Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

L-Phenylalanyl-L-alanine dihydrate

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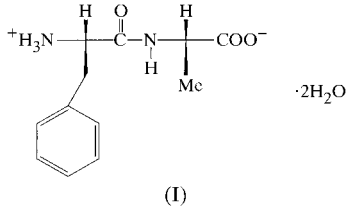
Received 11 October 2000
Accepted 22 January 2001

A new type of molecular arrangement for dipeptides is observed in the crystal structure of L-phenylalanyl-L-alanine dihydrate, $C_{12}H_{16}N_2O_3\cdot 2H_2O$. Two L-Phe and two L-Ala side chains aggregate into large hydrophobic columns within a three-dimensional hydrogen-bond network.

Comment

Dipeptides with two hydrophobic residues (L-Ala, L-Val, L-Leu, L-Ile, L-Met and L-Phe) have a high propensity to form cocrystals with organic solvent molecules. The structures of these solvates are invariably divided into distinct hydrophobic and hydrophilic layers (Görbitz, 1999, and references therein). When organic solvents are not used for crystallization purposes, a much more heterogeneous group of crystal-packing arrangements results. Structures with two-dimensional layers of peptide main chains have been observed [L-Met-L-Met (Stenkamp & Jensen, 1975), L-Leu-L-Ala tetrahydrate (Görbitz, 1997) and L-Phe-L-Val (Görbitz, 2000)], as well as honeycomb patterns with hexagonally symmetric hydrophobic columns along an ∼10 Å long *c* axis [L-Val-L-Ala (Görbitz & Gundersen, 1996*a*), L-Leu-L-Val 0.75-hydrate (Görbitz & Gundersen, 1996*b*), and L-Val-L-Val, L-Ala-L-Val and L-Ile-L-Ala (Görbitz, 2001)]. The L-Leu/Phe-L-Leu/Phe series, on the other hand, form structures with hydrophilic columns and one-dimensional hydrogen-bond patterns (Görbitz, 2001). L-Ala-L-Ala (Fletterick *et al.*, 1971) has a unique combination of hydrophobic columns and tetragonal symmetry.



(I)

All bond lengths and angles for L-Phe-L-Ala dihydrate, (I), shown in Fig. 1, are normal. The peptide main chain is fairly extended and the L-Phe side chain is in the common *gauche*$^-$ conformation. The aromatic ring is perfectly planar; the r.m.s. distance of ring C atoms from the ring plane is just 0.0021 Å.

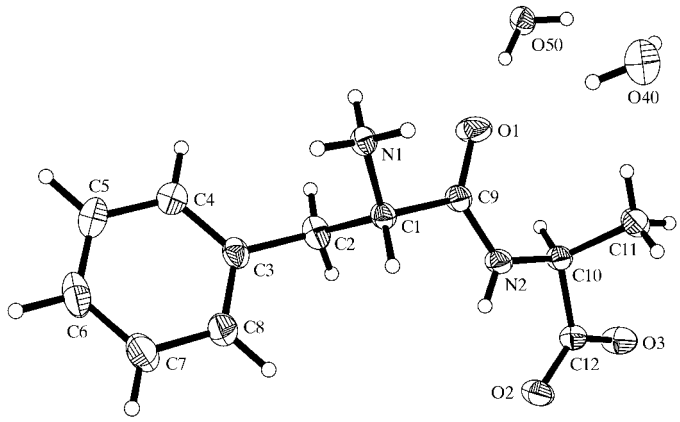


Figure 1
The structure of L-Phe-L-Ala dihydrate with the atomic numbering indicated. Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as spheres of arbitrary size.

The crystal structure and unit cell are depicted in Fig. 2. The molecular arrangment is new for dipeptides, but it is reminiscent of the L-Ala-L-Ala structure (Fletterick *et al.*, 1971) in that groups of four side chains constitute hydrophobic columns within a rectangular hydrogen-bond pattern. The types of hydrogen bonds are, however, completely different in the two structures. All three amino H atoms in L-Ala-L-Ala are donated to C-terminal carboxylate groups, while only one such interaction is present in the title structure, in which it generates a pleated head-to-tail chain parallel to the *b* axis. There are no other direct contacts between the peptide molecules. Hydrogen-bond parameters are given in Table 2. It is interesting to note that O50 is involved in four short hydrogen bonds [$d(O\cdots H) < 2.0$ Å] as a link between charged amino and carboxylate groups. O40, on the other hand, participates

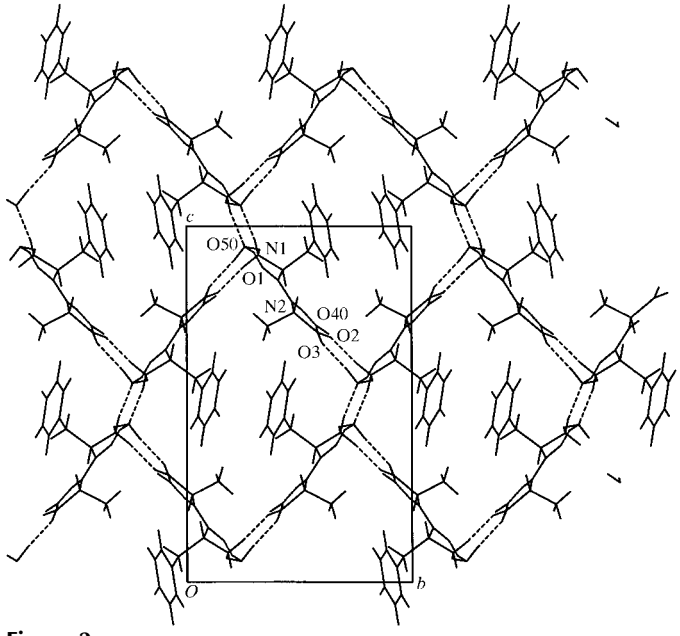


Figure 2
The unit cell and molecular packing viewed along the *a* axis. Hydrogen bonds are shown as dashed lines.

