

## L-Leucyl-L-isoleucine 0.75 hydrate

Carl Henrik Görbitz

Department of Chemistry, University of Oslo,  
PO Box 1033 Blindern, N-0315 Oslo, NorwayCorrespondence e-mail:  
c.h.gorbitz@kjemi.uio.no

## Key indicators

Single-crystal X-ray study  
 $T = 105\text{ K}$   
Mean  $\sigma(\text{C}-\text{C}) = 0.007\text{ \AA}$   
Disorder in main residue  
 $R$  factor = 0.053  
 $wR$  factor = 0.139  
Data-to-parameter ratio = 10.4For details of how these key indicators were  
automatically derived from the article, see  
<http://journals.iucr.org/e>.

The title compound,  $\text{C}_{12}\text{H}_{24}\text{N}_2\text{O}_3 \cdot 0.75\text{H}_2\text{O}$ , crystallizes in the hexagonal space group  $P6_2$  with four peptide molecules in the asymmetric unit ( $Z = 24$ ). The structure is very similar to the structure of L-Leu-L-Val-0.75H<sub>2</sub>O [Görbitz & Gundersen (1996). *Acta Chem. Scand.* **50**, 537–543] and is characterized by a honeycomb-shaped hydrogen-bond pattern with large hydrophobic columns running parallel to the  $c$  axis.

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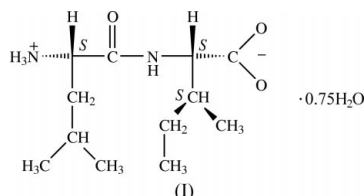
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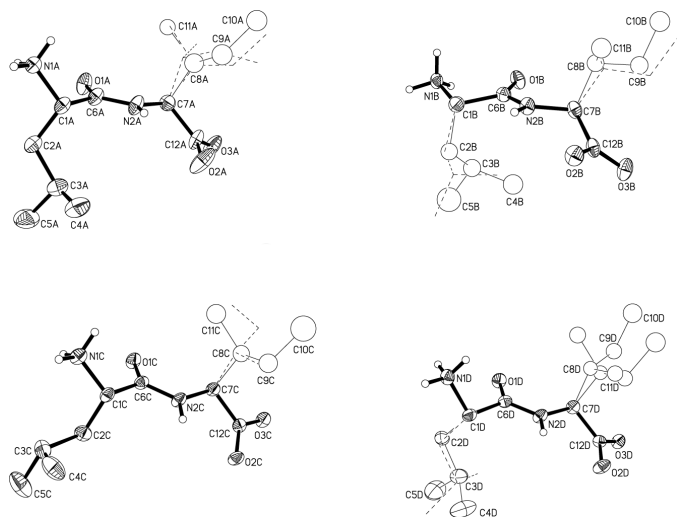
## Comment

In early work on the crystal structures of short linear peptides we focused on the systematic segregation of hydrophobic and hydrophilic groups into separate regions (Görbitz & Etter, 1992). Two different modes were identified: (i) formation of distinct hydrophobic and hydrophilic layers or (ii) formation of small hydrophobic columns along a short (5–6 Å) crystallographic axis. L-Leu-L-Val-0.75H<sub>2</sub>O (LV; Görbitz & Gundersen, 1996*a*), one of the first compounds to be investigated as part of a 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), was the first structure to break this pattern, as it was found to contain large hydrophobic columns parallel to a 11.723 (9) Å hexagonal axis [space group  $P6_2$ ,  $a = 29.212$  (16) Å]. Four peptide molecules (and three water molecules) in the asymmetric unit produced an unprecedented  $Z$  value of 24 for a chiral organic molecule.

Seven hydrophobic dipeptides studied later, including L-Val-L-Ala (Görbitz & Gundersen, 1996*b*), L-Ala-L-Val (Görbitz, 2002), L-Ile-L-Ala, L-Ala-L-Ile, L-Val-L-Val, L-Val-L-Ile and L-Ile-L-Val (Görbitz, 2003), were also found to possess hexagonal symmetry and sizable hydrophobic columns, but in space group  $P6_1$  with just one peptide molecule in the asymmetric unit ( $a \sim 14.5\text{ \AA}$  and  $c \sim 10.0\text{ \AA}$ ). Within this group, called the VA class after its first member L-Val-L-Ala (Görbitz & Gundersen, 1996*b*), Val and Ile residues can be interchanged without major modifications of the crystal packing arrangement. It was thus no great surprise to find that the crystal structure of L-Leu-L-Ile (LI), (I), shown in Figs. 1 and 2, is very similar to the structure of LV (Görbitz & Gundersen, 1996*a*).



