

Water molecules in the crystal
structure of tricyclic acyclovirKinga Suwińska,^{a*} Bożenna Golankiewicz^b and Wojciech Zielenkiewicz^a^aInstitute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, PL-01 224 Warszawa, Poland, and ^bInstitute of Bioorganic Chemistry, Polish Academy of Sciences, Z. Noskowskiego 12/14, PL-61 704 Poznań, Poland
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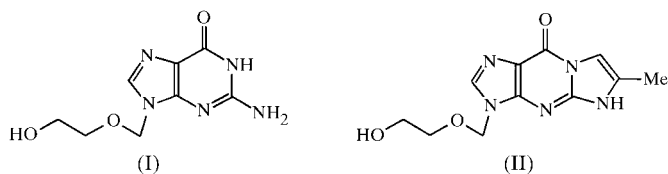
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The biologically important molecule tricyclic acyclovir, presented here as 3-[(2-hydroxyethoxy)methyl]-6-methyl-3*H*-imidazo[1,2-*a*]purin-9(5*H*)-one dihydrate, $C_{11}H_{13}N_5O_3 \cdot 2H_2O$, shows conformational flexibility, which is observed in the solid state as two symmetrically independent molecules with different side-chain conformations. Additionally, one of these molecules exhibits side-chain disorder, such that there are three different conformations in the crystal. Water molecules found in the crystal form $(H_2O)_8$ clusters which are located between molecules of tricyclic acyclovir. The complex hydrogen-bond network formed between water and tricyclic acyclovir in the solid state may be related to the solvation of the molecules in solution.

Comment

Acyclovir, (I), has been demonstrated to be of great clinical importance as an antiherpetic agent (Elion *et al.*, 1997). Tricyclic acyclovir, (II), in which the exocyclic amine group of (I) is incorporated into a new fused ring, was expected to be inactive, but instead exhibits potent and selective antiherpes activity. The spectrum of its activity is narrower than that of acyclovir and this results in a higher selectivity index compared with acyclovir itself (Boryski *et al.*, 1988; Golankiewicz, 1996). Recently, complex physicochemical studies of the title compound, (II)·2*H*₂O, were undertaken and these included the determination of aqueous solubilities, infinite-dilution activity coefficients and octanol–water partition coefficients, as well as other thermodynamic properties of the



compound in aqueous solution (Zielenkiewicz *et al.*, 1998, 1999). Thermogravimetric studies (Perlovich & Zielenkiewicz, 1998) have demonstrated that, in crystalline (II), there are

always solvent molecules present, independent of the solvent used (water or water/organic-solvent mixture). The present study was undertaken to determine the nature of the solvation

