L-Leu-L-Val·¾H₂O: A Hexagonal Crystal Structure with Z=24

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Görbitz, C. H. and Gundersen, E., 1996. L-Leu-L-Val·¾H₂O: A Hexagonal Crystal Structure with $Z=24$. – Acta Chem. Scand. 50: 537–543 © Acta Chemica Scandinavica 1996.

L-Leu-L-Val crystallizes in the hexagonal space group $P6_2$ with four peptide molecules and three solvent water molecules in the asymmetric unit. It is the first linear peptide to have $Z=24$. The structure was solved with direct methods and refined to a final R-factor 0.048 and $R_w=0.039$ using 5311 unique reflections ($I>3.0\ \sigma I$) collected at 120 K. Cell parameters: $a=29.212(16)$, $c=11.723(9)$ Å. The four dipeptides have different conformations and form a complex three-dimensional hydrogen-bond network in the crystal with a unique packing pattern unlike all those found for other structures of linear peptides. The most salient feature is the aggregation of side chains into two different types of hydrophobic columns parallel to the hexagonal axis.

When molecules undergo aggregation to form the systematic lattice of a crystal, it occurs in such a way so as to optimize hydrogen bonding, but under the condition that favourable hydrophobic interactions are also attained. For molecules with distinct hydrophobic as well as hydrophilic moieties, characteristic patterns are observed in which the hydrophobic groups usually segregate into two-dimensional layers or one-dimensional columns. Dipeptides with two hydrophobic side chains possess a dual hydrophilic/hydrophobic character which makes them particularly interesting for studies of such packing interactions in the solid phase. In a survey of the crystal structures of short linear peptides[1] it was found that among the dipeptides there was a conspicuous under-representation of these molecules. The only two structures were L-Ala-L-Ala,[2] which does not have a very distinct hydrophobic character, and L-Met-L-Met.[3] Recently the structure of a DMSO solvate of L-Leu-L-Leu has also been reported.[4] In our laboratory we have carried out crystallizations of several hydrophobic dipeptides. All of them share a common crystal habit in forming needle-shaped crystals which were frequently far too thin for diffraction experiments. Still, we managed to collect data for some compounds, and the results of these investigations will be presented in a short series of papers. The highest quality crystals were obtained for the title compound, which is the first structure in this series.

Nomenclature. The four unique peptide molecules are called Molecules 1, 2, 3 and 4. The abbreviations Lx and

Vx ($x=1$, 2, 3, 4) are used for the Leu and Val side chains of Molecules 1, 2, 3 and 4, respectively. The symbol $d(\text{X}-\text{Y})$ is used to denote the X–Y bond length, while $\alpha(\text{X}-\text{Y}-\text{Z})$ is used for the X–Y–Z bond angle.

Experimental

Preparation. The crystals were grown by vapour diffusion of acetonitrile into 30 μL of an aqueous solution containing about 2 mg of the peptide. NMR spectra of the needle-shaped crystals showed that they were devoid of acetonitrile solvent.

Data collection. The large hexagonal cell was found from the initial Polaroid photograph, and was confirmed by Weissenberg films before data collection. Experimental conditions are given in Table 1. Cell parameters were determined from 25 general reflections with $25<2\theta<35°$.

Refinement. From the systematic absences (00l, $l=3n$) two enantiomorphous space groups $P6_2$ and $P6_4$ were possible. The former was arbitrarily chosen and later shown to be correct. The structure was solved by direct methods using SIR92.[5] Only reflections with $2\theta<50°$ were used, and the number of permuted phases was increased from 5 (default) to 11. The correct solution, with four peptide molecules in the asymmetric unit, was obtained from trial structure number 905, and the subsequent least-squares Fourier cycles identified all the heavy atoms, including three solvent molecules, and even some (C$^\alpha$-)H atoms. The program assigned correct atom types to all but four atoms. The final R-factor for this isotropic refinement was 0.101 for 3399 reflections.

Table 1. Crystal data, intensity collection and structure refinement.

