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SHORT COMMUNICATIONS

Molecular Structure of Aib-Containing Oligopeptides, Boc–(Leu$_3$–Aib)$_2$–OBzl and Boc–(Leu$_3$–Aib)$_3$–OBzl

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An α-aminoisobutyric acid·(Aib) residue is a sterically noble amino acid residue. Due to steric hindrance of the two methyl moieties linked to C_α atom, torsional angles, ϕ and ψ, of Aib residue are severely restricted to the region including both α-helix ($\phi = \pm 57°$, $\psi = \pm 47°$) and 3_{10}-helix ($\phi = \pm 60°$, $\psi = \pm 30°$).[1] Because of this restriction, Aib residues promote helical folding (α- or 3_{10}-helix) in peptides. In fact, peptide fragments in membrane channel-forming polypeptides like alamethicin and suzukacillin contain a high proportion of Aib residue and well recognized to form α- and 3_{10}-helical structures.[2] By utilizing the nature of Aib residue to promote helical folding in peptide, one of the authors (M. Narita) succeeded in improving the solubility of protected peptide fragments.[3] Boc–(Leu$_3$–Aib)$_n$–OBzl ($n = 2, 3$) is one of the oligopeptides prepared to demonstrate the above usefulness of Aib residues.

The IR absorption spectra of these peptides in methylene chloride showed strong bands at 3340—3320 cm^{-1} and 1665—1659 cm^{-1}, indicating a helical structure (3_{10}- or α-helix)[3] ((a) and (b) in Figure 1). Recently, we suc-

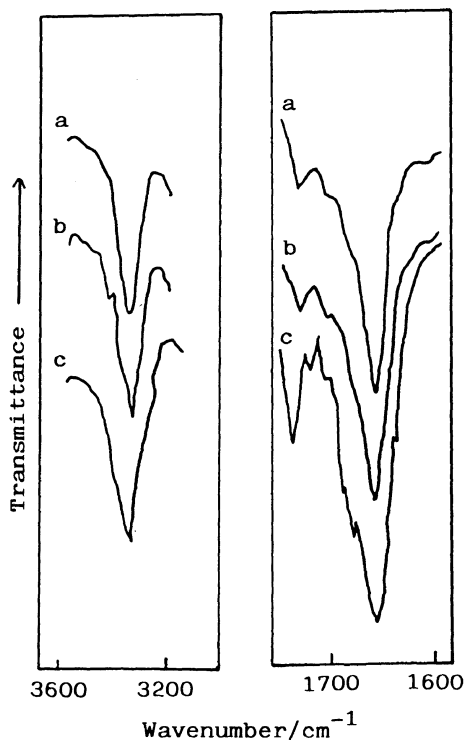

Figure 1. IR absorption spectra of Boc–(Leu$_3$–Aib)$_n$–OBzl. (a) $n = 3$ and (b) $n = 2$ in methylene chloride, (c) $n = 2$ in single crystals.

ceeded in growing single crystals of these oligopeptides from a solution of methanol and water (for the octapeptide) or methanol and hexane (for the dodecapeptide). The IR spectra of the octapeptide crystal ((c) in Figure 1) essentially agreed with those observed in methylene chloride, suggesting a helical conformation of this peptide in the solid state.

Determination of detailed lattice constants and X-ray intensity measurements of these crystals were carried out using a full-automatic four-circle goniometer. The crystal data were shown in Table I. Because of a fairly large molecular weight and no heavy atoms in a unit cell, the structure analyses of these peptides are very difficult to conduct. Therefore, in this paper, we determined only the helical structure (3_{10}- or α-helix) by utilizing three-dimensional X-ray intensity data.

