Acta Crystallographica Section C
Crystal Structure
Communications
ISSN 0108-2701

N-(L-2-Aminobutyryl)-L-alanine and 2-(L-alanylamino)-L-butyric acid 0.33-hydrate

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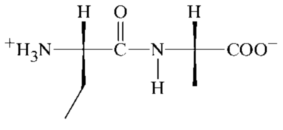
Received 8 May 2002
Accepted 2 July 2002
Online 31 July 2002

The crystal structure of *N*-(L-2-aminobutyryl)-L-alanine, $C_7H_{14}N_2O_3$, is closely related to the structure of L-alanyl-L-alanine, both being tetragonal, while the retro-analogue 2-(L-alanylamino)-L-butyric acid 0.33-hydrate, $C_7H_{14}N_2O_3\cdot0.33H_2O$, forms a new type of molecular columnar structure with three peptide molecules in the asymmetric unit.

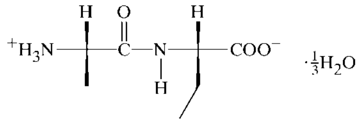
Comment

Recent investigations into the structures of dipeptides with two hydrophobic residues (Ala, Val, Leu, Ile or Phe; the stereochemical indicator L is common to all residues discussed in this paper and so is omitted) have revealed a diverse set of hydrogen-bond and crystal-packing arrangements [see Görbitz (2002*a*) for an overview and a complete set of references]. Some patterns, however, recur in two or more structures. One example is the hexagonally symmetric hydrophobic columns with empty central channels first observed for Val–Ala (Görbitz & Gundersen, 1996), which were subsequently found not only for the retro-analogue Ala–Val (Görbitz, 2002*b*), but also for a series of other dipeptides containing Ala, Val and Ile residues (Görbitz, 2002*c*). Finding such stable motifs is a key element in establishing peptides as useful model molecules for the design of materials by crystal engineering (Desiraju, 2001).

The size of the pores in a Val–Ala class structure is inversely related to the bulk of the two side chains. Val–Ala (Görbitz & Gundersen, 1996) and Ala–Val (Görbitz, 2002*b*) possess the largest known pores, with diameters of around 5 Å. Both these dipeptides have a total of four side-chain C atoms. In order to see if still larger pores could be attained by reducing the number of side-chain C atoms to three, crystal structure investigations were undertaken for the two title compounds, *N*-(L-2-aminobutyryl)-L-alanine or Abu–Ala, (I) (Fig. 1), and 2-(L-alanylamino)-L-butyric acid 0.33-hydrate or Ala–Abu, (II) (Fig. 2). Regarding a further reduction of the number of side-chain C atoms to two, the structure of Ala–Ala (Fletterick *et al.*, 1971) is the only peptide structure in the Cambridge Structural Database (Version 5.23 of April 2002; Allen & Kennard, 1993) with tetragonal symmetry, and is not a member of the Val–Ala class.



(I)



(II)

The crystal packing of (I) is shown together with that of Ala–Ala (Fletterick *et al.*, 1971) in Fig. 3. The two structures are almost indistinguishable, except that the empty central channels of the Ala_1 hydrophobic columns in Ala–Ala are filled by Abu_2 C^γ methyl groups in (I). The calculated density for (I) (1.379 Mg m^{-3}) is well above the value of 1.276 Mg m^{-3} for Ala–Ala (Fletterick *et al.*, 1971), which used to be the highest value observed for a hydrophobic dipeptide.

The main peptide chain of (I) is in an extended conformation (Fig. 1) and the bond lengths and angles are normal. To avoid steric conflict, there is a 1:1 disorder of the Abu side chain (Fig. 4). The somewhat unusual torsion angles associated with the two alternative orientations, −81.8 (7) and 79.1 (8)° (Table 1), have the curious effect of placing the two C^γ methyl positions on top of each other when viewed along the *c* axis, as

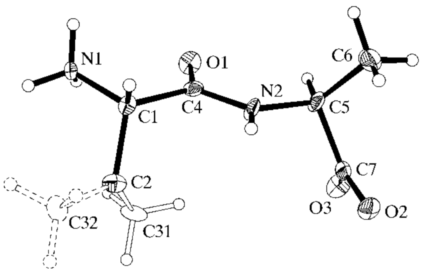


Figure 1
A view of the molecule of (I) with the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Two alternative Abu side-chain orientations, each with occupancy 0.5, are shown. The H atoms bonded to C2 have been omitted for clarity.

