

Crystal structure and Hirshfeld surface analysis of a third polymorph of 2,6-dimethoxybenzoic acid

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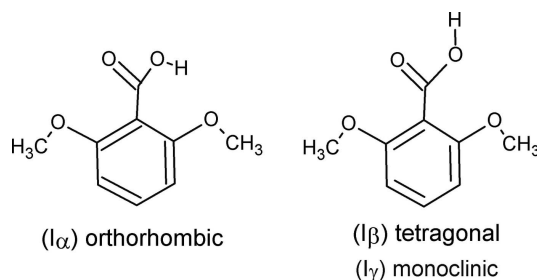
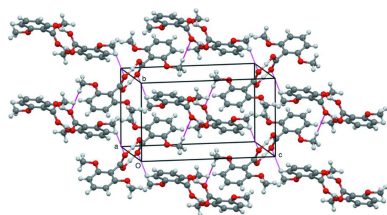
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A third crystalline form of the title compound, $C_9H_{10}O_4$, crystallizing in the centrosymmetric monoclinic space group $P2_1/c$, has been identified during screening for co-crystals. The asymmetric unit comprises a non-planar independent molecule with a synplanar conformation of the OH group. The sterically bulky *o*-methoxy substituents force the carboxy group to be twisted away from the plane of the benzene ring by $74.10(6)^\circ$. The carboxy group exhibits the acidic H atom disordered over two sites between two O atoms. A similar situation has been found for the second tetragonal polymorph reported [Portalone (2011). *Acta Cryst.* E67, o3394–o3395], in which molecules with the OH group in a synplanar conformation form dimeric units *via* strong $O-H\cdots O$ hydrogen bonds. In contrast, in the first orthorhombic form reported [Swaminathan *et al.* (1976). *Acta Cryst.* B32, 1897–1900; Bryan & White (1982). *Acta Cryst.* B38, 1014–1016; Portalone (2009). *Acta Cryst.* E65, o327–o328], the molecular components do not form conventional dimeric units, as an antiplanar conformation adopted by the OH group favors the association of molecules in chains stabilized by linear $O-H\cdots O$ hydrogen bonds.

1. Chemical context

Until now, two polymorphs are known for 2,6-dimethoxybenzoic acid. Polymorph ($I\alpha$) crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit (Swaminathan *et al.*, 1976; Bryan & White, 1982; Portalone, 2009). As a result of the antiplanar conformation adopted by the OH group, the molecular components are associated in the crystal in chains stabilized by linear $O-H\cdots O$ hydrogen bonds. Polymorph ($I\beta$) crystallizes in the tetragonal space group $P4_12_12$ with one molecule in the asymmetric unit (Portalone, 2011). In the crystal of the second polymorph, the synplanar conformation of the OH group favours the formation of dimers through $O-H\cdots O$ hydrogen bonds. In this article, it is reported the crystal structure of a third polymorph, ($I\gamma$), of 2,6-dimethoxybenzoic acid produced unexpectedly during an attempt to synthesize co-crystals of 5-fluorouracil with the title compound.



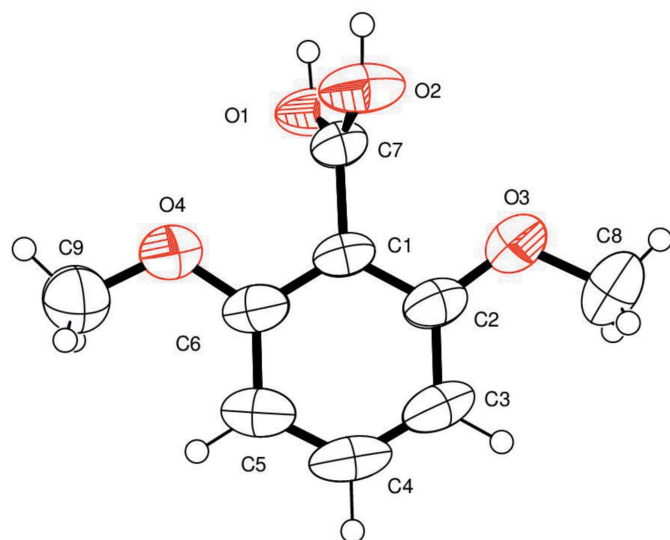


Figure 1
The molecular structure of (*I* γ), showing the atom-labeling scheme. Displacement ellipsoids are at the 50% probability level.

