Journal of Structural Chemistry. Vol. 59, No. 3, pp. 646-651, 2018.

CRYSTAL STRUCTURE AND PROPERTIES OF LEVOFLOXACINIUM 2-THIOBARBITURATE TRIHYDRATE

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The structure of levofloxacinium 2-thiobarbiturate trihydrate $LevoH_2^+Htba^-\cdot 3H_2O$ (**I**) (LevoH is levofloxacin, H_2tba is 2-thiobarbituric acid) is determined (CIF file CCDC No. 1547466); its thermal decomposition and IR spectrum are studied. The crystals of **I** are triclinic: $a = 8.670(1)$ Å, $b = 9.605(1)$ Å, $c = 15.786(2)$ Å, $\alpha = 89.144(5)°$, $\beta = 88.279(5)°$, $\gamma = 76.068(5)°$, $V = 1275.4(3)$ Å^3, space group $P1$, $Z = 2$. The unit cell of **I** contains two $LevoH_2^+$ ions, two $Htba^-$ ions, and six H_2O molecules. The absolute structure of the crystal and the configuration of the chiral center in a levofloxacin molecule S are determined. Experiments for generating the second optical harmonics gave a positive result. Intermolecular hydrogen bonds (HBs) N–H···O and O–H···O in **I** form a bilayer system along the *ab* diagonal with hydrophilic moieties within a layer and hydrophobic moieties directed outward. The structure is stabilized by multiple HBs and the π–π interaction between the $Htba^-$ and $LevoH_2^+$ ions and between the $LevoH_2^+$ ions.

DOI: 10.1134/S0022476618030204

Keywords: levofloxacin, 2-thiobarbituric acid, salt, crystal structure, absolute structure, thermal stability, IR spectrum.

Fluoroquinolones are one of the classes of synthetic antibiotics that are most broadly used in clinical practice [1, 2]. An important representative of this class is levofloxacin (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]1,4-benzoxazine-6-carboxylic acid (LevoH, Fig. 1) applied, inter alia, in treating the urinary infectious diseases and pneumonia. Due to its low bioavailability large LevoH doses are needed [3], but it is marginally

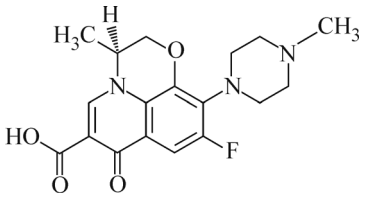

Fig. 1. Graphical formula of levofloxacin (LevoH, $C_{18}H_{20}FN_3O_4$).

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Translated from *Zhurnal Strukturnoi Khimii*, Vol. 59, No. 3, pp. 668-673, March-April, 2018. Original article submitted July 3, 2017; revised September 21, 2017.

soluble in water. To improve solubility it can be transformed in other compounds, for example, organic salts [4]. Noncentrosymmetric crystals of levofloxacin are a nonlinear optical (NLO) material [5] and its salts can also exhibit NLO properties. Within the systematic study of the structure of fluoroquinolone salts, levofloxacinium 2-thiobarbiturate trihydrate $LevoH_2^+Htba^-\cdot 3H_2O$ (**I**) was characterized by single crystal XRD.

EXPERIMENTAL

Levofloxacin hemihydrate $LevoH\cdot 1/2H_2O$ (Zhejiang Kangyu Pharmaceutical Co., Ltd, China) and H_2tba (chemically pure) were used without additional purification.

Synthesis of $LevoH_2^+Htba^-\cdot 3H_2O$ (I). A mixture of 0.54 mmol of $LevoH\cdot 1/2H_2O$ and 0.54 mmol of H_2tba was dissolved in 5 ml of water at 80 °C. The solution was cooled to room temperature and then kept in a refrigerator at 4 °C for 2 days. A pale pink precipitate in the form of platy crystals was filtered off, washed with 1 ml of water, 1 ml of acetone, and dried in the air until constant weight. The yield was 43%. A single crystal for XRD was selected from the bulk precipitate.

