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SYNTHESIS AND STRUCTURE OF $C_{17}H_{22}FN_3O_3^{2+} \cdot CuCl_4^{2-}$

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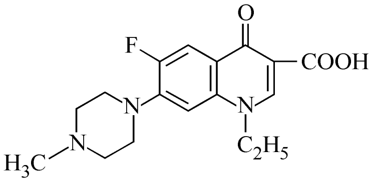
A new compound $C_{17}H_{22}FN_3O_3^{2+} \cdot CuCl_4^{2-}$ [pefloxacindium tetrachlorocuprate(II)], $C_{17}H_{20}FN_3O_3$ — 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(4-methyl-1-piperazinyl)-3-quinoline carboxylic acid (pefloxacin, PefH) is synthesized and characterized by single crystal X-ray diffraction technique. The crystal structure of the compound contains one $PefH_3^{2+}$ cation and one $CuCl_4^{2-}$ anion. The supramolecular architecture of the crystal is determined.

Keywords: fluoroquinolone, pefloxacin, copper chloride, crystal structure, hydrogen bonds, π–π-interaction.

One of the most important fluoroquinolones is pefloxacin (Pef, $C_{17}H_{20}FN_3O_3$) that belongs to the best fluoroquinolones of the third generation [1].



Graphical formula of pefloxacin

Many pharmacological and toxicological properties of drugs change due to the interaction with metals. Copper ions Cu^{2+} are likely to be most studied in this aspect. This is caused by that low molecular copper complexes have a beneficial effect in the treatment of some diseases, for instance, tuberculosis, cancer, and gastric ulcer [2].

An insight into various intermolecular interactions is of great essence in supramolecular chemistry and crystal engineering. The comprehension of structural motifs generated by these interactions can be applied to design novel materials with useful physical and chemical properties. Hydrogen bonding and π-stacking interactions between aromatic rings largely determine the topology and conformation of molecular ensembles in the solid state [3, 4]. Weak interactions involving fluorine also affect the supramolecular organization of the substance. An analysis of different interactions in fluoroquinolone compounds is especially important to understand their effect on the human body because they can control conformational and structural features of the drug, which are responsible of the curative effect. At present, the design and synthesis of multicomponent crystals of fluoroquinolones has been paid much attention [5, 6].

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We synthesized a new compound $C_{17}H_{22}FN_3O_3^{2+} \cdot CuCl_4^{2-}$ (pefloxacindium tetrachlorocuprate (II)), $C_{17}H_{20}FN_3O_3$ is 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(4-methyl-1-piperazinyl)-3-quinoline carboxylic acid (PefH, pefloxacin) and determined its crystal structure.

Experimental. PefH, used in the synthesis, in the form of a white powder was isolated in air from the solution obtained by dissolving PefH·CH_3SO_3H·$2H_2O$ pefloxacin methanesulfonate dihydrate (Nakoda Chemicals Ltd., India) in excess of 0.1 M ammonia solution.

Synthesis of $C_{17}H_{22}FN_3O_3^{2+} \cdot CuCl_4^{2-}$. In 4 ml of 6 M hydrochloric acid 0.30 g of pefloxacin was dissolved. Then an equimolar amount of $CuCl_2 \cdot 2H_2O$ was gradually added to the solution under heating. Crimson crystals of the compound were isolated in the form of thin needles on slow cooling or evaporating of the solution.

