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The hydrogen-bonding network in deacetylcephalothin

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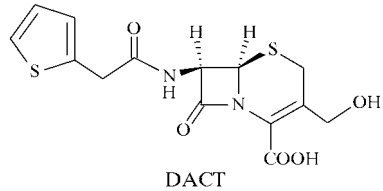
The structural analysis of deacetylcephalothin [systematic name: (6*R*,7*R*)-3-hydroxymethyl-8-oxo-7-(2-thiophen-2-yl-acetylamino)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid], $C_{14}H_{14}N_2O_5S_2$, shows that the geometry of the central bicyclic moiety is close to the geometry exhibited by other biologically active cephalosporin antibiotics. The molecules are arranged in a helical chain running parallel to the 2_1 axis *via* a strong O—H···O hydrogen bond. The main helices are zipped together *via* N—H···O interactions, forming infinite layers. The supramolecular architecture is stabilized by O—H···S and C—H···O hydrogen bonds.

Comment

The cephalosporins are widely used broad-spectrum antibiotics, exhibiting antibacterial activity against Gram-positive and Gram-negative bacteria (Dollery, 1999). In humans and animals, after parenteral administration of cephalothin [systematic name: (6*R*,7*R*)-3-acetoxymethyl-8-oxo-7-(2-thiophen-2-ylacetylamino)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid], the metabolite deacetylcephalothin, DACT, is formed (Katzung, 2001). Microbiological tests showed that DACT exhibits lower activity than the parent drug (Lee *et al.*, 1963). In general, the decrease of biological activity was attributed to the blocking of the carboxyl substituent (Flynn, 1972). On the basis of NMR and IR studies, it was proposed that, in solution, the O1—H hydroxyl group in DACT can form an intramolecular hydrogen bond with the carbonyl O2 atom and in this manner protect the COOH group (Zimniak *et al.*, 1998). In order to elucidate the nature of the hydrogen bonds in DACT in the solid state, the present crystallographic study has been performed. The structure of the sodium salt of cephalothin was determined by van Meerssche *et al.* (1979).

The asymmetric unit of the title compound contains one DACT molecule, confirmed as the *R*,*R* isomer (Fig. 1). Analysis of the bicyclo[4.2.0]octene ring shows that the six-membered dihydrothiazine ring displays an envelope conformation, with atom S1 lying 0.9027 (6) Å out of the plane defined by the remaining atoms of the ring and the C3—S1—C4—N1 torsion angle being 56.5 (2)°. The four-membered β-lactam ring is folded along the C8···N1 line, and the C4—C8—N1—C7 torsion angle is 166.9 (3)°. The geometry of the Δ^3-cephem core (cephem is 5-thia-1-azabicyclo[4.2.0]oct-2-en-8-one) in DACT was compared with that observed for other structurally characterized active cephalosporins derived from the Cambridge Structural Database (CSD, Version 5.26 of August 2005; Allen, 2002). It was found that the overall geometry and conformation of the Δ^3-cephem core in DACT are close to those in retrieved structures (Table 1).



DACT

Some geometric parameters were found to correlate with the antimicrobial activity of cephalosporins. The most commonly reported are the pyramidality of atom N1 (Woodward, 1980), the distance between atom C6 of the carboxyl group and β-lactam atom O4 (Cohen, 1983), and the O4···N1—C5—C6 torsion angle (Nangia *et al.*, 1996). In the molecule of DACT, atom N1 is displaced from the plane defined by atoms C4/C5/C8 by 0.214 (3) Å and Cohen's and Nangia's parameters are 3.186 (4) Å and 40.1 (3)°, respectively. These values are within the ranges postulated for active cephalosporins of 0.15–0.25 Å, 3.1–3.6 Å and 30–160°, respectively (Nangia *et al.*, 1996).

The molecular packing of DACT involves strong intermolecular hydrogen bonds (Table 2), resulting in a two-dimensional supramolecular structure that has been examined using graph-set descriptors (Etter, 1990; Bernstein *et al.*, 1995). The molecules of DACT are linked head-to-tail *via* strong

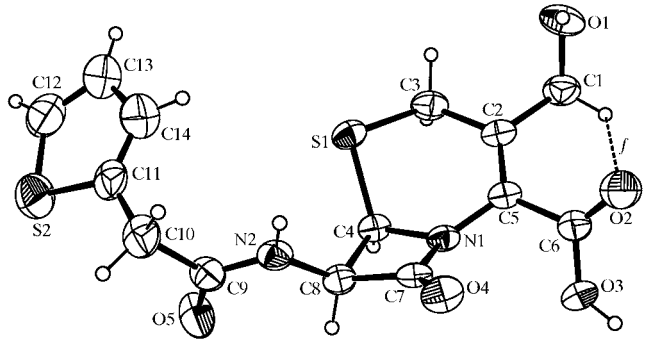


Figure 1
The molecule of DACT with the atom-numbering scheme. Only the major orientation of the disordered thiophene ring is shown. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The intramolecular hydrogen bond (motif *f*) is indicated by a dashed line.

