ISSN 0036-0236, Russian Journal of Inorganic Chemistry, 2016, Vol. 61, No. 11, pp. 1419–1422. © Pleiades Publishing, Ltd., 2016.
Original Russian Text © N.N. Golovnev, A.D. Vasil'ev, 2016, published in Zhurnal Neorganicheskoi Khimii, 2016, Vol. 61, No. 11, pp. 1472–1475.

COORDINATION COMPOUNDS

Structure of Two New Compounds of Fluoroquinolone Antibiotics with Mineral Acids

N. N. Golovnev[a, *] and A. D. Vasil'ev[a, b]

[a] *Siberian Federal University, Svobodnyi pr. 79, Krasnoyarsk, 660041 Russia*
[b] *Kirenskii Institute of Physics, Siberian Branch, Russian Academy of Sciences, Akademgorodok 50/38, Krasnoyarsk, 660036 Russia*
**e-mail: ngolovnev@sfu-kras.ru*

Received May 23, 2015

Abstract—New compounds of sparfloxacin ($C_{19}H_{22}F_2N_4O_3$, SfH) and levofloxacin ($C_{18}H_{20}FN_3O_4$, LevoH) with mineral acids, namely, sparfloxacinium bromide (SfH · HBr, **I**) and levofloxacindium diperchlorate (LevoH · $2HClO_4$, **II**), have been synthesized and characterized by X-ray diffraction. Crystallographic data are $a = 7.7151(7)$ Å, $b = 26.109(3)$ Å, $c = 10.008(1)$ Å, $\beta = 103.556(1)°$, $V = 1959.7(3)$ Å^3, space group $P2_1/n$, $Z = 4$ for **I** and $a = 9.727(6)$ Å, $b = 20.440(12)$ Å, $c = 12.286(7)$ Å, $\beta = 104.327(8)°$, $V = 2367(2)$Å^3, space group $P2_1$, $Z = 4$ for **II**. The structures of these compounds are stabilized by intra- and intermolecular hydrogen bonds and π–π interaction between SfH_2^+ or $LevoH_3^{2+}$ ions.

DOI: 10.1134/S0036023616110073

Fluoroquinolones selectively inhibit DNA gyrase, a microbial cell enzyme responsible for the normal biosynthesis and DNA replication of bacteria. They are the most important class of synthetic antibiotics [1]. Among its representatives are sparfoxancin ($C_{19}H_{22}F_2N_4O_3$, SfH) [2, 3] and levofloxacin or S-ofloxacin ($C_{18}H_{20}FN_3O_4$, LevoH) [1, 4]. Their application in medicine is complicated by a low solubility in water, hygroscopicity, and the formation of polymorphic and hydrated forms [5–7]. Ionic compounds of fluoroquinolones are better soluble and crystallized [8–12] and can be suitable ingredients of new medicines. Within the framework of the systematic study of their molecular and supramolecular structure, two new compounds, such as sparfloxacinium bromide SfH · HBr (**I**) and levofloxacindium diperchlorate LevoH · $2HClO_4$ (**II**) have been synthesized and characterized by X-ray diffraction.

EXPERIMENTAL

Sparfloxacin $C_{19}H_{22}F_2N_4O_3$ (Sigma; ≥98% pure), levofloxacin semi-hydrate $C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$ (Zhejiang Kangyu Pharmaceutical, China), HBr (chemically pure), and $HClO_4$ (chemically pure) were used without additional purification.

Synthesis. Compound **I** was synthesized by adding 2 M HBr drop by drop to a suspension of SfH (0.20 g) in water (5 mL) until pH 2–3 was attained. Compound **II** was synthesized by adding 10 M $HClO_4$ (3 mL) to LevoH (0.20 g). The formed yellow crystalline precipitates were filtered out, washed with acetone, and dried in air. Single crystals of compounds **I** and **II** precipitated during the slow evaporation of water from the resulting filtrates at room temperature.

