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Chemistry

α-Helix and mixed $3_{10}/\alpha$-helix in cocrystallized conformers of Boc-Aib-Val-Aib-Aib-Val-Val-Val-Aib-Val-Aib-OMe

(peptide crystal structure/head-to-tail hydrogen bonds/helix unwinding/helix aggregation)

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ABSTRACT **Two molecules of Boc-Aib-Val-Aib-Aib-Val-Val-Val-Aib-Val-Aib-OMe (where Boc is *t*-butoxycarbonyl and Aib is α-aminoisobutyryl) cocrystallize in a triclinic cell with different helical conformations. One molecule is completely α-helical with seven 5→1 intramolecular hydrogen bonds. It forms three head-to-tail NH···O=C hydrogen bonds to other molecules of the same conformation. The second molecule has a mixed $3_{10}/\alpha$-helix conformation with three 4→1 hydrogen bonds and four 5→1 hydrogen bonds; furthermore, there is a helix reversal at both termini. The second molecule forms only two head-to-tail hydrogen bonds with molecules of the same type, and the N(3)H group does not participate in any hydrogen bonding. The two different types of helices occur in alternate sheets in the crystal, where each sheet is composed of adjacent rods of helices formed by head-to-tail hydrogen bonding. Within each sheet, containing helices of only one type of conformation, the helices aggregate in a parallel mode. Between the sheets of different helices, the aggregation is antiparallel. The peptide, with formula $C_{51}H_{92}N_{10}O_{13}$, crystallizes in space group *P*1 with $Z = 2$ and cell parameters $a = 10.047 \pm 0.002$ Å, $b = 16.684 \pm 0.003$ Å, $c = 19.198 \pm 0.004$ Å, $\alpha = 80.30° \pm 0.01°$, $\beta = 85.74° \pm 0.01°$, and $\gamma = 83.03° \pm 0.01°$; overall agreement factor $R = 6.7\%$ for 6053 data ($|F_o| > 3\sigma$) and 0.96-Å resolution.**

Apolar peptides containing α-aminoisobutyric (Aib) residues form helices, either 3_{10}-helices or α-helices or a combination of both. Recently, a crystallographic study of polymorphs (different crystal forms) of Boc-Trp-Ile-Ala-Aib-Ile-Val-Aib-Leu-Aib-Pro-OMe (where Boc is *t*-butoxycarbonyl) showed predominantly α-helix in the triclinic crystal and a shift to predominantly 3_{10}-helix in the monoclinic crystal (1). The shift in the form of the helix was accompanied by small changes, 1° to 9°, in the torsion angles ϕ and ψ. In each crystal, the neighboring helices associated in a parallel mode rather than the commonly occurring antiparallel mode found in proteins (2).

The present report describes the structure of the decapeptide Boc-Aib-Val-Aib-Aib-Val-Val-Val-Aib-Val-Aib-OMe, which crystallizes in a triclinic cell with two molecules in the same cell, each with a different helical conformation. The packing is antiparallel. The different helical conformations occurred despite necessarily identical factors such as sequence, length of molecule, nature of solvent, and crystallizing conditions.

EXPERIMENTAL PROCEDURES

The decapeptide was synthesized by conventional solution-phase procedures, purified by reverse-phase HPLC on a C_{18} column, and crystallized from CH_3OH/H_2O. The crystals were stable after drying. X-ray data were collected from a dry, diamond-shaped plate (0.4 × 0.4 × 0.1 mm) with a four-circle automated diffractometer using Cu Kα radiation and a graphite monochromator. The θ–2θ scan technique was used with a 2.0° scan, variable scan speed of 5°/min to 15°/min, and $2\theta_{max} = 107°$, although the number of reflections measured with intensities $>3\sigma(F)$ was relatively small in the 2θ range 100° to 107°. The total number of unique reflections measured was 7813, of which 6053 had intensities $>3\sigma(F)$ to a resolution of 0.96 Å. Three reflections monitored after every 60 measurements remained constant within 4% during the data collection. Lorentz and polarization corrections were applied to the data. The space group is *P*1 with the cell dimensions shown in the *Abstract*. There are two independent peptide molecules per cell, there is no cocrystallized solvent, and the calculated density is 1.113 g/cm^3, based on a molecular weight of 1053.36 for $C_{51}H_{92}N_{10}O_{13}$ and cell volume $V = 3144.1$ Å^3.

