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Extent of Helical Induction Caused by Introducing α-Aminoisobutyric Acid into an Oligovaline Sequence

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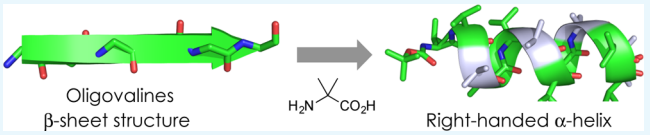
Supporting Information

ABSTRACT: The preferred conformations of a dodecapeptide composed of L-valine (L-Val) and α-aminoisobutyric acid (Aib) residues, Boc-(L-Val-L-Val-Aib)$_4$-OMe (**3**), were analyzed in solution and in the crystalline state. Peptide **3** predominantly folded into a mixture of α- and 3$_{10}$-(*P*) helical structures in solution and a (*P*) α helix in the crystalline state.



1. INTRODUCTION

In proteins, helices are abundant and important secondary structures, which recognize macromolecules, such as other proteins and DNA. Helical peptides that mimic proteins are capable of inhibiting protein−protein interactions, and a variety of helix-stabilizing methods have been developed to aid the production of such peptides. As representative techniques, the introduction of α,α-disubstituted α-amino acids (dAA)[1] or cyclic β-amino acids[2] into short oligopeptides and side-chain stapling[3] can all help to stabilize helical structures. In particular, α-aminoisobutyric acid (Aib) is the simplest dAA, and it is commonly used as a helical promoter.[4] We have previously reported that the introduction of Aib residues into natural amino acid sequences stabilized helical structures. For example, the oligopeptides Boc-(L-Leu-L-Leu-Aib)$_n$-OMe (n = 3 or 4) preferentially form stable right-handed (*P*) helical structures.[5,6] These peptides are able to act as organocatalysts for asymmetric reaction, such as enantioselective epoxidation catalysts of α,β-unsaturated ketones[6] and Michael addition of a malonate.[7] Furthermore, the amphipathic peptides R-(L-Xaa-L-Xaa-Aib)$_3$-NH$_2$ (R = FAM-β-Ala and Xaa = Arg or R = H and Xaa = Lys) were also folded into stable helical structures and were used as antimicrobial peptides[8] and cell-penetrating peptides,[9] respectively. In addition, we have recently reported that the azidolysine (Azl)-based peptide Boc-(L-Azl-L-Azl-Aib)$_3$-OMe formed a stable helical structure, and the azide groups could be replaced with several functional groups via click reactions without influencing the peptide's helical structure.[10] Thus, the insertion of Aib residues into α-amino acid-based oligopeptides is useful for stabilizing helical structures and providing a variety of functions. However, there have not been any reports about the secondary structural changes that occur when Aib residues are introduced into oligopeptides that form extended β-sheet structures. In general, oligopeptides composed of β-branched amino acids, such as valine (Val) and isoleucine (Ile), form β-sheet structures with extended conformations. In particular, oligovalines have a strong tendency to form β-sheet conformations.[11] In this study, we designed a dodecapeptide composed of L-Val and Aib residues, Boc-(L-Val-L-Val-Aib)$_4$-OMe (**3**), and analyzed its preferred conformations in solution and in the crystalline state.

2. RESULTS AND DISCUSSION

The dodecapeptide Boc-(L-Val-L-Val-Aib)$_4$-OMe (**3**) was synthesized using conventional solution-phase methods according to a fragment condensation strategy, in which 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) hydrochloride and 1-hydroxybenzotriazole (HOBt) hydrate were used as coupling reagents. Briefly, alkaline hydrolysis of the tripeptide Boc-L-Val-L-Val-Aib-OMe (**1**) afforded the acid **1-COOH**, whereas Boc deprotection by trifluoroacetic acid furnished the amine **1-NH$_2$**. The amine **1-NH$_2$** was coupled with **1-COOH** to give the hexapeptide Boc-(L-Val-L-Val-Aib)$_2$-OMe (**2**). The dodecapeptide **3** was prepared in a manner similar to that used to prepare the hexapeptide (Scheme 1).

