Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Two modifications of L-alanyl-L-tyrosyl-L-alanine with different solvent molecules in the crystal lattice

Lilianna Chęcińska,[a,b]* Diana Förster,[a] Wolfgang Morgenroth[c,d,e] and Peter Luger[a]

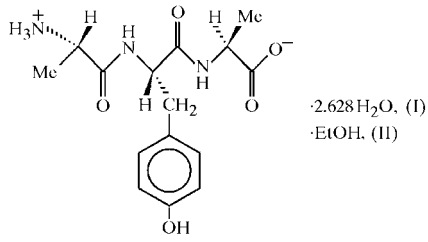
[a]Institute for Chemistry and Biochemistry/Crystallography, Free University Berlin, Takustraße 6, 14195 Berlin, Germany, [b]Department of Crystallography and Crystal Chemistry, University of Łódź, Pomorska 149/153, 90 236 Łódź, Poland, [c]Department of Chemistry, Aarhus University, Langelandsgade 140, 80 000 Aarhus C, Denmark, [d]Institute for Inorganic Chemistry, Georg August University, Tammannstraße 4, 37077 Göttingen, Germany, and [e]c/o DESY/HASYLAB, Notkestraße 85, 22603 Hamburg, Germany
Correspondence e-mail: lilach@uni.lodz.pl

Received 10 April 2006
Accepted 19 May 2006
Online 14 July 2006

The low-temperature crystal and molecular structure analyses of two modifications of L-alanyl-L-tyrosyl-L-alanine with water, $C_{15}H_{21}N_3O_5\cdot2.63H_2O$ [(I), at 9 K], and ethanol, $C_{15}H_{21}N_3O_5\cdot C_2H_5O$ [(II), at 20 K], solvent molecules in the crystal lattice show that the overall conformations of both modifications of the title tripeptide are practically the same. Moreover, despite the presence of different solvent molecules in the crystal lattice, the specific intermolecular interactions characteristic for individual tripeptide molecules of (I) and (II) are conserved. The crystal packing of the two modifications of Ala-Tyr-Ala differ from each other only in the solvent region. The tight arrangements of tripeptide molecules seem to be responsible for similar displacement parameters for all non-H atoms, despite the different distances from the molecular centre of mass. Comparison of the displacement parameters between the room- and low-temperature structures shows that an average U_{eq} value decrease of about 80% takes place at 9 K [for (I)] and 20 K [for (II)] with respect to room temperature.

Comment

In our ongoing comparative charge–density studies of oligopeptides, we became interested in the structures of tripeptides of the type L-Ala-*Xxx*-L-Ala, where *Xxx* is one of the 20 naturally encoded amino acids. First results have recently been obtained for *Xxx* = L-Ala (Rödel *et al.*, 2006) and *Xxx* = Gly (Förster *et al.*, 2005). In this paper, we describe the crystal and molecular structures of two modifications of L-alanyl-L-tyrosyl-L-alanine [L-Ala-L-Tyr-L-Ala, AYA; symbol according to the one-letter notation for amino acid sequences (IUPAC–IUB Commission on Biochemical Nomenclature, 1968)] with water, (I), and ethanol, (II), solvent molecules in the crystal structure. The different solvates were obtained using two crystallization routes for the title tripeptide (see *Experimental*).



The measurement temperature of 9 K [for (I)], realised by the recently installed He gas stream low-temperature set-up (Helijet) at beamline D3 of HASYLAB (DESY, Hamburg, Germany), is not often observed in the literature. It prompted us to compare the equivalent isotropic displacement parameters of non-H atoms for the title tripeptide molecule at room temperature and at low temperature. Moreover, special attention has been focused on the molecular conformations of L-Ala-L-Tyr-L-Ala in comparison with the crystal structures of the analogous tripeptides previously reported (Förster *et al.*, 2005; Padiyar & Seshadri, 1996; Fawcett *et al.*, 1975). We are also interested in crystal packing arrangements that are