The structure was solved by direct phase determination (3) using the random-tangent formula procedure in the SHELXTL computer program.‡ In 1000 trials, trial 684 had the best "combined figure of merit." In the resulting Fourier map, three groupings of atoms, consisting of 47, 18, and 9 peaks found among the strongest 110 peaks, were recognized as fragments of helices. The 47- and 18-atom fragments did not have continuous backbones, but four and three possible NH···O=C hydrogen bonds, respectively, arranged in a parallel fashion in each fragment, were prominently displayed. The positions of almost all of the remaining 74 C, N, and O atoms were found by means of partial structure development (4) in one cycle. The few remaining atoms were located in a difference map. One hundred eighty-four H atoms were placed in idealized positions on the C and N atoms and allowed to ride with the atom to which they are bonded during the least-squares refinement. Full-matrix least-squares refinement with anisotropic thermal factors for the 148 C, N, and O atoms (1336 parameters) was calculated in blocks with 668 parameters per cycle by refining alternately one of the two peptide molecules in each cycle. The final agreement factors for the 6053 data $>3\sigma(F)$ were $R = 0.067$ and $R_w = 0.058$ (where $w = [\sigma^2(F) + \text{abs}(g)F^2]^{-1}$; $g = 0.00025$). For all 7813 data, $R = 0.090$ and $R_w = 0.061$. The final difference map was featureless, with maximum excursions of +0.24 and −0.26 e/Å^3.

Fractional coordinates for the C, N, and O atoms in the two independent molecules are listed in Table 1. Bond lengths and angles (estimated SD, approximately 0.015 Å for bonds and

Abbreviations: Aib, α-aminoisobutyryl (α-aminoisobutyric residue); Boc, *t*-butoxycarbonyl.

‡Sheldrick, G. M. (1981) SHELXTL, An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data (Univ. of Göttingen, Göttingen, F.R.G.).

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Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$)