The dominant conformations of the synthesized peptides **1**−**3** in solution were analyzed based on their Fourier transform infrared (FT-IR), ^{1}H nuclear magnetic resonance (NMR), and circular dichroism (CD) spectra. Figure 1 shows the IR spectra of the tri- (**1**), hexa- (**2**), and dodecapeptide (**3**) in the 3200−3500 cm^{-1} region (the amide A NH-stretching region) at a peptide concentration of 5.0 mM in $CDCl_3$ solution. In the spectra, the weak bands in the 3425−3438 cm^{-1} region were assigned to free (solvated) peptide NH groups, and the strong bands in the 3325−3340 cm^{-1} region were assigned to peptide NH groups with N−H···O═C intramolecular hydrogen bonds. These IR spectra are similar to those of helical peptides containing Aib residues.[12]

In the ^{1}H NMR spectra of the dodecapeptide **3**, the N-terminal urethane-type N(1)H proton signal was unambiguously determined by the high-field position but the remaining eleven peptide NH protons could not be assigned. Figure 2

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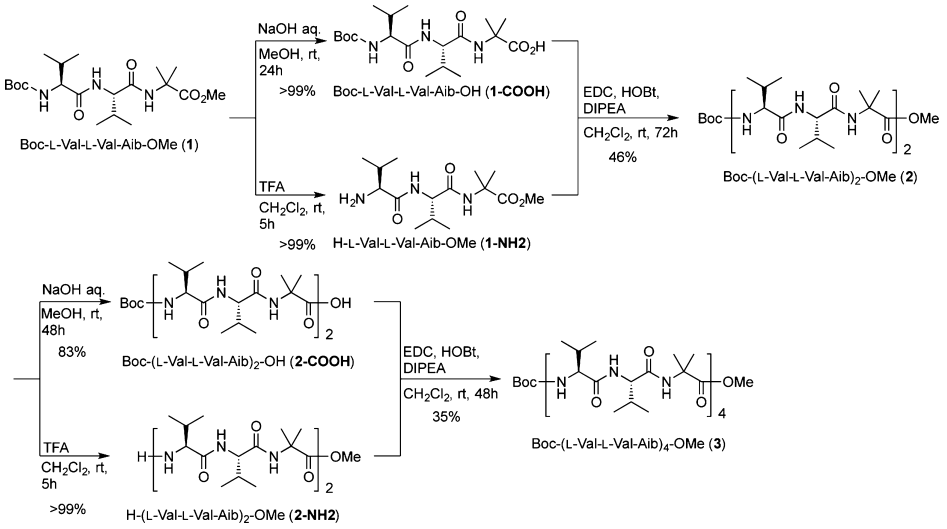
Scheme 1. Synthesis of Peptides 1−3



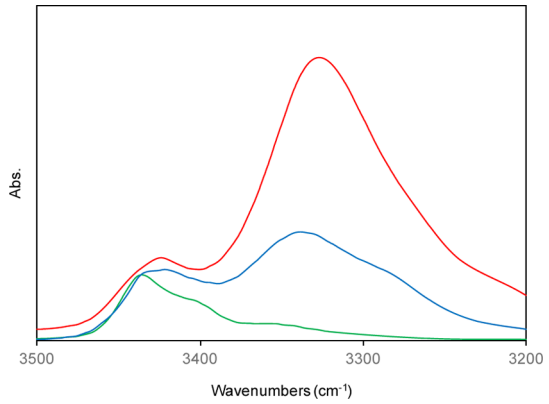


Figure 1. IR spectra of peptides **1** (green), **2** (blue), and **3** (red) in $CDCl_3$ solution (peptide concentration: 5.0 mM).

