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# Aggregation studies in crystals of apolar helical peptides: Boc-Aib-Val-Ala-Leu-Aib-Val-Ala-Leu-Aib-OMe

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Dedicated to the memory of Professor Choh Hao Li

In the crystal, the backbone of Boc-(Aib-Val-Ala-Leu)$_2$-Aib-OMe adopts a helical form with four α-type hydrogen bonds in the middle, flanked by $3_{10}$-type hydrogen bonds at either end. The helical molecules stack in columns with head-to-tail hydrogen bonds, either directly between NH and CO, or bridged by solvent molecules. The packing of the helices is parallel, even in space group $P2_1$. Cell parameters are $a = 9.837(2)$ Å, $b = 15.565(3)$ Å, $c = 20.087(5)$ Å, $\beta = 96.42(2)°$, $d_{calc} = 1.091$ g/cm$^3$ for $C_{46}H_{83}N_9O_{12} \cdot 1.5H_2O \cdot 0.67CH_3OH$. There appears to be some hydration of the backbone in this apolar helix.

*Key words:* Aib residues; $3_{10}$-helix/α-helix; parallel packing of helices; crystal structure; head-to-tail hydrogen bonds; hydration of backbone

The role of specific peptide residues in promoting helix formation and the nature of the aggregation of helices is being studied with X-ray diffraction analyses of model synthetic apolar peptides containing 9–16 residues (1–4). Factors which may be important are the type of residue, the specific sequence, and the polarity of the solvent from which crystals are grown. All the model peptides studied have ~30% Aib (α-aminoisobutyric acid) content to mimic natural membrane active peptides like zervamicin IIA (5). The sequence in the apolar 1–10 analog (1, 3) and the apolar 1–16 analog (2) of zervamicin IIA has the characteristic of having residues with large side-chains such as Ile, Val, and Leu interspersed with one or two residues with small side-chains such as Ala and Aib. The resulting helix has all the large side-chains on one side and the small side-chains on the other.

A decapeptide with the sequence Boc-(Aib-Ala-Leu)$_3$Aib-OMe also has the large leucyl side-chains on one side of the helix and the small side-chains of Aib and Ala on the other side (4). For this sequence, however, water molecules have invaded into the backbone on the side of the small side-chains and caused this peptide to mimic an amphiphilic helix. An aqueous channel is formed by the antiparallel aggregation of the helices.

The present peptide, Boc-(Aib-Val-Ala-Leu)$_2$-Aib-OMe, has an alternation of small and large side-chains. It forms a predominantly alpha-helix and aggregates with the helices parallel to each other in a mode similar to the zervamicin IIA analogs (1–3).

There is only minimal solvation of the backbone.

## EXPERIMENTAL PROCEDURE

Boc-(Aib-Val-Ala-Leu)$_2$-Aib-OMe was synthesized by conventional solution-phase procedures and crystals were grown from $CH_3OH/H_2O$ solution in the form of prisms with tapered corners. A crystal of size 1.30 × 0.40 × 0.50 mm, sealed in a thin-walled glass capillary with a small amount of mother liquor, was used to collect X-ray diffraction data on an automated diffractometer using CuK$\alpha$ radiation and a graphite monochromater ($\lambda = 1.54178$ Å). The $\theta$–$2\theta$ scan technique was used with a scan of $2.0° + 2\theta(\alpha_1) - 2\theta(\alpha_2)$, a variable scan rate between 6°/min and 27°/min, depending upon the diffracted intensity, and $2\theta_{max} = 110°$, for a total of 4024 independent reflections and 3249 reflections with intensities greater than $3\sigma(F)$. Three reflections 0 0 6, 0 3 1, and 4 0 0, monitored after every 60 measurements, remained constant within 3% during the data collection. Lorentz, polarization, and absorption corrections were applied to the data. The cell parameters are a = 9.837(2) Å, b = 15.565(3) Å, c = 20.087(5) Å, and $\beta$ = 96.42(2)° for space P2$_1$. The calculated density for Z = 2, V = 3056.0 Å$^3$, mol wt = 954.23 + 59.84 for $C_{46}H_{83}N_9O_{12}\cdot 1.5\text{-}H_2O\cdot 0.67CH_3OH$ is 1.091 g/cm$^3$.

