Acta Cryst E CRYSTALLOGRAPHIC COMMUNICATIONS

ISSN 2056-9890

A new solvate of epalerstat, a drug for diabetic neuropathy

Okky Dwichandra Putra, Daiki Umeda, Kaori Fukuzawa, Mihoko Gunji and Etsuo Yonemochi*

School of Pharmacy and Pharmaceutical Sciences, Hoshi University, 2-4-41, Ebara, Shinagawa, Tokyo 145-8501, Japan. *Correspondence e-mail: e-yonemochi@hoshi.ac.jp

Received 20 July 2017
Accepted 21 July 2017

Edited by H. Stoeckli-Evans, University of Neuchâtel, Switzerland

Keywords: crystal structure; epalerstat; acetone; monosolvate; isotypic; hydrogen bonding.

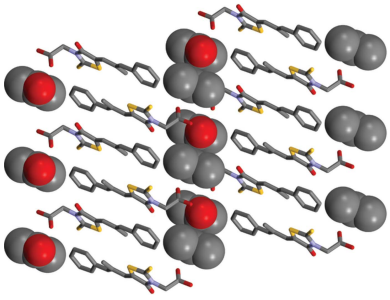
CCDC reference: 1563705

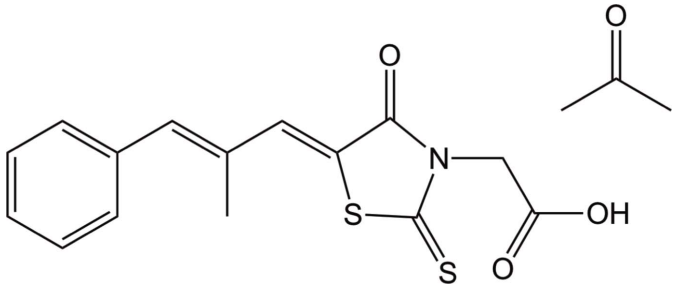
Supporting information: this article has supporting information at journals.iucr.org/e

Epalerstat {systematic name: (5*Z*)-5-[(2*E*)-2-methyl-3-phenylprop-2-en-1-ylidene]-4-oxo-2-sulfanylidene-1,3-thiazolidine-3-acetic acid} crystallized as an acetone monosolvate, $C_{15}H_{13}NO_3S_2{\cdot}C_3H_6O$. In the epalerstat molecule, the methylpropylenediene moiety is inclined to the phenyl ring and the five-membered rhodamine ring by 21.4 (4) and 4.7 (4)°, respectively. In addition, the acetic acid moiety is found to be almost normal to the rhodamine ring, making a dihedral angle of 85.1 (2)°. In the crystal, a pair of O—H···O hydrogen bonds between the carboxylic acid groups of epalerstat molecules form inversion dimers with an $R_2^2(8)$ loop. The dimers are linked by pairs of C—H···O hydrogen bonds, enclosing $R_2^2(20)$ loops, forming chains propagating along the [101] direction. In addition, the acetone molecules are linked to the chain by a C—H···O hydrogen bond. Epalerstat acetone monosolvate was found to be isotypic with epalerstat tertrahydrofuran solvate [Umeda *et al.* (2017). *Acta Cryst.* E**73**, 941–944].

1. Chemical context

Investigation of solid forms of pharmaceuticals has attracted a great deal of attention as different crystal forms may imply different physicochemical properties (Putra *et al.*, 2016*a*,*b*). Moreover, pharmaceutical processing stages during manufacturing, such as crystallization, can lead to the unexpected occurrence of new crystalline phases (Putra *et al.*, 2016*c*). One of the important classes of pharmaceutical solids that can occur during crystallization is solvates. Solvates are defined as multi-component crystalline systems in which solvent molecules are included within the crystal structure in either a stoichiometric or non-stoichiometric manner (Griesser, 2006). It has been estimated statistically that around 33% of organic compounds have the ability to form solvates with organic solvents (Clarke *et al.*, 2010).





Herein, we report on the crystal structure of a new solvate form of epalerstat, namely epalerstat acetone monosolvate. Epalerstat [systematic name: (5*Z*)-5-[(2*E*)-2-methyl-3-

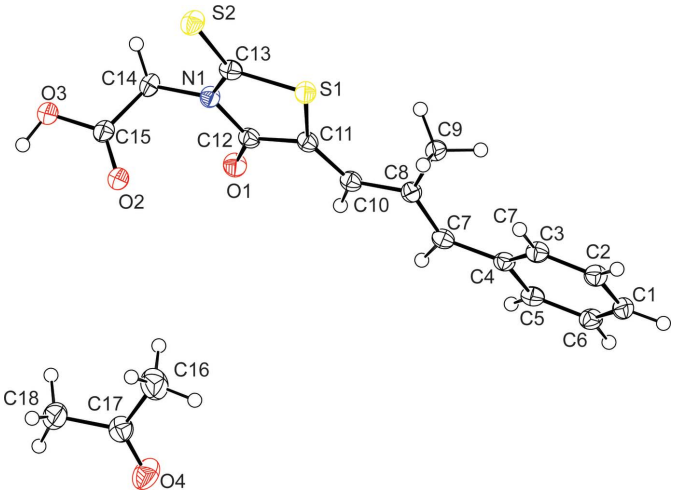


Figure 1
The molecular structure of epalerstat acetone monosolvate, with the atom labelling and displacement ellipsoids drawn at the 50% probability level.