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O3—H3O···O5^{i} hydrogen bonds, forming a helix with a $C(10)$ pattern around the 2_1 screw axis [symmetry code: (i) $-x, y+\frac{1}{2}, 1-z$; motif *a* in Fig. 2]. These main helices are further zipped together *via* the hydroxymethyl group, acting as both hydrogen-bond acceptor and donor. An O1^{ii}···H2N—N2 bond [the $C(9)$ motif *b*] is formed by the peptide N2—H2N group and, simultaneously, the O1—H1O group is engaged in a hydrogen bond with atom S1^{ii} of the dihydrothiazine ring, resulting in the $C(6)$ motif *c* [symmetry code: (ii) $1-x, y+\frac{1}{2}, 1-z$]. Motif *a* and motifs *b* or *c* combine to form layers of fused rings parallel to the (001) plane, with the second-level graph descriptors $N_2(ab) = C_2^2(11)[R_4^4(38)]$ and $N_2(ac) = C_2^2(14)[R_4^4(30)]$.

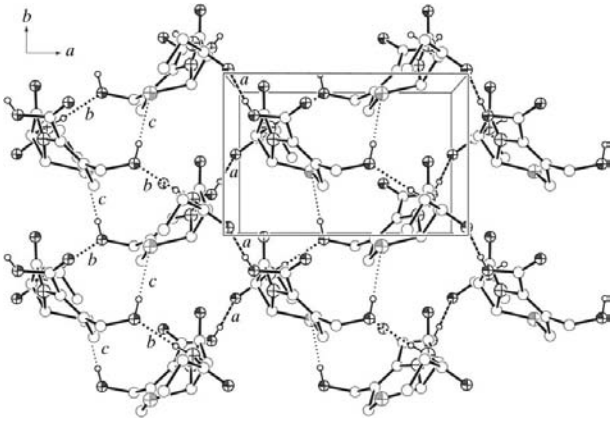

Figure 2
A packing diagram, showing the layered hydrogen-bond structure of DACT with assigned graph-set motifs, viewed along the *c* axis. Thiophene rings and the remaining H atoms have been omitted for clarity.

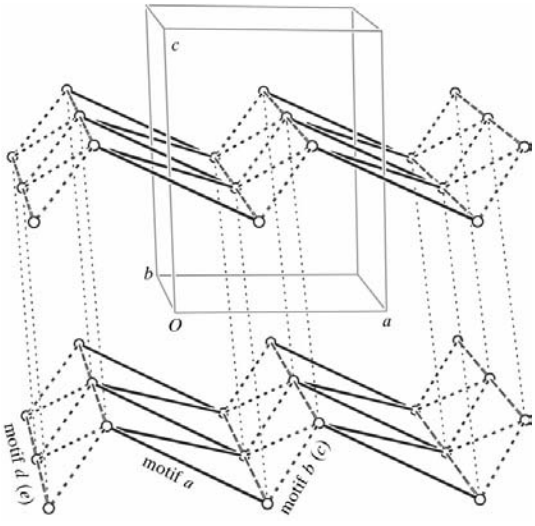

Figure 3
The topology of the hydrogen-bonded structure of DACT, represented by connections of molecule centres of gravity (motif *a* solid lines; motifs *b* and *c* dotted lines; motifs *d* and *e* dashed lines). Thin dotted lines indicate interlayer C—H···O interactions.

The two-dimensional structure is additionally stabilized by weak C—H···O hydrogen bonds between molecules related by translation symmetry in the [010] direction, as shown schematically in Fig. 3 (motifs *d* and *e*) (Steiner, 2002). These bonds are formed by two H atoms of the dihydrothiazine ring (H3*A* and H4) and lactam atom O4^{iii} [symmetry code: (iii) $x, y-1, z$], acting as a double acceptor, and tighten the helix, joining consecutive coils. Adjacent sheets are linked by very weak hydrogen-bond interactions between aromatic C—H donors of the thiophene ring and atom O2 of the carboxyl group, leading to a three-dimensional supramolecular network (Fig. 3).

Thus, in the solid state, all the potential strong hydrogen-bond donor centres of DACT are engaged in the intermolecular interactions that are decisive for supramolecular assembly. They do not form the intramolecular O—H···O bonds that were previously postulated for solutions (Zimniak *et al.*, 1998). The only intramolecular interaction observed in DACT is a weak C1—H1*A*···O2 interaction, depicted as motif *f* in Fig. 1.

