

## CRYSTAL STRUCTURE OF TWO IONIC SPARFLOXACIN COMPOUNDS

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The structure of two new ionic compounds of sparfloxacin ( $C_{19}H_{22}F_2N_4O_3$ , SfH),  $SfH_3[ZnCl_4] \cdot 1.5H_2O$  (**I**) and  $SfH_3[CdBr_4] \cdot H_2O$  (**II**), is determined. Crystallographic data are as follows: for **I**  $a = 14.505(3) \text{ \AA}$ ,  $b = 12.615(3) \text{ \AA}$ ,  $c = 29.118(7) \text{ \AA}$ ,  $V = 5254(4) \text{ \AA}^3$ , space group  $Pbca$ ,  $Z = 8$ ; for **II**  $a = 13.2822(5) \text{ \AA}$ ,  $b = 10.2564(4) \text{ \AA}$ ,  $c = 21.3250(8) \text{ \AA}$ ,  $\beta = 100.7248(4)^\circ$ ,  $V = 2854.3(3) \text{ \AA}^3$ , space group  $P2_1/n$ ,  $Z = 4$ . The structures of the compounds are stabilized by intra- and intermolecular hydrogen bonds and the structure of **I** is additionally stabilized by the  $\pi$ - $\pi$  interaction between the  $SfH_3^{2+}$  ions.

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Sparfloxacin ( $C_{19}H_{22}F_2N_4O_3$ , SfH) is one of the most important synthetic antibiotics of the fluoroquinolone group characterized by a high antibacterial activity, which promotes its increasing use in clinical practice [1, 2]. Mutual transformations of SfH polymorphs [3] make it essential to look for new drug ingredients, in particular, those based on metal-containing sparfloxacin compounds, which can additionally possess anticancer and antimicrobial activities [4-6]. Data on the synthesis and structural study of sparfloxacin compounds will be useful to determine the relationship between their structure and the curative effect and in handling the substance.

Previously, the compounds of the sparfloxacindi-ium cation with tetrahalide anions of doubly charged metal ions (Cu, Co, Zn, Cd, Hg) were synthesized, their crystallographic parameters were determined, and their thermal stability and IR spectra were studied [7]. In this work, we determined the structure of two ionic sparfloxacin compounds: hydrates of sparfloxacindi-ium tetrachloridozincate(II)  $SfH_3[ZnCl_4] \cdot 1.5H_2O$  and sparfloxacindi-ium tetrabromocadmiate(II)  $SfH_3[CdBr_4] \cdot H_2O$ .

### EXPERIMENTAL

We used sparfloxacin (Sigma-Aldrich, CAS No. 110871-86-8, basic substance content  $\geq 98\%$ ), HBr, HCl,  $CdBr_2$ , and  $ZnCl_2$  (all reagents are chemically pure).

**Synthesis of  $SfH_3[ZnCl_4] \cdot 1.5H_2O$  (I).** In 4 ml of 8 M HCl, 0.30 g of sparfloxacin was dissolved, then on heating the aqueous solution of  $ZnCl_2$  was gradually added to the prepared solution. In order to increase the yield of the compound, we provided the molar ratio  $SfH:ZnCl_2 = 1:5$ . The yellow crystals isolated on slow cooling or evaporation of the solution. The yield of the compound with respect to sparfloxacin was 60-70%.

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**Synthesis of  $\text{SfH}_3[\text{CdBr}_4]\cdot\text{H}_2\text{O}$  (II).** In 5 ml of 6 M HBr, 0.30 g of sparfloxacin was dissolved, then, on heating, solid  $\text{CdBr}_2$  was gradually added to the prepared solution. The molar ratio  $\text{SfH}:\text{CdBr}_2 = 1:3$ . The yellow crystals were isolated on evaporation of the solution. The yield with respect to sparfloxacin was 50-60%.

**Single crystal X-ray diffraction study.** For the structural study, we selected the crystals of **I** and **II** of  $0.28 \times 0.23 \times 0.18$  mm and  $0.366 \times 0.324 \times 0.227$  mm respectively. The reflection intensities were measured on a SMART APEX II X-ray single crystal diffractometer with a CCD detector (Bruker AXS),  $\text{MoK}_\alpha$  radiation at 298 K. The experimental absorption corrections were applied using the SADABS software [8] by multiscanning. The structure model was determined by direct methods and refined using the SHELXTL software [9]. The positions of hydrogen atoms in the sparfloxacinium cation were determined from difference electron density maps and were further idealized and refined with reference to the main atoms.

