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The 1:1 hydrate of diflunisal

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Key indicators

Single-crystal X-ray study
T = 298 K
Mean σ(C–C) = 0.004 Å
H-atom completeness 91%
Disorder in main residue
R factor = 0.050
wR factor = 0.178
Data-to-parameter ratio = 9.9

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

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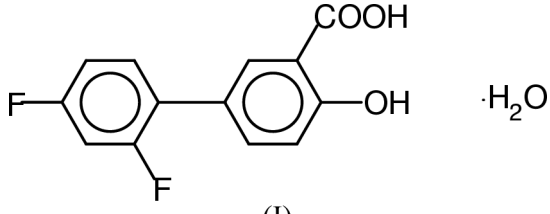
2′,4′-Difluoro-4-hydroxybiphenyl-3-carboxylic acid (diflunisal) hydrate, $C_{13}H_8F_2O_3\cdot H_2O$, forms a monoclinic crystal lattice with special channels parallel to the twofold screw axes along the *b* direction. These channels are occupied by disordered water molecules. The crystal lattice consists of dimers of diflunisal, in which two molecules are linked together by a pair of hydrogen bonds between their respective carboxyl groups.

Comment

Diflunisal is a difluorphenyl derivative of acetyl salicylic acid (aspirin), which is used therapeutically as an anti-inflammatory drug similar to aspirin. The structure of unsolvated diflunisal was described earlier (Kim & Park, 1996). However, this new investigation displays properties of clathrate materials and includes in the crystal lattice solvent molecules. Here, the structure of its hydrate, (I), is reported. The investigated structure is characterized as a packing of the diflunisal dimers, which are obtained by energetically equivalent hydrogen bonds between two adjacent molecules (Table 1). Probably, atom O2 takes part in forming not only the intermolecular bonds but also the intramolecular ones O1—H10···O2.



(I)

The conformation state of a diflunisal molecule may be characterized as follows: the phenyl planes are tilted round the C1—C8 bond by a dihedral angle of 43.9 (1)°. Similar values of angles have been reported for π-stacking interactions in nucleic acids (Langlet *et al.*, 1981; Rein, 1978; Claverie, 1978). For comparison, the planes of benzene molecules in an orthorhombic crystal, which are situated 5.81 Å apart, form a dihedral angle of 29° (Bacon *et al.*, 1964). It should be noted that theoretical analysis of the structure of benzene clusters (Sun & Bernstein, 1996) yields dihedral angles between planes of benzene molecules corresponding to approximately 40°, where the molecules are packed in a herring-bone fashion.

In diflunisal, the hydroxyl group is tilted towards the carbonyl group: the torsion angle C3—C4—O1—H1O is 3 (3)°. The geometry of the carboxyl group differs slightly from a planar arrangement [torsion angle O2—C7—O3—H2O is 2 (2)°] and is approximately coplanar with the phenyl fragment [torsion angle O3—C7—C3—C2 is 0.7 (4)°]. The F

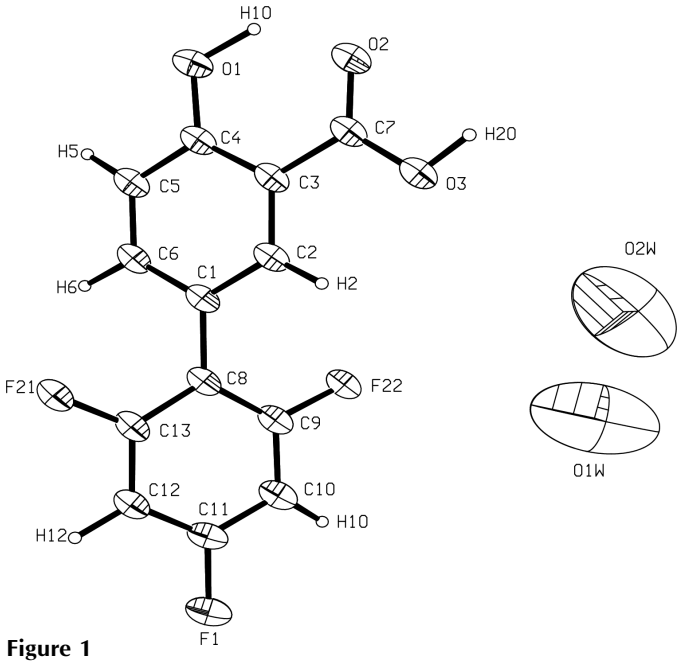


Figure 1
A view of diflunisal hydrate with the atomic numbering scheme. Displacement ellipsoids are drawn at the 20% probability level.