Single-crystal X-ray diffraction analysis. Single crystals of **I** and **II** selected for structural characterization were 0.18 × 0.14 × 0.07 and 0.43 × 0.38 × 0.21 mm in size, respectively. Reflection intensities were measured on a SMART APEX II X-ray single-crystal diffractometer with a Bruker AXS CCD detector (MoK_α radiation) at 298 K. Experimental corrections for absorption were applied using the SADABS software [13] by the multi-scan method. The structural model was solved by direct methods and refined in the anisotropic approximation for non-hydrogen atoms using the SHELXTL software suite [14]. The structures of compounds **I** and **II** were deposited with the Cambridge Structure Database (nos. 1047052 and 1047051, respectively). The data can be accessed at www.ccdc.cam.ac.uk/data_request/cif.

The positions of all hydrogen atoms in compounds **I** and **II** were determined from difference electron density syntheses and further refined as bonded with fixed distances. Some parameters of X-ray diffraction experiment and refinement details for their structures are given in Table 1.

Table 1. Parameters of X-ray experiment and details of structure refinement for compounds **I** and **II**

Formula	$C_{19}H_{23}BrF_2N_4O_3$ (**I**)	$C_{18}H_{22}Cl_2FN_3O_8$ (**II**)
Space group, Z	$P2_1/n$, 4	$P2_1$, 4
$2\theta_{max}$, deg	50	50
a, b, c, Å; β, deg	7.7151(7), 26.109(3), 10.008(1); 103.556(1)	9.727(6), 20.440(12), 12.286(7); 104.327(8)
V, Å^3	1959.7(3)	2367(2)
ρ, g/cm^3	1.604	1.578
μ, mm^{-1}	2.146	0.351
Total measured reflections	14261	17505
Independent reflections	3448	8263
Number of reflections with $F > 4\sigma_F$	2046	5387
h, k, l ranges	$-9 \le h \le 9$, $-31 \le k \le 30$, $-11 \le l \le 11$	$-11 \le h \le 11$, $-24 \le k \le 24$, $-14 \le l \le 14$
Refined parameters	257	654
$R1$ [$F_o > 4\sigma(F_o)$]	0.055	0.063
$wR2$	0.113	0.163
GOOF	1.02	1.04
Flack parameter	–	–0.09(6)
$\Delta\rho_{max}/\Delta\rho_{min}$, e/Å^3	0.79/–0.50	0.50/–0.36
$(\Delta/\sigma)_{max}$	0.0	0.01

RESULTS AND DISCUSSION

The asymmetric part of the crystal unit cell of compound **I** contains one SfH_2^+ ion and one Br^- ion. The two six-membered rings (N1–C2–C3–C4–C10–C9 and C5–C6–C7–C8–C9–C10) in the SfH_2^+ cation are nearly planar, and the third ring N2–C14–C15–N3–C16–C17 has a "chair" conformation (Fig. 1). The N4 atom is bonded to two hydrogen atoms located in the plane of the two first rings. The SfH_2^+ cation also contains the C11–C12–C13 three-membered ring bonded to the N1 atom. The interatomic distances and bond angles in compound **I** coincide with the values obtained for sparfoxacin [7, 15] and its derivatives [2, 16].

