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Pearls on a string: a Z' = 7 structure for glycyl-L-valine

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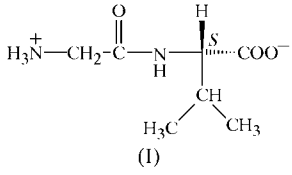
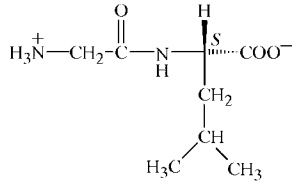
The title peptide, $C_7H_{14}N_2O_3$, crystallizes with seven independent molecules in the asymmetric unit. All have essentially the same overall conformation, but some flexibility is exhibited by the glycine residue. It appears that the high Z' value, observed only three times before for an organic compound, permits formation of shorter hydrogen bonds in one of the two head-to-tail chains involving the N-terminal amino groups and the C-terminal carboxylate groups than found in a hypothetical model structure of glycyl-L-valine with Z' = 1, and that it furthermore alleviates strain associated with an eclipsed orientation of the amino group.

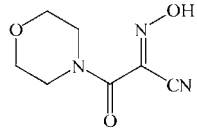
Comment

Among dipeptides constructed from the 20 natural amino acids, the Gly–Xaa series of crystal structures, where Xaa is any amino acid, is the most complete for a specific N-terminal amino acid, with 13 entries in the Cambridge Structural Database (CSD, Version 5.27 of November 2005; Allen, 2002). In a student project, we sought to expand this group of structures towards completeness by crystallization of the title compound, Gly-L-Val, (I).

Thin flakes of (I) obtained by slow evaporation were generally of low quality, but a specimen usable for data collection was found after a number of tests. The initial observation of a 44 Å unit-cell axis indicated that this was an unusual dipeptide crystal, a suspicion that was subsequently verified when structure determination revealed seven independent peptide molecules in the asymmetric unit, labelled *A* to *G* (Fig. 1). All seven molecules have essentially the same conformation, but with some torsion angle variations, in particular for rotation about the C1—C2 bond (ψ_1) (Table 1 and Fig. 2). It is interesting to note that the main chain conformation of Gly-L-Leu [(II); Pattabhi *et al.*, 1974] can be seen to represent an average of the seven Gly-L-Val conformations (Table 1), and the closely related monoclinic structure of (II) provides some clues as to why (I) has crystallized with Z' = 7.


(I)


(II)


(III)

As seen for (II), the crystal structure of (I) is divided into hydrophobic and hydrophilic layers (Fig. 3), and we first suspected that the side-chain modification going from Leu to Val rendered efficient packing of the side chain difficult with Z' limited to 1. To test this hypothesis, a molecular modelling program (*SYBYL*; Tripos, 2005) was used to construct a theoretical Gly-L-Val structure with Z' = 1, based on (II) but adapted to the correct space group, $P2_12_12_1$. This model showed no unfavourable short contacts or large voids compared with the structure of (I).

Our attention then turned to the hydrogen-bonding pattern, with contacts listed in Table 2. Atoms H1 and H3 are involved in head-to-tail chains within a hydrophilic sheet that also comprises the N2—H4···O3 interactions. Two such antiparallel sheets are interconnected by N1—H2···O3 hydrogen bonds and thus generate a hydrophilic layer (Fig. 3). A peculiarity of (II) is the eclipsed conformation of the amino group, as reflected by the H3—N1—C1—C2 torsion angle in Table 1, which is required to minimize the H···O distance in the N1—H3···O2 interaction (Table 2). In (I), two different rotational modes are observed for the amino group, one with

