(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_{10}H_{12}ClNO_{2}, without any co-crystallized substances. In the enantiopure title compound, the molecules arrange themselves in an orthorhombic crystal structure (space group P_{21}2_{1}2_{1}). In the crystal, strong hydrogen bonds and C–H⋯Cl bonds interconnect the zwitterionic molecules.

1. Chemical context

(R)-Baclofen, an unnatural β-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).
H molecules. Parallel to the hydrogen bonding, T-shaped C—
parallel to (001), which yields a layered formation of baclofen
molecules, resulting in a two-dimensional network
parallel, additional hydrogen bonding occurs with neighboring
ammonium group of the neighboring baclofen molecule. In
H within the molecules [C9—H9

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—σ interactions occur along the layers of aromatic rings
within the molecules [C9—H9 . . . Cg1 ⅛ = 2.74 Å; C6—H6 . . .

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 range of racemic baclofenium co-crystal structures with various carboxylic acids were published by Báthori & Kilin-
kissa (2015; refcodes: LUSXAA, LUSXEE, LUSXII, LUSXUU, LUSXOO, LUSYAB) and Malapile et al. (2021; refcodes: LABJJL, LABJJI, LABJUX, LABKAE, LABKEI, LABKIM, LABKOS). Additionally, Gendron et al.
(2019; refcode: WONSIE01) presented the crystal structure of
(R)-baclofenium 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 1H NMR. Enanti-
opure (R)-baclofen was purchased from aber GmbH (Karls-
Crystalline structure of (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 Uiso(H) = 1.2Ueq(C) (methylene groups, aryl CH, methine groups). The structure was refined as a two-component inversion twin (BASF 0.04470).

### Table 2

| Crystal data                  | Chemical formula | C₁₀H₁₂ClNO₂ |
|-------------------------------|------------------|-------------|
| Mₐ                           |                  | 213.66      |
| Crystal system, space group   | Orthorhombic, P2₁,2₁,2₁ |
| Temperature (K)               | 123              |
| a, b, c (Å)                   | 6.8913 (5), 7.6898 (5), 19.7527 (14) |
| \( V (Å³) \)                  | 1046.75 (13)     |
| Z                             | 4                |
| Radiation type                | Mo Kα            |
| \( \mu \) (mm⁻¹)              | 0.34             |
| Crystal size (mm)             | 0.27 \( \times \) 0.19 \( \times \) 0.16 |

| Data collection               | Bruker D8 QUEST diffractometer |
|-------------------------------| Multi-scan (SADABS2016/2; SHELXTL, 2015) |
| \( T_{\text{min}}, T_{\text{max}} \) | 0.662, 0.747 |
| No. of measured, independent and observed \( | \( | F^2 | > 2σ(F) \) reflections | 0.042 |
| \( \sin(θ/λ)_{\text{max}} \) (Å⁻¹) | 0.756 |

Refinement

| \( R[F^2 > 2σ(F^2)] \), \( wR(F^2) \), \( S \) | 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_{max}, Δρ_{min} (e Å⁻³) | 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), SHELXTL (Sheldrick, 2015a), SHELXL2014/7 (Sheldrick, 2015b) and ORTEP-3 for Windows (Farrugia, 2012).

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**(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: *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

C₁₀H₁₂ClNO₂

Mr = 213.66

Orthorhombic, *P*2₁2₁2₁

*a* = 6.8913 (5) Å

*b* = 7.6898 (5) Å

*c* = 19.7527 (14) Å

*V* = 1046.75 (13) Å³

*Z* = 4

*F*(000) = 448

*D*ₐ = 1.356 Mg m⁻³

Mo *Kα* radiation, *λ* = 0.71073 Å

Cell parameters from 9871 reflections

θ = 2.8–33.0°

*µ* = 0.34 mm⁻¹

*T* = 123 K

Block, colourless

0.27 × 0.19 × 0.16 mm

Data collection

Bruker D8 QUEST
diffractometer

Radiation source: microfocus sealed tube

Detector resolution: 10.4167 pixels mm⁻¹

*θ* and *ω* 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*σ*(*I*)

