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The Helix-Promoting Ability of Oligo-α-aminoisobutyric Acids at the Carboxyl Termini of Oligo-L-leucines

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ABSTRACT: Oligo(Leu)s containing an oligo(Aib) segment at their C terminus, Boc-Leu$_m$-Aib$_n$-OBzl (m = 4, n = 1, 1; m = 4, 7, and 10, n = 3, **2–4**; m = 4, 7, n = 5, **5** and **6**), were prepared to investigate the helix-promoting ability of the C-terminal oligo(Aib) segments for oligo(Leu)s. It has been shown that peptides **2–6** have excellent solubility in various organic solvents. From conformational studies by IR absorption spectroscopy, it has been suggested that peptides **2–6** have a helical structure in dichloromethane solution. It has also been indicated from the CD spectra in MeOH that peptides **3**, **4**, and **6** have a helical structure in the solvent. From conformational analyses of IR absorption spectra for their solid samples obtained by slow evaporation of the solvent from dichloromethane solution, it has been indicated that peptides **2–6** have little or no contribution of a β-sheet structure and a large contribution of intramolecularly hydrogen-bonded structures, probably with a large contribution of a helical structure, in the solid state. It is in contrast that peptide **1** and oligo(Leu)s (Boc-Leu$_n$-OBzl, n = 4–6 and 9; **7–10**) have a β-sheet structure in the solid state. These results indicate that the oligo(Aib) segments have a helix-promoting ability toward the N-terminal direction. From conformational studies by IR absorption spectra for the solid samples of peptides **2–6** obtained by slow evaporation of solvent from MeOH solution, it has been indicated that the helical structure of the peptides is relatively unstable in MeOH compared to that in dichloromethane and that only the peptides equal to or larger than dodecapeptide have a stable helical structure in concentrated MeOH solution. This result suggests that the oligo(Aib) segments promote helical folding through preventing the β-sheet construction of the neighboring oligo(Leu) segment.

Regardless[1] of the predicted secondary structure of oligopeptides to be a helical structure, oligopeptides usually have a β-sheet structure[2,3] because of a relatively large critical size of peptides for the development of a stable helical structure in the solid state. The critical size is assumed to be at an eicosapeptide level.[4,5] The β-sheet structure causes insolubility of peptides equal to or larger than an octa- or nonapeptide in most organic solvents and prevents further elongation of the peptide chain.[2,3,6–11] If the construction of the β-sheet structure is prevented by any method, peptide chain elongation would be carried out without an insolubility problem, and conformational transition from an unordered to a helical structure would be observed during peptide chain elongation.

It has been well-known that Aib residues promote helicity and solubility in peptides.[2,9–20] Replacement of some amino acid residues with Aib residues in a peptide sequence has been used to stabilize a helical structure of the peptide.[21] The ability of the Aib residue to promote helical folding in oligopeptides is due to the restriction[12] of the values of the backbone dihedral angles ϕ and ψ of the Aib residue to the narrow region of conformational map which includes helical structures. NMR studies of oligo(Leu)s containing an Aib residue have indicated that one Aib residue initiates helical folding in oligo(Leu)s toward the C-terminal direction from the Aib residue.[22] It was also indicated that the helical promoting ability of the Aib residue toward the N-terminal direction is rather weak. It is expected that an oligo(Aib) segment has a stronger helix-promoting ability than one Aib residue. It has been known that oligo(Aib)s have a stable 3_{10} helix due to the restriction of the values of the backbone dihedral angles ϕ and ψ of the Aib residue, although the stability of the helix depends on the peptide chain length.[18,19] To design and synthesize a peptide in a helical structure, it is desirable for the peptide sequence to have a helix-promoting segment at the C terminus because peptides are usually synthesized from the C terminal to the N-terminal direction. This paper investigates the helix-promoting ability of oligo(Aib) segments at the C terminus of oligo(Leu)s. Oligo(Leu)s containing an oligo(Aib) segment at their C terminus, Boc-Leu$_m$-Aib$_n$-OBzl (m = 4, n = 1, 1; m = 4, 7, and 10, n = 3, **2–4**; m = 4, 7, n = 5, **5** and **6**), are prepared, and their conformations are investigated.