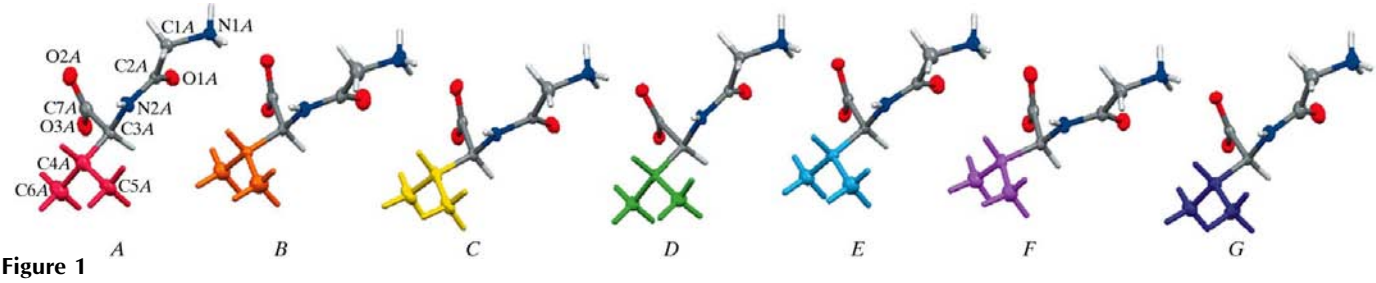


Figure 1
The asymmetric unit of (I). Displacement ellipsoids are drawn at the 50% probability level. Atomic numbering is shown for molecule *A* only. The valyl side chain is shaded differently for molecules *A*, *B*, *C*, *D*, *E*, *F* and *G*.

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H3—N1—C1—C2 < 0° for molecules *B*, *C*, *E* and *F*, and one with H3—N1—C1—C2 > 0° for molecules *A*, *D* and *G*. The fully eclipsed conformation is thus avoided and, at the same time, the associated hydrogen bonds are significantly shorter overall than in (II) (while hydrogen bonds involving atoms H1 and H2 are unchanged).

A further effect of this rearrangement can be seen as a reduction of the structural periodicity along the head-to-tail chains from 6.369 Å for (II) (*a* axis) to 6.299 Å for (I) (*c* axis/7). On the other hand, the shorter N2—H4···O3 hydrogen bond in (I) compared with (II) is most probably attributable mainly to more efficient packing of Val than Leu side chains, indicated by a shorter cell axis [5.5238 (7) Å for (I) and 5.565 Å for (II)], as only molecules of the same kind (*A*···*A*, *etc.*) are involved.

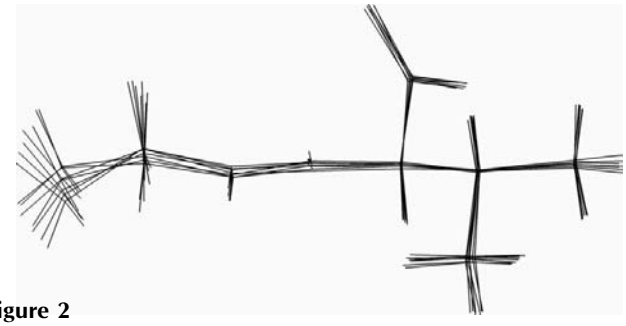

Figure 2
Overlap diagram of the seven molecules in the asymmetric unit of (I) after best fit to the average structure (not shown).