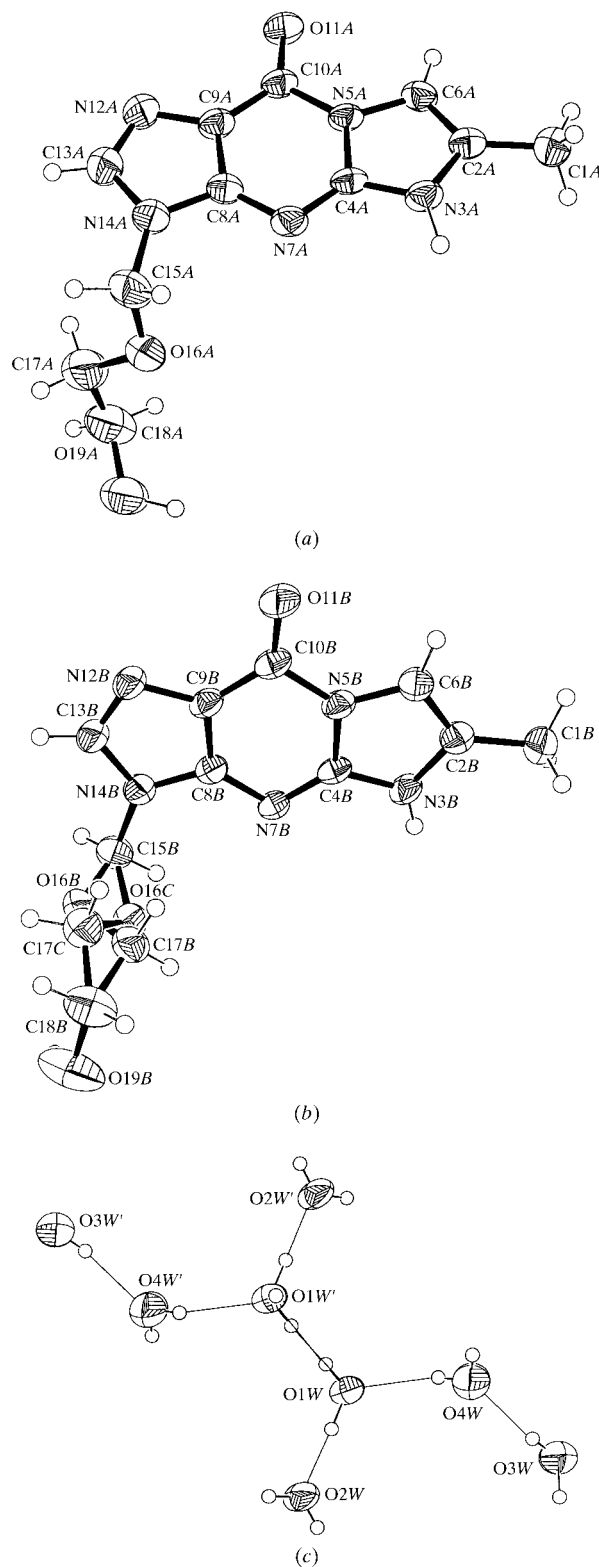


Figure 1

The molecular structures of (a) molecule A, (b) molecule B and the disordered conformer C, and (c) the $(H_2O)_8$ cluster in (II). Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

of (II) in the solid state and we hope it will contribute to an understanding of the relationships between the structures and thermodynamic parameters of the compounds examined.

The two symmetry-independent molecules of (II) have different conformations, *A* and *B*, and additionally, the (2-hydroxyethoxy)methyl side chain in molecule *B* is conformationally disordered, with two different conformations, *B* and *C*, observed in the crystal structure (Fig. 1). The distribution of the different conformers *A*:*B*:*C* in the crystal is 4:3:1. Conformations *A* and *C* are fairly similar, but not identical, while conformation *B* is different. For conformations *A* and *C*, the corresponding torsion angles C13—N14—C15—O16 and C8—N14—C15—O16 are, respectively, anticlinal and synclinal, according to the notation of Klyne & Prelog (1960), while for conformation *B*, the analogous torsion angles are reversed. In both cases, this leads to a partially folded conformation of the (2-hydroxyethoxy)methyl side chain. Details of the two types of conformations are given in Table 1 (it should be noted that in centrosymmetric space groups, the signs of the torsion angles in Table 1 may be reversed). When compared with (I), where three symmetry-independent molecules are also found, the side-chain conformations of two of the molecules of (I) are similar to those of molecules *A* and *C*, but the third molecule adopts a different conformation, with the side chain more fully extended (Birnbau *et al.*, 1984).

The bond lengths and angles of the guanine moiety (Table 1) are in good agreement with values derived from other crystal structure analyses and those found for (I). The differences are

for N7—C8 in molecule *A*, which is 0.019 Å shorter, and C8—C9 in both molecules, which is 0.019 (molecule *A*) and 0.014 Å (molecule *B*) longer, than in (I). Bonds C4—N5 and N5—C6 are elongated by approximately 0.02 Å because of the additional ring fusion in (II). For the bond angles, the differences are at C4 for both molecules, where the N3—C4—N5 angles are more acute and the N3—C4—N7 angles are more obtuse than in (I). This is again related to the presence of the additional fused ring.

The 12 atoms involved in the formation of the three condensed rings are planar. The r.m.s. deviations of the fitted atoms are 0.021 Å and 0.007 Å for molecules *A* and *B*, respectively. In addition, the ring systems of molecules *A* and *B* are coplanar. The molecules are almost parallel, with the angle between the planes of the two molecules being 4.41 (7)°, and the largest deviations from planarity are for atoms C6*A* [0.039 (2) Å] and C13*B* [0.013 (2) Å]. The atoms substituted directly to the condensed ring systems are displaced from the r.m.s. planes by -0.012 (3), -0.054 (2) and 0.095 (3) Å for C1*A*, O11*A* and C15*A*, respectively, and by 0.003 (3), -0.017 (2) and -0.055 (3) Å for C1*B*, O11*B* and C15*B*, respectively.

