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STRUCTURE OF THE OXONIUM COMPOUND OF PEFLOXACINIUM HEXACHLORIDOSTANNATE(IV)

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The structure of tris{hexachloridostannate(IV)}-hexachloride-tetrakis(pefloxacinium)-tetraoxonium undecahydrate (CCDC 1551760) $4\mathrm{PefH}_3^{2+}$, $4\mathrm{H_3O}^+$, $3\mathrm{SnCl}_6^{2-}$, $6\mathrm{Cl}^-$, $11\mathrm{H_2O}$ (**I**), (PefH is pefloxacin) is determined. The **I** crystals are triclinic: $a = 13.5474(10)$ Å, $b = 15.2859(11)$ Å, $c = 15.6586(11)$ Å, $\alpha = 94.467(1)°$, $\beta = 105.477(1)°$, $\gamma = 111.560(1)°$, $V = 2849.9(4)$ Å^3, space group $P\overline{1}$, $Z = 1$. The structure is stabilized by multiple intermolecular hydrogen bonds and π–π-interactions between the PefH_3^{2+} ions.

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Keywords: pefloxacinium cation, oxonium cation, chloride ion, hexachloridostannate(IV) anion, ionic compound, crystal structure.

1-Ethyl-6-fluoro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid or simply pefloxacin (PefH, Fig. 1) is an effective antimicrobial agent of the fluoroquinolone group with a broad spectrum of the bactericidal action [1, 2]. Because of its low solubility [3] its salts are used, usually pefloxacinium methanesulfonate $\mathrm{PefH_2(CH_3SO_3)}$. A further search for other PefH salts with improved physical properties is of practical interest. The protolytic equilibrium in aqueous solutions of fluoroquinolones can be represented as [4]

$$\mathrm{QH}_3^{2+} \leftrightarrow \mathrm{QH}_2^{2+} \leftrightarrow \mathrm{QH} \leftrightarrow \mathrm{Q}^-.$$

In a strongly acidic medium fluoroquinolones (QHs) are protonated and form well crystallizing salts containing QH_2^+ and QH_3^{2+} cations.

Within the systematic study of supramolecular organization patterns in the ionic compounds of fluoroquinolones we synthesized a new $4\mathrm{PefH}_3^{2+}$, $4\mathrm{H_3O}^+$, $3\mathrm{SnCl}_6^{2-}$, $6\mathrm{Cl}^-$, $11\mathrm{H_2O}$ compound (**I**) and determined its crystal structure by single crystal XRD.

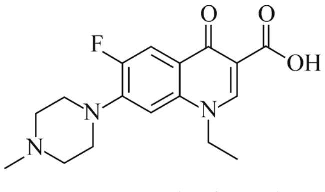

Fig. 1. Structural formula of pefloxacin (PefH, $\mathrm{C_{17}H_{20}FN_3O_3}$).

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So far, only one *fluoroquinolone* compound with the oxonium ion H_3O^+, $Ni(EnrH)_2^{2+}$, 2EnrH, $SiW_{12}O_{40}^{4-}$, $2H_3O^+$ (EnrH is enrofloxacin) [5] (CCDC code ODAFOO) has been structurally characterized; it exhibits the anticancer activity. Fluoroquinolone salts readily form hydrates [4]. The hydrates of acid salts, including those containing H_3O^+ oxonium cations or other $H(H_2O)_n^+$ ions, can possess high proton conductivity. Note that the search for new proton conductors is important now [6]. The structure of only one compound containing simultaneously fluoroquinolone and the $SnCl_6^{2-}$ anion, $\{[K_2(CfH)_2]^{2+}\times [SnCl_6^{2-}]\}_n$, where CfH is ciprofloxacin [7] (code ONEJEX) has been determined.

EXPERIMENTAL

Pefloxacin (CAS 70458-92-3, Sigma-Aldrich, ≥98%), $SnCl_4\cdot 5H_2O$ (CAS 10026-06-9, Sigma-Aldrich, 98%), and 12M HCl (chemically pure) were used without additional purification.

Synthesis of I. 0.2 g (0.6 mmol) of PefH was dissolved in 2 ml of HCl on heating. A hot solution (~80 °C) prepared by dissolving 0.42 g (1.2 mmol) of $SnCl_4\cdot 5H_2O$ in 2 ml of HCl was added dropwise to the obtained solution. The yellow solution was slowly cooled to room temperature and kept for 24 h at room temperature. Then, the solution with the yellow crystalline precipitate was filtered. Yellow single crystals of compound **I** were obtained by slow evaporation of the filtrate during 2-3 weeks, filtered off, and dried between filter paper sheets.