Experimental Section

General procedures for peptide synthesis were described in a previous paper.[9] The coupling reaction of Boc-Leu-Aib$_{n-1}$-OH with H-Aib-OBzl was carried out by a method described in the literature.[20] The uncorrected capillary melting points are reported. The amino acid compositions of acid hydrolysates were determined with a Shimadzu HPLC LC-3A all amino acid analysis system. The acid hydrolyses of the peptides were carried out with propionic acid/12 M HCl (volume ratio, 2/1) for 2 days at 110 °C. The IR spectra of the peptides in the solid state were recorded

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Table I
Synthetic Results and Physical Properties of Peptides 2–6

compd	yield, %[a]	recrystallization solvent	mp, °C	$[\alpha]_D^{31}$ (c = 1.0, CH_2Cl_2)
2	97[b]		164–166	−12.0
3	42	CCl_4	251–252	−19.4
4	57	EtOH/water	>270	−18.0
5	41	AcOEt/hexane	200–202	−6.0
6	57	EtOH/water	204–205	−16.0

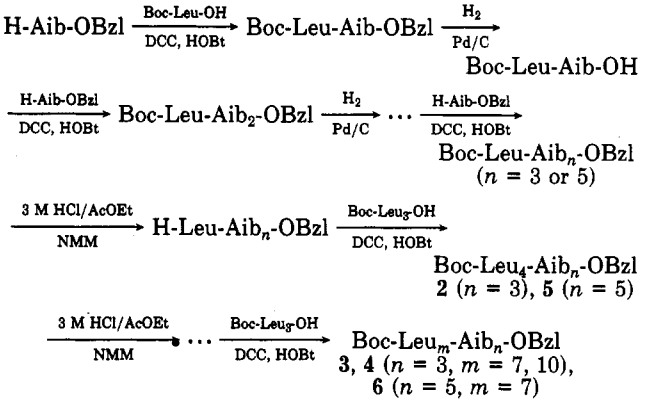
[a] Coupling yields in final steps. [b] Recrystallization was not carried out.

with a JEOL JIR-100 FT-IR spectrophotometer applying minimum shear stress in Nujor mull. The IR spectra of the peptides in dichloromethane were recorded at room temperature with the same instrument by employing 0.5-mm and 5-mm path length cells with potassium bromide windows. The CD spectra were obtained by using a JASCO J-40AS recording spectropolarimeter and using cylindrical fused quartz cells of 0.2-mm path length at 1 mg/mL concentration of the samples at room temperature. Band intensities are expressed as molar ellipticities $[\theta]$ (deg cm^2 dmol^{-1}). Other analytical instruments and conditions were described in a previous paper.[9]

Results and Discussion

Synthesis of Peptides 1–6. Starting from H-Aib-OBzl as the amino component, peptide 1 was prepared by the usual stepwise elongation of the peptide chain using Boc-Leu-OH as the acid component.[9] The coupling reactions were mediated by DCC, and liberation of the amino group from Boc-Leu$_n$-Aib-OBzl was performed by treatment with 3 M HCl/AcOEt, followed by treatment with NMM. The peptides 2–6 were prepared as shown in Scheme I. For the preparation of Boc-Leu-Aib$_n$-OBzl, the stepwise elongation from the C-terminal Aib residue was not employed since deprotection of the Boc group from Boc-Aib$_n$-OBzl with 3 M HCl/AcOEt and TFA/dichloromethane (1/3, v/v) resulted in poor yields. Boc-Leu-Aib$_n$-OBzl (n = 2–5) was prepared by the coupling reaction of Boc-Leu-Aib$_{n-1}$-OH with H-Aib-OBzl in DMF using DCC and HOBt as coupling reagents. The concentration of reactants in DMF affected the coupling yield, and the reaction in high concentration gave a high yield (55–77%)