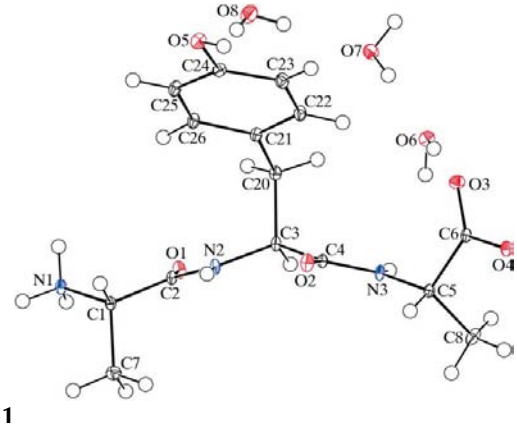


Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

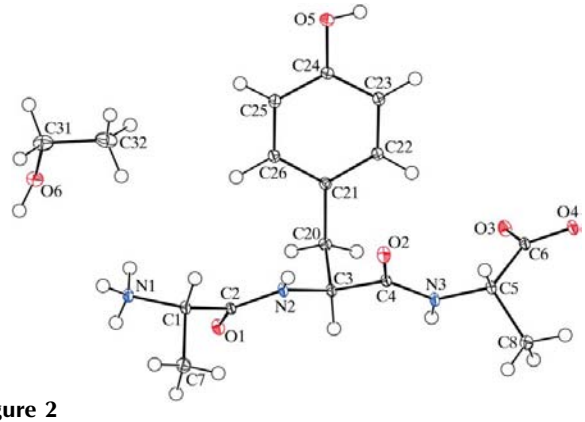


Figure 2
The molecular structure of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

  DOI: 10.1107/S0108270106018750

influenced by the presence of different solvent molecules in the crystal lattice.

The molecular structures, with the atom-numbering schemes, of both modifications of Ala-Tyr-Ala, *viz.* (I) and (II), are shown in Figs. 1 and 2. The asymmetric unit of (I) consists of one tripeptide molecule and an average of 2.6 water molecules (1 + 1 + 0.6), while for (II), the solvent consists of one ethanol molecule. In both cases, the Ala-Tyr-Ala molecules exist as zwitterions. Selected bond lengths and angles are given in Tables 1 and 3. The bond distances observed for both modifications are in good agreement and need no detailed disccussion. Table 5 presents the torsion angles, which characterize the backbone conformation of the tripeptide molecules. Among these, the C4—N3—C5—C6 and C4—N3—C5—C8 angles differ by slightly more than 15°, whereas the rest agree to within 10°. Hence, the molecular conformations are basically alike for both modifications. This means that the presence of different solvent molecules does not significantly disturb the overall conformation of the L-Ala-L-Tyr-L-Ala tripeptide.

Considering all published crystal structures of the type Ala-*Xxx*-Ala (where *Xxx* is one of the 20 naturally encoded amino acids), our special interest is focused on the conformation of the main peptide chain. It was found that the principal difference in the conformation of two independent molecules of trialanine is seen at the carboxyl terminal groups. Such a deformation is attributed to the requirements of hydrogen bonds and is reflected in the two values of the ψ_3 angle [symbols in agreement with IUPAC–IUB Commission on Biochemical Nomenclature (1970)]. The substantial variations (about 90° and more) between two forms of L-alanylglycyl-L-alanine, namely the hydrate and the solvent-free form, are visible for the ψ_1 and φ_3 torsion angles. Taking into consideration all the above-mentioned tripeptide structures, it seems that the essential conformational differences are noticeable for the $N_{pep}—C_\alpha$ bonds, described by the φ_2 and φ_3 torsion parameters (Table 5), while all remaining backbone torsion angles are conserved and differ at most by 30–35°.

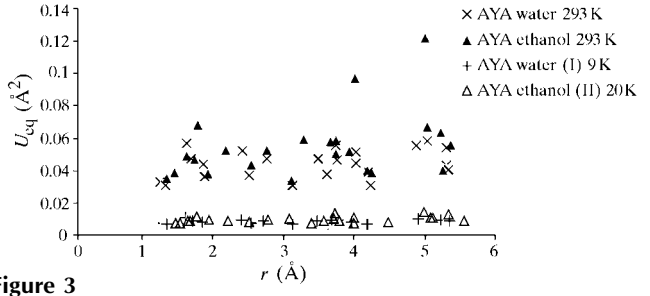


Figure 3
Equivalent isotropic displacement parameters U_{eq} (Å^2) plotted *versus* the corresponding atomic distances r (Å) from the molecular centre of mass for the water and ethanol modifications of AYA at room temperature and at 9 K [*viz.* (I)] and 20 K [*viz.* (II)].