Formula	$C_{11}H_{22}N_2O_3 \cdot \frac{1}{4}H_2O$
Formula weight/g mol^{-1}	243.82
Crystal size/mm	$0.70 \times 0.60 \times 0.60$
Color, habit	Colorless needle
Crystal system	Hexagonal
Space group	$P6_2$ (No. 171)
Cell dimensions/Å	$a = b = 29.212(16)$
	$c = 11.723(9)$
Volume/Å^3	8663 (11)
Z	24
D_{calc}/g cm^{-3}	1.121
Diffractometer	Nicolet P3
Radiation	Mo $K\alpha$ ($\lambda = 0.71069$ Å)
Monochromator	Graphite crystal
T/K	120
Scan mode	ω
Scan speed/° min^{-1}	3.0
Scan range/°	$2\theta_{\alpha 1} - 0.7$ to $2\theta_{\alpha 2} + 0.8$
2θ range/°	5.0–60.0
Background/scan ratio	0.70
Standard reflections	3 measured every 96 reflections
Variation in standard intensities (%)	<3.3
Index ranges	$0 \leqslant h,k \leqslant 35$
	$0 \leqslant l \leqslant 16$
No. of reflections measured	9256
No. of independent reflections	8776
R_{int}	0.027
No. of observed reflections $[I > 3\sigma(I)]$ $(= n)$	5311
Absorption correction	None
Refinement	On F
No. of parameters $(= p)$	869
$R = \Sigma|\Delta F|/\Sigma|F_0|$ [a]	0.048
$R_w = [\Sigma w(\Delta F)^2/\Sigma w(F_0)^2]^{1/2}$ [b]	0.039
$S = [\Sigma w(F_0^2 - F_c^2)/(n-p)]^{1/2}$	1.61
Residual electron density/e Å^{-3}	$+0.21, -0.26$

[a] $\Delta F = |F_0| - |F_c|$. [b] $w = 1/[\sigma^2(F_0) + 0.0004F_0^2]$.

Further least-squares refinement of the structure was an unusually time-consuming procedure for a small-molecule crystallographer, partly as a result of the disorder which was unravelled for the Leu side chains in Molecules 2 and 4 (L2 and L4). The distribution between the most populated (major) and the least populated (minor) conformation is 0.846:0.154 for L2 and 0.828:0.172 for L4. Unless otherwise noticed, the most populated conformations are used in tables and figures.

The model used in the final cycles of least-squares refinement incorporated the following parameters: (1) fractional coordinates for heavy atoms, with two alternative positions for C-atoms in L2 and L4 side chains; (2) fractional coordinates for H-atoms, except those on disordered side chains which were treated as riding atoms with fixed $d_{C-H} = 0.98$ Å; (3) anisotropic thermal parameters for the main-chain and ordered-side-chain heavy atoms; (4) anisotropic thermal parameters for C-atoms in the most populated side-chain conformation of L2 and L4, except C$^\beta$-atoms which were kept isotropic after splitting; (5) two isotropic parameters for each of the least populated side-chain conformations of L2 and L4, one for C$^\beta$ and C$^\gamma$ and one for C$^{\delta 1}$ and C$^{\delta 2}$; (6) one common isotropic temperature factor for the

three H-atoms in each amino and each methyl group. Other H-atoms were assigned an isotropic temperature factor U_{iso} equal to U_{eq} for the bonded atom. Details on the refinement are given in Table 1. Atomic scattering factors were taken from Ref. 6.

Cambridge Structural Database (CSD). Peptide structures were retrieved from the CSD (April 1995 release)[7] by means of the program QUEST. A maximum R-factor of 0.10 was used. The main-chain and side-chain conformations were studied with the GSTAT program. The structures of D-amino acids were inverted before being used in the statistics.

Results and discussion

An ORTEP[8] drawing of the asymmetric unit is shown in Fig. 1. The four peptide molecules with atomic numbering are depicted in Fig. 2. Molecular geometry is given in Table 2.

Bond lengths and bond angles. There are no remarkable values, but $d(C1-C2)$ and $d(C3-C4)$ are noticeably shorter in Molecule 1 than corresponding bonds in the
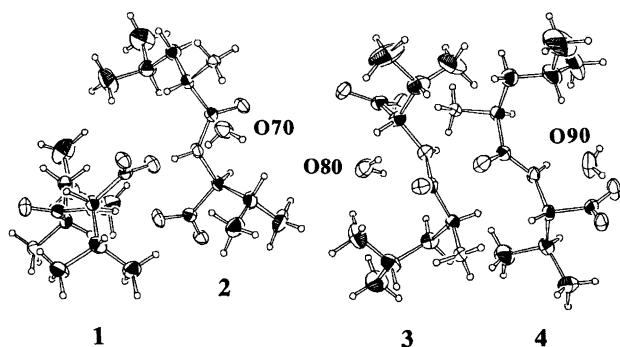
Fig. 1. The asymmetric unit with four dipeptide molecules with designators indicated, and three solvent water molecules with atomic numbering of the oxygen atoms. Thermal ellipsoids for heavy atoms are shown at 50% probability with shading for C atoms. H atoms are shown as spheres of arbitrary size.