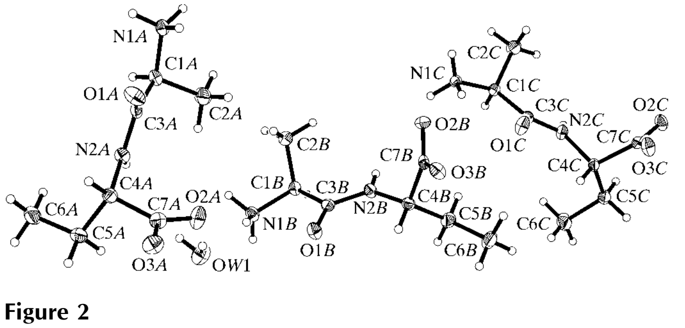


Figure 2
A view of the three independent molecules of (II) with the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

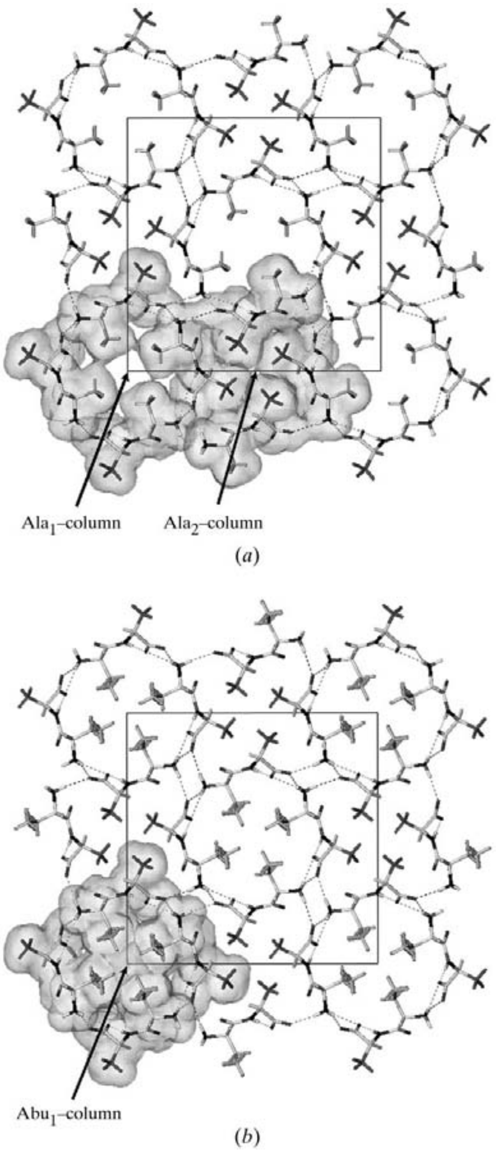


Figure 3
The molecular packing and unit cells of (*a*) Ala–Ala (Fletterick *et al.*, 1971) and (*b*) (I), both viewed along the *c* axis. A volume contour surface surrounds selected molecules in each structure to illustrate the presence of two types of hydrophobic columns. Atoms in the side chain of residue 2 are shown in a darker tone than those in the side chain of residue 1.

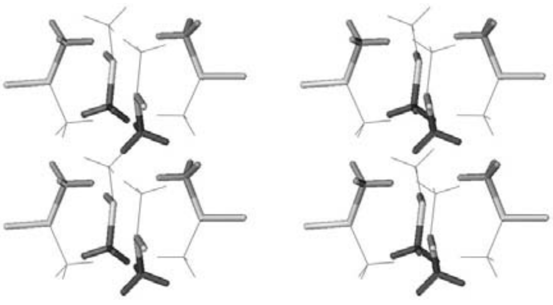


Figure 4
A stereodrawing of the hydrophobic interactions of an Abu column in the structure of (I). Alternative side-chain positions prohibited by steric conflict are shown by fine lines. Directly opposing mutually exclusive methyl positions have H$\cdots$H separations as little as 1.09 Å.

