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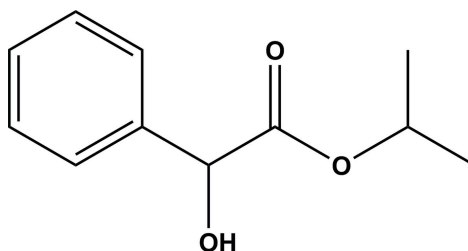
Crystal structure of isopropyl 2-hydroxy-2-phenylacetate: a pharmacopoeia reference standard

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The title compound, C₁₁H₁₄O₃, is used as a pharmacopoeia reference standard for determining impurities in the drug Pregabalin, used for the treatment of epilepsy and diabetic neuropathic pain. The molecule is far from being planar, with the dihedral angle between the planes of the aromatic ring and the carboxyl fragment (O—C=O) being 76.1 (6)°. The isopropyl substituent is located in a synperiplanar position relative to the C=O bond and is turned so that the C—O—C—H torsion angle is −43.7°. In the crystal, bifurcated O—H···(O,O) hydrogen bonds, enclosing R₁²(5) ring motifs, lead to the formation of chains propagating along the *c*-axis direction. Inversion-related chains are linked by the C—H···O hydrogen bonds, forming undulating layers lying parallel to the *bc* plane.

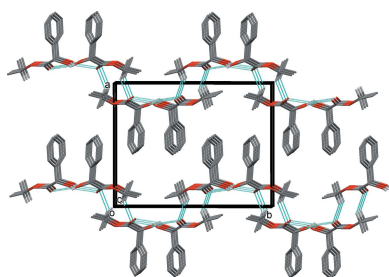
1. Chemical context

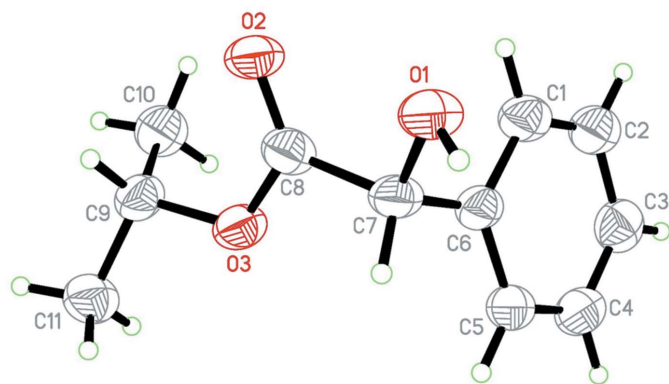
Pharmacopoeia reference standards are used widely for identification and quantitative determination of an active ingredient and undesirable impurity contents in many drug substances (European Pharmacopoeia Supplement, 2017). The title compound is used as the pharmacopoeia reference standard for the determining the level of impurities in Pregabalin (European Pharmacopoeia Supplement, 2016). This drug, sold under the trade mark 'Lyrica' (Silverman, 2016) is used for the treatment of epilepsy and diabetic neuropathic pains. Until now, its molecular and crystal structure were unknown.



2. Structural commentary

The molecular structure of the title compound is shown in Fig. 1. The hydroxyl group is situated in the *-sc* position relative to the C1—C6 endocyclic bond; torsion angle C1—C6—C7—O1 being −46.2 (6)°. The ester substituent at atom C7 has a *+sc*-orientation with respect to bond C1—C6 bond, with torsion angle C1—C6—C7—C8 = 71.2 (6)°, and it is turned in such way that the dihedral angle between the planes




Figure 1

The molecular structure of the title compound, showing the atom labelling. Displacement ellipsoids are drawn at the 50% probability level.

