Differences in Hydration and Association of Helical Boc-Val-Ala-Leu-Aib-Val-Ala-Leu-(Val-Ala-Leu-Aib)$_2$-OMe·xH_2O in Two Crystalline Polymorphs†

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The 15-residue apolar peptide, Boc-Val-Ala-Leu-Aib-Val-Ala-Leu-(Val-Ala-Leu-Aib)$_2$-OMe has been crystallized from 2-propanol–water (form I). The crystal parameters for I are as follows: $C_{74}H_{133}N_{15}O_{18}·2H_2O$, space group $P2_1$, a = 9.185 (6) Å, b = 47.410 (3) Å, c = 10.325 (9) Å, β = 91.47 (2)°, Z = 2, R = 6.3% for 4532 reflections observed >3$\sigma(F)$, resolution 0.94 Å. The structure is almost completely α-helical with eleven 5→1 hydrogen bonds and one 4→1 hydrogen bond near the N-terminus. The structure has been compared with a polymorph (form II) obtained from methanol–water (Karle, I. L.; Flippen-Anderson, J. L.; Uma, K.; Sukumar, M.; Balaram, P., *J. Am. Chem. Soc.* 1990, *112*, 9350–9356). The two forms differ in the extent of hydration; form I contains two water molecules in the head-to-tail region of helical columns, while form II is more extensively solvated, with the equivalent of 7.5 water molecules. The three-dimensional packing of helices is completely parallel in I and antiparallel in II.

α-Aminoisobutyric acid (Aib) is an important constituent of many membrane active fungal peptides.[1,2] Extensive studies of the stereochemistry of Aib-containing peptides[3-6] have been motivated by attempts to develop structure–activity correlations for membrane channel forming peptides[7,8] and the possibility of using stereochemically constrained residues in designing conformationally rigid analogs of biologically active peptides.[9-12] The ability of α-aminoisobutyryl residues to stabilize helical conformations in oligopeptides has permitted the detailed structural analysis of peptide helices in crystals at high resolution.[13,14] These studies have provided several useful insights into packing and solvation of helices in the solid state, in addition to allowing the detailed stereochemical characterization (α, 3_{10}, or mixed $3_{10}/\alpha$) of helices.[13-17] The stereochemical rigidity of Aib-containing peptide helices extends into solution,[18] suggesting that these residues could be effectively employed in the construction of conformationally rigid, secondary structure modules, in the de novo design of synthetic protein mimics.[19-22] This strategy to construct synthetic proteins rests on the ability to synthesize and characterize relatively long helical segments, which can then be assembled into larger structures.[23] This paper describes the structure of a model 15-residue peptide, Boc-Val-Ala-Leu-Aib-Val-Ala-Leu-(Val-Ala-Leu-Aib)$_2$-OMe, crystallized from 2-pro-

† This paper is dedicated to Professor Ralph Hirschmann on the occasion of his 70th birthday. It has been a pleasure to know him.

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Table I. Diffraction Data for Two Polymorphs of Boc-Val-Ala-Leu-Aib-Val-Ala-Leu-(Val-Ala-Leu-Aib)$_2$-OMe-xH$_2$O

	I (present paper)	II (ref 24)
empirical formula	$C_{74}H_{133}N_{15}O_{16}\cdot 2H_2O$	$C_{74}H_{133}N_{15}O_{16}\cdot 7.5H_2O$
crystallizing solvent	2-propanol-H_2O	methanol-H_2O
crystal size, mm	0.15 × 0.25 × 0.25	0.65 × 0.30 × 0.15
space group	$P2_1$	$C222_1$
cell parameters		
a, Å	9.185 (6)	18.348 (5)
b, Å	47.410 (3)	47.382 (11)
c, Å	10.325 (9)	24.157 (5)
β, deg	β = 91.47 (2)	
vol, Å^3	4495	21001 (9)
Z	2	8
mol wt	1520.98 + 36.03	1520.98 + 135.12
density, g/cm	1.150	1.048
resolution, Å	0.94	1.00
independent reflections	5724	5909
obsd refl ($\|F_o\| > 3\sigma(F)$)	4532	3147
no. parameters refined	979	1045
no. data to no. parameters ratio	4.6:1.0	3.0:1.0
final R indices (obsd data), %	6.3	10.6
goodness-of-fit	1.2	12.2
max diff, e/Å^3	0.35	0.36
min diff (hole), e/Å^3	−0.41	−0.31

