

Received 3 November 2021

Accepted 1 December 2021

Edited by C. Schulzke, Universität Greifswald,  
Germany**Keywords:** crystal structure; (*R*)-baclofen;  
enantiopure; hydrogen bonds.**CCDC reference:** 2125567**Supporting information:** this article has  
supporting information at journals.iucr.org/e

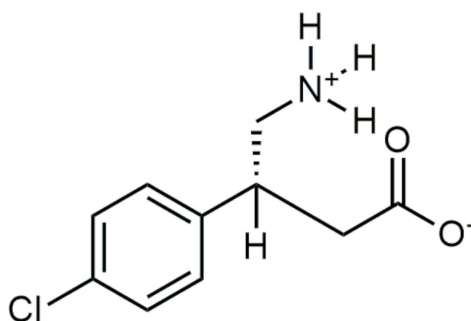
# (*R*)-Baclofen [(*R*)-4-amino-3-(4-chlorophenyl)-butanoic acid]

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This article provides the first single-crystal XRD-based structure of enantiopure (*R*)-baclofen (form C), C<sub>10</sub>H<sub>12</sub>ClNO<sub>2</sub>, without any co-crystallized substances. In the enantiopure title compound, the molecules arrange themselves in an orthorhombic crystal structure (space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>). In the crystal, strong hydrogen bonds and C—H···Cl bonds interconnect the zwitterionic molecules.

## 1. Chemical context

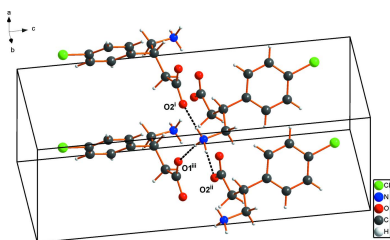
(*R*)-Baclofen, an unnatural  $\beta$ -amino acid and artificial GABA receptor agonist, is a frequently used non-addictive drug to treat muscle spasticity (Dario & Tomei, 2004). Although baclofen is conventionally applied as a racemic mixture, only the (*R*)-enantiomer actually mediates a therapeutic effect (Olpe *et al.*, 1978). In addition, baclofen has been recently approved in France as an alternative medication to treat alcohol dependence (Reade, 2021). Considering those new developments, the establishment of synthetic routes towards enantiopure (*R*)-baclofen were discussed recently (Córdova-Villanueva *et al.*, 2018; Gendron *et al.*, 2019).

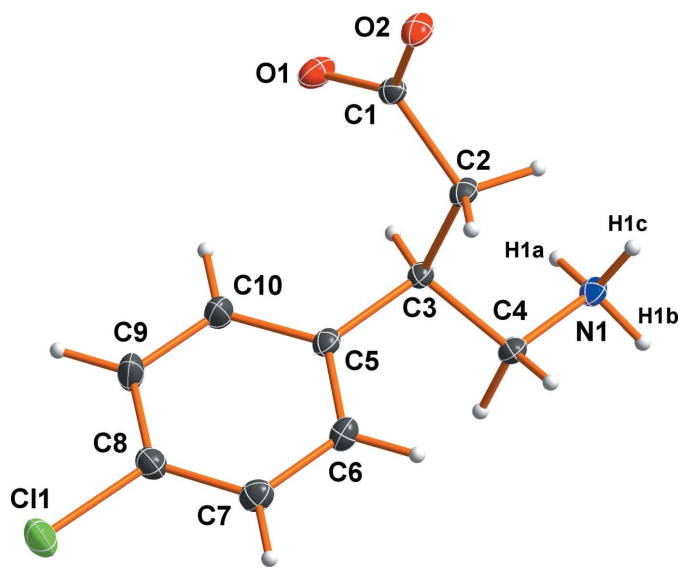


## 2. Structural commentary

The molecular structure of the title compound is shown in Fig. 1. A partial packing diagram is shown in Fig. 2.

A prediction of crystal forms of the title compound was previously presented by Couvrat *et al.* (2021), which is based on detailed XRPD-studies and Rietveld refinement. Based on the available XRPD-data, three forms, *A*, *B* and *C*, were observed, of which form *C* is considered to be the most stable form at higher temperatures. The (*R*)-baclofen crystal analyzed in this work corresponds to the newly predicted polymorphic form *C* presented by Couvrat *et al.* (2021).