Fig. 3 presents equivalent displacement parameters (U_{eq} values) of all non H-atoms plotted *versus* their distances (r) from the molecular centre of mass for both modifications of Ala-Tyr-Ala, for the data sets measured at room temperature (Chęcińska *et al.*, 2006) and at temperatures of 9 K [*viz.* (I)] and 20 K [*viz.* (II)]. The diagram reveals the influence of temperature on the refined model. It is interesting to note that, at all temperatures, there is no significant tendency for the U_{eq} values to increase for the outer atoms [with the exception of two outliers, C8 and O3, of the room-temperature structure of (II)], as is frequently observed for room-temperature structures (Meserschmidt *et al.*, 2003; Wagner *et al.*, 2002). The reason is obviously the tight integration of all tripeptide molecular fragments in intermolecular hydrogen bonding, as will be discussed later. The average U_{eq} values calculated for all non-H atoms at room temperature are 0.044 (9) and 0.055 (20) Å^2 for (I) and (II), respectively; the corresponding averages at 9 and 20 K are 0.0086 (14) and 0.0098 (20) Å^2 for (I) and (II), respectively. Thus, compared with room temperature, an average decrease in U_{eq} of 80% has taken place at the lower temperatures. Similar reductions of displacement parameters when going to ultra-low temperatures of 10–20 K have frequently been observed, for example, in our studies on an ergoline derivative (~80%; Luger & Zobel, 1993) and for an 18-crown-6–$KClO_4$ complex (85–90%; Luger *et al.*, 1992).

It is worth mentioning the unusually high fraction of significant reflections with $I > 2\sigma(I)$, which is between 98 and 99% for both data sets. This is of course the result of the very favourable experimental conditions, especially the low data-collection temperature, which favours an intensity increase of the high-order reflections.

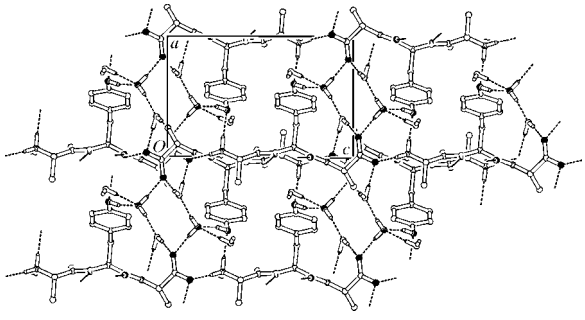


Figure 4
Part of the crystal structure of (I), showing the hydrogen-bonding network, projected on to the *ac* plane. N and O atoms are shaded. For clarity, H atoms bonded to C atoms have been omitted.

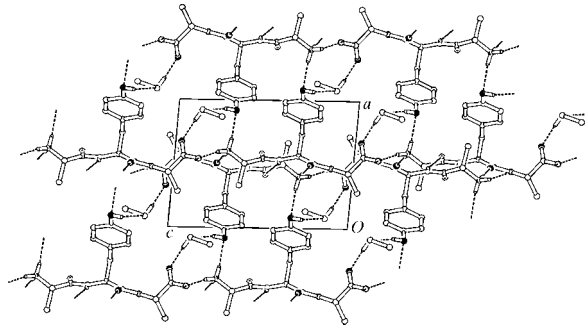


Figure 5
Part of the crystal structure of (II), showing the hydrogen-bonding network, projected on to the *ac* plane. N and O atoms are shaded. For clarity, H atoms bonded to C atoms have been omitted.

