Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

The 1:1 inclusion compounds zolmitriptan–benzene and zolmitriptan–phenol

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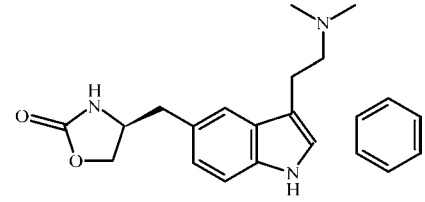
Received 1 May 2007
Accepted 31 May 2007
Online 23 June 2007

In the benzene and phenol solvates of (*S*)-4-{3-[2-(dimethylamino)ethyl]-1*H*-indol-5-ylmethyl}oxazolidin-2-one, *viz*. $C_{16}H_{21}N_3O_2\cdot C_6H_6$, (I), and $C_{16}H_{21}N_3O_2\cdot C_6H_5OH$, (II), the host molecule has three linked residues, namely a planar indole ring system, an ethylamine side chain and an oxazolidinone system. It has comparable features to that of sumatriptan, although the side-chain orientations of (I) and (II) differ from those of sumatriptan. Both (I) and (II) have host–guest-type structures. The host molecule in (I) and (II) has an L-shaped form, with the oxazolidinone ring occupying the base and the remainder of the molecule forming the upright section. In (I), each benzene guest molecule is surrounded by four host molecules, and these molecules are linked by a combination of N—H···N, N—H···O and C—H···O hydrogen bonds into chains of edge-fused $R_4^4(33)$ rings. In (II), two independent molecules are present in the asymmetric unit, with similar conformations. The heterocyclic components are connected through N—H···N, N—H···O and C—H···O interactions to form chains of edge-fused $R_6^4(38)$ rings, from which the phenol guest molecules are pendent, linked by O—H···O hydrogen bonds. The structures are further stabilized by extensive C—H···π interactions.

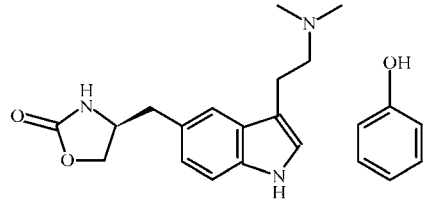
Comment

Zolmitriptan is an effective drug for the treatment of migraine headaches, which are believed to result from dilation of the blood vessels in the brain. The structure and its mechanism of action are comparable to that of sumatriptan (Ravikumar *et al.*, 2004). We have previously reported the crystal structure of zolmitriptan (Ravikumar *et al.*, 2007) and its chloroform solvate (Sridhar *et al.*, 2007). In an attempt to understand the effect on drug polymorphism in the light of host–guest structural mechanisms, we crystallized two inclusion compounds and their crystal structures are presented here.

The molecule of zolmitriptan consists of three linked residues, *viz*. a planar indole ring system, an ethylamine side chain and an oxazolidinone unit. Compound (I) contains molecules



(I)



(II)

of zolmitriptan (host) and benzene (guest) (Fig. 1). Compound (II) consists of two independent molecules (*A* and *B*) of zolmitriptan (host) and phenol (guest) (1:1) in the asymmetric unit (Fig. 2). In both structures, the host molecule acquires an L-shaped conformation, with the oxazolidinone ring occupying the base and the rest of the molecule forming the upright section. The side chains of compounds (I) and (II) exhibit some relatively large conformational differences from those of the parent (pure) zolmitriptan and its chloroform solvate. Interestingly, the indole ring system remains planar in all the structures. Another noteworthy point is that the oxazolidinone ring in each of the present structures is almost planar, unlike in the parent molecule and its chloroform solvate, where the ring adopts a twist conformation. Furthermore, the orientation of the oxazolidinone side chain is synclinal with respect to the indole ring system in (I) and (II)

