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The α-Helical Conformation of the Aib-Containing Oligopeptide, Boc-(Leu$_3$-Aib)$_2$-OBzl

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The octapeptide Boc-(Leu$_3$-Aib)$_2$-OBzl crystallizes in the space group $P2_1$, with a=11.450(2), b=27.915(7), c=11.255(2) Å, β=116.95(1)°, and Z=2. The crystal structure has been solved by direct methods and refined to an R value of 0.08. The peptide back-bone, except for the C-terminal Aib residue, folds into a right-handed α-helical conformation, stabilized by four intramolecular (5→1) hydrogen bonds and two intermolecular hydrogen bonds between molecules related by the 2_1 symmetry along the b direction. In order to determine the helical conformation definitively, the helical parameters (unit height h and unit twist θ) at each amino-acid residue were derived from the bond lengths, bond angles, and torsional angles of the peptide main chain. The average values of these parameters for seven residues (h=1.57 Å and θ=99.0°) showed much better agreement with those for an α-helix (h=1.5 Å and θ=100°) rather than with those for a 3_{10}-helix (h=2.0 Å and θ=120°). Peptide helices are arranged in columns in head-to-tail fashion. These columns are packed in parallel with respect to their helical direction. Between neighbouring chains of helices only hydrophobic contacts are found.

The membrane-channel-forming polypeptides, alamethicin and suzukacillin, contain a high proportion of α-aminoisobutyric acid (Aib) residues. As a result of the steric hindrance of the two methyl moieties linked to a C$_\alpha$ atom, the torsional angles, ϕ and ψ, of an Aib residue are severely restricted to the values near those associated with either the right- or left-handed α-helix ($\phi=\pm57°$, $\psi=\pm47°$) and the 3_{10}-helix ($\phi=\pm60°$, $\psi=\pm30°$).[1] Therefore, Aib-containing oligopeptides have shown a high tendency to the above helical conformations,[1] especially the 3_{10}-helical conformation. At least, up to pentapeptides, they have all been shown to adopt the 3_{10}-helix with the exception of Boc-Aib-Pro-Val-Aib-Val-OMe, in which the helix is stabilized by two types of hydrogen bonds, 5→1 and 4→1, indicating an α-helix and a 3_{10}-helix respectively.[2] Although the difference in the torsional angles of ϕ and ψ between the α-helix and the 3_{10}-helix is very small, the type of helix is important in many aspects. For example, the helical type affects its length and radius and also the distribution of hydrophobic amino-acid residues on the surface of a helix. These factors are very important in any study of the design of three-dimensional structures of peptides using the Aib residues.

Recently, Narita and Doi succeeded in improving the solubility of protected peptide fragments by utilizing the nature of the Aib residue to promote helical folding in peptides.[3] Boc-(Leu$_3$-Aib)$_2$-OBzl is one of the oligopeptides they prepared to demonstrate the above usefulness of Aib residues. The IR absorption spectra of the peptide both in dichloromethane and in the single-crystal state showed strong intensity bands at 3340—3320 cm^{-1} (amide A) and 1665—1659 cm^{-1} (amide I). This indicated a helical conformation (3_{10}- or α-helix) in both the solution and the crystal state.[4]

In our preliminary single crystal study of Boc-(Leu$_3$-Aib)$_2$-OBzl, the α-helical conformation was deduced from the intensity distribution of the meridional (0k0) and near-meridional reflections with the spacing in the range of 1.4—2.2 Å and by comparison of the molecular size and the lattice dimensions.[4] In this paper, we will discuss in detail the molecular and crystal structure of this oligopeptide and will also discuss its helical type by using helical parameters calculated from the bond lengths, bond angles, and torsional angles of the peptide main chain for each residue.