phenylprop-2-en-1-ylidene]-4-oxo-2-sulfanylidene-1,3-thiazolidine-3-acetic acid), is an aldose reductase inhibitor and is used for the treatment of diabetic neuropathy, a complication symptom in diabetes mellitus (Miyamoto, 2002). Pharmacologically, epalerstat acts to inhibit the synthesis of sorbitol from glucose (Ramirez & Borja, 2008). The abundant occurrences of solvates in epalerstat itself is not surprising because of the imbalance between the hydrogen-bond donors and acceptors in its molecular structure. Previously, the crystal structures of the methanol mono- and disolvate (Igarashi *et al.*, 2015; Nagase *et al.*, 2016), the ethanol monosolvate (Ishida *et al.*, 1989, 1990), the dimethylformamide monosolvate (Putra *et al.*, 2017), the dimethylsulfoxide disolvate (Putra *et al.*, 2017) and the tetrahydrofuran monosolvate (Umeda *et al.*, 2017) have been reported.

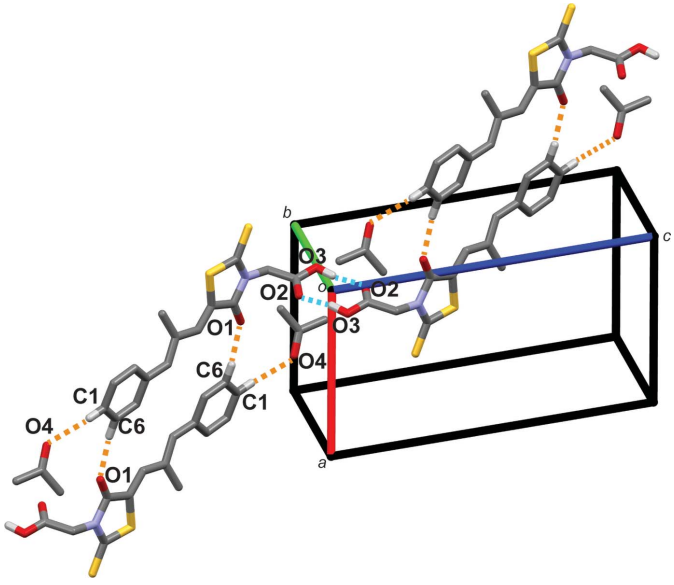


Figure 2
A view along the *b* axis of the crystal packing of the title compound. Blue and orange dashed lines represent O—H···O and C—H···O hydrogen bonds, respectively. Only H atoms involved in these interactions have been included.

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3*A*···O2^{i}	0.91 (3)	1.75 (3)	2.645 (2)	171 (3)
C6—H6···O1^{ii}	0.95	2.50	3.440 (3)	168
C1—H1···O4^{iii}	0.95	2.58	3.525 (3)	171

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

2. Structural commentary

The molecular structure of epalerstat acetone monosolvate is illustrated in Fig. 1. The values of the bond distances, bond angles and dihedral angles are normal according the *Mogul* geometry check within the CSD software (Bruno *et al.*, 2004; Groom *et al.*, 2016). The mean plane of the methylpropylenediene (C7–C10) moiety is inclined to the phenyl ring (C1–C6) and the five-membered rhodamine ring (S1/S2/O1/N1/C11–C13) by 21.4 (4) and 4.7 (4)°, respectively. The mean plane of the acetic acid moiety (O2/O3/C14/C15) is almost normal to the rhodamine ring, making a dihedral angle of 85.1 (2) °.

3. Supramolecular features

In the crystal, the epalerstat molecule is connected to two adjacent epalerstat molecules and one solvent molecule *via* both conventional and non-conventional hydrogen bonds. The details of the hydrogen bonds and hydrogen bonding architecture are listed and presented in Table 1 and Fig. 2, respectively. A pair of O3—H3*A*···O2^{ii} hydrogen bonds is observed between two carboxylic acid moieties forming an inversion dimer with an $R_2^2(8)$ loop. This dimer is linked to adjacent dimers by a pair of C6—H6···O1^{ii} hydrogen bonds, which enclose $R_2^2(20)$ loops, and form chains along direction [101]. In addition, acetone molecules are linked to the chain by a C1—H1···O4^{iii} hydrogen bond (Table 1 and Fig. 2).

