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L-Isoleucyl-L-serine 0.33-hydrate, L-phenylalanyl-L-serine and L-methionyl-L-serine 0.34-hydrate

Carl Henrik Görbitz,* Marius Bruvoll, Selma Dizdarevic, Nina Fimland, Jasmina Hafizovic, Helen Therese Kalfjøs, Alexander Krivokapic and Kristian Vestli

Department of Chemistry, University of Oslo, PO Box 1033, Blindern, N-0315 Oslo, Norway
Correspondence e-mail: c.h.gorbitz@kjemi.uio.no

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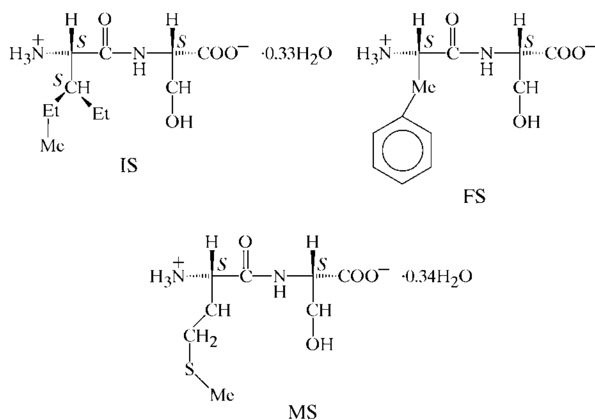
The structures of the title dipeptides, $C_9H_{18}N_2O_4\cdot0.33H_2O$, $C_{12}H_{16}N_2O_4$ and $C_8H_{16}N_2O_4S\cdot0.34H_2O$, complete a series of investigations focused on L-Xaa-L-serine peptides, where Xaa is a hydrophobic residue. All three structures are divided into hydrophilic and hydrophobic layers. The hydrophilic layers are thin for L-phenylalanyl-L-serine, rendered possible by an unusual peptide conformation, and thick for L-isoleucyl-L-serine and L-methionyl-L-serine, which include cocrystallized water molecules on the twofold axes.

Comment

In a series of papers, we have focused on the crystal structures of dipeptides with two hydrophobic residues (Görbitz, 2003, and references therein). Recently, this investigation was extended to include compounds with one hydrophobic and one hydrophilic residue (Netland *et al.*, 2004). The most interesting structure of such a mixed dipeptide is L-leucyl-L-serine (LS), which was found to form a completely new type of



nanoporous structure (Görbitz *et al.*, 2005). Glycyl-L-serine (Görbitz, 1999) and L-alanyl-L-serine (Jones *et al.*, 1978) are not isostructural with LS. Furthermore, we have previously shown that L-valyl-L-serine crystallizes as a layered trihydrate (VS-3w) from aqueous solutions (Johansen *et al.*, 2005), but that a nanoporous structure related, not to LS, but to the L-valyl-L-alanine family of isostructural dipeptides (Görbitz, 2003), is obtained when trifluoroethanol is used as the solvent (Görbitz, 2005). It is nevertheless conceivable that L-isoleucyl-L-serine (IS), L-phenylalanyl-L-serine (FS) or L-methionyl-L-serine (MS) could form crystals with LS-type packing arrangements. We present here the structures of these three dipeptides.

The crystal structures of IS, FS and MS are shown in Fig. 1, while torsion angles and hydrogen-bonding data are listed in Tables 1–6. There is an intramolecular hydrogen bond for FS; equivalent interactions occur for L-alanyl-L-threonine (Netland *et al.*, 2004) and LS (Görbitz *et al.*, 2005). The unit cells and the crystal-packing arrangements are shown in Figs.

