

(*R,R*)-Disynephrine ether bis(hydrogen sulfate)William Arbuckle,^a Alan R. Kennedy^{b*} and Catriona A. Morrison^b^aSchering-Plough Research Institute, Newhouse, Motherwell ML1 5SH, Scotland, and ^bDepartment of Pure & Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, Scotland

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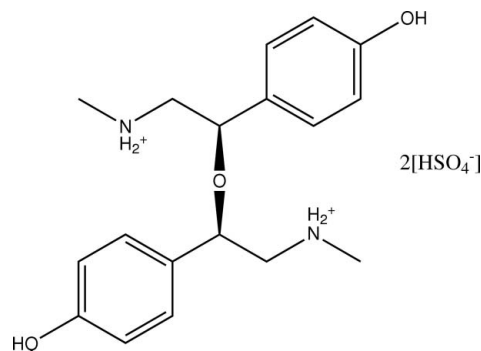
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Key indicators: single-crystal X-ray study; $T = 123$ K; mean $\sigma(\text{C}-\text{C}) = 0.004$ Å; R factor = 0.043; wR factor = 0.111; data-to-parameter ratio = 14.9.

The asymmetric unit of the title compound [systematic name: (*R,R*)-2,4-bis(4-hydroxyphenyl)-*N,N'*-dimethyl-3-oxapentane-1,5-diammonium bis(hydrogen sulfate)], $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_3^{2+} \cdot 2\text{HSO}_4^-$, contains one half-cation and one hydrogen sulfate anion. The cation has crystallographically imposed twofold symmetry with the rotation axis passing through the central ether O atom. Hydrogen bonds between the hydroxy group and amine H atoms of the cation to two hydrogen sulfate anions link the three ions in a ring motif. A three-dimensional network is accomplished by additional $\text{O}-\text{H} \cdots \text{O}$ hydrogen bonds between the anions and by $\text{N}-\text{H} \cdots \text{O}$ hydrogen bonds between the cations. Disorder with equally occupied sites affects the H-atom position in the anion.

Related literature

For the preparation and structure of the equivalent bromide salt, see: Mukhopadhyay & Dattagupta (1984, 1988). For recent examples of synephrine use, see: Blanck *et al.* (2007); Haller *et al.* (2008). For general background, see: Bruce (2007); Jacques *et al.* (1981).

**Experimental***Crystal data*

$\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_3^{2+} \cdot 2\text{HSO}_4^-$
 $M_r = 512.54$
 Monoclinic, $C2$
 $a = 13.7204$ (9) Å
 $b = 11.5853$ (5) Å
 $c = 7.6579$ (5) Å
 $\beta = 116.413$ (8)°

$V = 1090.19$ (13) Å³
 $Z = 2$
 Mo $K\alpha$ radiation
 $\mu = 0.31$ mm⁻¹
 $T = 123$ K
 $0.23 \times 0.15 \times 0.11$ mm

Data collection

Oxford Diffraction Gemini S CCD diffractometer
 Absorption correction: multi-scan (ABSPACK; Oxford Diffraction, 2007)

$T_{\min} = 0.974$, $T_{\max} = 1.000$
 (expected range = 0.942–0.967)
 5888 measured reflections
 2401 independent reflections
 2034 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.027$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.043$
 $wR(F^2) = 0.111$
 $S = 1.03$
 2401 reflections
 161 parameters
 1 restraint

H atoms treated by a mixture of independent and constrained refinement
 $\Delta\rho_{\max} = 0.57$ e Å⁻³
 $\Delta\rho_{\min} = -0.43$ e Å⁻³
 Absolute structure: Flack (1983), 1032 Friedel pairs
 Flack parameter: 0.08 (11)

