Journal of Structural Chemistry. Vol. 54, No. 2, pp. 377-382, 2013

CRYSTAL STRUCTURE OF ENROFLOXACINIUM TETRABROMIDODICHLORIDOSTANNATE(IV) MONOHYDRATE

© **N. N. Golovnev,[1] M. S. Molokeev,[2] I. I. Golovneva,[1] and G. A. Glushchenko[2]**

UDC 541.49:549.251:548.737

A new compound $EnrH_3[SnBr_{3.46}Cl_{2.54}]\cdot H_2O$, where $EnrH_3^{2+}$ is the enrofloxacinium cation ($C_{19}H_{24}FN_3O_3^{2+}$), is synthesized and its crystal and molecular structure is determined. Crystallographic data for enrofloxacinium tetrabromidodichloridostannate(IV) monohydrate are as follows: $a = 17.1262(19)$ Å, $b = 10.3435(11)$ Å, $c = 17.2582(19)$ Å, $\beta = 119.203(1)°$, $V = 2640.5(4)$ Å^3, space group $P2_1/c$, $Z = 4$. Hydrogen bonds form a branched three-dimensional network linking $EnrH_3^{2+}$, $[SnBr_{3.46}Cl_{2.54}]^{2-}$, and water molecules. The structure is also stabilized by the π–π interaction of $EnrH_3^{2+}$ aromatic rings.

DOI: 10.1134/S0022476613020157

Keywords: crystal structure, enrofloxacinium cation, tetrabromidodichloridostannate(IV) anion , hydrogen bonds.

In human organism, tin is a normal body component. The greatest amount of it is contained in tooth enamel (up to 93 mg/kg), nails (up to 12 mg/kg), and bones (up to 1.4 mg/kg). Tin enters in the composition of the digestive enzyme gastrin, effects the activity of flavin enzymes, can strengthen the growth processes. Its compounds are used in toothpastes, in the therapy of yellow plague, as the ingredients of radiopharmaceuticals and anticancer agents [1, 2]. Anticancer activity of mixed-ligand bromide chloride complexes of Sn(IV) has been revealed [3]. The structural features, reactivity, and biological activity of organotin compounds have extensively been studied over the past three decades. However, complexes with biologically active ligands are poorly examined, in particular, there are no data at all for the complexes with representatives of an important class of synthetic antibiotics: fluoroquinolones. In the past several years, fluoroquinolones attract keen interest of the scientific community due to practical and fundamental aspects. Indeed, their adoption is an important step in therapy [4].

One representative of this most successful group of synthetic antibiotics is enrofloxacin ($C_{19}H_{22}FN_3O_3$ — 1-cyclopropyl-7-(4-ethylpiperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, EnrH). It exhibits a wide range of activity against a large number of gram-negative and gram-positive bacteria, including those resistant to β-lactame antibiotics and sulfonamides. It is used in treating infections of the urinary tract, pyelonephritis, veneral diseases, prostatitis, skin and histologic infections [5]. Enrofloxacin was the first fluoroquinolone that came to be applied in veterinary to treat urinary and respiratory tracts, skin infections. It is widely used in the production of poultry meat in order to control respiratory and enteric infections [6].

[1]Siberian Federal University, Krasnoyarsk; ngolovnev@sfu-kras.ru. [2]L. V. Kirensky Institute of Physics, Siberian Division, Russian Academy of Sciences, Krasnoyarsk. Translated from *Zhurnal Strukturnoi Khimii*, Vol. 54, No. 2, pp. 317-322, March-April, 2013. Original article submitted April 13; revised June 18, 2012.

In this work, a new compound–enrofloxacinium tetrabromidodichloridostannate(IV) $EnrH_3[SnBr_{3.46}Cl_{2.54}]\cdot H_2O$ was synthesized and its crystal structure was determined.

EXPERIMENTAL

In the work, the following reagents were used: enrofloxacin (Fluka, basic substance content ≥98%), HBr (chemically pure), $SnCl_4\cdot 5H_2O$ (chemically pure).