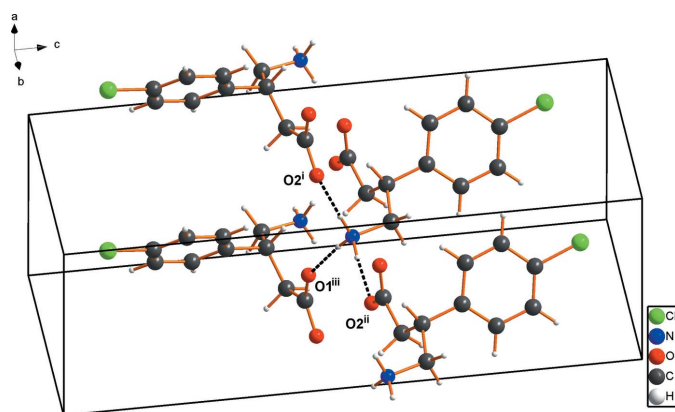


**Figure 1**  
The molecular structure of (*R*)-baclofen with displacement ellipsoids shown at the 50% probability level.

The molecules crystallize in a zwitterionic configuration, forming an ammonium and a carboxylate residue. The N-bound hydrogen atoms were located and refined freely. Bond lengths and angles fall into the typically observed ranges for organic molecules without any strain.

### 3. Supramolecular features

In the crystal of enantiopure (*R*)-baclofen form *C*, short N—H···O hydrogen bonds occur between the carboxylate and the ammonium group of the neighboring baclofen molecule. In parallel, additional hydrogen bonding occurs with neighboring baclofen molecules, resulting in a two-dimensional network parallel to (001), which yields a layered formation of baclofen molecules. Parallel to the hydrogen bonding, T-shaped C—H··· $\pi$  interactions occur along the layers of aromatic rings within the molecules [C9—H9···Cg1<sup>viii</sup> = 2.74 Å; C6—H6···



**Figure 2**  
Partial packing diagram of (*R*)-baclofen form *C*.

**Table 1**  
Hydrogen-bond geometry (Å, °).

<i>D</i> —H··· <i>A</i>	<i>D</i> —H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> —H··· <i>A</i>
N1—H1A···O2 <sup>i</sup>	0.91 (3)	1.91 (3)	2.820 (2)	176 (3)
N1—H1B···O2 <sup>ii</sup>	0.93 (3)	1.80 (3)	2.7149 (19)	168 (2)
N1—H1C···O1 <sup>iii</sup>	0.85 (3)	1.93 (3)	2.775 (2)	174 (3)
N1—H1B···Cl1 <sup>iv</sup>	0.93 (3)	2.95 (2)	3.3192 (14)	105.3 (16)
C4—H4A···Cl1 <sup>v</sup>	0.99	2.73	3.6306 (19)	152
C4—H4B···Cl1 <sup>vi</sup>	0.99	2.81	3.5668 (19)	134

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

Cg1<sup>ix</sup> = 3.24 Å; symmetry codes: (viii)  $-x + 2, y - \frac{1}{2}, -z + \frac{3}{2}$ ; (ix)  $-x + 1, y + \frac{1}{2}, -z + \frac{3}{2}$ ; Cg1 is the centroid of the C5—C10 benzene ring]. The interaction planes both form angles of 67° with the plane of the corresponding benzene ring (C5—C10).

The combination of both effects yields the observed structure of form *C* of (*R*)-baclofen. In contrast, the cohesion of the apparently less stable form *A* is ensured by  $\pi$ — $\pi$  interactions.

Hydrogen-bond geometry data as well as non-classical C—H···Cl interaction data are summarized in Table 1.

### 4. Database survey

Using the CSD database (version 5.42 updates 2 and 3; Groom *et al.*, 2016), a search for the title compound's structure and names used in this article was conducted with *CONQUEST* (version 2021.2.0; Bruno *et al.*, 2002).

While the crystal structures of (*R*)- and (*S*)-baclofenium hydrochloride were reported in the early 1980s (Chang *et al.*, 1981, 1982; refcodes: CRBMZB, CRBMZC10), studies on the phase behavior of pure baclofen have gained attention just recently. This is particularly relevant for the crystal structure of enantiomerically pure (*R*)-baclofen since X-ray powder diffraction studies were recently described by Couvrat *et al.* (2021). A total of three polymorphic forms (*A*, *B* and *C*) of (*R*)-baclofen were analyzed by X-ray powder diffraction, form *C* being identified as previously unknown. Based on this nomenclature, the crystal structure of form *C* is reported in this study. For the crystal structure of racemic baclofen, see Maniukiewicz *et al.* (2016; refcode: AQEKUE). A further array of racemic baclofenium co-crystal structures with various carboxylic acids were published by Báthori & Kilinkissa (2015; refcodes: LUSXAA, LUSXEE, LUSXII, LUSXUU, LUSXOO, LUSYAB) and Malapile *et al.* (2021; refcodes: LABJIL, LABJOR, LABJUX, LABKAE, LABKEI, LABKIM, LABKOS). Additionally, Gendron *et al.* (2019; refcode: WONSIE01) presented the crystal structure of (*R*)-baclofen hydrogenium maleate.