The fairly extended conformations of the LI main chains (torsion angles listed in Table 1) are very similar to those

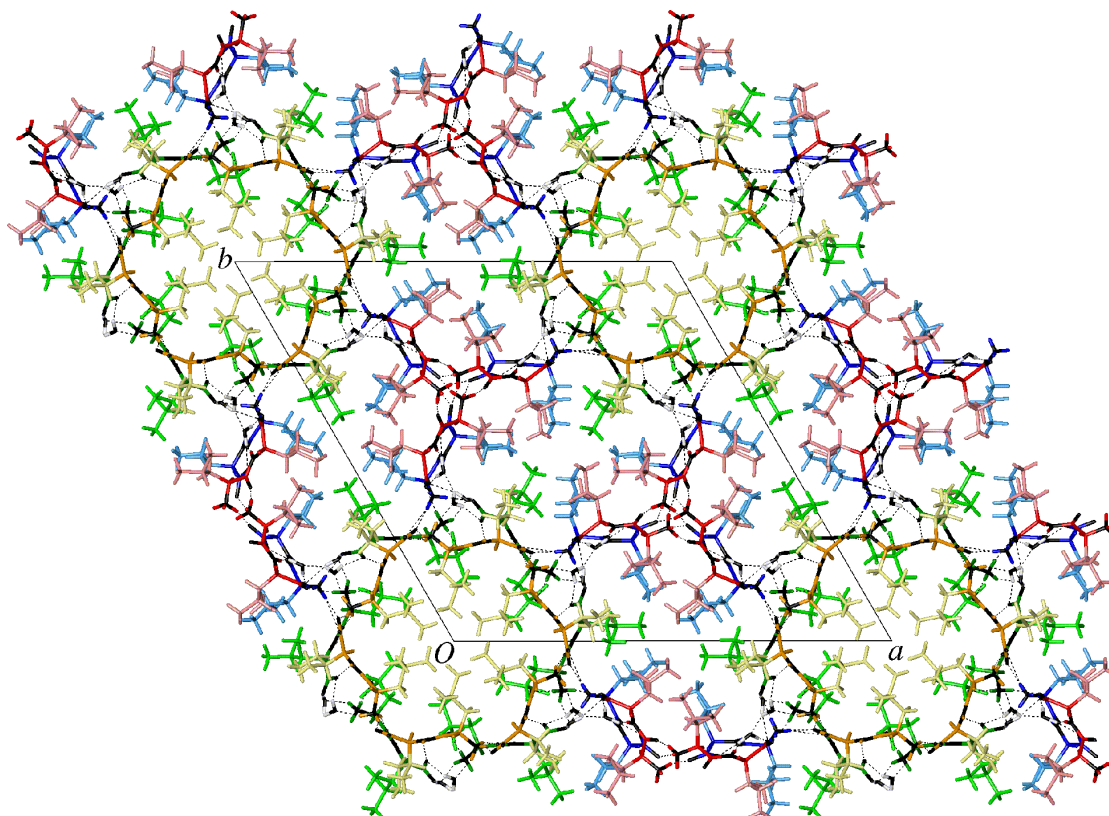

**Figure 1**

Independent views of the four peptide molecules in the asymmetric unit of LI. Displacement ellipsoids are shown at the 50% probability level, essential H atoms are shown as spheres of arbitrary size. The major components for disordered side chains are shown with open circles and full lines, except for the Leu side chain in molecule *D* which was refined anisotropically; the principal ellipses of the displacement tensor have thus been included. The minor components are shown as dashed lines. Molecule *D* has 0.50 occupancy for each of the two Ile rotamers.

observed previously for LV. The main difference between the two structures lies in the type and amount of side chain

disorder. Two LV peptide molecules, corresponding to molecules *A* and *D* in LI, had a major and a minor position for the Leu side chain, with  $\chi^1/\chi^{2,1}, \chi^{2,1}$  torsion angles *trans/gauche+*, *trans* and *trans/trans, gauche-*, respectively. All Val side chains were ordered. For LI an equivalent disorder is present for molecule *D*, but not for *A* (Table 2). Instead, two alternative orientations have been refined for the Leu side chain of molecule *B*, both strictly belonging to the same *gauche+/gauche+*, *trans* conformation, but separated by 13–18° dihedral rotations. As is evident from Fig. 1, all Ile side chains are also disordered, with three positions for molecule *A* and two positions for molecules *B*, *C* and *D*. The major orientations at the  $C^\alpha-C^\beta$  bonds listed in Table 3 are the same as for the Val side chains of the corresponding molecules in LV, except for molecule *A* which has  $\chi^{1,1}, \chi^{1,2}$  *gauche+*, *gauche-*. In this case, a *gauche-*, *trans* conformation was found in LV.

