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Key indicators

Powder X-ray study
T = 298 K
Mean $\sigma(C-C)$ = 0.002 Å
R factor = 0.033
wR factor = 0.038
Data-to-parameter ratio = 3.85

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

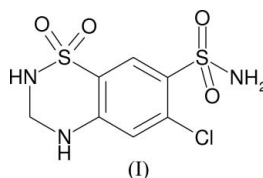
Powder study of hydrochlorothiazide form II

The crystal structure of hydrochlorothiazide form II, $C_7H_8ClN_3O_4S_2$, was solved by simulated annealing from laboratory X-ray powder diffraction data collected at room temperature to 1.76 Å resolution. Subsequent Rietveld refinement yielded an R_{wp} of 0.0376 to 1.49 Å resolution. The molecules crystallize in the space group $P2_1/c$ with one molecule in the asymmetric unit. The structure is stabilized by three $N-H \cdots N$ and one $N-H \cdots O$ hydrogen-bonded intermolecular interaction.

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Comment

Hydrochlorothiazide (HCT) is a thiazide diuretic which is known to crystallize in at least one non-solvated form (Dupont & Dideberg, 1972). A polycrystalline sample of a second polymorph of HCT, form II, (I), was produced using a modified precipitation technique in which an acetone solution of HCT was added to distilled water containing hydroxypropylmethylcellulose (grade E5LV, Dow Chemicals, USA) under



agitation. The resulting precipitate was immediately isolated from solution by membrane filtration. The sample was identified as a new form using multisample X-ray powder diffraction analysis (Florence *et al.*, 2003). The sample was

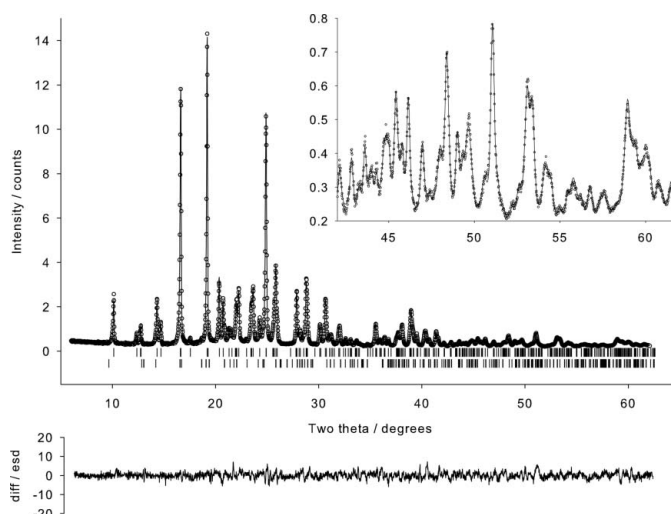


Figure 1
Final observed (points), calculated (line) and difference $[(y_{obs} - y_{calc}) / \sigma(y_{obs})]$ profiles for the Rietveld refinement of the title compound.

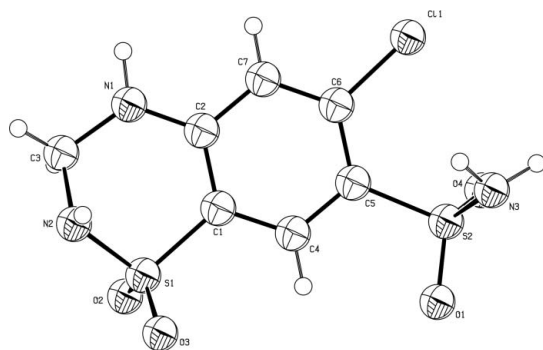


Figure 2
The molecular structure with the atom-numbering scheme. Isotropic displacement spheres are shown at the 50% probability level.