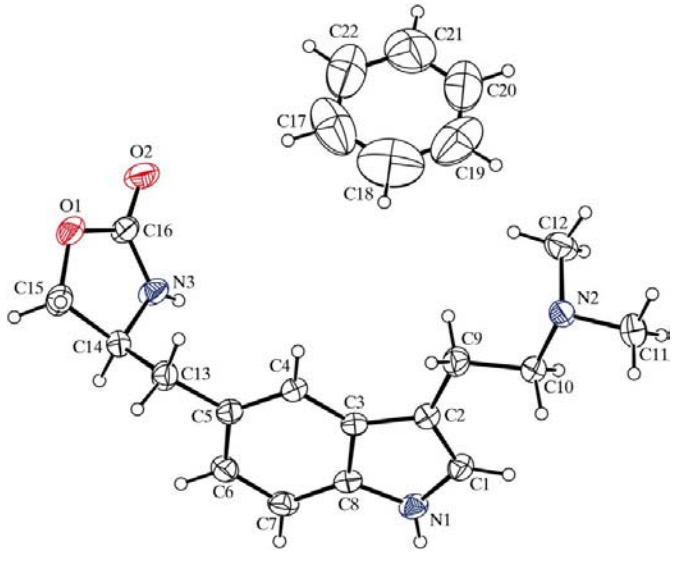


Figure 1
The asymmetric unit of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

 DOI: 10.1107/S0108270107026790

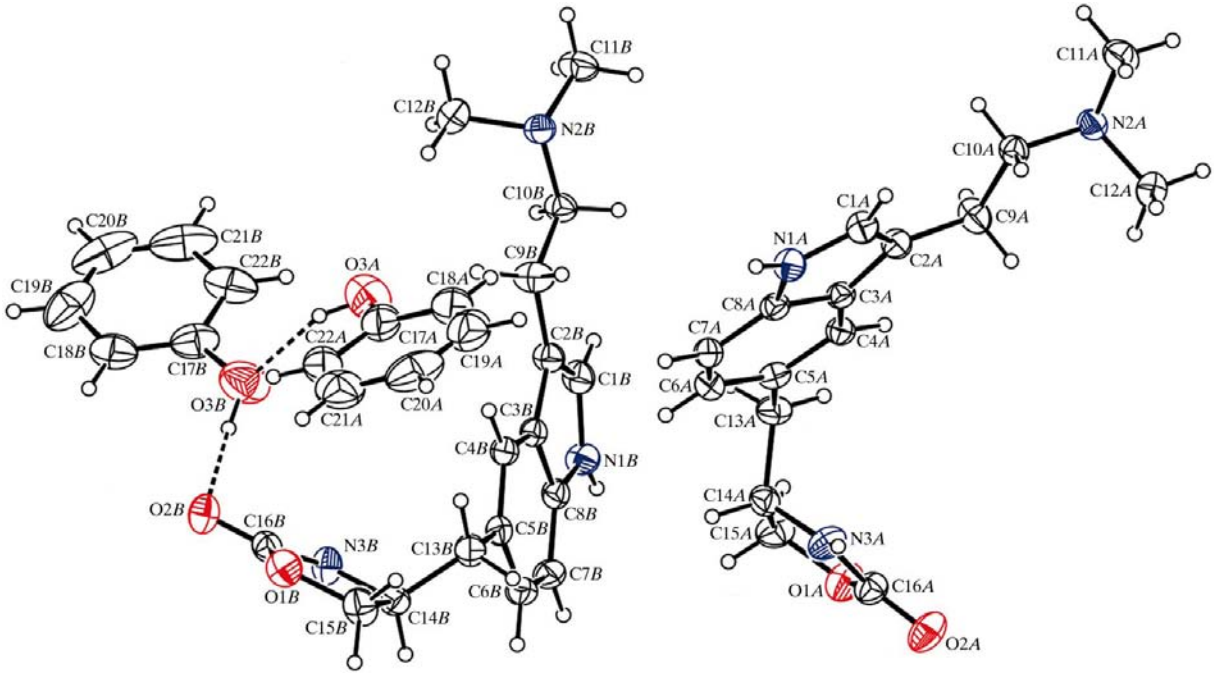


Figure 2
The independent components of (II), showing the atom-labelling scheme and the O—H···O hydrogen bonding (dashed lines) within the asymmetric unit. Displacement ellipsoids are drawn at the 30% probability level.