Scheme I



as described for the coupling reaction of Boc-Leu-Aib-OH with H-Aib-OMe.[20] Removal of the Bzl group from Boc-Leu-Aib$_n$-OBzl (n = 1–4) was performed by hydrogenolysis using Pd/C as a catalyst. Peptides 2–6 were obtained by the coupling reaction of Boc-Leu$_3$-OH with H-Leu$_m$-Aib$_n$-OBzl in dichloromethane using DCC and HOBt as coupling reagents. All the coupling reactions were monitored by HPLC on a gel filtration column.[9] The coupling yields of peptides 2–6 in the final coupling reactions are listed in Table I together with recrystallization solvents and physical properties of the peptides. Relatively low yields of these peptides are attributable to the purification step because their excellent solubility in most of organic solvents made their recrystallization rather difficult. The data of elemental and amino acid analyses of the peptides shown in Table II are in good agreement with the calculated values.

Solubility Properties of Peptides 1–6. The solubility properties of peptides 1–6 were listed in Table III together with those of oligoleucines, Boc-Leu$_n$-OBzl (n = 4–6 and 9, 7–10), which were examined before.[6] Peptide 1 is soluble in high-polar solvents, but in low-polar or nonpolar solvents such as ethyl acetate or benzene, it is soluble only at high temperatures. These solubility properties are comparable to those of peptide 8. On the other hand, peptides 2 and 3 have excellent solubility in most organic solvents. It is

Table II
Elemental and Amino Acid Analyses of Peptides 2–6

compd	formula	found (calcd) C, %	H, %	N, %	found (calcd) Leu/Aib ratio
2	$C_{48}H_{81}N_7O_{10}\cdot 0.5H_2O$	62.39 (62.31)	9.05 (8.95)	10.85 (10.60)	4.00/2.80 (4/3)
3	$C_{66}H_{114}N_{10}O_{13}\cdot 0.5H_2O$	62.72 (62.68)	9.30 (9.16)	11.12 (11.08)	7.00/2.91 (7/3)
4	$C_{84}H_{147}N_{13}O_{16}\cdot 2H_2O$	61.92 (61.85)	9.39 (9.33)	10.82 (11.16)	10.0/2.69 (10/3)
5	$C_{56}H_{95}N_9O_{12}\cdot 0.5H_2O$	61.51 (61.40)	9.09 (8.83)	11.66 (11.51)	4.00/4.66 (4/5)
6	$C_{74}H_{128}N_{12}O_{15}\cdot 3H_2O$	60.19 (60.06)	9.14 (9.13)	11.40 (11.36)	7.00/4.58 (7/5)

Table III
Solubility Properties[a] of the Peptides (c = 1.0 g/dL)

compd[b]	solvent[a] DMF	MeOH	EtOH	CH_2Cl_2	AcOEt	$CHCl_3$	benzene	CCl_4
1 (5)	A	A	A	A	B	A	B	B
2 (7)	A	A	A	A	A	A	A	A
3 (10)	A	A	A	A	A	A	A	B
4 (13)	A	B	B	A	A	A	A	A
5 (9)	A	A	A	A	A	A	A	A
6 (12)	A	A	A	A	A	A	A	A
7 (4)	A	A	A	A	A	A	A	A
8 (5)	A	A	B	A	B	A	B	C
9 (6)	B	B	B	D	D	C	D	D
10 (9)	D	D	D	D	D	D	D	D

[a] Solubility: A, soluble at room temperature; B, soluble at 80 °C or refluxing temperature; C, partially soluble at 80 °C or refluxing temperature; D, practically insoluble at 80 °C or refluxing temperature. [b] Number of amino acid residues of the peptide in parentheses.