Table 1 lists the parameters of the experiment and the refinement results for the structures of the compounds.

The structures of **I** and **II** have been deposited with the Cambridge Structural Database under numbers 1005412 and 1005411 respectively. The data are available through the website [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

The asymmetric part of the unit cell of the crystal of **I** contains one  $\text{C}_{19}\text{H}_{24}\text{F}_2\text{N}_4\text{O}_3^{2+}$  ion, one  $\text{ZnCl}_4^{2-}$  ion, and two crystallization water molecules, one of which is disordered over two positions, and, in total, has the site occupancy factor  $\text{sof} = 0.5$ . The six-membered C2–C3–C4–C10–C9–N1 and C5–C6–C7–C8–C9–C10 rings (Fig. 1) have a planar structure with a maximum deviation of the atoms from the ring plane of  $0.052(4)$  Å (C9); they are turned relative to each other by  $6.2^\circ$ . The O1, O2, O3, and C1 atoms are also close to the first of these planes with a maximum deviation of  $0.07(1)$  Å (O2).

The structures of **I** and  $\text{SfH}_3[\text{CuBr}_4]\cdot\text{H}_2\text{O}$  [10] differ little despite a less distorted  $\text{ZnCl}_4$  tetrahedron as compared with  $\text{CuBr}_4$  and the presence of an additional (disordered) water molecule in **I**. They have the same symmetry and arrangement of ions in the crystal, similar unit cell parameters. The main difference is that in  $\text{SfH}_3[\text{CuBr}_4]\cdot\text{H}_2\text{O}$  the water

**TABLE 1.** Main Crystallographic Characteristics and Parameters of the Experiment

Crystallographic data		
Chemical formula	$(\text{C}_{19}\text{H}_{24}\text{F}_2\text{N}_4\text{O}_3)[\text{ZnCl}_4]\cdot 1.5\text{H}_2\text{O}$	$(\text{C}_{19}\text{H}_{24}\text{F}_2\text{N}_4\text{O}_3)[\text{CdBr}_4]\cdot\text{H}_2\text{O}$
Space group; <i>Z</i>	<i>Pbca</i> ; 8	<i>P2<sub>1</sub>/n</i> ; 4
<i>a, b, c</i> , Å	14.305(3), 12.615(3), 29.118(7)	13.2822(5), 10.2564(4), 21.3250(8)
$\beta$ , deg	90.00	100.7248(4)
<i>V</i> , Å <sup>3</sup>	5254.4(2)	2854.3(2)
<i>d</i> , g/cm <sup>3</sup>	1.589	1.865
$\mu$ , mm <sup>-1</sup>	1.39	6.395
Parameters of data collection		
Total number of measured / indep. reflections	39907 / 5376	26453 / 7207
Number of reflections with $F > 4\sigma_F$	2919	5341
$2\theta_{\text{max}}$ , deg	52.84	57
<i>h, k, l</i>	-17→17, -15→15, -36→36	-17→17, -13→13, -28→28
Refinement results		
Number of refined parameters	325	316
<i>R1</i> [ $F_0 > 4\sigma(F_0)$ ]	0.0649	0.0309
<i>wR2</i>	0.1808	0.0618
<i>GOOF</i>	1.035	1.029
$\Delta\rho_{\text{max}} / \Delta\rho_{\text{min}}$ , e/Å <sup>3</sup>	0.74 / -0.70	1.00 / -0.79
$(\Delta/\sigma)_{\text{max}}$	0.00	0.10

**TABLE 2.** Geometric Characteristics of the D–H...A Hydrogen Bonds (bond lengths  $d$ , Å; angles, deg) in the Structure of **I**