The structures of oligopeptides offer the possibility of a wide variety of potential intermolecular interactions. Additionally, the number of hydrogen bonds increases due to the presence of the solvent molecules (water and ethanol) in the crystal lattice. To facilitate better understanding of the similarities and differences in the crystal packing of (I) and (II), we now describe the hydrogen-bonding networks, first separately for the tripeptide molecules and then together with solvent. The hydrogen-bonding geometries are presented in Tables 2 and 4, for (I) and (II), respectively. Examining the specific intermolecular interactions characteristic for individual tripeptide molecules of (I) and (II) indicates that they are very similar in both cases. Ala-Tyr-Ala possesses six potential hydrogen-bonding donors (–NH or –OH) and five O atoms (–OH, C═O or –COO^-), which are acceptors. As a result, the crystal structures of (I) and (II) contain three ammonium N—H···O intermolecular hydrogen bonds. Based on geometric criteria, the N1—H11*C*···O2^{iv} hydrogen bond (see Table 4 for symmetry code) seems to be the strongest, with a donor–acceptor distance of 2.748 (1) Å for structure (II). The remaining ammonium N—H···O interactions are characterized by somewhat longer N···O distances, which are in the range 2.786 (1)–2.873 (1) Å. The amide N—H bonds form the next set of interactions, which are typical for tripeptide molecules. Their geometries are roughly comparable for the water and ethanol modifications. In conclusion, it is worth mentioning that, considering only interactions between the tripeptide molecules, the hydrogen-bonded motifs are the same in both structures. The hydroxyl group (O5—H15) of the tyrosine fragment acts as a hydrogen-bond donor to O atoms of the solvent molecule, water and ethanol in (I) and (II), respectively. These O—H···O hydrogen bonds appear to be the strongest of all non-covalent interactions in the present structures.

In the crystal structure of Ala-Tyr-Ala, (I), there are two fully occupied water molecules. Each of them is involved in two interactions as a donor: atom O7 is an acceptor twice, whereas atom O6 is an acceptor only once. The third water molecule, which appears approximately twice every three unit cells, participates in only one hydrogen bond (O8—H81···O7). In contrast, the hydrogen-bonding network of (II), with ethanol as the solvent, is rather simple. Atom O6 of the ethanol molecule participates in the above-mentioned interaction with the tyrosine hydroxyl group (O5—H15···O6^{i}), as well as in an O6—H16···O3 interaction. Figs. 4 and 5 present the crystal packing of the reported structures projected on to the *ac* plane.

In closing, it can be seen from the figures that the arrangements of the molecules of these two modifications of Ala-Tyr-Ala, *viz.* (I) and (II), differ from each other only in the solvent region.

Experimental

The title tripeptide L-alanyl-L-tyrosyl-L-alanine was obtained from Bachem (Germany). Crystallization from water by slow evaporation yielded crystals of modification (I). Crystals of modification (II) were prepared by diffusion of ethanol into an aqueous solution of the tripeptide at room temperature.

Modification (I), at 9 K

Crystal data

$C_{15}H_{21}N_3O_5·2.628H_2O$
M_r = 370.69
Monoclinic, $P2_1$
a = 8.121 (3) Å
b = 9.299 (4) Å
c = 12.532 (5) Å
β = 91.21 (2)°
V = 946.2 (7) Å^3
Z = 2
D_x = 1.301 Mg m^{-3}
Synchrotron radiation
λ = 0.50 Å
μ = 0.06 mm^{-1}
T = 9 (2) K
Needle, colourless
0.54 × 0.25 × 0.13 mm

Data collection

Huber diffractometer with MarCCD detector
φ scans
9540 measured reflections
5019 independent reflections
4945 reflections with $I > 2\sigma(I)$
R_{int} = 0.044
θ_{max} = 25.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.024
$wR(F^2)$ = 0.068; S = 1.11
5019 reflections
344 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0499P)^2 + 0.0316P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.45 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}