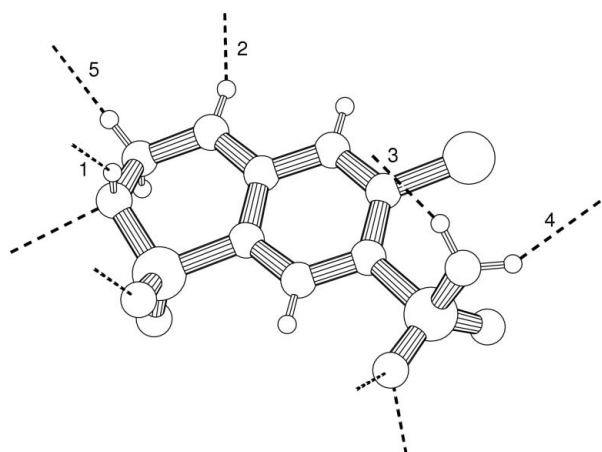


Figure 3
Packing diagram illustrating intermolecular contacts (dashed lines) in the structure of (I). Unique contacts are labelled as follows: 1: N2...O3 = 2.905 (4) Å, O3 in the molecule at $(-x, 1 - y, -z)$; 2: N1...O1 = 2.920 (3) Å, O1 in the molecule at $(x, 1/2 - y, -1/2 + z)$; 3: N3...O1 = 3.121 (3) Å, O1 in the molecule at $(1 - x, 1/2 + y, 1/2 - z)$; 4: N3...N2 = 3.214 (2) Å, N2 in the molecule at $(1 + x, 1/2 - y, 1/2 + z)$; 5: C3...O2 = 3.416 (3) Å, O2 in the molecule at $(-x, 1/2 + y, -1/2 - z)$. Contacts calculated and illustrated using *PLATON* (Spek, 2003; program version 280604).

found to contain a trace amount of HCT form I (Dupont & Dideberg, 1972).

The crystal structure of (I) was solved by simulated annealing using laboratory X-ray powder diffraction data (Fig. 1). The compound crystallizes in space group $P2_1/c$ with one molecule in the asymmetric unit (Fig. 2). In (I), the N2/S1/C1/C2/N1/C3 ring in HCT displays a non-planar conformation, atoms N2 and C3 having the largest deviations [0.458 (1) and -0.266 (1) Å, respectively] from the least-squares plane through the aromatic ring. The sulfonamide side chain adopts a torsion angle N3—S2—C5—C6 = 59.53 (19)°, such that O1 eclipses H4, and atoms O4 and N3 are staggered with respect to Cl1. In HCT form I (Dupont & Dideberg, 1972), this group is rotated by approximately 120° compared with (I), such that the amine group lies on the opposite side of the benzothiazine ring system.

The crystal structure is stabilized by a series of intermolecular contacts including three N—H...N hydrogen bonds

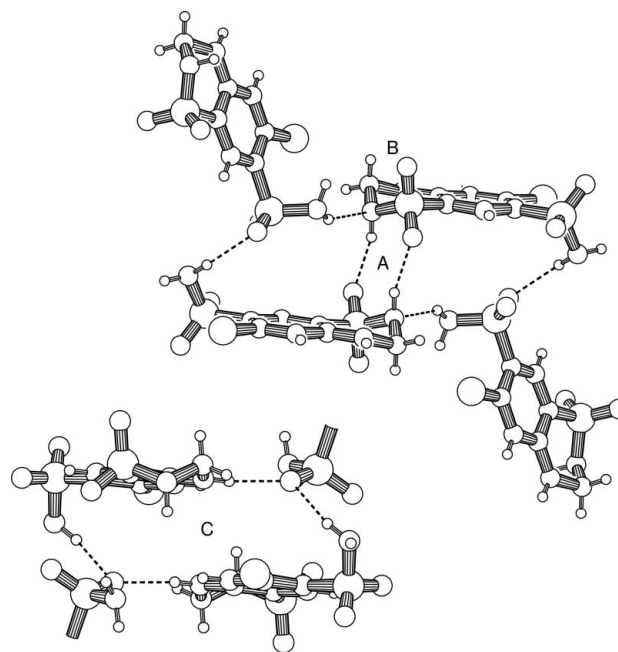


Figure 4
(Top) The $R_2^2(8)$ (labelled A) and $R_4^4(24)$ (labelled B) motifs within the structure of (I). (Bottom left) The $R_4^2(20)$ motif, shown with atoms not involved in the motif omitted for clarity.

