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Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: MU1306). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Cyclic Water Pentamers in L-Leucyl-L-alanine Tetrahydrate

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Abstract

The structure of the title compound, $C_9H_{18}N_2O_3.4H_2O$, contains a very unusual and elaborate system of hydrogen-bonded water molecules which includes cyclic water pentamers with idealized hydrogen-bond cooperativity. The solvent molecules form columns in the crystal, as do hydrophobic aggregates of peptide side chains. Both these units are located between hydrophilic sheets formed by the peptide main chains. The sheets contain two head-to-tail hydrogen-bonded chains, one of which is interrupted by a bridging water molecule that is functionally different from those constituting the core of the water channels.

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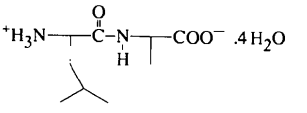
Comment

In the crystal structures of dipeptides, two of the three $-NH_3^+$ H atoms are often donated to the C-terminal carboxylate group, generating two head-to-tail hydrogen-bonded chains in a well defined hydrophilic sheet. Between the sheets are layers with a more or less distinct hydrophobic character depending on the types of amino acid residues involved. We have previously pointed out (Görbitz & Gundersen, 1996*a*) that some modification of this pattern is required when both dipeptide side chains are devoid of hydrogen-bond acceptors, since the third amino H atom would otherwise not be used in hydrogen bonding which is indeed what happens in the structure of L-Met-L-Met (Stenkamp & Jensen, 1975). One possibility is inclusion of an organic solvent molecule that can fit into the hydrophobic layer and provide the necessary hydrogen-bond acceptor. This occurs in L-Leu-L-Val.2-propanol (Görbitz & Gundersen, 1997), L-Leu-L-Leu.DMSO (Mitra & Subramanian, 1994) and L-Leu-L-Ala.DMSO (Mitra, Govindasamy & Subramanian, 1996). Alternatively, the layered crystal build-up may be abandoned with formation of columnar structures in hexagonal space groups, as for L-Val-L-Ala (Görbitz & Gundersen, 1996*a*) and L-Leu-L-Val.0.75H_2O (Görbitz & Gundersen, 1996*b*). Among the hydrophobic dipeptides we have investigated, L-Leu-L-Ala, (I), is the only compound that does not crystallize as elongated needles, and a comparison of its molecular-packing arrangement and hydrogen-bond pattern with those of the previously determined structures is of interest.



(I)

The molecular structure of L-Leu-L-Ala and the crystal packing are shown in Fig. 1. Bond angles for the solvent water molecules and selected torsion angles are listed in Table 1. All bond lengths and bond angles are normal. The peptide main chain is slightly folded with φ_2 (C6—N2—C7—C9) = −66.88 (8)°, while the L-Leu side chain is in the most common conformation (Görbitz & Gundersen, 1996*b*), with χ^1 (N1—C1—C2—C3) *gauche*$^-$ and $\chi^{2,1}/\chi^{2,2}$ (C1—C2—C3—C4/C5) *gauche*$^-$/*trans*). Both subunits have different conformations from those observed for L-Leu-L-Ala in the recently published DMSO solvate (Mitra *et al.*, 1996). It can be seen from Fig. 1 that the four co-crystallized water molecules, *W*40, *W*50, *W*60 and *W*70 (atom O40 is in *W*40 *etc.*), in the asymmetric unit form water columns parallel to the *a* axis, while two Leu and two Ala side chains aggregate into hydrophobic columns. Hydrogen bonds between peptide main chains generate wave-like sheets which are seen edge-on in Fig. 1. Hydrogen-bond parameters are listed in Table 2.