panol–water (I) and compares the conformation and solvation with that of a polymorph (II) obtained earlier from methanol–water.[24] While the crystals of polymorph I are stable for several weeks in the dry state, the crystals of polymorph II exist as stable colorless plates only when surrounded by a large amount of mother liquor. The two polymorphs differ in the extent of hydration and also show subtle differences in the peptide helix with respect to the intrahelical hydrogen bonding pattern near the N-terminus.

Experimental Section

The model peptide was synthesized by a conventional solution-phase procedure by a fragment condensation approach.[25] After purifying the peptide by high-performance liquid chromatography, crystals were grown by slow evaporation from a 2-propanol–H_2O solution.

X-ray diffraction data were collected with Cu Kα radiation from a dry crystal at 228 K on an automated four-circle diffractometer with a graphite monochromator (Nicolet R3). Three reflections used as standards, monitored after every 97 measurements, remained constant within 4% during the data collection. The θ–2θ scan technique was used with $2\theta_{max}$ = 110°, a scan width of 2.0° + $2\theta(\alpha_2) - 2\theta(\alpha_1)$, scan speed of 14.6°/min and index ranges h: −9 to +10; k: 0 to 49; and l: −10 to +1. Cell parameters for the two polymorphs and other diffraction data are shown in Table I. The present structure was solved by using the molecule in the earlier structure as a vector search model in the PATSEE computer program[26] contained in the SHELXTL package of computer programs.[27] Due to the large number of parameters, full-matrix anisotropic least-squares refinement was performed on the C, N, and O atoms in two blocks (residues 1–7 and residues 8–15 with the two water oxygens refined in each block). The weighting scheme was $w = [\sigma^2(F) + 0.0010F^2]^{-1}$. Hydrogen atoms were placed in idealized positions, with N–H and C–H = 0.96 Å and allowed to ride with the C or N atom to which each was bonded for the final cycles of refinement. The thermal factor for the hydrogen atoms was fixed at U_{iso} = 0.125. The side chain in Leu 14 has high thermal parameters and, in addition, the C$^\delta$ atoms occupy all three conformational positions on the C$^\gamma$(14) atom. Occupancies for atoms C$^{\delta 2}$(14) and C$^{\delta 2'}$(14) are ~$^2/_3$ and ~$^1/_3$ for sites with χ^2 near 50° and −72°, respectively. The final R factor is 6.3% for 4532 independent data measured >3$\sigma(F)$. Fractional coordinates are listed in the supplementary material, and torsional angles are listed in Table II.

Results

The Helix. The molecule folds into an almost complete α-helix with eleven 5→1 hydrogen bonds in the crystal form I from 2-propanol–H_2O. The 5→1 hydrogen bonds run successively beginning with N(5)H; N(4)H does not participate in any hydrogen bonding and N(3)H makes a 4→1 hydrogen bond with carbonyl O(0) from the Boc group (Table III). The initial 3_{10} turn stabilized by a 4→1 hydrogen bond at the N-terminus of a long helix is a fairly common feature in peptides and proteins.[28] The φ and ψ values (Table II) lie close to the values expected for ideal α-helices with somewhat greater distortions for the Val(12), Ala(13) and Leu(14) residues. The crystal form II reported earlier[24] adopts a complete α-helical conformation with twelve 5→1 hydrogen bonds. The φ and ψ values for form II are also listed in Table II for comparison. The overall conformation in the two forms is very similar with the four Leu side chains extended on one side of the helix and the four Val side chains extended on the other side. Only the terminal carbomethoxy group differs by a 180° rotation in the two crystalline forms.