Table 1

Hydrogen-bond geometry (Å, °).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
$\text{O1}-\text{H1} \cdots \text{O3}^{\text{i}}$	0.84	1.95	2.739 (3)	155
$\text{N1}-\text{H1N} \cdots \text{O4}^{\text{ii}}$	0.83 (3)	1.93 (3)	2.700 (4)	153 (3)
$\text{N1}-\text{H2N} \cdots \text{O1}^{\text{iii}}$	0.82 (3)	2.27 (3)	2.999 (3)	149 (3)
$\text{O5}-\text{H1S} \cdots \text{O5}^{\text{iv}}$	0.91	1.65	2.502 (6)	155
$\text{O6}-\text{H2S} \cdots \text{O6}^{\text{i}}$	1.05	1.60	2.493 (5)	139

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

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2007); cell refinement: *CrysAlis CCD*; data reduction: *CrysAlis RED* (Oxford Diffraction, 2007); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: WM2243).

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supporting information

Acta Cryst. (2009). E65, o1768–o1769 [doi:10.1107/S1600536809025288]

(*R,R*)-Disynephrine ether bis(hydrogen sulfate)**William Arbuckle, Alan R. Kennedy and Catriona A. Morrison****S1. Comment**

Synephrine (systematic name 2-hydroxy-2-(4-hydroxyphenyl)-*N*-methylethanamine) is a member of the phenylethylamine drug family and it is often found in products marketed as "traditional medicines" or "weight-loss" pills (Blanck *et al.*, 2007; Haller *et al.*, 2008). An attempt to prepare the sulfate salt of a racemic sample gave instead only the title compound, di-synephrine ether di-hydrogen sulfate, presumably *via* a variation of the well known S_N^2 condensation reaction (Mukhopadhyay & Dattagupta, 1988; Bruice, 2007).

The salt crystallizes in space group $C2$, with half a cation and one hydrogen sulfate anion in the asymmetric unit. The twofold rotation axis passes through O2, the etheric O atom (Fig. 1). The (*R,R*) conformation was assigned after refinement of the Flack parameter (0.08 (11)). The bulk sample is presumably thus a conglomerate (Jacques *et al.*, 1981). Similar symmetry is seen in the molecular structure of the analogous bromide salt (Mukhopadhyay & Dattagupta, 1988). Despite the gross structural similarities imposed by the identical symmetries, the two salts do have somewhat different conformations. This is best illustrated by the C8—C7—C7*—C8* torsion angle ($-28.7(3)^\circ$ here and -11.3° in the Br salt). Disorder effects the H atom position in the [HSO₄] anion, with equally occupied proton sites (50:50) associated with both O5 and O6.

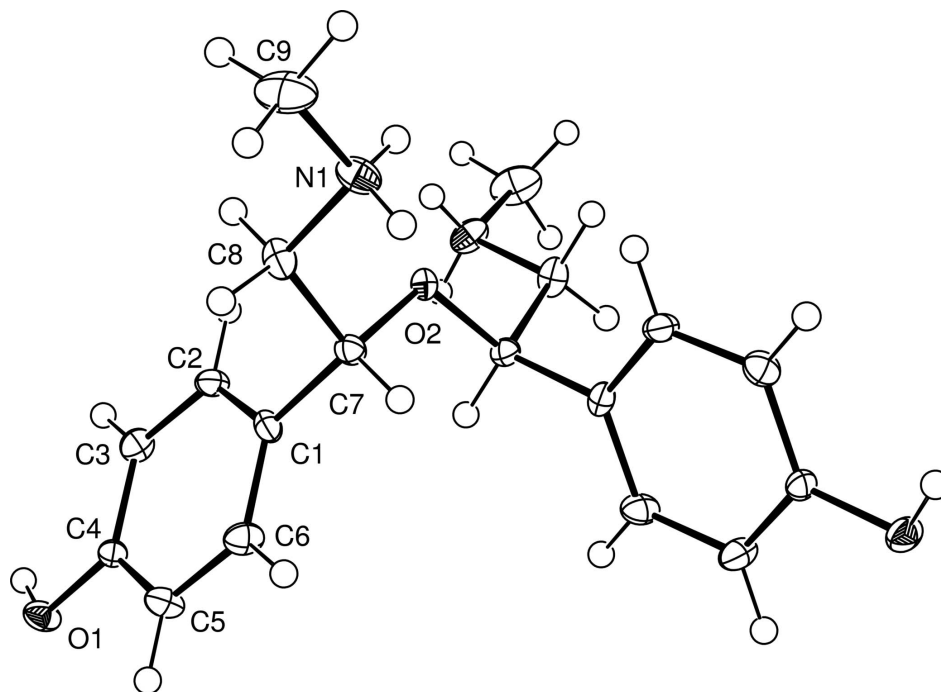
Hydrogen bonds (Table 1) from the cation's hydroxy and amine H atoms to two [HSO₄] anions link the three ions (one cation and two anions) in a ring motif (Fig. 2). Further anion to anion hydrogen bonded interactions give columns of [HSO₄] lying along the *c* direction and complete a hydrogen bonded network in the *ac* plane (Fig. 3). A final, weaker cation to cation interaction between the NH₂ and –OH links these planes in the *b* direction.