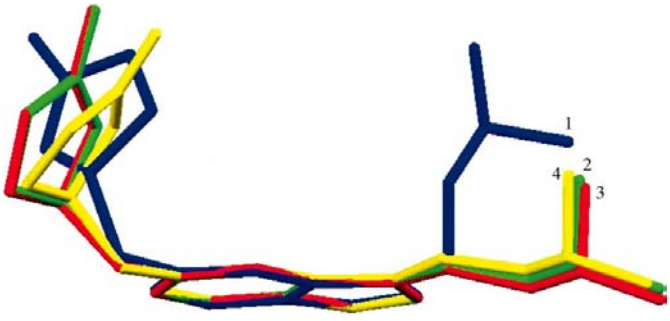


Figure 3
A least-squares fit of (I) (labelled 2; green in the electronic version of the paper; r.m.s. deviation = 0.0315 Å) and (II) (labelled 3, red, 0.0311 Å) along with pure zolmitriptan (labelled 1, blue) and its chloroform solvate (labelled 4, yellow, 0.0344 Å) based on atoms C1–C8 and N1.

(Tables 1 and 3), whereas, in pure zolmitriptan, the value deviates significantly [C4—C5—C13—C14 = 95.6 (3)°]. The ethylamine side chain of the host molecule has an extended conformation in both (I) and (II). This can be seen clearly in terms of their C2—C9—C10—N2 torsion angles (Tables 1 and 3). In (I), with respect to the indole ring system, the planes of the ethylamine group and the oxazolidinone ring make dihedral angles of 53.7 (1) and 64.4 (1)°, respectively [54.0 (1) and 64.8 (1)° for molecule *A* of (II), and 54.0 (1) and 62.8 (1)° for molecule *B*]. Similarly, the dihedral angle between the planes of the oxazolidinone ring and the ethylamine group is 74.4 (1)° [75.9 (1) and 74.4 (1)°, respectively, for molecules *A* and *B* of (II)]. Again, these values are predominantly different from those of pure zolmitriptan [30.0 (1)°]. This significant conformational change could be attributed to the guest molecules present in the respective compounds. An overlay fitting of the

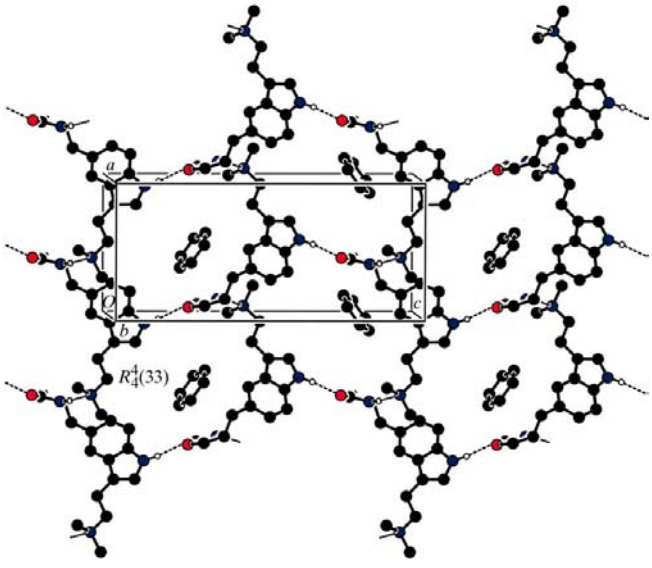


Figure 4
Part of the crystal structure of (I), highlighting the formation of a chain of $R_4^4(33)$ edge-fused rings along the *b* axis. Dashed lines indicate hydrogen bonds. For the sake of clarity, H atoms not involved in the motifs shown have been omitted.

indole ring system of compounds (I) and (II) along with pure zolmitriptan and its chloroform solvate is shown in Fig. 3.