The crystal packing arrangement of LI (Fig. 2) contains two different types of hydrophobic columns. The column along the hexagonal axis, with contributions from the Leu side chains of molecules *C* and *D*, is an exact copy of the one found in LV. The column carries some superficial similarity to those of the VA-class (Görbitz & Gundersen, 1996*b*; Görbitz, 2003), but at a detailed level hydrogen-bonding patterns and other molecular interactions are quite different. The LI column also lacks the central open channel typical for the VA-class; what remains is only a 0.8 Å wide slit that cannot be entered by solvent molecules. The second type of hydrophobic column,


**Figure 2**

The unit cell and crystal packing of LI viewed along the *c* axis. Color key: Molecule *A* blue; molecule *B* red; molecule *C* green; molecule *D* orange. Side chains have the same color as the main chain, but in a lighter tone. All N and O atoms, including those in cocrystallized water molecules, are depicted in black. Hydrogen bonds are indicated by dashed lines.

with elliptical shape, has twofold screw symmetry and involves all the remaining Leu and Val side chains.

Despite the lack of obvious channels or voids in the structure, the calculated crystal density is only  $1.121 \text{ Mg m}^{-3}$ , which is, for instance, slightly lower than the density of the nanoporous structure of L-Val-L-Ile ( $1.210$  and  $1.182 \text{ Mg m}^{-3}$  with and without inclusion of solvent trapped in channels; Görbitz, 2003).

Hydrogen-bond parameters are listed in Table 4. The intermolecular interactions of LI correspond closely to those already described for LV (Görbitz & Gundersen, 1996a).

## Experimental

The crystals used for the previous investigation of LV were grown by vapour diffusion of acetonitrile into an aqueous solution of the peptide (Görbitz & Gundersen, 1996a). The crystals of LI were much more difficult to obtain, and the equivalent experiment yielded only extremely thin, wool-like fibres. Useful crystals, in the shape of needles, were eventually grown by fast evaporation of an aqueous solution at elevated temperature ( $333 \text{ K}$ ), the same technique used for crystallizing several other hydrophobic dipeptides (Görbitz, 2001).

### Crystal data

$\text{C}_{12}\text{H}_{24}\text{N}_2\text{O}_3 \cdot 0.75\text{H}_2\text{O}$   
 $M_r = 258.01$   
 Hexagonal,  $P6_2$   
 $a = 29.633 (7) \text{ \AA}$   
 $c = 12.035 (3) \text{ \AA}$   
 $V = 9152 (4) \text{ \AA}^3$   
 $Z = 24$   
 $D_x = 1.124 \text{ Mg m}^{-3}$

Mo  $K\alpha$  radiation  
 Cell parameters from 8248 reflections  
 $\theta = 1.4\text{--}27.1^\circ$   
 $\mu = 0.08 \text{ mm}^{-1}$   
 $T = 105 (2) \text{ K}$   
 Flat needle, colorless  
 $0.95 \times 0.25 \times 0.10 \text{ mm}$

### Data collection

Bruker SMART CCD diffractometer  
 $\omega$  scans  
 Absorption correction: multi-scan (SADABS; Sheldrick, 1996)  
 $T_{\min} = 0.822$ ,  $T_{\max} = 0.992$   
 54361 measured reflections

7027 independent reflections  
 5101 reflections with  $I > 2\sigma(I)$   
 $R_{\text{int}} = 0.084$   
 $\theta_{\max} = 27.1^\circ$   
 $h = -33 \rightarrow 37$   
 $k = -37 \rightarrow 36$   
 $l = -15 \rightarrow 15$

### Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.053$   
 $wR(F^2) = 0.139$   
 $S = 1.06$   
 7027 reflections  
 678 parameters  
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.065P)^2 + 3.8347P]$   
 where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\max} = 0.002$   
 $\Delta\rho_{\max} = 0.35 \text{ e \AA}^{-3}$   
 $\Delta\rho_{\min} = -0.33 \text{ e \AA}^{-3}$

**Table 1**

Main-chain torsion angles ( $^\circ$ ) for LI.

