

2'-Deoxy-2',2'-difluorocytidine mono-
hydrochloride (Gemcitabine hydrochloride)

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Key indicators

Single-crystal X-ray study

$T = 298\text{ K}$

Mean $\sigma(\text{C}-\text{C}) = 0.005\text{ \AA}$

R factor = 0.060

wR factor = 0.060

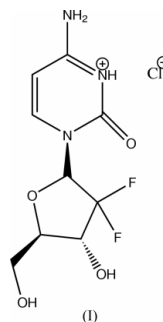
Data-to-parameter ratio = 10.9

For details of how these key indicators were
automatically derived from the article, see
<http://journals.iucr.org/e>.

Gemcitabine hydrochloride (2'-deoxy-2',2'-difluorocytidine hydrochloride), $\text{C}_9\text{H}_{12}\text{N}_3\text{F}_2\text{O}_4^+\cdot\text{Cl}^-$, is a β -nucleoside that is of pharmaceutical interest as an antitumor agent. The N atom of the cytidine ring is protonated due to salt formation. The sugar residue adopts a C3'-*endo* and C4'-*exo* conformation. In the asymmetric unit, gemcitabine cations and chloride ions are linked by $\text{N}-\text{H}\cdots\text{Cl}$ hydrogen bonds. In the crystal structure, screw-related gemcitabine cations are linked by $\text{O}-\text{H}\cdots\text{O}$ hydrogen bonds to form molecular columns along the c axis and adjacent columns are interlinked by $\text{N}-\text{H}\cdots\text{Cl}$ and $\text{O}-\text{H}\cdots\text{Cl}$ hydrogen bonds.

Comment

In the title compound, gemcitabine hydrochloride (henceforth referred to as GH), (I), the gemcitabine cation is protonated at N3 (Fig. 1), as observed in 2'-deoxycytidine hydrochloride (henceforth referred to as DCH) (Subramanian & Hunt, 1970).



The bond lengths in GH are normal (Allen *et al.*, 1987) and are comparable with those of DCH (Subramanian & Hunt, 1970) and β -cytidine (henceforth referred to as BC) (Ward, 1993). The sugar residue of GH adopts a C3'-*endo* and C4'-*exo* conformation; C3' is displaced *endo* by 0.183 (4) \AA and C4' is displaced *exo* by 0.343 (4) \AA from the weighted least-squares plane through the rest of the ring atoms. In the sugar residue of DCH (Subramanian & Hunt, 1970), C3' is displaced *endo* by 0.361 \AA and C2' is 0.245 \AA *exo*. The conformation of the C5'–C4' bond is better described by the torsion angles (Shefter & Trueblood, 1965) $\text{O5}'-\text{C5}'-\text{C4}'-\text{O1}'$ [-63.2 (4) $^\circ$] and $\text{O5}'-\text{C5}'-\text{C4}'-\text{C3}'$ [52.9 (5) $^\circ$]. The $\text{C6}-\text{N1}-\text{C1}'-\text{O1}'$ torsion angle, describing the relative orientation of the sugar and base (Sundaralingam & Jensen, 1965), is 46.3 (4) $^\circ$ in GH, while it is 0 and 18.1 (4) $^\circ$ in DCH and BC, respectively. The length of the $\text{N1}-\text{C1}'$ bond is found to be longer if this torsion angle is less. This is attributed to the repulsive forces between the electrons in the bonds $\text{N1}-\text{C6}$ and $\text{C1}'-\text{O1}'$ (Subramanian & Hunt, 1970). This is evident from the $\text{N1}-\text{C1}'$ bond

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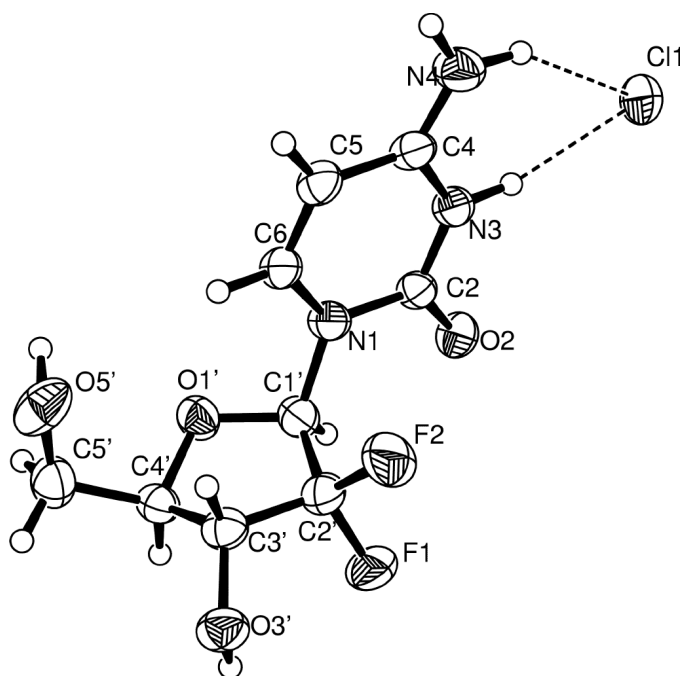


Figure 1
The structure of gemcitabine hydrochloride, showing 50% probability displacement ellipsoids and the atom-numbering scheme.