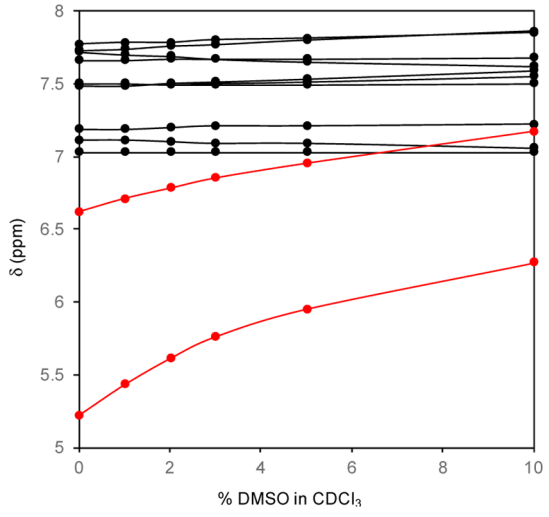


Figure 2. Plots of chemical shift values of the NH protons of peptide **3** as a function of the concentration of DMSO-d_6 (v/v) in $CDCl_3$ solution (peptide concentration: 5.0 mM).

shows a solvent perturbation experiment involving the addition of the strong H-bond acceptor solvent dimethyl sulfoxide (DMSO-d_6) [0−10% (v/v)]. Two NH chemical shifts in the high-field positions were sensitive to the addition of DMSO-d_6. These results are indicative of a 3_{10}- or α-helical structure in solution.[13]

The CD spectra of the dodecapeptide **3** in 2,2,2-trifluoroethanol (TFE) showed negative maxima at 207 and 222 nm indicating that **3** formed a right-handed (*P*) helical structure. Judging from the $R([\theta]_{222}/[\theta]_{208})$ value,[14] the secondary structure of **3** (R = 0.64) was a mixture of α- and 3_{10}-helical structures (Figure 3). This spectrum is similar to that of Boc-(L-Leu-L-Leu-Aib)$_4$-OMe (R = 0.51).[15]

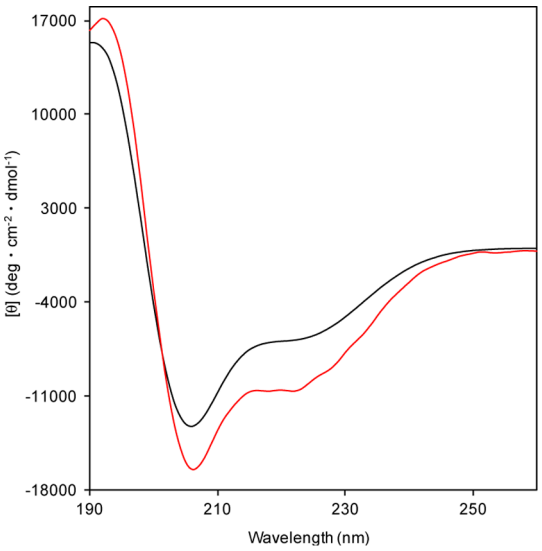


Figure 3. CD spectra of the dodecapeptide **3** (red) and Boc-(L-Leu-L-Leu-Aib)$_4$-OMe (black) in TFE solution (peptide concentration: 0.1 mM).

Peptide **3** formed good crystals for X-ray crystallographic analysis after the slow evaporation of methanol/water at room temperature. Its crystal and diffraction parameters, selected backbone and side-chain torsion angles, and intra- and intermolecular hydrogen-bond parameters are listed in the Supporting Information.[16−19] The asymmetric unit in **3** contained two (*P*) α-helical structures with a flipped C-terminal Aib(12) residue (Figure 4a). The conformations of

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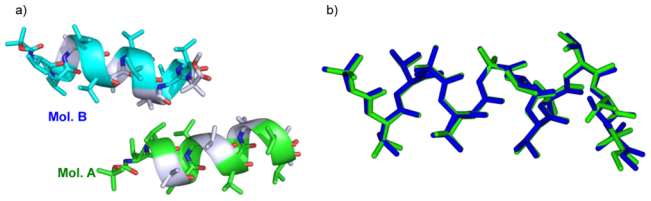

Figure 4. (a) X-ray diffraction structure of **3**. The methanol molecules have been omitted. (b) Superimposed structures of molecules **A** (green) and **B** (blue).

molecules **A** and **B** were well-matched, except for small differences in their side-chain conformations (Figure 4b). The mean ϕ and ψ torsion angles of the residues (2−11) were −63.1° and −39.9° for **A** and −62.6° and −40.7° for **B**, which are close to those of an ideal (*P*) α-helix (−60° and −45°, respectively). Regarding the intramolecular hydrogen bonds in molecules **A** and **B**, eight $i \leftarrow i + 4$ type hydrogen bonds were observed, respectively. In packing mode, molecules **A** and **B** were connected by intermolecular hydrogen bonds via methanol molecules, forming chains with head-to-tail alignments (···**A**···**A**···**A**··· and ···**B**···**B**···**B**···).

