were used without additional purification.

Synthesis of (C₁₇H₂₀FN₃O₃)₂[CoCl₄]₂·3H₂O (I). 0.30 g of CfH·HCl·H₂O were dissolved in 3 ml of 11 M HCl, then to the prepared solution CoCl₂·6H₂O was gradually added until the CoCl₂/CfH molar ratio reached 2:1. Crystals of the compound were isolated immediately or by evaporation of the solution.

Synthesis of C₁₇H₂₀FN₃O₃[CoCl₄]·H₂O (II). The only difference in the synthesis conditions from those described above was that the compound was crystallized from a hot (70-80°C) solution.

SINGLE CRYSTAL X-RAY DIFFRACTION STUDY OF COMPOUNDS I AND II

The first crystallization yielded light blue crystals with the orthorhombic symmetry (**I**) and the second one yielded light blue crystals with the trigonal symmetry (**II**). The crystals of **II** quickly decompose in the air, but the accelerated measurement allowed us to collect sufficiently good experimental material.

In both cases, the reflection intensities were measured on an X-ray single crystal SMART APEX II diffractometer with a CCD detector (Bruker AXS), MoK_α radiation, at 298 K. Experimental absorption corrections were introduced using the SADABS software [4] by the multi-scan method. The structure model was determined by direct methods (SHELXS) and refined using the SHELXTL program package [5]. The positions of hydrogen atoms in ciprofloxacindi-um cations were determined from difference electron density maps and were further idealized and refined with reference to the main atoms. Finally, it appeared that the structure of the crystals of **I** is formed from two independent molecular CfH_3^{2+} ciprofloxacindium cations, two polyatomic $CoCl_4^{2-}$ anions, and three molecules of crystallization water, while the crystals of **II** contain all these three components in their asymmetric part. Table 1 lists the parameters of the experiment and the results of the structure refinement. The structures of **I** and **II** were deposited with the Cambridge Crystallographic Data Centre (CCDC) under Nos. 878995 and 878993 respectively. The data can be obtained through the following website: www.ccdc.cam.ac.uk/ data_request/cif.

The refinement showed that the studied sample of compound **I** is racemically twinned in a 3/1 ratio. Fig. 1 depicts the CfH_3^{2+} ion with atom numbering; in both compounds (**I** and **II**) it has almost the same conformation. The main difference is the rotation of the N2–C14–C15–N3–C16–C17 ring with *chair* conformation around the C7–N2 bond. Thus, an angle between the plane of the C5–C6–C7–C8–C9–C10 ring and the plane drawn through the C14, C15, C16, C17 atoms is 32.8(3)° (molecule *A*) and 31.9(3)° (molecule *B*) in the case of **I** and 46.7(1)° (molecule *C*) in the case of **II**. Other geometric parameters of the molecules are given in Table 2. Bond lengths and angles in both compounds almost do not differ from those determined for CfH_3^{2+} $[CuCl_4]^{2-}$·H₂O [6] and CfH_3^{2+}·$[CuBr_4]^{2-}$·H₂O [7], which also contain the ciprofloxacindi-um cation.

Two independent molecules *A* and *B* in the crystal of **I** have an antiparallel location to each other of the head–tail type; these pairs are arranged mutually perpendicular (Fig. 2). The bond in molecular pairs is due to the π–π interaction of planar rings of the CfH_3^{2+} ions. The calculated characteristics of this interaction [8] are given in Table 3.