(contacts 1–3, Fig. 3), one N—H...O hydrogen bond (contact 4) and a C—H...O contact (contact 5). Contact 1 forms a centrosymmetric $R_2^2(8)$ dimer motif (Fig. 4, A), whilst contacts 3 and 4 produce a larger $R_4^4(24)$ motif (Fig. 4, B) connecting four molecules of HCT. Contacts 2 and 3 also combine to produce an $R_4^2(20)$ ring motif (Fig. 4, C).

Experimental

A sample of (I), obtained using the method described in the *Comment*, was lightly ground in a mortar, loaded into a 0.7 mm borosilicate glass capillary and mounted on the diffractometer. Data were collected from a sample in a rotating 0.7 mm borosilicate glass capillary using a variable count time scheme (Shankland *et al.*, 1997; Hill & Madsen, 2002).

Crystal data

$C_7H_8ClN_3O_4S_2$
 $M_r = 297.75$
Monoclinic, $P2_1/c$
 $a = 9.4884$ (5) Å
 $b = 8.3334$ (4) Å
 $c = 15.1309$ (7) Å
 $\beta = 113.2087$ (19)°
 $V = 1099.59$ (9) Å³
 $Z = 4$

$D_x = 1.799$ Mg m⁻³
Cu $K\alpha_1$ radiation
 $\mu = 6.75$ mm⁻¹
 $T = 298$ K
Specimen shape: cylinder
12 × 0.7 mm
Specimen prepared at 298 K
Particle morphology: visual estimate, prisms, white

Data collection

Bruker AXS D8 Advance diffractometer
Specimen mounting: 0.7 mm borosilicate capillary
Specimen mounted in transmission mode

Scan method: step
Absorption correction: none
 $2\theta_{\min} = 5.0$, $2\theta_{\max} = 65.0$
Increment in $2\theta = 0.017$ °

Refinement

| | |
|---|---|
| Refinement on I_{net} | 355 reflections |
| $R_p = 0.033$ | 92 parameters |
| $R_{\text{wp}} = 0.038$ | Only H-atom coordinates refined |
| $R_{\text{exp}} = 0.023$ | Weighting scheme based on |
| $R_B = 0.013$ | measured s.u.'s $1/\sigma(Y_{\text{obs}})^2$ |
| $S = 1.64$ | $(\Delta/\sigma)_{\text{max}} = 0.005$ |
| Excluded region(s): 62.1 to 65.0% due to poor signal-to-noise | Preferred orientation correction: a spherical harmonics-based |
| Profile function: fundamental parameters with axial divergence correction | preferred orientation correction was applied with <i>TOPAS</i> during the Rietveld refinement |

Table 1

Selected geometric parameters (\AA , $^\circ$).

| | | | |
|----------|-------------|----------|-------------|
| C1—C6 | 1.730 (2) | S2—O4 | 1.429 (3) |
| S1—O2 | 1.425 (3) | S2—N3 | 1.633 (2) |
| S1—O3 | 1.426 (2) | S2—C5 | 1.772 (2) |
| S1—N2 | 1.6438 (16) | N1—C2 | 1.358 (2) |
| S1—C1 | 1.7650 (17) | N1—C3 | 1.473 (2) |
| S2—O1 | 1.428 (2) | N2—C3 | 1.441 (2) |
| O2—S1—O3 | 119.4 (2) | C2—N1—C3 | 123.27 (16) |
| O2—S1—N2 | 110.42 (13) | S1—N2—C3 | 113.58 (11) |
| O2—S1—C1 | 108.92 (17) | S1—C1—C2 | 119.80 (11) |
| O3—S1—N2 | 106.39 (18) | S1—C1—C4 | 119.55 (11) |
| O3—S1—C1 | 109.25 (10) | N1—C2—C1 | 121.84 (13) |
| N2—S1—C1 | 100.90 (10) | N1—C2—C7 | 120.34 (13) |
| O1—S2—O4 | 122.35 (19) | N1—C3—N2 | 108.10 (11) |
| O1—S2—N3 | 106.27 (14) | S2—C5—C4 | 117.40 (12) |
| O1—S2—C5 | 105.68 (13) | S2—C5—C6 | 124.83 (13) |
| O4—S2—N3 | 107.67 (14) | C1—C6—C5 | 121.28 (16) |
| O4—S2—C5 | 108.82 (13) | C1—C6—C7 | 117.16 (14) |
| N3—S2—C5 | 104.75 (10) | | |