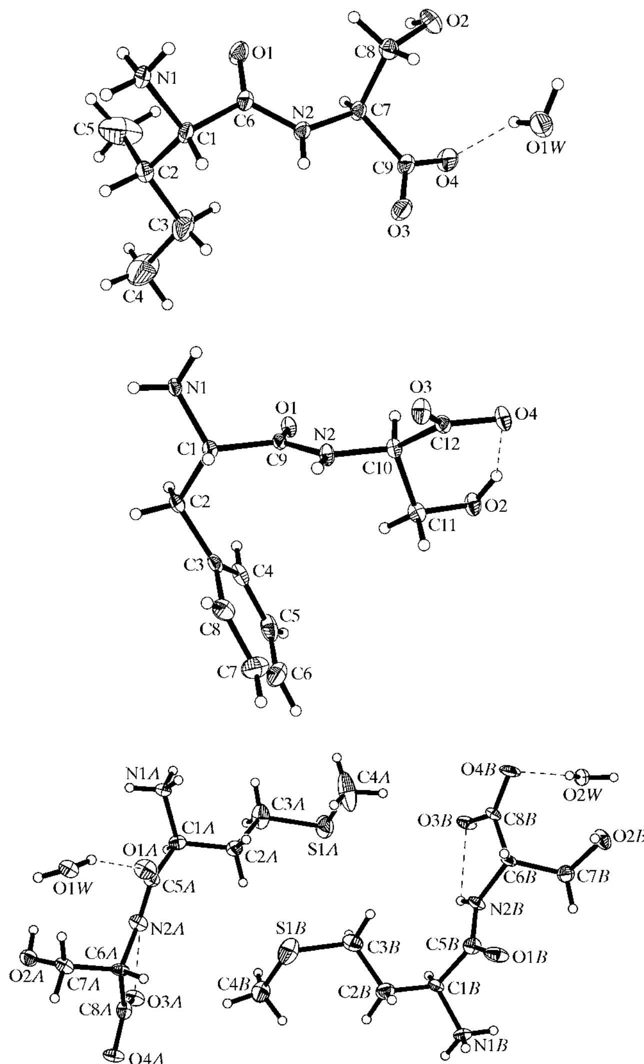


Figure 1
The structures of IS (top), FS (middle) and MS (bottom), with the atomic numbering schemes. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary size. Hydrogen bonds are indicated by dashed lines.

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2–4. All structures are non-porous and are divided into hydrophobic and hydrophilic layers. Each hydrophilic layer can in turn be divided into two hydrogen-bonded sheets, but the construction of individual sheets and the way they are connected differ.

An FS sheet includes intermolecular amino–carboxylate, amino–carbonyl and amide–hydroxyl interactions (Fig. 5 and Table 4). Two sheets are joined tightly together by N1—H3···O4 hydrogen bonds into a compact hydrophilic double layer. This is a rare motif in the structures of enantiopure L–L dipeptides, since it requires that the main chains adopt unusual conformations with both side chains on the same side of the peptide plane. In FS, this is achieved primarily by the 146° φ_2 torsion angle (C9—N2—C10—C12; Table 3), which may be compared with the values of around −163° for IS and MS (Tables 1 and 5) that are typical for dipeptides in extended conformations.

The sheets of IS and MS (Fig. 5) are rather similar to the sheets of VS-3w (Johansen *et al.*, 2005) and L-glutamyl-L-aspartic acid (Eggleston & Hodgson, 1985). Short >N2—H4···O1═C< contacts are, however, missing for IS and MS, while interactions involving the serine side chains have been added. In contrast with FS, adjacent sheets are not in direct contact through amino–carboxylate interactions. The presence of such hydrogen bonds is only compatible with a small inter-sheet separation, which in each case is effectively prevented by peptide main-chain conformations that put side chains on

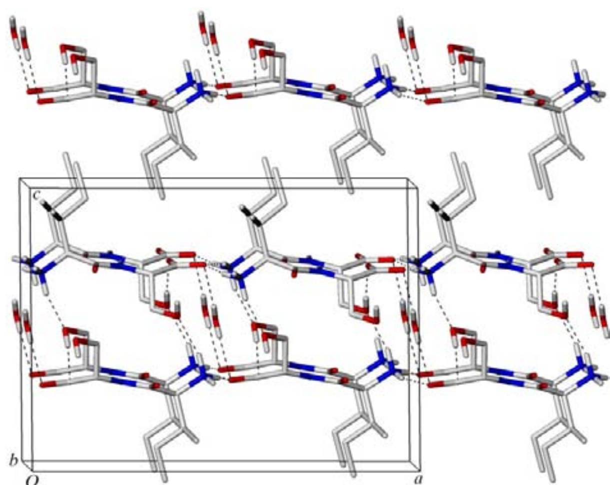

Figure 2
The unit cell and crystal packing of IS, viewed along the *b* axis.