Materials and Methods

The Boc-(Leu$_3$-Aib)$_2$-OBzl was prepared by the step-by-step elongation and fragment condensation methods. The procedures have been reported in detail elsewhere.[3] Boc-(Leu$_3$-Aib)$_2$-OBzl powder (40 mg) was dissolved in 30 ml of aqueous methanol (methanol:water=2:1 by volume) at 50 °C. Subsequently, the solution was cooled slowly to room temperature. After several days, transparent, plate-like single crystals were obtained. The lattice parameters and diffraction intensities were measured on a Rigaku four-circle diffractometer with Ni-filtered Cu $K\alpha$ radiation (λ=1.542 Å). The lattice parameters were refined by the least-squares fit using 20 reflections in the 2θ range of 40—50°. By using the ω-scan mode for reflections with 2θ values less than 30°, and by using the 2θ-ω-scan mode for the other reflections, the intensities of 3391 reflections were collected up to 100° in 2θ. The intensity measurements were carried out at scan speeds of 8° min^{-1} for reflections with $0<F_o^2<200$, 4° min^{-1} for $200<F_o^2<600$, and 2° min^{-1} for $600<F_o^2$. The scan width was $\Delta\omega=(1.2+0.45\tan\theta)°$. Three reference reflections, monitored every 100 reflections, showed no significant intensity deterioration during the data collection. Corrections were made for the

Table 1. Fractional Coordinates and Equivalent Isotropic Temperature Factors for Non-Hydrogen Atoms of Boc–(Leu$_3$–Aib)$_2$–OBzl, with Estimated Standard Deviations in Parentheses

	Atom	x	y	z	B_{eq}/Å^2
Boc					
	C_1	0.8522(26)	−0.3000(9)	1.3014(26)	14.36
	C_2	0.9702(26)	−0.3704(8)	1.4062(23)	13.00
	C_3	1.0681(27)	−0.2885(11)	1.4626(23)	16.58
	C_4	0.9800(22)	−0.3207(7)	1.3585(19)	10.22
	O_1	1.0229(13)	−0.3287(4)	1.2565(12)	9.30
	C_5	1.0526(17)	−0.2943(5)	1.1953(17)	7.34
	O_2	1.0348(12)	−0.2520(4)	1.1991(11)	8.10
Leul 1					
	N	1.1018(12)	−0.3125(4)	1.1127(12)	6.47
	C_α	1.1619(15)	−0.2803(5)	1.0538(16)	6.26
	C′	1.0668(15)	−0.2483(4)	0.9616(15)	6.22
	O	1.0986(11)	−0.2049(4)	0.9532(11)	7.36
	C_β	1.2308(15)	−0.3094(5)	0.9855(17)	7.22
	C_γ	1.3087(16)	−0.2835(6)	0.9321(20)	8.28
	C_{δ_1}	1.4221(21)	−0.2610(9)	1.0347(29)	14.25
	C_{δ_2}	1.3445(25)	−0.3139(8)	0.8486(26)	13.54
Leu 2					
	N	0.9455(11)	−0.2622(4)	0.8787(12)	6.06
	C_α	0.8467(16)	−0.2285(5)	0.7812(16)	6.97
	C′	0.8322(14)	−0.1847(5)	0.8462(16)	6.55
	O	0.8260(16)	−0.1441(3)	0.8012(11)	7.71
	C_β	0.7214(16)	−0.2532(6)	0.7017(20)	8.91
	C_γ	0.6142(17)	−0.2218(6)	0.5929(22)	11.54
	C_{δ_1}	0.4933(28)	−0.2226(13)	0.6054(29)	20.72
	C_{δ_2}	0.5543(32)	−0.2422(9)	0.4544(26)	17.60
Leu 3					
	N	0.8176(13)	−0.1905(5)	0.9632(14)	7.51
	C_α	0.8027(15)	−0.1490(5)	1.0307(17)	6.41
	C′	0.9254(15)	−0.1188(4)	1.0873(15)	5.64
	O	0.9205(10)	−0.0751(3)	1.0791(10)	6.38
	C_β	0.7661(18)	−0.1671(6)	1.1438(20)	8.39
	C_γ	0.7446(20)	−0.1265(7)	1.2217(22)	10.47
	C_{δ_1}	0.6279(20)	−0.0946(7)	1.1441(25)	11.45
	C_{δ_2}	0.7481(27)	−0.1483(10)	1.3453(26)	15.03
Aib 1					
	N	1.0468(12)	−0.1387(4)	1.1511(11)	6.29
	C_α	1.1716(13)	−0.1128(5)	1.2108(14)	5.61
	C′	1.1749(14)	−0.0793(4)	1.1038(15)	5.81
	O	1.2113(10)	−0.0386(4)	1.1294(10)	6.97
	C_{β_1}	1.1821(16)	−0.0850(6)	1.3319(16)	7.41
	C_{β_2}	1.2813(15)	−0.1490(6)	1.2511(17)	7.69
Leu 4					
	N	1.1389(12)	−0.0984(4)	0.9842(12)	6.26
	C_α	1.1473(14)	−0.0688(5)	0.8767(15)	5.75
	C′	1.0597(13)	−0.0286(5)	0.8374(14)	5.08
	O	1.0907(10)	0.0095(4)	0.8078(12)	8.28
	C_β	1.1191(16)	−0.1024(6)	0.7553(16)	6.92
	C_γ	1.2152(17)	−0.1392(7)	0.7714(17)	8.21
	C_{δ_1}	1.1662(22)	−0.1735(7)	0.6597(21)	11.25
	C_{δ_2}	1.3396(22)	−0.1161(9)	0.7776(27)	13.27
Leu 5					
	N	0.9433(10)	−0.0319(4)	0.8346(11)	5.39
	C_α	0.8423(12)	0.0070(5)	0.7935(14)	5.12
	C′	0.8729(14)	0.0439(4)	0.8956(15)	5.51
	O	0.8415(10)	0.0847(3)	0.8662(9)	6.95
	C_β	0.7086(13)	−0.0144(5)	0.7475(14)	5.37
	C_γ	0.6482(15)	−0.0455(6)	0.6203(17)	7.67

