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Two polymorphs of *N*-(2,6-difluorophenyl)formamide

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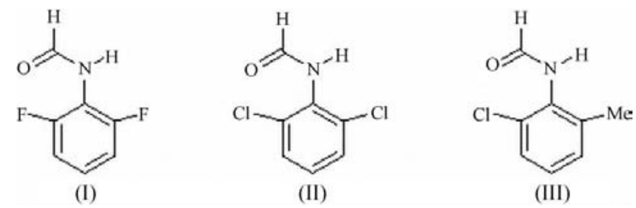
The structures of two distinct polymorphic forms of *N*-(2,6-difluorophenyl)formamide, $C_7H_5F_2NO$, have been studied using single crystals obtained under different crystallizing conditions. The two forms crystallize in different space groups, *viz.* form (I*a*) in the orthorhombic *Pbca* and form (I*b*) in the monoclinic $P2_1$ space group. Each polymorph crystallizes with one complete molecule in the asymmetric unit and they have a similar molecular geometry, showing a *trans* conformation with the formamide group being out of the plane of the aromatic ring. The packing arrangements of the two polymorphs are quite different, with form (I*a*) having molecules that are stacked in an alternating arrangement, linked into chains of N—H···O hydrogen bonds along the crystallographic *a* direction, while form (I*b*) has its N—H···O hydrogen-bonded molecules stacked in a linear fashion. A theoretical study of the two structures allows information to be gained regarding other contributing interactions, such as π–π and weak C—H···F, in their crystal structures.

Comment

The use of F atoms or the induction of F-containing groups into organic compounds has been shown to be useful in modulating physical, chemical and biological properties of target compounds (Thayer, 2006; Zheng *et al.*, 2007; Ravikumar *et al.*, 2003). Formamides have also been used as simple theoretical and experimental models for important chemical and biological compounds, as has been mentioned in our previous publications (Omondi *et al.*, 2005, 2008; Omondi, Levendis *et al.*, 2009, and references therein), and those with at least a C—F bond would probably be just as useful, if not more useful, in the sense that they fall into the category of organic compounds that are commonly found in pharmaceuticals and agrochemicals (Thayer, 2006).

The primary molecular packing of formamides is dominated by N—H···O hydrogen bonds (Ferguson *et al.*, 1998; Boeyens *et al.*, 1988; Godwa *et al.*, 2000). As part of the study on polymorphism and phase transformations in *N*-(2,6-disubstituted aryl)formamides (Omondi *et al.*, 2005), in which the effect of chloro/methyl exchange and the role of weak interactions on their structural and thermal properties were investigated, *N*-(2,6-difluorophenyl)formamide, (I), was also found to exist in two structural phases [*viz.* forms (I*a*) and (I*b*)] (Fig. 1) similar to those of *N*-(2,6-dichlorophenyl)formamide, (II), and *N*-(2-chloro-6-methylphenyl)formamide, (III) (Omondi *et al.*, 2005). The crystals of the two forms of compounds (II) and (III) were obtained at different temperatures, orthorhombic forms (II*a*) and (III*a*) at room temperature from solution and monoclinic forms (II*b*) and (III*b*) at high temperature by sublimation. Recently, we have also reported on the crystal structure of *N*-(2,6-dibromophenyl)formamide (Omondi, Lemmerer *et al.*, 2009), which forms hydrogen-bonded chains similar to forms (II*b*) and (III*b*) (Omondi *et al.*, 2005), compound (I*b*) in this report and *N*-(2,6-dimethylphenyl)formamide (Omondi *et al.*, 2005). In a related study, *N*-(2,6-disubstituted phenyl)thioformamides (Omondi, Lemmerer *et al.*, 2009) were found to exist in only one known phase, but adopted a *cis* conformation, different from that of the *N*-(2,6-disubstituted phenyl)formamides.