S2. Experimental

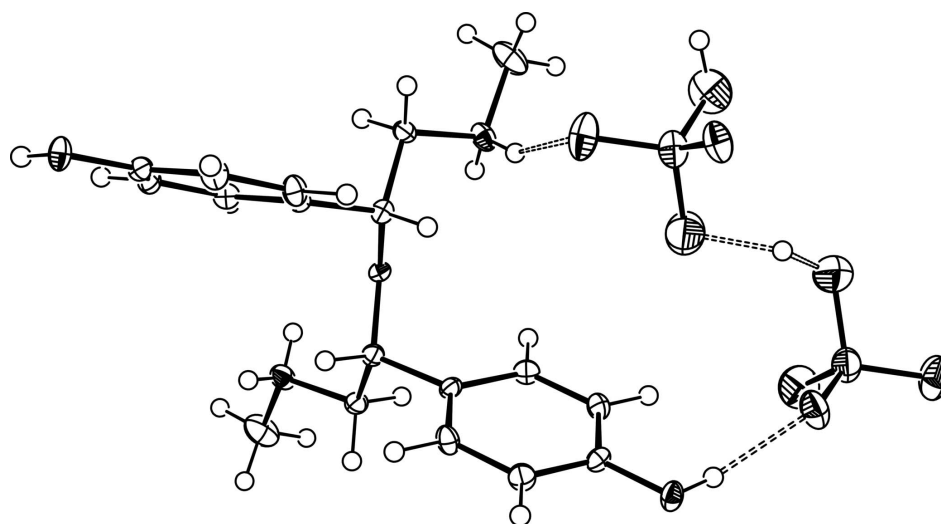
The title compound was obtained on treating an aqueous solution of (+/-)synephrine with dilute sulfuric acid. Single-crystals were obtained by allowing the solvent of the reaction mixture to evaporate at 295 K. ¹H NMR (DMSO-*d*₆) 9.67 (2H, s br, OH); 8.40 (4H, s br, NH₂); 7.07 (4H, d, *sp*² CH); 6.80 (4H, d, *sp*² CH); 4.20 (2H, dd, OCH); 3.32 (2H, m, CH₂); 2.99 (2H, m, CH₂); 2.57 (6H, t, Me).

S3. Refinement

Amine H atoms were found by difference synthesis and refined isotropically. All other H atoms of the cation were positioned geometrically at distances of 0.95, 1.00, 0.99, 0.98 and 0.84 Å from the parent atoms for CH(ar), CH(*sp*³), CH₂, CH₃ and ROH groups respectively. For these groups a riding model was used with $U_{\text{iso}}(\text{H})$ values constrained to be 1.2 times U_{eq} of the parent atom for CH and CH₂ groups and 1.5 times U_{eq} of the parent atom for OH and CH₃ groups. The anion's proton was found by difference synthesis to be disordered over two equally occupied sites. These were placed as found and constrained to ride on the parent O atoms with $U_{\text{iso}}(\text{H})$ equal to 1.5 times U_{eq} of the parent atom.