3.1. Discussion

Interestingly, the new solvate reported here is isotypic with epalerstat tetrahydrofuran monosolvate (Umeda *et al.*, 2017). Both solvates crystallize in the triclinic system with the same space group, $P\overline{1}$. As illustrated in Fig. 3, they have a similar molecular arrangement and the solvent molecules are located in similar pockets in the unit cell. The unit cell similarity index (Π) and the mean elongation (ε) values were calculated (Fábián & Kálmán, 1999) and found to be $\Pi = 0.0016$ and $\varepsilon = 0.0005$. As the Π and ε values are nearly zero, epalerstat acetone monosolvate and tetrahydrofuran monosolvate have isostructural crystals. The solvent-occupied spaces, in which the solvent molecules were deleted from the crystal structure, and the voids were calculated using the contact surface

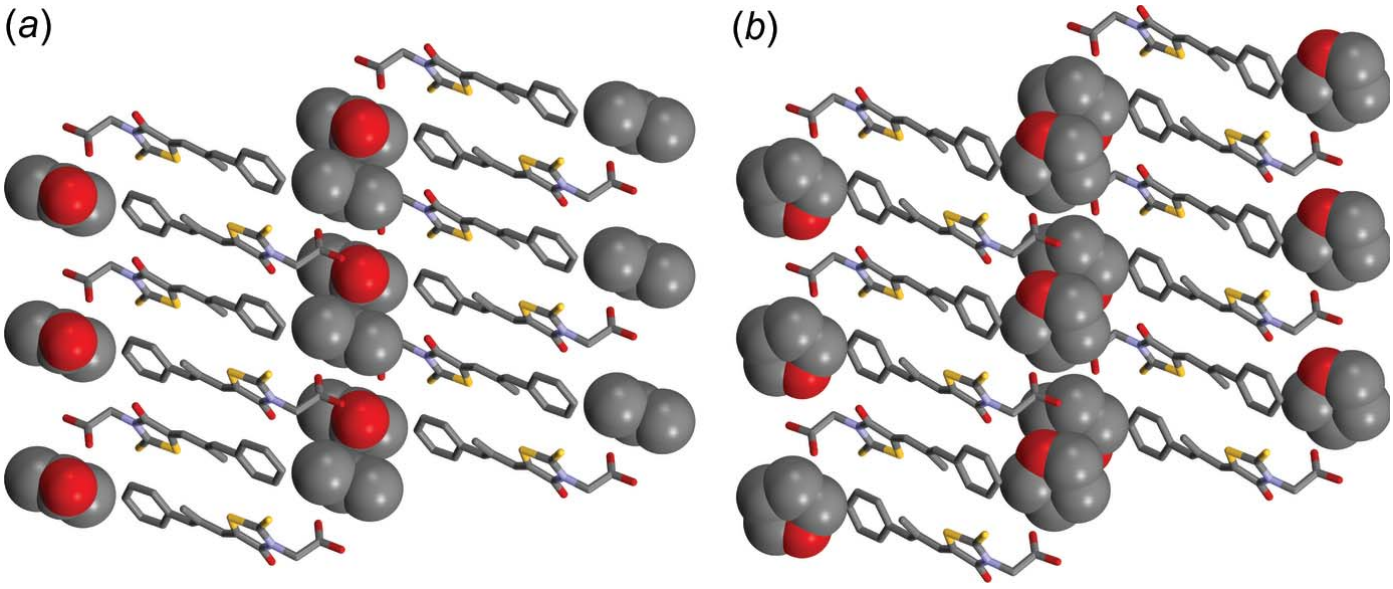


Figure 3
The packing view along the *b* axis of (*a*) epalerstat acetone monosolvate and (*b*) epalerstat tetrahydrofuran monosolvate shows the isostructurality between the two solvates. H atoms have been omitted for clarity, and the epalerstat molecules and the solvent molecules are drawn as capped sticks and spacefill models, respectively.

method with probe radius and approximate grid spacing set equal to 1.2 and 0.7 Å, respectively (Putra *et al.*, 2016*d;* Macrae *et al.*, 2008). The solvent occupied spaces for the acetone and tetrahydrofuran solvates are 199.86 and 221.89 Å^3, respectively. As expected, the larger occupied space in epalerstat tetrahydrofuran solvate corresponds to the larger solvent molecule. Interestingly, both solvents occupy nearly the same percentage of the total volume of the unit cell; the acetone and tetrahydrofuran molecules occupy 22.2 and 23.8%, respectively.