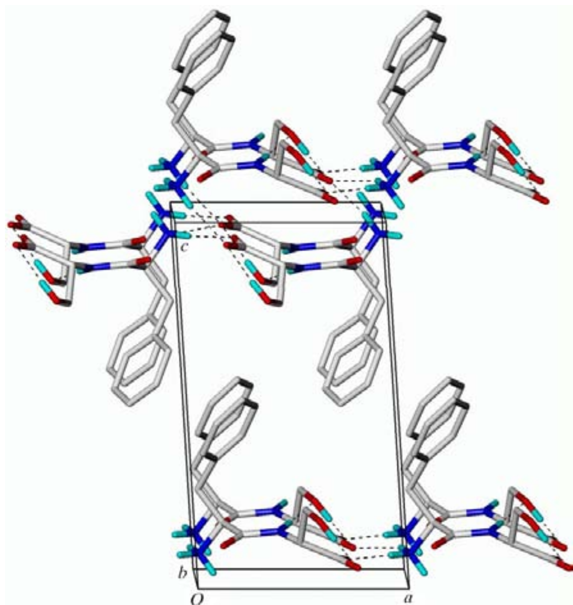

Figure 3
The unit cell and crystal packing of FS, viewed along the *b* axis.

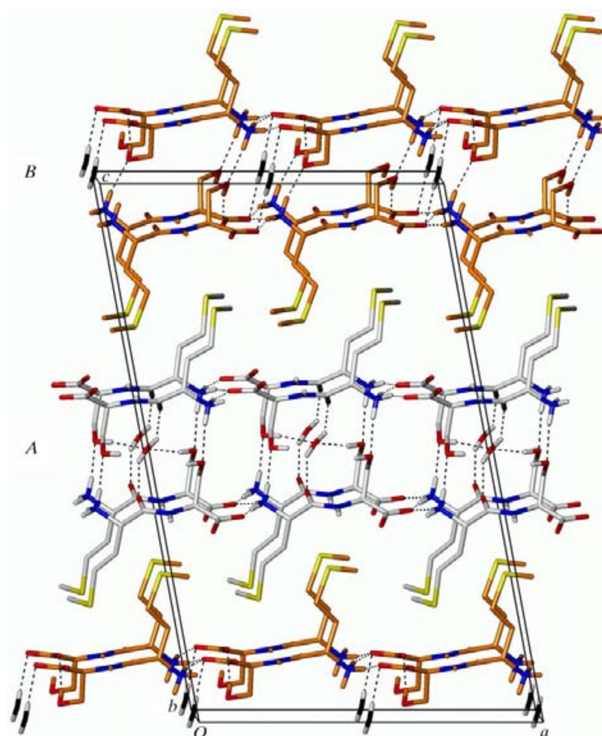

Figure 4
The unit cell and crystal packing of MS. viewed along the *b* axis. The letter *A* identifies a hydrophilic layer generated by peptide *A* molecules, while *B* identifies a corresponding layer generated by peptide *B* molecules, shown in a darker tone.

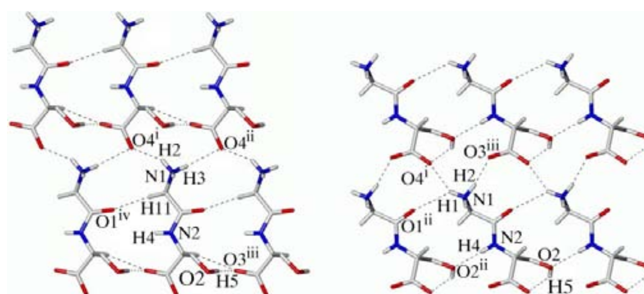

Figure 5
Hydrogen-bonded sheets in the structures of IS (left) and FS (right). The hydrophobic side chains and the methylene H atoms of the serine side chains have been omitted for clarity. [For IS, symmetry codes: (i) $x - \frac{1}{2}$, $\frac{1}{2} + y$, z; (ii) $x - \frac{1}{2}$, $y - \frac{1}{2}$, z; (iii) x, $y - 1$, z; (iv) x, $1 + y$, z. For FS, symmetry codes: (i) $1 + x$, $1 + y$, z; (ii) x, $1 + y$, z; (iii) $1 + x$, y, z.]