Single crystal XRD. The intensities of X-ray reflections from the crystal of 0.40×0.30×0.12 mm were measured at 150 K on a SMART APEX II single crystal diffractometer with a CCD detector (Bruker AXS), MoK_α radiation, $\lambda = 0.71073$ Å. The experiments showed that the crystal belongs to the triclinic symmetry. Since the LevoH molecule is chiral and the compound used for the synthesis was pure, we decided to determine and refine the structure in the noncentrosymmetric space group $P1$. The refinement was stable and gave low R factors ($R_B = 4.15\%$) and atomic thermal ellipsoids.

The main crystallographic characteristics of **I** and the parameters of the experiment are as follows: molecular formula $C_{18}H_{21}FN_3O_4^+$, $C_4H_3N_2O_2S^-$, $3(H_2O)$, chemical formula $C_{22}H_{30}FN_5O_9S$, $a = 8.670(1)$ Å, $b = 9.605(1)$ Å, $c = 15.786(2)$ Å, $\alpha = 89.144(5)°$, $\beta = 88.279(5)°$, $\gamma = 76.068(5)°$, $V = 1275.4(3)$ Å^3, space group $P1$, $Z = 2$, $D_x = 1.457$ g/cm^3, $\mu = 0.195$ mm^{-1}, $2\theta_{max} = 55.05°$; 15194 measured reflections, 10753 independent reflections, 9109 reflections with $F > 4\sigma(F)$, $-11 \le h \le 11$, $-12 \le k \le 12$, $-20 \le l \le 20$, $R_{int} = 0.0223$, weight scheme $w = 1/[\sigma^2(F_0^2) + (0.0570P)^2]$, 727 refined parameters, $R1[F_0 > 4\sigma(F_0)] = 0.0415$, $wR2[F_0 > 4\sigma(F_0)] = 0.1000$, $R1_{all} = 0.0517$, $wR2_{all} = 0.1075$, $GOOF = 1.016$, $\Delta\rho_{max}/\Delta\rho_{min} =$ $= 0.310/-0.282$ e/Å^3, $(\Delta/\sigma)_{max} = 0.001$, Flack parameter 0.03(5).

The structure has been deposited with the Cambridge Structural Database under CCDC number 1547466. The data are available via the website www.ccdc.cam.ac.uk/data_request/cif. The powder X-ray diffraction pattern of a polycrystalline sample of **I** at room temperature (Bruker D8 ADVANCE diffractometer (Multiple-Access Center of the Institute of Physics, Siberian Branch, Russian Academy of Sciences), VANTEC linear detector, CuK_α radiation) coincided with that calculated from the single crystal data, which confirmed the identity of the polycrystalline substance with the single crystal examined.

A crystal unit cell of **I** contains two $LevoH_2^+$ ions, two $Htba^-$ ions, and six H_2O molecules (Fig. 2). Neutral levofloxacin molecules have a bipolar structure where the carboxyl group is deprotonated and the >NMe group of the piperazinyl ring (N1A and N1B atoms) is protonated $>N(Me)H^+$ [4]. When compound **I** forms, the proton transfers from the C5 atom of thiobarbituric acid to the deprotonated carboxyl group of the zwitterion of neutral levofloxacin to form the $Htba^-$ anion and the $LevoH_2^+$ cation. After protonation, the LevoH geometric parameters did not change and also coincided with those previously determined for the $LevoH_2^+$ ion [4, 6]. The main bond lengths and bond angles in the $Htba^-$ ion in **I** coincided with those previously obtained in [7-10]. The configuration of the chiral centers of independent molecules (C15 atoms) determined from the S crystal absolute structure is the same as in the initial levofloxacin molecule. As usual [6], the morpholine ring has an *envelope* conformation and the piperazine ring has a *chair* conformation.

