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COORDINATION COMPOUNDS

Sparfloxacindium Tetrabromidocuprate(II) Monohydrate Crystal Structure

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Abstract—Structure solution has been carried out for a compound containing doubly charged sparfloxacindium cation, namely $((C_{19}H_{24}F_2N_4O_3)[CuBr_4] \cdot H_2O$ (**I**), where $C_{19}H_{22}F_2N_4O_3$ is sparfloxacin. The crystals of **I** are orthorhombic with $a = 14.533(4)$ Å, $b = 12.557(4)$ Å, $c = 29.370(9)$ Å, $V = 2360(3)$ Å^3, space group *Pbca*, $Z = 8$. In compound **I**, unlike in similar compounds of other fluoroquinolones, the second proton is attached to the sparfloxacin through the amino nitrogen atom instead of being attached through the ketone oxygen atom. This specific protonation feature of SfH is manifested in the specifics of supramolecular organization of **I**.

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Fluoroquinolones constitute a very important class of antibiotics. They are capable of selectively inhibiting DNA gyrase, the key enzyme of a microbial cell responsible for the normal biosynthesis and replication of bacterial DNA. Sparfloxacin ($C_{19}H_{24}F_2N_4O_3$, **SfH**) (Fig. 1) is the first aminodifluoroquinolone that shows high activity against gram-positive *Streptococcus pneumoniae* and *Mycobacterium tuberculosis* species [1]. Sparfloxacin has a higher activity than that of monofluoroquionolones, good pharmacokinetic properties, and bioavailability, and thereby its clinical use is ever increasing [2, 3].

The use of sparfloxacin is complicated by its polymorphism [4], so that the preparation of new medicaments comprising seems to be topical. Metal-containing compounds of sparfloxacin are expected to be more specific in their anticancer and antimicrobial activities [1, 5, 6]. Anion Sf^-, as other similar fluoroquinolone anions, is capable of adding at least three H^+ ions [7]. An additional NH_2 group contained therein makes it possible to bind the fourth proton. The sequence in which its electron-donating centers are protonated in acidic media (where cationic species are formed) yet remains unclear. Compounds containing fluoroquinolone cations are usually well crystallizable and suitable for structure determination (see, e.g., [8–12]). The preparation and structural study of fluoroquinolone compounds would help understanding correlations between their structures and their therapeutic effects.

Here, we determine the structure of a new compound, namely, sparfloxacindium tetrabromidocuprate(II) monohydrate $SfH_3[CuBr_4] \cdot H_2O$ (**I**). Mixed-ligand copper complexes containing sparfloxacin and 1,10-phenanthroline have been shown to have anticancer activity [1].

EXPERIMENTAL

The chemicals used were sparfloxacin (Sigma, ≥98%), HBr (chemically pure grade), and $CuBr_2$ (pure grade).

Synthesis of I. In 4 mL of 6 M HBr, 0.30 g sparfloxacin was dissolved; to the resulting solution, $CuBr_2$ was then slowly added under heating. The molar ratio $SfH : CuBr_2$ was 1 : 5. Dark violet crystals of the desired compound were separated upon slow cooling or concentration of the solution. The yield of the compounds based on sparfloxacin was 60–70%.

X-ray diffraction experiment. The structure was solved from a $0.16 \times 0.28 \times 0.47$ mm crystal. Reflection intensities were measured on a SMART APEX II single-crystal diffractometer equipped with a CCD detector (BRUKER AXC) using MoK_α radiation.

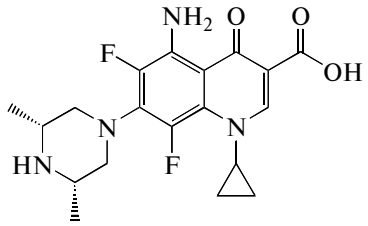

Fig. 1. Sparfloxacin structure.