### 5. Synthesis and crystallization

Crystals of the title compound were grown from a saturated aqueous solution containing enantiopure (*R*)-baclofen, which was evaporated slowly by a stream of dry argon at 313 K. The purity of the (*R*)-baclofen was verified *via* <sup>1</sup>H NMR. Enantiopure (*R*)-baclofen was purchased from *abcr GmbH* (Karls-

**Table 2**  
Experimental details.

Crystal data	
Chemical formula	C <sub>10</sub> H <sub>12</sub> ClNO <sub>2</sub>
<i>M<sub>r</sub></i>	213.66
Crystal system, space group	Orthorhombic, <i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Temperature (K)	123
<i>a</i> , <i>b</i> , <i>c</i> (Å)	6.8913 (5), 7.6898 (5), 19.7527 (14)
<i>V</i> (Å <sup>3</sup> )	1046.75 (13)
<i>Z</i>	4
Radiation type	Mo <i>K</i> α
μ (mm <sup>-1</sup> )	0.34
Crystal size (mm)	0.27 × 0.19 × 0.16
Data collection	
Diffractometer	Bruker D8 QUEST diffractometer
Absorption correction	Multi-scan ( <i>SADABS2016/2</i> ; Krause <i>et al.</i> , 2015)
<i>T</i> <sub>min</sub> , <i>T</i> <sub>max</sub>	0.662, 0.747
No. of measured, independent and observed [ <i>I</i> > 2σ( <i>I</i> )] reflections	23624, 3796, 3447
<i>R</i> <sub>int</sub>	0.042
(sin θ/λ) <sub>max</sub> (Å <sup>-1</sup> )	0.756
Refinement	
<i>R</i> [ <i>F</i> <sup>2</sup> > 2σ( <i>F</i> <sup>2</sup> )], <i>wR</i> ( <i>F</i> <sup>2</sup> ), <i>S</i>	0.033, 0.082, 1.07
No. of reflections	3796
No. of parameters	140
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Δρ <sub>max</sub> , Δρ <sub>min</sub> (e Å <sup>-3</sup> )	0.36, -0.30
Absolute structure	Refined as an inversion twin
Absolute structure parameter	0.04 (6)

Computer programs: *APEX2* and *APEX2* (Bruker, 2003), *SAINT* (Bruker, 2003), *SHELXT* (Sheldrick, 2015a), *SHELXL2014/7* (Sheldrick, 2015b) and *ORTEP-3 for Windows* (Farrugia, 2012).

ruhe, Germany) under the name (*R*)-4-amino-3-(4-chlorophenyl)butanoic acid.

## 6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. The N-bound hydrogen atoms were found in difference syntheses, and refined freely. All C-bound H atoms were positioned geometrically and refined using a riding model, with C–H = 0.99 Å (methylene groups), 1.00 Å (methine groups) or 0.95 Å (aryl CH) and with *U*<sub>iso</sub>(H) = 1.2*U*<sub>eq</sub>(C) (methylene groups, aryl CH, methine groups). The structure was refined as a two-component inversion twin (BASF 0.04470).

## Acknowledgements

Funding by the Central SME Innovation Programme (ZIM, project No. ZF4402103CR9) is gratefully acknowledged. The authors thank Isabel Schicht and Sandra Diederich for experimental and technical support.

## Funding information

Funding for this research was provided by: Bundesministerium für Wirtschaft und Energie (grant No. ZF4402103CR9 to Dr Jan von Langermann).

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## supporting information

*Acta Cryst.* (2022). E78, 33-35 [https://doi.org/10.1107/S2056989021012809]

**(R)-Baclofen [(R)-4-amino-3-(4-chlorophenyl)butanoic acid]**

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**Computing details**

Data collection: *APEX2* (Bruker, 2003); cell refinement: *APEX2* (Bruker, 2003); data reduction: *S SAINT* (Bruker, 2003); program(s) used to solve structure: *SHELXT* (Sheldrick, 2015a); program(s) used to refine structure: *SHELXL2014/7* (Sheldrick, 2015b); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 2012); software used to prepare material for publication: *SHELXL2014/7* (Sheldrick, 2015b).