The selected crimson crystal with linear dimensions of 0.12 mm×0.13 mm×0.42 mm was placed into the goniometer of an X-ray SMART APEX II (Bruker) autodiffractometer with a two-dimensional CCD-detector (MoK_α radiation, graphite monochromator). At 295 K by ω–φ scanning in a range to $2\theta = 56°$ 19825 reflections were measured, 5304 out of them being independent ($R_{\text{int}} = 0.025$). Crystallographic characteristics are as follows: $a = 14.055(1)$ Å, $b = 12.136(1)$ Å, $c = 12.922(1)$ Å, $\beta = 94.040(1)°$, $V = 2198.7(3)$ Å^3, $P2_1/c$ space group, $Z = 4$, $d_{\text{calc}} = 1.633$ g/cm^3. Absorption corrections were introduced using the SADABS program [7] that employs repeated measurements of the same reflections at different crystal orientations. The structural model was solved by direct methods and refined in the anisotropic approximation of thermal vibrations of non-hydrogen atoms using the SHELXTL program package [8]. Hydrogen atoms were located from electron density difference syntheses. The hydrogen atoms bonded to carbon atoms were refined with reference to the corresponding atoms; coordinates of the others were refined freely. Isotropic thermal parameters of all H were 1.2 of the U_{eq} value of the bonded atom. Hence, the maximum and minimum values of the difference electron density were 0.38 e/Å^3 and –0.38 e/Å^3, $R1 = 0.028$ (against 4399 $|F| > 4\sigma(F)$ and 0.038 over all independent reflections); $wR2 = 0.076$; $GOOF = 1.035$.

CIF file containing full information on the studied structure was deposited with CCDC, No. 714683, where it is available on request: www.ccdc.cam.ac.uk/data_request/cif.

Results and discussion. Fig. 1 shows the molecular structure of $C_{17}H_{22}FN_3O_3^{2+} \cdot CuCl_4^{2-}$ (molecular weight is 540.74). The lengths of C–O, C–N, C–F, and C–C bonds within errors coincided with those found previously for other pefloxacin compounds: $(PefH_2^+)PtCl_4^{2-} \cdot 2H_2O$, $(PefH_2^+)CH_3SO_3^- \cdot 2H_2O$, $(PefH_2^+)CH_3SO_3^- \cdot 0.1H_2O$, and $Ag(H_2O)Pef \cdot 3H_2O$ [9]. The corresponding bond angles were also slightly different. The crystal of the compound contains $PefH_3^{2+}$ and $CuCl_4^{2-}$ ions. The latter ion represents a distorted tetrahedron {d(Cu–Cl) = 2.2029(6)-2.2984(5) Å, $\angle Cl_iCuCl_j = 100.93(2)$-127.94(2)°}, while the $PefH_3^{2+}$ ion is a planar fragment composed of aromatic rings with side chains (non-hydrogen atoms are out of the plane not more than by 0.068(2) Å, except C12 with an outrun of 0.121(2) Å) and the piperazine ring with *chair* conformation, whose parameters, in accordance with [10], are as follows: $Q = 0.578(2)$ Å, $\theta = 4.5(2)°$, $\varphi = 16(2)°$ (Fig. 1). The terminal N3 atom is protonated. To the carbonyl O1 atom H1 hydrogen is also bonded, which forms an intramolecular hydrogen bond with O2 of the carboxyl group: O1–H1…O2. Another intramolecular bond C14–H14A…F also closing the six-membered ring binds F and C14 atoms. The C14–H14A protons are acidic, as compared to other C–H protons, due to the inductive effect of the nearest N2 atom, and therefore they form hydrogen bonds [4]. Table 1 lists the parameters of hydrogen bonds.

In the crystal, pefloxacin molecules form pairs (Fig. 2) bound by the π–π interaction between the aromatic rings of molecules. Table 2 presents the calculated geometric parameters of this interaction [11]. The presence of complex $CuCl_4^{2-}$ ions in the structure results in the formation of hydrogen bonds involving chlorine atoms that form zigzag chains of alternating pefloxacin molecules and $CuCl_4^{2-}$ ions with the [2 0 –1] axial direction. These chains are linked with each other by the described above π–π interaction so that two pefloxacin molecules successive in the chain are bonded to different