Synthesis of $C_{19}H_{24}FN_3O_3[SnBr_{3.46}Cl_{2.54}]\cdot H_2O$ (1). 0.2 g of EnrH were dissolved in 3 ml of concentrated HBr. To the prepared yellow solution 0.2 g of $SnCl_4\cdot 5H_2O$ were added. The molar ratio $EnrH:SnCl_4 = 1:1$. Initially, a light yellow rubber-like precipitate formed, which after short grinding with a glass rod turned into a fine light yellow precipitate; it was filtered, washed with acetone, and left to dry in the air until constant weight. Light yellow single crystals of the compound were isolated by evaporation of the filtrate.

Single crystal X-ray diffraction study. The X-ray diffraction experiment was performed on a SMART APEXII X-ray single crystal diffractometer with a two-dimensional detector using monochromatic MoK_α radiation, λ = 0.7106 Å. The data were collected at 100 K in order to increase the intensities of large-angle reflections.

Main crystallographic characteristics and parameters of the experiment are listed in Table 1.

The X-ray absorption by the crystal was taken into account based on the analysis of the intensities of equivalent reflections. After this, the intensities of equivalent reflections were averaged, and subsequently only independent reflections were used.

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

Chemical formula	$C_{19}H_{24}FN_3O_3[SnBr_{3.46}Cl_{2.54}]\cdot H_2O$
M_r	864.66
Space group, Z	$P2_1/c$, 4
a, b, c, Å; β, deg	17.1262(19), 10.3435(11), 17.2582(19); 119.203(1)
V, Å^3	2668.6(5)
d_x, g/cm^3	2.147
μ, mm^{-1}	6.429
Wavelength λ, Å	MoK_α, 0.7106
Temperature of experiment, K	100(0.1)
Number of measured/independ. reflections, N_1	25384/7178
Number of reflections with $I > 2\sigma(I)$, N_2	4030
Absorption accounting	Multiscanning
R_{int}	0.0989
$2\theta_{max}$, deg	59.58
h, k, l	$-23 \le h \le 23$, $-14 \le k \le 14$, $-23 \le l \le 24$
R [over N_1 reflections]	0.1247
R [over N_2 reflections]	0.0513
$wR(F^2)$ [over N_1 reflections]	0.1036
$wR(F^2)$ [over N_2 reflections]	0.0844
S	1.009
Weight scheme	$w=1/[\sigma^2(F_0^2) + (0.0308P)^2+0P]$, where $P = \max(F_0^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	< 0.004
$\Delta\rho_{max}/\Delta\rho_{min}$, e/Å^3	1.251/–1.143
Extinction coefficient (SHELX-97)	< 0.0004 was not introduced

The model was determined using the SHELXS software [7] by direct methods. The coordinates of all non-hydrogen atoms were found. The structure was refined by the least-squares method using the SHELXL97 software [8]. At first, it was suggested that with an excess of HBr Sn(IV) formed a polyatomic $SnBr_6^{2-}$ anion, which is contained in 24 compounds presented in the Cambridge Structural Database (CCDC) [9]. However, the thermal parameters of all Br atoms were abnormally high, and the anisotropic refinement failed to improve the refinement. Therefore, it was suggested that in addition to Br atoms compound **1** contained Cl atoms, and this hypothesis was supported by the results of X-ray fluorescence analysis. The X-ray fluorescence data (Bruker S4 Pioneer) confirmed the presence of chlorine in the substance, but its content declined after each 10 min measurement and decreased from 4.91 wt.% (the 1st measurement) to 2.39 wt.% (the 5th measurement). These data are indirectly supported by an increase in the content of bromine from 42.7 wt.% to 45.0.wt % in the sample under investigation. For $C_{19}H_{24}FN_3O_3[SnBr_{3.46}Cl_{2.54}]\cdot H_2O$, it was calculated (wt.%): Br 31.97, Cl 10.41. Apparently, under X-ray radiation a rapid decomposition of the compound with the removal of gaseous HCl occurs.

The occupancies of Br/Cl sites were refined taking into account that the sum of Br and Cl occupancies at one site equals unity. As a result, the *R* factor sharply decreased, and the anisotropic thermal parameters took ordinary values. Thermal parameters of all the other non-hydrogen atoms were also refined anisotropically. From difference electron density maps, the maxima corresponding to all hydrogen atoms, except those belonging to water molecule, were determined. The coordinates of all hydrogen atoms were further idealized, and for all of them only one isotropic thermal parameter was refined in order to reduce the number of refined parameters.The refinement was stopped at $R = 5.13\%$ for 7178 strong reflections with $F^2 > 2\sigma(F^2)$. The extinction coefficient was not refined due to its low value.