Although the $LevoH_2^+$ ion is chiral, sometimes crystallographers erroneously choose a centrosymmetric space group for structure models. For instance, wrong P-1 and *Fddd* groups were chosen for $[Zn_2(Levo)_2(odpa)]\cdot 5.5H_2O$, where odpa is

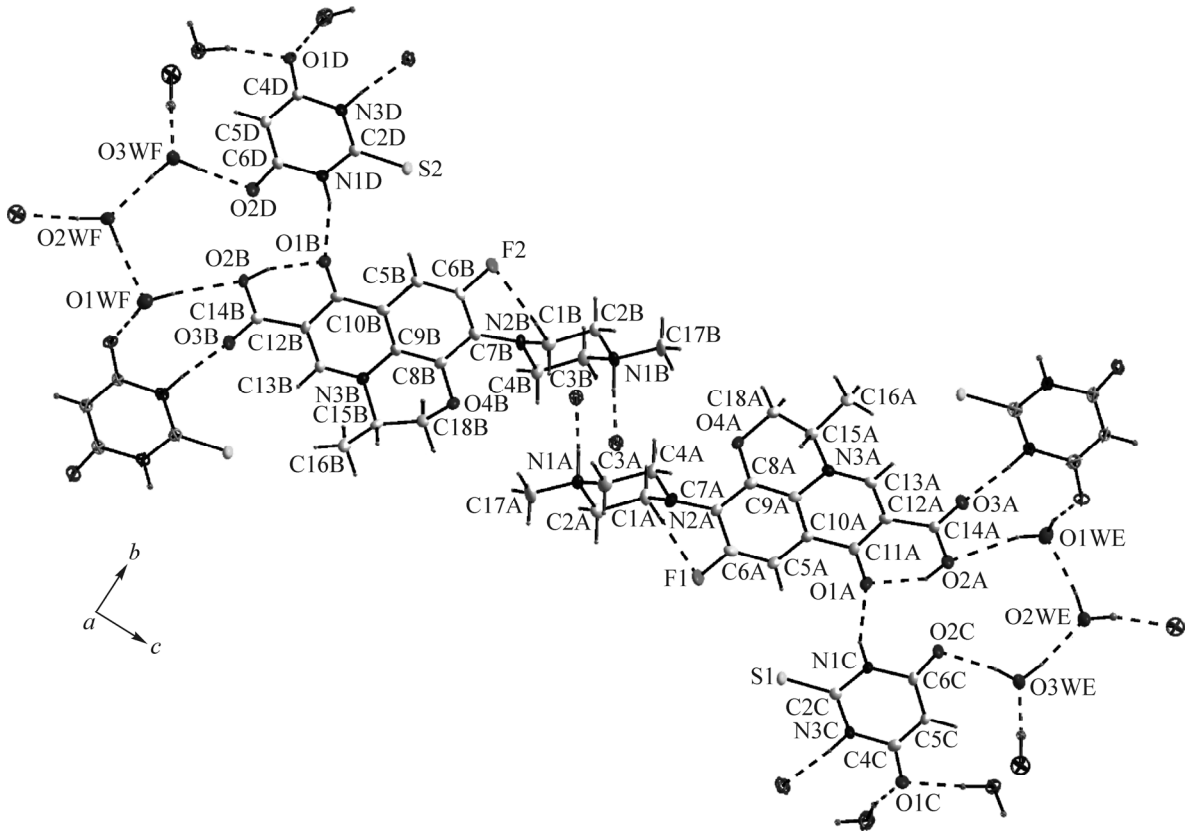

Fig. 2. Structure of $LevoH_2(Htba)\cdot 3H_2O$. The atoms that have not undergone translational transformations are denoted by symbols. Their neighboring atoms generated by translational symmetry elements are shown by their three main ellipsoids. The bonds between these two types of atoms and HBs are shown by dashed lines. The atomic thermal ellipsoids are shown at the 50% probability level, except for the hydrogen atoms shown by spheres.