opposing sides of the peptide plane (Figs. 2 and 4). The sheets are instead connected by two types of bridges, one involving the cocrystallized water molecules and one involving the serine side chain.

There is a small difference between the independent hydrophobic layers in the MS structure. Layers formed by the peptide *B* molecules are largely identical to the IS layers, while in layers formed by *A* molecules, the hydroxyl H atoms of the serine side chains are donated to the water molecules embedded in the layer rather than to the main-chain carboxylate groups. Water molecule 1, in the *A* layer, is thus fixed by a total of four hydrogen bonds, and the refined occupancy is 1.00. Water molecule 2 and the water molecule of IS are not hydrogen-bond acceptors and thus are not fixed to the same extent. The refined occupancies are 0.354 (18) and 0.668 (9), respectively.

The methionine side chains in the two molecules of MS have different conformations: N1—C1—C2—C3 is *gauche*− and *trans* in molecules *A* and *B*, respectively, while both molecules have C1—C2—C3—S *trans* and C2—C3—S—C4 *gauche*− (Table 5). The hydrophobic layers, with contributions from both *A* and *B* molecules, contain C—H···S interactions that may be described as weak hydrogen bonds. The associated H···S distances range upwards from 2.90 Å for C3*B*—H32*B*···S1*A*(x, $y+1$, z).

Experimental

The title compounds were obtained from Bachem. Crystals were grown by diffusion of acetonitrile into 40 µl of an aqueous solution containing about 1 mg of the respective peptide.

Dipeptide IS

Crystal data

$C_9H_{18}N_2O_4\cdot0.33H_2O$
M_r = 224.27
Monoclinic, $C2$
a = 16.9692 (11) Å
b = 5.2167 (3) Å
c = 12.4065 (8) Å
β = 90.9420 (10)°
V = 1098.11 (12) Å^3
Z = 4
D_x = 1.357 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3409 reflections
θ = 2.4–28.3°
μ = 0.11 mm^{-1}
T = 105 (2) K
Needle, colourless
0.40 × 0.25 × 0.10 mm

Data collection

Siemens SMART CCD area-detector diffractometer
0.3° ω rotation scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.858, T_{max} = 0.989
4482 measured reflections
1454 independent reflections
1373 reflections with $I > 2\sigma(I)$
R_{int} = 0.023
θ_{max} = 28.3°
$h = -19 \rightarrow 22$
$k = -5 \rightarrow 6$
$l = -16 \rightarrow 16$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.091
S = 1.10
1454 reflections
162 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0524P)^2 + 0.4828P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 1
Selected torsion angles (°) for IS.

N1—C1—C6—N2	136.37 (16)	N1—C1—C2—C5	59.9 (3)
C1—C6—N2—C7	175.27 (14)	C1—C2—C3—C4	166.7 (3)
C6—N2—C7—C9	−162.77 (16)	N2—C7—C8—O2	−166.25 (15)
N2—C7—C9—O3	−17.1 (2)	C7—C8—O2—H5	45.9 (17)
N1—C1—C2—C3	−175.7 (2)		

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O2^{i}	0.92 (3)	1.95 (2)	2.8353 (17)	158 (2)
N1—H2···O4^{ii}	0.92 (3)	1.95 (3)	2.777 (2)	153 (2)
N1—H3···O4^{iii}	0.89 (3)	2.31 (3)	3.187 (2)	167 (2)
N1—H3···O3^{iii}	0.89 (3)	2.46 (2)	2.9983 (17)	120 (2)
N2—H4···O3	0.81 (4)	2.26 (2)	2.6132 (18)	106 (2)
O2—H5···O3^{iv}	0.86 (3)	1.88 (3)	2.7258 (18)	172 (2)
C1—H11···O1^{v}	1.00	2.31	3.302 (2)	174
C7—H71···O3^{iv}	1.00	2.44	3.240 (2)	137
O1*W*—H1*W*···O4	0.88 (5)	1.99 (4)	2.771 (17)	149 (4)