Experimental absorption corrections were applied using SADABS software [13] by a multi-scan method. The structure model was established by direct methods (SHELXS) and refined in the anisotropic approximation for non-hydrogen atoms (SHELXTL) [14]. All hydrogen atoms were located from difference electron-density syntheses and then refined in the bound form. Table 1 displays experimental details and the results of structure refinement. The structure of **I** was deposited with the Cambridge Structural Database (no. 963775; deposit@ccdc.cam.ac.uk or ttp://www.ccdc.cam.ac.uk/data_request/cif).

Table 1. Experimental details and structure-refinement parameters for **I**

T, K	298
Space group	*Pbca*
Z	8
$2\theta_{max}$, deg	42
a, b, c, Å	14.533(4), 12.557(4), 29.370(9)
V, Å^3	2360(3)
ρ_{calc}, g/cm^3	1.972
μ, mm^{-1}	6.852
Reflections measured	24488
Reflections unique	2818
Reflections with $F > 4\sigma F$	1968
h, k, and l ranges	$-14 \le h \le 14$, $-12 \le k \le 12$, $-29 \le l \le 29$
Parameters refined	314
$R1$ [$F_o > 4\sigma(F_o)$]	0.0424
$wR2$	0.0989
GOOF	1.037
$(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$, e/Å^3	0.90, –0.60

RESULTS AND DISCUSSION

In addition to SfH_3^{2+} and $CuBr_4^{2-}$ ions, the asymmetric portion of a unit cell in **I** contains a water molecule. The sparfloxacindium cation has three six-membered rings; two of these rings (N1–C2–C3–C4–C10–C9 and C5–C6–C7–C8–C9–C10) are virtually planar, while the (N2–C14–C15–N3–C16–C17) ring has a chair conformation (Fig. 2). SfH_3^{2+} also contains a three-membered ring C11–C12–C13, which is linked to atom N1. C–O, C–N, C–F, and C–C bond lengths and the relevant bond angles coincide, within the error bar, with the values found earlier for other sparfloxacin compounds [15]. The $CuBr_4^{2-}$ anion is a distorted tetrahedron (Cu–Br 2.361(2)–2.403(2) Å, angles Br_iCuBr_j 97.15(6)°–136.95(6)°). We earlier found the same variations of parameters for the complex $(CfH_3)[CuBr_4] \cdot H_2O$ (CfH stands for ciprofloxacin $C_{17}H_{18}FN_3O_3$) [11].

pK_a values for sparfloxacin were determined potentiometrically [4]. The value of 6.40 was assigned to the dissociation of a carboxy group, and 8.90 to the dissociation of the piperazine secondary amine (Fig. 1). We used concentrated HBr to prepare compound **I**, which additionally induced the protonation of the $-NH_2$ group. These acidities were found to protonate the atom O1 of the keto group in other fluoroquinolones [8–12, 15]. The absence of protonation of this atom for sparfloxacin may be due to the formation, by O1, of strong intramolecular hydrogen bonds (H-bonds) involving a hydrogen atom of the $-NH_3^+$ group and the H atom of the carboxy group (Fig. 2, Table 2). This specific protonation feature of SfH appreciably affects the character of H-bonds in the structure of **I** and leads to the formation of structure motifs such that have been hitherto unknown for fluoroquinolones. For example, the atom O1 is a double acceptor of intermolecular H-bonds and forms two six-membered rings C1–C3–C4–O1···H1–O2 and C4–C10–C5–N4–H42···O1 ($S(6)$ structure motifs) [16]. Intermolecular H-bonds involving a water molecule (Fig. 3) also form the six-membered ring Cu–Br4···Hw2–Ow–Hw1···Br3 (R_2^1). All hydrogen atoms of the water molecule and at the nitrogen atoms (except for that at N4) participate in intermolecular hydrogen bonding. Two shortened

