

An $\text{NH}_3^+ \cdots$ phenyl interaction in
L-phenylalanyl-L-valine

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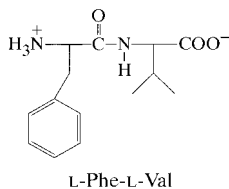
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One of the amino H atoms of L-phenylalanyl-L-valine, $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3$, participates in a rare secondary interaction in being accepted by the aromatic ring of the phenylalanine side chain. The phenyl group is also a donor in a weak hydrogen bond to the peptide carbonyl group.

Comment

Dipeptides with two hydrophobic residues (L-Ala, L-Val, L-Leu, L-Ile, L-Met, L-Phe) have a high propensity to form cocrystals with organic solvent molecules (Görbitz, 1999a, and references therein). The resulting structures are characterized by being divided into hydrophobic layers with peptide side chains, and hydrophilic layers with two head-to-tail hydrogen-bonded chains involving the N-terminal amino groups and the C-terminal carboxylate groups. The third amino H atom is accepted by the solvent molecule, which is embedded in the hydrophobic layer. Only one example has been found of a layered hydrophobic dipeptide structure completely devoid of solvent molecules. This is the structure of L-Met-L-Met (Stenkamp & Jensen, 1975), for which we previously stated that 'the last amino H atom is not used for hydrogen bonding' (Görbitz & Gundersen, 1996a). A closer inspection, however, reveals that an $\text{N}-\text{H} \cdots \text{S}$ interaction is in fact present [$d(\text{H} \cdots \text{S}) = 2.79(3) \text{ \AA}$, or 2.656 \AA with the $\text{N}-\text{H}$ distance normalized to 1.03 \AA], which means that the methionine side chain is a weak hydrogen-bond acceptor.



Unlike most other hydrophobic dipeptides, L-Phe-L-Val crystallizes as thin plates. This property sets it apart from the hexagonal needles of L-Ala-L-Val, L-Val-L-Val (Görbitz, 2001) and L-Leu-L-Val-0.75 H_2O (Görbitz & Gundersen, 1996b), and also from the very hydrophobic needles of the L-Leu/Phe-L-Leu/Phe series, which all form columnar structures (Görbitz,

2001). The structure of the title compound is clearly different in being divided into layers.

The hydrogen-bonding pattern involves two parallel head-to-tail chains, one for each carboxylate O atom (Fig. 2). Within each chain, alternate peptide molecules are related by a twofold screw axis. The third and last classical hydrogen bond also generates a chain, perpendicular to the first two, by connecting the peptide bond $>\text{N}-\text{H}$ with the *anti* lone pair of O3. The resulting pleated pattern is shared with five other dipeptides, namely L-Leu-L-Leu-2-methyl-2-propanol (Görbitz, 1999b), L-Ala-L-Phe-2(2-propanol) (Görbitz, 1999a), L-Leu-L-Val-methanol (Görbitz & Torgersen, 1999), L-Val-L-Glu (Eggleston, 1984) and L-Leu-L-Tyr (Krause *et al.*, 1993). The essential third amino H atom is accepted by a solvent molecule in the first three of these structures, and a normal functional group in a side chain in the last two. For L-Phe-L-Val, in contrast, the edge of the side chain phenyl group is the acceptor (Fig. 2). There are two $\text{H} \cdots \text{C}$ distances of 2.59 \AA (Table 2), with an $\text{H} \cdots$ centroid distance of 2.93 \AA . This is consistent with the fact that the title compound is only the second hydrophobic dipeptide which grows layered crystals devoid of solvent molecules.

Lately, much interest has been focused on the role of aromatic rings as hydrogen-bond acceptors (Desiraju & Steiner, 1999). A range of different donors can participate in $\text{X}-\text{H} \cdots \text{Ph}$ interactions, among them the positively charged amino group. It is, however, used very infrequently, as only 11 $-\text{NH}_3^+ \cdots \text{Ph}$ hydrogen bonds were found in the 866 structures in the Cambridge Structural Database (Allen & Kennard, 1993) that contain both groups. Six of them (Bakshi *et al.*, 1994; Bock *et al.*, 1997; Steiner *et al.*, 1997; Duatti *et al.*, 1991), as well as one in a recently reported structure (Steiner & Mason, 2000), occur in special systems with tetraphenylborate anions as acceptors. The H atoms involved are often located more or less directly above the ring center, with comparatively short $\text{H} \cdots$ centroid distances down to 2.13 \AA . Weaker interactions in which the H atom is shifted closer to the ring edge ($\text{H} \cdots$ centroid distances in the range $2.39-2.96 \text{ \AA}$) are found in