The mutual arrangement of H9 hydrogen atoms at C13*A* and C13*B* carbon atoms and $Cg_{2(A)}$ and $Cg_{2(B)}$ rings in two nearest perpendicular pairs is noteworthy (Fig. 2). The distance from H9A to the center of the $Cg_{2(B)}$ ring is 3.369 Å; a similar H9B–$Cg_{2(A)}$ distance is 3.239 Å. Therewith, the angle between the ring plane and an interval between H9 and the ring center differs from 90° only by 9° in both cases. This indicates an additional interaction of π orbitals of the rings with the hydrogen atoms bonding the pairs of molecules with each other. Such stacking interactions of the edge-to-plane type are proposed to consider [2, p. 57] as weak hydrogen bonds between the electron-deficient hydrogen atoms of one cyclic molecule and the electron-enriched π cloud of another.
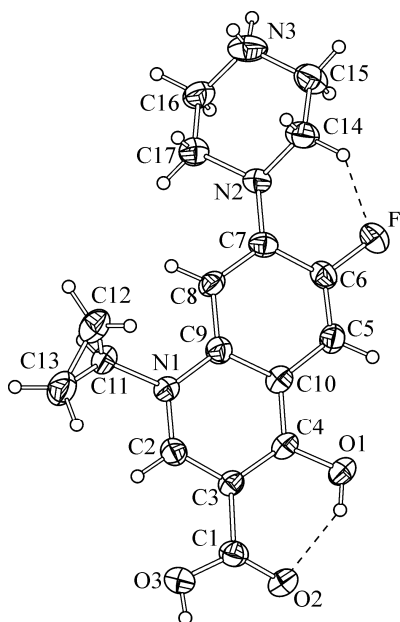
Fig. 1. CfH_3^{2+} cation with atom numbering. Intramolecular hydrogen bonds are denoted by dashed lines.
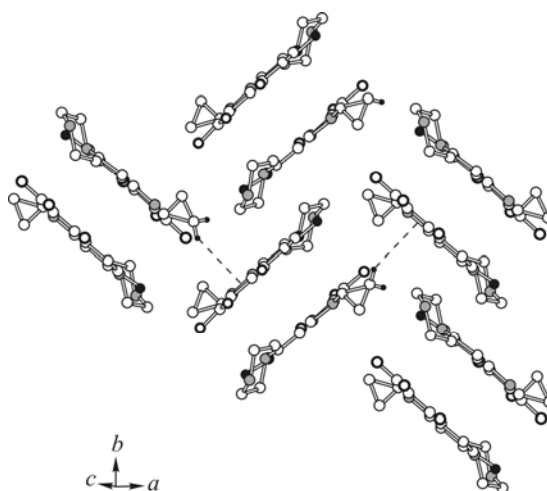

Fig. 2. Packing of the ciprofloxacindi-um ions in the crystal of **I**. Black circles are the F atoms, grey are N, bold are O. Dashed lines denote two contacts H9–Cg_2.

TABLE 1. Experimental Data and Parameters of the Refinement for the Structures of **I** and **II**

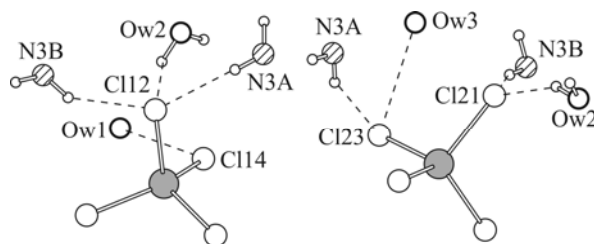| Formula	$(C_{17}H_{20}FN_3O_3)_2[CoCl_4]_2 \cdot 3H_2O$	$C_{17}H_{20}FN_3O_3[CoCl_4] \cdot H_2O$
Sample size, mm	0.40×0.30×0.20	0.41×0.35×0.24
Space group	$Pca2_1$	$P{-}1$
Z	4	2
$2\theta_{max}$, deg	52	52
a, b, c, Å	18.441(5), 9.030(3), 27.551(8)	9.305(3), 9.885(3), 12.999(4)
α, β, γ, deg	90, 90, 90	82.782(4), 72.954(4), 89.736(4)
V, Å^3	4588(4)	1133(1)
d, g/cm^3	1.625	1.619
μ, mm^{-1}	1.25	1.27
Total number of measured reflections	34914	6567
Number of independent reflections	8975	4211
Number of reflections with $F > 4\sigma_F$	5198	3288
Limits by h, k, l	$-22 \le h \le 22$; $-10 \le k \le 11$; $-33 \le l \le 33$	$-11 \le h \le 8$; $-12 \le k \le 12$; $-16 \le l \le 16$
	Refinement results	
Weight refinement on F^2	$w = [\sigma^2 + (0.0363P)^2 + 0.8661P]^{-1}$, where $P = (F_0^2 + 2F_c^2)/3$	$w = [\sigma^2 + (0.0423P)^2 + 0.36P]^{-1}$, where $P = (F_0^2 + 2F_c^2)/3$
Number of refined parameters	561	273
$R1$ [$F_0 > 4\sigma(F_0)$]	00490	0.0376
$wR2$	0.1080	0.0956
$GOOF$	1.006	1.050
Extinction coefficient	0.0003(1)	0.006(1)
$(\Delta\rho)_{max}$, e/Å^3	0.426	0.30
$(\Delta\rho)_{min}$, e/Å^3	−0.268	−0.31
$(\Delta/\sigma)_{max}$	0.000	0.000

Fig. 3. Hydrogen bonds in the crystal of **I** formed by the $CoCl_4^{2-}$ anion.

TABLE 2. Main Bond Lengths (*d*) and Angles (ω) in the Structures of **I** (*A,B*) and **II** (*C*).