three other peptides. There is a nice, but possibly coincidental, correlation between deviation from planarity at the peptide bond, reflected by the torsion angle ω, and the length of the peptide bond (Table 2). The parameters range from d(C–N) = 1.323 Å and $\omega = 179.0°$ for Molecule 2 to 1.345 Å and 164.8° for Molecule 3. The covalent geometry of the four carboxylate groups is quite variable, which can be readily explained by the nature and number of accepted hydrogen bonds by each group. The highest degree of asymmetry is seen for Molecule 2, with d(O22–C31) = 1.274 Å, d(O23–C31) = 1.236 Å, α(O22–C31–C27) = 115.4° and α(O23–C31–C27) =

120.1°. In this case O22 accepts two strong hydrogen bonds, while O23 participates in two weaker interactions. Details on the hydrogen-bond network and some interesting geometry differences associated with the Leu side chains are described in the sections below. The average d(C–H) for 54 refined H-atoms is 0.99 Å, while the averages for d(N–H) (16 bonds) and d(O–H) (6 bonds) are 0.94 Å and 0.79 Å, respectively. The estimated standard deviations for individual bond lengths to H are 0.03–0.04 Å, while the three statistical distributions all have standard deviation 0.06 Å.

Conformations. When there are two or more molecules in the asymmetric unit, one frequently observes only small differences between their covalent geometries. In contrast, the four Leu-Val molecules have significantly different main-chain conformations and variable side-chain orientations. This is evident from Fig. 2 and the data in Table 2. The four main chains are fairly extended in the common dipeptide fashion,[1] giving conformations characterized by the two side chains being located on opposite sides of the peptide plane.

Side-chain conformations. The Leu side chain has two rotatable bonds, giving a total of nine basic conformations. All of these are affected to some extent by steric conflict between the C^δ methyl groups and the main-chain atoms attached to C^α. When $\chi^{2,1}$ is *gauche*— (and $\chi^{2,2}$ is *gauche*+) there is always, regardless of the value for χ^1, two short interactions. Such conformations have
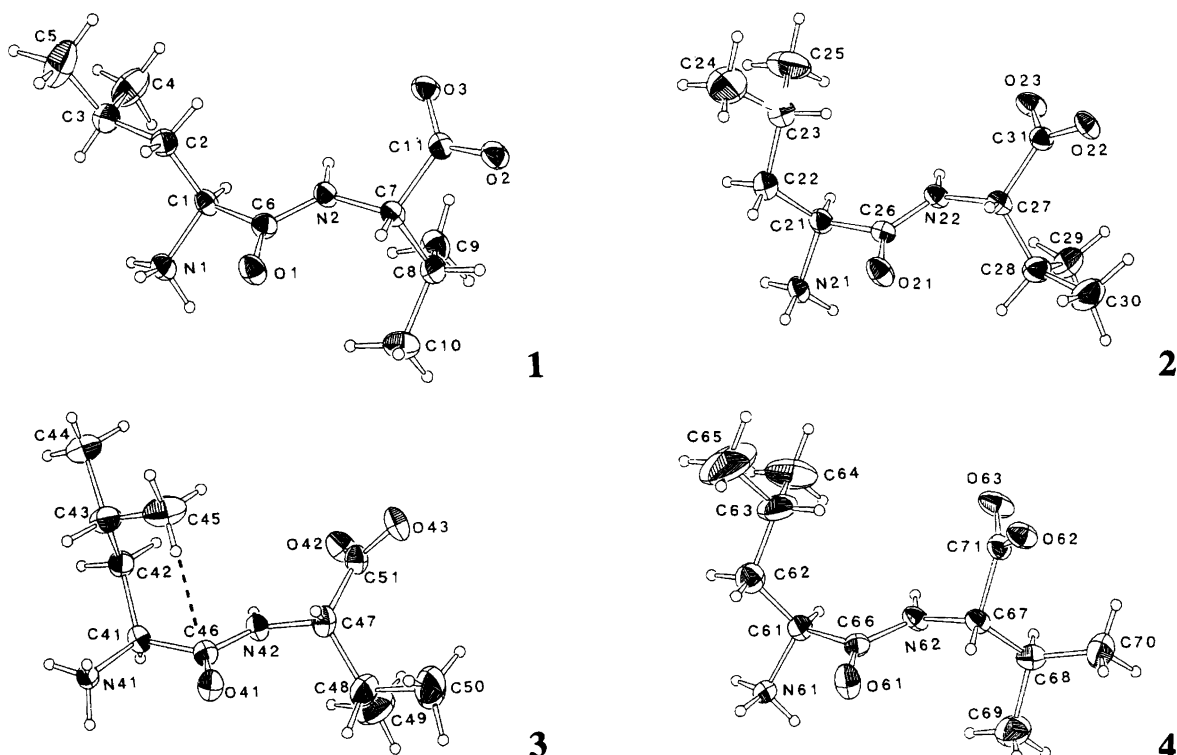