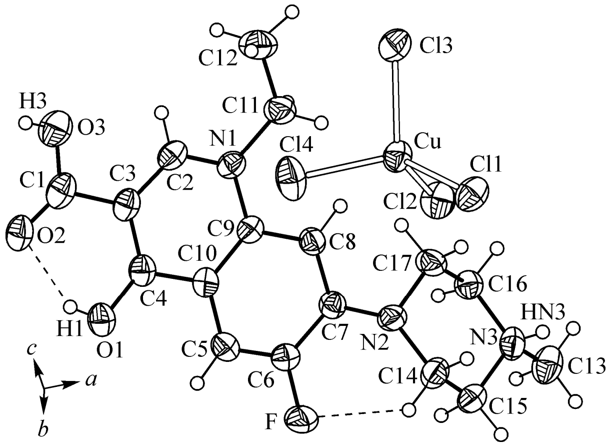

Fig. 1. Molecular structure of $C_{17}H_{22}FN_3O_3^{2+}\cdot CuCl_4^{2-}$. Intramolecular hydrogen bonds are shown by dashes. Thermal vibrations of atoms are shown by ellipsoids.

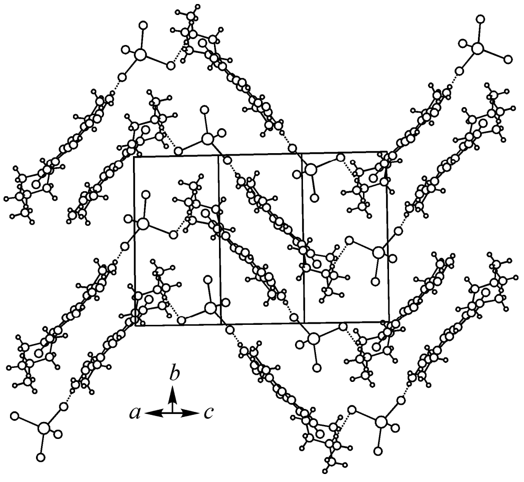

Fig. 2. Packing of molecular ions in the crystal cell. One of the layers is shown. Hydrogen bonds are shown by dashes.

TABLE 1. Parameters of Hydrogen Bonds in the $C_{17}H_{22}FN_3O_3^{2+}\cdot CuCl_4^{2-}$ Crystal

D–H…A	*d*(D–H)	*D*(H…A)	∠DHA	*d*(D…A)	Symmetry operations
O1–H1…O2	0.75(2)	1.93(2)	150(3)	2.603(2)	—
O3–H3…Cl3[a]	0.74(3)	2.26(3)	176(3)	2.997(2)	1–*x*, –*y*, 1–*z*
N3–HN3…Cl1[b]	0.84(2)	2.36(2)	176(2)	3.204(2)	2–*x*, 0,5+*y*, 0,5–*z*
C14–H14A…F	0.92(2)	2.28(1)	121(1)	2.853(2)	—

neighboring chains. Thus, with regard to the mentioned hydrogen bonds and π–π interaction of the plane–plane type [4], in the crystal, pefloxacin molecules and $CuCl_4^{2-}$ ions are packed into layers parallel to the *b* cell axis (Fig. 2).

On the whole, the structure of the compound is layered with a distance between the artomatic rings of the neighboring layers of about 3.4 Å, which indicates the interaction of π-electron systems. The tetrachlorocuprate(II) anion is located between the layers.

TABLE 2. Parameters of the π–π Interaction of $PefH_3^{2+}$ Molecular Ions in the $C_{17}H_{22}FN_3O_3^{2+} \cdot CuCl_4^{2-}$ Crystal. Interacting Molecules are Bound by the Center of Inversion

Cg_i–Cg_j	*d*(Cg–Cg), Å	α, deg	β, deg	γ, deg	Cg_i_p	Cg_j_p	Shift, Å
Cg_1–Cg_1	3.859(1)	0	28.05	28.05	3.4060(7)	3.4060(7)	1.815
Cg_1–Cg_2	3.682(1)	0.91(8)	21.57	21.64	3.4221(7)	3.4238(7)	—

Note. Cg_1 is the plane of the N1C2C3C4C10C9 ring; Cg_2 is the plane C5C6C7C8C9C10 ring.

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