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

Dipeptide FS

Crystal data

$C_{12}H_{16}N_2O_4$
M_r = 252.27
Monoclinic, $P2_1$
a = 7.6434 (7) Å
b = 5.7609 (5) Å
c = 13.4396 (12) Å
β = 93.754 (4)°
V = 590.51 (9) Å^3
Z = 2
D_x = 1.419 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3332 reflections
θ = 1.5–37.0°
μ = 0.11 mm^{-1}
T = 105 (2) K
Needle, colourless
0.70 × 0.15 × 0.15 mm

Data collection

Siemens SMART CCD area-detector diffractometer
0.3° ω rotation scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.820, T_{max} = 0.984
5381 measured reflections
2392 independent reflections
2268 reflections with $I > 2\sigma(I)$
R_{int} = 0.019
θ_{max} = 37.0°
$h = -12 \rightarrow 11$
$k = -9 \rightarrow 4$
$l = -17 \rightarrow 18$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.031
$wR(F^2)$ = 0.084
S = 1.06
2392 reflections
178 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0562P)^2 + 0.0336P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.35 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 3
Selected torsion angles (°) for FS.

N1—C1—C9—N2	126.45 (11)	C1—C2—C3—C4	−108.05 (13)
C1—C9—N2—C10	−179.18 (10)	C1—C2—C3—C8	74.17 (15)
C9—N2—C10—C12	146.35 (11)	N2—C10—C11—O2	167.83 (9)
N2—C10—C12—O3	−0.41 (17)	C10—C11—O2—H5	34.7 (14)
N1—C1—C2—C3	164.51 (10)		

Table 4
Hydrogen-bond geometry (Å, °) for FS.

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N1—H1···O4^{i}	0.89 (2)	2.11 (2)	2.8758 (12)	145 (2)
N1—H1···O1^{ii}	0.89 (2)	2.55 (2)	3.2262 (13)	134 (2)
N1—H2···O3^{iii}	0.92 (2)	1.88 (2)	2.7910 (12)	170 (2)
N1—H3···O4^{iv}	0.87 (2)	2.01 (2)	2.8384 (13)	160 (2)
N2—H4···O2^{ii}	0.85 (2)	2.05 (2)	2.8986 (13)	178 (2)
O2—H5···O4	0.85 (2)	2.01 (2)	2.7422 (13)	144 (2)

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

Dipeptide MS

Crystal data

$C_8H_{16}N_2O_4S\cdot 0.34H_2O$
$M_r = 242.41$
Monoclinic, $C2$
$a = 16.791$ (4) Å
$b = 5.0711$ (11) Å
$c = 26.851$ (6) Å
$\beta = 100.926$ (4)°
$V = 2244.8$ (8) Å^3
$Z = 8$
$D_x = 1.435$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3955 reflections
$\theta = 4.6$–$56.4°$
$\mu = 0.29$ mm^{-1}
$T = 105$ (2) K
Plate, colourless
0.45 × 0.22 × 0.03 mm

Data collection

Siemens SMART CCD area-detector diffractometer
0.3° ω rotation scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
$T_{min} = 0.744$, $T_{max} = 0.991$
3325 measured reflections
2849 independent reflections
2445 reflections with $I > 2\sigma(I)$
$R_{int} = 0.066$
$\theta_{max} = 28.2°$
$h = -22 \rightarrow 20$
$k = -3 \rightarrow 6$
$l = 0 \rightarrow 34$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.073$
$wR(F^2) = 0.201$
$S = 1.54$
2849 reflections
298 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0748P)^2 + 3.98P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.58$ e Å^{-3}
$\Delta\rho_{min} = -0.49$ e Å^{-3}

Table 5
Selected torsion angles (°) for MS.

