Research Article

Journal of PeptideScience

Received: 06 April 2010 Revised: 07 June 2010 Accepted: 10 June 2010 Published online in Wiley Online Library: 16 September 2010

(wileyonlinelibrary.com) DOI 10.1002/psc.1273

Conformations of peptides containing a chiral cyclic α,α-disubstituted α-amino acid within the sequence of Aib residues

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A single chiral cyclic α,α-disubstituted amino acid, (3*S*,4*S*)-1-amino-(3,4-dimethoxy)cyclopentanecarboxylic acid [(*S*,*S*)-Ac$_5$c^{dOM}], was placed at the *N*-terminal or *C*-terminal positions of achiral α-aminoisobutyric acid (Aib) peptide segments. The IR and ^{1}H NMR spectra indicated that the dominant conformations of two peptides Cbz-[(*S*,*S*)-Ac$_5$c^{dOM}]-(Aib)$_4$-OEt (1) and Cbz-(Aib)$_4$-[(*S*,*S*)-Ac$_5$c^{dOM}]-OMe (2) in solution were helical structures. X-ray crystallographic analysis of 1 and 2 revealed that a left-handed (*M*) 3$_{10}$-helical structure was present in 1 and that a right-handed (*P*) 3$_{10}$-helical structure was present in 2 in their crystalline states. Copyright © 2010 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: α-aminoisobutyric acid; chiral cyclic α,α-disubstituted amino acid; conformational analysis; 3$_{10}$-helix; X-ray diffraction

Introduction

The α-helix is one of the most common protein secondary structures. It usually has a right-handed (*P*) screw sense because of the asymmetric center of the α-carbon of L-α-amino acids [1]. Several studies have attempted to control the helical screw sense of peptides [2–10], and we have recently reported that a chiral cyclic α,α-disubstituted α-amino acid bearing only side-chain chiral centers, (3*S*,4*S*)-1-amino-(3,4-dimethoxy)cyclopentanecarboxylic acid [(*S*,*S*)-Ac$_5$c^{dOM}] [11] controls the left-handed (*M*) helical-screw sense of its homopeptides [12]. Incidentally, α-aminoisobutyric acid (Aib) is widely used as a strong helical inducer; however, it does not exhibit a helical-screw sense bias because Aib is an achiral amino acid [13–15]. Toniolo and Benedetti reported the positional effect of a C$^\alpha$-chiral amino acid residue {C$^\alpha$-trisubstituted (L-Val) or C$^\alpha$-tetrasubstituted [L-(αMe)Val: α-methyl-L-valine]} on the screw sense of a preceding and following achiral 3$_{10}$-helical sequence composed of Aib residues [3,4]. Furthermore, we have reported on the preferred conformations of pentapeptides consisting of one chiral α-ethylated α,α-disubstituted α-amino acid and four Aib residues [16]. Although the effects of single C$^\alpha$-chiral amino-acid residues on Aib sequences have been studied, the influence of the side-chain chiral centers of chiral amino acids has not been reported. Here, we studied whether the attachment of a chiral amino acid bearing only side-chain chiral centers was able to control the helical-screw sense of Aib-based peptides that do not exhibit a screw bias in solution and/or in the solid state. That is to say, we have designed and synthesized two pentapeptides, Cbz-[(*S*,*S*)-Ac$_5$c^{dOM}]-(Aib)$_4$-OEt (**1**) (Cbz: benzyloxycarbonyl; OEt: ethyl ester) and Cbz-(Aib)$_4$-[(*S*,*S*)-Ac$_5$c^{dOM}]-OMe (**2**) (OMe: methyl ester), and studied their preferred conformations in solution and in the crystalline state (Figure 1).

Materials and Methods

Synthesis and Characterization of Peptides

The synthesis of peptides **1** and **2** was carried out by the stepwise solution-phase method using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) hydrochloride and 1-hydroxybenzotriazole hydrate as coupling reagents. All compounds were purified by column chromatography on silica gel.

Cbz-[(S,S)-Ac$_5$c^{dOM}]-(Aib)$_4$-OEt (**1**). Colorless crystals; mp 181–183 °C; $[\alpha]_D^{24}$ = +53.16 (*c* = 1.0, $CHCl_3$); IR (in $CDCl_3$) 3423, 3350, 2986, 2938, 1734, 1668, 1534 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.47 (m, 7H), 7.17 (br s, 1H), 6.45 (br s, 1H), 5.91 (br s, 1H), 5.11 (dd, *J* = 12.2, 22.7 Hz, 2H), 4.09 (q, *J* = 7.0 Hz, 2H), 3.84 (m, 1H), 3.78 (m, 1H), 3.37 (s, 3H), 3.34 (s, 3H), 2.56 (dd, *J* = 5.0, 14.5 Hz, 1H), 2.26–2.35 (m, 2H), 1.89 (d, *J* = 15.6 Hz, 1H), 1.41–1.52 (m, 24H), 1.22 (t, *J* = 7.0 Hz, 3H): HR-ESI(+)-MS calcd for $C_{34}H_{53}O_{10}N_5Na$ (M^+ + Na), 714.3690: found 714.3812.

