

L-Isoleucyl-L-phenylalanine dihydrate

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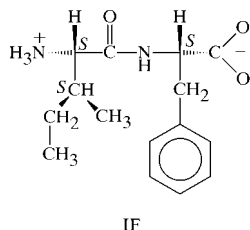
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The structure of the title compound, $C_{15}H_{22}N_2O_3 \cdot 2H_2O$, was derived from data collected on a very thin twinned needle. The peptide molecule is in a rare conformation normally associated with hydrophobic dipeptides that form nanotubes. Nevertheless, the present structure is divided into hydrophobic and hydrophilic layers.

Comment

L-Ile-L-Phe (IF) has been investigated as part of a systematic survey of dipeptides constructed from the five hydrophobic amino acid residues L-Ala, L-Val, L-Ile, L-Leu and L-Phe (Görbitz, 2003, and references therein). The peptide crystallized as a dihydrate and the molecular structure is shown in Fig. 1. While the vast majority of dipeptides have main-chain conformations in which one side chain is above the peptide plane and one is below, the opposite situation is observed for IF. The property of having both side chains on the same side of the peptide plane gives absolute values for the $C_1^\beta-C_1^\alpha \cdots C_2^\alpha-C_2^\beta$ (θ) torsion angle of less than 90° . For IF, the $C_2-C_1 \cdots C_7-C_8$ angle is $16.0(5)^\circ$. The C_1-C_4 and $C_1-C_6-O_1-N_2-C_7$ chains are both planar and form a dihedral angle [$69.0(3)^\circ$] that is not significantly different from that formed by the latter chain and the plane of the phenyl ring [$69.6(1)^\circ$]. The dihedral angle formed by the C_1-C_4 chain and the phenyl ring is $29.5(3)^\circ$.



The limited number of dipeptides with conformations similar to IF usually have two large hydrophobic side chains (Phe, Leu or Ile) and form nanotubular structures with hydrophilic channels. This group has been called the FF class after L-Phe-L-Phe and includes L-Leu-L-Leu, L-Leu-L-Phe (LF), L-Phe-L-Leu (Görbitz, 2001) and L-Ile-L-Leu (Görbitz, 2004). L-Trp-Gly (Emge *et al.*, 2000; Birkedal *et al.*, 2002) is an

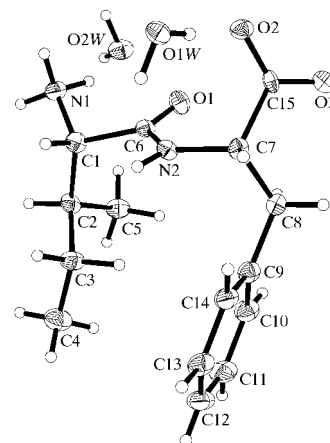


Figure 1

The molecular structure of $IF \cdot 2H_2O$. Displacement ellipsoids are shown at the 50% probability level and H atoms are drawn as spheres of arbitrary size.

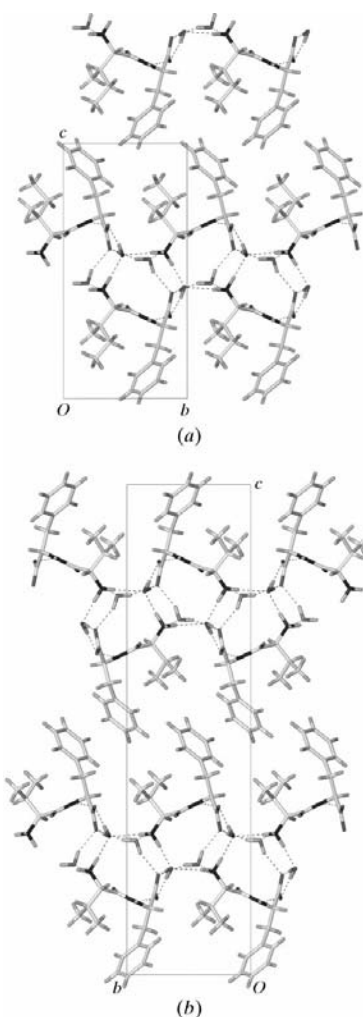
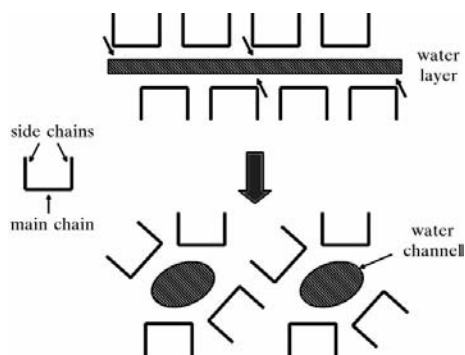


Figure 2

The unit cell and crystal packing of (a) $IF \cdot 2H_2O$ and (b) VF (Görbitz, 2002). Each structure is viewed along the a axis. Hydrogen bonds are shown as dashed lines.