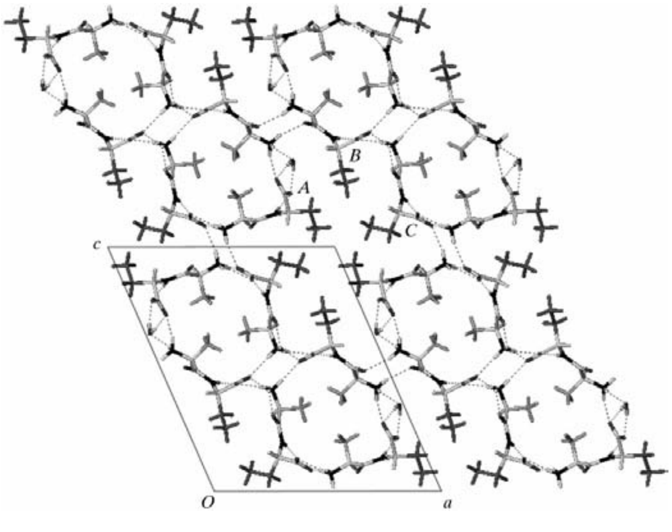


Figure 5
The molecular packing and unit cell of (II), viewed along the *b* axis. Atoms in the Abu side chain are shown in a darker tone than those in the Ala side chain. The three peptide molecules in the asymmetric unit are labelled *A*, *B* and *C*.

in Fig. 3. The shortest intermolecular H$\cdots$H contact between the four molecules related by fourfold symmetry is 2.44 Å, while H$\cdots$H contacts between quartets related by translation along the *c* axis start at 2.80 Å. As for Ala–Ala, the tetragonal symmetry renders possible the formation of three strong $-NH_3^+\cdots{}^-OOC-$ hydrogen bonds (Table 2), which set these two structures apart from all other structures of hydrophobic dipeptides.

As is evident from Fig. 3, the columns formed by Ala$_2$ in the Ala–Ala structure (Fletterick *et al.*, 1971) are more densely packed than the Ala$_1$ columns. Compared with (I), it thus seemed less likely that (II) would retain an Ala–Ala class structure. Indeed, Fig. 5 shows a completely new type of packing pattern that combines elements from the Ala–Ala class, such as the separation of residue 1 and residue 2 side chains into independent columns, with elements from the Val–Ala class, such as the pseudo-hexagonal arrangement of Ala$_1$ columns around Abu$_2$ columns. A unique feature of (II) is a cocrystallized water molecule that is essential for completing the hydrogen-bond network in the crystal. The result is a well defined structure with $D_x = 1.282$ Mg m^{-3}.

The three peptide molecules in the asymmetric unit of (II) are in extended conformations with normal bond lengths and angles, and are not related by pseudosymmetry. They differ mainly in the orientation of the Abu side chain, which is *trans* for molecule *B* but *gauche* for molecules *A* and *C* (Fig. 2 and Tables 3 and 4). The observation of $Z' = 3$ is actually quite rare for peptides, and only eight other examples were found in the Cambridge Structural Database (Allen & Kennard, 1993).

In conclusion, since neither (I) nor (II) form Val–Ala class structures, the largest known hydrophobic pores still occur in the structures of Val–Ala (Görbitz & Gundersen, 1996) and Ala–Val (Görbitz, 2002*b*).

Experimental

Both title compounds were obtained from Bachem and used as received. Crystals were grown by rapid evaporation of aqueous solutions at ambient temperature. The crystals of (II) were of high quality, but the crystals of (I) were usually twinned and/or displayed obvious orientational disorder for layers along the *c* axis. The specimen selected for data collection was fairly small, but not twinned.