2. Structural commentary

The title compound (*I* γ) crystallizes in the monoclinic centrosymmetric space group $P2_1/c$, and the asymmetric unit comprises a non-planar independent molecule. The carboxy group is twisted away from the plane of the benzene ring by $74.10(6)^\circ$ because of a significant steric hindrance of the two *o*-methoxy substituents (Fig. 1). The above angle between the planes is comparable with that found for the orthorhombic form, $56.12(9)^\circ$, and for the tetragonal form, $65.72(15)^\circ$. The

Table 1
Hydrogen-bond geometry (\AA , $^\circ$).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$O1-H1\cdots O2^i$	0.86 (6)	1.79 (6)	2.6411 (15)	174 (4)
$O2-H2\cdots O1^i$	0.81 (6)	1.84 (6)	2.6411 (15)	167 (5)
$C9-H9A\cdots O2^{ii}$	0.97	2.60	3.571 (3)	178

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

carboxy group, in which OH adopts a synplanar conformation similar to that observed for the tetragonal form, exhibits the carboxy H atom disordered over two sites between two O atoms. The pattern of bond lengths and bond angles of the phenyl ring is consistent with that reported in the structure determination of the two previously determined polymorphs, and a comparison of the present results with those obtained for similar benzene derivatives (Colapietro *et al.*, 1984; Irrera *et al.*, 2012; Portalone, 2012) shows no appreciable effects of the crystal environment on the ring deformation induced by substituents.

3. Supramolecular features

Analysis of the crystal packing of (*I* γ), (Fig. 2), shows that the molecular components form the conventional dimeric units observed in benzoic acids (Leiserowitz, 1976; Kanters *et al.*, 1991; Moorthy *et al.*, 2002). Indeed, the crystal structure is stabilized by strong intermolecular O—H \cdots O hydrogen bonds, which link inversion-related molecules into homodimers (Table 1). These homodimers are then joined by weak C—H \cdots O intermolecular interactions of graph-set motif

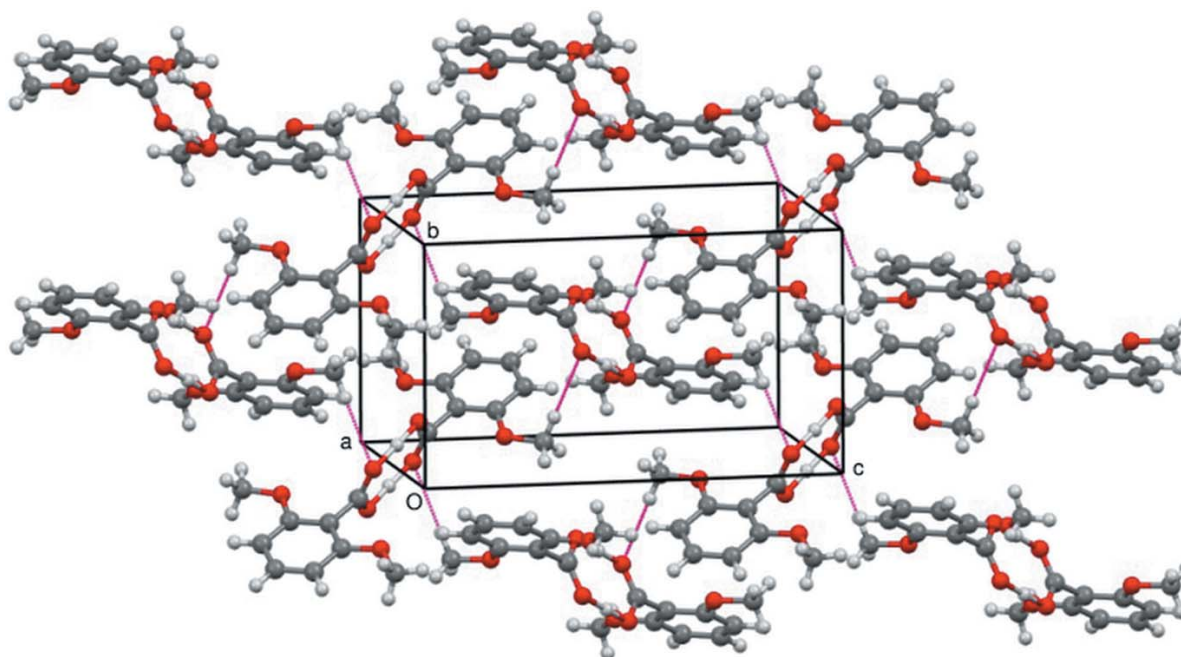


Figure 2
Crystal packing diagram for (*I* γ) viewed approximately down the *a* axis. All atoms are shown as small spheres of arbitrary radii. Hydrogen bonding is indicated by red dashed lines.