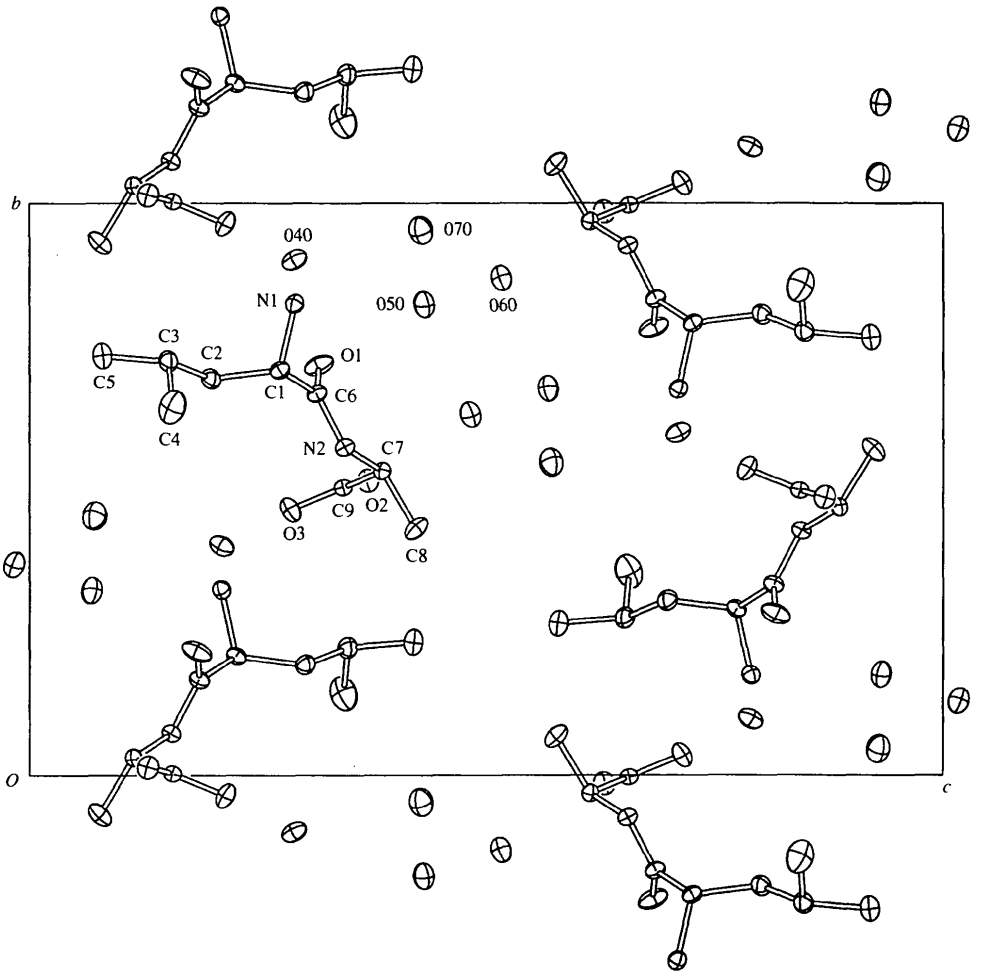


Fig. 1. The molecular structure of L-Leu-Ala with crystal packing viewed along the *a* axis. H atoms have been omitted for clarity and displacement ellipsoids are drawn at the 50% probability level. Atom numbering is given for the dipeptide and four solvent water molecules in the asymmetric unit.

Within the hydrophilic sheets, two amino H atoms, with C′—C^{α}—N—H torsion angles *gauche*$^{+}$ and *trans*, participate in hydrogen bonds. This is a commonly observed pattern in dipeptide structures. Water molecule *W*40 forms an integral part of the sheet as a bridge between charged N- and C-terminal functional groups, thus interrupting one of the two head-to-tail hydrogen-bonded chains. Although the bridging functionality of a solvent water molecule is not uncommon (Görbitz & Etter, 1992), the present sheet structure has not been found previously. Water molecule *W*40 donates its second H atom to the peptide-bond carbonyl group, which in dipeptides is often involved only in C^{α}—H···O=C interactions.

The third amino H atom, pointing out of the sheets, is donated to a solvent water molecule (*W*50), a type of hydrogen bond that also occurs in each of the two separate molecular layers in the 1:1 L-His-L-Ser-Gly-L-Glu hexahydrate complex (Suresh & Vijayan, 1985). Water molecules *W*50, *W*60 and *W*70 and their symmetry equivalents, related by a twofold screw axis, form the core of the water channel and are clearly different from water molecule *W*40 in that together they form only two hydrogen bonds to peptide molecules (Fig. 1). Extensive water···water hydrogen bonding creates a ribbon of fused cyclic water pentamers (Fig. 2). Each ring has five O—H···O bonds all running in the same direction. This favourable pattern takes full advantage of the cooperative effect and has been referred to as a homodromic cyclic system (Saenger, 1979). The hydrogen bonds are almost linear with O—H···O angles $> 170°$ and are quite short with an average O···O distance of 2.779 Å. It is remarkable that two such circles share the water molecules *W*50 and *W*60. Starting with *W*50···*W*70···*W*60′···*W*50″ and going in a clockwise direction in Fig. 2, the five ring O···O···O···O dihedral angles are −4.1, −14.4, 27.5, −30.4 and 20.5°, describing a puckered envelope conformation, with O60

positioned 0.81 Å above the least-squares plane defined by the other four ring O atoms. The ring structure is interesting from a theoretical point of view since it is very close to the global energy minimum for an isolated $(H_2O)_5$ cluster (Estrin, Paglieri, Corongiu & Clementi, 1996; Knochenmuss & Leutwyler, 1992; Xantheas, 1995). The two other ring systems in Fig. 2 have four or six hydrogen bonds, the latter in a very distorted chair shape.