The structure was solved directly by the random tangent procedure as contained in the SHELX84 package of programs[+], with the use of the tangent formula for direct phase determination (6). The initial E-map contained a fragment of the molecule consisting of 80% of the atoms which was expanded to the full structure by the partial structure procedure (7) and difference maps. The final cycles of full-matrix least-squares refinement were performed on the coordinates and anisotropic thermal parameters of C, N, and O atoms. Sixty-three hydrogen atoms in the peptide molecule were placed in idealized positions, and in the least-squares calculation they were allowed to ride with the C or N atoms to which they are bonded. Difference maps contained sizeable peaks that corresponded to alternate conformations for the side-chains of Val$^2$ and Leu$^4$ and for the OMe terminus and also partially occupied sites for water molecules. These atom positions were included in the least-squares refinement. Occupancy factors were refined for the disordered side-chains and partially occupied solvent sites. The hydrogen atoms associated with the C atoms in the disordered side-chains were not included in the refinement. The R-factors for 3249 data (greater than $3\sigma(F)$) are R = 0.081 and R$_w$ = 0.088. For all the 4024 data, they are R = 0.098 and R$_w$ = 0.090.

Fractional coordinates of C, N, and O atoms are listed in Table 1 with the atoms in partially occupied sites designated by †.

## RESULTS

### *Conformation of molecule*

A diagram of the peptide molecule in its predominant conformation, drawn by computer using the experimentally determined coordinates, is shown in Fig. 1. Alternate conformations for the side-chains of Val$^2$ and Leu$^4$, as well as for the terminal OMe group, are indicated in Fig. 2 by the dashed lines. For Val$^2$, the C$^\gamma$ atoms occur at all three possible conformations, that is, g$^+$, g$^-$, and t, although ~70° of the molecules in the crystal have the t, g$^-$ conformation while the t, g$^+$ and g$^+$, g$^-$ forms occur ~15% each. For Leu$^4$, in ~70% of the molecules, the side-chain has the g(tg) conformation and in ~30%, the side-chain has the t(tg$^-$) form. The g(tg) conformaton, occurring in the major conformer in Leu$^4$ and in Leu$^8$ that is not disordered, is the highly populated form found in peptides (8). The OMe terminus occurs about equally in two conformations

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[+] MicroVAX version of SHELXTL system of programs. Nicolet Analytical Instruments, Madison, Wisconsin.

[*] Supplementary material consisting of bond lengths, bond angles, anisotropic thermal parameters, and coordinates for H atoms will be deposited with the Cambridge Crystallographic Data File. Observed and calculated structure factors are available from I.L.K.