In both structures, oxazolidinone atom N3 acts as a hydrogen-bond donor to ethylamine atom N2 (Tables 2 and 4), so forming continuous screw-symmetric helical chains of *C*11 type (Bernstein *et al.*, 1995) along the *a* axis (Figs. 4 and 5). In (I), these chains are further connected into $R_4^4(33)$ rings through N—H···O and C—H···O hydrogen bonds along the

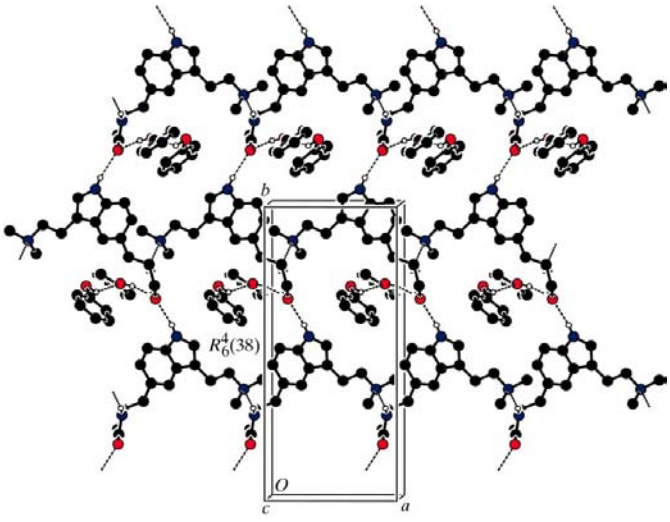


Figure 5
Part of the crystal structure of (II), highlighting the formation of a chain of $R_6^4(38)$ edge-fused rings along the *a* axis. Dashed lines indicate hydrogen bonds. For the sake of clarity, H atoms not involved in the motifs shown have been omitted.

c axis, forming a supramolecular network (Fig. 4). The guest benzene molecules are involved in C—H···π interactions with the indole ring system of the host molecules (Table 2). In (II), within the asymmetric unit, atom O3*A* of phenol guest molecule *A* acts as a hydrogen-bond donor, *via* H3*A*, to hydroxy atom O3*B* of phenol molecule *B*, and the pendent guest molecules are linked to ketone atom O2*B* of host molecule *B* *via* atom H5*D* (Table 4). In (II), these *A* and *B* chains are further interconnected *via* N—H···O and C—H···O interactions. The combination of these two independent molecules (*A* and *B*) then generates two-dimensional edge-fused $R_6^4(38)$ rings. This two-dimensional supramolecular network is further strengthened by extensive C—H···π interactions (Table 4). The centroids of the guest molecules (C17–C22 of *A*/*B*) lie 2.81 and 2.86 Å, respectively, from the H atoms of the pyrrole rings of the indole ring systems (H1*A* and H1*D*). These values agree well with those expected for typical C—H···π interactions (Guo *et al.*, 2005; Huang *et al.*, 2001), demonstrating C—H···π interactions in the inclusion compound. The C—H···π interactions in (I) and (II) are rather weak; however, they play a significant role in maintaining the conformational changes in the host molecules.

In conclusion, zolmitriptan produces inclusion compounds when it crystallizes from chloroform (Sridhar *et al.*, 2007), benzene and phenol (the present work), whereas crystallization from methanol (Ravikumar *et al.*, 2007), which presumably is not a preferred guest, does not produce an inclusion compound.

Experimental

Crystals of the two title compounds were grown from benzene [for (I)] and phenol [for (II)] solutions of zolmitriptan (1:1) by slow evaporation.