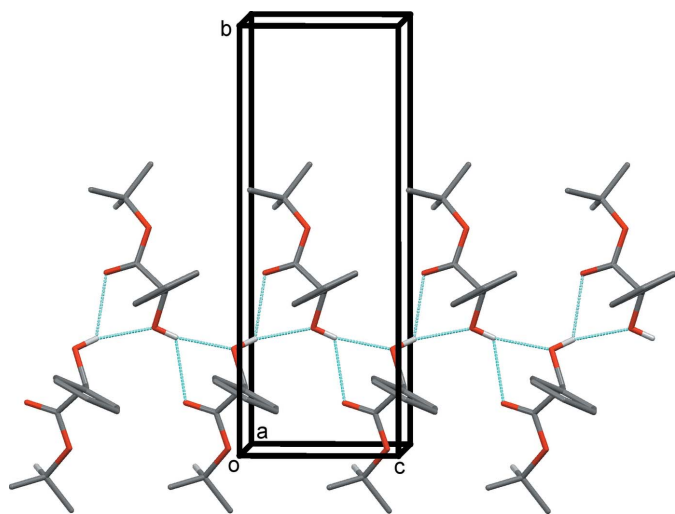
of the aromatic ring (C1–C6) and the carboxyl fragment (O3–C8=O2) is $76.1(6)^\circ$. The isopropyl substituent is located in a *syn*-periplanar position relative to the C8=O2 bond and is turned so that the C8–O3–C9–H9 torsion angle is -43.7° .

3. Supramolecular features

In the crystal, molecules are linked by bifurcated O–H···(O,O) hydrogen bonds, forming chains propagating along [001] and enclosing $R_1^2(5)$ ring motifs (Fig. 2 and Table 1). Neighbouring chains are linked by C–H···O hydrogen bonds, forming undulating layers lying parallel to the *bc* plane (Table 1 and Fig. 3).

4. Database survey

A search in the Cambridge Structural Database (Version 5.38, update February 2017; Groom *et al.*, 2016) for substructure


Figure 2

A partial view along the *a* axis of the crystal packing of the title compound, with the hydrogen bonds shown as dashed lines (see Table 1). For clarity, only H atoms H1O and H9 have been included.

Table 1

Hydrogen-bond geometry (Å, °).

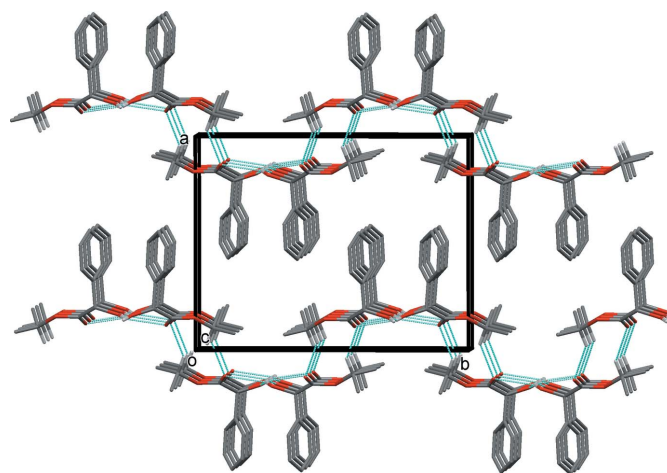
| <i>D</i> –H··· <i>A</i> | <i>D</i> –H | H··· <i>A</i> | <i>D</i> ··· <i>A</i> | <i>D</i> –H··· <i>A</i> |
|--------------------------|-------------|---------------|-----------------------|-------------------------|
| O1–H1O···O1 ⁱ | 0.83 (6) | 2.12 (5) | 2.903 (2) | 158 (5) |
| O1–H1O···O2 ⁱ | 0.83 (6) | 2.38 (6) | 2.930 (5) | 124 (5) |
| C9–H9···O2 ⁱⁱ | 1.00 | 2.53 | 3.379 (7) | 142 |

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

isopropyl 2-hydroxy-2-phenylacetate yielded three hits, *viz.* isopropyl 2,2-bis(4-bromophenyl)-2-hydroxyacetate (EFAFEY; Smith, 2012), 1-isopropyl 4-methyl 2-hydroxy-2-[2-[(methoxycarbonyl)amino]phenyl] succinate (MAZJAA; Suárez-Castillo *et al.*, 2012) and *syn*-isopropyl 2,3-dihydroxy-4-methyl-2-phenylpentanoate (MERRIL; Scholtis *et al.*, 2006). In the crystals of these three compounds, molecules are linked by pairs of O–H···O hydrogen bonds, forming inversion dimers.