Table 2

Hydrogen-bond geometry (\AA , $^\circ$).

| $D-H\cdots A$ | $D-H$ | $H\cdots A$ | $D\cdots A$ | $D-H\cdots A$ |
|----------------------------------|----------|-------------|-------------|---------------|
| N2—H5 \cdots O3 ⁱ | 0.95 (1) | 2.03 (1) | 2.905 (4) | 152 (1) |
| N1—H6 \cdots O1 ⁱⁱ | 0.94 (1) | 2.02 (1) | 2.920 (3) | 159 (1) |
| N3—H7 \cdots O1 ⁱⁱⁱ | 0.95 (1) | 2.21 (1) | 3.121 (3) | 161 (1) |
| N3—H8 \cdots N2 ^{iv} | 0.95 (1) | 2.37 (1) | 3.214 (2) | 149 (1) |
| C3—H1 \cdots O2 ^v | 0.95 (1) | 2.56 (1) | 3.416 (3) | 150 (1) |
| C4—H4 \cdots O1 | 0.95 (1) | 2.37 (1) | 2.803 (3) | 108 (1) |

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

The diffraction pattern indexed to a monoclinic cell [$M(20) = 25.9$, $F(20) = 70.7$; DICVOL-91; Boulton & Louer, 1991), and space group $P2_1/c$ was assigned from volume considerations and a statistical consideration of the systematic absences (Markvardsen *et al.*, 2001). The data set was background subtracted and truncated to $52.2^\circ 2\theta$ for Pawley (1981) fitting ($\chi^2_{\text{Pawley}} = 5.17$) and the structure was solved using the simulated annealing (SA) global optimization procedure (David *et al.*, 1998), which is now implemented in the *DASH* computer program (David *et al.*, 1998). The SA structure solution involved the optimization of one molecule of HCT, totaling 7 degrees of freedom. The best SA solution had a favourable $\chi^2_{\text{SA}}/\chi^2_{\text{Pawley}}$ ratio of 2.6, a chemically reasonable packing arrange-

ment and exhibited no significant misfit to the data. Prior to Rietveld refinement, atoms H7 and H8 were set to positions which satisfied the hydrogen bonding contacts within the structure. The solved structure was subsequently refined with data in the range $6.0\text{--}62.1^\circ 2\theta$ using a restrained Rietveld (1969) method, as implemented in *TOPAS* (Coelho, 2003), with the R_{wp} falling to 0.038 during the refinement. A joint refinement strategy was implemented, in which the structure of HCT form I (Dupont & Dideberg, 1972) was included to take account of the impurity peaks arising from the presence of a small amount (estimated at less than 5%) of this polymorph in the sample. In the course of the refinement, the form I unit-cell and peak-shape parameters were allowed to vary, whilst all atomic coordinates were fixed. All atomic positions (including H atoms) for the form II structure were refined, subject to a series of restraints on bond lengths, bond angles and planarity. $U_{\text{iso}}(\text{H})$ values were set at 0.044 \AA^2 . A spherical harmonics correction of intensities for preferred orientation was applied in the final refinement. The observed and calculated diffraction patterns for the refined crystal structure are shown in Fig. 1.

Data collection: *DIFFRAC* plus *XRD Commander* (Kienle & Jacob, 2003); cell refinement: *TOPAS* (Coelho, 2003); data reduction: *DASH* (David *et al.*, 2001); program(s) used to solve structure: *DASH*; program(s) used to refine structure: *TOPAS*; molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *enCIFer* (Allen *et al.*, 2004).