TABLE I

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

| | x | y | z | $U_{eq}^{*}$ |
|---|---|---|---|---|
| O | 4085(8) | 2195(7) | 996(4) | 101(3) |
| $C'(0)$ | 3414(14) | 2842(9) | 1256(6) | 83(5) |
| C(2) | 5263(16) | 2291(12) | 655(7) | 119(7) |
| C(3) | 6301(19) | 2641(16) | 1132(13) | 268(18) |
| C(4) | 5011(25) | 2835(14) | 82(8) | 249(14) |
| C(5) | 5593(17) | 1370(10) | 496(8) | 158(8) |
| O(0) | 3729(7) | 3614(7) | 1202(3) | 91(3) |
| N(1) | 2383(9) | 2546 | 1566(4) | 77(3) |
| $C^{\alpha}(1)$ | 1408(12) | 3110(7) | 1814(6) | 80(4) |
| $C'(1)$ | 2118(11) | 3781(8) | 2300(5) | 70(4) |
| O(1) | 1667(8) | 4518(6) | 2317(4) | 86(3) |
| $C^{\beta}(11)$ | 524(12) | 3554(9) | 1266(6) | 107(5) |
| $C^{\beta}(12)$ | 550(12) | 2546(9) | 2257(7) | 111(6) |
| N(2) | 3233(9) | 3545(7) | 2689(4) | 72(3) |
| $C^{\alpha}(2)$ | 3930(13) | 4128(9) | 3176(5) | 88(5) |
| $C'(2)$ | 4383(11) | 4934(9) | 2866(6) | 81(5) |
| O(2) | 4436(8) | 5635(7) | 3141(4) | 96(3) |
| $C^{\beta}(2)$ | 5038(19) | 3652(11) | 3635(7) | 132(7) |
| $C^{\gamma}(21)^{\dagger}$ | 5677(29) | 4222(16) | 4159(11) | 211(13) |
| $C^{\gamma}(22)^{\dagger}$ | 4317(49) | 3055(20) | 4116(16) | 132(19) |
| $C^{\gamma}(23)^{\dagger}$ | 6447(32) | 3487(21) | 3269(18) | 263(18) |
| N(3) | 4841(8) | 4867(7) | 2263(5) | 82(4) |
| $C^{\alpha}(3)$ | 5306(12) | 5619(8) | 1920(7) | 98(5) |
| $C'(3)$ | 4131(15) | 6260(9) | 1732(6) | 86(5) |
| O(3) | 4356(8) | 7034(7) | 1778(4) | 106(3) |
| $C^{\beta}(3)$ | 5899(18) | 5363(10) | 1315(8) | 167(9) |
| N(4) | 2876(12) | 5941(7) | 1536(4) | 87(4) |
| $C^{\alpha}(4)$ | 1782(15) | 6512(10) | 1388(6) | 101(5) |
| $C'(4)$ | 1409(11) | 6892(9) | 2016(9) | 106(6) |
| O(4) | 1049(8) | 7676(7) | 2068(4) | 114(4) |
| $C^{\beta}(4)^{\dagger}$ | 269(35) | 6078(15) | 1127(13) | 94(11) |
| $C^{\gamma}(4)^{\dagger}$ | 322(39) | 5893(19) | 462(16) | 134(15) |
| $C^{\delta}(41)^{\dagger}$ | −1068(30) | 5466(32) | 99(18) | 156(17) |
| $C^{\delta}(42)^{\dagger}$ | 367(39) | 6715(27) | −6(15) | 141(15) |
| $C^{\beta}(4')^{\dagger}$ | 1135(59) | 5879(33) | 942(24) | 84(19) |
| $C^{\gamma}(4')^{\dagger}$ | −379(33) | 6449(26) | 668(26) | 79(17) |
| $C^{\delta}(41')^{\dagger}$ | −1473(128) | 5600(96) | 246(31) | 266(41) |
| $C^{\delta}(42')^{\dagger}$ | −101(41) | 7201(41) | 249(29) | 97(20) |
| N(5) | 1380(8) | 6410(7) | 2586(5) | 86(4) |
| $C^{\alpha}(5)$ | 1077(12) | 6729(8) | 3237(7) | 94(5) |
| $C'(5)$ | 1928(14) | 7515(9) | 3448(6) | 88(5) |
| O(5) | 1462(9) | 8173(7) | 3643(5) | 134(5) |
| $C^{\beta}(51)$ | 1418(16) | 6021(10) | 3725(7) | 133(7) |
| $C^{\beta}(52)$ | −445(12) | 6961(10) | 3182(9) | 154(8) |
| N(6) | 3299(10) | 7450(7) | 3350(4) | 76(3) |
| $C^{\alpha}(6)$ | 4223(11) | 8156(8) | 3546(5) | 77(4) |
| $C'(6)$ | 3941(10) | 8906(8) | 3073(6) | 72(4) |
| O(6) | 3943(8) | 9646(7) | 3305(4) | 90(3) |
| $C^{\beta}(6)$ | 5766(12) | 7847(9) | 3608(6) | 90(5) |
| $C^{\gamma}(61)$ | 6052(13) | 7169(9) | 4126(6) | 111(5) |
| $C^{\gamma}(62)$ | 6722(11) | 8611(10) | 3743(6) | 112(6) |
| N(7) | 3699(7) | 8757(7) | 2433(4) | 63(3) |
| $C^{\alpha}(7)$ | 3409(11) | 9461(8) | 1950(6) | 79(4) |
| $C'(7)$ | 2215(11) | 9995(8) | 2051(5) | 72(4) |
| O(7) | 2139(8) | 10741(7) | 1886(5) | 110(4) |
| $C^{\beta}(7)$ | 3360(12) | 9110(9) | 1240(5) | 90(5) |
| N(8) | 1176(8) | 9580(7) | 2301(4) | 64(3) |
| $C^{\alpha}(8)$ | −92(10) | 10001(8) | 2395(6) | 74(4) |
| $C'(8)$ | −127(14) | 10421(9) | 3052(7) | 86(5) |
| O(8) | −1082(11) | 10836(9) | 3201(5) | 151(5) |
| $C^{\beta}(8)$ | −1259(11) | 9348(9) | 2280(6) | 93(5) |
| $C^{\gamma}(8)$ | −1510(15) | 8980(10) | 1595(9) | 134(7) |
| $C^{\delta}(81)$ | −2625(16) | 8252(12) | 1550(10) | 209(11) |
| $C^{\delta}(82)$ | −1902(22) | 9623(14) | 1029(9) | 234(13) |
| N(9) | 909(13) | 10282(8) | 3503(6) | 115(5) |
| $C^{\alpha}(9)$ | 948(17) | 10537(11) | 4192(8) | 129(7) |
| $C'(9)$ | 623(22) | 11521(13) | 4255(10) | 153(10) |
| O(9) | 1080(18) | 12036(11) | 3874(7) | 214(9) |
| $C(10)^{\dagger}$ | 365(59) | 12934(27) | 4163(42) | 354(37) |
| $C^{\beta}(91)$ | −23(22) | 9941(12) | 4571(8) | 196(11) |
| $C^{\beta}(92)$ | 2440(21) | 10543(14) | 4498(8) | 209(13) |
| O(10) | −166(13) | 11693(8) | 4724(5) | 162(6) |
| $C(10')^{\dagger}$ | −546(56) | 12709(28) | 4685(33) | 342(38) |
| W(1) | 4330(12) | 1778(8) | 2804(5) | 165(5) |
| $OM^{\dagger}$ | 6514(25) | 1290(21) | 3733(16) | 283(17) |
| $CM^{\dagger}$ | 6386(29) | 1101(27) | 4407(18) | 208(18) |
| $W(2)^{\dagger}$ | 6820(44) | 1459(52) | 2333(27) | 269(39) |
| $W(3)^{\dagger}$ | −1249(58) | 4489(31) | 2756(35) | 237(34) |

