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L-Phenylalanyl-L-isoleucine 0.88-hydrate

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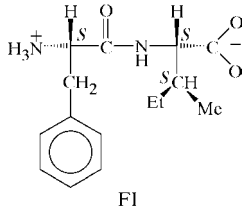
The asymmetric unit in the crystal structure of the title compound, $C_{15}H_{22}N_2O_3\cdot0.88H_2O$, contains two peptide molecules with completely different conformations. The structure is divided into hydrophobic and hydrophilic layers, with channels of water molecules at the layer interface.

Comment

A systematic survey has revealed that dipeptides constructed from two amino acid residues with large hydrophobic side chains may give porous structures with hydrophilic inner surfaces. This structural family has been referred to as the FF-class, after L-phenylalanyl-L-phenylalanine (FF; Görbitz, 2001), and includes L-leucyl-L-leucine (LL), L-leucyl-L-phenylalanine (LF), L-phenylalanyl-L-leucine (FL; Görbitz, 2001) and L-isoleucyl-L-leucine (IL; Görbitz, 2004*b*), as well as L-tryptophylglycine (WG; Emge *et al.*, 2000; Birkedal *et al.*, 2002). The size of the channel ranges from a rectangular 2.5 × 6.0 Å for LL, LF and IL, to circular with diameter 10 Å for FF. All peptide molecules which form this type of nanotube occur in unusual folded conformations that place both side chains on the same side of the plane defined by the peptide bond. The associated absolute values for the torsion angle θ ($C_1^\beta-C_1^\alpha\cdots C_2^\alpha-C_2^\beta$) are thus close to 0°. Conformations with low θ values are also observed for L-Ile-L-Phe (IF; Görbitz, 2004*a*), L-valyl-L-phenylalanine (VF, orthorhombic modification; Görbitz, 2002) and L-alanyl-L-tryptophane (AW; Emge *et al.*, 2000), but these three structures are divided into hydrophobic



FI

and hydrophilic layers, the latter including one (AW) or two (IF and VF) water molecules per peptide molecule. Against this background, the crystal structure of L-phenylalanyl-L-isoleucine, denoted FI, as the 0.88-hydrate is presented here.

The crystal structure of FI is depicted in Fig. 1 and selected torsion angles are given in Table 1. Just as for LL, LF, FL and IL, there are two peptide molecules in the asymmetric unit, *A* and *B*, but unlike the other four peptide structures the two molecules are completely different. Molecule *B* has the typical 'nanotube conformation', with θ (C2*B*—C1*B*···C10*B*—C11*B*) = −0.65 (19)° and C9*B*—N2*B*—C10*B*—C15*B* = 52.3 (2)°, while molecule *A* has a more elongated conformation, with θ (C2*A*—C1*A*···C10*A*—C11*A*) = −95.83 (17)° and C9*A*—N2*A*—C10*A*—C15*A* = −83.2 (2)°, which is stabilized by a weak intramolecular C4*A*—H41*A*···O2*A* hydrogen bond between the benzene ring and the carboxylate group (Table 2). The resulting structure (Fig. 2) is divided into wave-shaped hydrophobic and hydrophilic layers, but nevertheless incorporates obvious water-filled channels, although these are significantly reduced in size (to 1.8 × 4.0 Å) compared with the FF-class. The channels have partly hydrophilic and partly hydrophobic inner surfaces.

The L-Phe side chain in FI is in a *gauche*+ orientation for molecule *A* and in a *trans* orientation for molecule *B*. Both Ile side chains have the common *gauche*−/*trans*,*gauche*− conformation (for N2—C10—C11—C13/C12 and C10—C11—C13—C14), but are twisted about 30° away from the ideal staggered orientation at C10—C11 for molecule *B* to relieve what would have been a very close contact with the neighbouring molecule *B* along the *b* axis, to which it is related by the twofold screw (Fig. 2). The resulting intermolecular C14*B*—H20*B*···C8*B*($1-x,\ y-\frac{1}{2},\ -z$) interaction has a normal H···C distance of 2.97 Å. The twist also leads to additional intra- and intermolecular contacts (H···C ≥ 3.01 Å) involving the peptide *B* molecules.