Bond		*d*, Å	Bond		*d*, Å	Bond		*d*, Å
Co(1)–Cl(11)	**I**	2.232(2)	C(1)–O(3)	*A*	1.305(9)	C(4)–O(1)	*A*	1.329(7)
Co(1)–Cl(12)	**I**	2.294(2)		*B*	1.317(9)		*B*	1.335(7)
Co(1)–Cl(13)	**I**	2.255(2)		*C*	1.305(3)		*C*	1.329(3)
Co(1)–Cl(14)	**I**	2.268(2)	Co(2)–Cl(21)	**I**	2.293(2)	F–C(6)	*A*	1.360(8)
Co–Cl(1)	**II**	2.279(1)	Co(2)–Cl(22)	**I**	2.239(2)		*B*	1.361(7)
Co–Cl(2)	**II**	2.256(1)	Co(2)–Cl(23)	**I**	2.315(2)		*C*	1.350(3)
C(1)–O(2)	*A*	1.234(9)	Co(2)–Cl(24)	**I**	2.251(2)			
	B	1.230(8)	Co–Cl(3)	**II**	2.313(1)			
	C	1.214(3)	Co–Cl(4)	**II**	2.239(1)			

Angle		ω, deg	Angle		ω, deg	Angle		ω, deg
O(2)C(1)O(3)	*A*	123.6(8)	FC(6)C(7)	*A*	115.8(7)	FC(6)C(5)	*A*	119.1(7)
	B	122.8(8)		*B*	119.4(7)		*B*	116.7(6)
	C	124.6(2)		*C*	117.9(2)		*C*	118.5(2)
O(3)C(1)C(3)	*A*	114.9(8)	O(2)C(1)C(3)	*A*	121.5(8)	C(17)N(2)C(14)	*A*	111.0(5)
	B	114.0(7)		*B*	123.1(8)		*B*	111.9(6)
	C	113.7(2)		*C*	121.6(2)		*C*	110.7(2)
C(3)C(4)O(1)	*A*	121.5(7)	C(10)C(4)O(1)	*A*	118.4(7)			
	B	122.0(7)		*B*	117.1(7)			
	C	122.8(2)		*C*	117.5(2)			

TABLE 3. Parameters of the π–π Interaction of CfH_3^{2+} Ions in the Cof **I** (*A,B*) and **II** (*C*)

$Cg_i–Cg_j$	*d*, Å	α, deg	β, deg	Cg_i_p, Å	Cg_j_p, Å
$Cg_{1(A)}–Cg_{2(B)}$	3.634(4)	2.92	14.59	3.530	3.500
$Cg_{1(B)}–Cg_{2(A)}$	3.666(4)	1.27	14.32	3.550	3.552
$Cg_{2(A)}–Cg_{1(B)}$	3.666(4)	1.27	14.42	3.552	3.551
$Cg_{2(B)}–Cg_{1(A)}$	3.633(4)	2.92	13.67	3.500	3.530
$Cg_{1(C)}–Cg_{1(C)}$	3.567(2)	0	16.36	3.423	3.423

Note. Cg_1 ring: N1–C2–C3–C4–C10–C9; Cg_2 ring: C5–C6–C7–C8–C9–C10.

In addition to these interactions, the structure of **I** is determined by multiple hydrogen bonds with the participation of three independent water molecules, anions $CoCl_4^{2-}$, and cations CfH_3^{2+}. Although we have managed to detect the hydrogen atoms only in one water molecule, the O–Cl distances allow us to speak about the presence of such bonds in two other molecules, too, and the Ow1–Ow3 distance of 2.62 Å indicates the presence of a hydrogen bond also between these water
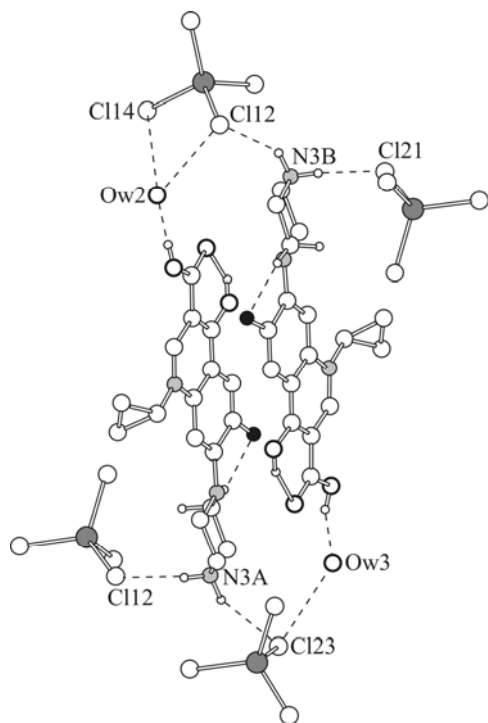
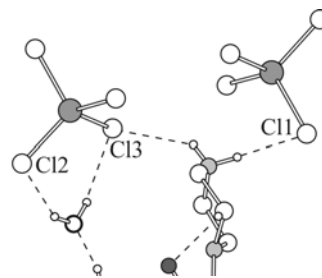**Fig. 4.** Hydrogen bonds with the participation of CfH_3^{2+} cations in **I**.