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

O1—C2	1.2442 (9)	N1—C1	1.4971 (9)
O2—C4	1.2444 (9)	N2—C2	1.3434 (9)
O3—C6	1.2568 (9)	N2—C3	1.4622 (9)
O4—C6	1.2859 (8)	N3—C4	1.3463 (9)
O5—C24	1.3840 (10)	N3—C5	1.4598 (9)
C2—N2—C3	120.41 (6)	N3—C4—C3	114.97 (6)
C4—N3—C5	121.63 (6)	N3—C5—C6	113.04 (6)
N1—C1—C2	107.77 (5)	O3—C6—C5	120.53 (6)
N2—C2—C1	115.60 (6)	O4—C6—C5	114.91 (6)
N2—C3—C4	108.28 (5)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O5—H15···O7^{i}	0.86 (2)	1.79 (2)	2.629 (1)	165 (2)
O6—H61···O3	0.84 (2)	2.02 (2)	2.847 (1)	172 (2)
O6—H62···O4^{ii}	0.89 (2)	1.93 (3)	2.821 (1)	176 (2)
O7—H71···O3^{iii}	0.86 (2)	1.90 (2)	2.746 (1)	173 (2)
O7—H72···O6	0.80 (2)	1.97 (2)	2.771 (1)	175 (3)
O8—H81···O7	0.80 (4)	2.12 (4)	2.916 (1)	173 (4)
N1—H11*A*···O4^{iv}	0.96 (2)	1.88 (2)	2.827 (1)	175 (2)
N1—H11*B*···O5^{v}	0.88 (2)	1.91 (2)	2.792 (1)	174 (2)
N1—H11*C*···O2^{vi}	0.88 (2)	1.97 (2)	2.821 (1)	163 (2)
N2—H12···O1^{vii}	0.88 (2)	2.10 (2)	2.947 (2)	160 (2)
N3—H13···O4^{ii}	0.82 (2)	2.21 (2)	3.028 (2)	172 (2)

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

Modification (II), at 20 K

Crystal data

$C_{15}H_{21}N_3O_5·C_2H_6O$
M_r = 369.42
Monoclinic, $P2_1$
a = 8.845 (2) Å
b = 9.057 (2) Å
c = 12.364 (3) Å
β = 94.56 (3)°
V = 987.3 (4) Å^3
Z = 2
D_x = 1.243 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 20 (2) K
Prism, colourless
0.4 × 0.25 × 0.2 mm

Data collection

Huber four-circle diffractometer with Bruker SMART Apex CCD area-detector
φ scans
9710 measured reflections
5258 independent reflections
5178 reflections with $I > 2\sigma(I)$
$R_{int} = 0.035$
$\theta_{max} = 37.0°$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.029$
$wR(F^2) = 0.077$
$S = 1.10$
5258 reflections
343 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0564P)^2 + 0.0452P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.50$ e Å^{-3}
$\Delta\rho_{min} = -0.19$ e Å^{-3}

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

O1—C2	1.2434 (9)	N1—C1	1.4993 (10)
O2—C4	1.2457 (9)	N2—C2	1.3451 (9)
O3—C6	1.2594 (9)	N2—C3	1.4612 (9)
O4—C6	1.2811 (9)	N3—C4	1.3399 (9)
O5—C24	1.3809 (10)	N3—C5	1.4627 (9)
C2—N2—C3	121.87 (6)	N3—C4—C3	115.88 (6)
C4—N3—C5	122.22 (6)	N3—C5—C6	111.62 (6)
N1—C1—C2	108.19 (6)	O3—C6—C5	119.36 (6)
N2—C2—C1	115.64 (6)	O4—C6—C5	115.58 (6)
N2—C3—C4	107.40 (6)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O5—H15···O6^{i}	0.81 (2)	1.83 (2)	2.627 (1)	169 (2)
O6—H16···O3^{ii}	0.87 (3)	1.82 (3)	2.689 (1)	176 (3)
N1—H11*A*···O4^{ii}	0.95 (2)	1.85 (2)	2.786 (1)	170 (2)
N1—H11*B*···O5^{iii}	0.83 (2)	2.04 (2)	2.873 (1)	174 (2)
N1—H11*C*···O2^{iv}	0.80 (2)	1.95 (2)	2.748 (1)	178 (2)
N2—H12···O1^{v}	0.85 (2)	2.18 (2)	2.975 (1)	156 (2)
N3—H13···O4^{vi}	0.85 (1)	2.13 (1)	2.963 (1)	167 (2)

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

One water molecule appears to be partially occupied in the crystal structure of (I). A common occupancy factor for the O atom (O8) and the two H atoms (H81 and H82) was refined freely to 0.628 (4) without any restraints. Due to the absence of significant anomalous scattering effects, 4464 and 4366 Friedel pairs were merged for (I) and (II), respectively. The absolute configuration of the purchased material was known.

Data collection: *MarCCD* (Paulmann & Morgenroth, 2006) for (I); *SMART* (Bruker, 2001) for (II). Cell refinement: *XDS* (Kabsch, 1993) for (I); *SMART* for (II). Data reduction: *XDS* for (I); *SAINT* (Bruker, 2001) and *SADABS* (Bruker, 2001) for (II). For both compounds, program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *PLATON*.