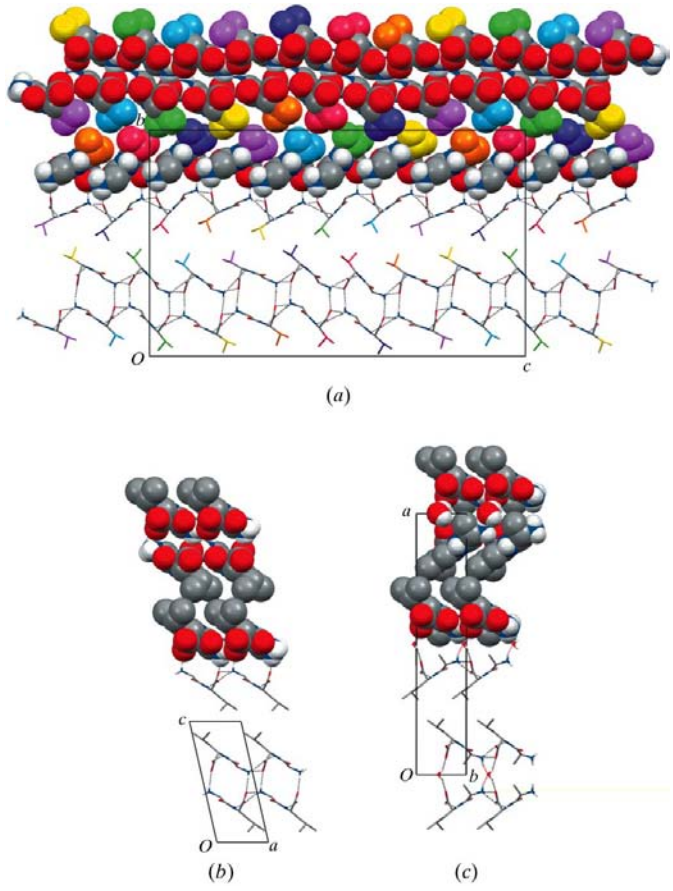

Figure 3
(*a*) The molecular packing and unit cell of (I), viewed along the *a* axis. Hydrogen bonds are indicated by dashed lines and H atoms not involved in such interactions have been omitted for clarity. Half the molecules are shown in a space-filling representation. The shading is similar to that in Fig. 1. (*b*) The crystal structure of Gly-L-Leu (Pattabhi *et al.*, 1974), viewed along the *b* axis. (*c*) The crystal structure of L-Ala-L-Leu (Görbitz, 1999), viewed along the *c* axis.

The monclinic *C*2 structure of L-Ala-L-Leu hemihydrate (Görbitz, 1999) is related to both (I) and (II) (Fig. 3), with essentially the same molecular conformation. Space for the extra methyl side chain at the N-terminus residue is nicely provided by insertion of extra water molecules in the hydrophilic layers. Water thus replaces atom O3 as the acceptor in the N1—H2···O3 interaction, and at the same time the two hydrogen-bonded sheets in a single layer (see above) switch from antiparallel to parallel orientation to provide carboxylate acceptors for both water H atoms.

There are only three other structures in the CSD with $Z' = 7$. Two of these are peptides, *viz.* *L*-Met-L-Ala in space group $P6_1$ (Görbitz, 2003) and Boc-L-Phe-L-Leu-OBzl, a protected dipeptide fragment of enkephalin, in space group $P2_1$ (Antolić *et al.*, 1999). In both cases, the seven molecules exhibit a mixture of conformations, particularly with regard to the side chains, but also with extensive flexibility for the peptide main chains. The third compound, 2-cyano-2-isonitroso-*N*-morpholinylacetamide [(III); Eddings *et al.*, 2004], shares the $P2_12_12_1$ space group with (I) and, with its 7.3 × 14.4 × 54.8 Å unit cell, shows some of the same packing features, but not the division into hydrophobic and hydrophilic layers as seen for (I). In (III), there is a 4:3 distribution between two different chair conformations for the six-membered ring.

Experimental

The title peptide was obtained from Bachem. Crystals in the shape of extremely thin plates were obtained by slow evaporation of an aqueous solution.

Crystal data

$C_7H_{14}N_2O_3$
M_r = 174.20
Orthorhombic, $P2_12_12_1$
a = 5.5238 (7) Å
b = 26.581 (3) Å
c = 44.093 (5) Å
V = 6474.0 (14) Å^3
Z = 28
D_x = 1.251 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 105 (2) K
Plate, colourless
0.75 × 0.25 × 0.01 mm

Data collection

Siemens SMART CCD area-detector diffractometer
ω scans
35141 measured reflections
6579 independent reflections
4122 reflections with $I > 2\sigma(I)$
R_{int} = 0.125
θ_{max} = 25.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.073
$wR(F^2)$ = 0.172
S = 1.28
6579 reflections
765 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.048P)^2 + 2.98P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.009
$\Delta\rho_{max}$ = 0.34 e Å^{-3}
$\Delta\rho_{min}$ = −0.35 e Å^{-3}
Extinction correction: *SHELXTL* (Bruker, 2000)
Extinction coefficient: 0.00086 (13)

Table 1
Torsion angles (°) for the seven independent peptide molecules in (I), corresponding torsion angles for Gly-L-Leu (Pattabhi *et al.*, 1974), and r.m.s. values (Å) compared with the average structure of (I).