4,4′-oxydiphthalate (CCDC 861272, IGUCOE, $R_B = 6.72\%$, with the disordered C12, C13, C12A, C13A, C30, C31, C30A, C31A atoms) [11], and $\{[Cu(Levo)_2][Cu_2Br_3]\cdot 2H_2O\}_n$ (CCDC 274841, WARXAP, $R_B = 15.07\%$, anomalous thermal ellipsoids of the C13, C14, C18, and N3 atoms) [12]. Non-centrosymmetry of the crystal of **I** is confirmed by visual observations of generating the second optical harmonics (Nd:YAG laser, $\lambda = 1064$ nm). Organic substances with NLO properties have some advantages as compared to inorganic ones [13], hence, in the future we intend to determine the NLO characteristics of compound **I**.

In each $LevoH_2^+$ cation two intramolecular hydrogen bonds (HBs) C–H···F, O–H···O (Fig. 2) form supramolecular motifs S(6) (Fig. 3) typical of fluoroquinolones [14-16]. Multiple intermolecular HBs N–H···O, O–H···O (Fig. 3*a*, Table 1) form a bilayer structure in the plane of the *a*-*b* and *c* vectors, with hydrophilic moieties located within a layer and hydrophobic moieties directed outward (Fig. 3*b*). The cyclic supramolecular motifs $R_6^6(20)$, $R_6^5(14)$, $R_6^4(12)$, $R_5^4(10)$ can be identified in the layers.

The $LevoH_2^+$ ion contains two HB donors (O–H of the carboxyl group; the $(CH_3)NH^+$ group of the piperazinyl ring) and eight HB acceptors (three N atoms, four O atoms, and one F atom [4]). However, both HB donors and only three HB acceptors, namely, O1, O2, and O3 atoms, are involved in intermolecular HBs (Fig. 3*a*). The H atom of the COOH group, as in other fluoroquinolones [14-16], forms a strong intramolecular HB $O2_{carboxyl}$–H···$O1_{ketone}$ bond which decreases its capability of intermolecular interactions. In compound **I** it is involved in intermolecular HBs only with independent cation A (Table 1, Fig. 3*a*). Water molecules form many intermolecular HBs (Fig. 3*a*). The structure is additionally stabilized by the