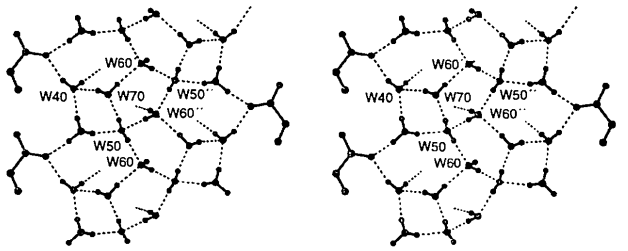


Fig. 2. Stereodiagram showing hydrogen bonds to and between the four solvent water molecules *W*40, *W*50, *W*60 and *W*70. Both N-terminal amino groups and C-terminal carboxylate groups have been included where appropriate. Symmetry codes: (′) $1+x, y, z$; (″) $\frac{1}{2}+x, \frac{1}{2}-y, 2-z$. Thus, *W*50′ and *W*60′ are related to *W*50 and *W*60, respectively, by a twofold screw axis in the **a** direction.

Water molecule *W*70 is engaged in only three hydrogen bonds since O70 accepts only one H atom. It is thus the best acceptor and O50—H···O70 is the shortest water–water contact (Table 3). As can be seen from Fig. 1, O70 also has the largest thermal vibrations, since *W*70 is not anchored to any peptide molecule. *W*50 and *W*60 are each engaged in four hydrogen bonds with approximately tetrahedral configurations [O···O(*W*)···O/N angles in the range 89–126° for *W*50 and 102–118° for *W*60]. The tetrahedron around *W*40 is more distorted (angular range 88–146°).

Although about 50% of all dipeptide structures in the Cambridge Structural Database (Allen & Kennard, 1993) are hydrates (Görbitz & Etter, 1992), the number of water molecules for each peptide molecule is always one or two, with D,L-His-L,D-His pentahydrate (Krause, Baures & Eggleston, 1991) as the sole exception. Other examples of high hydration in crystal structures of short linear peptides include L-Arg-Gly-L-Asp tetrahydrate (Eggleston & Feldman, 1990), L-Asp-L-Arg-L-Val-L-Tyr tetrahydrate (Feldman & Eggleston, 1990) and the 1:1 L-His-L-Ser–Gly-L-Glu hexahydrate complex (Suresh & Vijayan, 1985) mentioned above. Cyclic water systems occur only in the first of these structures, which has two different pentagons of water molecules sharing three hydrogen bonds. These systems are not homodromic, however, as hydrogen bonds are oriented in alternating directions (Saenger, 1979). Cyclic pentamers are abundant in the structures of various clathrate hydrates (Davidson, 1973) and occur in ices III, V and IX (of which only IX is fully ordered) (Savage, 1986).

Experimental

The jar received from Sigma (labelled as the peptide dihydrate) contained large crystals (several mm) which extinguished well when rotated in a polarizing microscope, but had very obvious faults and fractures. Attempts to grow new and better crystals by several techniques were completely unsuccessful. By carefully choosing one specimen from the original sample, and using rather long exposure times (60 s) for each frame during data acquisition, we were nevertheless able to collect high-quality reflection data.

Crystal data

$C_9H_{18}N_2O_3.4H_2O$
$M_r = 274.32$
Orthorhombic
$P2_12_12_1$
$a = 6.1863\ (2)$ Å
$b = 12.5481\ (4)$ Å
$c = 19.8831\ (6)$ Å
$V = 1543.45\ (8)$ Å^3
$Z = 4$
$D_x = 1.181$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 8192 reflections
$\mu = 0.100$ mm^{-1}
$T = 150\ (2)$ K
Block
0.50 × 0.35 × 0.10 mm
Colourless

Data collection

Siemens SMART CCD diffractometer
Sets of exsposures each taken over 0.6° ω rotation scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
$T_{min} = 0.946$, $T_{max} = 0.990$
23 659 measured reflections
7988 independent reflections
7250 reflections with $I > 2\sigma(I)$
$R_{int} = 0.0251$
$\theta_{max} = 38.24°$
$h = -10 \rightarrow 10$
$k = -21 \rightarrow 17$
$l = -33 \rightarrow 34$

