Intermolecular O—H···O hydrogen bonding in the three independent molecules of 
(2S)-3-(4-hydroxyphenyl)-2-(1-oxoisooindolin-2-yl)propanoic acid

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Intermolecular $\text{O} - \text{H} \cdots \text{O}$ hydrogen bonding in the three independent molecules of (2S)-3-(4-hydroxy-phenyl)-2-(1-oxoisindolin-2-yl)-propanoic acid

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The title compound, C$_{17}$H$_{15}$NO$_4$, derived from l-tyrosine, crystallizes with three independent molecules which differ in the conformation of the asymmetric unit: the N—C—C—C$_{\text{ipso}}$ torsion angles are $-71.7(5)$, $-63.6(6)$ and $-52.5(5)^\circ$, respectively. Deformations in the phenol ring hydroxy O—H sets the primary hydrogen-bonding systems assemble with graph ipso the conformation of the asymmetric unit: the N—C—C—C$_{\text{ipso}}$ combination with C—H interactions. Phenol crystallizes with three independent molecules in the asymmetric unit and intermolecular hydrogen-bonding environments. Intermolecular O—H$\cdots$O hydrogen bonds, with O—O distances in the range 2.607 (4)—2.809 (4) Å, are present in combination with C—H$\cdots$O and C—H$\cdots$π$_{\text{arom}}$ interactions. The primary hydrogen-bonding systems assemble with graph sets $R_3^2(8)$ and $R_7^2(22)$.

Comment

Phenol and related monosubstituted aromatic compounds have attracted considerable interest in gas-phase electron diffraction experiments and ab initio calculations in order to probe bond-angle deformations arising from electronic effects due to the nature of the phenyl ring substituent (Portalone et al., 1992; Ramondo et al., 1995). These investigations facilitate comparison with microwave and solid-state studies, although the experimental geometries in the ‘free’ molecule and crystal structure usually differ due to solid-state intra- and intermolecular interactions. Phenol crystallizes with three independent molecules in the asymmetric unit and intermolecular O—H$\cdots$O hydrogen bonds form a helical array of approximate $3_1$ symmetry (Zavodnik et al., 1987). Many hydrocarbons containing a single OH substituent, e.g. menthol (Bombicz et al., 1999) and 5α-dinosteran-29-ol (Brock et al., 1994), crystallize with more than one molecule in the asymmetric unit or in space groups with three- or fourfold axes in the absence of other significant interactions.

Amino acid derivatives are a major class of chiral compounds with a wide range of applications in medicinal chemistry. Tyrosine, H$_2$N(H)C$^*(R)$COOH (R is 4-hydroxy-benzyl) and related compounds (Brykjadal et al., 1974; Dahouei et al., 1999) have attracted considerable interest in biological studies (Kawai et al., 1999). The title compound, (I), which contains the isoindolyl group (Allin et al., 1996; McNab et al., 1997; Takahashi & Hatanaka, 1997) is synthesized from l-tyrosine and forms part of a study of the hydrogen-bonding interactions in a phthalimidine series (Brady et al., 1998; Gallagher & Murphy, 1999; Gallagher & Brady, 2000; Gallagher et al., 2000).

![Diagram](image)

Compound (I) crystallizes in space group $P2_1_2_1_2_1$ (No. 19) with three independent molecules, A, B and C, in the asymmetric unit which differ in conformation but retain the same configuration (S) at the (H)C$^*(R)$COOH chiral centre. The absolute structure can be deduced from the known absolute configuration of l-tyrosine used in the synthesis. Views of the three independent molecules, with the atomic numbering schemes, are given in Fig. 1 and selected dimensions are in Table 1.

The r.m.s. deviations for the superposition of the non-H atoms of any pair of molecules in (I) using PLATON (Spek, 1998) are 0.28 (A/B pair), 1.05 (A/C pair) and 0.56 Å (B/C pair). Crystal structures with several molecules present in the asymmetric unit are relatively common (Gallagher et al., 1998). There are ca 45 molecules in the Cambridge Structural Database (Allen & Kennard, 1993) with $Z = 12$ or more molecules in the asymmetric unit in space group $P2_1_2_1_2_1$, of which N-acyetyl-L-leucine-l-tyrosine methyl ester is a relevant example (Karle & Flippin-Anderson, 1989).

