The complex of flunixin and meglumine

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The flunixin–meglumine complex [(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxy-N-methyl–1-hexanaminium 2-[2-methyl-3-(trifluoromethyl)anilino]nicotinate], $C_7H_{18}NO_5^+ \cdot C_{14}H_{10}F_3N_2O_2^-$, is a non-steroidal anti-inflammatory drug (NSAID) and a non-narcotic analgesic drug with antipyretic activities. In its crystal structure, the meglumine cations are linked through O—H···O and N—H···O hydrogen bonds to form layers parallel to the *ab* plane. The flunixin anions are arranged between the two cationic layers and are linked to the cations through O—H···O hydrogen bonds.

Comment

Flunixin in the form of the meglumine salt, (I), is a non-steroidal anti-inflammatory drug (NSAID) and a non-narcotic analgesic drug with antipyretic activities. It is used in veterinary medicine (including food-producing animals) but not in human medicine. With regard to meglumine, it can be regarded as an excipient, which has the purpose of increasing the solubility of flunixin. In order to assess the possible mutagenicity of flunixin–meglumine *in vivo*, crystals of the complex were grown. The X-ray structure of the complex may be useful in assessing its mutagenicity.

(I)
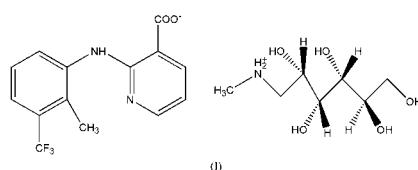
In the meglumine cation, the configuration of four chiral centers C19, C18, C17 and C16 has been chosen as *S*, *R*, *R* and *R*, respectively (Fig. 1), on the basis of the starting material, D-(+)-glucose. The specific optical rotation ($-9°$) of the title complex agrees with that in USP24 (-9 to $-12°$). In the flunixin anion, the sum of the bond angles around N2 is 357.7°, indicative of the sp^2 character of that atom, but the angle C5—N2—C6 [130.7 (2)°] deviates significantly from the ideal value of 120°. In the anion, the dihedral angle between the two aromatic rings is 26.1 (1)°. The carboxylate substituent is twisted out of the pyridine plane by 20.7 (1)° and this conformation is stabilized by the N2—H2N···O2 intramolecular hydrogen bond. In the asymmetric unit, the cation and anion are involved in an O4—H4O···O1 hydrogen bond.

In the crystal structure, all hydroxyl groups act as simultaneous hydrogen-bond donors and acceptors. The cations are linked through O—H···O and N—H···O hydrogen bonds (Table 2), forming layers parallel to the *ab* plane (Fig. 2). The
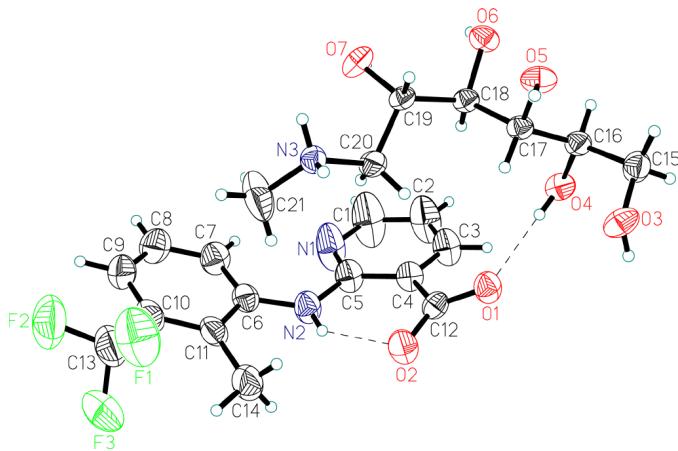
Figure 1
A view of the title complex, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

anions, which are arranged between the two cationic layers, are linked to the cations through O—H···O hydrogen bonds involving the hydroxyl groups and carboxylate O atoms (Table 2).

Experimental

A powder of the title compound (obtained from the Zhejiang Hisoar Pharmacy and Chemistry Limited Company, China) was dissolved in aqueous chloroform and methanol solution (2:5). Slow evaporation of the aqueous solution at room temperature yielded single crystals suitable for X-ray structure analysis.