Refinement

Refinement on F^2
$R(F) = 0.0380$
$wR(F^2) = 0.0905$
$S = 1.142$
7987 reflections
224 parameters
All N—H and O—H H atoms refined
$w = 1/[\sigma^2(F_o^2) + (0.0365P)^2 + 0.16P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = -0.009$
$\Delta\rho_{max} = 0.348$ e Å^{-3}
$\Delta\rho_{min} = -0.164$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters* (°)

H401—O40—H402	105 (2)	H601—O60—H602	106 (2)
H501—O50—H502	110 (2)	H701—O70—H702	104 (2)
N1—C1—C2—C3	−66.58 (8)	N1—C1—C6—N2	136.12 (7)
C1—C2—C3—C4	−72.16 (10)	C6—N2—C7—C9	−66.88 (8)
C1—C2—C3—C5	165.12 (7)	N2—C7—C9—O2	147.74 (6)
C1—C6—N2—C7	−177.94 (6)	N2—C7—C9—O3	−35.98 (9)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O40	0.84 (2)	1.94 (2)	2.758 (1)	166 (1)
N1—H2···O50	0.89 (1)	1.97 (1)	2.826 (1)	162 (1)
N1—H3···O3^{i}	0.91 (1)	1.87 (1)	2.773 (1)	170 (1)
N2—H4···O2^{ii}	0.88 (2)	2.02 (2)	2.872 (1)	164 (1)
O40—H401···O3^{iii}	0.85 (2)	1.85 (2)	2.663 (1)	158 (2)

O40—H402···O1^{ii}	0.88 (2)	1.78 (2)	2.659 (1)	176 (2)
O50—H501···O60	0.82 (2)	1.94 (2)	2.755 (1)	174 (2)
O50—H502···O70	0.81 (2)	1.92 (2)	2.726 (1)	170 (2)
O60—H601···O2^{iv}	0.82 (2)	1.90 (2)	2.718 (1)	172 (2)
O60—H602···O50^{v}	0.84 (3)	1.98 (3)	2.812 (1)	178 (3)
O70—H701···O40	0.80 (2)	2.09 (2)	2.861 (1)	165 (2)
O70—H702···O60^{ii}	0.85 (2)	1.95 (2)	2.790 (1)	171 (2)

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

The data collection nominally covered over a hemisphere of reciprocal space, by a combination of five sets of exposures, two with the detector set at $2\theta = 30°$ and three with $2\theta = 55°$. Each set had a different φ angle for the crystal and each exposure covered 0.6° in ω. The crystal-to-detector distance was 4.97 cm. No intensity decay was observed. Coverage of the unique set was over 99% complete to at least 70° in 2θ. H atoms bonded to O or N atoms were located by difference Fourier calculations and refined isotropically; other H atoms were placed geometrically and refined with a riding model (including free rotation about C—C bonds for methyl groups), but with the C—H distances free to refine. All H atoms connected to the same C atom were given the same shifts. U_{iso} values were constrained to be $1.2U_{eq}$ of the carrier atom, except that a free variable for U_{iso} was refined for each methyl group.

Data collection: *SMART* (Siemens, 1995). Cell refinement: *SAINT* (Siemens, 1995). Data reduction: *SAINT*. Program(s) used to solve structure: *SHELXTL* (Sheldrick, 1994). Program(s) used to refine structure: *SHELXTL*. Molecular graphics: *SHELXTL*. Software used to prepare material for publication: *SHELXTL*.

The purchase of the Siemens SMART diffractometer was made possible through support from The Research Council of Norway (NFR).

Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: AB1443). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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5,7-Dichlorokynurenic Acid Hydrate, an Antagonist for the Glycine Binding Site on the NMDA Receptor

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Abstract

The structure of 5,7-dichlorokynurenic acid hydrate (IUPAC name: 5,7-dichloro-4-oxo-1,4-dihydro-2-quinolinecarboxylic acid hydrate), $C_{10}H_5Cl_2NO_3.H_2O$, has been determined by X-ray analysis. The molecule exists as a keto tautomer. All hydrogen-bond donors and acceptors take part in the hydrogen-bonding network which connects molecules into a three-dimensional array. Graph-set analysis shows that there are both rings and chains in the network; however, there are no carboxylic acid dimers. The O—H portion of the carboxylic acid group is in a *trans* orientation with respect to the N—H group of the bicyclic ring system; the plane of the carboxylic group makes an angle of 7.6 (2)° with the plane of the heterocyclic ring.

Comment

There is increasing evidence that the amino acid glycine acts as an endogenous co-agonist at a specific strychnine-insensitive site on the NMDA (*N*-methyl-D-aspartate) receptor of the excitatory amino acid receptor