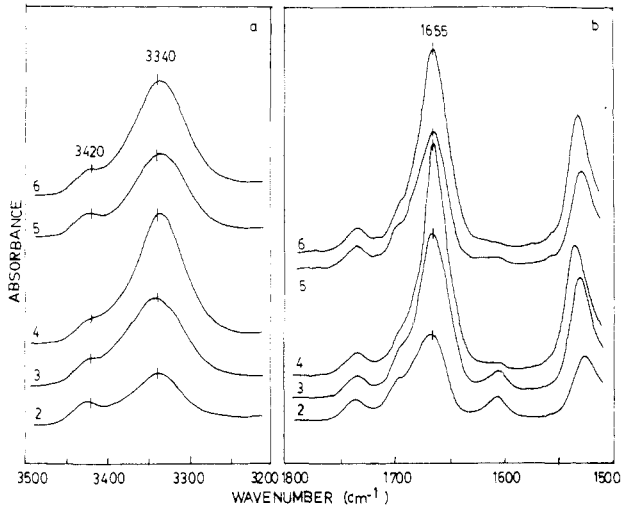


Figure 1. IR absorption spectra in amide A (a) and amide I and amide II (b) regions of peptides **2–6** in dichloromethane at 1 mM concentration. The absorption band at 1604 cm^{-1} is due to the solvent.

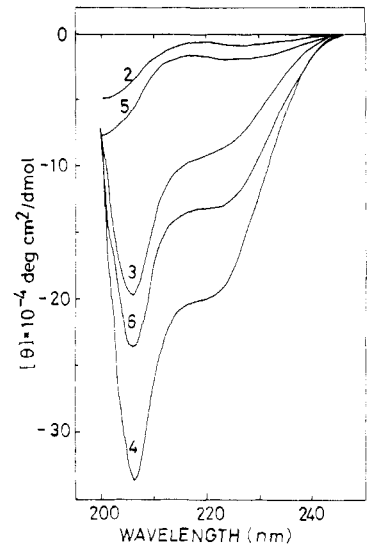


Figure 2. CD spectra of peptides **2–6** in MeOH.

remarkable when their solubility properties are compared to those of peptides **9** and **10** which are scarcely soluble or completely insoluble in most organic solvents, although peptides **9** and **10** have a similar chain length to that of peptides **2** and **3**, respectively. Furthermore, peptide **4** has far better solubility than peptide **10**, although both peptides have an oligo(Leu) segment with a similar chain length. Peptides **5** and **6** also have excellent solubility. We have already reported that a peptide equal to or larger than octa- or nonapeptide in a β-sheet structure is insoluble in most organic solvents, but a peptide in an unordered or a helical structure is soluble in various organic solvents regardless of its chain length.[9,10,23] The excellent solubility of peptides **2–6** suggests that peptides **2–6** do not have a β-sheet structure as their preferable conformation.

Conformation of Peptides 2–6 in Solution. Conformational analyses of peptides **2–6** were carried out by IR absorption spectra in dichloromethane over a wide range of concentrations (0.1–10 mM). The IR absorption spectra at 1 mM concentration are shown in Figure 1 in the most significant spectral regions for conformational assignments (3500–3200 cm^{-1}, amide A; 1800–1600 cm^{-1}, amide I;[24,25] and 1600–1500 cm^{-1}, amide II). These spectra have a similar pattern of the absorption bands. The bands around 1736, 1699, and 1665 cm^{-1} in the amide I region are attributed to the CO groups of the Bzl ester, Boc urethane, and amide in a helical or an unordered structure, respectively. Two broad bands in the amide A region around 3420 and 3340 cm^{-1} are attributed to free and hydrogen-bonded NH, respectively.[9,10,26,27] The intensities of the bands around 3420 and 3340 cm^{-1} of peptides **2–6** showed little dependence on the concentration, indicating that the band around 3340 cm^{-1} is due to the intramolecularly hydrogen-bonded NH.[26,27] In contrast to the fact that the band around 3420 cm^{-1} shows comparable intensity for every peptide, the intensity of the band around 3340 cm^{-1} increases with increasing the peptide chain length. This fact indicates that these peptides have an equal number of free NH and an increasing number of intramolecularly hydrogen-bonded NH with increasing the peptide chain length, suggesting that these peptides are a series of successively intramolecularly hydrogen-bonded species, probably in a helical structure. It has already been shown that peptides **1**, **7**, and **8** also have a helix-like structure in the solvent.[9,10,26] This fact indicates that oligopeptides, equal to or larger than tetrapeptide, consisting of amino acids which prefer to assume a helical structure, really have a considerable contribution of helical structure in dichloromethane. It is obvious that the Aib_3 and Aib_5 segments at the C terminus of the oligo(Leu)s at least prevented the β-sheet construction of the oligo(Leu)s to allow the peptides to assume a helical structure. It is also probable that the N-terminal NH protons of the helical oligo(Aib) segment would initiate helical folding by hydrogen bonding with CO of the neighboring Leu residues in a helix-promoting solvent.

