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Structure of Benzyloxycarbonyl-L-isoleucyl-L-alanyl-α-aminoisobutyryl-α-aminoisobutyrate Methyl Ester, Z-L-Ile-L-Ala-Aib-Aib-OMe

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Abstract. $C_{26}H_{40}N_4O_7$, $M_r = 520{\cdot}6$, tetragonal, $P4_32_12$, $a = 10{\cdot}433$ (1), $c = 54{\cdot}476$ (7) Å, $V = 5930$ (1) Å^3, $Z = 8$, $D_m = 1{\cdot}155$ (3), $D_x = 1{\cdot}166$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 0{\cdot}665$ mm^{-1}, $F(000) = 2240$, $T = 295$ K, $R = 0{\cdot}057$ for 2037 observed reflections. The tetrapeptide adopts a type II β-turn conformation with an extremely weak 4→1 intramolecular hydrogen bond [3·479 (7) Å]. The molecules are held together in the crystal by three kinds of N—H···O intermolecular hydrogen bonds.

Introduction. The title Aib-containing tetrapeptide is a fragment of the naturally occurring antibiotic trichopolyn, of which the stereochemistry will be correlated with its function in a biomembrane (Fujita, Takaishi, Okamura, Fujita, Fuji, Hiratsuka, Komatsu & Arita, 1981). Several types of backbone conformations for the related peptides have been reported so far, *e.g.* a type II β-turn for *N*-acetyl-L-Ala-Aib-L-Ala-O-methyl ester (Jung, Bruckner, Bosch, Winter, Schaal & Strahle, 1983), a type III β-turn for Z-L-Ala-Aib-Aib-OH (Taga, Itoh, Machida, Fujita & Ichihara, 1990) and other types for Z-L-Ala-Aib-OH (Taga, Itoh, Machida, Fujita & Ichihara, 1989) and *N-tert*-butyloxycarbonyl-L-Ala-Aib-OH (Bosch, Voges, Jung & Winter, 1983). The present X-ray work of the synthesized title tetrapeptide was undertaken for the purpose of comparing its structure with those already determined for related peptides.

Experimental. Colorless crystals grown from ethyl acetate solution by slow evaporation; D_m measured by flotation; crystal dimensions 0·2 × 0·2 × 0·3 mm; Rigaku AFC-5RU diffractometer using graphite-monochromated Cu $K\alpha$ radiation; cell parameters determined by least-squares refinement of the setting angles of 24 reflections ($19 < \theta < 20°$). 3091 reflections ($0 \le h \le 11$, $0 < k \le 11$, $0 \le l \le 61$) collected with $2\theta < 120°$; 2θ–ω scans at speeds of 8° min^{-1} were made over a range of $(1{\cdot}0 + 0{\cdot}50\tan\theta)°$; three standard reflections showed no significant fluctuation during data collection; data corrected for Lorentz and polarization factors, but not for absorption. Structure solved with *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). Space group $P4_32_12$ was chosen on the basis of the known absolute configuration of the amino acid residues. Anisotropic non-H atoms and isotropic H atoms refined by full-matrix least squares based upon F with $w = [\sigma^2(F_o) + (0{\cdot}023F_o)^2]^{-1}$; all H atoms located by difference Fourier syntheses. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV). Final R value was 0·057 ($wR = 0{\cdot}076$, $S = 1{\cdot}7$) for 2037 unique reflections with $F_o > 3\sigma(F_o)$; parameter shifts were less than $0{\cdot}1\sigma$, and max. and min. residual densities were 0·3 and −0·2 e Å^{-3}, respectively.

All computations performed on a FACOM M780 in the Data Processing Center of Kyoto University, using the progam *KPPXRAY* (Taga, Higashi & Iizuka, 1985).

Discussion. Final atomic parameters are listed in Table 1.* The molecular structure is shown in Fig. 1. Bond distances and angles listed in Table 2 are similar to those observed in other Aib-containing peptides.