**(R)-4-amino-3-(4-chlorophenyl)butanoic acid***Crystal data*

$C_{10}H_{12}ClNO_2$

$M_r = 213.66$

Orthorhombic,  $P2_12_12_1$

$a = 6.8913$  (5) Å

$b = 7.6898$  (5) Å

$c = 19.7527$  (14) Å

$V = 1046.75$  (13) Å<sup>3</sup>

$Z = 4$

$F(000) = 448$

$D_x = 1.356$  Mg m<sup>-3</sup>

Mo  $K\alpha$  radiation,  $\lambda = 0.71073$  Å

Cell parameters from 9871 reflections

$\theta = 2.8$ – $33.0^\circ$

$\mu = 0.34$  mm<sup>-1</sup>

$T = 123$  K

Block, colourless

$0.27 \times 0.19 \times 0.16$  mm

*Data collection*

Bruker D8 QUEST

diffractometer

Radiation source: microfocus sealed tube

Detector resolution: 10.4167 pixels mm<sup>-1</sup>

phi and  $\omega$  scans

Absorption correction: multi-scan

(*SADABS2016/2*; Krause *et al.*, 2015)

$T_{\min} = 0.662$ ,  $T_{\max} = 0.747$

23624 measured reflections

3796 independent reflections

3447 reflections with  $I > 2\sigma(I)$

$R_{\text{int}} = 0.042$

$\theta_{\max} = 32.5^\circ$ ,  $\theta_{\min} = 2.1^\circ$

$h = -10 \rightarrow 10$

$k = -11 \rightarrow 11$

$l = -29 \rightarrow 29$

*Refinement*

Refinement on  $F^2$

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.033$

$wR(F^2) = 0.082$

$S = 1.07$

3796 reflections

140 parameters

0 restraints

Primary atom site location: dual

Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0372P)^2 + 0.2629P]$

where  $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} = 0.001$

$\Delta\rho_{\max} = 0.36$  e Å<sup>-3</sup>

$\Delta\rho_{\min} = -0.30$  e Å<sup>-3</sup>

Absolute structure: Refined as an inversion twin

Absolute structure parameter: 0.04 (6)

*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.

Least-squares planes (x,y,z in crystal coordinates) and deviations from them (\* indicates atom used to define plane)

3.7985 (0.0046) x + 6.4064 (0.0034) y + 0.9085 (0.0146) z = 5.2962 (0.0108)

\* 0.0030 (0.0012) C5 \* -0.0067 (0.0012) C6 \* 0.0039 (0.0013) C7 \* 0.0025 (0.0013) C8 \* -0.0062 (0.0014) C9 \* 0.0035 (0.0014) C10 2.7365 (0.0020) H9\_\$8 3.2353 (0.0036) H6\_\$9

Rms deviation of fitted atoms = 0.0046

3.7985 (0.0045) x - 6.4064 (0.0034) y + 0.9085 (0.0145) z = 0.4604 (0.0136)

Angle to previous plane (with approximate esd) = 67.162 ( 0.045 )

\* -0.0030 (0.0012) C5\_\$8 \* 0.0067 (0.0012) C6\_\$8 \* -0.0039 (0.0013) C7\_\$8 \* -0.0025 (0.0014) C8\_\$8 \* 0.0062 (0.0014) C9\_\$8 \* -0.0035 (0.0014) C10\_\$8

Rms deviation of fitted atoms = 0.0046

3.7985 (0.0045) x + 6.4064 (0.0034) y - 0.9085 (0.0145) z = 7.2622 (0.0039)

Angle to previous plane (with approximate esd) = 66.899 ( 0.045 )

\* -0.0030 (0.0012) C5\_\$6 \* 0.0067 (0.0012) C6\_\$6 \* -0.0039 (0.0013) C7\_\$6 \* -0.0025 (0.0013) C8\_\$6 \* 0.0062 (0.0014) C9\_\$6 \* -0.0035 (0.0014) C10\_\$6