Table 1. (Continued)

	Atom	x	y	z	$B_{eq}/Å^2$
	$C_{\delta 1}$	0.6145(21)	−0.0141(7)	0.4964(17)	10.61
	$C_{\delta 2}$	0.5352(16)	−0.0740(7)	0.6088(22)	10.52
Leu 6					
	N	0.9368(11)	0.0301(4)	1.0266(11)	5.30
	C_α	0.9768(13)	0.0664(5)	1.1335(14)	5.17
	C′	1.0952(13)	0.0933(4)	1.1478(13)	5.07
	O	1.1139(10)	0.1349(4)	1.1859(11)	6.98
	C_β	1.0006(14)	0.0416(6)	1.2651(14)	5.93
	C_γ	0.8831(13)	0.0185(6)	1.2672(15)	6.44
	$C_{\delta 1}$	0.7762(17)	0.0487(8)	1.2410(22)	10.23
	$C_{\delta 2}$	0.9281(21)	−0.0045(7)	1.4126(19)	10.18
Aib 2					
	N	1.1900(12)	0.0705(4)	1.1296(12)	6.14
	C_α	1.3079(12)	0.0907(5)	1.1361(13)	5.28
	C′	1.3839(15)	0.1170(5)	1.2675(17)	6.90
	O	1.4490(12)	0.1497(4)	1.2850(12)	9.72
	$C_{\beta 1}$	1.3943(15)	0.0495(6)	1.1314(18)	7.75
	$C_{\beta 2}$	1.2713(16)	0.1262(6)	1.0219(16)	7.94
OBzl					
	O_1	1.3817(11)	0.0935(4)	1.3717(10)	7.69
	C_1	1.4527(18)	0.1178(7)	1.4960(17)	10.19
	C_2	1.4236(15)	0.0872(6)	1.5952(15)	7.38
	C_3	1.3321(16)	0.0552(6)	1.5676(17)	8.55
	C_4	1.3051(19)	0.0325(7)	1.6637(19)	10.10
	C_5	1.3840(20)	0.0426(7)	1.7921(19)	9.85
	C_6	1.4772(19)	0.0749(7)	1.8267(18)	9.66
	C_7	1.5044(16)	0.0994(6)	1.7327(17)	8.23

Lorentz and polarization factors, but not for the absorption effect. A total of 2863 reflections greater than $3\sigma(F_o)$ were used in the following analysis.

The density was measured by means of a flotation method using a solution of carbon tetrachloride and toluene. On the basis of the measured density and the unit cell volume, the unit cell can be said to contain two oligopeptide molecules.