5. Synthesis and crystallization

To a solution of (*2RS*)-2-hydroxy-2-phenylacetic acid (15.22 g, 0.1 mol; racemic mandelic acid) in 50 ml propan-2-ol was added 0.5 ml of concentrated H₂SO₄, and the mixture was refluxed for 5 h (Fig. 4). The excess of propan-2-ol was removed *in vacuo*. The reaction mixture was diluted with cold water and Na₂CO₃ was added to adjust the pH to 8. The solution was extracted with CH₂Cl₂ (3 × 30 ml). The organic layers were combined and the solvent extracted by distillation (at reduced pressure at the end). The residue was distilled *in vacuo*, and a fraction with a boiling point of 361–363 K/4 mm Hg was taken, and then left for several hours in the refrigerator at *ca* 278 K, giving finally the title compound as colourless needle-like crystals (yield of 17.67 g, 91%; m.p. 306.9–307.3 K).


Figure 3

A view along the *c* axis of the crystal packing of the title compound, with the hydrogen bonds shown as dashed lines (see Table 1). For clarity, only H atoms H1O and H9 have been included.

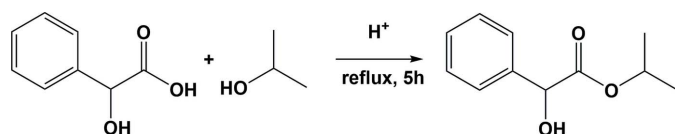


Figure 4
Reaction scheme

6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. All of the H atoms could all be located from difference-Fourier maps. The hydroxyl H atom was refined with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{O})$. The C-bound H atoms were included in calculated positions and treated as riding: C–H = 0.93–0.97 Å, with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C-methyl})$ and $1.2U_{\text{eq}}(\text{C})$ for other H atoms.

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Table 2

Experimental details.

| | |
|--|--|
| Crystal data | |
| Chemical formula | $\text{C}_{11}\text{H}_{14}\text{O}_3$ |
| M_r | 194.22 |
| Crystal system, space group | Monoclinic, $P2_1/c$ |
| Temperature (K) | 100 |
| a, b, c (Å) | 11.872 (3), 15.165 (4), 5.6079 (11) |
| β (°) | 91.41 (2) |
| V (Å ³) | 1009.3 (4) |
| Z | 4 |
| Radiation type | Mo $K\alpha$ |
| μ (mm ⁻¹) | 0.09 |
| Crystal size (mm) | 0.20 × 0.08 × 0.06 |
| Data collection | |
| Diffractometer | Agilent Xcalibur Sapphire3 |
| Absorption correction | Multi-scan (<i>CrysAlis RED</i> ; Agilent, 2012) |
| $T_{\text{min}}, T_{\text{max}}$ | 0.357, 1.000 |
| No. of measured, independent and observed [$I > 2\sigma(I)$] reflections | 5292, 1761, 922 |
| R_{int} | 0.101 |
| $(\sin \theta/\lambda)_{\text{max}}$ (Å ⁻¹) | 0.594 |
| Refinement | |
| $R[F^2 > 2\sigma(F^2)], wR(F^2), S$ | 0.090, 0.255, 1.03 |
| No. of reflections | 1761 |
| No. of parameters | 132 |
| 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) | 0.30, -0.26 |

Computer programs: *CrysAlis CCD* and *CrysAlis RED* (Agilent, 2012), *SHELXS2014* (Sheldrick, 2008), *SHELXL2014* (Sheldrick, 2015), *ORTEP-3 for Windows* (Farrugia, 2012), *Mercury* (Macrae *et al.*, 2008), *PLATON* (Spek, 2009) and *pubCIF* (Westrip, 2010).