Graphical representation of all crystal structures and molecules was made using the DIAMOND software [10]. The structure was deposited with the Cambridge Crystallographic Data Centre under No. 865975. The data can be obtained via the following web-site: www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

In the literature, the data on the synthesis of ionic compounds of enrofloxacin with $EnrH_2^+$ or $EnrH_2^{2+}$ cations are absent. The Cambridge Structural Database [9] contains information for only one ionic compound: 2-hydroxy ethanolamine enrofloxacinate, in which enrofloxacin is in the form of the Enr^- anion. The pK_a values for enrofloxacin (pK_{a1} = 5.94±0.09, pK_{a2} = 8.70±0.44) [11] are similar to those obtained for ciprofloxacin [12], thus it can be supposed that the $EnrH_3^{2+}$ ion will dominate in the solution with the HCl concentration of above 4–5 M and can be precipitated by appropriate anions in the form of salts.

An independent part of the cell of compound **1** contains one $EnrH_3^{2+}$ cation, one $SnBr_{3.46}Cl_{2.54}^{2-}$ anion, and one water molecule (Fig. 1). In the compound studied the lengths of C–O, C–N, C–F, and C–C bonds and the respective bond angles coincided with those found previously for other compounds of enrofloxacin [9]. Protonation of the O1 atom is confirmed by the elongation of the respective C4–O1 bond to 1.324(7) Å as compared to unprotonated O1 in 2-hydroxy ethanolamine enrofloxacinate (1.241 Å) [13]. The C1–O2 and C1–O3 distances in the deprotonated carboxyl group of 2-hydroxy ethanolamine enrofloxacinate are approximately the same (1.24 Å and 1.25 Å). In **1**, *d*(C1–O2) = 1.236(7) Å and *d*(C1–O3) = 1.317(7) Å, which in the first case corresponds to a double bond and in the second one to a single bond and is explained by proton bonding to the O3 atom.

The $[SnBr_{3.46}Cl_{2.54}]^{2-}$ anions are distorted octahedra {*d*(Sn–Br/Cl) = 2.4901(12)÷2.5741(10) Å}; 12 Br/Cl–Cd–Br/Cl angles are in a range of 85.89(3)÷93.46(3)°; 3 are in a range of 173.60(3)÷177.66(4)°. The $EnrH_3^{2+}$ ion contains a planar moiety comprised of aromatic rings and a piperazine ring with *chair* conformation (Fig. 1). The N3 nitrogen atom is protonated. To the carbonyl O1 atom, a hydrogen atom is bonded (HO1) which forms an intramolecular hydrogen bond with O2 oxygen of the carboxyl group. An intramolecular C14–H14A···F hydrogen bond forms another six-membered ring. The

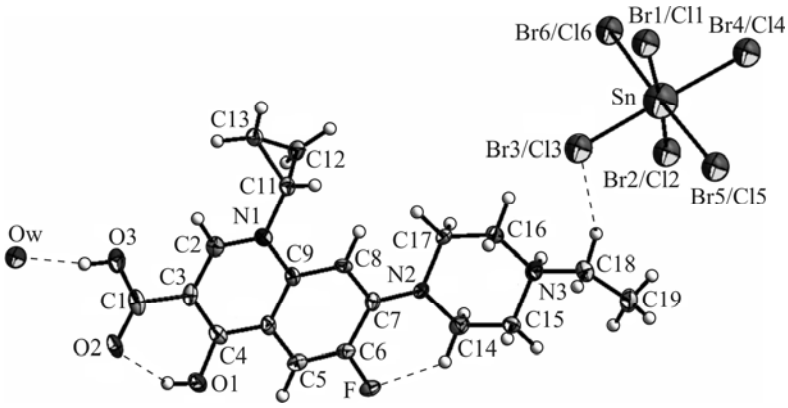

Fig. 1. Independent part of the cell of $C_{19}H_{24}FN_3O_3[SnBr_{3.46}Cl_{2.54}]\cdot H_2O$. Hydrogen bonds are denoted by dashed lines.