Single crystal XRD. A 0.40×0.38×0.12 mm crystal was selected for the structural investigation. The reflection intensities were measured on a SMART APEX II X-ray single crystal diffractometer (Bruker AXS) with a CCD detector, MoK_α radiation at 296 K. Experimental absorption corrections were applied using the SADABS software [8] by the multi-scan method. The structure model was determined by direct methods (SHELXT [9]) and refined using the SHELXL software [10].

The main crystallographic characteristics of **I** and the parameters of the experiment are as follows: molecular formula $4(C_{17}H_{22}FN_3O_3^{2+})$, $3(Cl_6Sn^{2-})$, $6(Cl^-)$, $11(H_2O)$, $4(H_3O^+)$, chemical formula $C_{68}H_{122}Cl_{24}F_4N_{12}O_{27}Sn_3$, $M_r = 2822.77$, $a = 13.5474(10)$ Å, $b = 15.2859(11)$ Å, $c = 15.6586(11)$ Å, $\alpha = 94.467(1)°$, $\beta = 105.477(1)°$, $\gamma = 111.560(1)°$, $V = 2849.9(4)$ Å^3, space group $P\overline{1}$, $Z = 1$, $D_x = 1.645$ g/cm^3, $\mu = 1.291$ mm^{-1}, $2\theta_{max} = 51.6°$; 22385 measured reflections, 10890 independent reflections, 7344 reflections with $F > 4\sigma(F)$, $-16 \le h \le 16$, $-18 \le k \le 18$, $-19 \le l \le 19$, weight scheme $w = [\sigma^2 + (0.0297P)^2]^{-1}$ (where $P = (\max(F_0^2, 0) + 2F_c^2)/3$), 698 refined parameters, $R1[F_0 > 4\sigma(F_0)] = 0.0399$, $wR2[F_0 > 4\sigma(F_0)] = 0.0835$, $GOOF = 1.009$, $\Delta\rho_{max}/\Delta\rho_{min} = 0.95/-0.40$ e/Å^3, $(\Delta/\sigma)_{max} = 0.006$.

The structure has been deposited with the Cambridge Structural Database under number CCDC-1551760. The data are available via the website www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

The electron density maps showed that a crystal unit cell contains four pefloxacin molecules, three octahedral $SnCl_6$ groups (with Sn atoms at special positions), six chlorine atoms, and 16 peaks assigned to the oxygen atoms (supposedly, of water molecules). All the H atoms near seven independent oxygen atoms and in the pefloxacin molecules were reliably identified from difference electron density maps; they were refined with the riding model after the refinement of the non-hydrogen atoms in the structure. The refined site occupancy of the eighth (O6) atom slightly differs from 0.5 because there is not enough water to fill this site. There is only one site for the considered water molecule in the structure; the second oxygen ″site″ is symmetrically transformed by the inversion center, as for any other atom in the structure. The positions of the hydrogen atoms in this molecule were calculated from the environment and possible hydrogen bonds; they are shown in Fig. 2.

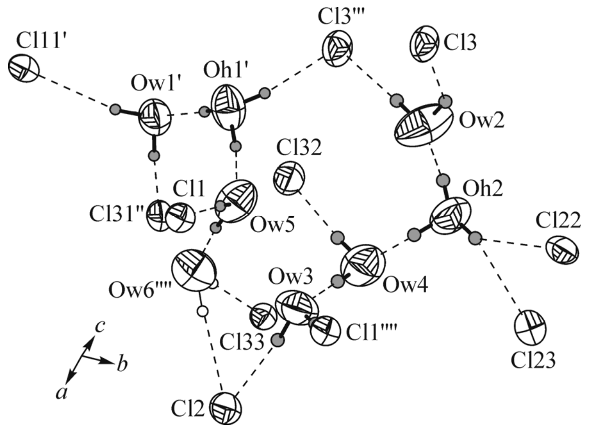

Fig. 2. Scheme of HBs between the water molecules and the oxonium cations in the structure. A single prime in the atomic notation means the [*x*, *y*–1, *z*] transformation; a double prime means [–*x*, –*y*, –*z*]; a triple prime [–*x*, –*y*, 1–*z*]; a quadruple prime means [1–*x*, –*y*, 1–*z*].