Atom	Molecule A mean value (SD)				Molecule B mean value (SD)			
	x	*y*	*z*	U_{eq}†	*x*	*y*	*z*	U_{eq}†
C(OBu^t)-1	10283 (12)	6018 (8)	−2317 (7)	82 (4)	817 (11)	−1958 (9)	2392 (8)	91 (4)
C(OBu^t)-2	10490 (14)	6898 (6)	−2619 (5)	147 (7)	−392 (10)	−1616 (7)	2834 (5)	95 (5)
C(OBu^t)-3	11588 (12)	5471 (7)	−2247 (6)	133 (6)	811 (11)	−1659 (7)	1606 (5)	113 (5)
C(OBu^t)-4	9275 (13)	5728 (5)	−2718 (4)	135 (6)	999 (11)	−2880 (5)	2568 (5)	125 (5)
O(OBu^t)	9721 (6)	6098 (4)	−1597 (4)	74 (3)	2058 (7)	−1749 (4)	2656 (4)	81 (3)
C′(0)	9481 (9)	5467 (5)	−1123 (5)	67 (4)	2267 (11)	−930 (7)	2592 (5)	73 (5)
O(0)	9328 (6)	4795 (4)	−1237 (4)	72 (3)	1588 (7)	−357 (5)	2321 (5)	98 (3)
N(1)	9436 (7)	5609 (5)	−462 (4)	53 (3)	3433 (7)	−925 (5)	2919 (4)	58 (3)
Cα(1)	9650 (8)	4999 (9)	158 (7)	54 (3)	4082 (9)	−157 (7)	2849 (6)	63 (4)
C′(1)	8576 (9)	4388 (6)	264 (5)	65 (4)	3202 (9)	449 (6)	3235 (5)	56 (4)
O(1)	8875 (6)	3669 (4)	315 (5)	67 (2)	3381 (6)	1190 (5)	3078 (4)	70 (2)
Cβ1(1)	11022 (8)	4491 (6)	92 (6)	77 (3)	5392 (9)	−406 (6)	3239 (6)	75 (3)
Cβ2(1)	9582 (9)	5427 (8)	797 (7)	84 (4)	4360 (10)	209 (8)	2064 (6)	89 (4)
N(2)	7293 (7)	4732 (5)	378 (5)	54 (3)	2360 (7)	194 (5)	3755 (5)	52 (3)
Cα(2)	6287 (8)	4162 (9)	593 (8)	46 (3)	1609 (8)	755 (7)	4168 (6)	51 (3)
C′(2)	6052 (8)	3713 (8)	7 (7)	51 (4)	2517 (10)	1216 (8)	4513 (7)	63 (4)
O(2)	5999 (6)	2979 (8)	125 (7)	58 (3)	2255 (5)	1955 (5)	4569 (4)	64 (3)
Cβ(2)	5000 (9)	4612 (8)	892 (6)	60 (4)	580 (9)	353 (8)	4678 (7)	69 (4)
Cγ1(2)	5229 (10)	5006 (8)	1523 (6)	81 (5)	−121 (10)	871 (10)	5174 (8)	102 (6)
Cγ2(2)	3941 (9)	4042 (9)	1089 (7)	83 (5)	−455 (10)	75 (9)	4262 (8)	101 (6)
N(3)	5920 (7)	4167 (5)	−647 (5)	53 (3)	3655 (7)	769 (6)	4769 (5)	56 (3)
Cα(3)	5737 (8)	3796 (7)	−1266 (6)	53 (4)	4596 (9)	1120 (8)	5127 (7)	62 (4)
C′(3)	6840 (10)	3049 (7)	−1282 (6)	55 (4)	4962 (9)	1952 (9)	4652 (9)	57 (4)
O(3)	6523 (5)	2403 (5)	−1381 (4)	59 (2)	5102 (6)	2529 (6)	4951 (5)	67 (3)
Cβ1(3)	4329 (9)	3533 (7)	−1215 (7)	77 (4)	5940 (9)	544 (8)	5167 (7)	79 (4)
Cβ2(3)	5977 (10)	4440 (7)	−1919 (6)	74 (4)	4033 (9)	1272 (7)	5860 (6)	75 (4)
N(4)	8099 (7)	3209 (5)	−1230 (5)	51 (3)	5236 (7)	1913 (9)	3987 (10)	56 (3)
Cα(4)	9228 (8)	2573 (6)	−1326 (7)	54 (4)	5725 (10)	2581 (8)	3505 (8)	65 (4)
C′(4)	9057 (8)	1783 (7)	−758 (6)	45 (3)	4769 (10)	3387 (9)	3544 (7)	61 (4)
O(4)	9279 (5)	1112 (5)	−931 (4)	60 (2)	5145 (6)	4049 (5)	3525 (5)	74 (3)
Cβ1(4)	10516 (8)	2906 (7)	−1138 (8)	83 (5)	7134 (9)	2717 (8)	3696 (8)	90 (5)
Cβ2(4)	9374 (10)	2368 (7)	−2069 (6)	78 (4)	5794 (10)	2417 (8)	2773 (7)	91 (5)
N(5)	8698 (6)	1904 (5)	−114 (5)	44 (3)	3438 (8)	3272 (6)	3563 (5)	59 (3)
Cα(5)	8584 (8)	1203 (7)	451 (6)	48 (3)	2426 (9)	3998 (7)	3528 (7)	60 (4)
C′(5)	7434 (9)	698 (7)	359 (6)	52 (4)	2328 (9)	4351 (9)	4199 (7)	58 (4)
O(5)	7569 (5)	−35 (5)	466 (4)	58 (2)	2199 (7)	5083 (6)	4190 (5)	79 (3)
Cβ(5)	8464 (9)	1453 (7)	1199 (7)	58 (4)	1044 (10)	3737 (8)	3365 (7)	73 (4)
Cγ1(5)	8219 (9)	755 (8)	1773 (6)	79 (4)	1167 (10)	3337 (9)	2698 (8)	104 (6)
Cγ2(5)	9708 (10)	1843 (10)	1318 (12)	86 (5)	1 (10)	4499 (9)	3308 (8)	111 (6)
N(6)	6275 (6)	1162 (5)	99 (5)	52 (3)	2391 (6)	3813 (6)	4807 (5)	53 (3)
Cα(6)	5207 (8)	686 (7)	−42 (8)	62 (4)	2320 (9)	4065 (7)	5490 (7)	59 (4)
C′(6)	5649 (9)	183 (8)	−606 (7)	61 (4)	3462 (9)	4619 (9)	5558 (7)	63 (4)
O(6)	5331 (6)	−522 (5)	−543 (5)	70 (3)	3255 (6)	5253 (6)	5767 (5)	81 (3)
Cβ(6)	3915 (9)	1278 (7)	−220 (8)	76 (4)	2364 (9)	3344 (8)	6087 (7)	58 (4)
Cγ1(6)	3454 (9)	1742 (8)	388 (8)	97 (5)	1139 (9)	2863 (8)	6107 (7)	82 (4)
Cγ2(6)	2852 (9)	769 (9)	−394 (10)	127 (7)	2477 (11)	3604 (10)	6814 (8)	98 (5)
N(7)	6335 (7)	534 (6)	−1179 (5)	57 (3)	4686 (7)	4268 (7)	5365 (7)	52 (3)
Cα(7)	6814 (10)	63 (8)	−1734 (6)	70 (4)	5845 (9)	4693 (7)	5401 (7)	60 (4)
C′(7)	7755 (9)	−679 (8)	−1460 (6)	55 (4)	5771 (9)	5510 (9)	4918 (9)	58 (4)
O(7)	7678 (6)	−1365 (5)	−1635 (4)	69 (3)	6113 (6)	6110 (5)	5108 (5)	69 (3)
Cβ(7)	7457 (12)	598 (9)	−2345 (7)	93 (5)	7159 (9)	4143 (7)	5273 (7)	72 (4)
Cγ1(7)	6420 (13)	1252 (9)	−2697 (8)	135 (7)	7265 (10)	3375 (9)	5846 (10)	111 (6)
Cγ2(7)	8054 (15)	95 (10)	−2929 (8)	155 (8)	8385 (10)	4601 (9)	5264 (10)	118 (6)
N(8)	8715 (6)	−581 (5)	−1033 (5)	51 (3)	5409 (7)	5512 (7)	4254 (6)	58 (3)
Cα(8)	9704 (8)	−1250 (7)	−732 (7)	55 (4)	5364 (9)	6231 (7)	3713 (7)	59 (4)
C′(8)	8991 (8)	−1954 (7)	−312 (6)	47 (4)	4495 (9)	6951 (8)	3960 (6)	53 (4)
O(8)	9460 (5)	−2649 (5)	−276 (4)	64 (3)	4773 (6)	7680 (5)	3733 (5)	71 (3)
Cβ1(8)	10498 (8)	−894 (7)	−234 (7)	67 (4)	4709 (11)	6016 (8)	3096 (7)	88 (5)
Cβ2(8)	10623 (9)	−1575 (11)	−1324 (12)	80 (5)	6784 (10)	6463 (9)	3502 (9)	88 (5)
N(9)	7867 (7)	−1740 (5)	79 (5)	45 (3)	3411 (8)	6812 (7)	4366 (6)	61 (3)
Cα(9)	7088 (8)	−2351 (6)	493 (6)	45 (3)	2512 (10)	7466 (7)	4618 (7)	65 (4)
C′(9)	6419 (8)	−2822 (7)	5 (6)	47 (3)	3314 (10)	7995 (9)	4995 (7)	72 (4)
O(9)	6320 (5)	−3562 (4)	203 (4)	57 (2)	3140 (7)	8726 (5)	4926 (5)	83 (3)
Cβ(9)	6126 (10)	−1971 (8)	1007 (7)	69 (4)	1334 (11)	7143 (8)	5102 (8)	83 (5)
Cγ1(9)	6816 (10)	−1762 (8)	1595 (7)	90 (5)	491 (11)	7862 (9)	5399 (9)	116 (6)