The hydrogen-bonding pattern in (II) (Table 2) is remarkable. It joins all the bases into infinite *ABAB*-type chains (Fig. 2). Each base of a molecule *A* is connected to adjacent molecules *B* by donating a proton in a hydrogen bond (N3*A*—H···N12*B*) and by accepting a proton in a hydrogen bond (N3*B*—H···O11*A*). Atoms N7 of both molecules and atom O11*B* are not involved in hydrogen bonding between the bases, although they are involved in hydrogen bonding with the water molecules. Each water molecule is involved in hydrogen bonds to molecules of (II) as well as to adjacent water molecules. In the crystal structure of (II), the water molecules form (H₂O)₈ clusters, wherein four symmetry-independent molecules interact with four others across a centre of symmetry. One of the H atoms of water molecule O1*W* is disordered, with a site-occupancy factor of 0.50. Fig. 1(c) shows the (H₂O)₈ cluster. The hydrogen bonds between (II) and water in the solid state may mimic those found in solution for the solvated molecule of (II).

Experimental

Compound (II)·2H₂O was synthesized as described by Boryski *et al.* (1988) and Golankiewicz *et al.* (1991). Recrystallization from aqueous solution afforded colourless crystals of (II)·2H₂O suitable for X-ray analysis.

Crystal data

C₁₁H₁₃N₅O₃·2H₂O
M_r = 299.30
 Triclinic, *P*1̄
a = 8.450 (1) Å
b = 11.665 (2) Å
c = 14.930 (3) Å
 α = 75.44 (2)°
 β = 76.65 (2)°
 γ = 86.44 (2)°
V = 1385.9 (4) Å³

Z = 4
D_x = 1.434 Mg m⁻³
 Mo *K*α radiation
 Cell parameters from 25 reflections
 θ = 5–12°
 μ = 0.12 mm⁻¹
T = 293 (2) K
 Block, colourless
 0.32 × 0.28 × 0.22 mm

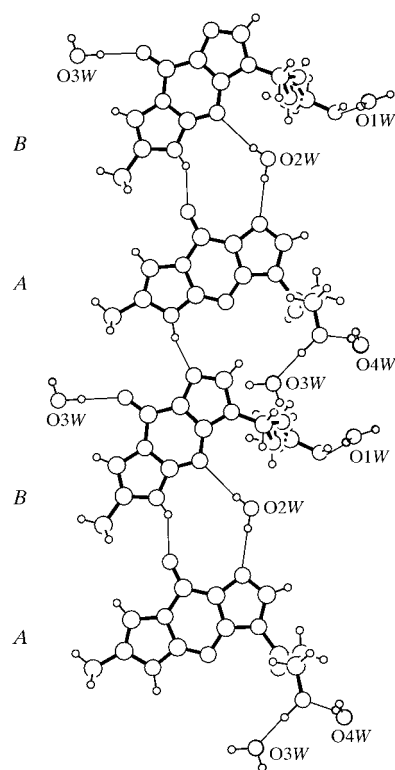


Figure 2

The hydrogen-bonding pattern in (II)·2H₂O, including the solvation of the molecules of (II) by water molecules. In water molecule O1*W*, only one of the alternate positions for the disordered H atoms is shown.

Table 1
Selected geometric parameters (Å, °).

C4A—N5A	1.389 (2)	C4B—N5B	1.381 (2)
N5A—C6A	1.405 (3)	N5B—C6B	1.393 (3)
N7A—C8A	1.336 (3)	N7B—C8B	1.357 (2)
C8A—C9A	1.395 (3)	C8B—C9B	1.390 (3)
N7A—C4A—N3A	127.11 (17)	N7B—C4B—N3B	127.55 (17)
N3A—C4A—N5A	106.59 (17)	N3B—C4B—N5B	105.70 (17)
C8A—N14A—C15A—O16A	−78.4 (3)		
C13A—N14A—C15A—O16A	100.2 (3)		
N14A—C15A—O16A—C17A	−87.1 (3)		
C15A—O16A—C17A—C18A	171.4 (2)		
O16A—C17A—C18A—O19A	67.5 (3)		
C8B—N14B—C15B—O16B	106.7 (2)		
C13B—N14B—C15B—O16B	−70.0 (3)		
N14B—C15B—O16B—C17B	−68.5 (3)		
C15B—O16B—C17B—C18B	178.8 (2)		
O16B—C17B—C18B—O19B	74.6 (4)		
C8B—N14B—C15B—O16C	65.0 (4)		
C13B—N14B—C15B—O16C	−111.7 (3)		
N14B—C15B—O16C—C17C	67.1 (7)		
C15B—O16C—C17C—C18B	171.2 (5)		
O16C—C17C—C18B—O19B	−59.5 (10)		