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supporting information

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Powder study of hydrochlorothiazide form II

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(I)

Crystal data

$C_7H_8ClN_3O_4S_2$

$M_r = 297.75$

Monoclinic, $P2_1/c$

Hall symbol: -P 2ybc

$a = 9.4884$ (5) Å

$b = 8.3334$ (4) Å

$c = 15.1309$ (7) Å

$\beta = 113.2087$ (19)°

$V = 1099.59$ (9) Å³

$Z = 4$

$F(000) = 608.0$

$D_x = 1.799$ Mg m⁻³

Cu $K\alpha_1$ radiation, $\lambda = 1.54056$ Å

$\mu = 6.75$ mm⁻¹

$T = 298$ K

Particle morphology: visual estimate, prisms white

cylinder, 12×0.7 mm

Specimen preparation: Prepared at 298 K

Data collection

Bruker AXS D8 Advance diffractometer

Radiation source: sealed X-ray tube, Bruker-AXS D8

Primary focussing, Ge 111 monochromator

Specimen mounting: 0.7 mm borosilicate capillary

Data collection mode: transmission

Scan method: step

$2\theta_{\min} = 5.0^\circ$, $2\theta_{\max} = 65.0^\circ$, $2\theta_{\text{step}} = 0.017^\circ$

Refinement

Least-squares matrix: selected elements only

$R_p = 0.033$

$R_{wp} = 0.038$

$R_{\text{exp}} = 0.023$

$R_{\text{Bragg}} = 0.013$

3529 data points

Excluded region(s): 62.1 to 65.0 due to poor signal to noise

Profile function: Fundamental parameters with axial divergence correction

92 parameters

47 restraints

1 constraint

Only H-atom coordinates refined

Weighting scheme based on measured s.u.'s

$1/\sigma(Y_{\text{obs}})^2$

$(\Delta/\sigma)_{\max} = 0.005$

Background function: Chebyshev polynomial

Preferred orientation correction: A spherical harmonics-based preferred orientation correction was applied with Topas during the Rietveld refinement.

Special details

Geometry. Bond distances, angles *etc.* have been calculated using the rounded fractional coordinates. All s.u.'s are estimated from the variances of the (full) variance-covariance matrix. The cell e.s.d.'s are taken into account in the estimation of distances, angles and torsion angles

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

| | <i>x</i> | <i>y</i> | <i>z</i> | $U_{\text{iso}}^*/U_{\text{eq}}$ |
|-----|--------------|---------------|---------------|----------------------------------|
| C11 | 0.75173 (15) | 0.1570 (3) | 0.12511 (14) | 0.0269 (4)* |
| S1 | 0.04110 (12) | 0.25043 (13) | -0.05257 (7) | 0.0269 (4)* |
| S2 | 0.53828 (12) | -0.00769 (14) | 0.22842 (7) | 0.0269 (4)* |
| O1 | 0.41184 (17) | -0.0340 (4) | 0.25537 (14) | 0.0269 (4)* |
| O2 | -0.0243 (4) | 0.1139 (3) | -0.1111 (2) | 0.0269 (4)* |
| O3 | -0.0117 (2) | 0.2956 (5) | 0.02000 (11) | 0.0269 (4)* |
| O4 | 0.6253 (3) | -0.1367 (3) | 0.21308 (19) | 0.0269 (4)* |
| N1 | 0.26907 (15) | 0.3922 (3) | -0.12379 (11) | 0.0269 (4)* |
| N2 | 0.02352 (17) | 0.41019 (14) | -0.11982 (8) | 0.0269 (4)* |
| N3 | 0.65720 (17) | 0.10948 (14) | 0.31064 (14) | 0.0269 (4)* |
| C1 | 0.24235 (12) | 0.2284 (2) | -0.00040 (9) | 0.0269 (4)* |
| C2 | 0.33184 (13) | 0.3004 (2) | -0.04357 (9) | 0.0269 (4)* |
| C3 | 0.10325 (14) | 0.39732 (15) | -0.18320 (9) | 0.0269 (4)* |
| C4 | 0.30954 (13) | 0.1390 (2) | 0.08259 (9) | 0.0269 (4)* |
| C5 | 0.46572 (15) | 0.1121 (2) | 0.12321 (12) | 0.0269 (4)* |
| C6 | 0.55492 (15) | 0.1828 (3) | 0.07942 (12) | 0.0269 (4)* |
| C7 | 0.49079 (13) | 0.2748 (2) | -0.00157 (9) | 0.0269 (4)* |
| H1 | 0.0814 (8) | 0.4892 (11) | -0.2234 (7) | 0.044* |
| H2 | 0.0707 (10) | 0.3011 (11) | -0.2187 (6) | 0.044* |
| H3 | 0.5541 (9) | 0.3160 (10) | -0.0320 (6) | 0.044* |
| H4 | 0.2476 (9) | 0.0937 (11) | 0.1121 (6) | 0.044* |
| H5 | 0.0555 (9) | 0.5041 (11) | -0.0813 (6) | 0.044* |
| H6 | 0.3375 (9) | 0.4321 (11) | -0.1498 (6) | 0.044* |
| H7 | 0.6580 (8) | 0.2158 (10) | 0.2881 (6) | 0.044* |
| H8 | 0.7567 (9) | 0.0647 (11) | 0.3389 (6) | 0.044* |