* $U_{eq} = 1/3 \Sigma\Sigma U_{ij} a_i^* a_j^* (a_i \cdot a_j)$

† Occupancy: $C^{\gamma}(21)$, 0.80; $C^{\gamma}(22)$, 0.35; $C^{\gamma}(23)$, 0.85; $C^{\beta}(4)$ to $C^{\delta}(42)$, 0.70; $C^{\beta}(4)'$ to $C^{\delta}(42)'$, 0.30; C(10), 0.50; C(10'), 0.50; OM, CM (MeOH), 0.67; W(2), 0.25; W(3), 0.25.

differing by ~180° around the $C^{\alpha}(9)$—$C'(9)$ bond. In each case, there is sufficient space in the lattice to accommodate the alternate conformations. In these atomic groupings, the nearest intermolecular C · · · O distance is 3.30 Å for $C^{\gamma}(22)$ · · · W(1) and the nearest intermolecular C · · · C distance is 3.56 Å for $C^{\delta}(41')$ · · · $C^{\beta}(3)$. The remainder of the sidegroups are reasonably rigid in a single conformation, although the thermal values $U_{eq}$ in Table I are 50%–100% larger for the molecule as a whole than in similar apolar molecules (1–4).

Bond lengths and angles have values consistent with those usually observed in peptides (8); however, those in or near the disordered regions have large errors due to the difficulty in the least-squares refinement procedure arising from closely spaced atomic sites and high thermal factors.