Rms deviation of fitted atoms = 0.0046

**Refinement.** Refined as a 2-component inversion twin (BASF 0.04470).

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ( $\text{\AA}^2$ )*

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
C11	0.90826 (7)	0.16066 (7)	0.88304 (2)	0.02370 (11)
N1	0.5842 (2)	0.60260 (18)	0.52352 (7)	0.0134 (2)
O1	0.76064 (19)	0.02092 (17)	0.54492 (7)	0.0194 (3)
O2	0.45342 (19)	-0.06602 (16)	0.53636 (7)	0.0178 (3)
C1	0.5825 (3)	0.0466 (2)	0.54937 (7)	0.0123 (3)
C2	0.5085 (2)	0.2255 (2)	0.57066 (9)	0.0147 (3)
H2A	0.4081	0.2098	0.6060	0.018*
H2B	0.4454	0.2809	0.5311	0.018*
C3	0.6643 (2)	0.3497 (2)	0.59801 (8)	0.0124 (3)
H3	0.7818	0.3378	0.5687	0.015*
C4	0.5966 (3)	0.5388 (2)	0.59429 (8)	0.0139 (3)
H4A	0.4674	0.5490	0.6159	0.017*
H4B	0.6882	0.6130	0.6199	0.017*
C5	0.7231 (2)	0.3034 (2)	0.67012 (8)	0.0134 (3)
C6	0.6148 (2)	0.3582 (2)	0.72594 (8)	0.0160 (3)
H6	0.5005	0.4248	0.7190	0.019*
C7	0.6719 (3)	0.3166 (2)	0.79192 (8)	0.0173 (3)
H7	0.5986	0.3560	0.8297	0.021*
C8	0.8370 (3)	0.2172 (2)	0.80119 (8)	0.0176 (3)
C9	0.9459 (3)	0.1590 (3)	0.74684 (9)	0.0223 (4)
H9	1.0580	0.0896	0.7540	0.027*
C10	0.8886 (3)	0.2037 (2)	0.68165 (8)	0.0200 (3)
H10	0.9639	0.1655	0.6442	0.024*
H1A	0.701 (5)	0.586 (4)	0.5031 (16)	0.044 (8)*
H1B	0.555 (4)	0.721 (3)	0.5245 (11)	0.022 (6)*

H1C	0.490 (4)	0.557 (4)	0.5021 (14)	0.029 (7)*
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*Atomic displacement parameters (Å<sup>2</sup>)*

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{12}$	$U^{13}$	$U^{23}$
C11	0.02181 (19)	0.0335 (2)	0.01578 (16)	0.0041 (2)	-0.00328 (16)	0.00057 (16)
N1	0.0134 (6)	0.0094 (6)	0.0174 (6)	0.0003 (5)	-0.0012 (5)	0.0000 (4)
O1	0.0152 (6)	0.0173 (6)	0.0258 (6)	0.0016 (5)	0.0031 (5)	-0.0055 (5)
O2	0.0167 (6)	0.0096 (5)	0.0272 (6)	-0.0011 (4)	-0.0027 (5)	-0.0011 (5)
C1	0.0156 (7)	0.0097 (6)	0.0117 (6)	0.0006 (6)	0.0003 (6)	0.0009 (5)
C2	0.0147 (7)	0.0091 (6)	0.0202 (7)	0.0006 (6)	-0.0025 (6)	-0.0018 (6)
C3	0.0130 (6)	0.0099 (6)	0.0144 (6)	0.0013 (6)	-0.0013 (5)	-0.0010 (5)
C4	0.0159 (7)	0.0104 (6)	0.0155 (6)	0.0015 (6)	-0.0012 (6)	-0.0012 (5)
C5	0.0133 (7)	0.0100 (7)	0.0169 (7)	0.0006 (5)	-0.0013 (5)	-0.0010 (5)
C6	0.0146 (7)	0.0146 (7)	0.0187 (7)	0.0028 (6)	0.0015 (5)	0.0012 (6)
C7	0.0186 (7)	0.0171 (8)	0.0163 (7)	0.0010 (7)	0.0029 (6)	0.0004 (6)
C8	0.0188 (8)	0.0188 (8)	0.0151 (7)	0.0001 (6)	-0.0025 (6)	0.0002 (6)
C9	0.0200 (9)	0.0276 (9)	0.0194 (7)	0.0115 (8)	-0.0034 (6)	0.0002 (7)
C10	0.0188 (8)	0.0243 (9)	0.0169 (7)	0.0090 (7)	-0.0015 (6)	-0.0030 (6)