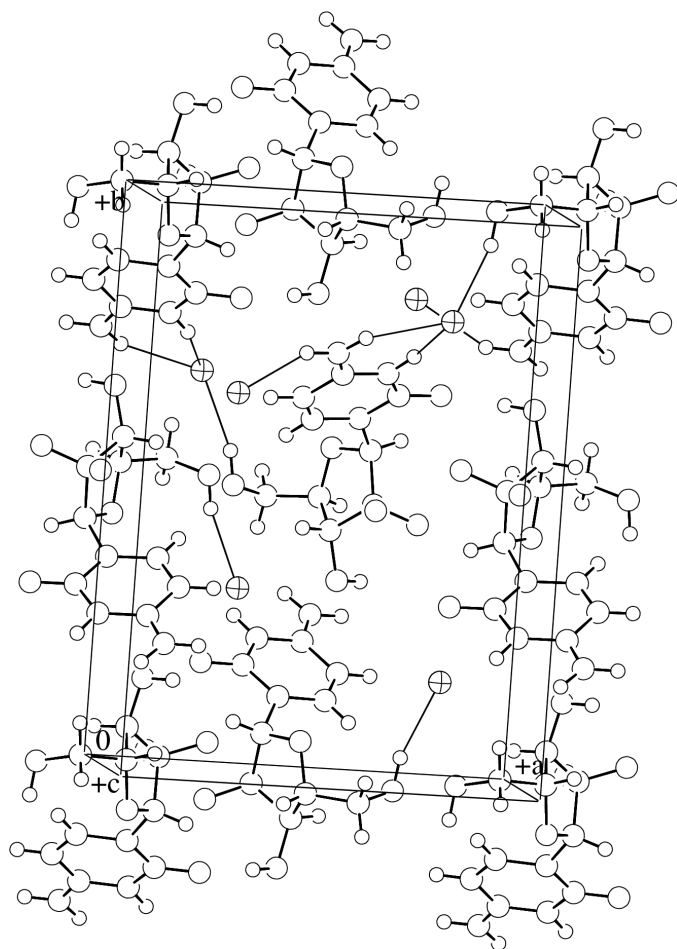


Figure 2
Packing of the molecules, viewed down the *c* axis. Hydrogen bonds are indicated by thin lines.

length in DCH [1.508 (3) Å], BC [1.490 (4) Å] and GH [1.449 (5) Å]. The absolute stereochemistry of atoms C1', C3' and C4' has been determined to be *R*, *R* and *R*, respectively, using anomalous dispersion of the Cl atom. The Flack paramDear Deter for the reported configuration is 0.00 (3), while that for the inverted structure is 0.98 (3).

In the asymmetric unit, the gemcitabine cation and chloride ion are linked by N3—H1···Cl1 and N4—H5···Cl1 hydrogen bonds. In addition to these hydrogen bonds, C1'—H6···O2 and C3'—H9···O5' weak intramolecular interactions are also observed. In the crystal structure, the screw-related gemcitabine cations are linked by O3'—H13···O2($\frac{1}{2} - x, -y, \frac{1}{2} + z$) hydrogen bonds involving the 3'-hydroxyl group of the sugar and the carbonyl oxygen of the base, to form molecular columns along the *c* axis. Adjacent molecular columns are interlinked by N4—H4···Cl1($\frac{1}{2} + x, \frac{1}{2} - y, -1 - z$) hydrogen bonds involving the amino group and O5'—H14···Cl1($\frac{1}{2} + x, \frac{1}{2} - y, -z$) hydrogen bonds involving the 5'-hydroxyl group, to form a molecular network. It is interesting to note that both the H atoms of the amino group participate in N—H···Cl hydrogen bonds in GH, while these H atoms in DCH are used to form N—H···Cl and N—H···O hydrogen bonds. Table 2 lists the geometry of hydrogen bonds and C—H···O interactions.

Experimental

The route reported by Chou *et al.* (1992) was adopted to prepare the title compound. Crystals suitable for X-ray diffraction study were grown from mixture of methanol and water (9:1).