**Figure 1**

The molecular structure and atomic labelling of the cation, showing 50% probability displacement ellipsoids. H atoms are shown as spheres of arbitrary radius.

**Figure 2**

The hydrogen-bonded ring motif between one cation and two anions in the structure of $[C_{18}H_{26}N_2O_3][SO_4H]_2$.

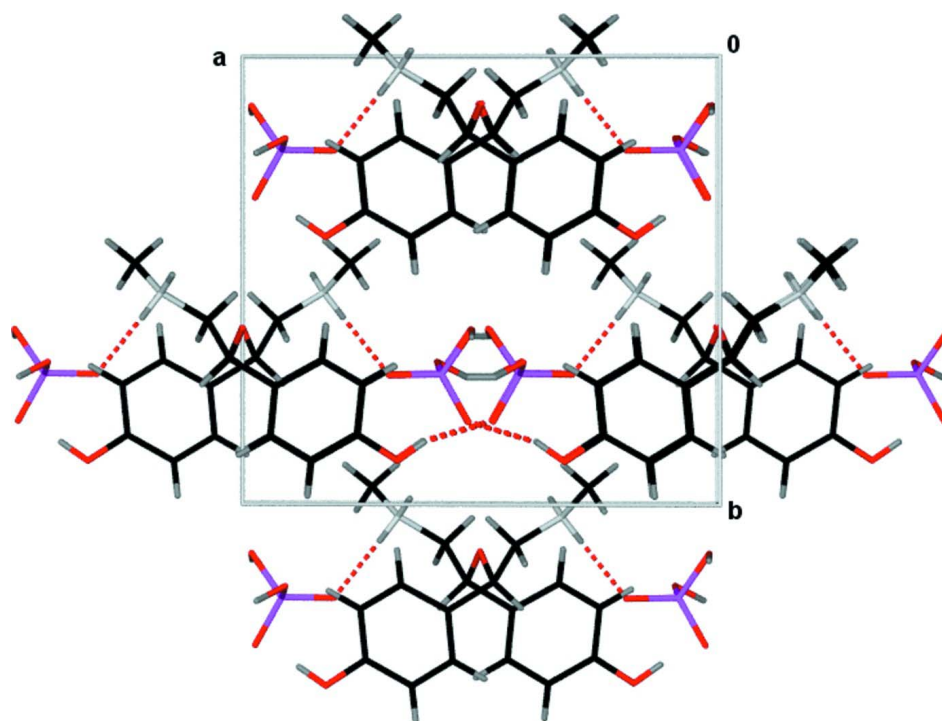


Figure 3

Packed structure viewed down the c -axis. S-atoms are pink and O-atoms are red. Hydrogen-bonding is shown as dashed lines.

(*R,R*)-2,4-bis(4-hydroxyphenyl)-*N,N'*-dimethyl-3-oxapentane-1,5-diammonium bis(hydrogen sulfate)

Crystal data

$C_{18}H_{26}N_2O_3^{2+} \cdot 2HSO_4^-$

$M_r = 512.54$

Monoclinic, $C2$

Hall symbol: $C 2y$

$a = 13.7204 (9) \text{ \AA}$

$b = 11.5853 (5) \text{ \AA}$

$c = 7.6579 (5) \text{ \AA}$

$\beta = 116.413 (8)^\circ$

$V = 1090.19 (13) \text{ \AA}^3$

$Z = 2$

$F(000) = 540$

$D_x = 1.561 \text{ Mg m}^{-3}$

Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$

Cell parameters from 3122 reflections

$\theta = 2.4\text{--}29.1^\circ$

$\mu = 0.31 \text{ mm}^{-1}$

$T = 123 \text{ K}$

Prism, colourless

$0.23 \times 0.15 \times 0.11 \text{ mm}$

Data collection

Oxford Diffraction Gemini S CCD
diffractometer

Radiation source: fine-focus sealed tube

Graphite monochromator

ω scans

Absorption correction: multi-scan

(ABSPACK; Oxford Diffraction, 2007)