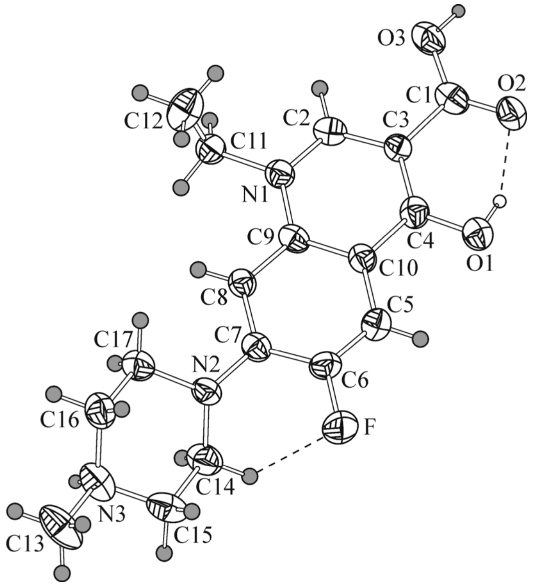

Fig. 3. Pefloxacinium dication.

The analysis of the structure model established that in the asymmetric unit of the crystal cell the negative charge exceeded the positive charge by two units. In two cases, the detailed analysis of the electron density allowed us to suppose the presence of three hydrogen atoms at the water O atoms, i.e., the existence of two oxonium ions H_3O^+ in the structure. Both oxonium ions have a pyramidal coordination; they were subsequently refined with fixed O–H and H–H distances (as for the water molecules). The oxygen atoms of the H_3O^+ ions are hereafter denoted as Oh1 and Oh2 (Fig. 2). The bond lengths and bond angles for the PefH_3^{2+} ion in **I** (Table 1) coincide with those previously determined for its *d* metal tetrahalides [11-13]. The Sn–Cl distances in the SnCl_6^{2-} ions vary from 2.4107(11) Å to 2.4456(10) Å and the maximum difference of Cl–Sn–Cl angles from 90° is 1.5°, which agrees with the SnCl_6^{2-} geometric parameters in the other compounds [14].

The protonation of neutral dipolar molecules (zwitterions) of fluoroquinolones, including PefH, first occurs at the O atom of the deprotonated carboxyl group; the second proton is bonded to the O1 atom of the ketone group [4, 11-13]. As in all previous studies, all the C–C, C–N, C–F bond lengths did not noticeably change with PefH protonation, only the C4–O1 bond elongated due to the proton bonding to the O1 atom (Fig. 3). The conformations of independent PefH_3^{2+} ions are so much alike that they are almost inverse antipodes. The PefH_3^{2+} ion has the usual geometric structure [11-13] and consists of a planar bicyclic aromatic ring moiety and a piperazine ring with a *chair* conformation.

The parameters of hydrogen bonds (HBs) and shortened C–H···*Cl*(O, F) contacts in **I** are given in Table 1. There are two intramolecular HBs (O–H···O and C–H···F) typical of fluoroquinolones in the PefH_3^{2+} cation. The PefH_3^{2+} ion is involved only in two intermolecular HBs: N3–H···Cl and O3–H···Cl. All three H atoms of each oxonium ion are involved in HBs with both water molecules and chlorine atoms. The O atoms of the H_3O^+ ions are not HB acceptors. All O atoms of water molecules act as HB acceptors, being also HB donors through the H atoms bonded to them. The site occupancy ratio for the Ow6 atom is practically 0.5, and although the H atoms at Ow6 were not located, their HBs with *Cl* (Ow6–*Cl*2 of 3.335 Å) and *Cl*33 (Ow6–*Cl*33 of 2.531 Å) are quite possible (the hypothetical H atoms at Ow6 are shown by empty circles