The bond lengths and angles in the five-membered rings of the three independent molecules of (I) are similar to those reported previously (McNab et al., 1997; Kundu et al., 1999; Mukherjee et al., 2000; Gallagher & Brady, 2000) and in agreement with expected values (Orpen et al., 1994). The angles between the five- and six-membered rings of the isoindole systems are 0.96 (12), 2.87 (8) and 1.01 (7)$^\circ$ in molecules A, B and C, respectively, and the maximum deviation from planarity for an atom in either ring plane is 0.021 (3) Å for N1A in A, 0.021 (3) Å for C3B in B and 0.015 (3) Å for C10C in C. The carbonyl O3N atom is 0.067 (7) Å from the C$_{\text{N}}$ ring plane in A, 0.113 (7) Å in B and 0.020 (7) Å in C (n is A, B or C). Pyramidalization occurs, with N11n 0.118 (4), 0.121 (5) and 0.070 (5) Å from the C2n/C3n/C10n planes, and these values are comparable with those of 0.129 (2) Å in a D$_{2h}$-phenylalanine derivative (Brady et al., 1998) and 0.079 (2) Å in a D$_{2h}$-meta-tyrosine derivative (Gallagher & Murphy, 1999). The carboxylic acid group CO$_2$ is almost perpendicular to the C$_{\text{N}}$ ring plane [79.14 (18), 83.3 (2) and 83.0 (2)$^\circ$ in A, B and C, respectively] and the phenyl ring [79.14 (13), 68.39 (14) and 82.5 (2)$^\circ$ in A, B and C, respectively]. Geometrical
differences for O$_2$n—C$_{1n}$—C$_{2n}$—C$_{21n}$, with torsion angles of 132.3 (5), 113.0 (6) and 128.3 (6)$^\circ$, respectively, are due to the distinct local environments of A, B and C.

Intermolecular hydrogen bonding involving the phenol residues can be evidenced by analysis of the O$_{4n}$—C$_{14n}$—C$_{13n}$—O$_{2n}$ bond angles, which vary as 116.5 (4)/123.9 (4), 121.7 (5)/118.1 (4) and 122.4 (5)/118.6 (5)$^\circ$ in A, B and C, respectively, with the larger angles cisoid to their O—H bonds, reflecting the different demands of O—H⋯O hydrogen bonding at each O—H site (the H$_{4n}$—O$_{4n}$—C$_{14n}$—C$_{13n}$ angles are 169, 8 and 20$^\circ$). This deformation is also present in the meta-tyrosine derivative, where a 5$^\circ$ difference in the O—C—C$_{ortho}$$_{ortho}$ angles [117.2 (2)/122.2 (2)$^\circ$] results from strong intermolecular hydrogen bonding [the C—C angle is 118.9 (2)$^\circ$; Gallagher & Murphy, 1999]. In related alkyl—OH derivatives, the donor/acceptor ability of the alkyl—OH group in O—H⋯O intermolecular hydrogen bonding can be noted from the O—C—C angle in the chiral and racemic threonine forms [110.5 (2) and 105.52 (11)$^\circ$, respectively; Gallagher et al., 2000]. In tris(4-methoxy-phenyl)methanol, MeO—C—C$_{ortho}$$_{ortho}$ angles of 115.1 (3)/125.5 (3)$^\circ$ cisoid/transoid to a methoxy group are distinct (Ferguson et al., 1996) and similar in magnitude to the values of 116/124$^\circ$ reported in the electron diffraction study of anisole, C$_6$H$_5$OCH$_3$ (Seip & Seip, 1973).

The hydrogen bonding in (I) consists primarily of O—H⋯O interactions, with some C—H⋯O and C—H⋯π arene interactions, as detailed in Table 2. The intermolecular interactions are dominated by the O—H⋯O hydrogen bonds with all six O—H groups participating; O⋯O distances range from 2.607 (4) Å (O$_{4B}$⋯O$_{3C}$) to 2.809 (4) Å (O$_{4C}$⋯O$_{3B}$). The crystal structure can be considered as a molecular association of B and C through two O$_{phenol}$—H⋯O=O$_{indole}$ hydrogen bonds to form a dimer, with graph set $R_2^\infty(22)$ (Fig. 2). Mole-

**Figure 1**
Views of molecules A (top), B and C (bottom) of (I) with the atomic numbering schemes. Displacement ellipsoids are drawn at the 30% probability level. Suffixes have been omitted from the C-atom labels for clarity.