The peptide backbone (L-Ile^1-L-Ala^2-Aib^3-Aib^4) adopts a distorted type II β-turn conformation with the principal backbone torsion angles: $\varphi_1 = -115{\cdot}7$ (5), $\psi_1 = 97{\cdot}4$ (5), $\omega_2 = -178{\cdot}6$ (6), $\varphi_2 = -69{\cdot}3$ (5), $\psi_2 = 142{\cdot}1$ (4), $\omega_3 = 175{\cdot}2$ (4), $\varphi_3 = 60{\cdot}9$ (6), $\psi_3 = 24{\cdot}7$ (6), $\omega_4 = 168{\cdot}5$ (4) and $\varphi_4 = -49{\cdot}9$ (5)°. The torsion angles of the L-Ala^2-Aib^3

* Lists of atomic parameters for H atoms, anisotropic thermal parameters for non-H atoms and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53790 (8 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Atomic coordinates and equivalent isotropic temperature factors*

$B_{eq} = (4/3)\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}(Å^2)
C(1)	−0·1307 (6)	0·5389 (5)	0·2778 (1)	5·2 (2)
C(2)	−0·0541 (7)	0·5549 (6)	0·2975 (1)	6·3 (3)
C(3)	0·0302 (9)	0·4601 (7)	0·3055 (1)	7·9 (3)
C(4)	0·0357 (9)	0·3475 (7)	0·2929 (1)	8·3 (3)
C(5)	−0·0404 (10)	0·3280 (7)	0·2729 (1)	9·6 (4)
C(6)	−0·1220 (8)	0·4222 (7)	0·2656 (1)	7·9 (3)
C(7)	−0·2189 (6)	0·6413 (6)	0·2701 (1)	6·1 (2)
C(8)	−0·0963 (5)	0·7524 (5)	0·2400 (1)	4·4 (2)
C(9)	0·0506 (5)	0·8067 (5)	0·2071 (1)	4·3 (2)
C(10)	0·1320 (6)	0·7085 (6)	0·1929 (1)	5·7 (2)
C(11)	0·2560 (8)	0·7699 (9)	0·1849 (1)	8·8 (3)
C(12)	0·1510 (8)	0·5818 (7)	0·2077 (1)	8·3 (3)
C(13)	0·2091 (12)	0·5850 (10)	0·2308 (2)	13·1 (10)
C(14)	0·0103 (5)	0·9166 (5)	0·1900 (1)	4·2 (2)
C(15)	−0·0259 (5)	1·1453 (5)	0·1864 (1)	3·9 (2)
C(16)	−0·0399 (7)	1·2616 (6)	0·2037 (1)	5·9 (2)
C(17)	0·0717 (5)	1·1718 (5)	0·1666 (1)	4·0 (2)
C(18)	0·0938 (5)	1·2547 (6)	0·1240 (1)	3·9 (2)
C(19)	0·1736 (6)	1·3735 (6)	0·1292 (1)	6·0 (2)
C(20)	0·0016 (6)	1·2809 (7)	0·1029 (1)	6·0 (2)
C(21)	0·1780 (4)	1·1451 (5)	0·1145 (1)	3·4 (2)
C(22)	0·2020 (5)	0·9146 (5)	0·1071 (1)	4·6 (2)
C(23)	0·3369 (6)	0·8907 (6)	0·1170 (1)	5·9 (2)
C(24)	0·1162 (7)	0·7975 (6)	0·1124 (1)	6·9 (3)
C(25)	0·2058 (6)	0·9367 (6)	0·0797 (1)	4·8 (2)
C(26)	0·0942 (9)	1·0022 (10)	0·0449 (1)	10·5 (5)
N(1)	−0·0658 (4)	0·7501 (4)	0·2167 (1)	4·2 (1)
N(2)	0·0134 (4)	1·0332 (4)	0·2007 (1)	4·2 (1)
N(3)	0·0190 (4)	1·2137 (4)	0·1451 (1)	4·0 (1)
N(4)	0·1413 (4)	1·0254 (4)	0·1192 (1)	4·2 (1)
O(1)	−0·2005 (4)	0·6777 (4)	0·2443 (1)	5·6 (1)
O(2)	−0·0415 (4)	0·8098 (4)	0·2566 (1)	5·9 (2)
O(3)	−0·0242 (4)	0·9004 (4)	0·1692 (1)	5·7 (2)
O(4)	0·1863 (3)	1·1572 (4)	0·1695 (1)	5·1 (1)
O(5)	0·2699 (3)	1·1678 (4)	0·1007 (1)	4·7 (1)
O(6)	0·2963 (5)	0·9114 (5)	0·0675 (1)	7·2 (2)
O(7)	0·0976 (4)	0·9818 (5)	0·0712 (1)	6·6 (2)