4. Database survey

A search of the Cambridge Structural Database (CSD, V5.38, last update July 2017; Groom *et al.*, 2016) for epalerstat yielded 16 hits. They include the ethanol monosolvate (Ishida *et al.*, 1989, 1990), the methanol monosolvate (Igarashi *et al.*, 2015), the methanol disolvate (Nagase *et al.*, 2016), the dimethylformamide monosolvate (Putra *et al.*, 2017), the dimethylsulfoxide disolvate (Putra *et al.*, 2017), the tetrahydrofuran monosolvate (Umeda *et al.*, 2017), Form I: triclinic, $P\overline{1}$ (Igarashi *et al.*, 2013; Swapna *et al.*, 2016), Form II: monoclinic, *C*2/*c* (Swapna *et al.*, 2016), Form III: monoclinic, $P2_1/n$ (Swapna *et al.*, 2016), the co-crystal with caffeine (Putra *et al.*, 2017), a series of salt co-crystals with cytosine (Swapna & Nangia, 2017) and the *Z,Z* isomer (Swapna *et al.*, 2016).

5. Synthesis and crystallization

Epalerstat Form I (700 mg) was dissolved in 10 ml acetone and the clear solution was then kept for three days at room temperature. Epalerstat acetone monosolvate appeared concomitantly with epalerstat Form I and they could be distinguished visually based on their crystal habit. In this case, the title compound, epalerstat acetone monosolvate, and Form I appeared as yellow blocks and orange needle-like crystals, respectively.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{15}H_{13}NO_3S_2{\cdot}C_3H_6O$
M_r	377.46
Crystal system, space group	Triclinic, $P\overline{1}$
Temperature (K)	93
a, *b*, *c* (Å)	7.9623 (1), 8.1806 (2), 15.6919 (3)
α, β, γ (°)	97.852 (7), 99.837 (7), 113.206 (8)
V (Å^3)	901.83 (6)
Z	2
Radiation type	Cu *K*α
μ (mm^{-1})	2.87
Crystal size (mm)	0.35 × 0.24 × 0.10
Data collection	
Diffractometer	Rigaku R-AXIS RAPID II
Absorption correction	Multi-scan (*ABSCOR*; Higashi, 1995)
T_{min}, T_{max}	0.378, 0.750
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	10593, 3235, 2790
R_{int}	0.045
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.602
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.050, 0.137, 1.11
No. of reflections	3235
No. of parameters	233
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.73, −0.30

Computer programs: *PROCESS-AUTO* (Rigaku, 1998), *SHELXS2014* (Sheldrick, 2008), *Mercury* (Macrae *et al.*, 2008), *SHELXL2016* (Sheldrick, 2015) and *PLATON* (Spek, 2009).

6. Refinement details

Crystal data, data collection and structure refinement details are summarized in Table 2. The hydrogen atom attached to an oxygen atom was located in a difference-Fourier map and freely refined. The C-bound H atoms were included in calculated positions and treated using riding model: C—H = 0.9–1.0 Å with U_{iso}(H) = 1.5U_{iso}(C-methyl) and 1.2U_{iso}(C) for other H atoms. Initially the site occupancy factor of the acetone molecule was refined and determined to be 1.005 (4). In the final cycles of refinement the occupancy of the acetone molecule was fixed at 1.

Acknowledgements

We wish to thank for Professor Hiromasa Nagase (Hoshi University) for technical support during the single-crystal X-ray measurements.