TABLE 2. Hydrogen Bonds D–H···A, (Å, deg) in Compound **1**

D–H	*d*(D–H)	*d*(H···A)	∠DHA	*d*(D···A)	A
N3–H3	0.93	2.46	155.3	3.324(5)	Br6 [*x*, *y*–1, *z*]
O1–HO1	0.84	1.90	145.6	2.637(6)	O2
C14–H14A	0.99	2.02	130.5	2.763	F
O3–HO3	0.84	1.78	166.2	2.607(6)	Ow
C11–H11	1.0	2.81	135.1	3.586(6)	Br1
C18–H18B	0.99	2.85	140.7	3.674(6)	Br3 [1–*x*, *y*–1/2, 1/2–*z*]
C14–H14B	0.99	2.88	147.7	3.754(6)	Br4 [*x*, *y*–1, *z*]
C17–H17A	0.99	2.87	148.1	3.747(6)	Br4 [*x*, *y*–1, *z*]
C19–H19C	0.98	2.75	146.1	3.603(7)	Br6 [1–*x*, *y*–1/2, 1/2–*z*]

intramolecular motifs *S*(6) [14] typical of the ionic compounds of fluoroquinolones correspond to them. In addition to two intramolecular hydrogen bonds, there are 7 intermolecular hydrogen bonds in the structure of **1**. The Br2 and Br5 atoms do not participate in the formation of hydrogen bonds. Parameters of hydrogen bonds are given in Table 2.

The $EnrH_3^{2+}$ ions are engaged in hydrogen bonding with $[SnBr_{3.46}Cl_{2.54}]^{2-}$ anions. One of them forms at once three two-center hydrogen bonds, with two of them between carbon hydrogen atoms and one Br4 atom forming a supramolecular motif $R_2^1(6)$. N3–H3···Br6 and C19–H19C···Br6 interactions close two seven-membered rings [motifs $R_2^2(7)$]. Each of three other $EnrH_3^{2+}$ provides one hydrogen bond with bromine atoms forming the chains. The seventh hydrogen bond results from the O3–HO3···Ow interaction.

The existence of intermolecular hydrogen bonds between $EnrH_3^{2+}$ leads to the formation of staggered one-dimensional chains (Fig. 2) of enrofloxacin molecules. Due to this, three-dimensional channels of 8.1 Å in diameter form in the substance, in which $[SnBr_{3.46}Cl_{2.54}]^{2-}$ ions and water molecules are located.

The analysis of shortened intermolecular contacts by means of the PLATON software [15] revealed the presence of the π–π interaction between the aromatic systems of different molecules of the head–tail type [14], which is typical of the other compounds of fluoroquinolones [9]. Geometric parameters of this interaction are given in Table 3.

The comparison of the obtained structure of **1** with monohydrate structures containing a deprotonated cation of ciprofloxacin $C_{17}H_{22}FN_3O_3^{2+}CuCl_4^{2-}\cdot H_2O$ [16] and $C_{17}H_{22}FN_3O_3^{2+}CuBr_4^{2-}\cdot H_2O$ [17] showed a significant difference in the intermolecular motifs formed. The hexahalide $[SnBr_{3.46}Cl_{2.54}]^{2-}$ anion provides a different system of hydrogen bonds than that

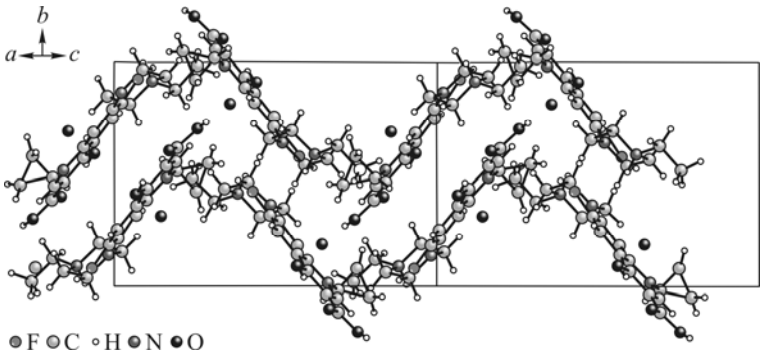

Fig. 2. Staggered one-dimensional chains of $EnrH_3^{2+}$ and oxygen atoms of water molecules in the formed channels. For simplicity, $[SnBr_{3.46}Cl_{2.54}]^{2-}$ anions in channels are not shown.