in just one short interaction (as a donor to a carboxylate group). The shortest interaction with O40 as acceptor has a peptide N—H bond as donor and d(O···H) = 2.186 (13) Å. Consequently, thermal motion is significantly greater for O40 (U_{eq} = 0.034 Å^2) than for the more fixed O50 (U_{eq} = 0.024 Å^2), as is also readily observed in Fig. 1.

Due to the comparatively long a axis (most dipeptides have an axis in the 5–6 Å range), the 'herring-bone' pattern generated by the aromatic rings is quite stretched out and unusual in that neighbouring rings related by a twofold screw axis make an angle of only 35.9°. The centroid–centroid separation is 5.15 Å and the shortest H···C distance for C_{ar}—H···C_{ar} contacts is 3.15 Å. There are no contacts between rings related by translation along the a axis.

Experimental

L-Phe-L-Ala was obtained from Sigma and was used as received. Needle-shaped crystals were grown by slow evaporation of an aqueous solution of the peptide at 276 K.

Crystal data

$C_{12}H_{16}N_2O_3\cdot 2H_2O$
M_r = 272.30
Orthorhombic, $P2_12_12_1$
a = 7.6541 (2) Å
b = 11.0918 (3) Å
c = 17.5990 (5) Å
V = 1494.12 (7) Å^3
Z = 4
D_x = 1.211 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 6235 reflections
θ = 2.2–35.0°
μ = 0.09 mm^{-1}
T = 150 (2) K
Needle, colourless
0.70 × 0.26 × 0.18 mm

Data collection

Siemens SMART CCD diffractometer
Sets of exposures each taken over 0.6° ω rotation scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.936, T_{max} = 0.983
19 962 measured reflections
3691 independent reflections (plus 2863 Friedel-related reflections)
5553 reflections with $I > 2\sigma(I)$
R_{int} = 0.021
θ_{max} = 35.0°
$h = -12 \rightarrow 11$
$k = -17 \rightarrow 17$
$l = -26 \rightarrow 28$
Intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.090
S = 1.02
6554 reflections
210 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0588P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.004
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}

Positional parameters were refined for H atoms involved in hydrogen bonds. Other H atoms were placed geometrically and refined with constraints to keep all C—H distances and C—C—H angles on any one C atom the same. Free rotation of the L-Ala methyl group was permitted. U_{iso} values were set at 1.2U_{eq} of the carrier atom or 1.5U_{eq} for water molecules. For the amino and methyl groups, two free variables were refined for U_{iso}. The absolute structure was known for the purchased material. The Flack x parameter [0.1 (5); Flack, 1983] does not allow this to be determined from the refinement (Flack & Bernadinelli, 2000).

Table 1
Selected geometric parameters (Å, °).

O1—C9	1.2369 (9)	N1—C1	1.4809 (10)
O2—C12	1.2515 (10)	N2—C9	1.3284 (9)
O3—C12	1.2580 (10)		
H401—O40—H402	108.8 (16)	H501—O50—H502	101.2 (13)
N1—C1—C9—N2	153.99 (7)	N2—C10—C12—O3	178.89 (7)
C1—C9—N2—C10	170.21 (7)	N1—C1—C2—C3	−62.08 (9)
C9—N2—C10—C12	−164.26 (7)	C1—C2—C3—C4	109.27 (9)
N2—C10—C12—O2	−2.32 (10)		

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O50^{i}	0.888 (13)	1.980 (13)	2.7879 (9)	150.5 (12)
N1—H2···O2^{ii}	0.914 (13)	1.802 (13)	2.7114 (9)	172.5 (12)
N1—H3···O50^{iii}	0.910 (13)	1.974 (12)	2.8440 (9)	159.3 (12)
N2—H4···O40^{iv}	0.825 (13)	2.186 (13)	2.9843 (9)	163.0 (12)
C1—H11···O40^{iv}	1.000 (12)	2.479 (12)	3.2920 (10)	138.1 (9)
O40—H401···O3^{v}	0.839 (19)	1.933 (19)	2.7679 (9)	172.9 (17)
O40—H402···O2^{ii}	0.829 (17)	2.462 (17)	3.0030 (10)	123.8 (14)
O40—H402···O1	0.829 (17)	2.721 (17)	3.4353 (11)	145.3 (15)
O50—H501···O3^{v}	0.834 (15)	1.850 (15)	2.6818 (9)	174.6 (14)
O50—H502···O1	0.834 (15)	1.930 (15)	2.7285 (8)	160.0 (14)

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

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 1997); 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).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DA1163). Services for accessing these data are described at the back of the journal.

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