Head-to-Tail Hydrogen Bonding. Figure 1 shows a comparison of the head-to-tail hydrogen bonding in crystals I and II.[24] The peptides are shown in nearly the same orientation. The direct N(1)H···O(13) hydrogen bond is the same in both. Water molecule W(2) is in a similar location in both, acting as a hydrogen bonding intermediary between N(2)H and O(13). Water molecules W(1) in I and W(5) in II both form hydrogen bonds with O(12), but their other hydrogen bonds are quite different. There are only two cocrystallized water molecules in I but in II there are six water molecules in the head-to-tail region, three of which are disordered among six water sites. (Only one position of each disordered water for II is shown in Figure 1.) As mentioned in the above section, a complete α-helix is formed in II.[24] In I the helix appears to adjust to fewer waters for hydrogen bond mediation by switching to a 3_{10}-type for N(3)H and by N(4)H not participating in any hydrogen bonding.

Interhelical Side-Chain Contacts. Figure 2 shows Leu···Val nearest contacts in a sheet in crystal I where the molecules are related by translation. Figure 3 shows molecules in a sheet in crystal II, where the molecules are related by a 2-fold rotation between Val···Val contacts or between Leu···Leu contacts. The right molecule in each figure is in nearly the same orientation. The dotted lines

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Table II. Torsional Angles[a,b]

	ϕ	ψ	ω	χ^1	χ^2
Val(1)	−51.8 (−55.5)[c]	−45.6 (−60.2)	−173.2	−67.4, 169.2	
Ala(2)	−63.6 (−65.5)	−32.5 (−38.5)	179.3		
Leu(3)	−65.9 (−64.8)	−51.7 (−40.3)	−179.3	−179.6	−173.2, 65.5
Aib(4)	−55.2 (−51.9)	−48.4 (−50.0)	−176.9		
Val(5)	−63.0 (−61.8)	−50.1 (−45.8)	−176.3	−67.5, 168.7	
Ala(6)	−61.1 (−60.3)	−42.9 (−39.5)	−177.3		
Leu(7)	−68.6 (−67.7)	−38.9 (−34.0)	175.8	−64.0	−178.9, −55.1
Val(8)	−63.9 (−69.5)	−45.1 (−45.1)	−179.2	−67.2, 169.9	
Ala(9)	−60.4 (−58.9)	−45.0 (−42.7)	178.8		
Leu(10)	−61.9 (−62.4)	−52.1 (−46.8)	−173.3	−73.5	162.8, −71.3
Aib(11)	−57.2 (−51.6)	−49.5 (−46.0)	−167.7		
Val(12)	−79.5 (−72.5)	−31.8 (−30.6)	178.3	−179.9, −60.5	
Ala(13)	−75.3 (−67.8)	−42.0 (−34.4)	−172.7		
Leu(14)	−81.2 (−87.3)	−28.5 (−20.0)	−169.3	−82.9	170.4, 49.5, 71.8[f]
Aib(15)	−56.3 (−57.5)	−41.0 (148.2)[d]	−171.5[e]		

[a] 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^1 and χ^2) are described in ref 38. [b] ESD's are ~1.0°. Values in parentheses correspond to form II crystallized from CH_3OH–H_2O.[24] [c] C′(0), N(1), C$^\alpha$(1), C′(1). [d] N(15), C$^\alpha$(15), C′(15), O(OMe). [e] C$^\alpha$(15), C′(15), O(OMe), C(OMe). [f] Disorder among C$^\delta$(14) atom positions.

