N—H···O=C hydrogen bonding and O···O=C repulsive interactions in *tert*-butoxycarbonyl-L-leucyl-L-alanine ethyl ester (Boc-L-Leu-L-Ala-OEt)

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The crystal structure of the title compound, $C_{16}H_{30}N_2O_5$, has been determined. In the asymmetric unit, there are three independent molecules which adopt extended β-sheet conformations. These molecules are linked together into an infinite column by six hydrogen bonds of the type –NH···O=C. All the ester C=O groups are perpendicular to the column axis. This orientation probably reflects a repulsive force between two electronegative O atoms, *viz*. O···O=C.

Comment

The title compound, (I), is a key starting material for compounds containing the amino-acid sequence -(Leu–Leu–Ala)$_n$–; such compounds have been extensively studied in our laboratory (Abe *et al.*, 2001; Ohyama, Oku, Hiroki *et al.*, 2000; Ohyama, Oku & Katakai, 2000; Oku *et al.*, 2000; Yasuno *et al.*, 2001).
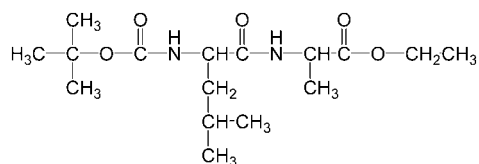
Boc-L-Leu-L-Ala-OEt

(I)

Our synthetic and spectroscopic studies of peptides have shown that, in the solid state, a critical size is needed to fold helices. For Leu- and Ala-based sequences, at least 10–14 residues are required to form a helical structure (Katakai 1977*a,b*, 1979; Katakai & Nakayama, 1977). Sequences shorter than this critical length invariably exist in the β-sheet conformation. To examine the sheet structure of (I) at a molecular level, the crystal structure of (I) has been determined.

The molecular structure of (I) is shown in Fig. 1. There are three independent molecules in the asymmetric unit. Each molecule adopts an extended β-sheet conformation and they are tightly linked together by six N—H···O=C hydrogen bonds, forming an infinite column along the *c* axis (Fig. 2). A similar type of packing was found in another peptide, *tert*-butoxycarbonyl-L-phenylalanyl-L-methionine methyl ester ethanol solvate (Doi *et al.*, 1994). A tight network of hydrogen bonds is an important factor for the crystallization of peptides. If such a network is absent then the crystals often melt at room temperature (Oku *et al.*, 2003).

In the crystal structure of (I), the three ester linkages are perpendicular to the hydrogen-bond direction. This orientation probably reflects the repulsion between two electronegative O atoms, such as an –O– (ester) and an O=C (amide, urethane and ester).
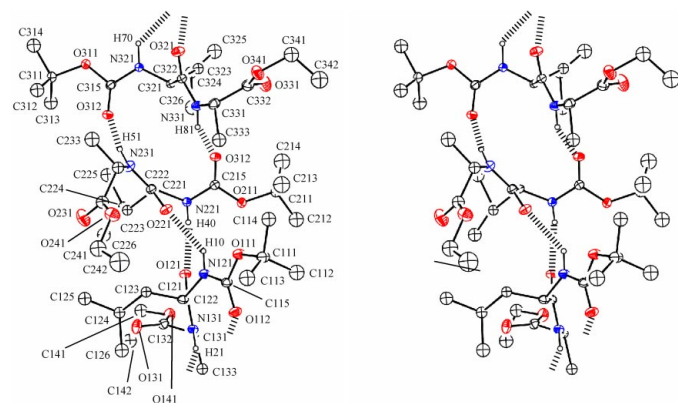
Figure 1
A view of (I) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 20% probability level. All H atoms have been omitted except those involved in hydrogen bonding, which are shown as spheres of arbitrary radii. Dashed lines indicate hydrogen bonds.
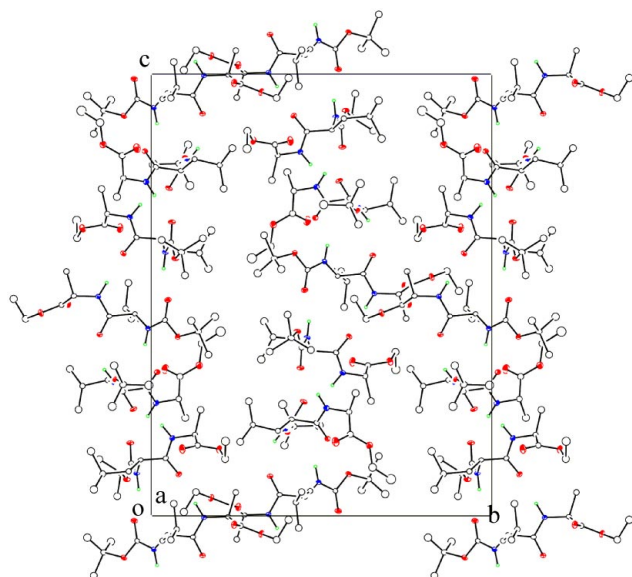