**Figure 2**
A view of the intermolecular interactions in (I), showing the interaction-intense $R_2^\infty(8)$ motif involving molecules A, B and C.
The title compound was prepared by the overnight reaction of l-tyrosine and o-phenaldehyde in refluxing acetonitrile (Allin et al., 1996). Filtration of the hot solution and subsequent slow cooling of the filtrate allowed the isolation of large colourless crystals of (I) [mp. 503–505 K (uncorrected)]. IR (KBr, \( \nu_{\text{cm}^{-1}} \)): 3339; (\( \nu_{\text{cm}^{-1}} \)-water): 1760, 1745, 1689; 1H NMR (400 MHz, \( \delta \), ppm): 3.06 (m, 2H, \( \text{CH}_{2} \)), 4.43 (br, s, 2H, \( \text{CH}_{2} \)), 5.02 (m, 1H, CH), 6.59–7.02 (m, 4H, \( \text{para-CH}_{3} \)), 7.35–7.39, 7.44–7.48, 7.49–7.55, 7.56–7.58 (m, 4H, \( \text{C}_{6}\text{H}_{5} \)), 9.20 (s, 1H, OH), 10.48 (s, 1H, OH).
Table 2
Hydrogen-bonding geometry (Å, °).

<table>
<thead>
<tr>
<th>D—H···A</th>
<th>D—H</th>
<th>H···A</th>
<th>D···A</th>
<th>D—H···A</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1A—H1A···O3A'</td>
<td>0.82</td>
<td>1.84</td>
<td>2.652 (4)</td>
<td>169</td>
</tr>
<tr>
<td>O1B—H1B···O3A'</td>
<td>0.82</td>
<td>2.00</td>
<td>2.716 (5)</td>
<td>147</td>
</tr>
<tr>
<td>O1C—H1C···O3B'</td>
<td>0.82</td>
<td>1.89</td>
<td>2.675 (5)</td>
<td>159</td>
</tr>
<tr>
<td>O4A—H4A···O1B</td>
<td>0.82</td>
<td>1.94</td>
<td>2.753 (5)</td>
<td>170</td>
</tr>
<tr>
<td>O4B—H4B···O3C</td>
<td>0.82</td>
<td>1.85</td>
<td>2.697 (4)</td>
<td>152</td>
</tr>
<tr>
<td>O4C—H4C···O3B</td>
<td>0.82</td>
<td>2.00</td>
<td>2.809 (4)</td>
<td>171</td>
</tr>
<tr>
<td>C10C—H10E···O1A''</td>
<td>0.97</td>
<td>2.50</td>
<td>3.284 (5)</td>
<td>138</td>
</tr>
<tr>
<td>C15A—H15A···O3C</td>
<td>0.93</td>
<td>2.54</td>
<td>3.425 (6)</td>
<td>160</td>
</tr>
<tr>
<td>C12B—H12B···O4A''</td>
<td>0.93</td>
<td>2.66</td>
<td>3.473 (5)</td>
<td>147</td>
</tr>
<tr>
<td>C15C—H15C···O2B*</td>
<td>0.93</td>
<td>2.65</td>
<td>3.569 (7)</td>
<td>173</td>
</tr>
<tr>
<td>CS4—H5A···Cg1v</td>
<td>0.93</td>
<td>2.86</td>
<td>3.716 (5)</td>
<td>153</td>
</tr>
</tbody>
</table>

Symmetry codes: (i) x − 1/4, y, z; (ii) x − 1/4, y, 1 − z; (iii) −1/2 − x, −y, 1/2 + z; (iv) −x, y − 1/2 − z; (v) −x, y − 1/2 − z; (vi) 1/2 − x, −y, 1/2 + z;

as a supplementary diagram. Refinement of the full data set with all Friedel reflections not unexpectedly gave an inconsistent Flack (1983) parameter [0.6 (16)] for this light-atom structure; for the final refinement, the Friedel reflections were merged.

Data collection: CAD-4-PC Software (Enraf–Nonius, 1992); cell refinement: CAD-4-PC Software; data reduction: DATR2D in NRCVAX96 (Gabe et al., 1989); program(s) used to solve structure: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: NRCVAX96 and SHELXL97; molecular graphics: ORTEP III (Burnett & Johnson, 1996), ORTEX (McArdle, 1995) and PLATON; software used to prepare material for publication: NRCVAX96, SHELXL97 and PREP8 (Ferguson, 1998).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1414). An additional figure is also available. Services for accessing these data are described at the back of the journal.

References