$R_2^2(6)$ between the methoxy and the carboxy groups of adjacent molecules to form a two-dimensional network parallel to the bc plane.

The Hirshfeld surface analysis (Spackman & Jayatilaka, 2009) was carried out using *CrystalExplorer* (Turner *et al.*, 2017). The surface enables the visualization of intermolecular contacts over the surface by different colors and color intensity, and shorter and longer contacts are indicated as red and blue spots, respectively. In Fig. 3 are shown the 3D Hirshfeld surface, modeled by choosing one of the two equally disordered components and mapped over d_{norm} , and the two-dimensional fingerprint plots, which give the contribution of the interatomic contacts to the Hirshfeld surface. The most prominent interactions, due to strong O—H...O hydrogen bonds, are shown by large and deep red spots on the surface. Small red spots on the surface indicate the areas where close-contact interactions due to weak C—H...O hydrogen bonds take place. The H...H contacts, representing van der Waals interactions, and the O...H/H...O contacts, representing intermolecular hydrogen bonds, are the most populated

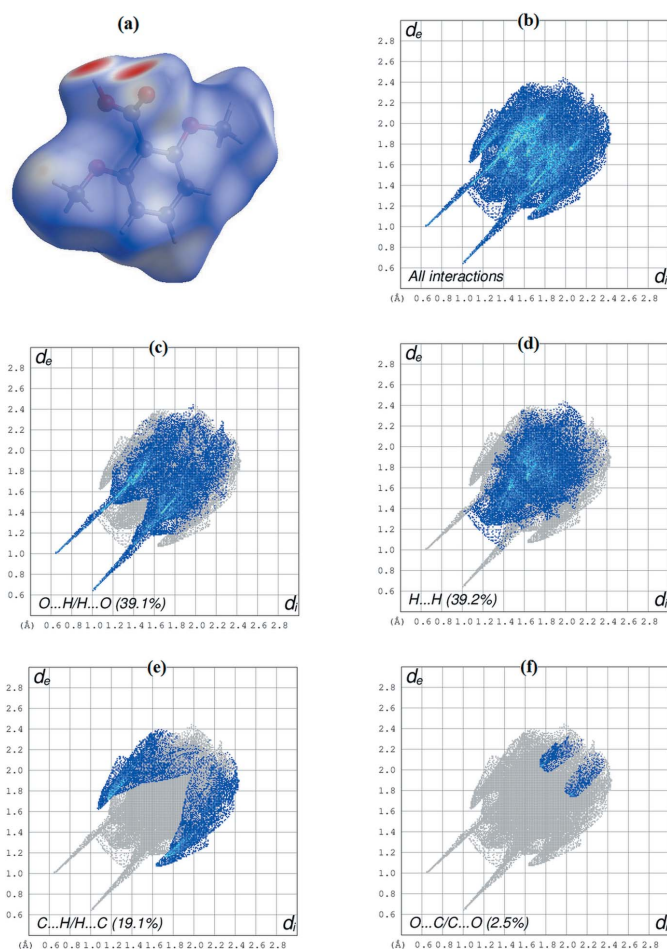


Figure 3
(a) A view of the three-dimensional Hirshfeld surface of the title compound mapped over d_{norm} with a fixed color scale of -0.742 (red) to 1.283 (blue) a.u. (b), (c), (d), (e) and (f): decomposed two-dimensional fingerprint plots for the title compound showing various close contacts and their proportional contributions.

Table 2
Experimental details.

Crystal data	
Chemical formula	$\text{C}_9\text{H}_{10}\text{O}_4$
M_r	182.17
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	298
a, b, c (Å)	7.7574 (10), 8.4763 (10), 14.3322 (19)
β (°)	97.526 (12)
V (Å ³)	934.3 (2)
Z	4
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	0.10
Crystal size (mm)	0.20 × 0.14 × 0.11
Data collection	
Diffractometer	Oxford Diffraction Xcalibur S CCD
Absorption correction	Multi-scan (<i>CrysAlis RED</i> ; Rigaku OD, 2018)
$T_{\text{min}}, T_{\text{max}}$	0.970, 0.999
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	9067, 2708, 1420
R_{int}	0.040
$(\sin \theta/\lambda)_{\text{max}}$ (Å ⁻¹)	0.704
Refinement	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.049, 0.132, 1.02
No. of reflections	2708
No. of parameters	134
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ (e Å ⁻³)	0.14, -0.12

Computer programs: *CrysAlis PRO* (Rigaku OD, 2018), *SIR2004* (Burla *et al.*, 2005), *SHELXL2014/7* (Sheldrick, 2015) and *WinGX* (Farrugia, 2012).

contacts and contribute 39.2 and 39.1% of the total intermolecular contacts, respectively. Other important contacts, such as C...H/H...C (19.1%), also supplement the overall crystal packing. The contributions of the O...C/C...O (2.5%) contacts are less significant.