Hydrogen bonds with O-atom acceptors are listed in Table 2, including three with C(π)—H donors (one intramolecular, see above). There are several similarities with the set of interactions found in the structures of the FF-class, and in

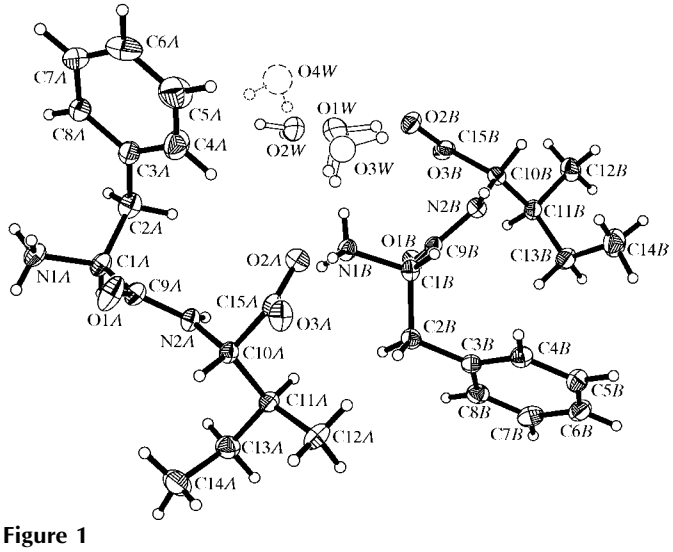


Figure 1
The molecular structure of FI, showing the atom-numbering scheme. Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as small spheres of arbitrary size. The drawing styles used for the water molecules reflect their occupancies: 0.709 (4) for O1*W* and O2*W*, 0.291 (4) for O3*W*, and 0.054 (4) for O4*W*.

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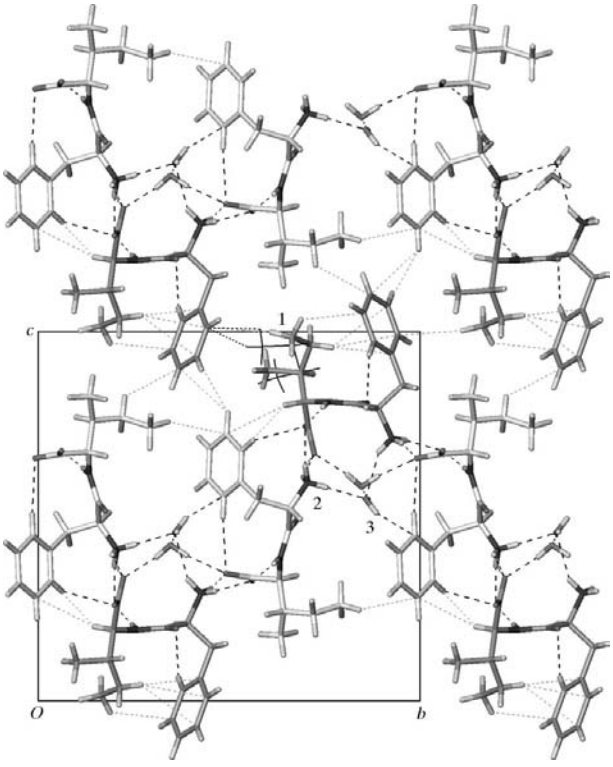

Figure 2
The molecular packing and unit cell of FI, viewed along the *a* axis. Water molecules with low occupancy have been omitted. Peptide molecule *B* is shown in a darker tone. Hydrogen bonds (Table 2) are shown as black dashed lines. C—H···C contacts with H···C distances of less than 3.2 Å and C—H···C angles greater than 120° are indicated by grey dashed lines. The line drawing shows the Ile side chain in a forced perfectly staggered orientation. Two of the very short C—H···C contacts (2.39 and 2.48 Å) are shown as black dotted lines. For a description of 1 (H20*B*), 2 and 3, see *Comment* text.

particular with LL, LF (Görbitz, 2001) and IL (Görbitz, 2004*b*), including the presence of a hydrogen bond between the two water molecules in the asymmetric unit, with atom O2*W* as the donor. The only major difference concerns the second H atom of O2*W*, which is donated to a carboxylate group in the three FF-class structures. In the FI structure, access to the corresponding carboxylate group (of molecule *B*) is blocked by the amino group of molecule *A* (2 in Fig. 2), and the pertinent H22*W* atom (3 in Fig. 2) points instead in the opposite direction, where it is accepted by the aromatic ring of the molecule *A* L-Phe side chain.

An L-leucine residue in a dipeptide can often be interchanged with an L-phenylalanine residue without major modifications to the crystal structure. An equivalent observation has been made for L-valine and L-isoleucine residues (Görbitz, 2004*c*). The FI structure, however, is not related to either L-leucyl-L-isoleucine (Görbitz, 2004*c*) or L-phenylalanyl-L-valine (Görbitz, 2000).

Experimental

The title compound was obtained from Bachem. Crystals were grown by rapid evaporation of an aqueous solution at elevated temperature (333 K), the same technique that was used for crystallizing compounds in the FF-class (Görbitz, 2001, 2004*b*).