An overlay of structures (I*a*) and (I*b*) (Fig. 2) reveals similar conformations for the two polymorphic forms. Only one case, that of *N*-phenylformamide, is known to exist as a *cis* and *trans* conformer in one crystal (Omondi *et al.*, 2008). Thioacetanilide (Michta *et al.*, 2008) was also found to have four independent molecules, all with a *trans* conformation, in the asymmetric unit. In this study, the terms *cis* and *trans* are used with reference to the orientation of the H atom attached to the N atom in relation to the O atom; when H1 is on the same side as O1 the term *cis* is used and *vice versa*. The angle

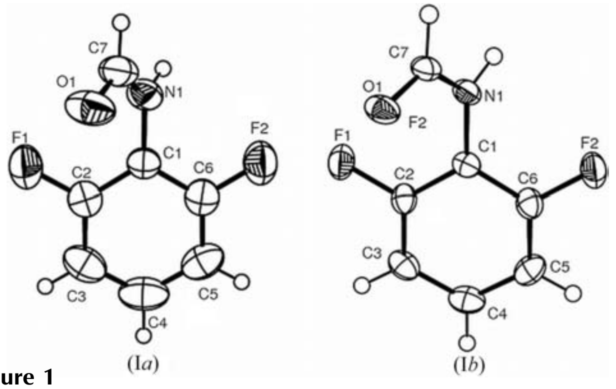


Figure 1
Views of forms (I*a*) and (I*b*), showing the atom-numbering schemes. Displacement ellipsoids are drawn at the 50% probability level.

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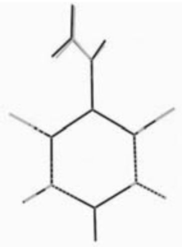

Figure 2
An overlay of the molecular structures of polymorphic forms (I*a*) and (I*b*).

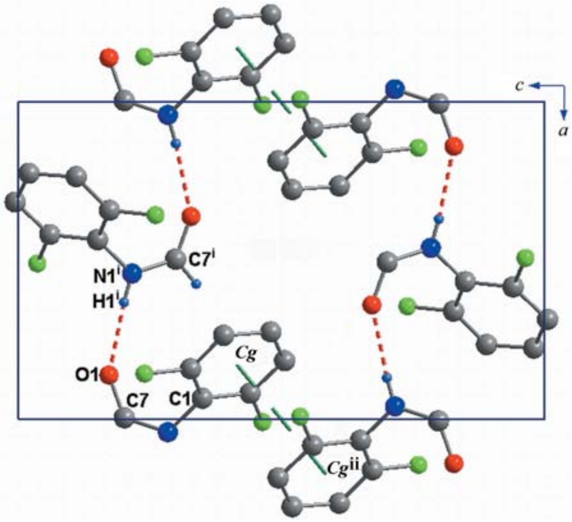

Figure 3
A view of polymorph (I*a*) down the crystallographic *b* axis, showing N—H$\cdots$O hydrogen-bonded chains (short dashed lines) that are linked by π–π intermolecular interactions (long dashed lines). [Symmetry codes: (i) $x - \frac{1}{2}, y, -z + \frac{3}{2}$; (ii) $-x + 2, -y + 1, -z + 1$.]

between the planes defined by the C1–C6 aryl ring and the C1—N1—C7—O1 formamide group is larger in form (I*a*) [60.2 (2)°] than in form (I*b*) [56.7 (3)°]. This is different from what has been observed in the previously reported two forms of each of compounds (II) and (III) (Omondi *et al.*, 2005) and also for the two forms of 2,6-dichloroacetanilide (Nagarajan *et al.*, 1986), where the structures of crystals of 'form *a*' have a lower value of this torsion angle compared with those of 'form *b*'. Bond distances and angles (Tables 1 and 3) for both polymorphs are comparable with those of similar structures from the literature (Omondi *et al.*, 2005, and references therein).

A comparison of the cell parameters of form (I*a*) with the room-temperature orthorhombic phases of (II) and (III) [(II*a*) and (III*a*)] reveals that the three compounds are isostructural and isomorphous with variations in the cell dimensions. The three structures have similar packing patterns. However, compounds (I*b*), (II*b*) and (III*b*) are not isostructural. Hydrogen-bonding patterns for the two title polymorphic forms are shown in Figs. 3, 4, 6 and 7, and the hydrogen-bond geometry is given in Tables 2 and 4.