Compound (I)

Crystal data

$C_{16}H_{21}N_3O_2{\cdot}C_6H_6$
M_r = 365.47
Orthorhombic, $P2_12_12_1$
a = 8.6938 (5) Å
b = 12.1331 (7) Å
c = 19.5321 (12) Å
V = 2060.3 (2) Å^3
Z = 4
Mo *K*α radiation
μ = 0.08 mm^{-1}
T = 273 (2) K
0.22 × 0.17 × 0.15 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
15000 measured reflections
2097 independent reflections
1995 reflections with $I > 2\sigma(I)$
R_{int} = 0.020

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.113
S = 1.29
2097 reflections
254 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (I).

C1—N1	1.374 (3)	C14—N3	1.445 (3)
C8—N1	1.366 (3)	C16—O2	1.213 (3)
C10—N2	1.458 (3)	C16—N3	1.321 (3)
C12—N2	1.462 (3)	C16—O1	1.348 (3)
N3—C14—C13	113.5 (2)	C11—N2—C10	109.56 (19)
O2—C16—O1	120.80 (19)	C11—N2—C12	109.3 (2)
C8—N1—C1	108.97 (18)		
C13—C5—C6—C7	−178.6 (2)	C4—C5—C13—C14	120.8 (2)
C1—C2—C9—C10	−6.7 (4)	C13—C14—C15—O1	117.2 (2)
C2—C9—C10—N2	177.3 (2)		

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

*Cg*1, *Cg*2 and *Cg*3 are the centroids of the C17–C22, C3–C8 and N1/C1–C3/C8 rings, respectively.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1N···O2^{i}	0.93 (3)	1.99 (3)	2.898 (3)	165 (2)
N3—H3N···N2^{ii}	0.84 (3)	2.10 (3)	2.933 (3)	171 (3)
C15—H15*A*···O2^{iii}	0.97	2.58	3.269 (3)	128
C1—H1···*Cg*1^{iv}	0.93	2.88	3.768	159
C11—H11*A*···*Cg*2^{v}	0.96	2.83	3.658	145
C13—H13*B*···*Cg*3^{vi}	0.96	2.87	3.699	144

Symmetry codes: (i) $-x+\frac{1}{2}, -y+1, z+\frac{1}{2}$; (ii) $x-1, y, z$; (iii) $-x, y+\frac{1}{2}, -z+\frac{1}{2}$; (iv) $-x, y+\frac{1}{2}, -z+\frac{3}{2}$; (v) $x+1, y, z$; (vi) $-x-1, y-\frac{1}{2}, -z+\frac{3}{2}$.

Compound (II)

Crystal data

$C_{16}H_{21}N_3O_2{\cdot}C_6H_6O$
M_r = 381.47
Monoclinic, $P2_1$
a = 8.7618 (13) Å
b = 19.506 (3) Å
c = 12.1767 (18) Å
β = 91.399 (2)°
V = 2080.5 (5) Å^3
Z = 4
Mo *K*α radiation
μ = 0.08 mm^{-1}
T = 293 (2) K
0.22 × 0.18 × 0.16 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
19466 measured reflections
3780 independent reflections
3521 reflections with $I > 2\sigma(I)$
R_{int} = 0.036

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.047$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.137$	$\Delta\rho_{max} = 0.23$ e Å^{-3}
$S = 1.19$	$\Delta\rho_{min} = -0.17$ e Å^{-3}
3780 reflections	
530 parameters	

Table 3
Selected geometric parameters (Å, °) for (II).