Table III. Hydrogen Bonds

type	donor	acceptor	N···O, Å	H···O,[a] Å	C=O···N angle, deg
heat-to-tail	N(1)	O(13)[b]	3.029	2.16	165.7
peptide-to-water	N(2)	W(2)[c]	2.819	1.93	
4→1	N(3)	O(0)	3.054	2.37	125.5
	N(4)[d]				
5→1	N(5)	O(1)	3.036	2.15	164.1
	N(6)	O(2)	2.941	2.08	146.8
	N(7)	O(3)	2.932	2.06	159.2
	N(8)	O(4)	3.151	2.27	152.4
	N(9)	O(5)	2.986	1.88	157.1
	N(10)	O(6)	2.933	2.06	154.9
	N(11)	O(7)	2.911	2.04	149.8
	N(12)	O(8)	3.001	2.13	156.8
	N(13)	O(9)	3.031	2.20	148.6
	N(14)	O(10)	2.976	2.11	156.4
	N(15)	O(11)	3.156	2.40	144.0
			O···O, Å		
water-to-peptide	W(1)	O(12)[e]	2.912		
or water	W(1)	O(14)[f]	2.871		
	W(2)	W(1)	2.749		
	W(2)	O(13)[b]	2.960		

[a] The H atoms were placed in idealized positions with the N–H distance equal to 0.96 Å. [b] Symmetry equivalent $2-x$, $^1/_2+y$, $1-z$ to coordinates listed in the supplementary material. [c] Symmetry equivalent $1+x$, y, z to coordinates listed in the supplementary material. [d] Atoms N(4) and O(15) do not participate in hydrogen bonding; N(4)···O(0) = 3.42 Å, angle C=O···N = 162°. [e] Symmetry equivalent $1-x$, $^1/_2+y$, $1-z$ to coordinates listed in the supplementary material. [f] Symmetry equivalent $1-x$, $^1/_2+y$, $2-z$ to coordinates listed in the supplementary material.

show intermolecular C···C contacts (~3.8 to 4.1 Å, a very few are <3.8 Å). In crystal I there are eleven such contacts while in crystal II, seven such contacts occur between Val···Val, or if the Leu···Leu contacts on the other side of the helix are examined, there are eight. In either case there are fewer C···C close approaches in II than in I. Even taking into account the occurrence of water molecules in some of the cavities (where C···O approaches are ≥3.9 Å), the packing is looser in II than in I. The larger calculated density, 1.15 g cm^{-3} in I as compared to 1.05 g cm^{-3} in II is consistent with more efficient packing in I.