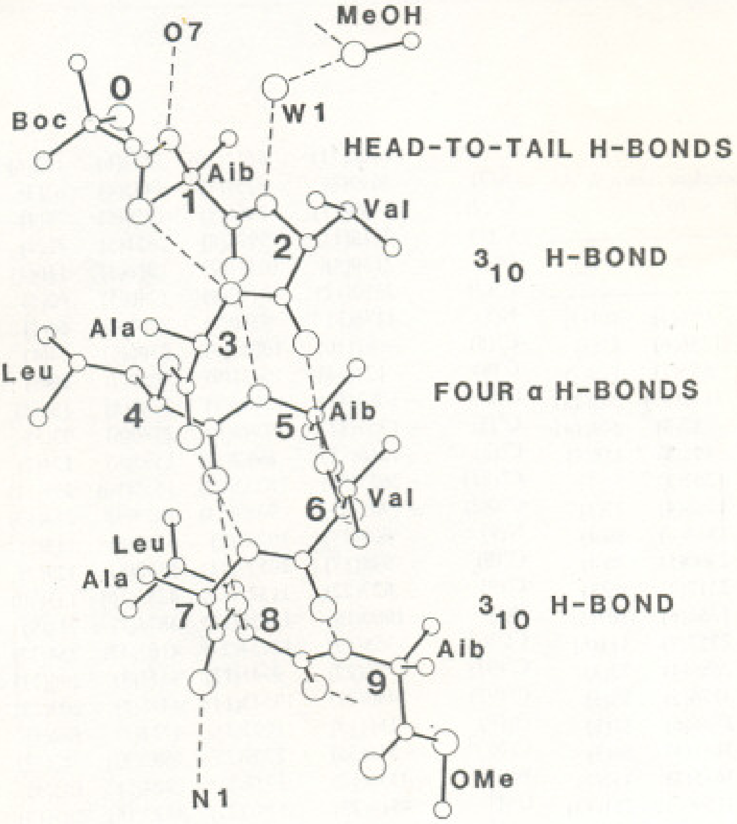

FIGURE 1

View along the helix of Boc-(Aib-Val-Ala-Leu)$_2$-Aib-OMe. Included are the $H_2O$ molecule in a fully occupied site and the $CH_3OH$ molecule in a partially occupied site (2/3) that bridge the head-to-tail hydrogen bonding. The $C^\alpha$ atoms are labeled 1–9. The number 0 is the position of an O atom in the Boc group at the amino terminus. Carbonyl oxygens O(5) and O(9) do not participate in hydrogen bonding. Only the major conformer is shown.

The backbone is a typical helix for an apolar peptide, containing four α-helix type hydrogen bonds in the center portion and flanked at either end with $3_{10}$-helix type hydrogen bonds. Conformational angles are listed in Table 2. Hydrogen bonds are shown in Figs. 1 and 3 and listed in Table 3. Water molecules have not been inserted into the backbone as occurred in Boc-(Aib-Ala-Leu)$_3$-Aib-OMe[4]. In that molecule, the large side-chains occurred on one side of the helix. On the other side, where side-chains consisted of only one methyl group, there was sufficient space for free access to the backbone by a water molecule. In the present molecule, Boc-(Aib-Val-Ala-Leu)$_2$-Aib-OMe, small and large side-chains alternate and the backbone is shielded more evenly by the hydrophobic groups. Even so, there appears to be some hydration. The coordinates of a possible $H_2O$ peak in the difference map have remained stable in least-squares refinement. That peak has been labeled as an O atom of a water molecule and the occupancy of that site has been determined by least-squares refinement to be ~0.25. This water molecule, W(3), resides in a void between parallel peptide molecules related by one unit cell translation in the *a* direction. Its only close approach to another atom is 3.094 Å to O(1). All other contacts to W(3) are greater than 3.7 Å. The probable hydrogen bond between W(3) and O(1) of the backbone is indicated in Fig. 3. Fig. 4 shows that O(1) is unshielded by neighboring hydrophobic side-chains and open to hydration.

### *Head-to-tail hydrogen bonding*

The apolar helical peptides studied thus far in this laboratory (1–4 and unpublished work), with 9–16 residues, form infinite helical columns by head-to-tail hydrogen bonding. Two molecules of such a column in the present structure are shown in Fig. 3. Back-