$T_{\min} = 0.974$, $T_{\max} = 1.000$

5888 measured reflections

2401 independent reflections

2034 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.027$

$\theta_{\max} = 28.0^\circ$, $\theta_{\min} = 2.4^\circ$

$h = -17 \rightarrow 16$

$k = -14 \rightarrow 14$

$l = -10 \rightarrow 10$

*Refinement*Refinement on F^2

Least-squares matrix: full

 $R[F^2 > 2\sigma(F^2)] = 0.043$ $wR(F^2) = 0.111$ $S = 1.03$

2401 reflections

161 parameters

1 restraint

Primary atom site location: structure-invariant
direct methodsSecondary atom site location: difference Fourier
mapHydrogen site location: inferred from
neighbouring sitesH atoms treated by a mixture of independent
and constrained refinement $w = 1/[\sigma^2(F_o^2) + (0.071P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$ $(\Delta/\sigma)_{\max} < 0.001$ $\Delta\rho_{\max} = 0.57 \text{ e } \text{\AA}^{-3}$ $\Delta\rho_{\min} = -0.43 \text{ e } \text{\AA}^{-3}$ Absolute structure: Flack (1983), 1032 Friedel
pairs

Absolute structure parameter: 0.08 (11)

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R -factor wR and goodness of fit S are based on F^2 , conventional R -factors R are based on F , with F set to zero for negative F^2 . The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating R -factors(gt) *etc.* and is not relevant to the choice of reflections for refinement. R -factors based on F^2 are statistically about twice as large as those based on F , and R -factors based on ALL data will be even larger.

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

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$	Occ. (<1)
S1	0.08291 (6)	0.20896 (7)	0.33257 (10)	0.0289 (2)	
O1	0.17446 (14)	0.40319 (17)	-0.2357 (3)	0.0181 (4)	
H1	0.1185	0.3616	-0.2796	0.027*	
O2	0.5000	0.1062 (2)	0.5000	0.0128 (5)	
O3	0.02688 (19)	0.31541 (19)	0.3192 (4)	0.0304 (6)	
O4	0.19286 (16)	0.2108 (3)	0.4864 (3)	0.0395 (6)	
O5	0.0193 (2)	0.1104 (2)	0.3550 (4)	0.0456 (7)	
H1S	0.0204	0.1255	0.4724	0.068*	0.50
O6	0.0896 (2)	0.1834 (3)	0.1477 (4)	0.0519 (8)	
H2S	0.0295	0.2160	0.0149	0.078*	0.50
N1	0.6712 (2)	0.0279 (2)	0.4186 (4)	0.0191 (5)	
C1	0.4315 (2)	0.2368 (2)	0.2158 (3)	0.0135 (6)	
C2	0.3329 (2)	0.1795 (2)	0.1126 (4)	0.0156 (6)	
H2	0.3247	0.1025	0.1470	0.019*	
C3	0.2473 (2)	0.2329 (2)	-0.0382 (4)	0.0166 (6)	
H3	0.1807	0.1927	-0.1078	0.020*	
C4	0.2581 (2)	0.3458 (2)	-0.0891 (4)	0.0139 (5)	
C5	0.3554 (2)	0.4041 (3)	0.0124 (4)	0.0182 (6)	
H5	0.3633	0.4812	-0.0217	0.022*	
C6	0.4414 (2)	0.3491 (2)	0.1646 (4)	0.0173 (6)	
H6	0.5079	0.3893	0.2346	0.021*	
C7	0.5277 (2)	0.1742 (2)	0.3714 (4)	0.0136 (5)	
H7	0.5851	0.2315	0.4495	0.016*	

