Acta Crystallographica Section E
Structure Reports
Online

ISSN 1600-5368

Hydrochlorothiazide–1,4-dioxane (1/1)

Andrea Johnston,[a] Alastair J. Florence[a]* and Alan R. Kennedy[b]

[a]Department of Pharmaceutical Sciences, University of Strathclyde, 27 Taylor Street, Glasgow G4 0NR, Scotland, and [b]WestCHEM, Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, Scotland

Correspondence e-mail:
alastair.florence@strath.ac.uk

Key indicators

Single-crystal X-ray study
T = 123 K
Mean σ(C–C) = 0.003 Å
R factor = 0.031
wR factor = 0.078
Data-to-parameter ratio = 15.4

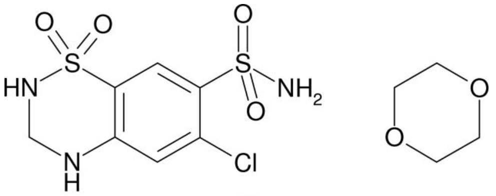
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 5 July 2005
Accepted 13 July 2005
Online 16 July 2005

Hydrochlorothiazide forms a 1:1 solvate with 1,4-dioxane, $C_7H_8ClN_3O_4S_2 \cdot C_4H_8O_2$ [systematic name: 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide–1,4-dioxane (1/1)]. The asymmetric unit comprises one molecule of hydrochlorothiazide and halves of two solvent molecules arranged around inversion centres. The structure contains a hydrogen-bonding network comprising three N—H···O and one N—H···N hydrogen bonds.

Comment

Hydrochlorothiazide (HCT) is a thiazide diuretic which is known to crystallize in at least one non-solvated form (Dupont & Dideberg, 1972). The title compound, (I), was produced during an automated parallel crystallization polymorph screen on HCT. The sample was identified as a novel form using multi-sample X-ray powder diffraction analysis of all recrystallized samples (Florence *et al.*, 2003). Subsequent manual recrystallization from a saturated 1:1 acetone/dioxane solution, by slow evaporation at 298 K, yielded samples of the HCT 1,4-dioxane solvate suitable for single-crystal X-ray analysis (Fig. 1).



(I)

In (I), the six-membered S1/N1/C1/N2/C2/C7 ring in HCT displays a half-chair conformation, atoms C1 and N1 having deviations of −0.134 (2) and 0.554 (2) Å, respectively, from the least-squares plane through atoms C2–C7. The sulfonamide side chain adopts an N3—S2—C5—C4 torsion angle of 57.55 (18)°, such that atom O3 eclipses atom H6, and atoms O4 and N3 are staggered with respect to atom Cl1. In the non-solvated structure, this group is rotated by approximately 120° compared with that in (I), such that the amine group lies on the opposite side of the benzothiadiazine ring system. Both centrosymmetric solvent molecules adopt chair conformations, with puckering parameters (Cremer & Pople, 1975) for rings A and B of $Q = 0.564$ (2) and 0.566 (2) Å, $\theta = 2.11$ (1) and 0.00° and φ = 0 and 0°, respectively.

The crystal structure is stabilized by a network of hydrogen bonds interconnecting (*a*) HCT molecules (Fig. 2, contacts 1 and 2), (*b*) HCT and solvent molecule A (contact 3), and (*c*) HCT and solvent molecule B (contact 4). Contact 1 forms an

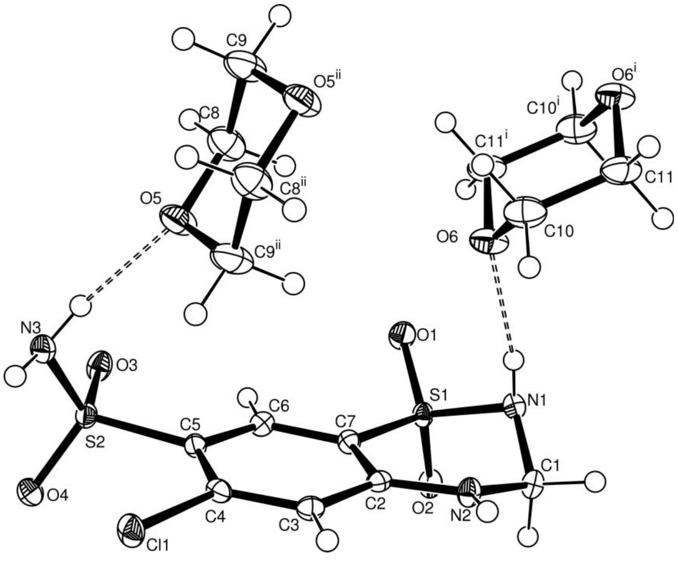


Figure 1
The asymmetric unit contents, expanded to complete the solvent molecules, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. Dashed lines indicate hydrogen-bond contacts. [Symmetry codes: (i) $1-x, -y, 1-z$; (ii) $-x, 1-y, 1-z$].