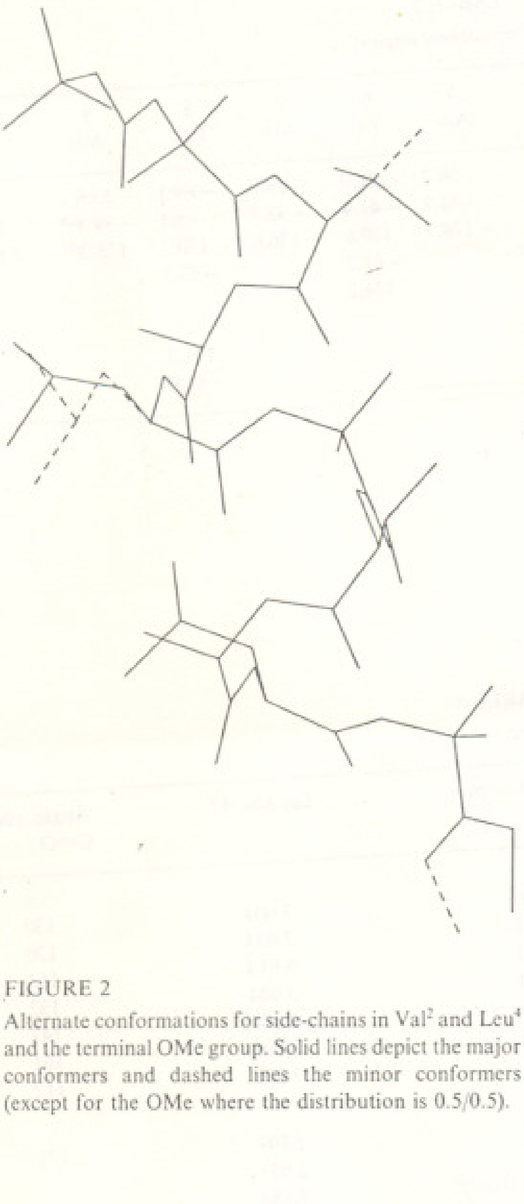

FIGURE 2

Alternate conformations for side-chains in Val$^2$ and Leu$^4$ and the terminal OMe group. Solid lines depict the major conformers and dashed lines the minor conformers (except for the OMe where the distribution is 0.5/0.5).

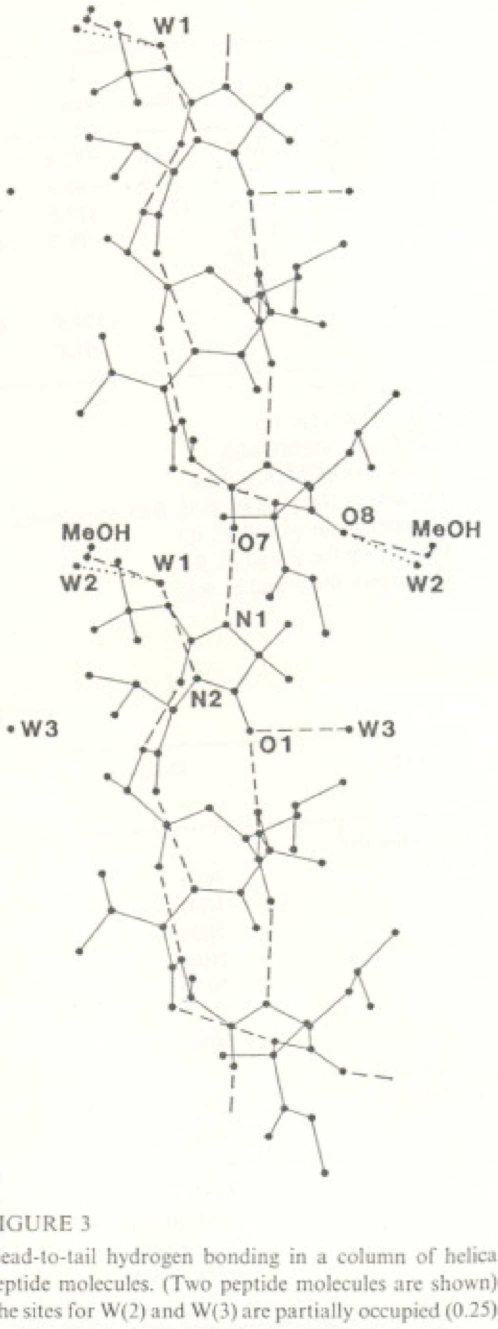

FIGURE 3

Head-to-tail hydrogen bonding in a column of helical peptide molecules. (Two peptide molecules are shown). The sites for W(2) and W(3) are partially occupied (0.25). Dashed and dotted lines indicate hydrogen bonds.

bone amides N(1)H and N(2)H are involved in direct hydrogen bonding with carbonyl O atoms of the molecule above or indirectly through water bridges or other cocrystallized solvent bridges, usually an alcohol molecule.