Table 1. *(Continued)*

Atom	Molecule A mean value (SD)				Molecule B mean value (SD)			
	x	y	z	U_{eq}†	x	y	z	U_{eq}†
Cγ2(9)	5032 (12)	−2477 (11)	1276 (8)	126 (7)	465 (12)	6728 (9)	4722 (10)	130 (7)
N(10)	5931 (6)	−2403 (5)	−576 (5)	47 (3)	4136 (9)	7521 (7)	5468 (6)	73 (4)
Cα(10)	5314 (9)	−2793 (7)	−1076 (6)	53 (4)	4230 (16)	8500 (11)	6259 (9)	94 (6)
C′(10)	4297 (10)	−3306 (9)	−702 (8)	67 (5)	4662 (9)	9145 (7)	6347 (6)	124 (4)
O(10)	4188 (7)	−4006 (7)	−809 (7)	88 (3)	5008 (13)	7831 (12)	5907 (15)	80 (5)
Cβ1(10)	4580 (9)	−2092 (7)	−1593 (6)	74 (4)	6178 (12)	8177 (10)	5451 (9)	113 (6)
Cβ2(10)	6377 (10)	−3258 (9)	−1489 (7)	82 (5)	5506 (13)	7172 (10)	6485 (9)	120 (7)
O(OMe)	3493 (6)	−2936 (9)	−228 (8)	73 (3)	3011 (9)	8329 (6)	6503 (5)	98 (4)
C(OMe)	2501 (10)	−3391 (8)	145 (9)	103 (5)	2177 (12)	8964 (10)	6819 (8)	133 (7)

The three equivalent C atoms of the *t*-butoxy (OBu^t) moiety of the Boc blocking group are numbered 2–4; the central C atom is numbered 1. Atoms of the carbonyl moiety of Boc (residue 0) and of amino acid residues 1–10 are identified according to conventions in ref. 5.
†$U_{eq} = \frac{1}{3}\sum\sum U_{ij}\, a_i^* a_j^* (\mathbf{a}_i \cdot \mathbf{a}_j)$.