C8	0.5734 (2)	0.0900 (3)	0.2748 (4)	0.0172 (6)
H8A	0.5165	0.0329	0.1989	0.021*
H8B	0.5928	0.1326	0.1827	0.021*
C9	0.7267 (3)	-0.0381 (3)	0.3240 (5)	0.0302 (7)
H9A	0.7837	-0.0864	0.4212	0.045*
H9B	0.7595	0.0155	0.2662	0.045*
H9C	0.6738	-0.0873	0.2216	0.045*
H1N	0.711 (2)	0.082 (3)	0.482 (4)	0.013 (8)*
H2N	0.648 (3)	-0.011 (3)	0.480 (4)	0.012 (8)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0228 (4)	0.0289 (4)	0.0312 (4)	0.0004 (4)	0.0086 (3)	-0.0031 (4)
O1	0.0142 (9)	0.0149 (9)	0.0191 (10)	0.0002 (8)	0.0019 (8)	0.0039 (8)
O2	0.0139 (12)	0.0143 (13)	0.0101 (11)	0.000	0.0053 (10)	0.000
O3	0.0196 (11)	0.0272 (12)	0.0420 (13)	0.0024 (9)	0.0117 (10)	-0.0016 (10)
O4	0.0275 (11)	0.0363 (12)	0.0388 (12)	0.0082 (14)	0.0005 (9)	0.0003 (14)
O5	0.0485 (16)	0.0330 (14)	0.0552 (17)	-0.0104 (13)	0.0231 (14)	-0.0060 (13)
O6	0.0427 (15)	0.072 (2)	0.0398 (14)	0.0081 (15)	0.0172 (13)	-0.0090 (13)
N1	0.0160 (12)	0.0187 (13)	0.0244 (12)	0.0036 (10)	0.0106 (11)	0.0065 (11)
C1	0.0139 (13)	0.0157 (15)	0.0108 (11)	0.0032 (9)	0.0054 (10)	0.0027 (9)
C2	0.0190 (13)	0.0106 (13)	0.0178 (12)	-0.0004 (10)	0.0088 (11)	0.0009 (9)
C3	0.0134 (13)	0.0172 (16)	0.0178 (12)	-0.0026 (10)	0.0057 (10)	-0.0019 (10)
C4	0.0164 (13)	0.0118 (12)	0.0125 (12)	0.0040 (10)	0.0055 (11)	0.0010 (10)
C5	0.0184 (14)	0.0138 (12)	0.0217 (14)	0.0003 (12)	0.0082 (12)	0.0044 (11)
C6	0.0135 (13)	0.0140 (13)	0.0224 (13)	-0.0030 (11)	0.0063 (11)	-0.0010 (11)
C7	0.0143 (12)	0.0120 (12)	0.0133 (12)	-0.0016 (9)	0.0053 (10)	0.0011 (9)
C8	0.0145 (13)	0.0239 (15)	0.0148 (12)	0.0049 (11)	0.0079 (10)	0.0031 (11)
C9	0.0292 (18)	0.0236 (17)	0.047 (2)	0.0087 (13)	0.0251 (16)	0.0051 (14)

Geometric parameters (Å, °)

S1—O3	1.433 (2)	C1—C7	1.513 (3)
S1—O4	1.443 (2)	C2—C3	1.375 (4)
S1—O6	1.488 (3)	C2—H2	0.9500
S1—O5	1.492 (3)	C3—C4	1.392 (4)
O1—C4	1.368 (3)	C3—H3	0.9500
O1—H1	0.8400	C4—C5	1.386 (4)
O2—C7	1.438 (3)	C5—C6	1.390 (4)
O2—C7 ⁱ	1.438 (3)	C5—H5	0.9500
O5—H1S	0.9095	C6—H6	0.9500
O6—H2S	1.0540	C7—C8	1.517 (4)
N1—C9	1.477 (4)	C7—H7	1.0000
N1—C8	1.489 (3)	C8—H8A	0.9900
N1—H1N	0.83 (3)	C8—H8B	0.9900
N1—H2N	0.82 (3)	C9—H9A	0.9800
C1—C6	1.383 (4)	C9—H9B	0.9800