In the present case, there is one direct hydrogen bond, N(1)H · · · O(7). The N(2)H group makes a hydrogen bond to W(1), which in turn donates a proton to the O in $CH_3OH$ and the proton in $CH_3OH$ is donated to carbonyl O(8) in the molecule above but displaced by one cell length to the left as viewed in Fig. 3. The $CH_3OH$ molecule occupies only ~ 0.67 of its sites in the lattice. In the remainder of the cells, W(2) with

TABLE 2

*Conformational angles*[a]

| | 1<br>Aib | 2<br>Val | 3<br>Ala | 4<br>Leu | 4′ | 5<br>Aib | 6<br>Val | 7<br>Ala | 8<br>Leu | 9<br>Aib | 9′ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $\phi$ | −55.9[b] | −58.2 | −64.6 | −72.4 | | −50.2 | −71.9 | −58.9 | −89.1 | −53.6 | |
| $\psi$ | −34.4 | −37.3 | −36.9 | −40.5 | | −44.7 | −41.9 | −32.7 | −8.1 | −39.3[c,h] | 139.4[c,h] |
| $\omega$ | −177.7 | 179.9 | 177.6 | 177.5 | | −178.7 | 179.6 | −176.6 | −170.7 | 178.3[d,h] | −174.3[d,h] |
| $\chi^1$ | | −175.8[e]<br>−71.6[e]<br>+78.3[e] | | −79.7[f] | 179.3[g] | | −61.2<br>174.2 | | −63.3 | | |
| $\chi^2$ | | | | −179.5[f]<br>−67.8[f] | −167.1[g]<br>68.2[g] | | | | 174.3<br>−61.0 | | |

[a] E.s.d.'s ~ 1.2°.

[b] $C'(0)N(1)C^{\alpha}(1)C'(1)$.

[c] $N(9)C^{\alpha}(9)C'(9)O(OMe)$.

[d] $C^{\alpha}(9)C'(9)O(OMe)C(OMe)$.

[e] Occupancy for $\chi^1$, 0.80, 0.35, 0.85 respectively.

[f] Occupancy for $\chi^1$ and $\chi^2$, 0.7.

[g] Occupancy for $\chi^1$ and $\chi^2$, 0.3.

[h] Occupancy for $\phi$ and $\omega$, 0.5.

TABLE 3

*Hydrogen bonds*

| Type | Donor | Acceptor | Length, Å° | Angle, (deg) C=O · · · N |
|---|---|---|---|---|
| Intramolecular | | | | |
| 4 → 1 | N(3) | O(0) | 3.004 | 130 |
| | N(4)[a] | O(1) | 3.033 | 120 |
| 5 → 1 | N(5) | O(1) | 3.014 | 163 |
| | N(6) | O(2) | 3.084 | 152 |
| | N(7) | O(3) | 3.088 | 147 |
| | N(8) | O(4) | 3.000 | 161 |
| 4 → 1 | N(9) | O(6) | 3.211 | 112 |
| Intermolecular | | | | |
| Head-to-tail | N(1) | O(7)[b] | 2.899 | 171 |
| | N(2) | W(1) | 2.953 | |
| | W(1) | O(M)[c](0.67)[d] | 2.788 | |
| | W(1) | W(2) (0.25)[d] | 2.768 | |
| | O(M)[c](0.67)[d] | O(8)[e] | 2.792 | |
| | W(2) (0.25)[d] | O(8)[e] | 2.726 | |
| Lateral | W(3) (0.25)[d] | O(1) | 3.094 | |

O(5) and O(9) do not participate in hydrogen bonding.

[a] O(1) is nearly the same distance from N(4) and N(5); however the H atom on N(4) is not ideally placed for a hydrogen bond.

[b] x, −1 + y, z (transformation of coordinates in Table 1 in order to obtain coordinates of acceptor atom).

[c] O(M) is the oxygen atom in $CH_3OH$ (solvent molecule).

[d] Occupancy in partially occupied sites.

[e] 1 + x, −1 + y, z (transformation of coordinates in Table 1 in order to obtain coordinates of acceptor atom).