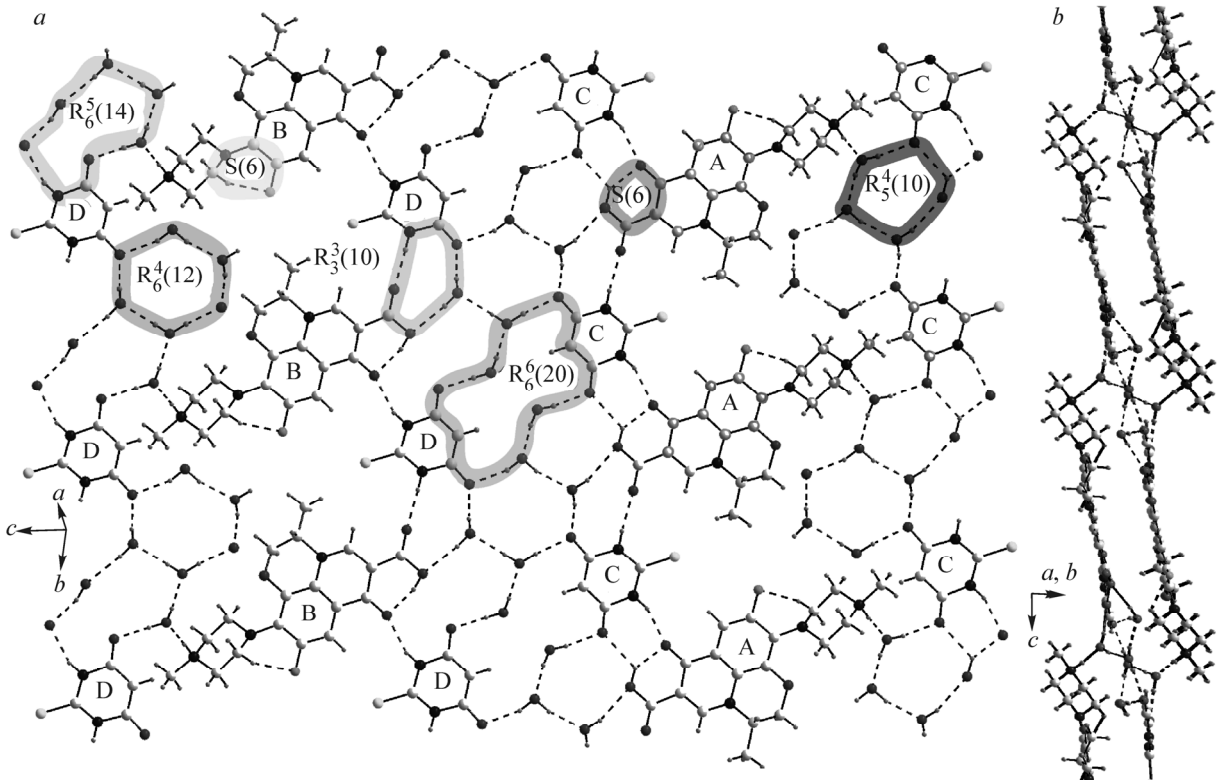

Fig. 3. Scheme of the hydrogen bonding in **I**: the projection perpendicular to the layer lying in the plane of *a*-*b* and *c* vectors (*a*); the view along the bilayer system in the *a*-*b* (*b*) direction. HBs are shown by dashed lines, the supramolecular motifs are marked by wide circles, the independent $LevoH_2^+$ (A, B) and $Htba^-$ (C, D) ions are marked by letters.

π–π interaction between the $Htba^-$ and $LevoH_2^+$ ions and between the $LevoH_2^+$ ions forming pairs (intercentroid distances range from 3.654(2) Å to 4.007(2) Å).

The thermal analysis of **I** was performed on a SDT-Q600 (TA Instruments, USA) apparatus in the air flow (50 ml/min) in a range of 22-350 °C at a heating rate of 10 deg/min. The composition of evolved gases was determined on a Nicolet380 (Thermo Scientific, USA) IR spectrometer combined with a thermal analyzer. The IR spectroscopic analysis of evolved gases indicates that the decomposition of compound **I** begins at ~50 °C with a loss of crystallization water (Fig. 4). The TG and DSC curves suggest two-stage dehydration accompanied by two endothermic effects at 79.2 °C and 113.4 °C. The total weight loss (9.50%) practically coincides with that calculated theoretically under the assumption of three water molecules lost ($-3H_2O$, $\Delta m_{calc} = 9.65\%$). At the first stage at ~100 °C $\Delta m = 6.5\%$, which agrees with a removal of two water molecules ($-2H_2O$, $\Delta m_{calc} = 6.44\%$). Complete dehydration of **I** occurs at 120 °C. In a range 120-250 °C the sample weight remains constant and at $T > 250$ °C the compound melts with decomposition and releases H_2O, CO_2, SO_2, NO gases. In terms of thermal stability, anhydrous compound **I** is better than LevoH whose melting/decomposition point ($T_{melt/decomp}$) is 226.4 °C [17], but close to H_2tba with $T_{melt/decomp} = 250.6$ °C [18].

A band at 3421 cm^{-1} in the IR spectrum (Nicolet 6700, Thermo Scientific, USA; the Multiple-Access Center of the Siberian Federal University) of **I** in KBr corresponds to υ(O–H) of the $LevoH_2^+$ carboxyl group [5, 19, 20]. A strong band at 1724 cm^{-1}, in accordance with [19, 20], was assigned to υ(C = O) in COOH, which also confirms the proton transfer from 2-thiobarbituric acid to levofloxacin as a result of the reaction between them and agrees with the XRD results.

The work was performed within the State Task of the Ministry of Education and Science of the Russian Federation to the Siberian Federal University for 2017-2019 (4.7666.2017/BCh).