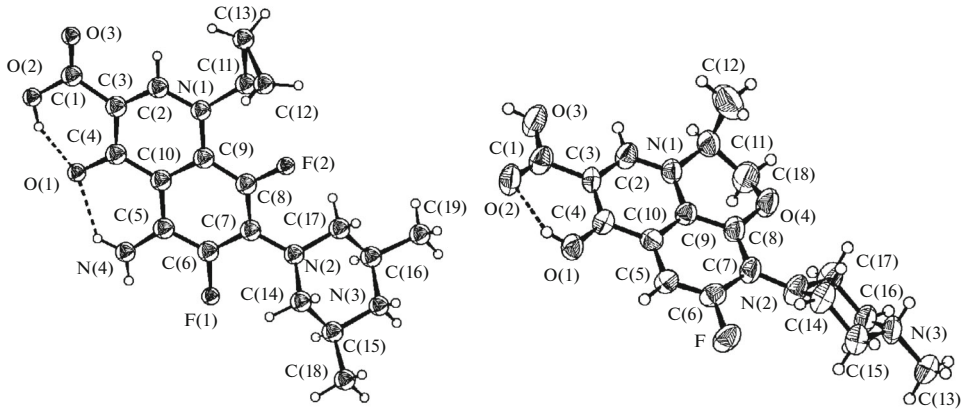

Fig. 1. Cations SfH_2^+ in compound **I** and $LevoH_3^{2+}$ in compound **II** with numbered atoms. Thermal oscillation ellipsoids are calculated with a 50-% confidence probability. Hereinafter, dashed lines are hydrogen bonds.

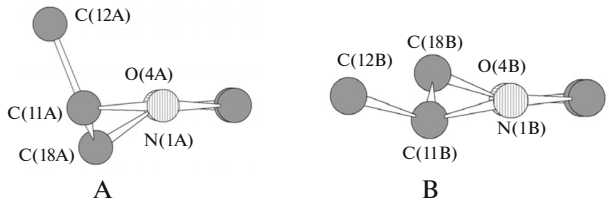

Fig. 2. Shape of the C8–C9–N1–C11–C18–O4 rings in the two independent $LevoH_3^{2+}$ ions in the structure of compound **II**.

The asymmetric part of the unit cell of in a crystal of compound **II** contains two $LevoH_3^{2+}$ cations (A and B) and four ClO_4^- anions. The bond lengths and bond angles in $LevoH_3^{2+}$ (Fig. 1) coincide with the literature data for levofloxacin [15] and its derivatives [12]. The oxygen atoms in ClO_4^- ions are strongly disordered, especially in the case of Cl4, so the OClO angles at the Cl1 atom are from 107.9(5)° to 110.3(5)°, and the Cl–O bond lengths are 1.411–1.448(7) Å, while these ranges for the Cl4 atom are 97.6°–118.1(13)° and 1.306–1.452(13) Å, respectively. The two independent $LevoH_3^{2+}$ cations have an ordinary structure [12]: the two six-membered rings N1–C2–C3–C4–C10–C9 and C5–C6–C7–C8–C9–C10 are nearly planar, and the third ring N2–C14–C15–N3–C16–C17 has a "chair" conformation. The fourth ring C8–C9–N1–C11–C18–O4 in cation **A** has an "envelope" conformation, where the C18 atom is 0.667 Å out of the plane, in which the other ring atoms lie (maximum deviation is 0.010(5) Å for N1), and the same ring in cation B has a "half-chair" conformation, where the atoms C11 (0.28 Å) and C18 (0.44 Å) deviate in different directions from the plane in which the other ring atoms lie nearly without any deviations (Fig. 2). The fourth rings alone do not obey the inversion bond between $LevoH_3^{2+}$ ions, thus causing a non-centrosymmetric character of the structure.

The structures of compounds I and II (Figs. 3 and 4) contain both intra- and intermolecular hydrogen bonds. The presence of an additional NH_2 group in SfH_2^+ in comparison with $LevoH_3^{2+}$ and the different natures of anions and the different degrees of protonation of fluoroquinolones have various effects on the hydrogen bonds in compounds **I** and **II**. The O1 atom in the SfH_2^+ ion is a double acceptor of intramolecular O2–H1···O1 and N4–H5···O1 hydrogen bonds, and Br^- is bonded to three SfH_2^+ cations via N–H···Br hydrogen bonds (Table 2) to form an infinite three-dimensional structure. Alongside with the intramolecular O1–H···O2 hydrogen bond typical for diprotonated fluoroquinolones [17, 18], the structure of