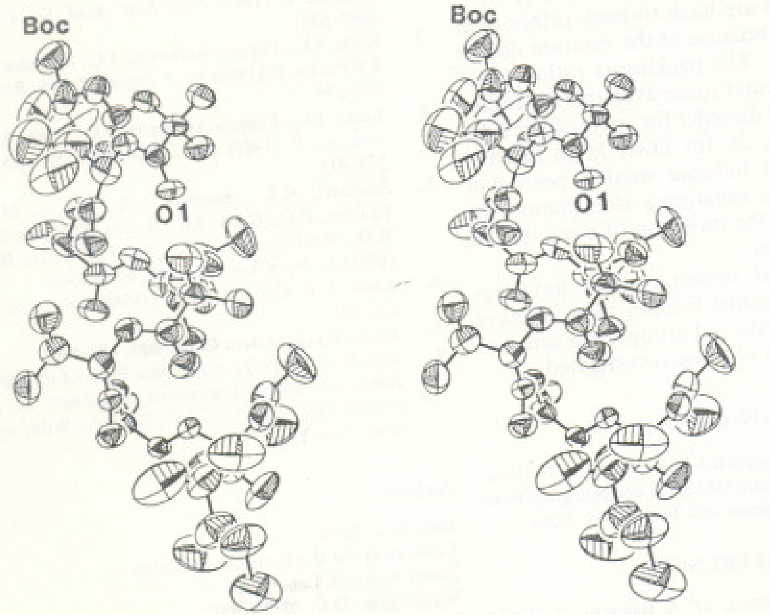

FIGURE 4

Stereo view of the peptide molecule with thermal ellipsoids at the 50% probability level. Note the exposure of O(1) to the outside environment and the possibility for a water molecule (W(3) in Fig. 3) to hydrate the backbone at this point.

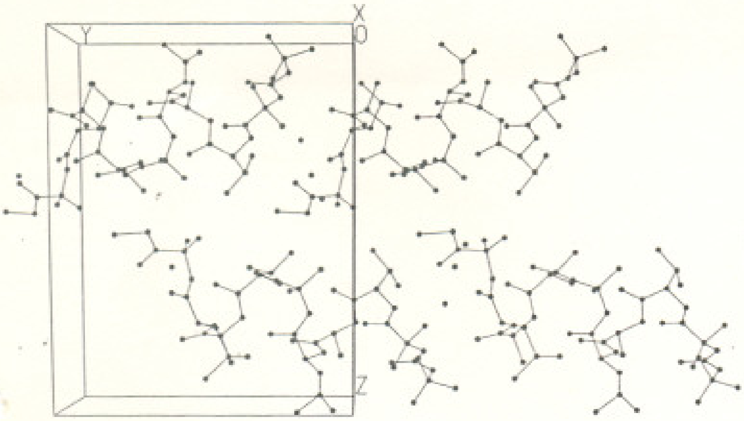

FIGURE 5

Packing of Boc-(Aib-Val-Ala-Leu)$_2$-Aib-OMe in P2$_1$ cell. Four peptide molecules are shown. The helices aggregate in a parallel mode, rather than antiparallel.

~ 0.25 occupancy in a site different than that occupied by $CH_3OH$, makes hydrogen bond bridges between W(1) and O(8). The coexistence of $CH_3OH$ and W(2) in a particular cell is probably possible, since the O(M) · · · W(2) distance is 2.87 Å. The partial occupancy of the solvent molecules is not due to the crystal drying in the atmosphere since a crystal surrounded by mother liquor in a capillary was used for data collection.

*Parallel aggregation of peptide molecules*

The present molecule provides another example of parallel packing of α-helices (1–3), even in space group P2$_1$. The helix axis is approximately parallel to the *b* axis of the cell (*b* axis unique). The length of the *a* axis, 9.837 Å, is large enough for only one helical molecule. Therefore, in the *a* direction the helices must pack in a parallel fashion simply by translation.

In the *c* direction, 20.087 Å, there is space for two helical molecules. The 2-fold screw axis of space group P2$_1$ passes between the helices. The resulting packing is shown in Fig. 5. The axes of neighboring helices are nearly parallel but the peptide molecules are shifted by 1/2 cell length in the *b* direction. The major difference between the packing here and in previously observed parallel motifs (1–3) is that the helices are back-to-back rather than back-to-front, because of the rotation due to the screw axes. The packing is rather loose with intermolecular space available for rather large positional disorder for some of the side-chains (see Fig. 2), for fairly large thermal parameters that indicate smaller positional disorder for the remaining side-chains (see Fig. 4), and for the inclusion of a number of solvent molecules.

All the helical molecules that have aggregated in a parallel fashion thus far have had Boc- and -OMe end groups. The effect of other end groups is being investigated.

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