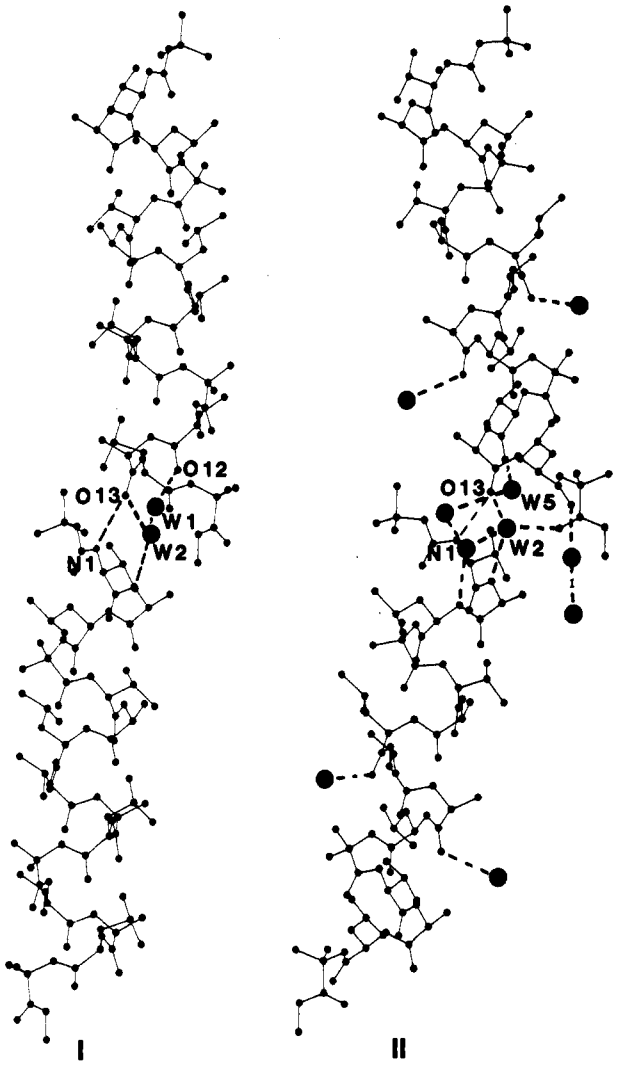

Figure 1. Head-to-tail hydrogen bonds between two molecules (related by a 2-fold screw axis) of Boc-Val-Ala-Leu-Aib-Val-Ala-Leu-(Val-Ala-Leu-Aib)$_2$-OMe in polymorph I ($P2_1$, with $2H_2O$) (present paper) and polymorph II ($C222_1$, with $7.5H_2O$) (see ref 24). The large black dots represent water molecules and the dashed lines represent hydrogen bonds.

Helix Assembly in Crystals. Peptide helices possess appreciable macrodipole moments.[29-31] Antiparallel helix packing in proteins has been rationalized by invoking

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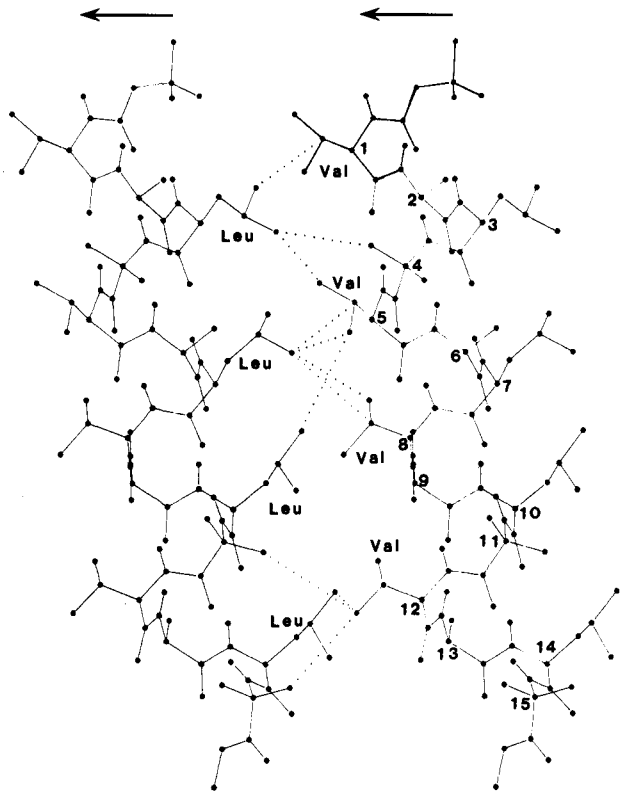

Figure 2. Two molecules of the 15-residue peptide in polymorph I that are related by translation along the ac diagonal. Dotted lines indicate nearest C···C distances (~3.8 to 4.1 Å) between neighboring molecules. Mostly Leu···Val van der Waals contacts are involved.