*R*ₐₙ = 0.042

θₘᵢₙ = 32.5°, θₘᵢₙ = 2.1°

*h* = −10→10

*k* = −11→11

*l* = −29→29

Refinement

Refinement on *F*²

Least-squares matrix: full

*R*(*F*² > 2*σ*(*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

\[ w = 1/[σ^2(F_c^2) + (0.0372P)^2 + 0.2629P] \]

where *P* = (*F*² + 2*F*c²)/3

(Δ/σ)ₘₐₓ = 0.001

Δρₘₐₓ = 0.36 e Å⁻³

Δρₘᵢₙ = −0.30 e Å⁻³

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)

\[3.7985 \pm (0.0045) x + 6.4064 \pm (0.0034) y + 0.9085 \pm (0.0145) z = 5.2962 \pm (0.0104)\]

* -0.0030 \pm (0.0012) C5 \* -0.0067 \pm (0.0012) C6 \* 0.0039 \pm (0.0013) C7 \* 0.0025 \pm (0.0013) C8 \* -0.0062 \pm (0.0014) C9 \* 0.0035 \pm (0.0014) C10 2.7365 \pm (0.0020) H9 \_8 3.2353 \pm (0.0036) H6 \_9

Rms deviation of fitted atoms = 0.0046

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

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

* -0.0030 \pm (0.0012) C5 \_8 \* 0.0067 \pm (0.0012) C6 \_8 \* -0.0039 \pm (0.0013) C7 \_8 \* -0.0025 \pm (0.0014) C8 \_8 \* 0.0062 \pm (0.0014) C9 \_8 \* -0.0035 \pm (0.0014) C10 \_8

Rms deviation of fitted atoms = 0.0046

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

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

* -0.0030 \pm (0.0012) C5 \_6 \* 0.0067 \pm (0.0012) C6 \_6 \* -0.0039 \pm (0.0013) C7 \_6 \* -0.0025 \pm (0.0013) C8 \_6 \* 0.0062 \pm (0.0014) C9 \_6 \* -0.0035 \pm (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 (Å²) |
|---|---|---|---|
| x  | y  | z  | Uiso/Ueq |
|---|---|---|---|
| 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)* |
Atomic displacement parameters (Å²)

|   | $U_{11}$   | $U_{22}$   | $U_{33}$   | $U_{12}$   | $U_{13}$   | $U_{23}$   |
|---|------------|------------|------------|------------|------------|------------|
| Cl1 | 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)   | 0.0158 (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, °)

| bond          | length (Å) | bond     | length (Å) | bond     | length (Å) |
|---------------|------------|----------|------------|----------|------------|
| C1—Cl1        | 1.7445 (17) | C3—H3    | 1.0000     | C4—H4A   | 0.9900     |
| N1—C4         | 0.91 (3)   | C4—H4B   | 0.9900     | C5—C10   | 1.394 (2)  |
| N1—H1A        | 0.93 (3)   | C5—C6    | 1.396 (2)  | C6—C7    | 1.398 (2)  |
| N1—H1B        | 0.85 (3)   | C6—H6    | 0.9500     | C7—C8    | 1.383 (3)  |
| N1—H1C        | 1.247 (2)  | C7—H7    | 0.9500     | C8—C9    | 1.384 (2)  |
| O1—Cl1        | 1.268 (2)  | C8—H8    | 0.9500     | C9—C10   | 1.390 (2)  |
| O2—Cl2        | 1.526 (2)  | C9—H9    | 0.9500     | C10—H10  | 0.9500     |
| C1—Cl1        | 1.535 (2)  | C10—H10  | 0.9500     |           |            |
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—Cl1 119.47 (13)
C5—C3—C4 110.37 (13)  C9—C8—Cl1 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  C9—C10—C5 121.32 (16)
C4—C3—H3 107.8  C9—C10—H10 119.3
C2—C3—H3 107.8  C5—C10—H10 119.3
N1—C4—C3 112.15 (12)  C5—C10—H10 119.3
N1—C4—H4A 109.2

Hydrogen-bond geometry (Å, °)

| D—H···A  | D—H  | H···A  | D···A  | D—H···A |
|----------|-------|--------|--------|---------|
| N1—H1A···O2i | 0.91 (3) | 1.91 (3) | 2.820 (2) | 176 (3) |
| N1—H1B···O2ii | 0.93 (3) | 1.80 (3) | 2.7149 (19) | 168 (2) |
| N1—H1C···O1iii | 0.85 (3) | 1.93 (3) | 2.775 (2) | 174 (3) |
| N1—H1B···Cl1iv | 0.93 (3) | 2.95 (2) | 3.3192 (14) | 105.3 (16) |
| C4—H4A···Cl1v | 0.99 | 2.73 | 3.6306 (19) | 152 |
| C4—H4B···Cl1vi | 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.