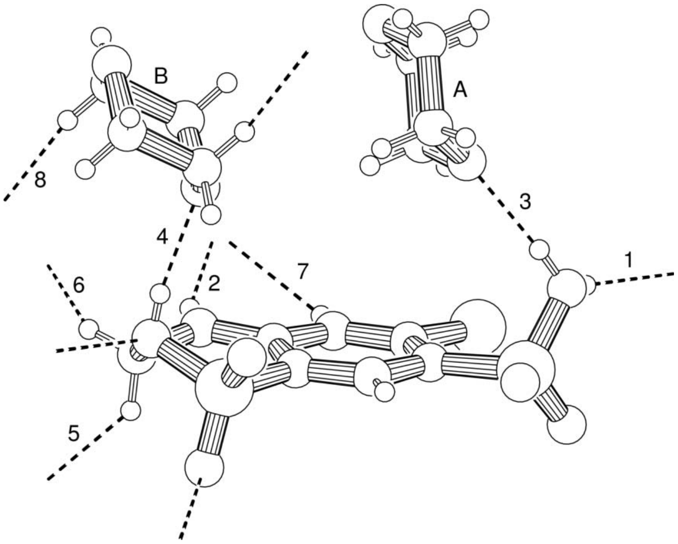


Figure 2
Intermolecular interactions in (I). Dashed lines indicate hydrogen bonds and unique contacts are labelled as follows: (1) N3···N1($-1+x, 1+y, z$) = 3.097 (3) Å; (2) N2···O2($-1+x, y, z$) = 3.032 (2) Å; (3) N3···O5 = 2.879 (2) Å; (4) N1···O6 = 2.848 (2) Å; (5) C1···O2($2-x, -y, -z$) = 3.304 (2) Å; (6) C1···O4($x, -1+y, z$) = 3.220 (2) Å; (7) C3···O2($-1+x, y, z$) = 3.285 (2) Å; (8) C11···O3($x, -1+y, z$) = 3.412 (2) Å. Contacts calculated and illustrated using *PLATON* (Spek, 2003; program version 280604)

infinite chain of HCT molecules, which combine with contact 2 to form layers of HCT molecules in the *ab* plane. Each HCT layer is connected to parallel layers of 1,4-dioxane (*via* contacts 3 and 4) and HCT molecules. Hydrophobic interactions between layers of HCT include offset face-to-face (off) π–π stacking between the ring formed by atoms C2–C7 [centroid–centroid distance = 4.192 (1) Å]. Compound (I) therefore adopts a stacked structure with alternating double layers of HCT, with single layers of solvent stacked in the *c* direction (Fig. 3). Three C—H···O contacts also exist between HCT molecules (Fig. 2, contacts 5–7), with a fourth connecting 1,4-dioxane molecule B to atom O3 of HCT (contact 8).