References

Bruno, I. J., Cole, J. C., Kessler, M., Luo, J., Motherwell, W. D. S., Purkis, L. H., Smith, B. R., Taylor, R., Cooper, R. I., Harris, S. E. & Orpen, A. G. (2004). *J. Chem. Inf. Comput. Sci.* **44**, 2133–2144.
Clarke, H. D., Arora, K. K., Bass, H., Kavuru, P., Ong, T. T., Pujari, T., Wojtas, L. & Zaworotko, M. J. (2010). *Cryst. Growth Des.* **10**, 2152–2167.
Fábián, L. & Kálmán, A. (1999). *Acta Cryst.* B**55**, 1099–1108.
Griesser, U. J. (2006). *Polymorphism: In the Pharmaceutical Industry*, edited by R. Hilfiker, pp. 211–233. Weinheim: Wiley-Vch Verlag GmbH & Co. KGaA.
Groom, C. R., Bruno, I. J., Lightfoot, M. P. & Ward, S. C. (2016). *Acta Cryst.* B**72**, 171–179.
Higashi, T. (1995). *ABSCOR*. Rigaku Corporation, Tokyo, Japan.
Igarashi, R., Nagase, H., Furuishi, T., Endo, T., Tomono, K. & Ueda, H. (2013). *X-ray Struct. Anal. Online*, **29**, 23–24.
Igarashi, R., Nagase, H., Furuishi, T., Tomono, K., Endo, T. & Ueda, H. (2015). *X-ray Struct. Anal. Online*, **31**, 1–2.
Ishida, T., In, Y., Inoue, M., Tanaka, C. & Hamanaka, N. (1990). *J. Chem. Soc. Perkin Trans. 2*, pp. 1085–1091.
Ishida, T., In, Y., Inoue, M., Ueno, Y., Tanaka, C. & Hamanaka, N. (1989). *Tetrahedron Lett.* **30**, 959–962.
Macrae, C. F., Bruno, I. J., Chisholm, J. A., Edgington, P. R., McCabe, P., Pidcock, E., Rodriguez-Monge, L., Taylor, R., van de Streek, J. & Wood, P. A. (2008). *J. Appl. Cryst.* **41**, 466–470.
Miyamoto, S. (2002). *Chem. Bio. Info. J*, **2**, 74–85.
Nagase, H., Kobayashi, M., Ueda, H., Furuishi, T., Gunji, M., Endo, T. & Yonemochi, E. (2016). *X-ray Struct. Anal. Online*, **32**, 7–9.
Putra, O. D., Yonemochi, E. & Uekusa, H. (2016*d*). *Cryst. Growth Des.* **16**, 6568–6573.
Putra, O. D., Furuishi, T., Yonemochi, E., Terada, K. & Uekusa, H. (2016*a*). *Cryst. Growth Des.* **16**, 3577–3581.
Putra, O. D., Umeda, D., Nugraha, Y. P., Furuishi, T., Nagase, H., Fukuzawa, K., Uekusa, H. & Yonemochi, E. (2017). *CrystEngComm*, **19**, 2614–2622.
Putra, O. D., Yoshida, T., Umeda, D., Gunji, M., Uekusa, H. & Yonemochi, E. (2016*c*). *Cryst. Growth Des.* **16**, 6714–6718.
Putra, O. D., Yoshida, T., Umeda, D., Higashi, K., Uekusa, H. & Yonemochi, E. (2016*b*). *Cryst. Growth Des.* **16**, 5223–5229.
Ramirez, M. A. & Borja, N. L. (2008). *Pharmacotherapy*, **28**, 646–655.
Rigaku (1998). *PROCESS-AUTO*. Rigaku Corporation, Tokyo, Japan.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Sheldrick, G. M. (2015). *Acta Cryst.* C**71**, 3–8.
Spek, A. L. (2009). *Acta Cryst.* D**65**, 148–155.
Swapna, B. & Nangia, A. (2017). *Cryst. Growth Des.* **17**, 3350–3360.
Swapna, B., Suresh, K. & Nangia, A. (2016). *Chem. Commun.* **52**, 4037–4040.
Umeda, D., Putra, O. D., Gunji, M., Fukuzawa, K. & Yonemochi, E. (2017). *Acta Cryst.* E**73**, 941–944.

supporting information

Acta Cryst. (2017). E**73**, 1264-1267 [https://doi.org/10.1107/S2056989017010751]

A new solvate of epalerstat, a drug for diabetic neuropathy

Okky Dwichandra Putra, Daiki Umeda, Kaori Fukuzawa, Mihoko Gunji and Etsuo Yonemochi

Computing details

Data collection: *PROCESS-AUTO* (Rigaku, 1998); cell refinement: *PROCESS-AUTO* (Rigaku, 1998); data reduction: *PROCESS-AUTO* (Rigaku, 1998); program(s) used to solve structure: *SHELXS2014* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2016* (Sheldrick, 2015); molecular graphics: *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXL2016* (Sheldrick, 2015) and *PLATON* (Spek, 2009).

(5*Z*)-5-[(2*E*)-2-Methyl-3-phenylprop-2-en-1-ylidene]-4-oxo-2-sulfanylidene-1,3-thiazolidine-3-acetic acid acetone monosolvate

Crystal data

$C_{15}H_{13}NO_3S_2 \cdot C_3H_6O$
$M_r = 377.46$
Triclinic, $P\overline{1}$
$a = 7.9623$ (1) Å
$b = 8.1806$ (2) Å
$c = 15.6919$ (3) Å
$\alpha = 97.852$ (7)°
$\beta = 99.837$ (7)°
$\gamma = 113.206$ (8)°
$V = 901.83$ (6) Å^3
$Z = 2$
$F(000) = 396$
$D_x = 1.390$ Mg m^{-3}
Cu $K\alpha$ radiation, $\lambda = 1.54187$ Å
Cell parameters from 10593 reflections
$\theta = 5.9$–$68.2°$
$\mu = 2.87$ mm^{-1}
$T = 93$ K
Block, yellow
0.35 × 0.24 × 0.10 mm