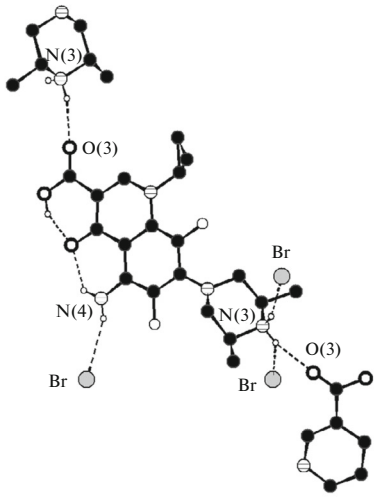

Fig. 3. Hydrogen bonds in the structure of compound **I**. Nitrogen atoms are horizontally shaded, and bromine atoms are shown as grey circles.

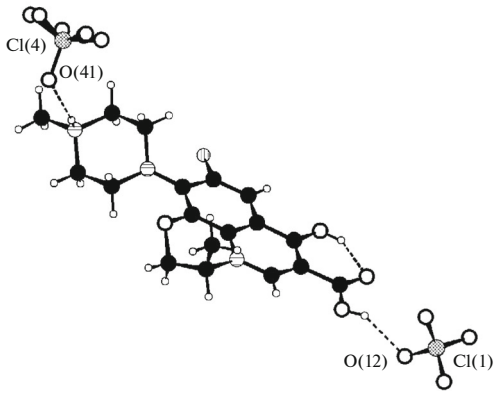

Fig. 4. Hydrogen bonds in the structure of compound II. Nitrogen atoms are horizontally shaded.

compound **II** contains four intermolecular hydrogen bonds like N3–H···O and O3–H···O. In this case, these bonds link each $LevoH_3^{2+}$ cation to two ClO_4^- ions (Fig. 4). C14–H···F hydrogen bonds typical for fluoroquinolones [17] are formed in both structures.

The SfH_2^+ cations in the structure of compound **I** are arranged in pairs in an antiparallel fashion through the inversion center and are bonded via "head-to-tail" π–π-interaction [19] (Table 3). Cations A and B in compound **II** are also linked into pairs via "head-to-tail" π–π-interaction, and the structural units consisting of two $LevoH_3^{2+}$ cations and four ClO_4^-, anions are bonded only by van der Waals forces. The geometric parameters of π–π-interactions in compounds **I** and **II** are close to the values found in some other fluoroquinolone derivatives [8–11, 17].

Table 2. Geometric parameters of D–H···A hydrogen bonds (*d*, Å; angles, deg) in the structures of compounds **I** and **II**

D–H	D–H	H···A	∠DHA	D···A	A	Symmetry codes for atom A
Compound **I**						
O2–H1	0.95	1.61	154	2.498(5)	O1	x, y, z
N3–H2	0.98	2.43	160	3.371(4)	Br	$x - 0.5, 0.5 - y, z - 0.5$
N3–H3	0.98	2.26	132	3.006(5)	O3	$0.5 - x, 0.5 + y, 1.5 - z$
N3–H3	0.98	2.66	126	3.342(4)	Br	x, y, z
N4–H4	0.98	2.60	157	3.518(4)	Br	$x - 0.5, 0.5 - y, z + 0.5$
N4–H5	0.98	1.94	128	2.654(5)	O1	x, y, z
C14–H12	0.97	2.38	115	2.932(4)	F1	x, y, z
Compound **II**						
O1A–H1A	0.95	1.77	143	2.597(8)	O2A	x, y, z
O3A–H3A	0.95	1.86	146	2.702(9)	O12	$x - 1, y, z - 1$
N3A–HN3A	0.98	1.99	150	2.876(12)	O41	$x + 1, y, z$
O1B–H1B	0.95	1.77	142	2.586(9)	O2B	x, y, z
O3B–H3B	0.95	1.74	163	2.665(10)	O21	$x + 1, y, z$
N3B–HN3B	0.98	1.83	171	2.807(12)	O31	$-x, y - 0.5, -z$
C14A–H14A	0.97	2.31	116	2.877(12)	FA	x, y, z
C14B–H14B	0.97	2.33	115	2.878(11)	FB	x, y, z