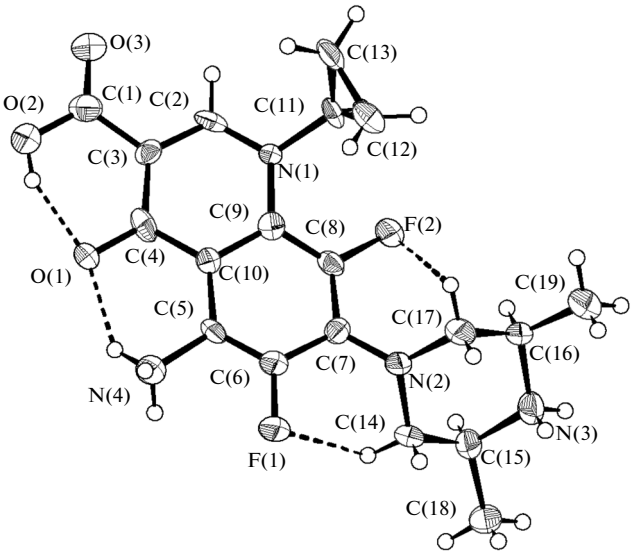

Fig. 2. SfH_3^{2+} ion with atom numbering. Intramolecular hydrogen bonds are shown by dashed lines. Thermal vibration ellipsoids are calculated with 50% confidential probability.

Table 2. Geometric parameters of D–H···A hydrogen bonds (bond lengths, Å; angles, deg) in the structure of **I**

D–H	D–H	H···A	D···A	Angle DHA	A	Transformation for atom A
O2–H1	0.82	1.82	2.578(8)	153	O1	x, y, z
N3–H31	0.90	2.42	3.318(7)	172	Br2	$1 - x, 0.5 + y, 0.5 - z$
N3–H32	0.90	2.48	3.337(7)	160	Br1	x, y, z
N4–H41	0.89	1.88	2.74(1)	160	Ow	$0.5 + x, y, 0.5 - z$
N4–H42	0.89	1.93	2.628(9)	134	O1	x, y, z
N4–H43	0.89	2.38	3.236(7)	161	Br3	$1 - x, y - 0.5, 0.5 - z$
C14–H14A	0.97	2.32	2.800(9)	110	F1	x, y, z
C17–H17B	0.97	2.31	2.790(9)	110	F2	x, y, z
Ow–Hw1	0.90	2.56	3.437(8)	165	Br3	x, y, z
Ow–Hw2	0.90	2.99	3.533(6)	121	Br4	x, y, z

Table 3. π–π interaction parameters in **I**

Cg_i–Cg_j	d, Å	α, deg	β, deg	Cg_i_p, Å	Δ, Å
Cg_1–Cg_1	3.704(5)	0	24.45	3.372(3)	1.533
Cg_1–Cg_2	3.802(5)	5.4(4)	27.60	3.428(3)	–
Cg_2–Cg_1	3.803(5)	5.4(4)	25.63	3.370(4)	–

distances (F1···H14A (2.32(1) Å) and F2···H17B (2.31(1) Å)) may be regarded as weak H-bonds closing two similar six-membered rings, which correspond to the $S(6)$ motif (Fig. 2). The H14A and H17B protons, which are bonded to atoms C14 and C17, respectively, are "acidic" [16] compared to the other C–H protons due to the inductive effect of the nearest neighboring atom N2 and, therefore, form an H-bond of this type. Such the rings are also typical of other fluoroquinolones [8–12].