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

D—H...A	D—H	H...A	D...A	D—H...A
N3A—H3A...N12B ⁱ	0.98 (2)	1.85 (2)	2.800 (2)	163.4 (19)
N3B—H3B...O11A	0.86 (2)	1.98 (2)	2.747 (2)	148 (2)
O19B—H19B...O19B ⁱⁱ	0.82	2.02	2.671 (4)	135
O19A—H19A...O3W ⁱⁱⁱ	1.02 (4)	1.71 (4)	2.731 (2)	177 (3)
O1W—H1WB...O19B ^{iv}	0.89	1.84	2.706 (2)	164
O2W—H2WA...N12A ^v	0.84	1.96	2.797 (2)	177
O2W—H2WB...N7B ^v	0.78	2.21	2.982 (2)	173
O3W—H3WB...O11B ^{vi}	0.97	1.85	2.8219 (18)	176
O4W—H4WB...O19A ^{vii}	0.82	2.00	2.738 (2)	149
O1W—H1WA...O2W	1.00	1.69	2.679	170
O1W—H1WC...O1W ^{viii}	0.82	1.99	2.808 (2)	175
O3W—H3WA...O4W	0.84	1.94	2.751	163
O4W—H4WA...O1W	0.77	2.11	2.852	163

Symmetry codes: (i) $x - 1, y - 1, z$; (ii) $-x, 1 - y, 2 - z$; (iii) $-1 - x, -y, 1 - z$; (iv) $x, y, z - 1$; (v) $-x, 1 - y, 1 - z$; (vi) $x, y - 1, z$; (vii) $2 + x, y, z - 1$; (viii) $1 - x, 1 - y, -z$.

Data collection

Enraf-Nonius CAD-4 diffractometer
 $\omega/2\theta$ scans
 8414 measured reflections
 8047 independent reflections
 4182 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.023$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.062$
 $wR(F^2) = 0.155$
 $S = 1.02$
 8047 reflections
 389 parameters
 H atoms treated by a mixture of independent and constrained refinement

$\theta_{\text{max}} = 30^\circ$
 $h = -11 \rightarrow 11$
 $k = 0 \rightarrow 16$
 $l = -20 \rightarrow 20$
 3 standard reflections
 frequency: 60 min
 intensity decay: 0.3%

$w = 1/[\sigma^2(F_o^2) + (0.0709P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} = 0.016$
 $\Delta\rho_{\text{max}} = 0.26 \text{ e \AA}^{-3}$
 $\Delta\rho_{\text{min}} = -0.20 \text{ e \AA}^{-3}$
 Extinction correction: *SHELXL97* (Sheldrick, 1997)
 Extinction coefficient: 0.0050 (13)

Side-chain disorder in molecule *B* was observed as a shortening of the O16—C17 bond, with unusual displacement parameters for these two atoms. At the same time, residual maxima in the difference electron-density maps were observed. A ratio of 3:1 for conforma-

tions *B* and *C* was established by subsequent refinement of site-occupancy factors and was kept constant in the final stages of the refinement. The disorder for the H atoms of the O1W molecule was found from a difference Fourier synthesis as three maxima with tetrahedral geometry around the O atom. Using a starting model with H1WA and H1WB only resulted in a very high displacement parameter for H1WB, while the U_{iso} value of H1WA refined to the expected value of 0.08 \AA^2 . An additional maximum of approximately 0.4 e \AA^{-3} , with tetragonal angles to H1WA and H1WB, was also observed. Additionally, the short distance [2.816 (3) Å] between atom O1W and its partner related by a centre of symmetry suggested formation of an O1W...O1W hydrogen bond. Refinement of the model with three H atoms, two of which (H1WB and H1WC, where H1WC was introduced in the observed electron-density maximum) had site-occupancy factors of 0.5 and U_{eq} defined as indicated below, improved the refinement and the expected hydrogen bond was found as O1W—H1WC...O1W. H atoms bonded to C atoms were calculated in their ideal positions and refined as riding, with $U_{\text{iso}} = 1.5U_{\text{eq}}$ of the attached C atom for CH₃ groups and $1.2U_{\text{eq}}$ for other C atoms. H atoms bonded to non-water O or N atoms were found in difference electron-density maps and only their coordinates were refined, with $U_{\text{iso}} = 1.2U_{\text{eq}}$ for those attached to N and $1.5U_{\text{eq}}$ for those attached to O. The H atoms of the water molecules were found in difference electron-density maps and refined as riding, with $U_{\text{iso}} = 1.5U_{\text{eq}}$ of the parent O atom.

Data collection: *CAD-4 Software* (Enraf-Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *SDP* (Frenz, 1985); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976) and *ATOMS* (Dowty, 1998); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1107). Services for accessing these data are described at the back of the journal.

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