Fig. 2. Individual ORTEP-drawings (50% probability spheres) of the four peptide molecules with atomic numbering indicated. A short H···O contact for Molecule 3 has been dotted.

Table 2. Bond lengths (in Å), bond angles (in °) and selected torsion angles (in °).

Atoms	Molecule 1	Molecule 2[a]	Molecule 3	Molecule 4[a]
O1–C6[b]	1.228(4)	1.234(4)	1.229(4)	1.227(4)
O2–C11	1.258(4)	1.274(4)	1.250(4)	1.258(4)
O3–C11	1.251(4)	1.236(4)	1.260(4)	1.241(4)
N1–C1	1.504(4)	1.503(4)	1.493(4)	1.496(4)
N2–C6	1.332(4)	1.323(4)	1.345(4)	1.333(4)
N2–C7	1.460(4)	1.463(4)	1.458(4)	1.454(4)
C1–C2	1.518(5)	1.546(5)	1.535(5)	1.537(6)
C1–C6	1.535(5)	1.528(5)	1.521(4)	1.530(4)
C2–C3	1.519(5)	1.522(7)	1.527(5)	1.505(10)
C3–C4	1.498(6)	1.534(7)	1.536(6)	1.538(11)
C3–C5	1.543(6)	1.537(8)	1.514(6)	1.533(10)
C7–C8	1.557(5)	1.544(5)	1.550(5)	1.542(5)
C7–C11	1.544(5)	1.526(4)	1.537(5)	1.537(5)
C8–C9	1.514(6)	1.532(6)	1.498(8)	1.516(6)
C8–C10	1.521(6)	1.513(6)	1.530(8)	1.524(5)
C6–N2–C7	122.8(3)	121.0(3)	122.0(3)	125.7(3)
N1–C1–C2	110.9(3)	109.5(3)	110.7(3)	108.2(3)
N1–C1–C6	106.4(3)	106.7(3)	107.5(3)	107.9(3)
C2–C1–C6	110.7(3)	109.3(3)	115.4(3)	110.4(3)
C1–C2–C3	115.6(3)	114.7(4)	118.4(3)	114.3(5)
C2–C3–C4	113.0(3)	110.6(4)	108.1(4)	111.8(6)
C2–C3–C5	109.8(4)	112.6(5)	113.7(3)	110.1(7)
C4–C3–C5	109.7(4)	109.5(5)	109.0(4)	111.0(7)
O1–C6–N2	125.6(3)	123.7(3)	123.3(3)	124.8(3)
O1–C6–C1	120.8(3)	118.5(3)	121.5(3)	120.6(3)
N2–C6–C1	113.5(3)	117.6(3)	115.2(3)	114.6(3)
N2–C7–C8	111.1(3)	111.2(3)	111.2(3)	110.3(3)
N2–C7–C11	111.5(3)	109.3(3)	107.1(3)	109.1(3)
C8–C7–C11	109.4(3)	112.7(3)	114.8(3)	110.2(3)
C7–C8–C9	111.8(3)	112.3(3)	113.1(4)	110.7(3)
C7–C8–C10	111.1(3)	111.7(3)	109.3(4)	112.1(3)
C9–C8–C10	110.6(3)	112.0(4)	114.0(4)	111.3(3)
O2–C11–O3	125.2(3)	124.5(3)	124.4(3)	125.1(3)
O2–C11–C7	114.9(3)	115.4(3)	118.6(3)	116.8(3)
O3–C11–C7	119.9(3)	120.1(3)	117.1(3)	118.0(3)
ψ_1 (N1–C1–C6–N2)	142.9(4)	129.1(4)	175.3(4)	131.7(4)
ω_1 (C1–C6–N2–C7)	−174.4(4)	179.0(4)	164.8(4)	173.4(5)
ϕ_2 (C6–N2–C7–C11)	−141.4(4)	−157.0(4)	−148.2(4)	−116.3(4)
ψ_T (N2–C7–C11–O3)	−14.3(3)	−24.4(3)	−32.9(3)	−46.6(3)
χ_1^1 (N1–C1–C2–C3)	−60.2(3)	−179.0(5)	54.3(3)	−173.5(6)
$\chi_1^{2,1}$ (C1–C2–C3–C5)	172.0(5)	66.1(5)	63.4(4)	66.8(6)
$\chi_1^{2,2}$ (C1–C2–C3–C4)	−65.2(4)	−171.0(6)	−175.5(5)	−169.3(8)
χ_2^1 (N2–C7–C8–C10)	−76.2(3)	−157.4(4)	−168.5(5)	170.2(4)
χ_2^2 (N2–C7–C8–C9)	47.9(3)	75.8(4)	63.4(4)	−64.8(3)