Crystal data

$C_{15}H_{22}N_2O_3\cdot0.88H_2O$
M_r = 294.24
Monoclinic, $P2_1$
a = 5.5634 (3) Å
b = 17.0558 (9) Å
c = 16.6859 (9) Å
β = 96.7440 (10)°
V = 1572.34 (15) Å^3
Z = 4
D_x = 1.243 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 6894 reflections
θ = 1.7–27.1°
μ = 0.09 mm^{-1}
T = 105 (2) K
Needle, colourless
0.75 × 0.15 × 0.12 mm

Data collection

Siemens SMART CCD area-detector diffractometer
ω rotation scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.899, T_{max} = 0.989
10 060 measured reflections
3570 independent reflections
3378 reflections with $I > 2\sigma(I)$
R_{int} = 0.025
θ_{max} = 27.1°
$h = -7 \rightarrow 7$
$k = -13 \rightarrow 21$
$l = -21 \rightarrow 20$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.029
$wR(F^2)$ = 0.077
S = 1.00
3570 reflections
434 parameters
H atoms treated by a mixture of restrained and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0431P)^2 + 0.3167P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}

Table 1
Selected torsion angles (°).

	Molecule *A*	Molecule *B*
N1—C1—C9—N2	164.38 (17)	114.94 (17)
C1—C9—N2—C10	−178.54 (16)	−171.42 (15)
C9—N2—C10—C15	−83.2 (2)	52.3 (2)
N2—C10—C15—O2	−41.0 (2)	44.7 (2)
N1—C1—C2—C3	57.2 (2)	173.66 (15)
C1—C2—C3—C4	84.8 (2)	64.3 (2)
C1—C2—C3—C8	−92.7 (2)	−116.06 (19)
N2—C10—C11—C12	175.79 (16)	−152.49 (16)
N2—C10—C11—C13	−57.9 (2)	−26.6 (2)
C10—C11—C13—C14	−54.3 (2)	−66.3 (2)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1*A*—H1*A*···O2*W*^{i}	0.85 (3)	1.94 (3)	2.765 (3)	163 (3)
N1*A*—H2*A*···O2*B*^{i}	0.89 (2)	2.04 (3)	2.839 (2)	150 (2)
N1*A*—H3*A*···O3*B*^{ii}	0.91 (3)	1.92 (3)	2.799 (2)	162 (2)
N2*A*—H4*A*···O3*A*^{iii}	0.90 (2)	2.03 (3)	2.908 (2)	167 (2)
C1*A*—H11*A*···O1*A*^{iii}	1.02 (2)	2.46 (2)	3.290 (2)	138.3 (18)
C4*A*—H41*A*···O2*A*	0.95	2.64	3.560 (3)	165
C8*A*—H81*A*···O3*B*^{ii}	0.95	2.51	3.322 (3)	143
N1*B*—H1*B*···O2*W*	0.86 (3)	2.20 (3)	2.969 (3)	149 (2)
N1*B*—H2*B*···O3*A*^{iii}	0.89 (2)	1.91 (3)	2.754 (2)	157 (2)
N1*B*—H3*B*···O2*A*	0.90 (3)	1.80 (3)	2.691 (2)	170 (2)
N2*B*—H4*B*···O3*B*^{iv}	0.85 (2)	2.00 (3)	2.831 (2)	165 (2)
C1*B*—H11*B*···O1*B*^{iv}	0.98 (2)	2.40 (2)	3.263 (2)	146.2 (19)
C4*B*—H41*B*···O1*B*^{iv}	0.95	2.62	3.521 (2)	158
O1*W*—H11*W*···O2*B*^{iv}	0.85 (3)	1.85 (3)	2.694 (3)	172 (4)
O1*W*—H12*W*···O2*A*	0.85 (3)	1.98 (3)	2.818 (3)	167 (5)
O2*W*—H21*W*···O1*W*^{iii}	0.85 (3)	1.91 (3)	2.703 (4)	154 (3)
O2*W*—H22*W*···C4*A*	0.85 (3)	2.49 (3)	3.282 (4)	156 (4)

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

Heavy atoms other than the low-occupancy water atoms O3*W* and O4*W* were refined anisotropically. Positional parameters were refined

for H atoms involved in short hydrogen bonds (H···O < 2.50 Å), with water-molecule geometries being restrained by DFIX 0.85 0.01 commands for the O—H distances and DFIX 1.35 0.01 commands for the H···H distances (giving H—O—H angles close to 105°). H atoms bonded to O3*W* and O4*W* were introduced in positions giving the best possible hydrogen-bonding geometry (with O—H = 0.85 Å) and refined as riding. The remaining H atoms were positioned geometrically and refined with constraints to keep all C—H distances and C—C—H angles on one C atom the same. U_{iso}(H) values were set at $1.2U_{eq}$(C) or $1.5U_{eq}$(N, C_{Me} and O). In the absence of significant anomalous scattering effects, 1585 Friedel pairs were merged. The absolute configuration was known for the purchased material.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT-Plus* (Bruker, 2001); data reduction: *SAINT-Plus*; program(s) used to solve structure: *SHELXTL* (Bruker, 2000); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA1081). Services for accessing these data are described at the back of the journal.

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