Crystal data

$C_7H_{18}NO_5^+ \cdot C_{14}H_{10}F_3N_2O_2^-$
$M_r = 491.46$
Monoclinic, $P2_1$
$a = 9.910 (1)$ Å
$b = 6.914 (1)$ Å
$c = 16.578 (2)$ Å
$\beta = 91.86 (1)°$
$V = 1135.2 (2)$ Å^3
$Z = 2$

$D_x = 1.438$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 28 reflections
$\theta = 3.7–14.8°$
$\mu = 0.12$ mm^{-1}
$T = 296 (2)$ K
Prism, colourless
$0.52 \times 0.52 \times 0.38$ mm

Data collection

Siemens $P4$ diffractometer
ω scans
Absorption correction: none
6316 measured reflections
3269 independent reflections
2594 reflections with $I > 2\sigma(I)$
$R_{int} = 0.014$

$\theta_{max} = 29.0°$
$h = -12 \rightarrow 13$
$k = -8 \rightarrow 9$
$l = -22 \rightarrow 22$
3 standard reflections
every 97 reflections
intensity decay: 1.9%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.033$
$wR(F^2) = 0.085$
$S = 0.98$
3269 reflections
327 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0534P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.20$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}
Extinction correction: SHELXL97
Extinction coefficient: 0.022 (3)
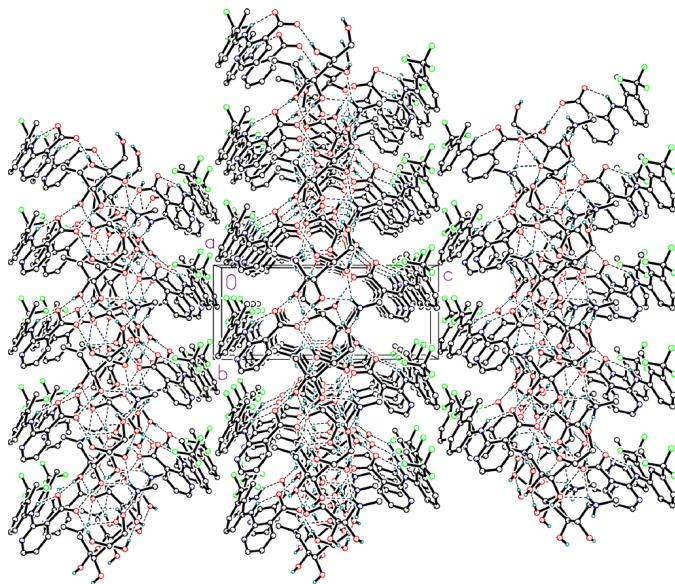
Figure 2
Packing of the title complex, viewed down the a axis.

Table 1
Selected geometric parameters (Å, °).

O1—C12	1.255 (2)	N1—C5	1.332 (3)
O2—C12	1.257 (2)	N1—C1	1.334 (4)
O3—C15	1.430 (3)	N2—C5	1.378 (3)
O4—C16	1.421 (2)	N2—C6	1.399 (3)
O5—C17	1.423 (2)	N3—C21	1.446 (3)
O6—C18	1.420 (2)	N3—C20	1.502 (2)
O7—C19	1.413 (2)		
C5—N2—C6	130.7 (2)		
C3—C4—C12—O1	18.5 (3)	C5—C4—C12—O2	21.5 (3)

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2N···O2	0.85 (2)	1.97 (2)	2.670 (2)	139 (2)
O4—H4O···O1	0.82	2.00	2.818 (2)	175
O6—H6O···O1^i	0.82	1.95	2.757 (2)	170
O7—H7O···O2^i	0.82	1.79	2.591 (2)	166
O3—H3O···O4^{ii}	0.82	1.99	2.792 (2)	168
O5—H5O···O7^{iii}	0.82	1.79	2.608 (2)	178
N3—H3NA···O3^{iv}	0.86 (2)	2.01 (2)	2.776 (2)	148 (2)
N3—H3NB···O5^{iii}	0.87 (3)	2.05 (2)	2.767 (2)	139 (3)
N3—H3NB···O6^{iii}	0.87 (3)	2.16 (2)	2.894 (2)	142 (3)

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

H atoms on N2 and N3 were located in a difference Fourier map and their parameters refined with N—H distances restrained to 0.86 (1) Å. The hydroxyl H atoms were located in a difference Fourier map and refined using a rotating-group model, with $U_{iso}(H) = 1.2U_{eq}(N)$. The positions of the C-bound H atoms were calculated geometrically and refined using a riding model [C—H = 0.93–0.98 Å and $U_{iso}(H) = 1.2U_{eq}(C)$]. A rotating-group model was also used for the methyl groups.

Data collection: XSCANS (Siemens, 1994); cell refinement: XSCANS; data reduction: SHELXTL (Siemens, 1991); program(s)

used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

References

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