[a] Values for atoms in the most populated L-Leu side-chain conformation. [b] Parameter in Molecule 1, equivalent parameters in Molecules 2–4 are listed.

never been observed in crystal structures and are not included in Table 3, which summarizes side-chain geometries. There are two common conformations for Leu side chains which each involves only a mild conflict with H^α. The most frequent is gauche − /trans,gauche − ($\chi^1/\chi^{2,1},\chi^{2,2}$), which is also observed for L1. The second is trans/gauche + ,trans, which occurs for the major conformations of the disordered Leu side chains of Molecules 2 and 4, as shown for L4 in Fig. 3. The rare minor conformations trans/trans,gauche − (four previous observations, Table 3) are affected by considerable strain from short H⋯O (carbonyl) contacts. Deviations from the normal covalent geometries are evident for the bond angles, particularly α(C26, C21, C22) = 123.7(10)° and

α(C66, C61, C62) = 118.0(8)°. There is also substantial twisting from the ideal staggered conformations at the C^β–C^γ bond. For L2 $\chi^{2,1}$ and $\chi^{2,2}$ are 156(3)°, −78(2)°, respectively, and 158(3)°, −86(2)° for L4. The values for χ^1 are −177(2)° for L2 and −172(2)° for L4.

The gauche + /gauche + ,trans combination for L3 is also very uncommon, found previously in only four crystal structures. The H⋯O (carbonyl) contact can be seen in Fig. 2. The distances in the refined structure are 2.71 Å for d(H⋯O41) and 2.70 Å for d(H⋯C46). When the C^δ–H distance is normalized[9] from 0.91 Å to the neutron diffraction value for methyl groups, 1.06 Å,[10] the contact distance is reduced to 2.61 and 2.65 Å, respectively. It can readily be seen from Table 2 how the

Table 3. Side chain conformations in L-Leu-L-Val·$\frac{3}{4}H_2O$ and in peptides retrieved from the Cambridge Structural Database (CSD).[7]

Torsion angles	L-Leu-L-Val	CSD[b]
$\chi^1/\chi^{2,1}$, $\chi^{2,2}$	Leu	
g^+/g^+, t	1 (3)[a]	4
g^+/t, g^-	–	1
g^-/g^+, t	–	11
g^-/t, g^-	1 (1)	132
t/g^+, t	2 (2, 4)[c]	54
t/t, g^-	2 (2, 4)[d]	4
$\chi^{1,1}$, $\chi^{1,2}$	Val	
g^+, t	2 (2, 3)	30
t, g^-	1 (4)	185
g^-, g^+	1 (1)	64

[a] Molecule designator in parenthesis. [b] Combined figures for N-terminal, central and C-terminal residues. No significant distributional differences were found between these three groups. [c] Most populated conformations. [d] Least populated conformations.

bond lengths, and in particular the bond angles of the L3 side chain, have been modified to avoid an even shorter distance. Thus, α(C42–C41–C46) and α(C41–C42–C43) are 115.4 and 118.4°, respectively, while the averages for equivalent angles in Molecules 1, 2 and 4 are 110.1 and 114.9°. If all bond lengths and bond angles in Molecule 3 are adjusted to the average values for Molecules 1, 2 and 4, and the torsion angles are put in idealized staggered positions, d(H⋯O41) is 1.99 Å and d(H⋯C46) is 2.03 Å. The peptide bond in
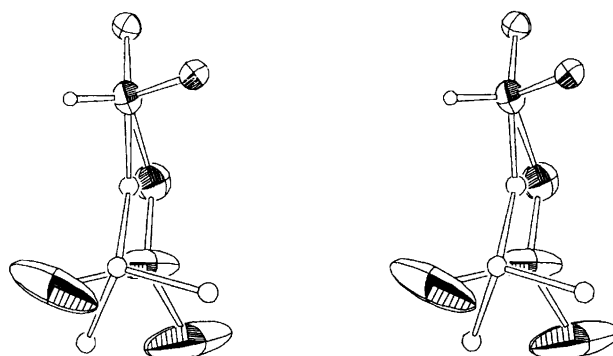

Fig. 3. Stereoview of the disordered Leu side chain in Molecule 4. C atoms in the least-populated side-chain conformation are shown as spheres of arbitrary size, as is the H^α atom. Other H atoms have been left out for clarity. The N61 atom is unshaded.