3. CONCLUSIONS

We designed and synthesized a dodecapeptide-containing L-Val and Aib residues, Boc-(L-Val-L-Val-Aib)$_4$-OMe (**3**), to investigate the influence of the helical promoter Aib on β-sheet structures. The conformation of **3** was analyzed based on its FT-IR, ^{1}H NMR, and CD spectra in solution and X-ray diffraction analysis in the crystalline state. Peptide **3** predominantly folded into a mixture of α- and 3_{10}-(*P*) helical structures in solution and a (*P*) α helix in the crystalline state. Although oligopeptides composed of β-branched amino acids form β-sheet structures with extended conformations, the insertion of Aib residues into β-sheet-forming peptide sequences could change the conformations of helical structures. Thus, we revealed that the insertion of Aib residues into oligopeptides not only stabilized their helical structures but also markedly altered their secondary structures (from βsheets to helical structures). Not only helical but also unique secondary structures will be created by the combination of natural L- and/or D-amino acids and Aib residues,[20] and these findings will be invaluable for the de novo design of peptide-based organic and bioorganic molecules.

4. EXPERIMENTAL SECTION

4.1. General. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz in $CDCl_3$ (tetramethylsilane as an internal standard). FT-IR spectra were recorded at 1 cm^{-1} resolution, with an average of 256 scans used for the $CDCl_3$ solution method (0.1 mm path length for NaCl cell). High-resolution mass spectra were recorded with LCMS-IT-TOF spectrometer. CD spectra were recorded using a 1.0 mm path length cell in TFE.

4.2. Synthesis of Tripeptide 1. The tripeptide **1** was prepared by conventional solution-phase peptide synthesis strategy. Colorless crystals; mp 177−179 °C; $[\alpha]_D^{24}$ = −95.7 (*c* 0.25, $CHCl_3$); IR ($CDCl_3$, cm^{-1}): 3437, 2969, 2934, 2875, 1738, 1705, 1671; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.66 (s, 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 4.99 (d, *J* = 7.2 Hz, 1H), 4.21−4.18 (m, 1H), 3.91 (dd, *J* = 6.8 Hz, 1H), 3.70 (s, 3H), 2.23−2.17 (m, 2H), 1.53 (s, 3H), 1.51 (s, 3H), 1.45 (s, 9H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 171.6, 167.0, 156.1, 80.4, 60.5, 58.3, 56.4, 52.5, 50.2, 30.3, 30.2, 28.3, 24.8, 24.7, 19.3, 19.2, 17.7, 17.5; [HR-ESI(+)-TOF] *m*/*z*: calcd for $C_{20}H_{37}N_3O_6Na$ $[M + Na]^+$, 438.2575; found, 438.2591.