Torsion angle	A	B	C	D
N1—C1—C6—N2 ( $\psi_1$ )	130.0 (4)	165.0 (5)	145.9 (3)	126.1 (3)
C1—C6—N2—C7 ( $\omega_1$ )	173.9 (3)	162.5 (3)	−174.3 (3)	177.0 (3)
C6—N2—C7—C12 ( $\varphi_2$ )	−137.2 (4)	−148.8 (3)	−145.4 (3)	−146.4 (3)
N2—C7—C12—O2 ( $\psi_T$ )	−22.9 (6)	−32.4 (4)	−11.2 (5)	−26.0 (5)

**Table 2**

Torsion angles ( $^\circ$ ) for Leu side chains.

Torsion angle	A	B <sup>a</sup>	C	D <sup>b</sup>
N1—C1—C2—C3 ( $\chi_1^{1,1}$ )	−177.8 (4)	71.7 (6) [58.0 (13)]	−57.0 (5)	−175.2 (6) [−176.7 (17)]
C1—C2—C3—C4 ( $\chi_1^{2,1}$ )	64.3 (6)	87.1 (7) [64.5 (17)]	−62.4 (5)	66.9 (7) [−77 (3)]
C1—C2—C3—C5 ( $\xi_1^{2,2}$ )	−172.4 (4)	−151.1 (6) [−169.0 (13)]	174.8 (4)	−169.4 (6) [159 (3)]

Notes: (a) Values for 0.710 (10) and [0.290 (10)] occupancy components; (b) values for 0.868 (10) and [0.132 (10)] occupancy components.

**Table 3**

Torsion angles ( $^\circ$ ) for Ile side chains.

Torsion angle	A <sup>a</sup>	B <sup>b</sup>	C <sup>c</sup>	D <sup>d</sup>
N2—C7—C8—C9 ( $\chi_2^{1,1}$ )	60.8 (9) [80.2 (15)] {177.6 (7)}	−162.0 (5) [−174.5 (7)]	65.6 (8) [−156.5 (6)]	−161.5 (5) [63.9 (7)]
N2—C7—C8—C11 ( $\chi_2^{1,2}$ )	−67.6 (9) [−46.2 (18)] {50.0 (10)}	77.7 (7) [44.8 (11)]	−62.8 (7) [75.6 (8)]	73.1 (6) [−64.5 (7)]
C7—C8—C9—C10 ( $\chi_2^2$ )	166.7 (9) [167 (2)] [−84.4 (13)]	173.2 (13) [175.3 (9)]	173.2 (8) [71.8 (10)]	−178.7 (7) [177.9 (7)]

Notes: (a) Values for 0.484 (17), [0.240 (18)] and {0.278 (8)} occupancy components; (b) values for 0.565 (14) and [0.435 (14)] occupancy components; (c) values for 0.534 (8) and [0.446 (8)] occupancy components; (d) values for 0.502 (8) and [0.498 (8)] occupancy components.

**Table 4**

Hydrogen-bonding geometry ( $\text{\AA}$ ,  $^\circ$ ).