Data collection

Rigaku R-AXIS RAPID II diffractometer
Radiation source: rotating anode X-ray, RIGAKU
Detector resolution: 10.0 pixels mm^{-1}
ω scan
Absorption correction: multi-scan (ABSCOR; Higashi, 1995)
$T_{min} = 0.378$, $T_{max} = 0.750$
10593 measured reflections
3235 independent reflections
2790 reflections with $I > 2\sigma(I)$
$R_{int} = 0.045$
$\theta_{max} = 68.2°$, $\theta_{min} = 5.9°$
$h = -9 \rightarrow 9$
$k = -9 \rightarrow 9$
$l = -18 \rightarrow 18$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.050$
$wR(F^2) = 0.137$
$S = 1.11$
3235 reflections
233 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: mixed
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0886P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$

$\Delta\rho_{max} = 0.73$ e Å^{-3}
$\Delta\rho_{min} = -0.30$ e Å^{-3}

Special details

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

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
S1	0.32326 (7)	0.22776 (7)	0.40775 (3)	0.0232 (2)
S2	0.53005 (7)	0.15013 (8)	0.27814 (4)	0.0290 (2)
O1	−0.15383 (19)	−0.1417 (2)	0.26694 (9)	0.0270 (5)
O2	0.0245 (2)	0.0465 (2)	0.10793 (9)	0.0257 (5)
O3	0.0821 (2)	−0.1687 (2)	0.02943 (10)	0.0304 (5)
N1	0.1578 (2)	−0.0247 (2)	0.26497 (11)	0.0214 (5)
C1	−0.2491 (3)	0.5295 (3)	0.76805 (14)	0.0256 (7)
C2	−0.0768 (3)	0.6025 (3)	0.74641 (14)	0.0252 (7)
C3	−0.0449 (3)	0.5163 (3)	0.67266 (13)	0.0232 (6)
C4	−0.1877 (3)	0.3532 (3)	0.61713 (14)	0.0214 (6)
O4	0.3463 (2)	0.3068 (2)	0.03521 (11)	0.0438 (6)
C5	−0.3632 (3)	0.2835 (3)	0.63920 (14)	0.0235 (6)
C6	−0.3931 (3)	0.3700 (3)	0.71326 (14)	0.0252 (7)
C7	−0.1685 (3)	0.2516 (3)	0.53833 (13)	0.0216 (6)
C8	−0.0128 (3)	0.2508 (3)	0.51367 (13)	0.0215 (6)
C9	0.1858 (3)	0.3596 (3)	0.56879 (14)	0.0242 (6)
C10	−0.0467 (3)	0.1284 (3)	0.43048 (13)	0.0218 (6)
C11	0.0769 (3)	0.1067 (3)	0.38588 (13)	0.0211 (6)
C12	0.0075 (3)	−0.0322 (3)	0.30199 (13)	0.0220 (7)
C13	0.3343 (3)	0.1078 (3)	0.30963 (14)	0.0226 (6)
C14	0.1251 (3)	−0.1486 (3)	0.18203 (13)	0.0234 (6)
C15	0.0718 (3)	−0.0778 (3)	0.10282 (14)	0.0230 (6)
C16	0.6721 (4)	0.3855 (4)	0.08636 (16)	0.0463 (9)
C17	0.4865 (3)	0.2987 (3)	0.01874 (15)	0.0306 (7)
C18	0.4837 (4)	0.2023 (4)	−0.07037 (16)	0.0397 (8)
H1	−0.26853	0.58768	0.81968	0.0310*
H2	0.02089	0.71326	0.78271	0.0300*
H3	0.07467	0.56789	0.65942	0.0280*
H3A	0.034 (4)	−0.130 (4)	−0.016 (2)	0.066 (10)*
H5	−0.46298	0.17474	0.60237	0.0280*
H6	−0.51254	0.32025	0.72678	0.0300*
H7	−0.28463	0.17230	0.49709	0.0260*
H9A	0.24324	0.47371	0.54951	0.0360*
H9B	0.25903	0.28868	0.56141	0.0360*
H9C	0.18490	0.38731	0.63143	0.0360*
H10	−0.17563	0.05124	0.40288	0.0260*