4. Database survey

A search of crystal structure of 2,6-dimethoxy benzoic acid alone in the Cambridge Crystallographic Database (CSD version 5.41, May 2020 update; Groom *et al.*, 2016) yielded four hits as crystalline polymorphs. Three were for the orthorhombic polymorph: DMOXBA (Swaminathan *et al.*, 1976), DMOXBA01 (Bryan & White, 1982) and DMOXBA02 (Portalone, 2009); the fourth one was for the tetragonal polymorph: DMOXBA03 (Portalone, 2011).

5. Synthesis and crystallization

Polymorph (I γ) was formed from an unsuccessful co-crystallization between 2,6-dimethoxybenzoic acid and 5-fluorouracil. Colorless plate-like crystals were formed by the slow evaporation of an aqueous solution of 2,6-dimethoxybenzoic acid (1 mmol, Sigma Aldrich at 99% purity) and 5-fluorouracil (1 mmol, Sigma Aldrich at 99% purity) in a 1:1 molar ratio.

6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. All H atoms were identified in difference-Fourier maps, but in the refinement all C-bound H atoms were placed in calculated positions, with C–H = 0.97 Å, and refined as riding on their carrier atoms, with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C}_{\text{phenyl}})$ or $1.5U_{\text{eq}}(\text{C}_{\text{methyl}})$. A rotating group model was applied to the methyl groups. The remaining two halves of the disordered O-bound H atom, H1 and H2, were refined freely and their U_{iso} values were kept equal to $1.2U_{\text{eq}}(\text{O})$. Site-occupation factors of H1 and H2 refined to 0.53 (3) and 0.47 (3), respectively.

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Computing details

Data collection: *CrysAlis PRO* (Rigaku OD, 2018); cell refinement: *CrysAlis PRO* (Rigaku OD, 2018); data reduction: *CrysAlis PRO* (Rigaku OD, 2018); program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *SHELXL2014/7* (Sheldrick, 2015); molecular graphics: *WinGX* (Farrugia, 2012); software used to prepare material for publication: *WinGX* (Farrugia, 2012).

2,6-Dimethoxybenzoic acid.

Crystal data

$C_9H_{10}O_4$	$F(000) = 384$
$M_r = 182.17$	$D_x = 1.295 \text{ Mg m}^{-3}$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation, $\lambda = 0.710689 \text{ \AA}$
$a = 7.7574 (10) \text{ \AA}$	Cell parameters from 1806 reflections
$b = 8.4763 (10) \text{ \AA}$	$\theta = 2.9\text{--}32.6^\circ$
$c = 14.3322 (19) \text{ \AA}$	$\mu = 0.10 \text{ mm}^{-1}$
$\beta = 97.526 (12)^\circ$	$T = 298 \text{ K}$
$V = 934.3 (2) \text{ \AA}^3$	Tablets, colourless
$Z = 4$	$0.20 \times 0.14 \times 0.11 \text{ mm}$

Data collection

Oxford Diffraction Xcalibur S CCD diffractometer	9067 measured reflections
Radiation source: Enhance (Mo) X-ray source	2708 independent reflections
Graphite monochromator	1420 reflections with $I > 2\sigma(I)$
Detector resolution: 16.0696 pixels mm^{-1}	$R_{\text{int}} = 0.040$
ω and ϕ scans	$\theta_{\text{max}} = 30.0^\circ$, $\theta_{\text{min}} = 2.9^\circ$
Absorption correction: multi-scan (<i>CrysAlis RED</i> ; Rigaku OD, 2018)	$h = -10 \rightarrow 10$
$T_{\text{min}} = 0.970$, $T_{\text{max}} = 0.999$	$k = -11 \rightarrow 6$
	$l = -19 \rightarrow 20$