To indicate the solvent effect on peptide conformation, CD spectra of peptides **2–6** in MeOH were obtained. As shown in Figure 2, peptides **3**, **4**, and **6** exhibit a CD pattern of a helical structure with two negative bands at 206(π–π^*) and 220–225(n–π^*) nm. It has been reported that the ratio of the ellipticities $[\theta]_{n-\pi^*}/[\theta]_{\pi-\pi^*}$ is 0.9–1.0 for helical polypeptides, whereas it is about 0.7 for Aib-containing oligopeptides in a helical structure in MeOH.[28] The ratio of the ellipticities of the bands $[\theta]_{n-\pi^*}/[\theta]_{\pi-\pi^*}$ for peptides **3**, **4**, and **6**, are 0.46, 0.60, and 0.56, respectively. These peptides have a large contribution of helical structure in MeOH.[29] Peptides **2** and **5** exhibit a CD pattern of an unordered structure, although the small negative band at 227 nm suggests some contribution of an ordered structure to these peptides. This fact indicates that a polar solvent such as MeOH prevents the construction of a stable helical structure of oligopeptides equal to or smaller than nonapeptide.

Conformation of Peptides 1–6 in the Solid State. It has been reported that peptide conformation in the solid state is largely affected by the method to obtain the sample.[5,11] It has also been reported that a peptide in a helical structure in solution assumes a helical or a β-sheet structure in the solid sample obtained by slow evaporation of the solvent, according to the stability of the helical structure.[5] Therefore, to investigate the stability of the helical structure in dichloromethane, the conformational analysis of peptides **1–6** in the solid state by IR absorption spectroscopy was carried out for the samples obtained by slow evaporation of the solvent from dichloromethane solution. To detect the conformation of the peptides with a minimum influence of shear stress, the solid samples were weakly pulverized with Nujol by hand using an agate mortar for IR measurements.

As shown in Figure 3, the IR absorption spectra of peptides **1** and **7** show a strong band centered at about 1640 cm^{-1} in the amide I region and a broad band around

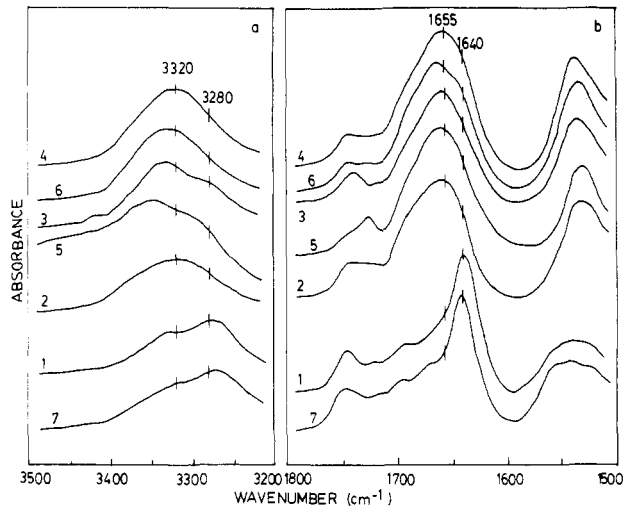


Figure 3. IR absorption spectra in amide A (a) and amide I and amide II (b) regions of peptides 1–7 for the solid samples obtained by slow evaporation of the solvent from dichloromethane solution.