D–H	$d(\text{D–H})$	$d(\text{H...A})$	$d(\text{D...A})$	$\angle\text{DHA}$	A	Transformation for A
O2–H2	0.95(1)	1.66(3)	2.552(6)	154(6)	O1	$x, y, z$
N3–H31	0.90	2.24	3.138(5)	177	Cl2	$[1-x, y+1/2, 1/2-z]$
N3–H32	0.90	2.34	3.200(5)	160	Cl1	$x, y, z$
N4–H41	0.89	2.35	3.206(5)	161	Cl3	$[1-x, y-1/2, 1/2-z]$
N4–H42	0.89	1.88	2.731(5)	158	Ow1	$[x+1/2, y, 1/2-z]$
N4–H43	0.89	1.90	2.630(6)	137	O1	$x, y, z$
Ow1–Hw11	0.95(1)	1.75(4)	2.66(4)	159(6)	Ow2B	$[1-x, 1-y, 1-z]$
Ow1–Hw11	0.95(1)	2.15(5)	3.08(5)	167(6)	Ow2A	$x, y, z$
Ow1–Hw11	0.95(1)	2.24(5)	3.18(5)	171(6)	Ow2A	$[1-x, 1-y, 1-z]$
Ow1–Hw12	0.95(1)	2.32(2)	3.267(2)	177(5)	Cl3	$x, y, z$
C14–H14A	0.97	2.31	2.826(6)	113	F1	$x, y, z$
C17–H17B	0.97	2.26	2.744(6)	110	F2	$x, y, z$

molecule Ow1 is linked by hydrogen bonds with two halogen atoms (Br) [10], while in **I** it is linked to one halogen atom (Cl) and an additional water molecule Ow2 (Fig. 1, Table 2). Since the latter is disordered, we failed to determine the position of its hydrogen atoms, however, the Ow2A...Cl and Ow2B...Cl distances (3.20 Å and 2.98 Å) make it possible to say that the fourth chlorine atom is also involved in hydrogen bonds, though not with the Ow1 molecule, as in CuBr<sub>4</sub> [10].

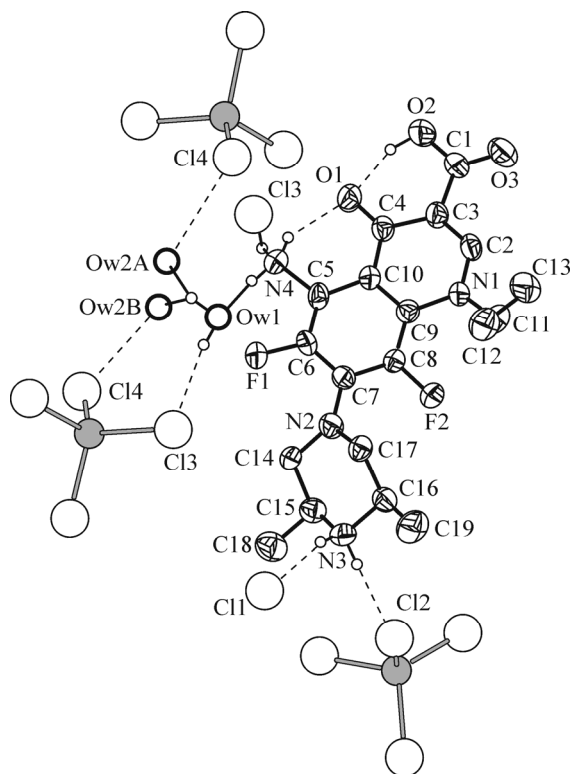
The sparfloxacinidinium ions in **I** are arranged in pairs, in which they are linked by the symmetry center and by the  $\pi$ – $\pi$  interaction of the planar N1–C2–C3–C4–C10–C9 (Cg1) and C5–C6–C7–C8–C9–C10 (Cg2) rings of a “head-to-tail” type (Table 3), characteristic of other ionic compounds of fluoroquinolones [10–17].