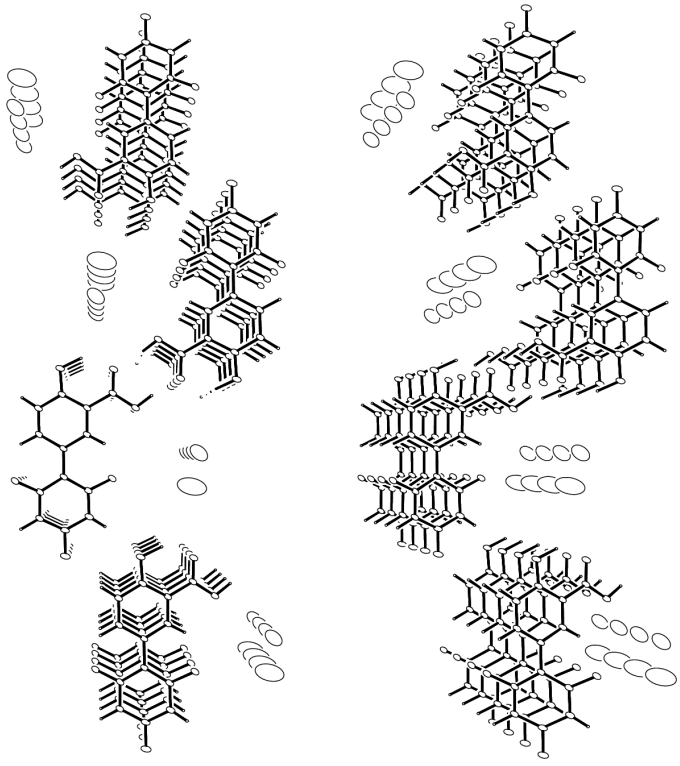


Figure 2
Fragment of the crystal packing looking down the *b* axis.

atoms in positions 2′- and 6′- are disordered. This means that the peaks found for F21 and F22 are a combination of a half-hydrogen peak with a half-fluorine peak even though the bond lengths found for the C—F bonds are normal. This may be explained by the fact that fluorine is a much heavier element compared to hydrogen (19:1), so the influence of hydrogen on the C—F bond will be negligible. The phenyl groups of neighbouring parallel molecules are stacked face-to-face and shifted by R_{shift} = 1.6 Å. The distance between these planes of the phenyl rings is R_b = 3.73 Å. These parameters are in good agreement with the values for the local energetic minimum calculated for benzene dimers: R_{shift}* = 1.6 Å and R_b* = 3.85 Å (Hobza *et al.*, 1993, 1994), and the relative orientation and packing of phenyl rings in diflunisal follow, in general, the rules of packing of benzene dimers. Out of four energetic minima calculated for benzene arrangements (parallel staggered PS; parallel displaced, PD; herring-bone, H; T-shape, T), in the present case, two such local energetic minima are realised (PD and H).

The characteristic (specific) property of the crystal lattice of diflunisal is the existence of channels along the twofold screw axes and parallel to the *b* direction. The geometry of these channels allows accommodation of solvent molecules of appropriate sizes. In the present case, the channels are filled by water molecules, which are situated in a disordered state. It should be noted that the solvate studied here is stable under room conditions. In order to check the stoichiometry of the solvate DSC and TG measurements were carried out at various heating rates (v = 1–20 K min^{-1}). The heat effect occurring during desolvation at v = 10 K min^{-1} and temperature interval from 353 to 383 K is 16 J mol^{-1}. The average mass losses achieved 7.1% and this corresponded to a stoichiometry of diflunisal:water of 1:1. This result is in a good agreement with the X-ray experiment. Considering the possible orientations of the water molecule in the two sites, a calculation has been carried out by using the *HYDROGEN* program (Nardelli, 1999). These results lead us to conclude that the water molecules in the channels form hydrogen bonds between themselves. However, these molecules (guests) are located at relatively long distances from host(diflunisal)-molecules and do not take part in specific host–guest interactions.

Experimental

The solvate was grown by crystallization of a saturated solution of diflunisal and in acetone by vapour diffusion of H_2O (Guillory, 1999).

Crystal data

$C_{13}H_8F_2O_3\cdot H_2O$
M_r = 268.21
Monoclinic, *C*2/*c*
a = 34.650 (2) Å
b = 3.730 (2) Å
c = 20.760 (2) Å
β = 110.47 (6)°
V = 2513.7 (14) Å^3
Z = 8
D_x = 1.417 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 25 reflections
θ = 12–16°
μ = 0.12 mm^{-1}
T = 298 (2) K
Needle, white
0.30 × 0.20 × 0.15 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
2306 measured reflections
2221 independent reflections
1127 reflections with $I > 2\sigma(I)$
R_{int} = 0.014
θ_{max} = 25.0°
$h = -1 \rightarrow 40$
$k = 0 \rightarrow 4$
$l = -24 \rightarrow 23$
3 standard reflections
frequency: 120 min
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.050$
$wR(F^2) = 0.178$
$S = 0.83$
2221 reflections
225 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.1388P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.072$
$\Delta\rho_{max} = 0.26$ e Å^{-3}
$\Delta\rho_{min} = -0.16$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0019 (10)

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H2O···O2^{i}	1.00 (4)	1.65 (4)	2.650 (3)	176 (4)
O1—H1O···O2	1.11 (6)	1.75 (6)	2.620 (4)	131 (4)

Symmetry code: (i) $\frac{1}{2} - x, \frac{1}{2} - y, 1 - z$.

All programs used in the solution, refinement and display of the structures are included in the *OSCAIL* program package (McArdle, 1993).

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *CAD*-4 *Software*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *OSCAIL* (McArdle, 1993).

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