1.0° for angles) do not show significant or systematic differences from expected values.§

RESULTS

Conformations of Helices. The two independent molecules that have crystallized side-by-side in a triclinic cell, devoid of any symmetry elements, have different conformations. In Fig. 1 they are shown separately in a similar orientation and in Fig. 2 they are superimposed with a best least-squares fit to atoms in residues 3 to 8. The conformational angles for the backbones and side chains are listed in Table 2, and the hydrogen bonds are listed in Table 3.

In molecule A, all seven intrahelical hydrogen bonds are of the 5→1 type; that is, the helix is completely an α-helix. Furthermore, molecule A forms three direct NH···O=C hydrogen bonds to other molecules of type A, related by translation, to form infinite columns of α-helix structure. The head-to-tail region meets in good register so that three intermolecular hydrogen bonds are formed: N(1)H···O(8), N(2)H···O(9), and N(3)H···O(10). The head-to-tail hydrogen-bonding motif is an extension of the α-helix hydrogen-bonding motif in the body of the helix (Fig. 3). All ten NH groups participate in hydrogen bonding. Since there are eleven C=O groups (an additional carbonyl is provided by the Boc terminal group), atom O(7) does not participate in a hydrogen bond.

The central part of molecule B, including the side chains, is entirely similar to molecule A. Amide groups N(6)H to N(9)H participate in four 5→1-type hydrogen bonds. The helix is elongated at both termini and, accordingly, amide groups N(4)H, N(5)H, and N(10)H form 4→1 hydrogen bonds, giving this molecule a mixed 3_{10}/α-helical character. At the Boc terminus, the helix is not only elongated but also unwound. The torsion angles ϕ and ψ for Aib-1 have changed signs from minus to plus, corresponding to a change in the handedness of the helix (Table 2). Nevertheless, head-to-tail hydrogen bonding between molecules of type B still occurs, between N(1)H and O(8) and between N(2)H and O(9) (Figs. 1 and 4). Amide N(3)H is not close enough to O(10) of the next molecule in a column, or to any other carbonyl oxygen, to participate in any hydrogen bonding. Carbonyl oxygens O(0) and O(6) also are not involved in hydrogen bonding. To our knowledge, this is the first reported occurrence of the reversal of the helix sense at an amino-terminal Aib residue in a helical peptide. Such reversals are often observed for the carboxyl-terminal Aib residue (6, 7).

Packing of Helices. Molecules of type A form an infinite column and molecules of type B form a different infinite column by head-to-tail hydrogen bonding (Fig. 4). In column A the axis of the column coincides with the helix axis of molecule A, which is parallel to the *b* axis of the unit cell. In column B, the helices of the molecules are somewhat longer than those in column A (see Fig. 2) and, accordingly, the helix axis is inclined by 10° with respect to the *b* axis in order to be accommodated within the cell length (Fig. 4).

The adjacent columns A and B are antiparallel to each other. However, in the direction perpendicular to that shown in Fig. 4, the cell is one molecule thick. Therefore the helices of abutting molecules A are parallel, and similarly for abutting molecules B, although the helix direction for molecules B is opposite to that for molecules A. There is no net polarity for the crystal.