Crystal Data: $C_{56}H_{96}N_8O_{11}$, F.W.=1057.4, monoclinic, space group $P2_1$, $Z=2$, $a=11.450(2)$, $b=27.915(7)$, $c=11.255(2)$ Å, $\beta=116.95(1)°$, $V=3207(1)$ Å^3, $D_x=1.093$, $D_m=1.09$ g cm^{-3}, $\rho(\text{Cu } K\alpha)=5.7$ cm^{-1}.

Determination and Refinement of the Structure

The direct method with the SAPI87[5] program based on MULTAN-80[6] was applied to the $P2_1$ space group. After several cycles of block-diagonal least-squares refinement starting from the coordinates of all the non-hydrogen atoms of the oligopeptide obtained by the direct method, difference Fourier syntheses revealed no significant peak. After an anisotropic refinement of the non-hydrogen atoms, the hydrogen atoms located on their calculated positions with isotropic temperature factors were included in the refinement. The quantity minimized was $\sum\omega(|F_o|-|F_c|)^2$, with $w=1.0$ for all reflections. After several cycles, some hydrogen atoms with unacceptable geometry were excluded from further calculations. The final R value was 0.083 ($R_w=0.077$) for all the non-hydrogen atoms and 28 hydrogen atoms. The final atomic parameters for the non-hydrogen atoms are given in Table 1.[7]

The atomic scattering factors were taken from International Tables for X-Ray Crystallography, Vol. IV.[8] Computations were done on a HITAC M-280H computer at the Computer Center, University of Tokyo, with the help of the programs in UNICS III.[9]

Results and Discussion

For the convenience of atom specification, all the residues are numbered in series from the N- to the C-terminus. Therefore, the molecule of Boc-(Leu$_3$ Aib)$_2$-OBzl is denoted as Boc-Leu1-Leu2-Leu3-Aib1-Leu4-Leu5-Leu6-Aib2-OBzl. The atomic names in the Leu and Aib residues are those given in the IUPAC-IUB recommendations,[10] while those in the protected groups at N- and C-termini are shown in Fig. 1.

Peptide-Backbone Conformation. A perspective view of the molecule is shown in Fig. 1, together with a part of the upper molecule related by the 2_1-symmetry. The bond distances, bond angles, and torsional angles (ϕ, ψ, ω) of the peptide main chain are given in Table 2. The bond lengths of C_i^α–C_i' in

Leu1 (1.43 Å), Leu2 (1.47 Å), Leu4 (1.43 Å), and Leu5 (1.46 Å) are slightly shorter, while those of C'_i–N_{i+1} in Leu2 (1.41 Å), Leu3 (1.36 Å), Leu5 (1.37 Å), and Leu6 (1.35 Å) are slightly longer, than the values of 1.53 Å and 1.32 Å respectively derived by Pauling et al.[11] Because of the contact between the two methyl moieties linked to the C^{α}_i atom and the carbonyl oxygen, the bond angles of C'_{i-1}–N_i–C^{α}_i (126° and 128°) and N_i–C^{α}_i–C'_i (108° and 108°) in the Aib residues are significantly different from those in the Leu residues.

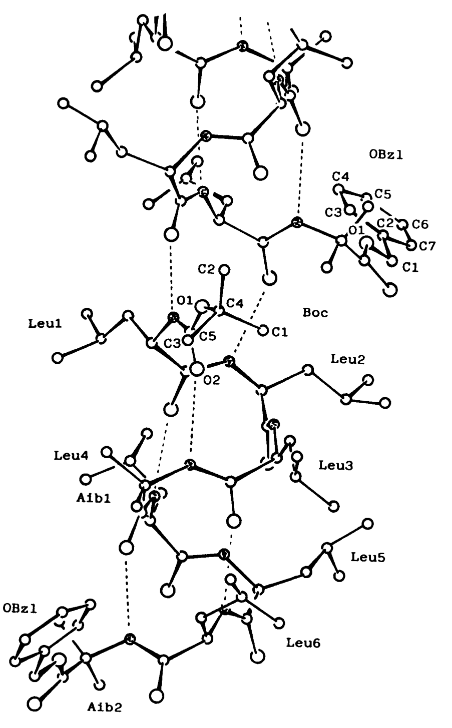

Fig. 1. Molecular structure of Boc–(Leu$_3$–Aib)$_2$–OBzl together with the atomic numbering in the terminal protected moieties (Boc and OBzl). The upper and lower side molecules are related to each other by a crystallographic 2_1 symmetry. Broken lines denote intra- and intermolecular hydrogen bonds.