Compound (I)

Crystal data

$C_7H_{14}N_2O_3$
M_r = 174.20
Tetragonal, *I*4
a = 17.9290 (12) Å
c = 5.2196 (5) Å
V = 1677.8 (2) Å^3
Z = 8
D_x = 1.379 Mg m^{-3}

Mo *K*α radiation
Cell parameters from 3540 reflections
θ = 1.6–27.1°
μ = 0.11 mm^{-1}
T = 105 (2) K
Needle, colourless
0.65 × 0.12 × 0.05 mm

Data collection

Bruker SMART CCD area-detector diffractometer
ω rotation scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.932, T_{max} = 0.995
5085 measured reflections

1029 independent reflections
1001 reflections with $I > 2\sigma(I)$
R_{int} = 0.041
θ_{max} = 27.1°
h = −22 → 16
k = −22 → 22
l = −6 → 6

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.079$
$wR(F^2) = 0.180$
S = 1.27
1029 reflections
121 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0203P)^2 + 13.6465P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.003$
$\Delta\rho_{max}$ = 0.36 e Å^{-3}
$\Delta\rho_{min}$ = −0.39 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (I).

O1—C4	1.230 (7)	N1—C1	1.497 (7)
O2—C7	1.265 (7)	N2—C4	1.351 (7)
O3—C7	1.233 (8)		
O3—C7—C5	119.0 (6)	O2—C7—C5	116.4 (6)
N1—C1—C4—N2	171.6 (5)	N2—C5—C7—O2	−71.7 (7)
C1—C4—N2—C5	176.5 (5)	N1—C1—C2—C31	79.1 (8)
C4—N2—C5—C7	−114.3 (6)	N1—C1—C2—C32	−81.8 (7)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O3^{i}	0.92	1.99	2.846 (7)	154
N1—H2···O2^{ii}	0.92	1.90	2.787 (7)	160
N1—H3···O2^{iii}	0.92	1.89	2.804 (6)	170
N2—H4···O3^{iv}	0.86	2.00	2.856 (7)	177
C1—H11···O1^{iv}	0.98	2.45	3.316 (7)	147

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

Compound (II)

Crystal data

$C_7H_{14}N_2O_3 \cdot 0.33H_2O$
M_r = 180.21
Monoclinic, $P2_1$
a = 15.4292 (5) Å
b = 5.4602 (2) Å
c = 18.1320 (6) Å
β = 113.505 (1)°
V = 1400.81 (8) Å^3
Z = 6

D_x = 1.282 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 7806 reflections
θ = 2.2–35.0°
μ = 0.10 mm^{-1}
T = 105 (2) K
Needle, colourless
1.30 × 0.12 × 0.08 mm

Data collection

Siemens SMART CCD area-detector diffractometer
ω rotation scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.876, T_{max} = 0.992
19 775 measured reflections

10 606 independent reflections
7926 reflections with $I > 2\sigma(I)$
R_{int} = 0.030
θ_{max} = 35°
h = −24 → 19
k = −8 → 8
l = −29 → 28

Table 3
Selected geometric parameters (Å, °) for (II).

O1*A*—C3*A*	1.2255 (14)	N1*B*—C1*B*	1.4946 (14)
O2*A*—C7*A*	1.2672 (14)	N2*B*—C3*B*	1.3301 (13)
O3*A*—C7*A*	1.2482 (14)	O1*C*—C3*C*	1.2298 (13)
N1*A*—C1*A*	1.4923 (14)	O2*C*—C7*C*	1.2624 (13)
N2*A*—C3*A*	1.3492 (14)	O3*C*—C7*C*	1.2503 (14)
O1*B*—C3*B*	1.2444 (13)	N1*C*—C1*C*	1.4945 (13)
O2*B*—C7*B*	1.2592 (13)	N2*C*—C3*C*	1.3394 (13)
O3*B*—C7*B*	1.2539 (13)		
O2*A*—C7*A*—C4*A*	117.96 (10)	O2*C*—C7*C*—C4*C*	117.90 (9)
O3*A*—C7*A*—C4*A*	116.28 (9)	O3*C*—C7*C*—C4*C*	118.00 (9)
O2*B*—C7*B*—C4*B*	117.25 (9)	H1*W*—O1*W*—H2*W*	105.8 (17)
O3*B*—C7*B*—C4*B*	117.58 (9)		
N1*A*—C1*A*—C3*A*—N2*A*	171.50 (8)	N2*B*—C4*B*—C7*B*—O2*B*	−38.19 (12)
C1*A*—C3*A*—N2*A*—C4*A*	170.07 (9)	N2*B*—C4*B*—C5*B*—C6*B*	−173.87 (9)
C3*A*—N2*A*—C4*A*—C7*A*	−77.26 (12)	N1*C*—C1*C*—C3*C*—N2*C*	172.27 (9)
N2*A*—C4*A*—C7*A*—O2*A*	−25.90 (14)	C1*C*—C3*C*—N2*C*—C4*C*	−171.04 (9)
N2*A*—C4*A*—C5*A*—C6*A*	−54.93 (13)	C3*C*—N2*C*—C4*C*—C7*C*	−96.62 (11)
N1*B*—C1*B*—C3*B*—N2*B*	170.04 (9)	N2*C*—C4*C*—C7*C*—O2*C*	−65.36 (11)
C1*B*—C3*B*—N2*B*—C4*B*	179.71 (9)	N2*C*—C4*C*—C5*C*—C6*C*	−62.38 (12)
C3*B*—N2*B*—C4*B*—C7*B*	−106.46 (11)		