In the crystal, (I*a*) has molecules linked by N—H$\cdots$O hydrogen bonds, forming chains of molecules related by a glide plane in the crystallographic *a* direction. This results in the formamide molecules pointing in alternating directions (Fig. 3). Adjacent N—H$\cdots$O hydrogen-bonded chains are held together through π–π interactions [$Cg\cdots Cg(-x + 2, -y + 1, -z + 1) = 3.903\ (5)$ Å]. The joining of molecules by N—H$\cdots$O and π–π intermolecular interactions results in (010) sheets. Neighbouring sheets interact with each other through very weak C—H$\cdots$F [H3$\cdots$F2$(-x + \frac{3}{2}, y + \frac{1}{2}, z) =$ 2.69 Å] interactions (Fig. 4).

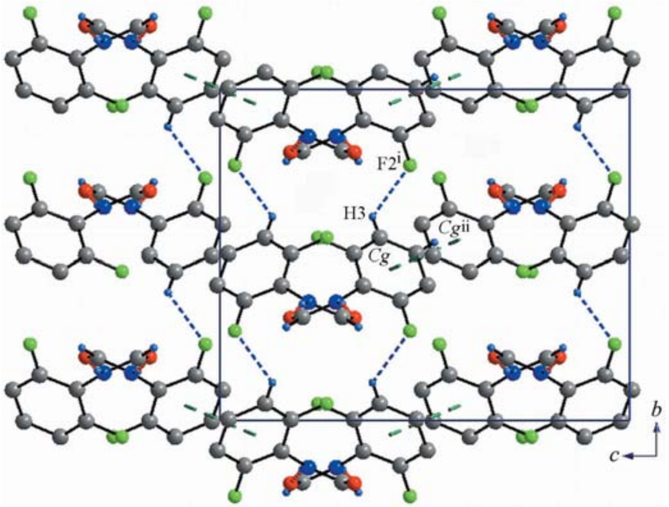

Figure 4
A view of polymorph (I*a*) down the crystallographic *a* axis, showing C—H$\cdots$F interactions (short dashed lines). [Symmetry code: (i) $-x + \frac{3}{2}, y + \frac{1}{2}, z$; (ii) $-x + 2, -y + 1, -z + 1$.]

The crystals of form (I*b*) were found to exist in the batch of crystals of *N*-(2,6-difluorophenyl)thioformamide. Since *N*-(2,6-difluorophenyl)formamide is a starting material in the synthesis of *N*-(2,6-difluorophenyl)thioformamide, it was assumed that unconverted *N*-(2,6-difluorophenyl)formamide from the reaction crystallized out under the influence of *N*-(2,6-difluorophenyl)thioformamide, thereby obtaining (I*b*). Attempts to grow crystals of (I*b*) under controlled conditions were not successful as only the starting crystals of *N*-(2,6-difluorophenyl)formamide and *N*-(2,6-difluorophenyl)thioformamide were obtained in their original forms. Attempts to convert (I*a*) to (I*b*) by sublimation of a powder of (I*a*) in a similar manner to converting (II*a*) and (III*a*) to (II*b*) and (III*b*), respectively, were also unsuccessful. Due to limited amounts of (I*b*), further studies (thermal and crystallographic) were not possible. Fig. 5 shows crystals of (I*b*) in a batch of crystals of *N*-(2,6-difluorophenyl)thioformamide.