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supporting information

Acta Cryst. (2017). E73, 771-773 [https://doi.org/10.1107/S2056989017005862]

Crystal structure of isopropyl 2-hydroxy-2-phenylacetate: a pharmacopoeia reference standard

Ivan Isaiev, Svitlana Shishkina, Igor Ukrainets and Elena Bevz

Computing details

Data collection: *CrysAlis CCD* (Agilent, 2012); cell refinement: *CrysAlis CCD* (Agilent, 2012); data reduction: *CrysAlis RED* (Agilent, 2012); program(s) used to solve structure: *SHELXS2014* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 2012) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXL2014* (Sheldrick, 2015), *PLATON* (Spek, 2009) and *publCIF* (Westrip, 2010).

Isopropyl 2-hydroxy-2-phenylacetate

Crystal data

$C_{11}H_{14}O_3$

$M_r = 194.22$

Monoclinic, $P2_1/c$

$a = 11.872$ (3) Å

$b = 15.165$ (4) Å

$c = 5.6079$ (11) Å

$\beta = 91.41$ (2)°

$V = 1009.3$ (4) Å³

$Z = 4$

$F(000) = 416$

$D_x = 1.278$ Mg m⁻³

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

Cell parameters from 403 reflections

$\theta = 4.3$ – 21.1 °

$\mu = 0.09$ mm⁻¹

$T = 100$ K

Needle, colourless

$0.20 \times 0.08 \times 0.06$ mm

Data collection

Agilent Xcalibur Sapphire3
diffractometer

Radiation source: Enhance (Mo) X-ray Source

Detector resolution: 16.1827 pixels mm⁻¹

ω -scan

Absorption correction: multi-scan
(*CrysAlis RED*; Agilent, 2012)

$T_{\min} = 0.357$, $T_{\max} = 1.000$

5292 measured reflections

1761 independent reflections

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

$R_{\text{int}} = 0.101$

$\theta_{\max} = 25.0$ °, $\theta_{\min} = 3.2$ °

$h = -14 \rightarrow 13$

$k = -17 \rightarrow 18$

$l = -5 \rightarrow 6$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.090$

$wR(F^2) = 0.255$

$S = 1.03$

1761 reflections

132 parameters

0 restraints

Primary atom site location: structure-invariant
direct methods

Secondary atom site location: difference Fourier
map

Hydrogen site location: difference Fourier map

H atoms treated by a mixture of independent
and constrained refinement

$$w = 1/[\sigma^2(F_o^2) + (0.1022P)^2]$$

where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$

$$\Delta\rho_{\max} = 0.30 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.26 \text{ e } \text{\AA}^{-3}$$

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)