H14A	0.02271	−0.26889	0.17941	0.0280*
H14B	0.24067	−0.16584	0.17988	0.0280*
H16A	0.66246	0.45979	0.13819	0.0690*
H16B	0.76964	0.46315	0.06051	0.0690*
H16C	0.70570	0.29014	0.10460	0.0690*
H18A	0.35396	0.14160	−0.10715	0.0590*
H18B	0.53261	0.11105	−0.06269	0.0590*
H18C	0.56266	0.29111	−0.09945	0.0590*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0185 (3)	0.0257 (3)	0.0223 (3)	0.0072 (2)	0.0049 (2)	0.0033 (2)
S2	0.0207 (3)	0.0327 (4)	0.0313 (3)	0.0088 (3)	0.0094 (2)	0.0041 (3)
O1	0.0193 (8)	0.0290 (9)	0.0267 (8)	0.0060 (7)	0.0039 (6)	0.0033 (7)
O2	0.0287 (8)	0.0273 (9)	0.0227 (8)	0.0147 (7)	0.0057 (6)	0.0029 (6)
O3	0.0355 (9)	0.0386 (10)	0.0221 (8)	0.0233 (8)	0.0047 (7)	0.0020 (7)
N1	0.0205 (9)	0.0223 (10)	0.0204 (9)	0.0082 (8)	0.0056 (7)	0.0036 (7)
C1	0.0304 (12)	0.0290 (13)	0.0238 (11)	0.0168 (10)	0.0099 (9)	0.0091 (9)
C2	0.0251 (11)	0.0242 (12)	0.0267 (11)	0.0115 (9)	0.0049 (9)	0.0056 (9)
C3	0.0196 (10)	0.0233 (12)	0.0266 (11)	0.0081 (9)	0.0064 (9)	0.0074 (9)
C4	0.0221 (11)	0.0232 (11)	0.0232 (11)	0.0123 (9)	0.0066 (9)	0.0091 (9)
O4	0.0331 (10)	0.0508 (11)	0.0447 (11)	0.0144 (8)	0.0180 (8)	0.0027 (9)
C5	0.0192 (10)	0.0248 (12)	0.0268 (11)	0.0099 (9)	0.0038 (9)	0.0073 (9)
C6	0.0205 (11)	0.0300 (13)	0.0281 (11)	0.0119 (9)	0.0082 (9)	0.0096 (10)
C7	0.0208 (11)	0.0199 (11)	0.0238 (11)	0.0083 (9)	0.0037 (9)	0.0073 (9)
C8	0.0231 (11)	0.0223 (11)	0.0217 (10)	0.0106 (9)	0.0074 (9)	0.0079 (9)
C9	0.0213 (11)	0.0293 (12)	0.0227 (10)	0.0122 (9)	0.0054 (9)	0.0040 (9)
C10	0.0205 (10)	0.0220 (11)	0.0232 (11)	0.0085 (9)	0.0052 (9)	0.0081 (9)
C11	0.0211 (11)	0.0212 (11)	0.0212 (10)	0.0085 (9)	0.0051 (8)	0.0077 (9)
C12	0.0216 (11)	0.0236 (12)	0.0226 (11)	0.0101 (9)	0.0056 (9)	0.0091 (9)
C13	0.0197 (11)	0.0227 (11)	0.0260 (11)	0.0089 (9)	0.0051 (9)	0.0082 (9)
C14	0.0251 (11)	0.0215 (11)	0.0230 (11)	0.0095 (9)	0.0084 (9)	0.0012 (9)
C15	0.0146 (10)	0.0261 (12)	0.0234 (11)	0.0058 (9)	0.0040 (8)	0.0000 (9)
C16	0.0394 (15)	0.0540 (18)	0.0356 (14)	0.0151 (13)	0.0027 (12)	0.0022 (13)
C17	0.0282 (13)	0.0318 (13)	0.0308 (12)	0.0100 (10)	0.0100 (10)	0.0089 (10)
C18	0.0330 (13)	0.0541 (17)	0.0317 (13)	0.0211 (12)	0.0078 (11)	0.0016 (12)

Geometric parameters (Å, º)

S1—C11	1.759 (3)	C11—C12	1.476 (3)
S1—C13	1.744 (2)	C14—C15	1.507 (3)
S2—C13	1.636 (3)	C1—H1	0.9500
O1—C12	1.213 (3)	C2—H2	0.9500
O2—C15	1.213 (3)	C3—H3	0.9500
O3—C15	1.316 (3)	C5—H5	0.9500
N1—C12	1.401 (3)	C6—H6	0.9500
N1—C13	1.377 (3)	C7—H7	0.9500