The hydrogen-bonded chains in compound (I*b*) are very similar to those of (II*b*) and (III*b*) (Omondi *et al.*, 2005). In these structures, molecules are stacked with the aryl rings arranged in a linear fashion on top of one another and related by translation along a short crystallographic axis [the *a* axis for (I*b*) and (II*b*) and the *b* axis for (III*b*)]. This results in the molecules being parallel to each other, forming chains through N—H$\cdots$O hydrogen bonding along the crystallographic *a* direction (Fig. 6). Neighbouring N—H$\cdots$O hydrogen-bonded chains in (I*b*) are further connected through C—H$\cdots$F intermolecular interactions [F2$\cdots$H5$(-x + 2, y + \frac{1}{2}, -z + 2) =$ 2.65 Å, F1$\cdots$H3$(-x, y + \frac{1}{2}, -z + 1) = 2.45$ Å] (Fig. 7). The

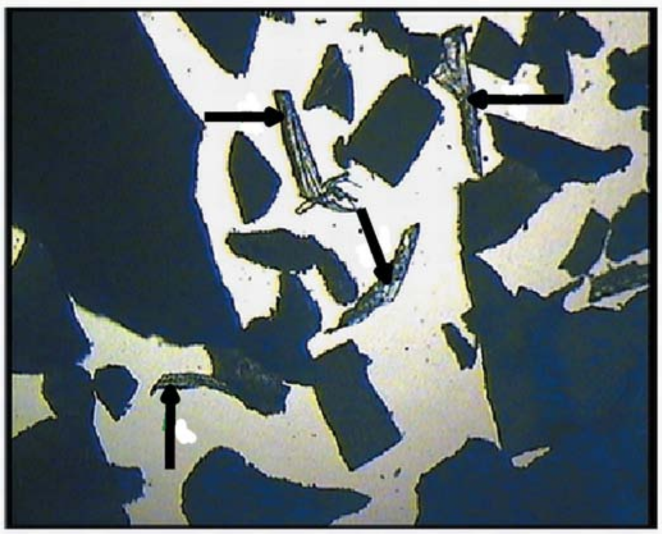

Figure 5
Crystals of polymorph (I*b*) (transparent, with dimensions of about 0.7 × 0.15 × 0.05 mm, indicated by arrows) in a batch of crystals of *N*-(2,6-difluorophenyl)thioformamide (dark patches).

second C—H⋯F interaction in (I*b*) is shorter (2.45 Å) than the lower limits set by Rowland & Taylor (1996) at 2.54 Å for normalized H-atom positions. This would be an indication that the interaction is only secondary and therefore exists as a result of the close proximity of neighbouring molecules caused by the N—H⋯O, the longer C—H⋯F and possibly a C—H⋯π intermolecular interaction [C2—F1⋯π ($-x+1$, $y+\frac{1}{2}$, $-z+1$): C2⋯π = 3.825 (2) Å and C2—F1⋯π = 143.27 (12)°].

The stability of the two polymorphs was assessed on the basis of the different intermolecular interactions involved in their crystal packing. Estimation and description of lattice energies by summation of potential energies between interacting atoms (or atom–atom interaction energies) were carried out using the *ZipOpec* module of the *OPIX* program suite (Gavezzotti, 2003) described by the UNI force field (Filippini & Gavezzotti, 1994) in a similar manner as was done for (II) and (III) (Omondi *et al.*, 2005). Values of −91.3 and −89.9 kJ mol^{-1} were obtained for the lattice energies of forms (I*a*) and (I*b*), respectively.

In addition to lattice energies, *ZipOpec* calculates molecule–molecule interaction energies to identify which molecular arrangements contribute most to the overall lattice stabilization. For compound (I*a*), the most stabilizing interaction is between molecules involved in the formation of the N—H⋯O chain (−35.2 kJ mol^{-1}), followed by molecules arranged in a π–π interaction configuration (−21.9 kJ mol^{-1}). The third most stabilizing interaction (−9.1 kJ mol^{-1}) brings neighbouring F and H atoms into close proximity to form C—H⋯F interactions. In (I*b*), the most stabilizing interaction is again between molecules involved in the N—H⋯O chain formation (−36.9 kJ mol^{-1}). The next most stabilizing geometries contribute −12.6 and −12.4 kJ mol^{-1} and involve molecules interacting *via* C—H⋯F and C—F⋯π interactions, respectively, towards lattice stability. As we mentioned previously (Omondi *et al.*, 2005), it seems like the π–π interaction configuration in (I*a*), which is not present in (I*b*), contributes to the preferential formation of (I*a*) at room temperature.