The asymmetric part of the unit cell of **II** contains one SfH<sub>3</sub><sup>2+</sup> ion, one CdBr<sub>4</sub><sup>2-</sup> ion, and a water molecule. In the CdBr<sub>4</sub><sup>2-</sup> anion, the Br–Cd–Br angles range from 101.85(1)° to 116.23(2)°, which agrees with the single crystal X-ray diffraction data [18]. Five hydrogen atoms at nitrogen atoms and the hydrogen of the hydroxide group are involved in seven hydrogen bonds, one of which (N4–H...O1) is intramolecular (Fig. 2, Table 4). Both hydrogen atoms of the water molecule are bonded to the Br atoms, and the oxygen atom (Ow) is an acceptor of the O2–H...O bond. Unlike **I** and SfH<sub>3</sub>[CuBr<sub>4</sub>].H<sub>2</sub>O [10], in **II** the SfH<sub>3</sub><sup>2+</sup> ion contains the O3–C1–O2H group turned by 180° around the C1–C3 bond. As a result, one of the intramolecular hydrogen bonds of the O–H...O type disappears, but three intermolecular H bonds with the CdBr<sub>4</sub><sup>2-</sup> ions are retained, although one of them is now formed by the N4 donor. The N3 donor via two hydrogen bonds links each initial SfH<sub>3</sub><sup>2+</sup> ion with the same other ion forming a six-membered ring ( $R_1^2$ ) and creates the N3–H...Br1 bond (Figs. 2 and 3). The second SfH<sub>3</sub><sup>2+</sup> ion is linked to the initial one by two intermolecular N3–H...O bonds with the involvement of the O1 and O3 atoms of the initial ion. Three of four Br ions are involved in hydrogen bonds (Fig. 3). Two of them (Br2, Br3), together with the water molecule, form a supramolecular motif  $R_2^1(6)$ .

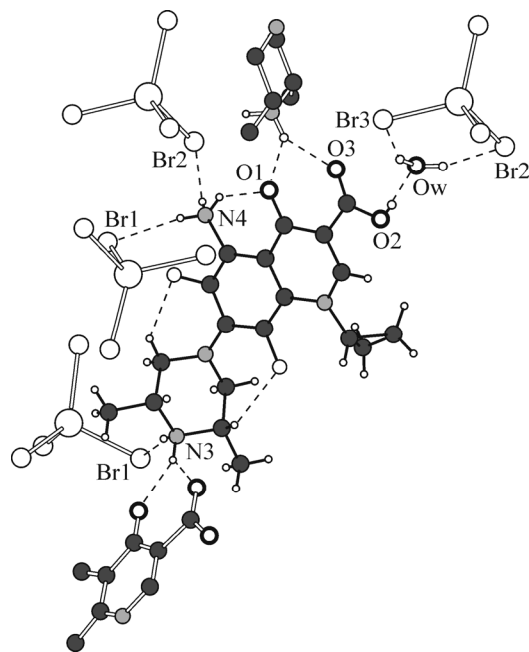
The common features in the structure of ionic compounds **I**, **II**, and SfH<sub>3</sub>[CuBr<sub>4</sub>].H<sub>2</sub>O can be noted [10]. The compounds consist of the SfH<sub>3</sub><sup>2+</sup>, MX<sub>4</sub><sup>2-</sup> ions (M = Zn, Cd, Cu; X = Cl or Br) and water molecules linked by hydrogen bonds

**TABLE 3.** Parameters of the  $\pi$ – $\pi$  Interactions in the Structure of **I**

Cg <sub>i</sub> –Cg <sub>j</sub>	$d$ , Å	$\alpha$ , deg	$\beta$ , deg	Cg <sub>i_p</sub> , Å	$\Delta$ , Å
Cg <sub>1</sub> –Cg <sub>1</sub>	3.610(3)	0	20.3	3.385(2)	1.253
Cg <sub>1</sub> –Cg <sub>2</sub>	3.884(3)	6.2(2)	30.4	3.449(2)	–
Cg <sub>2</sub> –Cg <sub>1</sub>	3.884(3)	6.2(2)	27.4	3.350(2)	–



**Fig. 1.** Hydrogen bonds in the structure of **I**. Hydrogen bonds are shown by dashed lines. The ellipsoids of thermal vibrations are calculated with confidence level of 50%.