Geometric parameters (\AA , $^\circ$)

| | | | |
|----------|-------------|----------|-------------|
| C11—C6 | 1.730 (2) | N2—H5 | 0.951 (9) |
| S1—O2 | 1.425 (3) | N3—H7 | 0.951 (8) |
| S1—O3 | 1.426 (2) | N3—H8 | 0.946 (9) |
| S1—N2 | 1.6438 (16) | C1—C2 | 1.3946 (19) |
| S1—C1 | 1.7650 (17) | C1—C4 | 1.381 (2) |
| S2—O1 | 1.428 (2) | C2—C7 | 1.4031 (19) |
| S2—O4 | 1.429 (3) | C4—C5 | 1.381 (2) |
| S2—N3 | 1.633 (2) | C5—C6 | 1.394 (2) |
| S2—C5 | 1.772 (2) | C6—C7 | 1.368 (2) |
| N1—C2 | 1.358 (2) | C3—H1 | 0.949 (9) |
| N1—C3 | 1.473 (2) | C3—H2 | 0.947 (9) |
| N2—C3 | 1.441 (2) | C4—H4 | 0.946 (9) |
| N1—H6 | 0.943 (9) | C7—H3 | 0.953 (9) |
| O2—S1—O3 | 119.4 (2) | S1—C1—C4 | 119.55 (11) |
| O2—S1—N2 | 110.42 (13) | C1—C2—C7 | 117.82 (13) |
| O2—S1—C1 | 108.92 (17) | N1—C2—C1 | 121.84 (13) |