All the peptide torsional angles, ω, showed a very good planarity. The values of the torsional angles, ϕ and ψ, showed that the octapeptide folds into a right-handed helix with the exception of the Aib2 residue at the C-terminus, in which the ϕ and ψ values belong to a left-handed helix. A change in the helical sense at the C-terminal Aib residue is usually observed in the oligopeptide helices with the protected moiety at the C-terminus.[12–14] This may be attributed to the bulky protected moiety linked to the Aib residue and the restricted conformation of the Aib residue. Since the ϕ and ψ values of an Aib residue are restricted to only two narrow regions, that is, near the right- or the left-handed α- (or 3_{10}-) helical regions, the helical sense of the C-terminus Aib residue has to be different from that of the preceding peptide region in order to avoid contact between the protected moiety and the rest of the molecule.

Since the allowed regions of torsional angles for the α-helix and the 3_{10}-helix almost entirely overlap in the ϕ–ψ map, it is not possible to decide a helical conformation on the basis of only the torsional angles in Table 2. Therefore, the helical conformation of Aib-containing oligopeptides have usually been determined by the intramolecular hydrogen bonding type, that is, the hydrogen bonds between the C=O group of Residue i and the N–H group of Residue $i+3$, which belong to the 3_{10}-helix, and those between Residue i and Residue $i+4$, which belong to the α-helix. However, even by the hydrogen-bonding type it is difficult to determine a helical structure definitively when the N–H groups of Residues $i+3$ and $i+4$ are both close to the C=O group of Residue i. In this study, therefore, the helical parameters were used as the criterion of the helical structure. They are the unit height (h) and the unit twist (θ), that is, the height per residue along the helical axis and the rotational angle per residue about the helical axis respectively. Assuming that each amino acid residue forms its own helix, the helical parameters are derived from its bond

Table 2. Bond Lengths, Bond Angles, and Torsional Angles of the Peptide Main Chain, together with Standard Deviations in Parentheses

	Leu 1	Leu 2	Leu 3	Leu 4	Leu 5	Leu 6	Aib 1	Aib 2
Bond length/Å								
N_i–C^{α}_i	1.46(2)	1.50(2)	1.44(2)	1.50(2)	1.50(2)	1.48(2)	1.46(2)	1.43(2)
C^{α}_i–C'_i	1.43(2)	1.47(2)	1.51(2)	1.43(2)	1.46(2)	1.49(2)	1.54(2)	1.52(2)
C'_i–N_{i+1}	1.33(2)	1.41(3)	1.36(2)	1.32(2)	1.37(2)	1.35(2)	1.33(2)	—
Bond angle/°								
C'_{i-1}–N_i–C^{α}_i	120(4)	122(1)	120(1)	119(1)	126(1)	120(1)	126(1)	128(1)
N_i–C^{α}_i–C'_i	111(1)	112(1)	111(2)	113(2)	113(1)	111(1)	108(1)	108(1)
C^{α}_i–C'_i–N_{i+1}	122(1)	117(1)	122(1)	121(1)	118(1)	120(1)	116(1)	—
Torsional angle/°								
ϕ(C'_{i-1}–N_i–C^{α}_i–C'_i	−66(2)	−53(2)	−66(2)	−65(2)	−76(2)	−76(2)	−53(2)	53(2)
ψ(N_i–C^{α}_i–C'_i–N_{i+1})	−40(2)	−47(2)	−43(2)	−35(2)	−33(2)	−36(2)	−46(2)	40(2)
ω(C^{α}_i–C'_i–N_{i+1}–C^{α}_{i+1})	−179(1)	−180(1)	−179(1)	−179(1)	176(1)	178(1)	−176(1)	—