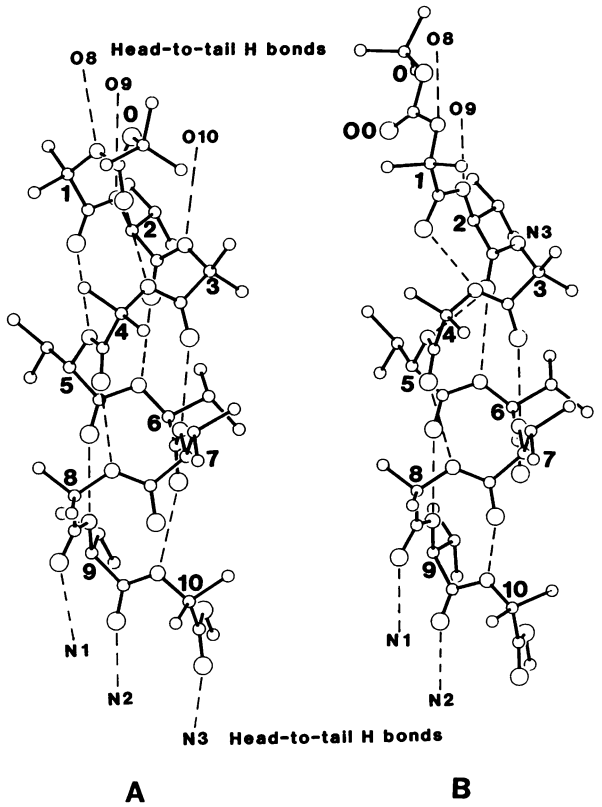

FIG. 1. Conformations of two independent Boc-Aib-Val-Aib-Aib-Val-Val-Val-Aib-Val-Aib-OMe molecules cocrystallized in a *P*1 cell. Molecule A is entirely α-helical; molecule B has 3_{10}-type hydrogen bonds near either end of the helix. Hydrogen bonds are indicated by dashed lines. The C^α atoms are labeled 1–10. The number 0 is at the position of an O atom in the Boc group.

§Supplementary material consisting of observed and calculated structure factors, anisotropic thermal factors, coordinates for H atoms, and bond angles is available from I.L.K.

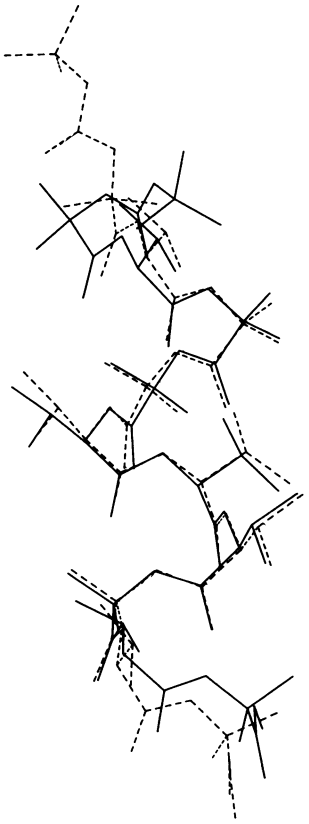

FIG. 2. Superposition of molecule A (solid line) and molecule B (dashed line).

There is no solvent in the cell and there are no lateral hydrogen bonds between molecules in different columns. There are only hydrophobic contacts. The packing of the side chains from adjacent molecules is not particularly efficient in this crystal or in most of the structures of apolar helical peptides. However, there is an orderly and efficient boundary between molecules A and B in this crystal. The view in Fig. 5 is rotated 45° about the *b* axis, as compared to that in Fig. 4. Side chains of Val-2, Val-6, and Val-9, all on the right side

Table 2. Torsion angles

Residue	Value,* degrees ϕ	ψ	ω	$\chi 1$
	Molecule A			
Aib-1A	−62.6†	−62.8	−170.4	
Val-2A	−68.1	−44.8	−177.7	−58.6, 177.8
Aib-3A	−49.5	−51.4	−172.6	
Aib-4A	−59.3	−43.5	−176.9	
Val-5A	−66.5	−38.1	175.6	−60.4, 174.7
Val-6A	−63.2	−43.0	178.5	−58.9, 177.7
Val-7A	−59.8	−44.9	−179.6	−65.8, 176.7
Aib-8A	−56.3	−39.3	179.0	
Val-9A	−66.9	−39.3	178.4	−72.1, 161.7
Aib-10A	+50.4	+44.5‡	179.9§	
	Molecule B			
Aib-1B	+68.0†	+24.7	174.2	
Val-2B	−57.7	−39.3	−178.4	−64.1, 173.5
Aib-3B	−50.6	−46.2	−173.1	
Aib-4B	−53.3	−43.5	−174.0	
Val-5B	−71.0	−40.1	179.5	−54.4, −178.5
Val-6B	−57.7	−50.9	−179.6	−63.3, 172.5
Val-7B	−61.8	−46.1	−176.4	−61.2, 176.5
Aib-8B	−54.2	−36.1	−179.1	
Val-9B	−53.8	−48.1	−179.6	−63.1, 175.3
Aib-10B	+48.3	+42.1‡	−177.0§	

The torsion angles for rotation about bonds of the peptide backbone (ϕ, ψ, and ω) and about bonds of the amino acid side chains (χ) are described in ref. 5.
*Estimated SD ≈ 1.0°.
†C′(0), N(1), Cα(1), C′(1).
‡N(10), Cα(10), C′(10), O(OMe).
§Cα(10), C′(10), O(OMe), C(OMe).