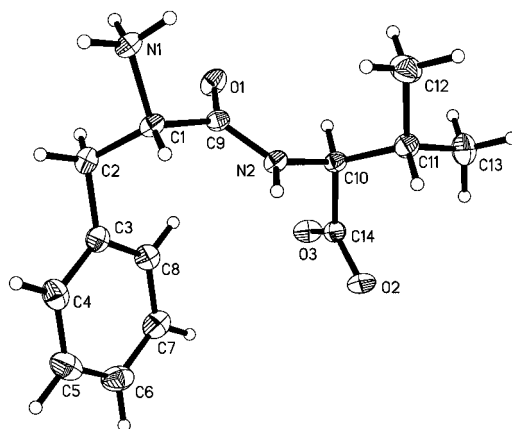


Figure 1

The structure of L-Phe-L-Val 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 molecular conformation is semi-extended; all bond lengths and bond angles are normal.

the structures of L-Tyr-L-Val hydrate (Ramakrishnan *et al.*, 1984), L-Tyr-L-Leu hydrate (Ramakrishnan & Viswamitra, 1988), pressinoic acid [a disulfide-linked hexapeptide constituting the cyclic moiety of Vasopressin; Langs *et al.* (1986)], a peptide derivative containing phenylglycine (Coudert *et al.*, 1996) and DL-*o*-tyrosine hydrochloride (Mostad *et al.*, 1977). The $-\text{NH}_3^+ \cdots \text{Ph}$ hydrogen bond found in the title structure is thus the sixth observed for a neutral acceptor. The rarity of this type of interaction can be explained by the fact that the amino group prefers to participate, whenever possible, in more traditional hydrogen bonds to strong acceptors, while the aromatic groups are more likely to be involved in interactions with weaker $X-\text{H}$ donors.

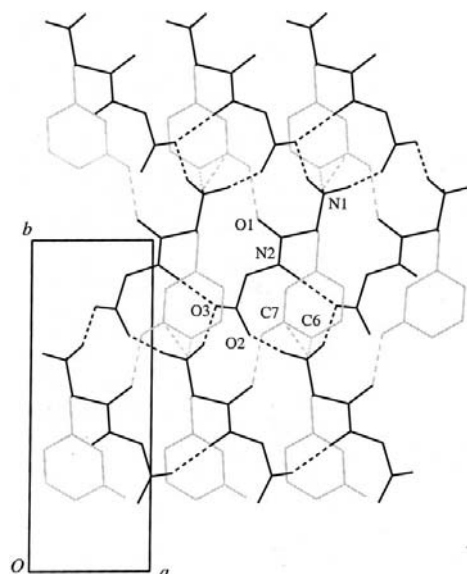


Figure 2

The hydrogen bonding in a hydrophilic layer. The view direction is approximately parallel to the z axis (only one face of the unit cell is shown). Peptide main chains and the three classical hydrogen bonds between them are shown in black. The L-Phe side chain and the hydrogen bonds associated with it are shown in a grey half-tone. The L-Leu side chain and all H atoms not directly involved in hydrogen bonding have been removed for clarity.

When the peptide carbonyl group does not accept H atoms from N-H or O-H donors, as in the present structure, it is frequently observed to participate in weaker $\text{C}\alpha-\text{H} \cdots \text{O}=\text{C}$ interactions. Such a contact is also present here, but it is very long (Table 2), and the aromatic ring is a donor in a shorter and more prominent hydrogen bond (Fig. 2).

In addition to their participation in hydrogen bonds as donors and acceptors, the phenyl rings are also engaged in aromatic stacking. A typical 'herring-bone' pattern is generated by rings related by a twofold screw axis parallel to the 5.1 \AA a axis. The centroid separation and interplanar angle are 5.68 \AA and 67.3° , respectively. The shortest $\text{H} \cdots \text{C}$ distances for $\text{C}(\text{ar})-\text{H} \cdots \text{C}(\text{ar})$ contacts are 3.0 \AA both for molecules related by the twofold screw and for molecules related by translation along the a axis. In conclusion, the phenyl group of L-Phe-L-Val is involved in intermolecular interactions to a much higher degree than usually observed in peptide structures.