C1—C2	1.395 (4)	C9—H9C	0.9800
O3—S1—O4	112.25 (15)	O1—C4—C3	122.1 (2)
O3—S1—O6	111.20 (16)	C5—C4—C3	119.8 (2)
O4—S1—O6	107.16 (15)	C4—C5—C6	119.6 (3)
O3—S1—O5	110.11 (14)	C4—C5—H5	120.2
O4—S1—O5	111.70 (16)	C6—C5—H5	120.2
O6—S1—O5	104.10 (17)	C1—C6—C5	121.0 (2)
C4—O1—H1	109.5	C1—C6—H6	119.5
C7—O2—C7 ⁱ	113.6 (3)	C5—C6—H6	119.5
S1—O5—H1S	102.3	O2—C7—C1	113.45 (19)
S1—O6—H2S	119.6	O2—C7—C8	105.9 (2)
C9—N1—C8	112.3 (2)	C1—C7—C8	109.2 (2)
C9—N1—H1N	109 (2)	O2—C7—H7	109.4
C8—N1—H1N	102 (2)	C1—C7—H7	109.4
C9—N1—H2N	114 (2)	C8—C7—H7	109.4
C8—N1—H2N	104 (2)	N1—C8—C7	112.5 (2)
H1N—N1—H2N	114 (3)	N1—C8—H8A	109.1
C6—C1—C2	118.7 (2)	C7—C8—H8A	109.1
C6—C1—C7	120.9 (2)	N1—C8—H8B	109.1
C2—C1—C7	120.3 (2)	C7—C8—H8B	109.1
C3—C2—C1	120.8 (2)	H8A—C8—H8B	107.8
C3—C2—H2	119.6	N1—C9—H9A	109.5
C1—C2—H2	119.6	N1—C9—H9B	109.5
C2—C3—C4	120.1 (2)	H9A—C9—H9B	109.5
C2—C3—H3	120.0	N1—C9—H9C	109.5
C4—C3—H3	120.0	H9A—C9—H9C	109.5
O1—C4—C5	118.1 (2)	H9B—C9—H9C	109.5
C6—C1—C2—C3	0.6 (4)	C7 ⁱ —O2—C7—C1	-70.07 (17)
C7—C1—C2—C3	-175.4 (2)	C7 ⁱ —O2—C7—C8	170.1 (2)
C1—C2—C3—C4	-0.4 (4)	C6—C1—C7—O2	139.0 (2)
C2—C3—C4—O1	-178.7 (2)	C2—C1—C7—O2	-45.1 (3)
C2—C3—C4—C5	0.2 (4)	C6—C1—C7—C8	-103.1 (3)
O1—C4—C5—C6	178.8 (2)	C2—C1—C7—C8	72.8 (3)
C3—C4—C5—C6	-0.1 (4)	C9—N1—C8—C7	-169.9 (2)
C2—C1—C6—C5	-0.5 (4)	O2—C7—C8—N1	-59.6 (3)
C7—C1—C6—C5	175.4 (2)	C1—C7—C8—N1	177.9 (2)
C4—C5—C6—C1	0.3 (4)		

Symmetry code: (i) $-x+1, y, -z+1$.

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

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
O1—H1 \cdots O3 ⁱⁱ	0.84	1.95	2.739 (3)	155
N1—H1N \cdots O4 ⁱ	0.83 (3)	1.93 (3)	2.700 (4)	153 (3)
N1—H2N \cdots O1 ⁱⁱⁱ	0.82 (3)	2.27 (3)	2.999 (3)	149 (3)

O5—H1S···O5 ^{iv}	0.91	1.65	2.502 (6)	155
O6—H2S···O6 ⁱⁱ	1.05	1.60	2.493 (5)	139

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