| | | | |
|-------------|--------------|--------------|--------------|
| O3—S1—N2 | 106.39 (18) | N1—C2—C7 | 120.34 (13) |
| O3—S1—C1 | 109.25 (10) | N1—C3—N2 | 108.10 (11) |
| N2—S1—C1 | 100.90 (10) | C1—C4—C5 | 121.48 (13) |
| O1—S2—O4 | 122.35 (19) | S2—C5—C4 | 117.40 (12) |
| O1—S2—N3 | 106.27 (14) | S2—C5—C6 | 124.83 (13) |
| O1—S2—C5 | 105.68 (13) | C4—C5—C6 | 117.77 (15) |
| O4—S2—N3 | 107.67 (14) | C11—C6—C5 | 121.28 (16) |
| O4—S2—C5 | 108.82 (13) | C11—C6—C7 | 117.16 (14) |
| N3—S2—C5 | 104.75 (10) | C5—C6—C7 | 121.56 (15) |
| C2—N1—C3 | 123.27 (16) | C2—C7—C6 | 120.67 (13) |
| S1—N2—C3 | 113.58 (11) | N1—C3—H1 | 109.0 (6) |
| C2—N1—H6 | 116.1 (6) | N1—C3—H2 | 110.7 (6) |
| C3—N1—H6 | 118.7 (5) | N2—C3—H1 | 109.1 (6) |
| S1—N2—H5 | 110.9 (5) | N2—C3—H2 | 107.5 (6) |
| C3—N2—H5 | 110.2 (6) | H1—C3—H2 | 112.3 (8) |
| S2—N3—H7 | 112.6 (5) | C1—C4—H4 | 119.6 (5) |
| S2—N3—H8 | 112.0 (6) | C5—C4—H4 | 118.9 (6) |
| H7—N3—H8 | 112.5 (8) | C2—C7—H3 | 119.7 (5) |
| C2—C1—C4 | 120.66 (12) | C6—C7—H3 | 119.5 (5) |
| S1—C1—C2 | 119.80 (11) | | |
| O2—S1—N2—C3 | -62.4 (2) | S1—N2—C3—N1 | -66.39 (16) |
| O3—S1—N2—C3 | 166.72 (13) | C2—C1—C4—C5 | -2.8 (2) |
| C1—S1—N2—C3 | 52.73 (12) | S1—C1—C2—C7 | -177.71 (12) |
| O2—S1—C1—C2 | 96.13 (19) | C4—C1—C2—N1 | -178.32 (17) |
| O2—S1—C1—C4 | -83.47 (19) | S1—C1—C2—N1 | 2.1 (2) |
| O3—S1—C1—C2 | -131.9 (2) | S1—C1—C4—C5 | 176.79 (13) |
| O3—S1—C1—C4 | 48.5 (2) | C4—C1—C2—C7 | 1.9 (2) |
| N2—S1—C1—C2 | -20.07 (15) | N1—C2—C7—C6 | 179.82 (19) |
| N2—S1—C1—C4 | 160.33 (13) | C1—C2—C7—C6 | -0.4 (2) |
| O1—S2—C5—C4 | -7.5 (2) | C1—C4—C5—S2 | -178.81 (13) |
| O1—S2—C5—C6 | 171.5 (2) | C1—C4—C5—C6 | 2.1 (3) |
| O4—S2—C5—C4 | 125.57 (18) | S2—C5—C6—C7 | -179.59 (15) |
| O4—S2—C5—C6 | -55.4 (2) | S2—C5—C6—C11 | 0.7 (3) |
| N3—S2—C5—C4 | -119.51 (15) | C4—C5—C6—C11 | 179.73 (17) |
| N3—S2—C5—C6 | 59.5 (2) | C4—C5—C6—C7 | -0.6 (3) |
| C3—N1—C2—C7 | 166.79 (16) | C5—C6—C7—C2 | -0.3 (3) |
| C3—N1—C2—C1 | -13.0 (3) | C11—C6—C7—C2 | 179.46 (16) |
| C2—N1—C3—N2 | 44.9 (2) | | |

Hydrogen-bond geometry (\AA , $^\circ$)

| $D-H\cdots A$ | $D-H$ | $H\cdots A$ | $D\cdots A$ | $D-H\cdots A$ |
|----------------------------------|----------|-------------|-------------|---------------|
| N2—H5 \cdots O3 ⁱ | 0.95 (1) | 2.03 (1) | 2.905 (4) | 152 (1) |
| N1—H6 \cdots O1 ⁱⁱ | 0.94 (1) | 2.02 (1) | 2.920 (3) | 159 (1) |
| N3—H7 \cdots O1 ⁱⁱⁱ | 0.95 (1) | 2.21 (1) | 3.121 (3) | 161 (1) |
| N3—H8 \cdots N2 ^{iv} | 0.95 (1) | 2.37 (1) | 3.214 (2) | 149 (1) |

| | | | | |
|-----------------------|----------|----------|-----------|---------|
| C3—H1…O2 ^v | 0.95 (1) | 2.56 (1) | 3.416 (3) | 150 (1) |
| C4—H4…O1 | 0.95 (1) | 2.37 (1) | 2.803 (3) | 108 (1) |

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