Experimental

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

Crystal data

$\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3$
 $M_r = 264.32$
 Orthorhombic, $P2_12_12_1$
 $a = 5.0955 (3) \text{ \AA}$
 $b = 13.2155 (7) \text{ \AA}$
 $c = 20.1670 (11) \text{ \AA}$
 $V = 1358.04 (13) \text{ \AA}^3$
 $Z = 4$
 $D_x = 1.293 \text{ Mg m}^{-3}$

Mo $K\alpha$ radiation
 Cell parameters from 6612 reflections
 $\theta = 2.54\text{--}27.82^\circ$
 $\mu = 0.091 \text{ mm}^{-1}$
 $T = 150 (2) \text{ K}$
 Plate, colourless
 $0.60 \times 0.60 \times 0.05 \text{ mm}$

Data collection

Siemens SMART CCD diffractometer
 1655 reflections with $I > 2\sigma(I)$
 Sets of exposures each taken over 0.3° ω rotation scans
 $R_{\text{int}} = 0.014$
 $\theta_{\text{max}} = 27.82^\circ$
 $h = -6 \rightarrow 6$
 $k = -17 \rightarrow 17$
 $l = -19 \rightarrow 26$
 Absorption correction: empirical (SADABS; Sheldrick, 1996)
 $T_{\text{min}} = 0.947$, $T_{\text{max}} = 0.995$
 8290 measured reflections

1741 independent reflections
 1655 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.014$
 $\theta_{\text{max}} = 27.82^\circ$
 $h = -6 \rightarrow 6$
 $k = -17 \rightarrow 17$
 $l = -19 \rightarrow 26$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.028$
 $wR(F^2) = 0.070$
 $S = 1.056$
 1741 reflections
 200 parameters
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0395P)^2 + 0.2794P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} = 0.007$
 $\Delta\rho_{\text{max}} = 0.19 \text{ e \AA}^{-3}$
 $\Delta\rho_{\text{min}} = -0.17 \text{ e \AA}^{-3}$
 Absolute structure: see below

Table 1

Selected geometric parameters (\AA , $^\circ$).

O1—C9	1.2298 (19)	N1—C1	1.4964 (18)
O2—C14	1.2500 (17)	N2—C9	1.3411 (18)
O3—C14	1.2623 (19)		
N1—C1—C9—N2	128.94 (13)	N1—C1—C2—C3	-173.05 (13)
C1—C9—N2—C10	178.82 (12)	C1—C2—C3—C4	110.58 (16)
C9—N2—C10—C14	-109.57 (14)	N2—C10—C11—C12	-59.34 (16)
N2—C10—C14—O2	-80.87 (15)	N2—C10—C11—C13	178.09 (13)
N2—C10—C14—O3	97.69 (15)		

Table 2

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

$D-\text{H} \cdots A$	$D-\text{H}$	$\text{H} \cdots A$	$D \cdots A$	$D-\text{H} \cdots A$
N1—H1 \cdots C6 ⁱ	0.95 (2)	2.59 (2)	3.523 (2)	170.4 (17)
N1—H1 \cdots C7 ⁱ	0.95 (2)	2.59 (2)	3.384 (2)	142.2 (18)
N1—H2 \cdots O2 ⁱ	1.00 (2)	1.72 (2)	2.6926 (18)	164 (2)
N1—H3 \cdots O3 ⁱⁱ	0.98 (2)	1.85 (2)	2.7662 (17)	154 (2)
N2—H4 \cdots O3 ⁱⁱⁱ	0.86 (2)	2.03 (2)	2.8907 (17)	179.2 (18)
C1—H11 \cdots O1 ⁱⁱⁱ	0.96	2.54	3.151 (2)	122
C7—H71 \cdots O1 ^{iv}	1.00	2.42	3.132 (2)	127

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

H atoms bonded to nitrogen were refined isotropically; other H atoms were placed geometrically and refined with constraints to keep all C—H distances and C—C—H angles on one C atom the same.

Free rotation of methyl groups was permitted. U_{iso} values were set at $1.2U_{\text{eq}}$ of the carrier atom or $1.5U_{\text{eq}}$ for methyl groups. Intensities were measured for 1120 Friedel pairs. The absolute structure could not be established; the value for the Flack x parameter was 0.4 (8) (Flack, 1983). Friedel pairs were therefore merged in the final refinements. NH_3^+ ···phenyl interactions in the Cambridge Structural Database [CSD version 5.19, April 2000; Allen & Kennard (1993)] were identified by searching for structures with at least one H ···C distance less than 2.8 Å. Additionally, the centroid—C ···H angle was constrained to be in the range 60–120° to avoid hits for groups such as Ph—OH where the hydroxylic O atom is the true acceptor. Two structures with such interactions were still returned by the search and were subsequently rejected. A search for structures using an H ···centroid distance less than 3.1 Å as the only search criterion produced the same results.

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*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ1429). Services for accessing these data are described at the back of the journal.

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