Table 3. Helical Parameters for Each Amino Acid in Boc-(Leu$_3$-Aib)$_2$-OBzl

	Leu 1	Leu 2	Leu 3	Aibl	Leu 4	Leu 5	Leu 6	Average
h/Å	1.55	1.64	1.51	1.69	1.74	1.48	1.39	1.57
θ/°	97.5	101.8	95.6	104.1	100.4	98.4	94.9	99.0

Table 4. Torsional Angles of Side Chains in Leu Residues, together with Estimated Standard Deviations in Parentheses

	χ_1	χ_2	χ_2'
Leu 1	−174(1)	66(2)	−168(2)
Leu 2	−177(1)	−127(2)	127(2)
Leu 3	−179(2)	66(2)	−165(2)
Leu 4	−68(2)	−71(2)	170(2)
Leu 5	−66(2)	−69(2)	164(1)
Leu 6	−64(2)	−58(2)	−179(1)

Table 5. Hydrogen-Bond Parameters

Hydrogen bond	Bond length/Å (N···O)	Bond angle/° (N-H···O)
Intermolecular		
N(Leu 1)···O(Leu 5)	2.93	172
N(Leu 2)···O(Leu 6)	2.97	154
Intramolecular		
N(Aib 1)···O2(Boc)	3.22	162
N(Leu 4)···O(Leu 1)	3.01	167
N(Leu 6)···O(Leu 3)	3.02	175
N(Aib 2)···O(Leu 4)	3.06	176

lengths, bond angles, and torsional angles by the method of Sugeta and Miyazawa.[15] These values for each residue except for the C-terminus Aib2 are shown in Table 3. The average values are h=1.57 Å and θ=99.0°. Since the helical parameters for the α-helix and the 3_{10}-helix are h=1.5 Å and θ=100°, and h=2.0 Å, and θ=120°, respectively, it is obvious that the molecular conformation of Boc-(Leu$_3$-Aib)$_2$-OBzl is not a 3_{10}-helix, but an α-helix. This finding agreed with our previous conclusion from the X-ray intensity distribution of the meridional reflections and the consideration of the lattice dimensions.[4]

Side-Chain Conformations. The torsional angles in the Leu side chains are given in Table 4. The torsional angle of χ_1 (N-C$_\alpha$-C$_\beta$-C$_\gamma$) is trans (Leul, Leu2, and Leu3) or gauche (Leu4, Leu5, and Leu6), while those of χ_2 and χ_2' (C$_\alpha$-C$_\beta$-C$_\gamma$-C$_{\delta_1}$ and C$_\alpha$-C$_\beta$-C$_\gamma$-C$_{\delta_2}$) are also trans or gauche, except in the Leu2 residue. The C$_{\delta_1}$ and C$_{\delta_2}$ atoms in the Leu2 residue cannot adopt either the trans or gauche conformation because of the short contact with the carbonyl oxygen atom of the Aib2 residue in the neighbouring molecule.

Hydrogen Bonds. The right-handed α-helical conformation of the peptide is stabilized by four intramolecular and two intermolecular hydrogen bonds (Fig. 1). The hydrogen-bond parameters are given in Table 5. All the lengths of the intramolecular hydrogen bonds are significantly longer than the mean value (2.9±0.1 Å)[16] usually observed in the peptide structures in which no Aib residues are included. This fact is also observed in other Aib-containing oligopeptides, such as Boc-(Ala-Aib)$_2$-Aib-OMe,[12] Boc-Leu-Aib-Pro-Val-Aib-OMe,[13] p-BrBz-(Aib)$_8$-O-t-Bu,[14] Boc-(Ala-Aib)$_2$-Ala-Glu(OBzl)-(Ala-Aib)$_2$-Ala-OMe,[17] and Boc-Leu-Aib-Pro-Val-Aib-Aib-Glu(OBzl)-Gln-Phl monohydrate.[18] This marked tendency of the Aib-containing peptides is probably due to the fact that the molecular conformations of these peptides are mainly determined by the stereochemical restrictions of the Aib residues rather than by the stabilization by the intramolecular hydrogen bonds. All the intramolecular hydrogen bonds listed in Table 5 are between the C=O group of Residue i and the N-H group of Residue i+4, which indicates the α-helical conformation. There is no hydrogen bond associated with N(Leu3) and N(Leu5). In the case of N(Leu3), there is no acceptor oxygen in the upper-peptide molecule because of the opposite helical sense at the C-terminal Aib2 residue. On the other hand, in the case of N(Leu5), the distance of 3.36 Å to the carbonyl oxygen in the Leu2 residue is