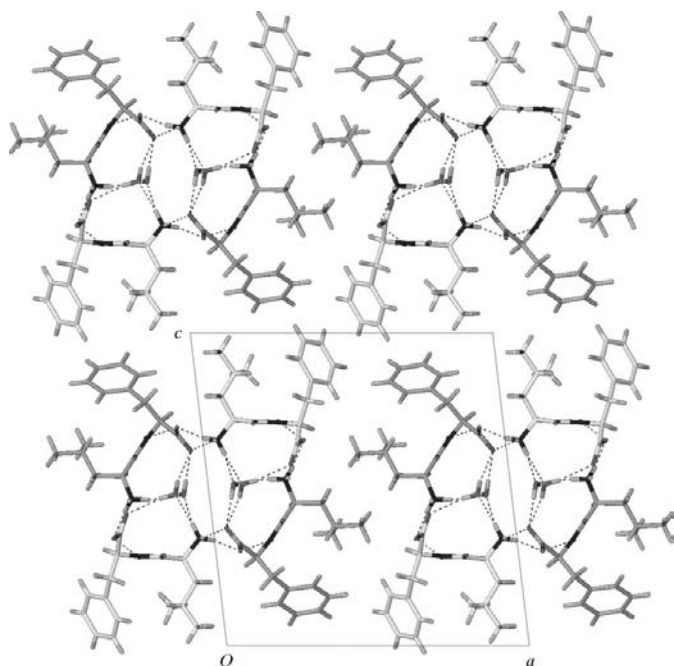
unexpected last member of the FF class. The distinctly hydrophobic title compound does not form channels, however, but rather hydrophobic and hydrophilic layers in exactly


Figure 3

A schematic illustration of the difference between the crystal structures of VF and IF and the FF class (Görbitz, 2001). Starting with VF/IF (top), every second peptide facing a water layer can undergo a rotation of $\sim 60^\circ$, as indicated by the small arrows, to yield the tubular patterns of LL/LF, with water molecules inside hydrophilic channels.

the same manner as L-Val–L-Phe dihydrate (VF, orthorhombic modification; Görbitz, 2002; Fig. 2). Similar hydrophilic layers were also found in L-Ala–L-Trp (AW; $\theta = 37.5^\circ$; Emge *et al.*, 2000), while L-Phe–L-Pro hydrate (Panneerselvam & Chacko, 1989) has a different crystal packing arrangement, despite having a low θ value (42.3°).

The $-\text{NH}_3^+\cdots\text{OOC}-$ hydrogen bond is the signature intermolecular interaction of crystal structures of linear unblocked peptides, where it generates the familiar head-to-tail peptide chains. The most unusual feature of the hydrogen-bond network of IF is the lack of such direct interactions between the charged terminal groups (Table 1). All amino H atoms are instead accepted by water molecules. In comparison, the hydrophilic region of AW is slightly contracted, as


Figure 4

The unit cell and crystal packing of LF (Görbitz, 2001). C atoms in molecules that have been rotated as described in Fig. 3 are shown in a darker tone.

reflected by the shrinkage of the unit-cell lengths [from $a = 5.6350$ (14) and 5.6595 (4) Å, and $b = 8.2897$ (18) and 8.3306 (6) Å for IF and VF, respectively, to $a = 4.9475$ (5) Å and $b = 8.2059$ (12) Å for AW]. Water molecule 2 (O2W in Fig. 1) is then eliminated, with concomitant formation of two traditional $-\text{NH}_3^+\cdots\text{OOC}-$ hydrogen bonds.

While the hydrophilic layers are identical in IF and VF, the additional terminal methyl group of the Ile residue modifies the contact interface at the centre of the hydrophobic region in such a way as to shift the space group from $P2_12_12_1$ for VF to $P2_1$ for IF (Fig. 2).

A schematic illustration of the transition from the layered IF and VF structures to members of the FF class is given in Fig. 3. In the process, the water content is reduced from two water molecules per peptide molecule (dihydrate) to just one (monohydrate). At the same time, the number of peptide molecules in the asymmetric unit is increased from one to two. LF is shown in Fig. 4 as an example of an FF-class structure. The water-filled channels are of rectangular shape, with van der Waals dimensions of 2.5×6.0 Å. The molecular conformations of VF, IF and LF are compared in Table 2, which lists relevant torsion angles in the three structures. VF and IF are very similar, but it is also clear that the special folded conformation is retained by LF in the FF class.

FF itself has hexagonal symmetry, a single molecule in the asymmetric unit and a channel with a 10 Å van der Waals diameter (Görbitz, 2001).

Experimental

Very thin needles of the title compound were obtained by fast evaporation of an aqueous solution at elevated temperature (333 K). The same technique was used for crystallizing compounds in the FF class (Görbitz, 2001).