The authors thank the Deutsche Forschungsgemeinschaft (DFG) for financial support of this work (grant Lu 222/24-2 and Lu 222/27-1).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3016). Services for accessing these data are described at the back of the journal.

References

Bruker (2001). *SMART*, *SAINT*, *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.
Chęcińska, L., Förster, D., Morgenroth, W. & Luger, P. (2006). Unpublished results.
Fawcett, J. K., Camerman, N. & Camerman, A. (1975). *Acta Cryst.* B**31**, 658–665.
Förster, D., Messerschmidt, M. & Luger, P. (2005). *Acta Cryst.* C**61**, o420–o421.
IUPAC–IUB Commission on Biochemical Nomenclature (1968). *Biochemistry*, **7**, 2703.
IUPAC–IUB Commission on Biochemical Nomenclature (1970). *Biochemistry*, **9**, 3471–3479.
Kabsch, W. (1993). *J. Appl. Cryst.* **26**, 795–800.
Luger, P., André, C., Rudert, R., Zobel, D., Knöchel, A. & Krause, A. (1992). *Acta Cryst.* B**48**, 33–37.
Luger, P. & Zobel, D. (1993). *Z. Kristallogr.* **206**, 183–200.
Meserschmidt, M., Meyer, M. & Luger, P. (2003). *J. Appl. Cryst.* **36**, 1452–1454.
Padiyar, G. S. & Seshadri, T. P. (1996). *Acta Cryst.* C**52**, 1693–1695.
Paulmann, C. & Morgenroth, W. (2006). *Hasylab Jahresbericht I*, pp. 1121–1122.
Rödel, E., Messerschmidt, M., Dittrich, B. & Luger, P. (2006). *Org. Biomol. Chem.* **4**, 475–481.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Wagner, A., Flaig, R., Zobel, D., Dittrich, B., Bombicz, P., Strümpel, M. & Luger, P. (2002). *J. Phys. Chem. A*, **106**, 6581–6590.

Table 5
A comparison of torsion angles (°) describing the conformations of the main chains of tripeptides Ala-*Xxx*-Ala.

ψ, ω and φ are defined in agreement with IUPAC–IUB Commission on Biochemical Nomenclature (1970).

Torsion angle	Symbol	(I)^{a}	(II)^{a}	AAA^{b}	AAA^{b}	AGA^{c}	AGA^{d}
N1—C1—C2—N2	ψ_1	155.20 (5)	147.31 (6)	152.7 (3)	162.2 (3)	−146.8 (2)	172.6 (2)
C1—C2—N2—C3	ω_1	178.39 (5)	177.49 (6)	175.2 (3)	−179.2 (3)	−173.5 (2)	−178.2 (2)
C2—N2—C3—C4	φ_2	−156.19 (5)	−166.37 (6)	−145.7 (3)	−156.2 (3)	86.4 (2)	91.7 (1)
N2—C3—C4—N3	ψ_2	147.39 (5)	156.88 (6)	145.5 (3)	149.9 (3)	−167.4 (2)	−151.9 (2)
C3—C4—N3—C5	ω_2	−179.08 (5)	172.63 (6)	176.6 (3)	173.0 (3)	−173.8 (2)	−176.9 (1)
C4—N3—C5—C6	φ_3	−90.75 (7)	−108.07 (7)	−147.0 (3)	−159.9 (3)	−159.1 (2)	−71.3 (2)
N3—C5—C6—O3	$\psi_{3,1}$	−7.41 (8)	−7.56 (9)	−9.7 (3)	−10.1 (3)	−5.0 (3)	−6.9 (1)
N3—C5—C6—O4	$\psi_{3,2}$	174.16 (5)	174.91 (6)	172.3 (3)	143.9 (3)	176.9 (3)	172.4 (2)
C4—N3—C5—C8		145.72 (6)	129.52 (7)				

References: (*a*) this work; (*b*) L-alanyl-L-alanyl-L-alanine hemihydrate (Fawcett *et al.*, 1975); (*c*) L-alanylglycyl-L-alanine monohydrate (Förster *et al.*, 2005); (*d*) L-alanylglycyl-L-alanine (Padiyar & Seshadri, 1996).