Experimental

The synthesis and properties of DACT were reported previously by Zimniak *et al.* (1998). Single crystals of DACT were obtained from anhydrous ethanol.

Crystal data

$C_{14}H_{14}N_2O_5S_2$
$M_r = 354.36$
Monoclinic, $P2_1$
$a = 9.6992\ (18)$ Å
$b = 6.4069\ (12)$ Å
$c = 12.919\ (2)$ Å
$\beta = 93.974\ (14)^\circ$
$V = 800.9\ (2)$ Å^3
$Z = 2$
$D_x = 1.469$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 30 reflections
$\theta = 12$–35°
$\mu = 0.36$ mm^{-1}
$T = 293\ (2)$ K
Prism, colourless
0.35 × 0.25 × 0.20 mm

Data collection

Siemens *P*3 diffractometer
Profile data from $\omega/2\theta$ scans
3986 measured reflections
2834 independent reflections
2623 reflections with $I > 2\sigma(I)$
$R_{int} = 0.034$
$\theta_{max} = 25.0^\circ$
$h = -11 \rightarrow 11$
$k = -7 \rightarrow 7$
$l = -15 \rightarrow 15$
2 standard reflections
every 70 reflections
intensity decay: 4.8%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.038$
$wR(F^2) = 0.090$
$S = 1.08$
2834 reflections
254 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0457P)^2 + 0.2079P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.18$ e Å^{-3}
$\Delta\rho_{min} = -0.18$ e Å^{-3}
Absolute structure: Flack (1983), with 1279 Friedel pairs
Flack parameter: −0.02 (9)

Since the absorption coefficient was comparatively low, no absorption correction was applied. The thiophene ring was found to be disordered over two positions related by rotation about the C10—C11 bond, with site-occupancy factors of 0.626 (4) and 0.374 (4) for the major and minor components, respectively. The alternative atoms

Table 1
Selected geometric parameters (Å, °) for DACT and the mean values for other cephalosporins retrieved from the CSD.

	DACT	Mean CSD†
S1—C3	1.810 (3)	1.82 (2)
S1—C4	1.813 (3)	1.797 (7)
O4—C7	1.201 (3)	1.208 (9)
N1—C4	1.457 (3)	1.47 (1)
N1—C5	1.402 (3)	1.41 (1)
N1—C7	1.381 (3)	1.37 (2)
C2—C5	1.344 (4)	1.34 (1)
C3—S1—C4	93.86 (12)	94 (2)
S1—C4—C8	115.72 (18)	116 (1)
C4—N1—C5	126.7 (2)	126 (1)
C4—N1—C7	94.3 (2)	95.0 (9)
C5—N1—C7	131.8 (2)	133 (2)
C3—S1—C4—N1	56.49 (19)	55 (4)
C4—C8—N1—C7	166.9 (3)	172 (4)

† Based on data for 27 structures with an *R* factor below 0.075 (36 Δ^3-cephem fragments) (CSD, Version 5.26 of August 2005; Allen, 2002).

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3O···O5^{i}	0.86 (4)	1.77 (4)	2.629 (3)	177 (4)
N2—H2N···O1^{ii}	0.80 (3)	2.05 (3)	2.841 (3)	172 (2)
O1—H1O···S1^{ii}	0.85 (4)	2.46 (4)	3.297 (2)	168 (4)
C3—H3*A*···O4^{iii}	0.97	2.53	3.362 (4)	144
C4—H4···O4^{iii}	0.98	2.52	3.322 (3)	139
C1—H1*A*···O2	0.97	2.43	3.072 (5)	124

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

C11 and C11*B* were fixed at the same sites with identical displacement parameters. The positions of H atoms attached to N and O atoms were refined freely but their isotropic displacement parameters were fixed at 1.2 and 1.5 times U_{eq} of the parent atom, respectively. The remaining H atoms were positioned geometrically and refined using a riding model, with U_{iso}(H) = 1.2 or 1.3U_{eq}(C). The absolute structure was established based on anomalous dispersion (1279 Friedel pairs) using the Flack parameter *x* (Flack, 1983; Flack & Bernardinelli, 1999, 2000).

Data collection: *P3*/*P4-PC Diffractometer Program* (Siemens, 1991); cell refinement: *P3*/*P4-PC Diffractometer Program*; data reduction: *XDISK* (Siemens, 1991); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996) and *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97* and *PLATON* (Spek, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ1751). Services for accessing these data are described at the back of the journal.

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