4.3. Synthesis of Hexapeptide 2. A solution of the tripeptide Boc-L-Val-L-Val-Aib-OMe (**1**) (415 mg, 1.0 mmol) and 1 M aqueous NaOH (2.0 mL, 2.0 mmol) in MeOH (10 mL) was stirred at room temperature for 24 h. The solution was neutralized with 1 M aqueous HCl and was extracted with AcOEt. Being dried over Na_2SO_4 and removing the solvent afforded the tripeptide-carboxylic acid **1-COOH**, which was used for the next reaction without further purification. Trifluoroacetic acid (1 mL) was added to a solution of **1** (415 mg, 1.0 mmol) in CH_2Cl_2 (5 mL), and then the mixture was stirred at room temperature for 5 h. Removing the solvent afforded the crude N-terminal free tripeptide **1-NH$_2$**, which was used without further purification. A mixture of EDC (230 mg, 1.2 mmol), HOBt (162 mg, 1.2 mmol), *N*,*N*-diisopropylethylamine (418 μL, 2.4 mmol), the above **1-COOH** (1.0 mmol), and the above **1-NH$_2$** (1.0 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 3 days. The solution was washed with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, before being dried over Na_2SO_4. After removing the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 1:5) to give the hexapeptide **2** in 46% yield. Colorless crystals; mp 200−203 °C; $[\alpha]_D^{24}$ = −27.4 (*c* 0.5, $CHCl_3$); IR ($CDCl_3$, cm^{-1}): 3437, 3340, 2968, 2935, 2875, 1736, 1703, 1665; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.30 (d, *J* = 9.2 Hz, 1H), 7.17 (s, 1H), 6.93 (d, *J* = 6.8 Hz, 1H), 6.44 (d, *J* = 5.2 Hz, 1H), 5.01 (d, *J* = 2.6 Hz, 1H), 4.42 (dd, *J* = 8.8, 5.2 Hz, 1H), 4.18 (dd, *J* = 6.4, 4.4 Hz, 1H), 3.95 (dd, *J* = 4.4 Hz, 1H), 3.82 (dd, *J* = 4.4, 2.6 Hz, 1H), 3.68 (3H, s), 2.50−2.44 (m, 2H), 2.30−2.20 (m, 2H), 1.53 (3H, s), 1.52 (3H, s), 1.50 (9H, s), 1.50 (3H, s), 1.48 (3H, s), 1.06 (d, *J* = 6.8 Hz, 6H), 1.05−1.04 (m, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 175.2, 172.1, 171.9, 170.9, 170.5, 157.0, 81.8, 62.1, 60.8, 60.0, 58.6, 57.1, 55.8, 52.0, 29.4, 29.2, 28.9, 28.2, 27.5, 25.2, 24.7, 23.7, 19.6, 19.3, 19.2, 18.0, 17.5, 17.4, 17.2; [HR-ESI(+)-TOF] *m*/*z*: calcd for $C_{34}H_{62}N_6O_9Na$ $[M + Na]^+$, 721.4470; found, 721.4502.

4.4. Synthesis of Dodecapeptide 3. The dodecapeptide **3** was prepared using a method similar to that described for the preparation of **2**. Yield 35%; colorless crystals; mp 302−304 °C; $[\alpha]_D^{24}$ = −16.9 (*c* 0.5, $CHCl_3$); IR ($CDCl_3$, cm^{-1}): 3425, 3325, 2967, 2936, 2876, 1734, 1703, 1656; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 4.8 Hz, 1H), 7.77 (s, 1H), 7.73 (s, 1H), 7.67 (d, *J* = 4.8 Hz, 1H), 7.53−7.51 (m, 3H), 7.21 (d, *J* = 5.6 Hz, 1H), 7.10 (d, *J* = 6.0 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.72 (br s, 1H), 5.39 (br s, 1H), 4.41 (dd, *J* = 9.0, 5.8 Hz, 1H), 4.25 (dd, *J* = 7.2, 5.6 Hz, 1H), 3.89−3.84 (m, 3H), 3.82−3.79 (m, 1H), 3.71−3.62 (m, 2H), 3.67 (s, 3H), 2.47−2.36 (m, 2H), 2.29−2.15 (m, 6H), 1.52−1.48 (m, 33H), 1.12−0.97 (m, 48H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 175.9, 175.5, 173.8, 173.8, 173.0, 172.7, 172.6, 172.3, 171.5, 171.0, 157.2, 81.7, 62.9, 62.7, 62.5, 62.3, 60.9, 60.7, 59.2, 57.0, 56.8, 56.6, 55.8, 51.9, 29.8, 29.6, 29.5, 29.2, 29.2, 28.9, 28.3, 27.5, 27.4, 25.2, 24.6, 23.4, 23.3, 23.0, 19.9, 19.7, 19.5, 19.4, 19.4, 19.3, 19.2, 19.1, 19.1, 19.0, 18.9, 18.5, 18.0, 18.0, 17.8; [HR-ESI(+)-TOF] *m*/*z*:

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calcd for $C_{62}H_{112}N_{12}O_{15}Na$ $[M + Na]^+$, 1287.8262; found, 1287.8333.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01030.

Crystallographic data and copies of the ^1H NMR and ^{13}C NMR spectra of the peptides (PDF)

Crystallographic data of peptide **3** (CIF)

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Notes

The authors declare no competing financial interest.

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