Crystal data

$\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_3 \cdot 2\text{H}_2\text{O}$
 $M_r = 314.38$
 Monoclinic, $P2_1$
 $a = 5.6350$ (14) Å
 $b = 8.2897$ (18) Å
 $c = 17.382$ (4) Å
 $\beta = 99.256$ (9) $^\circ$
 $V = 801.4$ (3) Å 3
 $Z = 2$
 $D_x = 1.303$ Mg m $^{-3}$

Mo $K\alpha$ radiation
 Cell parameters from 3020 reflections
 $\theta = 2.4$ – 26.4°
 $\mu = 0.10$ mm $^{-1}$
 $T = 105$ (2) K
 Needle, colourless
 $1.05 \times 0.01 \times 0.01$ mm

Data collection

Siemens SMART CCD diffractometer
 ω scans
 Absorption correction: multi-scan (SADABS; Sheldrick, 1996)
 $T_{\min} = 0.790$, $T_{\max} = 0.999$
 6941 measured reflections

1741 independent reflections
 1425 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.064$
 $\theta_{\text{max}} = 26.4^\circ$
 $h = -7 \rightarrow 7$
 $k = -8 \rightarrow 10$
 $l = -21 \rightarrow 20$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.039$
 $wR(F^2) = 0.082$
 $S = 1.08$
 1741 reflections
 230 parameters
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0398P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} = 0.005$
 $\Delta\rho_{\text{max}} = 0.31$ e Å $^{-3}$
 $\Delta\rho_{\text{min}} = -0.26$ e Å $^{-3}$
 Extinction correction: SHELXL97
 Extinction coefficient: 0.283 (15)

Table 1
Hydrogen-bonding 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—H1...O1W ⁱ	0.96	1.98	2.895 (5)	158
N1—H2...O2W	0.96	1.91	2.806 (5)	154
N1—H2...O1	0.96	2.28	2.711 (5)	106
N1—H3...O1W ⁱⁱ	0.96	1.83	2.787 (5)	175
N2—H4...O3 ⁱⁱⁱ	0.90	2.10	2.891 (5)	146
C1—H11...O1 ⁱⁱⁱ	1.07	2.48	3.491 (6)	158
O1W—H11W...O3 ⁱⁱⁱ	0.90	1.83	2.724 (4)	172
O1W—H12W...O2	0.90	1.75	2.651 (4)	174
O2W—H21W...O2 ⁱ	0.90	2.06	2.852 (4)	146
O2W—H22W...O2 ^{iv}	0.90	1.94	2.763 (4)	152

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

Table 2
Torsion angles (°) for IF, VF[†] and LF[‡].

Torsion angle [§]	IF	VF	LF(A) [¶]	LF(B)
N1—C1—C6—N2 (ψ_1)	150.0 (4)	151.35 (11)	125.0 (5)	124.3 (5)
C1—C6—N2—C7 (ω_1)	170.6 (3)	172.31 (11)	179.8 (4)	-174.2 (4)
C6—N2—C7—C12 (φ_2)	49.4 (5)	48.55 (16)	47.7 (6)	49.1 (6)
N2—C7—C12—O2 (ψ_r)	48.4 (5)	48.45 (16)	52.7 (7)	54.1 (6)
C2—C1...C7—C8 (θ)	16.0 (5)	19.97 (12)	-0.1 (5)	3.0 (5)
N1—C1—C2—C3 ($\chi_1^{1,1}$)	-163.6 (4)	-164.06 (11)	178.4	175.7 (4)
N1—C1—C2—C5 ($\chi_1^{1,2}$)	70.9 (5)	70.85 (15)		
C1—C2—C3—C4 ($\chi_1^{1,1}$)	171.6 (4)		-178.9 (5)	-175.2 (5)
C1—C2—C3—C5 ($\chi_1^{1,2}$)			59.3 (6)	61.5 (7)
N2—C7—C8—C9 (χ_2^1)	-50.5 (5)	-50.08 (16)	-61.0 (6)	-55.1 (6)
C7—C8—C9—C10 ($\chi_2^{2,1}$)	138.6 (4)	138.07 (13)	122.9 (5)	113.0 (5)

[†] Görbitz (2002). [‡] Görbitz (2001). [§] Atomic numbering refers to IF. [¶] The label in parentheses identifies the peptide molecule in the asymmetric unit.

The very thin needle used for data collection proved to be a merohedral twin. Twinning was handled in the refinement by a *SHELXTL* (Bruker, 2000) TWIN 1 0 0 0 $\bar{1}$ 0 $\bar{1}$ 0 $\bar{1}$ command. The fractional contribution was 0.50 for each component. Positional parameters for H atoms were refined only for the two water mol-

ecules. Restraints were applied to give O—H distances close to 0.90 Å and H—O—H angles close to 105°. Peptide H atoms were placed geometrically and included in the refinement with constraints. Free rotation was permitted for amino and methyl groups. U_{iso} values for H atoms were set at $1.2U_{\text{eq}}$ of the carrier atom, or $1.5U_{\text{eq}}$ for water, methyl and amino groups. In the absence of significant anomalous scattering effects, 1103 Friedel pairs were merged. The absolute configuration was known for the purchased material.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; 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*.

The purchase of the diffractometer was made possible by support from the Research Council of Norway (NFR)

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1649). Services for accessing these data are described at the back of the journal.

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