Table 3. Hydrogen bonds

Type	Donor	Acceptor	Length, Å	Angle, degrees (C=O···N)
		Molecule A		
Head-to-tail	N(1)	O(8)	2.990	154
	N(2)	O(9)	2.866	154
	N(3)	O(10)	3.300	140
α-Helix (5→1)	N(4)	O(0)	3.051	161
	N(5)	O(1)	3.215	153
	N(6)	O(2)	3.020	167
	N(7)	O(3)	3.104	159
	N(8)	O(4)	2.988	156
	N(9)	O(5)	3.033	156
	N(10)	O(6)	3.134	154
		Molecule B		
Head-to-tail	N(1)	O(8)	2.829	135
	N(2)	O(9)	3.099	138
3_{10}-Helix (4→1)	N(4)	O(1)	3.116	119
	N(5)	O(2)	2.971	122
α-Helix	N(6)	O(2)	3.228	165
	N(7)	O(3)	3.107	160
	N(8)	O(4)	3.058	150
	N(9)	O(5)	3.341	151
3_{10}-Helix	N(10)	O(7)	3.029	123

In molecule A, atom O(7) does not participate in any hydrogen bonding. In molecule B, atoms N(3), O(0), O(6), and O(10) do not participate in any hydrogen bonding.

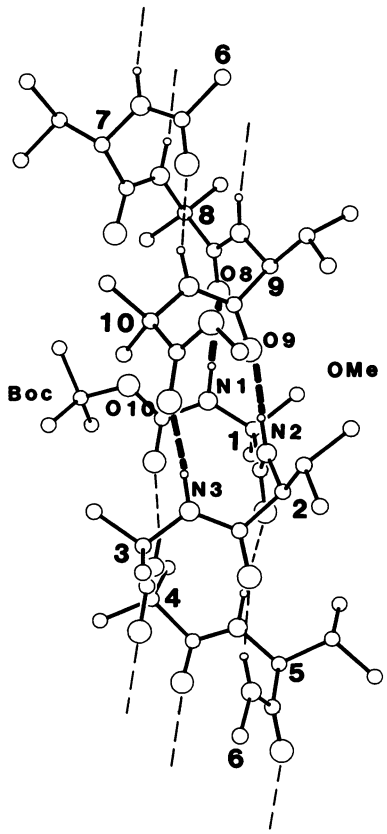

FIG. 3. Three direct NH···O=C head-to-tail hydrogen bonds (heavy dashed lines in middle of diagram), between two molecules of conformation A, that continue the α-helix motif.

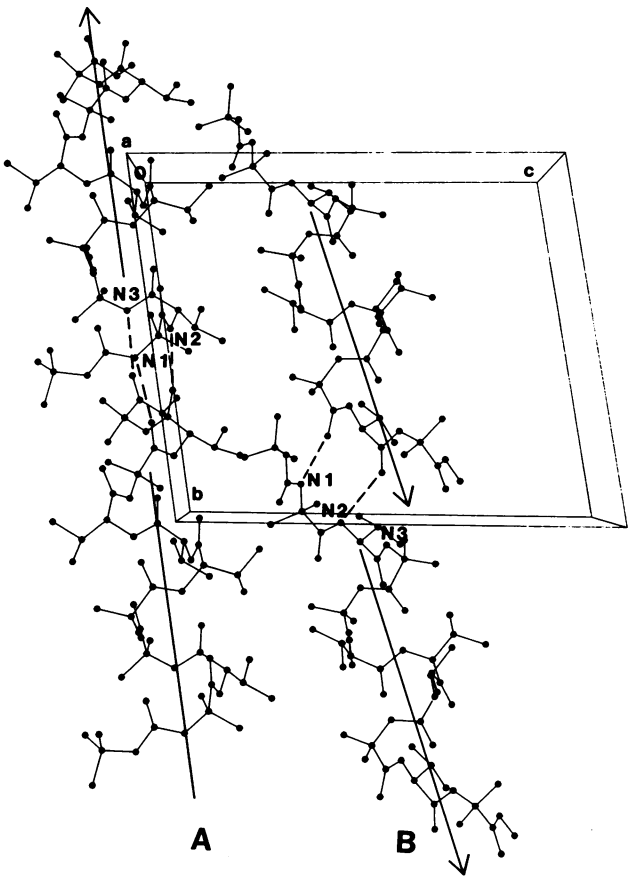

FIG. 4. Packing of helical columns of molecules A and B in crystal. Head-to-tail hydrogen bonds are shown by dashed lines. Arrows indicate the directions of the helix axes. The view is down the *a* axis of the unit cell.