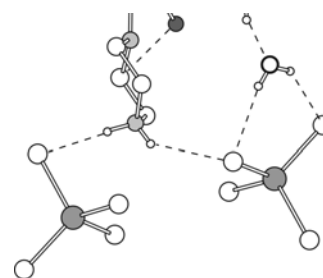**Fig. 5.** Fragment of the structure of triclinic phase **II**.

TABLE 4. Geometric Characteristics of D–H…A Hydrogen Bonds (bond lengths d, Å; angles, deg) and the Shortest Contacts in the Structures of **I** and **II**

D–H	d(D–H)	d(H…A)	∠DHA	d(D…A)	A	Transformation for the A atom (acceptor)
			$(C_{17}H_{20}FN_3O_3)_2[CoCl_4]_2 \cdot 3H_2O$ (**I**)			
O1A–H1A	0.82	1.86	147	2.589(8)	O2A	
O1B–H1B	0.82	1.83	147	2.560(7)	O2B	
O3A–H3A	0.82	1.82	164	2.614(9)	OW2	0.5–x, y, 0.5+z
O3B–H3B	0.82	1.88	154	2.642(7)	OW3	
Ow2–Hw2B	0.89(7)	2.60(9)	135(8)	3.288(7)	Cl12	
N3A–H15A	0.90	2.47	150	3.277(6)	Cl23	
N3B–H15B	0.90	2.31	144	3.088(6)	Cl12	1–x, –y, 0.5+z
N3A–H16A	0.90	2.34	156	3.182(5)	Cl12	x–0.5, 1–y, z
N3B–H16B	0.90	2.30	159	3.161(6)	Cl21	1–x, –y, 0.5+z
C14A–H11A	0.97	2.15	129	2.858(9)	FA	
C14B–H12B	0.97	2.12	129	2.835(10)	FB	
			$C_{17}H_{20}FN_3O_3[CoCl_4] \cdot H_2O$ (**II**)			
N3–H3A	0.90	2.28	177	3.178(3)	Cl1	–x, 1–y, –z
N3–H3B	0.90	2.54	140	3.285(3)	Cl3	x, 1+y, z
N3–H3B	0.90	2.96	118	3.481(3	Cl4	–x, 1–y, –z
O1–H1	0.82	1.94	144	2.645(3)	O2	
O1–H1	0.82	2.29	132	2.901(3)	O2	2–x, 1–y, 1–z
O3–H3	0.82	1.79	157	2.561(3)	OW	1–x, –y, 1–z
Ow–Hw1	0.89(1)	2.30(2)	168(3)	3.177(3)	Cl3	
Ow–Hw2	0.89(1)	2.44(2)	144(3)	3.212(3)	Cl2	

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molecules. Table 4 summarizes the hydrogen bond parameters; Fig. 3 and 4 depict the arrangement of interacting atomic groups. There are shortened C–H…Cl distances in the structure, which we do not consider in order not to complicate the discussion.

Main geometric parameters for the structure of **II** are listed in Table 2. Having a simpler structure, the centrosymmetric crystal of triclinic phase **II** is also formed from the CfH_3^{2+} ion pairs, which, in this case, are not independent because they are related by the symmetry center. The intrapair interaction is due to the π–π bonding of N1–C2–C3–C4–C10–C9 rings (Cg_1). Parameters of this interaction are given in Table 3. In this structure there is also an additional interaction between the π orbitals of planar rings and the $CoCl_4^{2-}$ anion through the Cl1 chlorine atom. The Co–Cl1$\cdots\pi$ interaction can be explained by the formation of a quadrupole by the aromatic ring, which can be represented as two oppositely directed dipoles [2]. Therewith, the distance between Cl1 and the ring center is 3.401(2) Å for Cg_1 and 3.758(2) Å for Cg_2. In the first case, the angle between the ring plane and the section of a straight line between Cl1 and the ring center is 77.3°, and in the second it is 62.1°.

Hydrogen bonds in the structure of **II** are shown in Fig. 5, and their geometric parameters are listed in Table 4. Continuous chains of CfH_3^{2+} cations formed by hydrogen bonds through the water molecules are arranged along the [111] direction in the crystal.

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