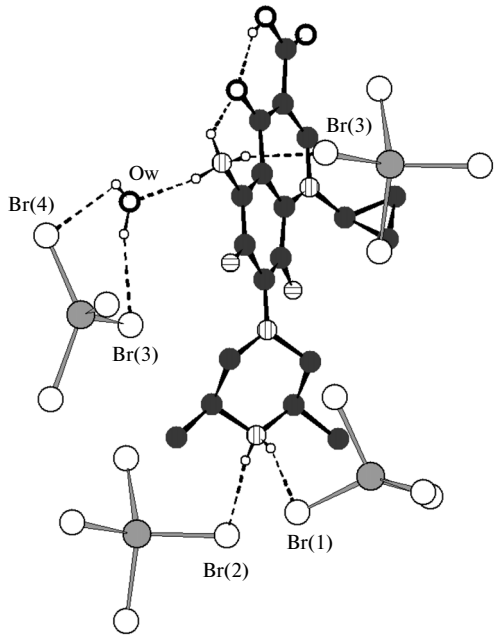

Fig. 3. Hydrogen bonds in the structure of **I**. N atoms are hatched by vertical lines and F atoms are hatched by horizontal lines.

We have been the first to determine the structure of a compound with the doubly-charged cation SfH_3^{2+}. Of the ten solved structures, the monoprotonated sparfloxacin SfH_2^+ is contained only in $(SfH_2^+)[BF_4^-] \cdot 0.63H_2O$ [7]. The proton H^+ in this compound is attached to the O atom of the deproptonated carboxy group instead of being attached to the N atom of the terminal $-NH_2$ group. The reduced basicity of the latter can arise from the strong electron-drawing properties of the near-lying fluoride ion and the aromatic system of the sparfloxacin.

The sparfloxacindium ions in a crystal of **I** are distributed in pairs, where they are related by centers of symmetry (Fig. 4). There are "heat-to-tail" supramolecular π–π interactions in the structure with participation of the ring N1–C2–C3–C4–C10–C9 (ring Cg_1) and the ring C5–C6–C7–C8–C9–C10 (ring Cg_2), which are also intrinsic to other ionic compounds of fluoroquinolones [8–12]. The calculated interaction parameters [17] are found in Table 3. Noteworthy, π–π interactions are absent in a similar ciprofloxacin compound $(CfH_3)[CuBr_4] \cdot H_2O$ [11]; that is, packing in crystals depends on the fluoroquinolone. Further, the structure-forming intermolecular contacts attendant to π–π interactions in **I** are also Cu–Br···π contacts, as judged from the interatomic distances and the arrangement of atoms. The Br1···(center of Cg_2) and Br4···(center of Cg_1) distances are 3.539(4) and 3.794(4) Å, respectively; the relevant Cu–Br···(center of ring) angles are 90.16(7)° and 89.05(7)°, respectively. The occurrence of these

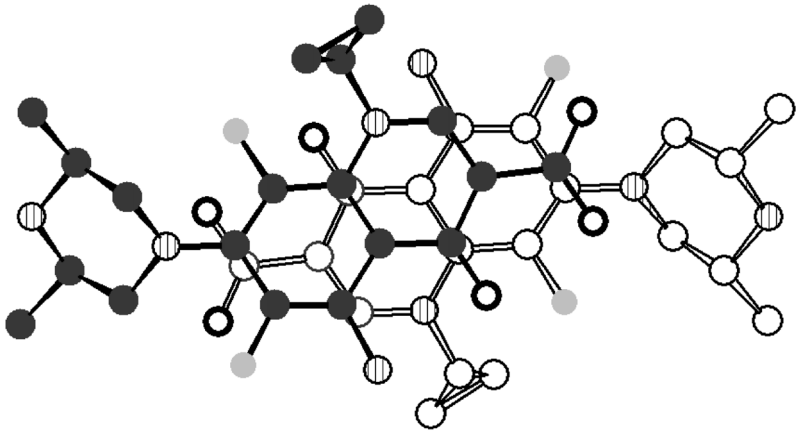

Fig. 4. Mutual positions of two SfH_3^{2+} ions related by a center of symmetry as projected onto a plane parallel to the planar rings. Interatomic bonds and C atoms in the higher lying molecules are indicated in black. The N atoms are hatched; the F atoms are shaded.

interactions may be due to a relatively high polarizability ("softness") of the bromine atom. C–F···π contacts are known to be significant for structure formation in bicyclic aromatic compounds even for the "hard" fluorine atom [18].

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