TABLE 1. Hydrogen Bonds (Å, deg) and Shortened Contacts in the Structure

D–H	*d*(D–H)	*d*(H···A)	∠DHA	*d*(D···A)	A	Transformation for A atom
N13–HN13	0.89(4)	2.46(4)	170(3)	3.343(4)	*Cl*31	*x*, *y*, *z*
O11–HO11	0.82	1.87	146	2.584(4)	*O*12	*x*, *y*, *z*
O13–HO13	0.82	2.12	162	2.912(3)	*Cl*2	1–*x*, 1–*y*, 1–*z*
N23–HN23	0.88(4)	2.19(4)	167(4)	3.048(4)	*Cl*1	*x*, 1+*y*, *z*
O21–HO21	0.82	1.83	145	2.546(4)	*O*22	*x*, *y*, *z*
O23–HO23	0.82	2.21	171	3.020(3)	*Cl*3	1–*x*, 1–*y*, –*z*
Ow1–Hw11	0.98(5)	2.48(3)	146(5)	3.332(3)	*Cl*31	–*x*, 1–*y*, –*z*
Ow1–Hw12	0.98(5)	2.36(4)	160(4)	3.295(3)	*Cl*11	*x*, *y*, *z*
Ow2–Hw21	0.95(5)	2.43(4)	136(3)	3.181(4)	*Cl*3	*x*, *y*, *z*
Ow2–Hw22	0.99(5)	2.16(4)	178(4)	3.147(4)	*Cl*3	*x*–1, *y*–1, *z*
Ow3–Hw31	0.98(5)	2.14(4)	172(5)	3.116(4)	*Cl*2	*x*, *y*, *z*
Ow3–Hw32	0.98(5)	2.43(4)	152(5)	3.324(4)	*Cl*1	–*x*, –*y*, 1–*z*
Ow4–Hw41	0.99(5)	1.64(6)	179(3)	2.631(6)	*O*w3	*x*, *y*, *z*
Ow4–Hw42	0.98(5)	2.29(4)	171(3)	3.264(4)	*Cl*32	*x*, *y*, *z*
Ow5–Hw51	0.98(5)	1.69(3)	164(4)	2.645(5)	*O*w6	1–*x*, –*y*, 1–*z*
Ow5–Hw52	0.98(5)	2.04(3)	174(5)	3.016(4)	*Cl*1	*x*, *y*, *z*
Oh1–Hh11	0.98(5)	1.47(4)	164(4)	2.429(5)	*O*w5	*x*, 1+*y*, *z*
Oh1–Hh12	0.98(5)	1.60(4)	169(4)	2.569(5)	*O*w1	*x*, *y*, *z*
Oh1–Hh13	0.98(5)	2.13(4)	170(3)	3.096(4)	*Cl*3	*x*–1, *y*, *z*
Oh2–Hh21	0.98(5)	1.52(4)	170(4)	2.494(5)	*O*w2	*x*, *y*, *z*
Oh2–Hh22	0.98(5)	1.44(4)	164(5)	2.403(6)	*O*w4	*x*, *y*, *z*
Oh2–Hh23	0.98(5)	2.61(4)	151(3)	3.502(4)	*Cl*22	*x*, *y*, *z*
Oh2–Hh23	0.98(5)	2.70(4)	119(3)	3.285(4)	*Cl*23	*x*, *y*, *z*
C12–H12	0.93	2.72	165	3.622(4)	*Cl*1	*x*, 1+*y*, *z*
C114–H11A	0.97	2.22	123	2.871(4)	*F*1	*x*, *y*, *z*
C114–H11A	0.97	2.91	133	3.651(4)	*Cl*3	*x*–1, *y*–1, *z*
C115–H11D	0.97	2.95	149	3.821(4)	*Cl*2	*x*–1, *y*, *z*
C113–H11F	0.96	2.84	152	3.720(5)	*Cl*2	*x*–1, *y*, *z*
C113–H11G	0.96	2.81	128	3.483(5)	*Cl*33	–*x*, –*y*, –*z*
C116–H11I	0.97	2.76	151	3.638(4)	*Cl*12	–*x*, 1–*y*, –*z*
C117–H11J	0.97	2.88	136	3.640(4)	*Cl*13	*x*, *y*, *z*
C117–H11K	0.97	2.86	141	3.666(4)	*Cl*11	*x*, *y*, *z*
C211–H21B	0.97	2.70	142	3.522(4)	*Cl*23	*x*, *y*, *z*
C212–H21D	0.96	2.57	158	3.472(5)	*O*21	1–*x*, 1–*y*, –*z*
C22–H22	0.93	2.84	167	3.751(4)	*Cl*33	*x*, *y*, *z*
C214–H21G	0.97	2.19	123	2.838(5)	*F*2	*x*, *y*, *z*
C215–H21I	0.97	2.89	133	3.627(4)	*Cl*2	*x*, 1+*y*, *z*
C213–H21O	0.96	2.91	151	3.776(5)	*Cl*1	1–*x*, 1–*y*, 1–*z*
C213–H21P	0.96	2.92	155	3.817(5)	*Cl*3	*x*, *y*, *z*
C216–H21L	0.97	2.93	137	3.700(4)	*Cl*21	1–*x*, 1–*y*, 1–*z*
C216–H21M	0.97	2.66	133	3.390(5)	*O*22	1–*x*, 1–*y*, –*z*
C217–H21J	0.97	2.78	133	3.517(4)	*Cl*22	1–*x*, 1–*y*, 1–*z*

The first digit in the atomic notation corresponds to the molecule number.

in Fig. 2). Therefore, all H atoms of water molecules are most likely to be involved in HBs. HBs form a three-dimensional infinite structure of compound **I**. The PefH$_3^{2+}$ ions are arranged in pairs by (head-to-tail) π–π interactions between both N1–

C2–C3–C4–C10–C9 rings and N1–C2–C3–C4–C10–C9 and C5–C6–C7–C8–C9–C10 rings (interplanar distances of 3.52-3.56 Å).

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