Table I. Crystal data for Boc–$(Leu_3–Aib)_n$–Obzl

n	2	3
Formula weight	1056	1480
Space group	$P2_1$	$P2_12_12_1$
a/Å	11.450 (2)	11.470 (5)
b/Å	27.915 (7)	20.870 (10)
c/Å	11.255 (1)	37.747 (17)
β/°	116.95 (1)	—
Z	2	4
D_x/g cm^{-3}	1.093	1.083
D_m/g cm^{-3}	1.09	1.10

First, in order to determine the molecular direction, it was assumed that these peptides have an α-helical structure, since the unit height per residue of α-helix (1.5 Å) is shorter than that of 3_{10}-helix (2.0 Å). Accordingly, the expected molecular length of the octapeptide is more than 12 Å and the dodecapeptide, 18 Å. Taking into account the lattice dimensions in Table I, the molecular direction should be parallel to the b-axis in the former case and the b- or c-axis in the latter case. To obtain more definitive evidence, cylindrical Patterson maps were synthesized in three cases. In each case, the molecular direction was assumed to be one of three crystal axes. As a result, only when the

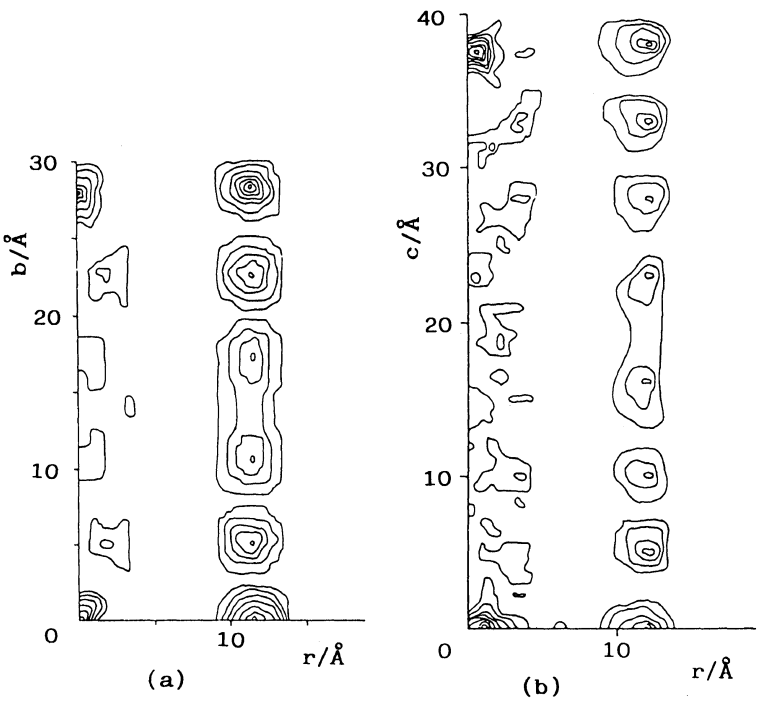

Figure 2. Cylindrical Patterson maps of Boc–$(Leu_3–Aib)_n$–OBzl. (a) $n=2$ and (b) $n=3$.

molecular direction coincided with the *b*-axis of the octapeptide or the *c*-axis of the dodecapeptide, the Patterson maps showed significant peaks aligned vertically at $r=0$ and 12 Å, which corresponded to the vectors of intra- and interhelical molecules, respectively (Figure 2). Since both molecules are not ideal helical-fibers, but finite molecules (less than 20 Å) with fairly large protecting group at N- and C-terminals, the obtained Patterson maps are too complicated to analyse minutely. However, from the vertically aligned peaks at $r=0$ and 12 Å, it is clear that the peptide molecules are parallel to the *b*-axis (octapeptide) or the *c*-axis (dodecapeptide) and also clear that the neighbouring molecules are separated by about 12 Å in both cases.

Secondly, we shall consider the helical conformation. Since the α-helical and 3_{10}-helical structures give meridional or near-meridional reflections with spacing about 1.5 and 2.0 Å, respectively, a search was made for the reflections in these regions. Figure 3 shows X-ray intensity distribution for meridional or near-meridional reflections in the range of 1.4—2.2 Å, that is, near (0 20 0) reflections in the case of the ocatapeptide and near (0 0 26) reflections in the case of the dodecapeptide.