Crystal data

$C_8H_{12}F_2N_3O_4^+ \cdot Cl^-$
 $M_r = 299.66$
Orthorhombic, $P2_12_12_1$
 $a = 11.4680$ (7) Å
 $b = 15.5987$ (9) Å
 $c = 6.706$ (2) Å
 $V = 1199.6$ (4) Å³
 $Z = 4$
 $D_x = 1.659$ Mg m⁻³

Cu K α radiation
Cell parameters from 25 reflections
 $\theta = 22.6$ – 24.8°
 $\mu = 3.27$ mm⁻¹
 $T = 298.2$ K
Block, colourless
0.50 × 0.50 × 0.40 mm

Data collection

Rigaku AFC-7S diffractometer
 ω - 2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
 $T_{min} = 0.175$, $T_{max} = 0.271$
2540 measured reflections
2083 independent reflections
2032 reflections with $F^2 > 2\sigma(F^2)$

$R_{int} = 0.028$
 $\theta_{max} = 67.9^\circ$
 $h = -13 \rightarrow 13$
 $k = -18 \rightarrow 18$
 $l = -7 \rightarrow 7$
3 standard reflections every 150 reflections
intensity decay: 1.3%

Refinement

Refinement on F
 $R = 0.060$
 $wR = 0.060$
 $S = 1.13$
2082 reflections
191 parameters
H atoms treated by a mixture of independent and constrained refinement
Weighting scheme: Chebychev polynomial with 3 parameters (Carruthers & Watkin, 1979): 2.0710, 1.3167 and 0.0135

$(\Delta/\sigma)_{max} = 0.041$
 $\Delta\rho_{max} = 0.77$ e Å⁻³
 $\Delta\rho_{min} = -0.57$ e Å⁻³
Extinction correction: Larson (1970), eq. 22
Extinction coefficient: 110 (9)
Absolute structure: Flack (1983), 828 Friedel pairs
Flack parameter = 0.00 (3)

Table 1
Selected geometric parameters (Å, °).

F1—C2'	1.371 (4)	N1—C6	1.393 (4)
F2—C2'	1.360 (5)	N1—C2	1.386 (5)
O2—C2	1.233 (4)	N1—C1'	1.449 (5)
O1'—C1'	1.409 (5)	N3—C4	1.360 (4)
O1'—C4'	1.441 (4)	N3—C2	1.361 (5)
O3'—C3'	1.406 (4)	N4—C4	1.295 (5)
O5'—C5'	1.410 (6)		
C1'—O1'—C4'	109.7 (3)	O1'—C1'—C2'	106.1 (3)
C2—N1—C1'	118.2 (3)	N1—C1'—C2'	112.5 (3)
C6—N1—C1'	119.7 (3)	F1—C2'—F2	104.5 (3)
C2—N1—C6	120.7 (3)	F1—C2'—C1'	109.3 (3)
C2—N3—C4	125.2 (3)	F1—C2'—C3'	111.2 (3)
O2—C2—N3	122.4 (3)	F2—C2'—C1'	112.3 (3)
O2—C2—N1	121.5 (3)	F2—C2'—C3'	114.0 (3)
N1—C2—N3	116.2 (3)	O3'—C3'—C2'	114.7 (3)
N3—C4—N4	118.8 (3)	O3'—C3'—C4'	116.1 (3)
N3—C4—C5	117.3 (3)	O1'—C4'—C3'	104.8 (3)
N4—C4—C5	124.0 (3)	O1'—C4'—C5'	107.5 (3)
N1—C6—C5	121.3 (3)	O5'—C5'—C4'	112.6 (4)
O1'—C1'—N1	109.2 (3)		

Table 2
Hydrogen-bonding geometry (Å, °).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N3—H1...C1	0.95	2.17	3.068 (3)	157
N4—H4...C1 ⁱ	0.95	2.29	3.158 (4)	151
N4—H5...C1	0.95	2.38	3.224 (4)	147
O3'—H13...O2 ⁱⁱ	0.94 (5)	1.90 (6)	2.829 (4)	173 (5)
O5'—H14...C1 ⁱⁱⁱ	0.93 (2)	2.31 (3)	3.212 (3)	165 (5)
C1'—H6...O2	0.95	2.35	2.734 (5)	103
C3'—H9...O5'	0.95	2.48	2.928 (4)	109

Symmetry codes: (i) $\frac{1}{2} + x, \frac{1}{2} - y, -1 - z$; (ii) $\frac{1}{2} - x, -y, \frac{1}{2} + z$; (iii) $\frac{1}{2} + x, \frac{1}{2} - y, -z$.

Atoms H13 and H14 were located in a difference map and their positional and isotropic displacement parameters were refined. Other H atoms were placed geometrically with C—H and N—H distances fixed at 0.95 Å and U_{iso} values set at $1.2U_{\text{eq}}$ of the bound atoms. Owing to the large fraction of weak data at higher angles, the completeness of the data is low (96%).

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1994); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1995); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1993); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*, 1996); molecular graphics: *CrystalStructure* (Rigaku/MS, 2003); software used to prepare material for publication: *CrystalStructure*.

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