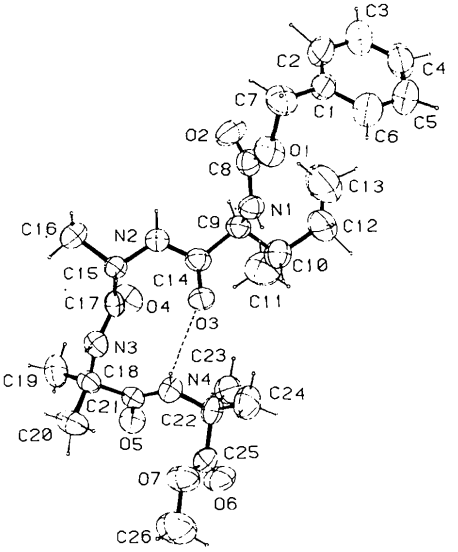

Fig. 1. Perspective view of the molecule with 50% probability thermal ellipsoids, showing the atom-numbering scheme.

corner residues deviate from that of an ideal type II β-turn ($\varphi_2 = -60$, $\psi_2 = 120$, $\varphi_3 = 80$, $\psi_3 = 0°$). A very weak 4→1 intramolecular hydrogen bond is observed between N(4) and O(3). The N···O distance is 3·479 (7) Å and the N—H···O angle is 146 (5)°.

Table 2. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

C(1)—C(2)	1·348 (8)	C(1)—C(6)	1·390 (9)
C(1)—C(7)	1·471 (8)	C(2)—C(3)	1·393 (10)
C(3)—C(4)	1·362 (10)	C(4)—C(5)	1·363 (10)
C(5)—C(6)	1·360 (11)	C(7)—O(1)	1·468 (8)
C(8)—N(1)	1·309 (8)	C(8)—O(1)	1·358 (7)
C(8)—O(2)	1·226 (7)	C(9)—C(10)	1·539 (8)
C(9)—C(14)	1·536 (7)	C(9)—N(1)	1·448 (7)
C(10)—C(11)	1·508 (10)	C(10)—C(12)	1·561 (9)
C(12)—C(13)	1·397 (13)	C(14)—N(2)	1·349 (7)
C(14)—O(3)	1·201 (8)	C(15)—C(16)	1·543 (8)
C(15)—C(17)	1·509 (8)	C(15)—N(2)	1·464 (7)
C(17)—N(3)	1·366 (7)	C(17)—O(4)	1·216 (6)
C(18)—C(19)	1·520 (9)	C(18)—C(20)	1·524 (8)
C(18)—C(21)	1·532 (8)	C(18)—N(3)	1·454 (7)
C(21)—N(4)	1·331 (7)	C(21)—O(5)	1·241 (6)
C(22)—C(23)	1·528 (8)	C(22)—C(24)	1·542 (8)
C(22)—C(25)	1·511 (8)	C(22)—N(4)	1·474 (7)
C(25)—O(6)	1·184 (8)	C(25)—O(7)	1·308 (8)
C(26)—O(7)	1·449 (8)		