Molecule 3 has $\omega = 164.8°$, but it is not clear to what extent and how this unusually large deviation from planarity may be related to the strained side-chain conformation. A search in the Cambridge Structural Database[7] revealed that only 3.9% of the 2226 *trans* peptide bonds had $|\omega| < 165°$.

All the three basic rotamers occur for the four Val side chains. Both V2 and V4 have *gauche+*, *trans* torsion angles for $\chi^{1,1}$, $\chi^{1,2}$, which is the least frequently observed Val conformation in the Cambridge Structural Database[7] (Table 3).

Hydrogen bonds. There is a total of 23 hydrogen bonds which have been listed and normalized[9] in Table 4. The

Table 4. Hydrogen bond distances (in Å) and angles (in °).

D–H⋯O	D–H	H⋯O[a]	H⋯O[b]	D⋯O	D–H⋯O
N1–H1⋯O43[i,c]	0.96(4)	1.82(2)	1.75	2.765(3)	170(3)
N1–H2⋯O80[i]	1.01(4)	1.83(3)	1.82	2.802(4)	158(3)
N1–H3⋯O21[i]	0.93(4)	1.96(3)	1.87	2.861(4)	162(3)
N2–H4⋯O23[ix]	0.90(3)	2.07(3)	1.94	2.942(3)	164(3)
N21–H21⋯O70[ix]	0.94(4)	1.78(3)	1.70	2.666(4)	155(3)
N21–H22⋯O22[ii]	0.95(4)	1.80(4)	1.73	2.686(4)	154(3)
N21–H23⋯O1[vi]	0.97(4)	1.99(4)	1.93	2.935(3)	165(3)
N22–H24⋯O3[ix]	1.00(4)	1.95(3)	1.92	2.854(3)	149(2)
N41–H41⋯O62[v]	0.93(4)	1.86(3)	1.77	2.808(3)	154(3)
N41–H42⋯O41[iii]	0.88(4)	2.01(3)	1.88	2.808(3)	150(3)
N41–H43⋯O62[iv]	0.96(4)	1.81(4)	1.74	2.745(4)	165(3)
N42–H44⋯O61[ix]	0.87(3)	2.10(3)	1.96	2.895(3)	152(3)
N61–H61⋯O2[vi]	0.86(4)	1.89(3)	1.72	2.746(3)	172(3)
N61–H62⋯O22[vii]	0.98(4)	1.85(3)	1.80	2.788(3)	160(3)
N61–H63⋯O42[ix]	1.05(4)	1.80(3)	1.82	2.833(3)	168(3)
N62–H64⋯O90[ix]	0.83(4)	2.18(3)	2.00	2.955(4)	155(3)
O70–H71⋯O90[viii]	0.77(4)	1.92(4)	1.75	2.663(4)	161(4)
O70–H72⋯O3[ix]	0.76(4)	2.08(4)	1.90	2.790(3)	157(4)
O80–H81⋯O2[vi]	0.85(4)	1.88(4)	1.78	2.727(3)	173(4)
O80–H82⋯O42[ix]	0.82(4)	2.24(4)	2.14	2.961(3)	146(3)
O90–H91⋯O43[vi]	0.69(5)	2.07(4)	1.92	2.741(3)	164(5)
O90–H92⋯O63[ix]	0.84(4)	1.91(4)	1.81	2.694(3)	156(4)
C1–H111⋯O23[ix]	0.93(3)	2.47(3)	2.36	3.214(4)	136(2)

[a] Refined H-atom positions. [b] Normalized[9] H-atom positions: d(O–H) = 0.95 Å, d(N–H) = 1.03 Å, d(C–H) = 1.10 Å.[10] [c] Symmetry codes: [i] y, $-x+y$, 2/3+z, [ii] $x-y$, x, 1/3+z, [iii] $1-y$, $x-y$, $-1/3+z$, [iv] $1-y$, $x-y$, 2/3+z, [v] $1-x+y$, $1-x$, 1/3+z, [vi] x, y, $-1+z$, [vii] $x-y$, x, $-2/3+z$, [viii] x, y, $1+z$, [ix] x, y, z.