C1*A*—N1*A*	1.370 (5)	C14*A*—N3*A*	1.432 (5)
C1*B*—N1*B*	1.379 (5)	C14*B*—N3*B*	1.444 (5)
C8*A*—N1*A*	1.368 (5)	C16*A*—O2*A*	1.217 (5)
C8*B*—N1*B*	1.367 (5)	C16*A*—N3*A*	1.329 (5)
C10*A*—N2*A*	1.473 (4)	C16*A*—O1*A*	1.350 (4)
C10*B*—N2*B*	1.467 (4)	C16*B*—O2*B*	1.220 (4)
C12*A*—N2*A*	1.476 (5)	C16*B*—N3*B*	1.327 (5)
C12*B*—N2*B*	1.458 (5)	C16*B*—O1*B*	1.345 (4)
N3*A*—C14*A*—C13*A*	113.3 (3)	C8*B*—N1*B*—C1*B*	108.9 (3)
N3*B*—C14*B*—C13*B*	114.0 (3)	C11*A*—N2*A*—C10*A*	109.6 (3)
O2*A*—C16*A*—O1*A*	120.7 (3)	C11*A*—N2*A*—C12*A*	109.2 (3)
O2*B*—C16*B*—O1*B*	120.9 (3)	C12*B*—N2*B*—C11*B*	109.2 (3)
C1*A*—N1*A*—C8*A*	109.1 (3)	C11*B*—N2*B*—C10*B*	109.1 (3)
C13*A*—C5*A*—C6*A*—C7*A*	−178.5 (3)	C2*B*—C9*B*—C10*B*—N2*B*	175.3 (3)
C13*B*—C5*B*—C6*B*—C7*B*	−178.7 (3)	C4*A*—C5*A*—C13*A*—C14*A*	122.3 (4)
C1*A*—C2*A*—C9*A*—C10*A*	−10.7 (6)	C13*A*—C14*A*—C15*A*—O1*A*	116.5 (3)
C1*B*—C2*B*—C9*B*—C10*B*	−4.2 (6)	C13*B*—C14*B*—C15*B*—O1*B*	115.8 (3)
C2*A*—C9*A*—C10*A*—N2*A*	178.2 (3)		

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

*Cg*1, *Cg*2, *Cg*3, *Cg*4 and *Cg*5 are the centroids of the C17*B*–C22*B*, C17*A*–C22*A*, C3*A*–C8*A*, C3*B*–C8*B* and N1*A*/C1*A*–C3*A*/C8*A* rings, respectively.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1*B*—H1*B*N···O2*B*^{i}	0.83 (4)	2.26 (4)	3.050 (4)	159 (4)
N3*A*—H3*A*N···N2*A*^{ii}	0.84 (4)	2.17 (4)	2.975 (4)	162 (3)
N3*B*—H3*B*N···N2*B*^{ii}	0.79 (4)	2.14 (5)	2.912 (4)	169 (4)
N1*A*—H1*A*N···O2*A*^{iii}	0.89 (5)	2.02 (5)	2.902 (4)	166 (4)
C15*A*—H15*A*···O2*B*^{i}	0.97	2.59	3.403 (5)	142
O3*A*—H3*A*···O3*B*	0.87 (6)	2.05 (7)	2.760 (6)	137 (9)
O3*B*—H5*D*···O2*B*	0.87 (5)	1.92 (4)	2.758 (5)	162 (10)
C1*A*—H1*A*···*Cg*1^{iv}	0.93	2.81	3.683	156
C1*B*—H1*D*···*Cg*2^{v}	0.93	2.86	3.747	160
C11*A*—H11*C*···*Cg*3^{ii}	0.96	2.80	3.648	148
C11*B*—H11*F*···*Cg*4^{ii}	0.96	2.92	3.733	143
C13*B*—H13*D*···*Cg*5^{vi}	0.97	2.81	3.666	148

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

In (I), the geometries of atoms C17–C22 were restrained, with distances set to a target value of 1.39 Å. H atoms attached to N and O atoms were located in a difference density map and were refined isotropically; distance restraints were also applied to the H atoms of the hydroxy groups in (II). All other H atoms were placed in geometrically idealized positions and allowed to ride on their parent atoms, with C—H distances in the range 0.93–0.98 Å, and with U_{iso}(H) values of $1.5U_{eq}$(C) for methyl H atoms and $1.2U_{eq}$(C) for all other H atoms. In the absence of significant anomalous scattering effects, Friedel pairs were merged. The absolute configuration of zolmitriptan was known in advance.

For both compounds, data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* and *PARST* (Nardelli, 1995).

The authors thank Dr J. S. Yadav, Director, IICT, Hyderabad, for his kind encouragement.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3041). Services for accessing these data are described at the back of the journal.

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