Refinement

Refinement on F^2	H atoms treated by a mixture of independent and constrained refinement
Least-squares matrix: full	$w = 1/[\sigma^2(F_o^2) + (0.0439P)^2 + 0.0492P]$
$R[F^2 > 2\sigma(F^2)] = 0.049$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.132$	$(\Delta/\sigma)_{\text{max}} < 0.001$
$S = 1.02$	$\Delta\rho_{\text{max}} = 0.14 \text{ e \AA}^{-3}$
2708 reflections	$\Delta\rho_{\text{min}} = -0.12 \text{ e \AA}^{-3}$
134 parameters	
0 restraints	
Hydrogen site location: mixed	

Extinction correction: SHELXL-2014/7
 (Sheldrick 2015\bbr000),
 $F_c^* = kFc[1 + 0.001x Fc^2 \lambda^3 / \sin(2\theta)]^{-1/4}$
 Extinction coefficient: 0.031 (4)

Special details

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

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

	x	y	z	U_{iso}^*/U_{eq}	Occ. (<1)
O1	0.50254 (16)	0.32576 (15)	0.56267 (9)	0.0726 (4)	
H1	0.446 (6)	0.372 (5)	0.515 (3)	0.087*	0.53 (3)
O2	0.68711 (16)	0.52450 (15)	0.57631 (9)	0.0776 (5)	
H2	0.643 (7)	0.571 (6)	0.530 (4)	0.093*	0.47 (3)
O3	0.94633 (16)	0.24939 (16)	0.59823 (10)	0.0827 (4)	
O4	0.50328 (18)	0.39851 (17)	0.76761 (9)	0.0900 (5)	
C1	0.73003 (19)	0.31878 (17)	0.68819 (11)	0.0531 (4)	
C2	0.8886 (2)	0.24603 (19)	0.68370 (13)	0.0622 (5)	
C3	0.9743 (2)	0.1717 (2)	0.76309 (15)	0.0767 (6)	
H3	1.0852	0.1199	0.7610	0.092*	
C4	0.8991 (3)	0.1731 (2)	0.84415 (15)	0.0836 (7)	
H4	0.9582	0.1201	0.8992	0.100*	
C5	0.7430 (3)	0.2467 (2)	0.85095 (13)	0.0782 (6)	
H5	0.6940	0.2474	0.9099	0.094*	
C6	0.6574 (2)	0.3199 (2)	0.77134 (12)	0.0648 (5)	
C7	0.63417 (19)	0.39559 (18)	0.60344 (10)	0.0508 (4)	
C8	1.1123 (3)	0.1829 (4)	0.5897 (2)	0.1261 (10)	
H8A	1.2012	0.2385	0.6310	0.158 (12)*	
H8B	1.1358	0.1925	0.5251	0.152 (12)*	
H8C	1.1129	0.0723	0.6072	0.169 (13)*	
C9	0.4198 (3)	0.4098 (3)	0.84841 (17)	0.0986 (7)	
H9A	0.3944	0.3048	0.8698	0.139 (10)*	
H9B	0.3122	0.4684	0.8337	0.129 (9)*	
H9C	0.4950	0.4641	0.8976	0.155 (12)*	

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0660 (8)	0.0702 (8)	0.0718 (8)	-0.0169 (6)	-0.0278 (6)	0.0167 (6)
O2	0.0747 (8)	0.0651 (8)	0.0823 (9)	-0.0180 (6)	-0.0302 (7)	0.0257 (7)
O3	0.0585 (8)	0.1008 (10)	0.0873 (10)	0.0180 (7)	0.0041 (6)	0.0170 (8)
O4	0.0984 (10)	0.1059 (11)	0.0659 (9)	0.0408 (8)	0.0118 (7)	0.0165 (7)
C1	0.0513 (8)	0.0503 (8)	0.0525 (9)	0.0003 (7)	-0.0128 (7)	0.0062 (7)
C2	0.0512 (9)	0.0611 (10)	0.0693 (12)	-0.0009 (7)	-0.0108 (8)	0.0098 (8)
C3	0.0579 (10)	0.0739 (12)	0.0904 (14)	0.0082 (9)	-0.0199 (10)	0.0192 (10)

C4	0.0835 (14)	0.0788 (13)	0.0775 (14)	0.0018 (11)	-0.0309 (11)	0.0234 (10)
C5	0.0925 (15)	0.0788 (12)	0.0580 (11)	0.0040 (11)	-0.0103 (9)	0.0152 (9)
C6	0.0712 (11)	0.0584 (10)	0.0599 (11)	0.0086 (8)	-0.0104 (9)	0.0068 (8)
C7	0.0461 (8)	0.0509 (8)	0.0522 (9)	0.0012 (7)	-0.0057 (6)	0.0047 (7)
C8	0.0704 (16)	0.173 (3)	0.138 (3)	0.0443 (17)	0.0250 (17)	0.037 (2)
C9	0.1151 (19)	0.0953 (17)	0.0891 (16)	0.0249 (15)	0.0273 (15)	0.0135 (14)