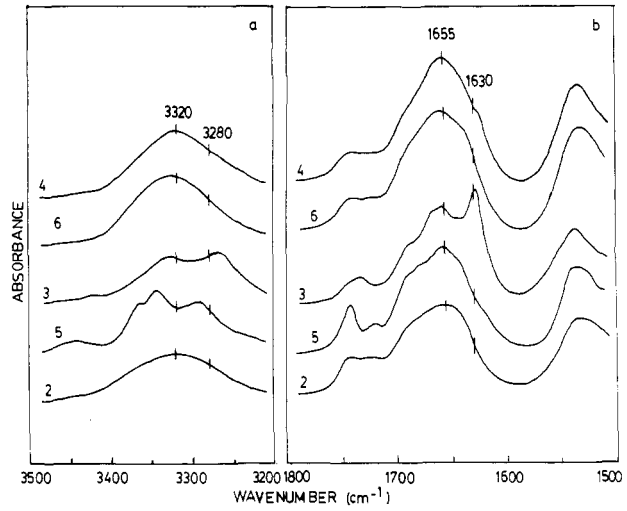


Figure 4. IR absorption spectra in amide A (a) and amide I and amide II (b) regions of peptides 2–6 for the solid samples obtained by slow evaporation of the solvent from MeOH solution.

3270 cm^{-1} in the amide A region, indicating that these peptides have a large contribution of β-sheet structure.[2-7,9-11,24-27,30] It has already been shown by IR absorption spectroscopy that peptides **1**, **7**, and **8** have an intramolecularly hydrogen-bonded structure, probably a helical one, in dichloromethane at 0.1–10 mM concentration.[9,10,26] It has also been shown by NMR study that in $CDCl_3$ the amide NH protons of peptide **7** are not intramolecularly but intermolecularly hydrogen bonded at 10–100 mM concentration.[22] The above result in this study indicates that peptides **1** and **7** transform into a β-sheet structure in concentrated dichloromethane solution. It is well-known that peptides **8–10** have a β-sheet structure in solid states.[6] These results indicate that, in dilute dichloromethane solution, the intramolecularly hydrogen-bonded structure of peptides **1**, **7**, and **8** is unstable and only in equilibrium with an unordered structure, and transforms into a β-sheet structure in concentrated dichloromethane solution. The same conformational behavior of peptide **1** as peptides **7** and **8** indicates that an Aib residue at the C terminus of the Leu_4 segment has no ability to stabilize a helical structure. The comparable solubility of peptide **1** with that of peptide **8** reflects well the preferable secondary structure of these peptides.

On the other hand, the IR spectra of peptides **2–6** show a broad band around 3320–3350 cm^{-1} in the amide A region attributable to a intramolecularly hydrogen-bonded amide NH. Furthermore, the spectra of peptides **2**, **4**, and **6** have no maximum around 3280 cm^{-1} attributable to a β-sheet structure. The spectra of peptides **2–6** also show a similar band around 1657–1662 cm^{-1} in amide I region attributable to amide CO in a helical or an unordered structure, although the band of peptide **2** is relatively broad. These results indicate that, in the solid state, peptides **2–6** have little or no contribution of β-sheet structure and a large contribution of intramolecularly hydrogen-bonded structures, probably with a large contribution of helical structure. It is suggested that the helical structure of peptides **2–6**, especially of peptides **4** and **6**, is stable in dichloromethane and maintained in the concentrated solution. This clearly contrasts the fact that peptide **1** and oligo(Leu)s **7–10** have a β-sheet structure in the solid state[6] and indicates that the Aib_3 and Aib_5 segments at the C-terminal site of oligo(Leu)s stabilize a helical structure. It is clear that the excellent solubility of peptides **2–6** is attributable to the conformational preference to a helical structure of these peptides.