D—H...A	D—H	H...A	D...A	D—H...A
N1A—H1A...O3C <sup>i</sup>	0.90	1.87	2.753 (4)	169
N1A—H2A...O3D <sup>ii</sup>	0.90	1.95	2.807 (4)	159
N1A—H3A...O2B	0.90	2.05	2.945 (4)	170
N2A—H4A...O1E <sup>ii</sup>	0.88	2.20	3.051 (5)	164
N1B—H1B...O1B <sup>iii</sup>	0.94	1.97	2.809 (4)	147
N1B—H2B...O3A <sup>iv</sup>	0.94	1.84	2.737 (4)	160
N1B—H3B...O3A <sup>v</sup>	0.94	1.82	2.685 (4)	152
N2B—H4B...O1A	0.88	2.04	2.897 (4)	163
N1C—H1C...O1G <sup>i</sup>	0.91	1.97	2.801 (5)	153
N1C—H2C...O1D <sup>i</sup>	0.91	1.98	2.869 (4)	169
N1C—H3C...O3B	0.91	1.86	2.750 (4)	167
N2C—H4C...O2D <sup>ii</sup>	0.88	2.14	2.991 (4)	163
C1C—H11C...O2D <sup>ii</sup>	1.00	2.43	3.208 (5)	135
N1D—H1D...O1F <sup>vi</sup>	0.91	1.84	2.664 (4)	149
N1D—H2D...O3D <sup>vi</sup>	0.91	1.91	2.741 (4)	150
N1D—H3D...O1C <sup>vi</sup>	0.91	2.17	3.040 (4)	159
N2D—H4D...O2C <sup>vii</sup>	0.88	2.10	2.863 (4)	145
O1E—H1E...O3B	0.91 (7)	1.84 (7)	2.752 (4)	171 (6)
O1E—H2E...O2A <sup>vii</sup>	0.95 (7)	1.79 (7)	2.702 (5)	160 (6)
O1F—H1F...O2C <sup>viii</sup>	0.87 (6)	1.96 (6)	2.790 (4)	161 (5)
O1F—H2F...O1E	0.90 (6)	1.85 (6)	2.681 (5)	152 (5)
O1G—H1G...O3C	0.82 (6)	1.93 (6)	2.746 (4)	168 (5)
O1G—H2G...O2B <sup>vi</sup>	0.82 (6)	2.02 (6)	2.815 (4)	163 (5)

Symmetry codes: (i)  $y, -x + y, z - \frac{1}{3}$ ; (ii)  $x, y, z - 1$ ; (iii)  $1 - y, x - y, z - \frac{1}{3}$ ; (iv)  $1 - y, x - y, \frac{2}{3} + z$ ; (v)  $1 - x + y, 1 - x, \frac{1}{3} + z$ ; (vi)  $x - y, x, \frac{1}{3} + z$ ; (vii)  $x, y, 1 + z$ ; (viii)  $y, -x + y, \frac{2}{3} + z$ .

In the absence of significant anomalous dispersion effects, Friedel pairs were averaged and the absolute configuration can not be determined from the crystallographic experiment. The disorder of Ile (C7—C11) and Leu (C1—C5) for the four molecules of the asymmetric unit is as follows: molecule A, Ile disordered over three positions with occupancies 0.484 (17), 0.240 (18) and 0.278 (8); molecule B, Ile disordered over two positions with occupancies 0.565 (14) and

0.435 (14), Leu disordered over two positions with occupancies 0.710 (10) and 0.290 (10); molecule *C*, Ile disordered over two positions with occupancies 0.534 (8) and 0.466 (8); molecule *D*, Ile disordered over two positions with occupancies 0.502 (8) and 0.498 (8), Leu disordered over two positions with occupancies 0.868 (10) and 0.132 (10). Positional parameters for H atoms were refined only for the three water molecules. Peptide H atoms were positioned geometrically and refined with riding-model constraints: C—H = 0.98–1.00 Å, terminal N—H = 0.90 Å and peptide link N—H = 0.88 Å.  $U_{\text{iso}}$  values for H atoms were  $1.2U_{\text{eq}}$  of the carrier atom, or  $1.5U_{\text{eq}}$  for water, methyl and amino groups.

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*.

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## References

- Bruker (1998). *SMART*. Version 5.054. Bruker AXS Inc., Madison, Wisconsin, USA.
- Bruker (2000). *SHELXTL*. Version 6.10. Bruker AXS Inc., Madison, Wisconsin, USA.
- Bruker (2001). *SAINT-Plus*. Version 6.22. Bruker AXS Inc., Madison, Wisconsin, USA.
- Görbitz, C. H. (2001). *Chem. Eur. J.* **7**, 5153–5159.
- Görbitz, C. H. (2002). *Acta Cryst.* **B58**, 849–854.
- Görbitz, C. H. (2003). *New J. Chem.* **27**, 1789–1793.
- Görbitz, C. H. & Etter, M. C. (1992). *Int. J. Peptide Protein Res.* **39**, 93–110.
- Görbitz, C. H. & Gundersen, E. (1996a). *Acta Chem. Scand.* **50**, 537–543.
- Görbitz, C. H. & Gundersen, E. (1996b). *Acta Cryst.* **C52**, 1764–1767.
- Sheldrick, G. M. (1996). *SADABS*. University of Göttingen, Germany.