Figure 2
A packing diagram of (I), projected down the a axis.

Experimental

The title peptide, (I), was prepared by conventional liquid-phase synthesis. Crystals of the title compound were successfully grown from dimethylformamide–water and methanol–water systems (Oku, Shichiri *et al.*, 2003; Ohyama, Oku, Hiroki *et al.* 2000; Ohyama *et al.*, 2001). Analytical data (m.p., ^{1}H NMR, ESI–MS and $[\alpha]_D^{20}$) are in accordance with the expected structure; $[\alpha]_D^{20} = -54.0°$ (c 0.1, methanol).

Crystal data

$C_{16}H_{30}N_2O_5$	Cu $K\alpha$ radiation
$M_r = 330.42$	Cell parameters from 11 533
Orthorhombic, $P2_12_12_1$	reflections
$a = 11.322$ (6) Å	$\theta = 5.6$–$67.8°$
$b = 19.903$ (9) Å	$\mu = 0.69$ mm^{-1}
$c = 25.828$ (16) Å	$T = 173.1$ K
$V = 5820$ (5) Å^3	Platelet, colourless
$Z = 12$	$0.30 \times 0.20 \times 0.20$ mm
$D_x = 1.131$ Mg m^{-3}	

Data collection

Rigaku R-AXIS RAPID diffractometer	5906 independent reflections
ω scans	4827 reflections with $F^2 > 2\sigma(F^2)$
Absorption correction: refined from ΔF (*DIFABS*; Walker & Stuart, 1983)	$R_{int} = 0.056$
	$\theta_{max} = 68.3°$
	$h = -13 \rightarrow 13$
$T_{min} = 0.848$, $T_{max} = 0.872$	$k = -23 \rightarrow 23$
105 756 measured reflections	$l = -30 \rightarrow 31$

Refinement

Refinement on F^2	All H-atom parameters refined
$R[F^2 > 2\sigma(F^2)] = 0.067$	$w = 1/[0.001F_o^2 + 3\sigma(F_o^2) + 0.5]/$
$wR(F^2) = 0.159$	$(4F_o^2)$
$S = 1.43$	$(\Delta/\sigma)_{max} = 0.006$
5906 reflections	$\Delta\rho_{max} = 0.58$ e Å^{-3}
552 parameters	$\Delta\rho_{min} = -0.38$ e Å^{-3}

Table 1
Selected torsion angles (°).

O111—C115—N121—C121	−166.6 (4)	C221—C222—N231—C231	168.5 (4)
C115—N121—C121—C122	−125.0 (4)	C222—N231—C231—C232	−57.2 (6)
N121—C121—C122—N131	129.8 (4)	N231—C231—C232—O241	138.4 (5)
C121—C122—N131—C131	174.6 (3)	C231—C232—O241—C241	179.5 (4)
C122—N131—C131—C132	−62.0 (5)	C315—N321—C321—C322	−104.8 (4)
N131—C131—C132—O141	154.5 (4)	N321—C321—C322—N331	142.0 (4)
C131—C132—O141—C141	170.3 (3)	C321—C322—N331—C331	170.4 (4)
O211—C215—N221—C221	173.5 (3)	C322—N331—C331—C332	−74.8 (5)
C215—N221—C221—C222	−65.8 (5)	N331—C331—C332—O341	158.3 (4)
N221—C221—C222—N231	154.9 (4)	C331—C332—O341—C341	177.8 (4)

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N121—H10$\cdots$O221	0.95	2.25	2.948 (5)	129
N131—H21$\cdots$O321^i	0.95	2.06	2.983 (5)	164
N221—H40$\cdots$O121	0.95	2.08	2.925 (4)	148
N231—H51$\cdots$O312	0.95	1.91	2.850 (5)	173
N321—H70$\cdots$O112^{ii}	0.95	1.96	2.865 (5)	158
N331—H81$\cdots$O212	0.95	2.08	2.945 (5)	151