Geometric parameters (Å, °)

O1—C7	1.2563 (17)	C3—C4	1.367 (3)
O1—H1	0.86 (6)	C3—H3	0.9700
O2—C7	1.2472 (18)	C4—C5	1.377 (3)
O2—H2	0.81 (6)	C4—H4	0.9700
O3—C2	1.359 (2)	C5—C6	1.389 (2)
O3—C8	1.425 (2)	C5—H5	0.9700
O4—C6	1.363 (2)	C8—H8A	0.9701
O4—C9	1.402 (2)	C8—H8B	0.9701
C1—C6	1.383 (2)	C8—H8C	0.9701
C1—C2	1.385 (2)	C9—H9A	0.9701
C1—C7	1.4885 (19)	C9—H9B	0.9701
C2—C3	1.391 (2)	C9—H9C	0.9701
C7—O1—H1	117 (3)	O4—C6—C1	115.07 (14)
C7—O2—H2	124 (3)	O4—C6—C5	124.95 (19)
C2—O3—C8	118.50 (17)	C1—C6—C5	119.97 (17)
C6—O4—C9	119.91 (16)	O2—C7—O1	123.27 (13)
C6—C1—C2	120.51 (14)	O2—C7—C1	119.20 (13)
C6—C1—C7	118.92 (14)	O1—C7—C1	117.53 (14)
C2—C1—C7	120.57 (16)	O3—C8—H8A	109.5
O3—C2—C1	115.62 (14)	O3—C8—H8B	109.5
O3—C2—C3	124.61 (17)	H8A—C8—H8B	109.5
C1—C2—C3	119.74 (18)	O3—C8—H8C	109.5
C4—C3—C2	118.64 (18)	H8A—C8—H8C	109.5
C4—C3—H3	120.7	H8B—C8—H8C	109.5
C2—C3—H3	120.7	O4—C9—H9A	109.5
C3—C4—C5	122.81 (16)	O4—C9—H9B	109.5
C3—C4—H4	118.6	H9A—C9—H9B	109.5
C5—C4—H4	118.6	O4—C9—H9C	109.5
C4—C5—C6	118.33 (19)	H9A—C9—H9C	109.5
C4—C5—H5	120.8	H9B—C9—H9C	109.5
C6—C5—H5	120.8		
C8—O3—C2—C1	177.2 (2)	C9—O4—C6—C5	0.1 (3)
C8—O3—C2—C3	-4.9 (3)	C2—C1—C6—O4	178.43 (14)
C6—C1—C2—O3	178.84 (15)	C7—C1—C6—O4	-2.2 (2)
C7—C1—C2—O3	-0.5 (2)	C2—C1—C6—C5	-0.5 (3)
C6—C1—C2—C3	0.9 (2)	C7—C1—C6—C5	178.92 (15)
C7—C1—C2—C3	-178.51 (14)	C4—C5—C6—O4	-179.32 (17)

O3—C2—C3—C4	-178.01 (17)	C4—C5—C6—C1	-0.5 (3)
C1—C2—C3—C4	-0.2 (3)	C6—C1—C7—O2	106.30 (19)
C2—C3—C4—C5	-0.8 (3)	C2—C1—C7—O2	-74.3 (2)
C3—C4—C5—C6	1.2 (3)	C6—C1—C7—O1	-73.7 (2)
C9—O4—C6—C1	-178.74 (18)	C2—C1—C7—O1	105.66 (18)

Hydrogen-bond geometry (Å, °)

<i>D</i> —H \cdots <i>A</i>	<i>D</i> —H	H \cdots <i>A</i>	<i>D</i> \cdots <i>A</i>	<i>D</i> —H \cdots <i>A</i>
O1—H1 \cdots O2 ⁱ	0.86 (6)	1.79 (6)	2.6411 (15)	174 (4)
O2—H2 \cdots O1 ⁱ	0.81 (6)	1.84 (6)	2.6411 (15)	167 (5)
C9—H9 <i>A</i> \cdots O2 ⁱⁱ	0.97	2.60	3.571 (3)	178

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $-x+1, y-1/2, -z+3/2$.