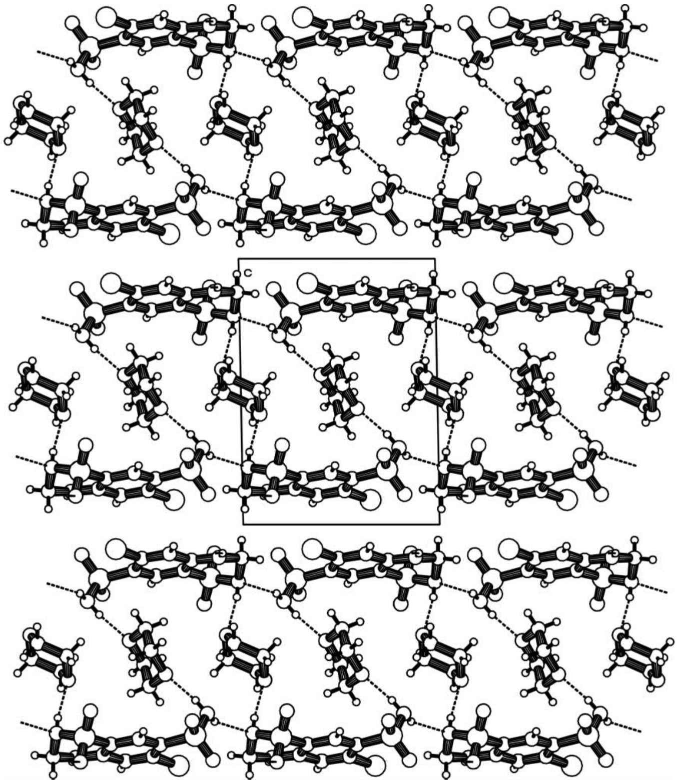


Figure 3
The crystal packing in the structure of (I); view down the *a* axis, showing the alternating layers of HCT and 1,4-dioxane molecules stacked along *c*. Hydrogen bonds are shown as dashed lines.

Experimental

A single-crystal sample of the title compound was recrystallized from a 1:1 acetone/1,4-dioxane solution by slow evaporation at 298 K.

Crystal data

$C_7H_8ClN_3O_4S_2 \cdot C_4H_8O_2$
M_r = 385.84
Triclinic, $P\overline{1}$
a = 6.6684 (2) Å
b = 9.8585 (3) Å
c = 12.9149 (4) Å
α = 87.046 (2)°
β = 78.017 (2)°
γ = 70.872 (2)°
V = 784.55 (4) Å^3

Z = 2
D_x = 1.633 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3105 reflections
θ = 1.0–27.1°
μ = 0.54 mm^{-1}
T = 123 (2) K
Plate, colourless
0.50 × 0.20 × 0.08 mm

Data collection

Nonius KappaCCD diffractometer
ω and φ scans
Absorption correction: none
12343 measured reflections
3445 independent reflections
2879 reflections with $I > 2\sigma(I)$

$R_{\rm int}$ = 0.035
$\theta_{\rm max}$ = 27.1°
$h = -8 \rightarrow 8$
$k = -12 \rightarrow 12$
$l = -16 \rightarrow 15$

o2574 Johnston *et al.* • $C_7H_8ClN_3O_4S_2 \cdot C_4H_8O_2$ *Acta Cryst.* (2005). E**61**, o2573–o2575

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.031$
$wR(F^2) = 0.078$
$S = 1.03$
3445 reflections
224 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0335P)^2 + 0.4818P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.35$ e Å^{-3}
$\Delta\rho_{min} = -0.43$ e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···O6	0.82 (2)	2.04 (2)	2.848 (2)	170 (2)
N2—H2N···O2^{i}	0.81 (2)	2.28 (3)	3.032 (2)	154 (2)
N3—H3N···N1^{ii}	0.81 (2)	2.35 (2)	3.097 (3)	155 (2)
N3—H4N···O5	0.87 (3)	2.02 (3)	2.879 (2)	170 (3)
C1—H1A···O2	0.99	2.60	2.980 (2)	103
C1—H1A···O2^{iii}	0.99	2.55	3.304 (2)	133
C1—H1B···O4^{iv}	0.99	2.41	3.220 (2)	139
C3—H3···O2^{i}	0.95	2.56	3.285 (2)	133
C6—H6···O3	0.95	2.38	2.800 (2)	107
C11—H11B···O3^{iv}	0.99	2.50	3.412 (2)	153

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

The amine H atoms were located in difference syntheses and were refined isotropically. All other H atoms were constrained to an idealized geometry using a riding model with $U_{iso}(H) = 1.2U_{eq}(C)$; for CH_2 groups, C—H = 0.99 Å, whilst for CH groups, C—H = 0.95 Å.

Data collection: *COLLECT* (Hooft, 1988) and *DENZO* (Otwinowski & Minor, 1997); cell refinement: *DENZO* and *COLLECT*; data reduction: *DENZO*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

We thank the Basic Technology Programme of the UK Research Councils for funding this work under the project Control and Prediction of the Organic Solid State (http://www.cposs.org.uk).

References

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Dupont, L. & Dideberg, O. (1972). *Acta Cryst.* B**28**, 2340–2347.
Florence, A. J., Baumgartner, B., Weston, C., Shankland, N., Kennedy, A. R., Shankland, K. & David, W. I. F. (2003). *J. Pharm. Sci.* **92**, 1930–1938.
Hooft, R. (1988). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.

Acta Cryst. (2005). E**61**, o2573–o2575 Johnston *et al.* • $C_7H_8ClN_3O_4S_2 \cdot C_4H_8O_2$ **o2575**