| | <i>x</i> | <i>y</i> | <i>z</i> | $U_{\text{iso}}^*/U_{\text{eq}}$ |
|------|------------|------------|------------|----------------------------------|
| O1 | 0.8289 (3) | 0.2748 (2) | 0.4019 (6) | 0.0456 (10) |
| H1O | 0.845 (4) | 0.252 (4) | 0.534 (10) | 0.068* |
| O2 | 0.8740 (3) | 0.4013 (2) | 0.0966 (6) | 0.0476 (11) |
| O3 | 0.8375 (3) | 0.5068 (2) | 0.3667 (6) | 0.0455 (10) |
| C1 | 0.5984 (5) | 0.3361 (3) | 0.3003 (9) | 0.0443 (14) |
| H1 | 0.6314 | 0.3108 | 0.1638 | 0.053* |
| C2 | 0.4827 (5) | 0.3407 (3) | 0.3113 (9) | 0.0479 (14) |
| H2 | 0.4368 | 0.3171 | 0.1856 | 0.057* |
| C3 | 0.4332 (5) | 0.3801 (3) | 0.5079 (9) | 0.0492 (15) |
| H3 | 0.3535 | 0.3852 | 0.5142 | 0.059* |
| C4 | 0.4998 (5) | 0.4111 (3) | 0.6910 (9) | 0.0467 (14) |
| H4 | 0.4658 | 0.4367 | 0.8262 | 0.056* |
| C5 | 0.6154 (5) | 0.4061 (3) | 0.6831 (9) | 0.0419 (13) |
| H5 | 0.6600 | 0.4286 | 0.8122 | 0.050* |
| C6 | 0.6684 (4) | 0.3679 (3) | 0.4857 (8) | 0.0387 (13) |
| C7 | 0.7937 (4) | 0.3603 (3) | 0.4744 (8) | 0.0403 (13) |
| H7 | 0.8283 | 0.3743 | 0.6343 | 0.048* |
| C8 | 0.8399 (4) | 0.4230 (3) | 0.2895 (9) | 0.0416 (13) |
| C9 | 0.8869 (5) | 0.5744 (3) | 0.2113 (9) | 0.0452 (14) |
| H9 | 0.9599 | 0.5521 | 0.1494 | 0.054* |
| C10 | 0.8087 (5) | 0.5957 (4) | 0.0050 (9) | 0.0565 (16) |
| H10A | 0.7346 | 0.6120 | 0.0649 | 0.085* |
| H10B | 0.8009 | 0.5440 | -0.0989 | 0.085* |
| H10C | 0.8394 | 0.6451 | -0.0856 | 0.085* |
| C11 | 0.9094 (5) | 0.6527 (3) | 0.3724 (9) | 0.0528 (15) |
| H11A | 0.9489 | 0.6329 | 0.5183 | 0.079* |
| H11B | 0.8378 | 0.6802 | 0.4136 | 0.079* |
| H11C | 0.9562 | 0.6956 | 0.2897 | 0.079* |

Atomic displacement parameters (\AA^2)

| | U^{11} | U^{22} | U^{33} | U^{12} | U^{13} | U^{23} |
|----|-----------|-----------|-------------|--------------|-------------|--------------|
| O1 | 0.074 (3) | 0.030 (2) | 0.0327 (19) | 0.0060 (18) | 0.0021 (18) | 0.0017 (15) |
| O2 | 0.074 (3) | 0.040 (2) | 0.0298 (19) | -0.0036 (18) | 0.0078 (18) | -0.0039 (15) |
| O3 | 0.068 (3) | 0.035 (2) | 0.0337 (19) | -0.0031 (18) | 0.0107 (17) | -0.0007 (15) |
| C1 | 0.062 (4) | 0.039 (3) | 0.031 (3) | 0.000 (3) | -0.003 (2) | 0.003 (2) |

| | | | | | | |
|-----|-----------|-----------|-----------|------------|------------|------------|
| C2 | 0.064 (4) | 0.042 (3) | 0.038 (3) | -0.001 (3) | -0.003 (3) | 0.005 (2) |
| C3 | 0.055 (4) | 0.046 (3) | 0.047 (3) | -0.001 (3) | -0.001 (3) | 0.009 (3) |
| C4 | 0.063 (4) | 0.036 (3) | 0.041 (3) | 0.004 (3) | 0.010 (3) | 0.001 (2) |
| C5 | 0.065 (4) | 0.027 (3) | 0.033 (3) | -0.004 (3) | 0.001 (2) | 0.003 (2) |
| C6 | 0.055 (4) | 0.033 (3) | 0.029 (3) | -0.004 (2) | 0.003 (2) | 0.003 (2) |
| C7 | 0.060 (4) | 0.031 (3) | 0.030 (3) | -0.001 (3) | 0.003 (2) | -0.004 (2) |
| C8 | 0.055 (4) | 0.034 (3) | 0.036 (3) | -0.002 (3) | -0.003 (2) | -0.002 (2) |
| C9 | 0.061 (4) | 0.038 (3) | 0.037 (3) | -0.006 (3) | 0.012 (2) | 0.001 (2) |
| C10 | 0.081 (4) | 0.051 (4) | 0.038 (3) | -0.015 (3) | 0.001 (3) | 0.010 (3) |
| C11 | 0.074 (4) | 0.039 (3) | 0.045 (3) | -0.008 (3) | 0.002 (3) | -0.001 (2) |