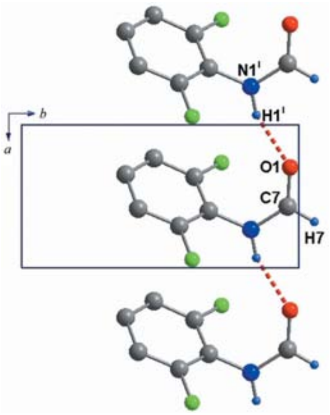

Figure 6
A view of polymorph (1*b*) down the crystallographic *c* axis, showing N—H⋯O hydrogen-bonded chains. [Symmetry code: (i) $x-1$, y, z.]

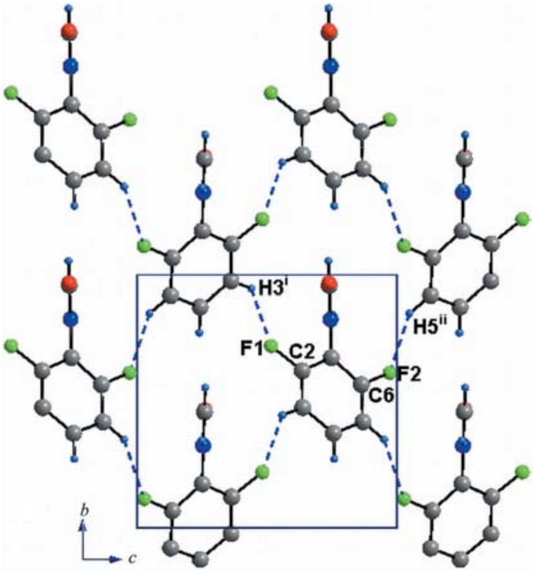

Figure 7
A view of polymorph (1*b*) down the crystallographic *a* axis, showing C—H⋯F interactions. [Symmetry codes: (i) $-x$, $y+\frac{1}{2}$, $1-z$; (ii) $-x+2$, $y+\frac{1}{2}$, $-x+2$.]

After standing for several weeks and even after heating [as observed by differential scanning calorimetry (DSC)], compound (I*b*) does not seem to revert to (I*a*), unlike the analogue of (III) (Omondi *et al.*, 2005). Should a transformation of (I*a*) to (I*b*) be found, we would speculate that the mechanism for such a transformation is similar to that proposed for the polymorphs of (II) and (III). In this case, C—H⋯F intermolecular interactions would play a similar role to Cl⋯Cl interactions in (II) and (III). The phase transformation of (II*a*) and (III*a*) involves rotation of the aryl group, leaving the N—H⋯O hydrogen-bonding chain intact with the aryl rings stacked along the short axis. The transformation of (II*a*) was said to be entropically driven as it reverts to form (II*a*) in large part because of the stabilizing π–π interactions, whereas there was no reverse change for compound (III), probably due to inhibition by intermolecular C—H⋯O interactions present in (III*b*) but not present in (II*b*).

Experimental

Polymorph (I*a*) was synthesized according to a known procedure (Ugi *et al.*, 1965). Commercially available 2,6-difluoro-*N*-phenylaniline (Aldrich, purity > 95%) was heated in a tenfold excess of formic acid for a period of 15 h at 363 K. The excess formic acid was then removed under vacuum to give a white solid, which was treated with dilute hydrochloric acid (0.1 *M* HCl, 10 ml) and ethyl acetate (60 ml). The organic layer was separated from the aqueous layer, dried over magnesium sulfate and filtered. Colourless needle-shaped crystals of (I*a*) were grown from the filtrate. The compound was obtained in good yields (over 80%). The purity of the compound was confirmed by NMR spectroscopy using a Bruker 300 MHz instrument. It was found to exist in solution (C_6D_6) as a mixture of *cis* and *trans* isomers in a 2:1 ratio. The second polymorph, (I*b*), could only be found as an impurity during the preparation of 2,6-difluoro-*N*-phenylthioamide. Efforts to produce (I*b*) experimentally by sublimation of (I*a*) or by seeding a solution of (I*a*) using crystals of *N*-(2,6-difluorophenyl)thioformamide were not successful.