The IR absorption spectra of peptides **2–6** in the solid state were also measured for the samples obtained from slow evaporation of the solvent from MeOH solution to investigate solvent effect on the conformation. As shown in Figure 4, except for peptide **3**, these spectra in the amide A, amide I, and amide II regions show a similar pattern of bands as the spectra for the samples obtained from dichloromethane solution, indicating that peptides **2** and **4–6** obtained from MeOH solution also have a similar conformation as the samples from dichloromethane solution. However, the bands around 1660 cm^{-1} in the amide I region were more broad and complicated with small shoulders, especially for peptides **2** and **5**, showing that several conformational species exist. The spectra of peptide **3** have a distinct band at 1628 cm^{-1} besides a broad band at 1656 cm^{-1} in the amide I region, and a band around 3269 cm^{-1} is larger than that around 3329 cm^{-1} in the amide A region, indicating that peptide **3** has a large contribution of β-sheet structure besides intramolecularly hydrogen-bonded structures. These results indicate that, in MeOH solution, the helical structure of peptides **3**, **4**, and **6**, especially of peptide **3**, is relatively unstable compared to that in dichloromethane solution. The CD spectra of these peptides in MeOH solution (Figure 2) actually show the expected conformation. The peptide segments temporarily in an unordered structure probably at the oligo(Leu) segments in dilute MeOH solution would transform into a β sheet or some intramolecularly hydrogen-bonded structures in concentrated solution. It was suggested that, in a polar solvent such as MeOH, the helical structure of these peptides would only be stable for the peptides equal to or larger than dodecapeptide. Initiation of helical folding by hydrogen bonding of the N-terminal NH protons of the Aib_3 or Aib_5 segment with CO of the neighboring Leu residues would not be predominant in MeOH solution.

It is concluded that the C-terminal oligo(Aib)s combined to oligo(Leu)s have a helix-promoting ability toward the N-terminal direction. They probably promote helical folding through preventing the β-sheet construction of the neighboring oligo(Leu) segment. Initiation of helical folding by hydrogen bonding of their N-terminal NH protons with CO of the neighboring Leu residues would not be predominant for the C-terminal Aib_3–Aib_5 segments because the stability of a helical structure of the peptides examined here depends on the solvent polarity and their peptide chain length. However, it is inferred that the

peptides containing an oligo(Aib) segment at their C terminus have a potential to assume a helical structure, when the N-terminal side segment of the Aib segment prefers a helical structure from its amino acid composition. Thus, a helical peptide would easily be designed and the synthesis of the peptide would be carried out without insolubility problem. For the functional investigation of a helical segment in proteins, it would be useful to keep the peptide fragment in a helical structure by introduction of an oligo(Aib) segment into the C-terminal site of the peptide.

Registry No. 1, 99593-00-7; 2, 117709-87-2; 3, 117709-88-3; 4, 117709-89-4; 5, 117709-90-7; 6, 117709-91-8; 7, 92782-17-7; 8, 92782-18-8; 9, 92782-19-9; 10, 92782-20-2; H-Aib-OBzl, 55456-40-1; BOC-Leu-OH, 13139-15-6; BOC-Leu_3-OH, 18868-20-7; BOC-Leu-Aib-OBzl, 79118-23-3; BOC-Leu-Aib_2-OBzl, 117709-92-9; BOC-Leu-Aib_3-OBzl, 117709-93-0; BOC-Leu-Aib_4-OBzl, 117709-94-1; BOC-Leu-Aib_5-OBzl, 117709-95-2; BOC-Leu-Aib-OH, 72485-34-8; BOC-Leu-Aib_2-OH, 117709-96-3; BOC-Leu-Aib_3-OH, 117709-97-4; BOC-Leu-Aib_4-OH, 117709-98-5; H-Leu-Aib_3-OBzl, 117709-99-6; H-Leu-Aib_5-OBzl, 117710-00-6; H-Leu_4-Aib_3-OBzl, 117710-01-7; H-Leu_4-Aib_5-OBzl, 117733-98-9; H-Leu_7-Aib_3-OBzl, 117710-02-8; H-Aib-OH, 62-57-7.

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