C(2)—C(1)—C(6)	116·8 (6)	C(2)—C(1)—C(7)	120·5 (5)
C(6)—C(1)—C(7)	122·7 (5)	C(1)—C(2)—C(3)	122·4 (6)
C(2)—C(3)—C(4)	118·8 (7)	C(3)—C(4)—C(5)	120·5 (8)
C(4)—C(5)—C(6)	119·4 (7)	C(1)—C(6)—C(5)	122·3 (6)
C(1)—C(7)—O(1)	112·3 (5)	N(1)—C(8)—O(1)	110·6 (5)
N(1)—C(8)—O(2)	127·7 (5)	O(1)—C(8)—O(2)	121·8 (5)
C(10)—C(9)—C(14)	110·1 (4)	C(10)—C(9)—N(1)	111·9 (4)
C(14)—C(9)—N(1)	107·1 (4)	C(9)—C(10)—C(11)	109·6 (5)
C(9)—C(10)—C(12)	112·0 (5)	C(11)—C(10)—C(12)	113·6 (6)
C(10)—C(12)—C(13)	120·0 (7)	C(9)—C(14)—N(2)	113·9 (5)
C(9)—C(14)—O(3)	123·3 (5)	N(2)—C(14)—O(3)	122·8 (5)
C(16)—C(15)—C(17)	110·9 (5)	C(16)—C(15)—N(2)	109·2 (4)
C(17)—C(15)—N(2)	109·7 (4)	C(15)—C(17)—N(3)	113·6 (4)
C(15)—C(17)—O(4)	123·2 (5)	N(3)—C(17)—O(4)	123·2 (5)
C(19)—C(18)—C(20)	109·9 (5)	C(19)—C(18)—C(21)	111·0 (4)
C(19)—C(18)—N(3)	112·7 (5)	C(20)—C(18)—C(21)	104·0 (5)
C(20)—C(18)—N(3)	108·1 (4)	C(21)—C(18)—N(3)	110·8 (5)
C(18)—C(21)—N(4)	118·1 (4)	C(18)—C(21)—O(5)	120·3 (5)
N(4)—C(21)—O(5)	121·2 (5)	C(23)—C(22)—C(24)	109·8 (5)
C(23)—C(22)—C(25)	110·5 (5)	C(23)—C(22)—N(4)	111·5 (4)
C(24)—C(22)—C(25)	108·7 (5)	C(24)—C(22)—N(4)	106·8 (4)
C(25)—C(22)—N(4)	109·5 (5)	C(22)—C(25)—O(6)	122·8 (6)
C(22)—C(25)—O(7)	112·5 (5)	O(6)—C(25)—O(7)	124·7 (6)
C(8)—N(1)—C(9)	123·1 (5)	C(14)—N(2)—C(15)	118·9 (5)
C(17)—N(3)—C(18)	123·8 (4)	C(21)—N(4)—C(22)	121·8 (5)
C(7)—O(1)—C(8)	114·7 (5)	C(25)—O(7)—C(26)	115·1 (6)

Such wide 4→1 hydrogen-bond distances in the type II β-turn conformation have been reported for *N*-acetyl-L-Ala-Aib-L-Ala-O-methyl ester (Jung, Bruckner, Bosch, Winter, Schaal & Strahle, 1983), *N-tert*-butyloxycarbonyl-L-Ala-Aib-L-Ala-O-methyl ester (Bosch, Jung, Voges & Winter, 1984) and their monothioated analogues (Bardi, Piazzesi, Toniolo, Jensen, Omar & Senning, 1988). According to theoretical calculations of the conformation energy of L-Ala-Aib-containing peptides, the type III β-turn is the most preferable conformation and a number of peptides do adopt the type III β-turn (Taga, Itoh, Machida, Fujita & Ichihara, 1990). The present peptide, however, adopts the type II β-turn conformation. Since the peptide bonds have no large geometrical constraints as observed in the proline-containing peptides, *e.g.* pivaloyl-L-Pro-Aib-*N*-methylamide (Prasad, Balaram & Balaram, 1982) and *N-p*-chlorobenzoyl-L-Pro-Aib-L-Ala-Aib-*O*-methyl ester (Cameron, Hanson & Taylor, 1982), the type II β-turn conformation would be stabilized by intermolecular interactions such as hydrogen bonds in the crystal structure.