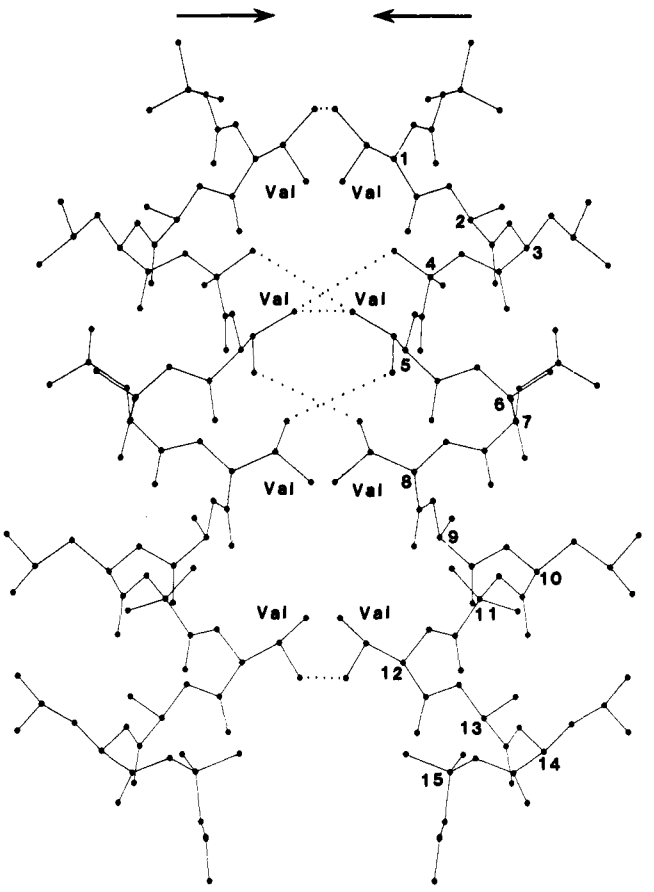

Figure 3. Two molecules of the 15-residue peptide in polymorph II[24] related by a 2-fold rotation axis. Dotted lines indicate nearest C···C distances (~3.8 to 4.1 Å) between neighboring molecules. Val···Val and Val···Aib van der Waals contacts are involved.

dipole–dipole interactions as an important determinant in protein folding.[30] Electrostatic energy calculations for helical peptides packed in crystals have led to the conclusion that antiparallel helix packing is overwhelmingly favored.[32] However, this has not been the case for 10–16 residue apolar peptide helices where many instances of completely parallel packing of helices has been observed in crystals. In a number of cases, the same peptide crystallized in different crystal forms has been found to have all parallel assemblies of helices in one crystal form and an antiparallel assembly in a different crystal form.[33,34] Similarly, for the present 15-residue peptide, there is completely parallel packing of helices in crystal I. In crystal II,[24] although there is parallel packing, in the sense of the helix direction, that occurs in sheets of one molecule thickness as shown in Figure 3, the adjacent sheets assemble in an antiparallel motif. The existence of a dipole moment in a helix does not appear to influence the packing direction of helices.

The demonstration that peptide helices can assemble in a completely parallel fashion[35] was instrumental in designing a peptide having chymotrypsin-like esterase activity.[36,37] In this peptide, four short parallel helical peptides were linked covalently at their carboxyl ends while their amino ends bore the serine protease catalytic site residues serine, histidine, and aspartic acid.

Concluding Remarks

A 15-residue apolar peptide has been shown to crystallize in different crystal forms in which completely parallel packing of helices occurs in one, and antiparallel packing occurs in the other. The association of helices is not governed by particular selectivities of the various side chains. Although both polymorphs contain water of crystallization, there is much more water around the head-to-tail region (and some additional water molecules laterally between the helices) in the crystal in which the packing is less efficient. Nevertheless, the conformation of the peptide molecule is nearly the same in both, that is, completely α-helical in one and one 5→1 hydrogen bond replaced by a 4→1 hydrogen bond in the other. It is important to note that the choice of solvent, and conse-

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quently the amount of cocrystallized water, has a profound effect on the stability of the crystals.

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Supplementary Material Available: Tables of atomic coordinates, bond lengths, bond angles, anisotropic displacement coefficients, and H atom coordinates (10 pages); observed and calculated structure factors (21 pages). Ordering information is given on any current masthead page.

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