Table 3. Parameters of π–π-interactions between the N1–C2–C3–C4–C10–C9 rings in compound **I** and the N1–C2–C3–C4–C10–C9 and C5–C6–C7–C8–C9–C10 rings in compound **II**

Compound	Cg_i–Cg_j	*d*, Å	α, deg	β, deg	Cg_i_p, Å	Δ, Å
I	Cg_1–Cg_1	3.664(3)	0	10.31	3.604(2)	0.656
II	Cg_{1A}–Cg_{2B}	3.779(5)	4.2(4)	22.80	3.396(3)	–
	Cg_{2A}–Cg_{1B}	3.861(5)	5.1(4)	23.67	3.429(3)	
	Cg_{1B}–Cg_{2A}	3.861(5)	5.1(4)	27.34	3.370(4)	
	Cg_{2B}–Cg_{1A}	3.780(5)	4.2(4)	26.02	3.484(3)	

ACKNOWLEDGMENTS

This work was performed in the Siberian Federal University within the state task of the Russian Ministry of Education and Science for 2014–2016 (project no. GKh-3).

REFERENCES

1. L. A. Mitsher, Chem. Rev. **105**, 559 (2005).
2. D. Shingnapurkar, R. Butcher, Z. Afrasiabi, et al., Inorg. Chem. Commun. **10**, 459 (2007).
3. G. E. Stein and D. H. Havlichek, Pharmacotherapy **17**, 1139 (1997).
4. E. N. Padeiskaya, *Prevention, Diagnosis, and Pharmacotherapy of Some Infectious Diseases* (Bioinform, Moscow, 2002) [in Russian].
5. C.-L. Zhang and Y. J. Wang, Chem. Eng. Data **53**, 1295 (2008).
6. M. Hewitt, M. T. D. Cronin, S. J. Enoch, et al., J. Chem. Inf. Model **49** (11), 2572 (2009).
7. A. Llinas, J. C. Burley, T. J. Prior, et al., Cryst. Growth Des. **8** (1), 114 (2008).
8. A. D. Vasiliev and N. N. Golovnev, J. Struct. Chem. **54**, 607 (2013).
9. N. N. Golovnev, I. I. Golovneva, M. S. Molokeev, and G. A. Glushchenko, J. Struct. Chem. **54**, 377 (2013).
10. N. N. Golovnev, S. D. Kirik, and A. D. Vasiliev, J. Mol. Struct. **1021**, 112 (2012).
11. A. D. Vasil'ev and N. N. Golovnev, Russ. J. Inorg. Chem. **57**, 248 (2012).
12. A. D. Vasiliev and N. N. Golovnev, J. Struct. Chem. **51**, 183 (2010).
13. G. M. Sheldrick, SADABS, Version 2.01 (Bruker, Madison, Wisconsin, USA, 2004).
14. G. M. Sheldrick, SHELXTL, Version 6.10 Bruker, Madison, Wisconsin, USA, 2004).
15. Cambridge Structural Database. Version 5.35 (Univ. of Cambridge, Cambridge (UK), 2013).
16. A. D. Vasil'ev and N. N. Golovnev, Russ. J. Inorg. Chem. **59**, 322 (2014).
17. M. D. Prasanna and T. N. G. Row, J. Mol. Struct. **559**, 255 (2001).
18. A. D. Vasiliev, N. N. Golovnev, M. S. Molokeev, and T. D. Churilov, J. Struct. Chem. **46**, 363 (2005).
19. J. W. Steed and J. L. Atwood, *Supramolecular Chemistry*, 1st Ed. (CRC Press, 2004; IKTs Akademkniga, Moscow, 2007).

Translated by E. Glushachenkova