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

Even at low temperature (173 K), with Cu $K\alpha$ radiation and an area detector, diffraction from the crystal was very weak and insufficient data were available for full anisotropic refinement. For non-H atoms, refinement was performed with anisotropic displacement parameters for the main chain atoms (Leu and Ala) and the non-methyl atoms of the Boc group; isotropic refiment was used for the side chains (Leu and Ala), for the methyl atoms of the Boc group and for the ethyl group. H atoms were positioned geometrically, with C—H = 0.95 Å. They were refined using a riding model, with U_{iso} values constrained to be $1.2U_{eq}$ of the carrier atom. In the absence of significant anomalous scattering effects, Friedel pairs were averaged and the absolute configuration could not be determined from the diffraction experiment. The absolute configuration of the compound was, however, confirmed from the spectroscopic data.

Data collection: *RAPID-AUTO* (Rigaku/MSC & Rigaku, 2003); cell refinement: *RAPID-AUTO*; data reduction: *CrystalStructure* (Rigaku/MSC & Rigaku, 2003); program(s) used to solve structure: *SIR*2002 (Burla *et al.*, 2003); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*, 1996); molecular graphics: *ORTEP* (Johnson, 1965); software used to prepare material for publication: *CrystalStructure*.

References

Abe, N., Oku, H., Yamada, K. & Katakai, R. (2001). *Peptide Science 2000*, edited by T. Shioiri, pp. 289–292. Osaka: The Japanese Peptide Society.

Burla, M. C., Camalli, M., Carrozzini, B., Casarano, G. L., Giacovazzo, C., Polidori, G. & Spagna, R. (2003). *J. Appl. Cryst.* **36**, 1103.

Doi, M., In, Y., Inoue, M. & Ishida, T. (1994). *Int. J. Peptide Protein Res.* **44**, 532–538.

Johnson, C. K. (1965). *ORTEP*. Oak Ridge National Laboratory, Tennessee, USA.

Katakai, R. (1977*a*). *J. Am. Chem. Soc.* **99**, 232–234.

Katakai, R. (1977*b*). *J. Chem. Soc. Perkin Trans.* 1, pp. 1193–1196.

Katakai, R. (1979). *J. Chem. Soc. Perkin. Trans.* 1, pp. 905–909.

Katakai, R. & Nakayama, Y. (1977). *J. Chem. Soc. Chem. Commun.* pp. 805–806.

Ohyama, T., Oku, H., Hiroki, A., Maekawa, Y., Yoshida, M. & Katakai, R. (2000). *Biopolymers*, **54**, 375–378.

Ohyama, T., Oku, H. & Katakai, R. (2000). *Peptide Science 1999*, edited by T. Shioiri, pp. 287–290. Osaka: The Japanese Peptide Society.

Ohyama, T., Oku, H., Yoshida, M. & Katakai, R. (2001). *Biopolymers*, **58**, 636–642.

Oku, H., Shichiri, K., Yamada, K. & Katakai, R. (2003). *Acta Cryst.* E**59**, *o*1413–*o*1415.

Oku, H., Tetsuka, Y., Ohyama, T. & Katakai, R. (2000). *Peptide Science 1999*, edited by T. Shioiri, pp. 291–294. Osaka: The Japanese Peptide Society.

Oku, H., Yamada, K. & Katakai, R. (2003). *Acta Cryst.* E**59**, *o*1130-*o*1132.

Rigaku/MSC & Rigaku (2003). *CrystalStructure* and *RAPID-AUTO*. Rigaku/MSC, 9009 New Trails Drive, The Woodlands, TX 77381-5209, USA, and Rigaku Corporation, 3-9-12 Akishima, Tokyo, Japan.

Walker, N. & Stuart, D. (1983). *Acta Cryst.* A**39**, 158–166.

Watkin, D. J., Prout, C. K., Carruthers, J. R. & Betteridge, P. W. (1996). *CRYSTALS*. Issue 10. Chemical Crystallography Laboratory, Oxford, England.

Yasuno, K., Oku, H., Yamada, K. & Katakai, R. (2001). *Peptide Science 2000*, edited by T. Shioiri, pp. 297–300. Osaka: The Japanese Peptide Society.