Table 5. Distribution of hydrogen-bond types.

Acceptor	Donor			
	$-NH_3^+$	$>NH$	H_2O	$C^\alpha H$
$-COO^-$	7	2	5	1
$>C=O$	3	1		
H_2O	2	1	1	

hydrogen-bond types are summarized in Table 5. In the previous survey on hydrogen bonding in dipeptides[1] it was found that in non-hydrated structures 9 out of 15 peptide bond carbonyl groups participated in classical H-bonds (not counting C–H donors), while a larger fraction, 15 out of 22 groups, accepted H-atoms in hydrates. This means that in either case several carbonyl groups lose the competition for (N⁻)H or (O⁻)H atoms.* In the present structure, however, all four carbonyl groups are involved in N–H⋯O interactions. Three have NH_3^+ donors, giving a H-bond type usually found in only one out of four dipeptide structures.[1] The carboxylate group of Molecule 1 accepts two H atoms from water molecules and two from $-NH_3^+$. A rather similar pattern occurs for Molecule 3, except that one $-NH_3^+$ is replaced by an amide $>N–H$. In the carboxylate group of Molecule 2, O22 participates in two short interactions with $-NH_3^+$ donors, while O23 is involved in two weaker H bonds, one of them an uncommon interaction with $C^\alpha–H$ in the *syn* direction. As has been described previously, this asymmetry in the H-bond pattern is transferred back to the covalent geometry of the group, which is also clearly asymmetric. The last carboxylate group, on Molecule 4, accepts only three H atoms.
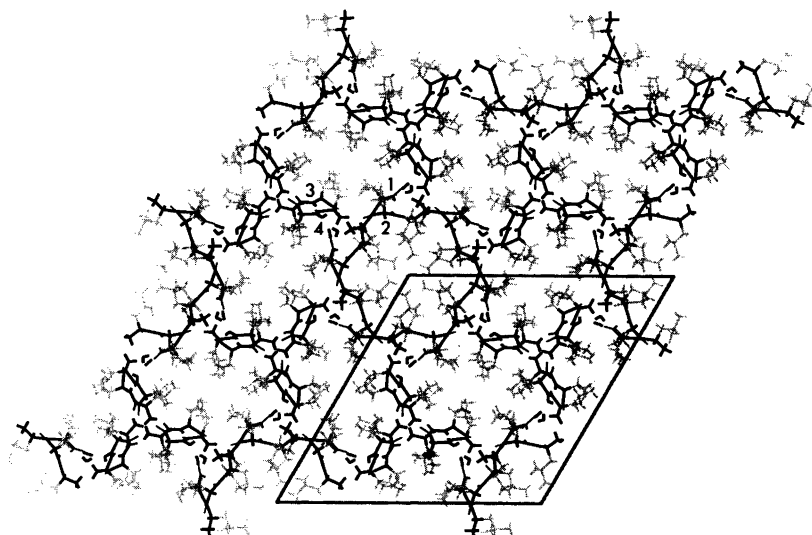
Solvent water molecules. The three solvent water molecules are shown in Fig. 1. All six H atoms are donated to carboxylate groups, except the O70–H⋯O90 water–water hydrogen bond (Table 4). O70 and O80 both accept H atoms from $-NH_3^+$ groups, and thus participate in what has been referred to as water-mediated salt bridges between $-NH_3^+$ and $-COO^-$. In addition to the H bond from O70, O90 also accepts a H atom from a peptide bond $>N–H$ donor. This type of interaction is rather uncommon and has previously been found for nine out of 114 water molecules in the hydrates of short linear peptides.[1] The refined O–H bond lengths for the water molecules appear in Table 4; the calculated bond angles are 113(4), 94(4) and 106(5)° for α(H–O70–H), α(H–O80–H) and α(H–O90–H), respectively.
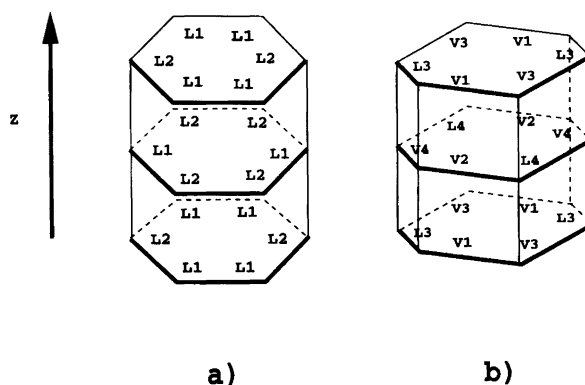

a) b)

Fig. 5. Schematic drawing of the buildup of the (a) hexagonal and (b) twofold symmetry hydrophobic columns. Abbreviations for Leu and Val side chains in Molecules 1–4 are used as described in the text.