TABLE 1. Geometric Parameters of the D–H···A Hydrogen Bonds (bond lengths *d*, Å; angles, deg) in the Structure of **I**

D–H	*d*(D–H)	*d*(H···A)	∠DHA	*d*(D···A)	A	Transformations for A atom
N1A–H0A	0.98	1.69	175	2.672(4)	O3WE O1A	*x*, *y*, *z*
N1C–H1C	0.86	1.98	158	2.793(5)	O3A	*x*, *y*, –1+*z*
N3C–H3C	0.86	1.99	171	2.841(4)	O1A	1+*x*, –1+*y*, –1+*z*
O2A–H02A	0.91(4)	1.80(4)	139(4)	2.561(4)	F1	*x*, *y*, *z*
C1A–H1AA	0.97	2.31	117	2.878(5)	O1C	*x*, *y*, *z*
O1WE–H11E	0.85(4)	1.96(4)	165(5)	2.784(5)	O2A	–1+*x*, 1+*y*, *z*
O1WE–H12E	0.88(3)	2.25(4)	164(3)	3.109(4)	O1D	*x*, *y*, –1+*z*
O2WE–H21E	0.88(3)	1.92(3)	162(4)	2.771(4)	O1WE	*x*, *y*, *z*
O2WE–H22E	0.87(5)	1.94(5)	163(4)	2.786(4)	O2WE	*x*, *y*, *z*
O3WE–H31E	0.86(4)	1.90(4)	171(6)	2.750(4)	O2C	*x*, *y*, *z*
O3WE–H32E	0.83(3)	1.85(3)	169(5)	2.665(4)	O3WF	*x*, *y*, *z*
N1B–H0B	0.98	1.67	176	2.646(4)	O1B	*x*, *y*, *z*
N1D–H1D	0.86	2.00	159	2.818(5)	O3B	*x*, *y*,1+*z*
N3D–H3D	0.86	2.00	169	2.849(5)	O1B	–1+*x*, 1+*y*, 1+*z*
O2B–H02B	0.84(4)	1.75(4)	161(4)	2.556(4)	F2	*x*, *y*, *z*
C1B–H1BB	0.97	2.32	118	2.901(5)	O1D	*x*, *y*, *z*
O1WF–H12F	0.85(4)	1.97(4)	176(5)	2.810(5)	O2B	1+*x*, –1+*y*, *z*
O1WF–H11F	0.87(4)	2.19(4)	172(4)	3.059(4)	O1D	*x*, *y*, 1+*z*
O2WF–H21F	0.90(3)	1.86(3)	172(4)	2.753(4)	O1WE	*x*, *y*, *z*
O2WF–H22F	0.85(5)	1.91(5)	173(4)	2.753(4)	O2WE	*x*, *y*, *z*
O3WF–H31F	0.89(4)	1.84(4)	170(5)	2.721(4)	O2D	*x*, *y*, *z*
O3WF–H32F	0.87(3)	1.79(3)	178(6)	2.652(5)	O2C	*x*, *y*, *z*
O2A–H02A	0.91(4)	2.27(4)	122(4)	2.860(4)		*x*, *y*, 1+*z*

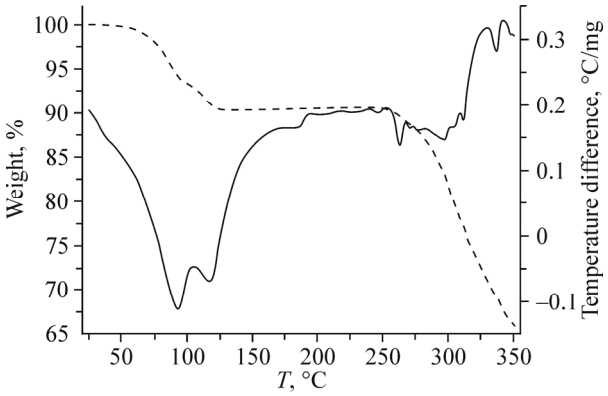

Fig. 4. TG and DSC curves for compound **I**.

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