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1*A*—H1*A*···O3*C*^{i}	0.952 (15)	1.868 (15)	2.7921 (12)	163.0 (13)
N1*A*—H2*A*···O2*C*^{ii}	0.890 (14)	1.934 (15)	2.8054 (12)	165.6 (12)
N1*A*—H3*A*···O2*C*^{iii}	0.910 (16)	1.912 (16)	2.7834 (13)	159.7 (13)
N2*A*—H4*A*···O3*A*^{iv}	0.834 (15)	2.067 (15)	2.8945 (13)	171.8 (13)
N1*B*—H1*B*···O1*B*^{v}	0.896 (14)	1.963 (15)	2.8327 (13)	163.3 (13)
N1*B*—H2*B*···O1*W*	0.898 (16)	2.001 (15)	2.7864 (14)	145.3 (12)
N1*B*—H3*B*···O2*A*^{iv}	0.950 (14)	1.820 (14)	2.7446 (12)	163.4 (12)
N2*B*—H4*B*···O3*B*^{iv}	0.855 (15)	2.053 (15)	2.9056 (12)	175.2 (13)
N1*C*—H1*C*···O3*B*^{iv}	0.944 (14)	1.805 (14)	2.7403 (12)	170.7 (12)
N1*C*—H2*C*···O2*B*	0.918 (16)	2.119 (14)	2.8619 (12)	137.3 (11)
N1*C*—H3*C*···O2*B*^{i}	0.837 (14)	1.929 (14)	2.7573 (12)	170.1 (14)
N2*C*—H4*C*···O3*C*^{iv}	0.874 (15)	1.995 (15)	2.8539 (12)	167.2 (12)
O1*W*—H1*W*···O2*A*	0.82 (2)	1.97 (2)	2.7835 (14)	171.1 (18)
O1*W*—H2*W*···O3*A*^{iv}	0.84 (2)	1.93 (2)	2.7548 (12)	168.1 (17)

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

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.037$
$wR(F^2) = 0.074$
$S = 0.94$
10 606 reflections
406 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0371P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.002$
$\Delta\rho_{\max} = 0.33$ e Å^{-3}
$\Delta\rho_{\min} = -0.27$ e Å^{-3}

Due to problems with the crystal quality for (I), the refinement converged at a considerably higher R factor than for (II), with higher s.u.'s for the geometric parameters. Isotropic refinement of H atoms was thus limited to those bonded to N and O atoms in (II); the remaining H atoms were placed geometrically and refined with C—H = 0.92–1.01 Å and N—H 0.86–0.92 Å. Free rotation of amino and methyl groups (without disorder) was permitted, and U_{iso} values were $1.2U_{\text{eq}}$ of the carrier atom, or $1.5U_{\text{eq}}$ for methyl and amino groups. Friedel pairs were merged in the final refinement of (I). The Flack parameter [−0.6 (4); Flack, 1983] for (II) did not allow the absolute structure, which was known for the purchased material, to be determined from the refinement (Flack & Bernadinelli, 2000).

For both compounds, data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); 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*.

The purchase of the Siemens SMART CCD 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: GD1209). Services for accessing these data are described at the back of the journal.

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