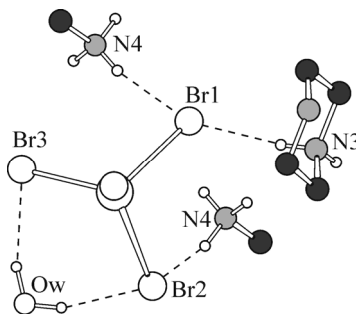


**Fig. 2.** Hydrogen bonds in the structure of **II**. The N atoms are shaded, the C atoms are blackened.

in the framework structures. The respective C–O, C–N, C–F, and C–C bond lengths and bond angles coincide with each other and with the values previously obtained for sparfloxacin [18], its trihydrate [3], and  $\text{SfH}_2[\text{BF}_4] \cdot 0.63\text{H}_2\text{O}$  [4]. In the  $\text{C}_{19}\text{H}_{24}\text{F}_2\text{N}_4\text{O}_3^{2+}$  cation, two six-membered N1–C2–C3–C4–C10–C9 and C5–C6–C7–C8–C9–C10 rings are almost planar and the third one, N2–C14–C15–N3–C16–C17, has a *chair* conformation (Fig. 1). In a strongly acidic medium, the second proton bonds to the N4 atom of the SfH molecule, instead of the O1 atom of the carbonyl group, as in other fluoroquinolones [11–17]. This behavior can be explained by more basic character of the N4 nitrogen atom and by the fact that the O1 atom forms

**TABLE 4.** Geometric Characteristics of the D–H...A Hydrogen Bonds (bond lengths  $d$ , Å; angles, deg) in the Structure of **II**

D–H	$d(\text{D–H})$	$d(\text{H...A})$	$\angle\text{DHA}$	$d(\text{D...A})$	A	Transformation for A atom
O2–H1	0.94(1)	1.69(1)	173(4)	2.626(3)	Ow	$-x, 1-y, -z$
N3–H3	0.90	2.52	170	3.409(2)	Br1	$1.5-x, y-0.5, 0.5-z$
N3–H4	0.90	2.02	135	2.729(3)	O1	$0.5+x, 0.5-y, 0.5+z$
N3–H4	0.90	2.07	140	2.823(3)	O3	$0.5+x, 0.5-y, 0.5+z$
N4–H5	0.89	2.50	165	3.370(2)	Br1	$x, y-1, z$
N4–H6	0.89	2.48	152	3.294(2)	Br2	$1-x, 1-y, -z$
N4–H7	0.89	1.79	143	2.556(3)	O1	$x, y, z$
N4–H7	0.89	2.99	115	3.455(2)	Br1	$1-x, 1-y, -z$
Ow–Hw1	0.95(1)	2.45(2)	157(3)	3.348(3)	Br2	$x, y, z$
Ow–Hw2	0.95(1)	2.50(2)	154(4)	3.383(3)	Br3	$x, y, z$
C17–H17	0.97	2.32	107	2.756(3)	F2	$x, y, z$
C14–H14	0.97	2.32	112	2.844(3)	F1	$x, y, z$



**Fig. 3.** Involvement of bromine atoms in hydrogen bonds.

a strong hydrogen bond with the hydrogen atom of  $-\text{NH}_3^+$ , and with the H atom of the carboxyl group in **I** (Fig. 1, Table 2) or the  $>\text{NH}_2^+$  group of the piperazinyl ring in **II** (Fig. 2 and Table 4). Therefore, the O1 atom is a double acceptor of hydrogen bonds and forms two six-membered rings. In **I**, two intramolecular hydrogen bonds  $\text{O2}-\text{H}\cdots\text{O1}$  and  $\text{N4}-\text{H}-\text{O1}$  form the rings corresponding to the supramolecular motif  $S(6)$  [19]; in **II**, the intramolecular hydrogen bond  $\text{N4}-\text{H}\cdots\text{O1}$  also forms  $S(6)$  and the intermolecular  $\text{N3}-\text{H}\cdots\text{O1}$  bond forms  $R_2^1(6)$ . In the  $\text{SfH}_3^{2+}$  cation of the studied compounds, there are weak intramolecular hydrogen bonds  $\text{C14}-\text{H14}\cdots\text{F}$  and  $\text{C17}-\text{H17}\cdots\text{F}$  (Tables 2 and 4, [10]). Unlike **I** and  $\text{SfH}_3[\text{CuBr}_4]\cdot\text{H}_2\text{O}$  [10], there are no  $\pi-\pi$ -interactions in **II**.

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