*Geometric parameters (Å, °)*

C11—C8	1.7445 (17)	C3—H3	1.0000
N1—C4	1.484 (2)	C4—H4A	0.9900
N1—H1A	0.91 (3)	C4—H4B	0.9900
N1—H1B	0.93 (3)	C5—C10	1.394 (2)
N1—H1C	0.85 (3)	C5—C6	1.396 (2)
O1—C1	1.247 (2)	C6—C7	1.398 (2)
O2—C1	1.268 (2)	C6—H6	0.9500
C1—C2	1.526 (2)	C7—C8	1.383 (3)
C2—C3	1.535 (2)	C7—H7	0.9500
C2—H2A	0.9900	C8—C9	1.384 (2)
C2—H2B	0.9900	C9—C10	1.390 (2)
C3—C5	1.523 (2)	C9—H9	0.9500
C3—C4	1.529 (2)	C10—H10	0.9500
C4—N1—H1A	109 (2)	C3—C4—H4A	109.2
C4—N1—H1B	108.4 (14)	N1—C4—H4B	109.2
H1A—N1—H1B	110 (3)	C3—C4—H4B	109.2
C4—N1—H1C	112.1 (19)	H4A—C4—H4B	107.9
H1A—N1—H1C	114 (2)	C10—C5—C6	118.31 (15)
H1B—N1—H1C	104 (2)	C10—C5—C3	119.94 (14)
O1—C1—O2	124.61 (16)	C6—C5—C3	121.76 (14)
O1—C1—C2	119.43 (15)	C5—C6—C7	121.13 (15)
O2—C1—C2	115.95 (15)	C5—C6—H6	119.4
C1—C2—C3	115.09 (14)	C7—C6—H6	119.4
C1—C2—H2A	108.5	C8—C7—C6	118.76 (15)
C3—C2—H2A	108.5	C8—C7—H7	120.6

C1—C2—H2B	108.5	C6—C7—H7	120.6
C3—C2—H2B	108.5	C7—C8—C9	121.46 (16)
H2A—C2—H2B	107.5	C7—C8—C11	119.47 (13)
C5—C3—C4	110.37 (13)	C9—C8—C11	119.07 (14)
C5—C3—C2	111.71 (14)	C8—C9—C10	119.01 (16)
C4—C3—C2	111.18 (13)	C8—C9—H9	120.5
C5—C3—H3	107.8	C10—C9—H9	120.5
C4—C3—H3	107.8	C9—C10—C5	121.32 (16)
C2—C3—H3	107.8	C9—C10—H10	119.3
N1—C4—C3	112.15 (12)	C5—C10—H10	119.3
N1—C4—H4A	109.2		
O1—C1—C2—C3	-11.2 (2)	C10—C5—C6—C7	0.9 (3)
O2—C1—C2—C3	169.78 (14)	C3—C5—C6—C7	-179.16 (16)
C1—C2—C3—C5	-76.36 (17)	C5—C6—C7—C8	-1.0 (3)
C1—C2—C3—C4	159.86 (13)	C6—C7—C8—C9	0.1 (3)
C5—C3—C4—N1	165.95 (14)	C6—C7—C8—C11	-178.86 (14)
C2—C3—C4—N1	-69.51 (18)	C7—C8—C9—C10	0.8 (3)
C4—C3—C5—C10	-138.39 (16)	C11—C8—C9—C10	179.81 (16)
C2—C3—C5—C10	97.37 (19)	C8—C9—C10—C5	-0.9 (3)
C4—C3—C5—C6	41.7 (2)	C6—C5—C10—C9	0.0 (3)
C2—C3—C5—C6	-82.53 (19)	C3—C5—C10—C9	-179.86 (18)

## Hydrogen-bond geometry (Å, °)

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N1—H1A...O2 <sup>i</sup>	0.91 (3)	1.91 (3)	2.820 (2)	176 (3)
N1—H1B...O2 <sup>ii</sup>	0.93 (3)	1.80 (3)	2.7149 (19)	168 (2)
N1—H1C...O1 <sup>iii</sup>	0.85 (3)	1.93 (3)	2.775 (2)	174 (3)
N1—H1B...C11 <sup>iv</sup>	0.93 (3)	2.95 (2)	3.3192 (14)	105.3 (16)
C4—H4A...C11 <sup>v</sup>	0.99	2.73	3.6306 (19)	152
C4—H4B...C11 <sup>vi</sup>	0.99	2.81	3.5668 (19)	134

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