N1—C14	1.451 (3)	C9—H9B	0.9800
O3—H3A	0.91 (3)	C9—H9C	0.9800
C1—C6	1.391 (3)	C9—H9A	0.9800
C1—C2	1.387 (4)	C10—H10	0.9500
C2—C3	1.386 (3)	C14—H14A	0.9900
C3—C4	1.407 (3)	C14—H14B	0.9900
C4—C5	1.410 (4)	C16—C17	1.499 (4)
C4—C7	1.459 (3)	C17—C18	1.501 (3)
O4—C17	1.212 (3)	C16—H16A	0.9800
C5—C6	1.382 (3)	C16—H16B	0.9800
C7—C8	1.363 (4)	C16—H16C	0.9800
C8—C10	1.445 (3)	C18—H18A	0.9800
C8—C9	1.501 (3)	C18—H18B	0.9800
C10—C11	1.352 (3)	C18—H18C	0.9800
C11—S1—C13	93.02 (11)	C4—C3—H3	120.00
C12—N1—C13	116.89 (18)	C4—C5—H5	119.00
C12—N1—C14	120.69 (18)	C6—C5—H5	119.00
C13—N1—C14	122.41 (19)	C1—C6—H6	120.00
C15—O3—H3A	107 (2)	C5—C6—H6	120.00
C2—C1—C6	119.2 (2)	C4—C7—H7	114.00
C1—C2—C3	121.0 (2)	C8—C7—H7	114.00
C2—C3—C4	120.7 (2)	C8—C9—H9A	109.00
C3—C4—C5	117.4 (2)	C8—C9—H9B	109.00
C5—C4—C7	117.6 (2)	C8—C9—H9C	109.00
C3—C4—C7	125.1 (2)	H9A—C9—H9B	109.00
C4—C5—C6	121.4 (2)	H9A—C9—H9C	109.00
C1—C6—C5	120.3 (2)	H9B—C9—H9C	109.00
C4—C7—C8	131.1 (2)	C8—C10—H10	115.00
C7—C8—C9	124.49 (19)	C11—C10—H10	115.00
C7—C8—C10	116.2 (2)	N1—C14—H14A	109.00
C9—C8—C10	119.2 (2)	N1—C14—H14B	109.00
C8—C10—C11	129.9 (2)	C15—C14—H14A	109.00
S1—C11—C12	109.41 (17)	C15—C14—H14B	109.00
C10—C11—C12	119.9 (2)	H14A—C14—H14B	108.00
S1—C11—C10	130.59 (17)	O4—C17—C16	121.6 (2)
O1—C12—C11	127.7 (2)	O4—C17—C18	121.9 (2)
N1—C12—C11	110.3 (2)	C16—C17—C18	116.5 (2)
O1—C12—N1	122.00 (19)	C17—C16—H16A	110.00
S1—C13—N1	110.27 (17)	C17—C16—H16B	109.00
S2—C13—N1	126.30 (17)	C17—C16—H16C	109.00
S1—C13—S2	123.43 (14)	H16A—C16—H16B	109.00
N1—C14—C15	111.81 (19)	H16A—C16—H16C	109.00
O2—C15—C14	123.1 (2)	H16B—C16—H16C	109.00
O3—C15—C14	111.3 (2)	C17—C18—H18A	109.00
O2—C15—O3	125.6 (2)	C17—C18—H18B	109.00
C2—C1—H1	120.00	C17—C18—H18C	110.00
C6—C1—H1	120.00	H18A—C18—H18B	109.00

C1—C2—H2	120.00	H18A—C18—H18C	109.00
C3—C2—H2	119.00	H18B—C18—H18C	109.00
C2—C3—H3	120.00		

C13—S1—C11—C10	−175.1 (2)	C2—C3—C4—C7	−179.8 (2)
C13—S1—C11—C12	1.91 (17)	C7—C4—C5—C6	179.3 (2)
C11—S1—C13—S2	177.60 (16)	C5—C4—C7—C8	−159.0 (2)
C11—S1—C13—N1	−2.90 (17)	C3—C4—C5—C6	−1.1 (3)
C14—N1—C13—S2	1.0 (3)	C3—C4—C7—C8	21.4 (4)
C14—N1—C12—C11	179.93 (18)	C4—C5—C6—C1	0.1 (4)
C12—N1—C13—S1	3.3 (2)	C4—C7—C8—C9	2.0 (4)
C13—N1—C12—O1	178.6 (2)	C4—C7—C8—C10	178.8 (2)
C14—N1—C12—O1	0.4 (3)	C9—C8—C10—C11	−8.4 (4)
C13—N1—C12—C11	−1.8 (3)	C7—C8—C10—C11	174.7 (2)
C13—N1—C14—C15	−93.1 (3)	C8—C10—C11—C12	178.6 (2)
C14—N1—C13—S1	−178.51 (15)	C8—C10—C11—S1	−4.7 (4)
C12—N1—C13—S2	−177.26 (17)	C10—C11—C12—O1	−3.6 (4)
C12—N1—C14—C15	85.1 (2)	C10—C11—C12—N1	176.9 (2)
C2—C1—C6—C5	1.3 (3)	S1—C11—C12—N1	−0.5 (2)
C6—C1—C2—C3	−1.8 (4)	S1—C11—C12—O1	179.0 (2)
C1—C2—C3—C4	0.8 (4)	N1—C14—C15—O2	−14.2 (3)
C2—C3—C4—C5	0.7 (3)	N1—C14—C15—O3	166.38 (19)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3*A*···O2^{i}	0.91 (3)	1.75 (3)	2.645 (2)	171 (3)
C6—H6···O1^{ii}	0.95	2.50	3.440 (3)	168
C1—H1···O4^{iii}	0.95	2.58	3.525 (3)	171

Symmetry codes: (i) −*x*, −*y*, −*z*; (ii) −*x*−1, −*y*, −*z*+1; (iii) −*x*, −*y*+1, −*z*+1.