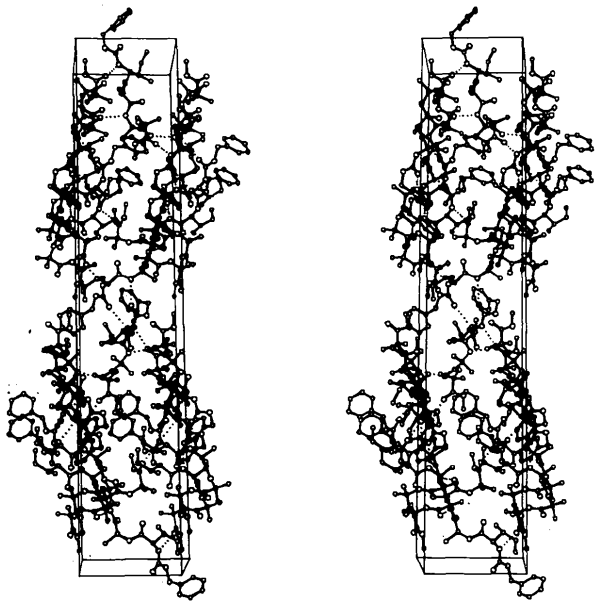

Fig. 2. Stereoview of the crystal structure. Dotted lines indicate intermolecular hydrogen bonds.

A stereoview of the structure is shown in Fig. 2. One molecule is hydrogen bonded to five adjacent molecules. All N and O atoms of the amide groups except for O(4) participate in hydrogen bonding, molecules being held together by three kinds of intermolecular hydrogen bonds: N(1)···O(6)($-\frac{1}{2}+x$, $\frac{3}{2}-y$, $\frac{1}{4}-z$) 2·895 (7), N(2)···O(2)($1-y$, $1-x$, $\frac{1}{2}-z$) 2·970 (7) and N(3)···O(5)($-\frac{1}{2}+x$, $\frac{5}{2}-y$, $\frac{1}{4}-z$) 2·887 (5) Å. In addition to these hydrogen bonds, van der Waals contacts between the hydrophobic isoleucine and *N*-terminal protecting groups stabilize the crystal structure. The isoleucyl side group adopts a conformation with χ_1[N(1)—C(9)—C(10)—C(12)] = −49·0 (6)° and χ_2[C(9)—C(10)—C(12)—C(13)] = −58·8 (9)°, while the *N*-terminal protecting group has torsion angles 125·2 (5) for O(1)—C(7)—C(1)—C(2), −76·7 (5) for C(8)—O(1)—C(7)—C(1), 161·9 (4) for C(7)—O(1)—C(8)—N(1) and −171·6 (4)° for O(1)—C(8)—N(1)—C(9). Short intermolecular distances are 3·660 (7) Å between C(3) and C(11)($1-y$, $1-x$, $\frac{1}{2}-z$) and 3·524 (8) Å between C(2) and C(20)($-\frac{3}{2}+y$, $\frac{1}{2}-x$, $\frac{1}{4}+z$). O(4) has a close intermolecular contact of 3·417 (8) Å to C(2)($1-y$, $1-x$, $\frac{1}{2}-z$).

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Structure of a New Cyclotetrapeptide Trapoxin A

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Abstract. $C_{34}H_{42}N_4O_6$, M_r = 602·73, triclinic, $P1$, a = 14·707 (2), b = 15·559 (2), c = 13·026 (1) Å, α = 112·23 (1), β = 97·25 (1), γ = 60·67 (1)°, V = 2399·1 (6) Å^3, Z = 3, D_x = 1·251 Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, μ = 0·71 mm^{-1}, $F(000)$ = 966, T = 295 K, R = 0·042 for 7802 observed reflections [$F_o > 3\sigma(F_o)$]. The structure of trapoxin A was determined as *cyclo*[-(*S*)-phenylalanyl-(*S*)-phenylalanyl-(*R*)-pipecolinyl-(2*S*,9*S*)-2-amino-8-oxo-9,10-epoxydecanoyl-]. There are three crystallographically independent molecules in the cell. These molecules are linked to each other by NH···O hydrogen bonds to form an infinite chain extending along the *a* axis.

Introduction. Trapoxin A (I) is a new cyclotetrapeptide. It was isolated from the culture broth of

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