TABLE 3. Parameters of the π–π Interaction of $EnrH_3^{2+}$ Cations in the Crystal of **1**

Cg_i–Cg_j	d(Cg–Cg), Å	α, deg	β, deg	γ, deg	Cg_i_p, Å	Shift, Å
Cg_1–Cg_1'	3.900	0	28.78	28.78	3.418	1.877
Cg_1–Cg_2'	3.736	3.1	23.15	21.95	3.465	1.877

Cg_1 is the C2C3C4C9C10N1 ring plane; Cg_2 is the C5C6C7C8C9C10 ring plane. Cg_1' and Cg_2' are produced by transformation [2–x, –y, 1–z].

in the compared compounds with tetrahalide anions. Since we failed to determine the coordinates of hydrogen atoms of water molecules, a more detailed comparison of the structure of the compounds under consideration is not possible. It can be supposed that the formation of one-dimensional staggered chains by enrofloxacindium ions occurs with the participation of hydrogen atoms of water, as for other monohydrate ionic compounds of fluoroquinolones [16, 17].

Therefore, the structure of **1** is stabilized by a network of hydrogen bonds and the π–π interaction and contains three-dimensional channels of 8.1 Å in diameter, in which $[SnBr_{3.46}Cl_{2.54}]^{2-}$ ions and water molecules are located. In the obtained substances, supramolecular $R_2^1(6)$ and $R_2^2(7)$ motifs appear, which were previously unknown for the ionic compounds of fluoroquinolones.

The work was supported by the grant of the President of the Russian Federation for the support of leading scientific schools of the Russian Federation (NSh-4828.2012.2) and the Federal Targeted Program "Scientific and Scientific Pedagogical Personnel of Innovative Russia, 2009-2013" (State contracts Nos. 02.740.11.0269 and 02.740.11.0629).

REFERENCES

1. L. Nagy, A. Szorcsik, and K. Kovacs, *Acta Pharm. Hungary*, **70**, No. 2, 53-71 (2000).
2. S. Tabassum and C. Pettinari, *J. Organometallic Chem.*, **691**, 1761-1766 (2006).
3. Yu. Li, Ya. Li, X. Niu, et al., *J. Inorg. Biochem.*, **102**, No. 9, 1731-1735 (2008).
4. L. A. Mitsher, *Chem. Rev.*, **105**, No. 2, 559-585 (2005).
5. A. Tarushi, C. P. Raptopoulou, V. Psycharis, et al., *Bioorg. Med. Chem.*, **18**, 2678-2685 (2010).
6. H. M. Otker and I. A. Balcioglu, *J. Hazardous Mater.*, **122**, 251-258 (2008).
7. G. M. Sheldrick, *Acta Crystallogr.*, **A46**, 467-473 (1990).
8. G. M. Sheldrick, *Shelxl-97*: *A Computer Program for Refinement of Crystal Structures*, Univ. Göttingen, Germany.
9. *Cambridge Structural Database*, *Version 5.32*, Univ. Cambridge, UK (2010).

10. K. Brandenburg and M. Berndt, *DIAMOND-Visual Crystal Structure Information System CRYSTAL IMPACT*, Postfach 1251, D-53002 Bonn.
11. M. Lizondo, M. Pons, M. Gallardo, et al., *J. Pharm. Biomed. Anal*., **15**, 1845-1849 (1997).
12. N. N. Golovnev, A. I. Petrov, N. V. Dorokhova, et al., *J. of Siberian Federal University*, **3**, No. 1, 58-63 (2010).
13. H.-X. Sun, Y. Li, and Y.-J. Pan, *Acta Crystallogr*., **E60**, o1694-o1696 (2004).
14. J. W. Steed and J. L. Atwood, *Supramolecular Chemistry*, 1/2, 2nd edition, Wiley (2009).
15. *PLATON*, *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands (2008).
16. A. D. Vasil'ev, N. N. Golovnev, M. S. Molokeev, et al., *J. Struct. Chem*., **46**, No. 2, 363-370 (2005).
17. A. D. Vasil'ev and N. N. Golovnev, *J. Struct. Chem*., **52**, No. 4, 809-812 (2011).