Polymorph (I*a*)

Crystal data

$C_7H_5F_2NO$
M_r = 157.12
Orthorhombic, *Pbca*
a = 8.5031 (15) Å
b = 11.387 (2) Å
c = 14.075 (3) Å
V = 1362.8 (4) Å^3
Z = 8
Mo *Kα* radiation
μ = 0.14 mm^{-1}
T = 298 K
0.5 × 0.16 × 0.1 mm

Data collection

Bruker SMART 1K CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2004)
$T_{\min}$ = 0.933, $T_{\max}$ = 0.986
8426 measured reflections
1637 independent reflections
1006 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.039

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.100
S = 1.02
1637 reflections
105 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}$ = 0.15 e Å^{-3}
$\Delta\rho_{\min}$ = −0.12 e Å^{-3}

Polymorph (I*b*)

Crystal data

$C_7H_5F_2NO$
M_r = 157.12
Monoclinic, *P*2$_1$
a = 4.468 (2) Å
b = 8.486 (3) Å
c = 8.8810 (10) Å
β = 100.698 (5)°
V = 330.88 (19) Å^3
Z = 2
Mo *Kα* radiation
μ = 0.14 mm^{-1}
T = 123 K
0.35 × 0.09 × 0.04 mm

Data collection

Bruker SMART 1K CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2004)
$T_{\min}$ = 0.951, $T_{\max}$ = 0.994
8100 measured reflections
843 independent reflections
710 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.040

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

C1—N1	1.4147 (19)	C7—N1	1.327 (2)
C7—O1	1.2178 (19)		
C6—C1—N1	121.51 (14)	O1—C7—N1	125.73 (15)
C2—C1—N1	122.39 (14)	C7—N1—C1	122.58 (14)
C2—C1—N1—C7	60.2 (2)		

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

D—H⋯*A*	*D*—H	H⋯*A*	*D*⋯*A*	*D*—H⋯*A*
N1—H1⋯O1$^{\rm i}$	0.801 (17)	2.050 (17)	2.843 (2)	170.2 (17)

Symmetry code: (i) $x + \frac{1}{2}, y, -z + \frac{3}{2}$.

Table 3
Selected bond and torsion angles (°) for polymorph (I*b*).

C6—C1—N1	121.7 (2)	O1—C7—N1	125.9 (2)
C2—C1—N1	122.5 (2)	C7—N1—C1	123.11 (17)
C2—C1—N1—C7	56.7 (3)		

Table 4
Hydrogen-bond geometry (Å, °) for polymorph (I*b*).

D—H⋯*A*	*D*—H	H⋯*A*	*D*⋯*A*	*D*—H⋯*A*
N1—H1⋯O1$^{\rm i}$	0.88 (3)	1.97 (3)	2.807 (3)	158 (3)

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

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.031
$wR(F^2)$ = 0.076
S = 1.08
843 reflections
104 parameters
2 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}$ = 0.19 e Å^{-3}
$\Delta\rho_{\min}$ = −0.21 e Å^{-3}

With the exception of the H atoms involved in hydrogen bonding (*i.e.* H1), all H atoms were positioned geometrically, with C—H = 0.95 Å, and allowed to ride on their parent atoms, with $U_{\rm iso}$(H) = 1.2$U_{\rm eq}$(C). Atom H1 was located in a difference map and refined freely. A rigid bond restraint with an s.u. of 0.001 was applied to the atomic displacement parameters of atoms C7 and O1 in the structures of (I*a*) and (I*b*), because the components of the displacement parameters in the direction of the bond between these atoms were slightly inconsistent.

For both polymorphs, data collection: *SMART* (Bruker, 2004); cell refinement: *SAINT* (Bruker, 2004); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3* (Farrugia, 1997), *PLATON* (Spek, 2009) and *DIAMOND* (Brandenburg & Putz, 2005); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GZ3168). Services for accessing these data are described at the back of the journal.

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