Torsion angle	*A*	*B*	*C*	*D*	*E*	*F*	*G*	Mean†	Gly-L-Leu
N1—C1—C2—N2 (ψ_1)	149.7 (5)	178.2 (5)	−178.9 (5)	153.4 (5)	162.1 (5)	−173.3 (5)	164.2 (5)	168 (14)	171.6
C1—C2—N2—C3 (ω_1)	170.5 (5)	173.1 (5)	166.0 (5)	168.1 (4)	171.4 (5)	171.8 (5)	164.2 (5)	169 (3)	168.7
C2—N2—C3—C7 (φ_2)	−63.3 (6)	−71.1 (6)	−64.6 (6)	−61.8 (6)	−64.6 (6)	−68.5 (6)	−60.6 (6)	−65 (4)	−64.9
N2—C3—C7—O2 (ψ_T)	−30.5 (7)	−26.3 (6)	−31.3 (6)	−35.8 (6)	−27.5 (6)	−29.3 (6)	−35.9 (6)	−31 (4)	−30.2
N2—C3—C4—C5 ($\chi_2^{1,1}$)	−61.3 (6)	−58.9 (6)	−58.9 (6)	−60.6 (5)	−61.7 (5)	−57.6 (6)	−60.0 (5)	−60 (2)	
N2—C3—C4—C6 ($\chi_2^{1,2}$)	174.2 (5)	176.9 (5)	177.0 (5)	175.8 (4)	173.8 (4)	178.5 (5)	175.7 (4)	176 (2)	
H3—N1—C1—C2	10.2	−14.1	−8.0	8.7	−4.0	−13.7	9.5	−2 (11)	−1.9
r.m.s.	0.105	0.060	0.106	0.085	0.049	0.099	0.091		0.032‡

† Sample standard deviation in parentheses. ‡ Calculated for main-chain atoms and C_2^{β}.

Table 2
Hydrogen-bond geometry (Å, °) for (I) and for corresponding interactions in the crystal structure of Gly-L-Leu (Pattabhi *et al.*, 1974); covalent N—H distances were set to 0.91 Å for amino groups and 0.88 Å for peptide bond amide groups.

D—H···*A*	Molecules†							Mean	Gly-L-Leu
N1—H1···O3	*A*···B^{i}	*B*···C^{i}	*C*···D^{i}	*D*···E^{i}	*E*···F^{i}	*F*···G^{i}	*G*···A^{ii}		
H···O	1.83	1.92	1.91	1.82	1.89	1.91	1.85	1.87	1.85
N···O	2.727 (6)	2.788 (6)	2.797 (6)	2.719 (6)	2.768 (7)	2.802 (6)	2.751 (7)	2.765	2.750
N—H···O	171	159	165	169	162	166	172	166	170
N1—H2···O2	*A*···G^{iii}	*B*···F^{iii}	*C*···E^{iii}	*D*···D^{iii}	*E*···C^{iii}	*F*···B^{iii}	*G*···A^{iii}		
H···O	1.75	1.82	1.84	1.77	1.78	1.83	1.81	1.80	1.80
N···O	2.652 (6)	2.707 (7)	2.741 (6)	2.676 (6)	2.673 (6)	2.740 (6)	2.714 (7)	2.700	2.704
N—H···O	171	166	172	173	165	177	173	171	174
N1—H3···O2	*A*···*B*	*B*···*C*	*C*···*D*	*D*···*E*	*E*···*F*	*F*···*G*	*G*···A^{iv}		
H···O	2.02	1.98	1.99	2.03	2.00	1.97	2.03	2.00	2.05
N···O	2.840 (6)	2.804 (7)	2.779 (6)	2.845 (6)	2.838 (7)	2.775 (6)	2.830 (7)	2.816	2.856
N—H···O	149	151	145	148	152	147	146	148	147
N2—H4···O3	*A*···A^{i}	*B*···B^{i}	*C*···C^{i}	*D*···D^{i}	*E*···E^{i}	*F*···F^{i}	*G*···G^{i}		
H···O	2.07	2.07	2.13	2.09	2.08	2.08	2.11	2.09	2.15
N···O	2.820 (6)	2.823 (6)	2.862 (6)	2.828 (6)	2.811 (6)	2.841 (6)	2.832 (6)	2.831	2.870
N—H···O	143	144	140	141	140	143	139	142	139

† Donor molecule–acceptor molecule; for designators see Fig. 1. Symmetry codes: (i) $x-1, y, z$; (ii) $x-1, y, z+1$; (iii) $x-\frac{1}{2}, \frac{3}{2}-y, 1-z$; (iv) $x, y, z+1$.

H atoms were positioned with idealized geometry, with amide H atoms in the peptide plane and fixed C—H and N—H distances of 0.98–1.00 and 0.88–0.91 Å, respectively. Rigid rotation was permitted for amino groups only. U_{iso}(H) values were $1.2U_{eq}$ of the carrier atom, or $1.5U_{eq}$(parent) for amino and methyl groups. In the absence of significant anomalous scattering effects, 4887 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*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ3047). Services for accessing these data are described at the back of the journal.

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