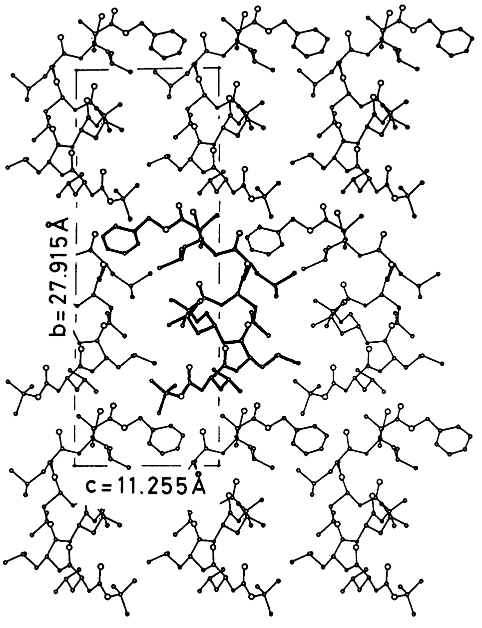

Fig. 2. Head-to-tail arrangement of Boc-(Leu$_3$-Aib)$_2$-OBzl molecules as viewed along the a direction. One molecule in a unit cell is drawn with bold lines.

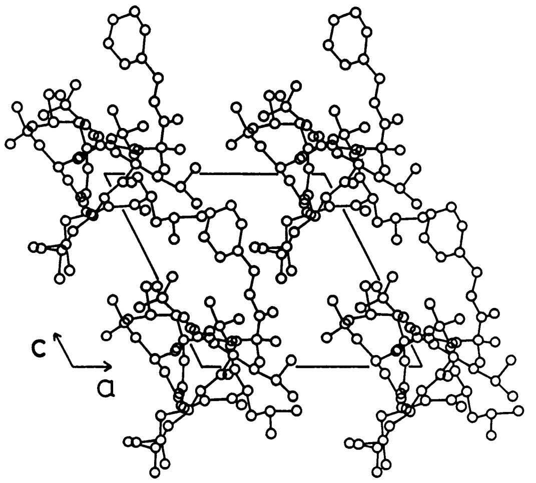

Fig. 3. Packing of octapeptide molecules in the crystal viewed along the *b* (helical) direction. For the sake of clarity only one molecule in the unit cell is shown.

fairly short, but too long as a hydrogen bond distance. In addition to the four intramolecular hydrogen bonds, two intermolecular hydrogen bonds, N(Leu1)···O(Leu5) of 2.93 Å and N(Leu2)···O(Leu6) of 2.97 Å, stabilize the helical conformation.

Crystal Structure of Boc-(Leu$_3$-Aib)$_2$-OBzl. Figure 2 shows the head-to-tail arrangement of the molecules as viewed along the *a* direction. The upper and lower molecules are related by the 2_1 symmetry along the *b*-axis and are linked head-to-tail by two intermolecular hydrogen bonds to form columns along this direction. These columns are arranged parallel with respect to their helical direction. The packing structure of Boc-(Leu$_3$-Aib)$_2$-OBzl molecules in the *ac*-plane is shown in Fig. 3. In this figure, only four equivalent molecules are illustrated; the molecules related by the 2_1 symmetry are omitted for the sake of clarity. Since the lattice dimensions of *a* and *c* are similar to each other, and since $\beta(=117°)$ is very close to 120°, the columns are packed pseudo-hexagonally. There is no hydrogen bond between laterally packed molecules, and only hydrophobic interactions stabilize the crystal structure. The benzyl moieties and the side chains of the Leu residues project from the helix core and interact with the neighbouring molecules (Figs. 2 and 3). The fairly short contacts between molecules are O(Leu5)···C7(OBzl) 3.47 Å, O(Leu5)···O1(Boc) 3.48 Å, O(Aib2)···C(Leu2) 3.39 Å, O(Aib2)···C(Leu1) 3.48 Å, and O(Leu6)···N(Leu1) 3.47 Å.

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