N1A—C1A—C5A—N2A	145.6 (5)	N1B—C1B—C5B—N2B	131.9 (5)
C1A—C5A—N2A—C6A	168.1 (5)	C1B—C5B—N2B—C6B	178.4 (5)
C5A—N2A—C6A—C8A	−164.8 (5)	C5B—N2B—C6B—C8B	−161.9 (5)
N2A—C6A—C8A—O3A	−8.0 (7)	N2B—C6B—C8B—O3B	−15.5 (7)
N1A—C1A—C2A—C3A	−64.2 (7)	N1B—C1B—C2B—C3B	−174.1 (5)
C1A—C2A—C3A—S1A	−173.9 (4)	C1B—C2B—C3B—S1B	176.3 (4)
C2A—C3A—S1A—C4A	−78.0 (6)	C2B—C3B—S1B—C4B	−73.8 (6)
N2A—C6A—C7A—O2A	64.7 (6)	N2B—C6B—C7B—O2B	−165.2 (5)
C6A—C7A—O2A—H5A	−66 (6)	C6B—C7B—O2B—H5B	52 (6)

Positional parameters were refined for IS and FS amino and amide H atoms, for IS and MS water molecules and for the hydroxyl groups in all three structures. Other H atoms were positioned with idealized geometry and with fixed $X-H$ distances (X = C or N) in the range 0.88–1.00 Å. U_{iso}(H) values were set at $1.2U_{eq}$ of the carrier atom, or $1.5U_{eq}$ for hydroxyl, amino and methyl groups and water molecules. The geometries of the two independent molecules in the MS structure were constrained by mild *SHELXTL* SAME 0.008 0.012 constraints, while DFIX constraints were used for the geometries of the water molecules. Due to the low crystal quality, the final R factor is rather

Table 6
Hydrogen-bond geometry (Å, °) for MS.

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N1A—H1A···O4A^{i}	0.89	2.03	2.818 (7)	148
N1A—H2A···O4A^{ii}	0.89	1.99	2.874 (7)	170
N1A—H3A···O2A^{iii}	0.89	1.93	2.815 (6)	171
N2A—H4A···O3A	0.86	2.17	2.582 (6)	109
O2A—H5A···O1W^{iv}	0.84 (3)	1.92 (3)	2.752 (5)	172 (8)
C6A—H61A···O3A^{v}	0.98	2.37	3.311 (6)	162
N1B—H1B···O2B^{vi}	0.89	1.97	2.824 (6)	161
N1B—H2B···O4B^{vii}	0.89	1.97	2.777 (7)	151
N1B—H3B···O4B^{viii}	0.89	2.17	3.041 (7)	167
N2B—H4B···O3B	0.86	2.23	2.600 (6)	106
O2B—H5B···O3B^{v}	0.84 (4)	1.87 (4)	2.671 (7)	160 (8)
C1B—H11B···O1B^{iv}	0.98	2.23	3.198 (7)	170
C3B—H32B···S1A^{v}	0.97	2.90	3.833 (7)	162
C6B—H61B···O3B^{v}	0.98	2.32	3.114 (6)	137
O1W—H1W···O1A	0.86 (3)	1.98 (4)	2.773 (5)	153 (6)
O2W—H2W···O4B	0.87 (3)	1.96 (4)	2.742 (7)	150 (5)

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

high for MS, and the presence of S atoms was not enough to give a reliable determination of the absolute structure; without merging of Friedel pairs, the Flack (1983) parameter was −0.1 (2). Accordingly, 476 Friedel pairs were merged in the final refinements, as were, in the absence of significant anomalous scattering effects, 700 and 339 Friedel pairs for IS and FS, respectively. The absolute configuration was known for the purchased materials.

For all compounds, data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT-Plus* (Bruker, 2001); data reduction: *SAINT-Plus*; program(s) used to solve structure: *SHELXTL* (Bruker, 2000); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

The purchase of the Siemens SMART CCD diffractometer was made possible through support from the Research Council of Norway (NFR)

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1882). Services for accessing these data are described at the back of the journal.

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