of molecule A, interweave between side chains of Aib-1, Aib-4, and Aib-8, all on the left side of molecule B. The shortest intermolecular contact is Cγ1(2A)···Cβ1(8B) = 3.67 Å. The sequences of the three Val residues and similarly of the three Aib residues involved in the close intermolecular packing have the repeat property of $i + 3$ or 4.

Conformation in Solution. The decapeptide Boc-Aib-Val-Aib-Aib-Val-Val-Val-Aib-Val-Aib-OMe has been studied in C^2HCl_3 and $(C^2H_3)_2SO$ solutions by 270-MHz ^1H NMR (8). In C^2HCl_3, the presence of eight intramolecularly hydrogen-bonded NH groups has been established, consistent with a 3_{10}-helical conformation. In $(C^2H_3)_2SO$, only seven solvent-shielded NH groups are observed, supporting either an α-helical conformation or a partially unfolded 3_{10}-helix.

DISCUSSION

The factors governing transitions between 3_{10}-helices and α-helices in apolar peptides containing Aib residues appear to be quite subtle. To eliminate the effects from the number of residues, the type of residue, and the sequence, a single decapeptide, Boc-Trp-Ile-Ala-Aib-Ile-Val-Aib-Leu-Aib-Pro-OMe, has been studied in various crystal forms (refs. 1 and 9 and unpublished work). The conformations of the backbone in the different crystalline polymorphs varied from a complete α-helix to a predominantly 3_{10}-helix. The possible remaining factors responsible for the $3_{10}/\alpha$ transitions may be the packing accommodations, the head-to-tail hydrogen-bonding motifs, the type and number of cocrystallized solvent molecules, and the polarity of the solvent from which the various crystals were grown.

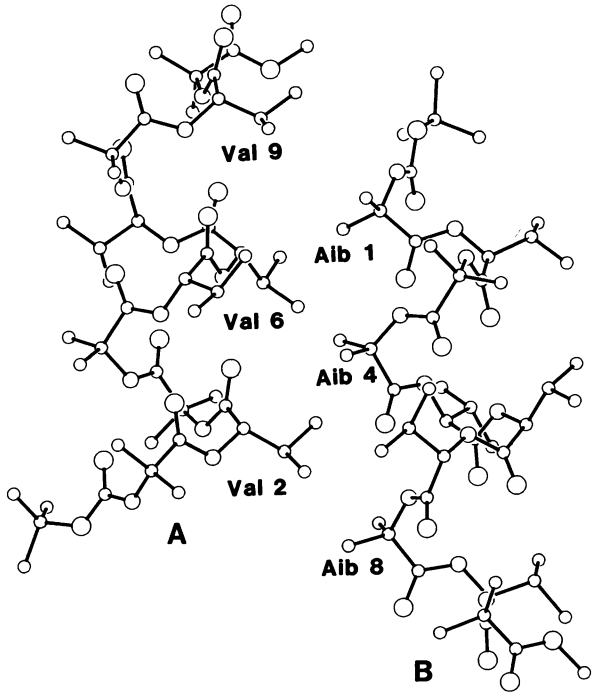

FIG. 5. Orderly packing between molecules A and B. The view is rotated 45° about the *b* axis relative to the view shown in Fig. 4.

Several more variables were eliminated in the present structure study. Since only one crystal was involved, the nature of the crystallizing solvent is not a factor. Furthermore, no solvent molecules were cocrystallized. The unit cell consists only of two independent peptide molecules with different conformations and different head-to-tail hydrogen bonding in an environment that is as nearly equivalent as possible for both conformers. Since there are no hydrogen bonds between the two conformers, the only interactions are hydrophobic attractions between nonpolar side chains. Neither the particular ordered interweaving of Val and Aib side chains shown in Fig. 5 nor the other, more random contacts between the molecules appear to indicate a reason for the existence of the two conformations for the backbone. This study has shown the apparent ease for the interconversion between the 3_{10}- and α-helical conformations and the apparent equality of their stability. An explanation for the $3_{10}/\alpha$ transition has not been established yet. The factors determining partial unwinding of the helix in one of the cocrystallized conformers remain to be understood.

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