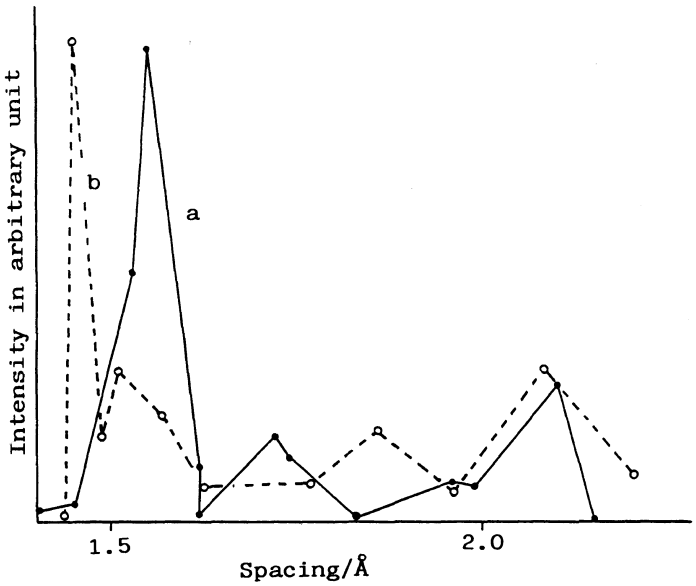

Figure 3. X-Ray intensity distribution of Boc–(Leu$_3$–Aib)$_n$–OBzl for near-meridional reflections in the range of 1.4—2.2A. (a) $n=2$ and (b) $n=3$.

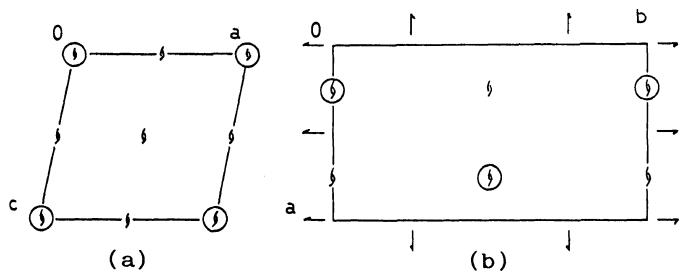

Figure 4. Crystal symmetries and molecular positions in a unit cell of Boc–(Leu$_3$–Aib)$_n$–OBzl. Circles denote molecular positions. (a) $n=2$ and (b) $n=3$.

The intensity distribution showed definitely that the α-helix is the molecular conformation in both peptides.

Taking into accout the separation (*ca.* 12 Å) between neighbouring molecules and lattice dimensions (*a* and *c*) perpendicular to the molecular axis, two octapeptide molecules in a unit cell must be aligned vertically. Therefore, they must be located on the 2_1 crystallographic axis (Figure 4(a)). Similarly, in the case of the dodecapeptide, two molecules located on the same 2_1 axis parallel to the *c*-direction and the other two molecules are generated by the 2_1 symmetry perpendicular to the *c*-direction (Figure 4(b)). Hence, the generated molecules are on the 2_1 axis and antiparallel to the former molecules. The lengths of two vertically aligned α-helices are 24 Å (= 12 Å × 2) for the octapeptide and 36 Å (= 18 Å × 2) for the dodecapeptide. These values are still within the corresponding lattice dimensions of 27.9 and 37.7 Å, respectively. In the case of the 3_{10}-helix, the lengths (32 and 48 Å) are beyond the corresponding lattice dimensions. In addition to the investigation of meridional reflections, it is also shown from the above consideration about lattice dimensions that the molecular structure of Boc–$(Leu_3$–Aib$)_n$–OBzl ($n=2$, 3) must be the α-helix.

To analyse the crystal structures of Boc–$(Leu_3$–Aib$)_n$–OBzl, we shall test various methods including the trial-and-error method on the base of the α-helical structure obtained in this study.

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