Fig. 4. View of the packing arrangement and the unit cell viewed along the *c*-axis. Leu and Val side chains are shown in a lighter colour to distinguish hydrophilic and hydrophobic regions in the crystal. Numbers identify the four crystallographically different dipetide molecules.

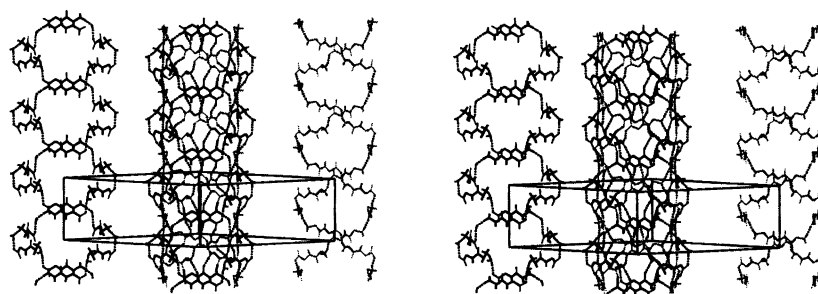* In these structures one often finds $C^\alpha–H\cdots O=C$ interactions.

Fig. 6. Stereoview of the hydrogen-bonded helices formed by Molecule 1 (left, black) and Molecule 2 (right, grey). Side chains have been left out for clarity. In the center figure both helices have been merged to give the hydrogen bonded network surrounding the hexagonal hydrophobic column.

Molecular packing. In crystal structures of organic compounds the occurrence of two molecules in the asymmetric unit is relatively common for monoclinic and orthorombic space groups, giving values for Z up to 8; higher values for Z are rare. The combination of an hexagonal space group with four molecules in the asymmetric for L-Leu-L-Val·¾H_2O gives $Z = 24$. Only six times has this value for Z been observed in the crystal structures of organic compounds, and just once for a peptide structure, a cyclic pentapeptide derivative.[11]

In the crystal structures of short linear peptides there are two modes of separating hydrophilic and hydrophobic groups.[1] For molecules with large hydrophobic side chains the crystals tend to be divided into two-dimensional hydrophobic and hydrophilic layers. With smaller hydrophobic entities one usually finds hydrophobic columns parallel to a short crystallographic axis in the range 4.5–6.0 Å (common) or 7.5–9.0 Å (less common). The crystal structure of L-Leu-L-Val·¾H_2O is the first example of a completely new packing pattern characterized by large hydrophobic columns parallel to a 10–12 Å hexagonal axis. In the present structure there are two distinct hydrophobic columns, one at the hexagonal axes and one around the twofold axes in the middle of the cell (Fig. 4). Each column has contributions from 12 different side chain as is illustrated schematically in Fig. 5. The hydrophobic columns are completely separated by the hydrophilic groups forming the three-dimensional hydrogen-bond network. The hexagonal column is surrounded by Molecules 1 and 2 only. Two independent Molecule 2 chains form right-handed double helices through head-to-tail hydrogen bonds. Molecule 1 also forms right-handed double helices, but the peptide chains are running in the opposite direction, and the peptide molecules are connected through water bridges. These patterns are illustrated in Fig. 6. The other kind of column centered at the two-fold axis is surrounded by the main chains of all four peptides in the asymmetric unit, with four H bonds between Molecules 3 and 4.

The shortest hydrophobic H···H distance is the V1–V3 contact C10–H···H–C50 = 2.34 Å. All other H···H distances exceed 2.46 Å.

It can be seen from Figs. 4 and 5 that the two

disordered side chains L2 and L4 are located in different hydrophobic columns. There are no hydrogen bonds or other interactions between Molecules 2 and 4. It appears, then, that these two very similar disorder phenomena occur completely independent of each other.

Supplementary material. Tables giving fractional coordinates for all atoms, anisotropic temperature parameters for heavy atoms, and the geometry of the least populated conformation of the disordered Leu side chains are available from the authors on request, also by e-mail: c.h.gorbitz@kjemi.uio.no

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