Geometric parameters (Å, °)

| | | | |
|-------------|------------|--------------|------------|
| O1—C7 | 1.424 (6) | C3—C4 | 1.364 (8) |
| O2—C8 | 1.211 (5) | C4—C5 | 1.376 (8) |
| O3—C8 | 1.343 (6) | C5—C6 | 1.412 (7) |
| O3—C9 | 1.476 (6) | C6—C7 | 1.495 (7) |
| C1—C2 | 1.378 (7) | C7—C8 | 1.519 (7) |
| C1—C6 | 1.401 (7) | C9—C10 | 1.501 (8) |
| C2—C3 | 1.397 (7) | C9—C11 | 1.512 (7) |
| C8—O3—C9 | 117.1 (4) | O1—C7—C6 | 112.4 (4) |
| C2—C1—C6 | 121.6 (5) | O1—C7—C8 | 105.2 (4) |
| C1—C2—C3 | 119.8 (5) | C6—C7—C8 | 110.9 (4) |
| C4—C3—C2 | 119.6 (6) | O2—C8—O3 | 123.8 (5) |
| C3—C4—C5 | 121.1 (5) | O2—C8—C7 | 125.0 (4) |
| C4—C5—C6 | 120.8 (5) | O3—C8—C7 | 111.2 (4) |
| C1—C6—C5 | 117.0 (5) | O3—C9—C10 | 111.0 (4) |
| C1—C6—C7 | 121.0 (5) | O3—C9—C11 | 105.0 (4) |
| C5—C6—C7 | 121.9 (5) | C10—C9—C11 | 112.9 (5) |
| C6—C1—C2—C3 | 1.9 (8) | C1—C6—C7—C8 | 71.2 (6) |
| C1—C2—C3—C4 | -2.1 (8) | C5—C6—C7—C8 | -109.5 (5) |
| C2—C3—C4—C5 | 1.4 (8) | C9—O3—C8—O2 | -4.3 (8) |
| C3—C4—C5—C6 | -0.5 (7) | C9—O3—C8—C7 | 176.1 (4) |
| C2—C1—C6—C5 | -0.9 (7) | O1—C7—C8—O2 | 15.9 (7) |
| C2—C1—C6—C7 | 178.4 (5) | C6—C7—C8—O2 | -105.9 (6) |
| C4—C5—C6—C1 | 0.2 (7) | O1—C7—C8—O3 | -164.5 (4) |
| C4—C5—C6—C7 | -179.1 (4) | C6—C7—C8—O3 | 73.7 (5) |
| C1—C6—C7—O1 | -46.2 (6) | C8—O3—C9—C10 | 76.8 (6) |
| C5—C6—C7—O1 | 133.0 (5) | C8—O3—C9—C11 | -160.9 (5) |

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—H1O \cdots O1 ⁱ | 0.83 (6) | 2.12 (5) | 2.903 (2) | 158 (5) |

| | | | | |
|--------------------------|----------|----------|-----------|---------|
| O1—H1O···O2 ⁱ | 0.83 (6) | 2.38 (6) | 2.930 (5) | 124 (5) |
| C9—H9···O2 ⁱⁱ | 1.00 | 2.53 | 3.379 (7) | 142 |

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