Cbz-(Aib)$_4$-[(S,S)-Ac$_5$c^{dOM}]-OMe (**2**). Colorless crystals; mp 155–157 °C; $[\alpha]_D^{22}$ = +23.7 (*c* = 1.40, $CHCl_3$); IR (in $CDCl_3$) 3425, 3351, 2991, 1742, 1707, 1692, 1639, 1548 cm^{-1}; ^{1}H NMR

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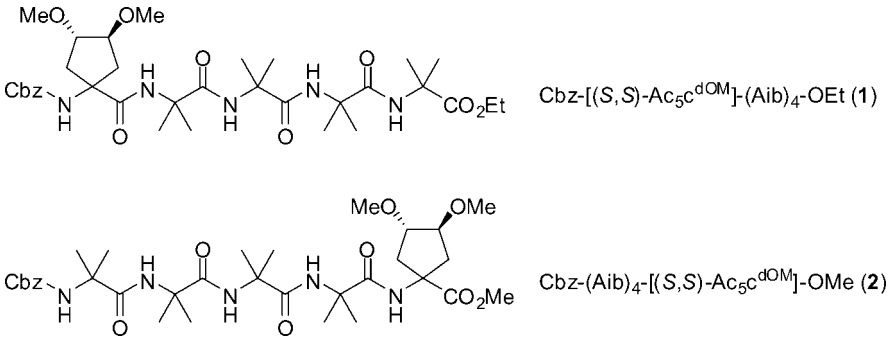

Figure 1. Structures of peptides **1** and **2**.

(400 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 7.34–7.39 (m, 6H), 7.21 (br s, 1H), 6.31 (br s, 1H), 5.22 (br s, 1H), 5.13 (dd, J = 12.1, 17.0 Hz, 2H), 3.94 (q, J = 7.3 Hz, 1H), 3.80 (q, J = 7.3 Hz, 1H), 3.68 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H), 2.93 (dd, J = 7.8, 14.0 Hz, 1H), 2.64 (dd, J = 7.2, 14.0 Hz, 1H), 2.09 (dd, J = 8.4, 14.0 Hz, 1H), 2.02 (dd, J = 8.1, 14.0 Hz, 1H), 1.30–1.49 (m, 24H): HR-ESI(+)-MS calcd. for $C_{33}H_{51}O_{10}N_5Na$ (M^+ + Na) 700.3533, found 700.3495; elemental analysis calcd for $C_{33}H_{51}O_{10}N_5$: C 58.48, H 7.58, N 10.33: found C 58.42, H 7.58, N 10.35.

FT-IR Spectra

FT-IR spectra were recorded on a *JASCO FT/IR-4100* spectrometer at 24 °C with a resolution of 1.0 cm^{-1}, an average of 32 scans used for the solution ($CDCl_3$) method and a 0.1 mm path length used for NaCl cells.

^{1}H NMR Spectra

^{1}H NMR spectra were recorded on a *Varian AS 400* spectrometer at 24 °C. Measurements were carried out in $CDCl_3$ with tetramethylsilane used as an internal standard. The TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl, radical) concentration ranged from 1.0 to 5.0 $\times$ 10^{-2}% (*w*/*v*).

CD Spectra

CD spectra were recorded with a *Jasco J-720 W* spectropolarimeter using a 1.0 mm path length cell. The data were expressed in terms of $[\theta]_M$, the total molar ellipticity (° cm^2 $dmol^{-1}$). 2,2,2-trifluoroethanol was used as a solvent.

X-ray Diffraction

Single crystals of **1** and **2** were grown from MeOH/H_2O for **1** and EtOH/H_2O for **2**. Data collection was performed on a Bruker AXS SMART 1000 CCD imaging plate diffractometer using graphite-monochromated Mo$K\alpha$ radiation. The crystal and collection parameters are listed in Table 1. All crystals remained stable during the X-ray-data collection. The structures of the crystals were solved using the SIR 92 [17] or the SHELXS 97 [18] direct method and expanded by the Fourier technique [19]. All non-H-atoms were given anisotropic thermal parameters, some H-atoms were refined isotropically, and the remaining H-atoms at the calculated positions were given isotropic thermal parameters. The final cycle of full-matrix least-squares refinement of **1** gave an R_1 factor of 0.0462 based on 1652 ($I > 2\sigma(I)$) reflections and an *Rw* factor of 0.0506 for all data. The R_1 factor of **2** was 0.0374 based on 4587 ($I > 2\sigma(I)$) reflections and an R_w factor of 0.0542 for all data. All data for peptides **1** and **2** have been deposited in the Cambridge Crystallographic Data Centre (CCDC) as a supplementary publication, and their CCDC reference numbers are CCDC-763135 and 763137, respectively [20].

Table 1. Crystal and diffraction parameters of pentapeptides **1** and **2**

	1	**2**
Empirical formula	$C_{34}H_{53}O_{10}N_5$	$C_{33}H_{51}O_{10}N_5$
M_r	691.82	677.79
Crystal dimensions (mm)	0.20 × 0.15 × 0.15	0.30 × 0.30 × 0.20
Crystal system	Monoclinic	Orthorhombic
	Lattice parameters	
a, *b*, *c* (Å)	10.425, 15.681, 11.718	11.614, 17.354, 17.932
α, β, γ (°)	90, 99.077, 90	90, 90, 90
V [Å^3]	1891.5	3614.3
Space group	$P2_1$	$P2_12_12_1$
Z value	2	4
D_{calc} (g/cm^3)	1.215	1.246
μ (Mo*K* α) (cm^{-1})	0.89	0.92
No. of observations	1652 ($I > 2\sigma(I)$)	4127 ($I > 2\sigma(I)$)
No. of variables	444	435
R_1, R_w	0.0462, 0.0506	0.0374, 0.0542
Solvent	MeOH/H_2O	EtOH/H_2O

Results and Discussion

FT-IR Spectra

At first, the preferred conformations of peptides **1** and **2** were studied in solution using the IR spectroscopic method. Figure 2 shows the IR spectra of **1** and **2** in the 3250–3500 cm^{-1} region at a peptide concentration of 1.0 mM in $CDCl_3$ solution. In the IR spectra, the weak bands in the 3420 cm^{-1} region were assigned to free (solvated) peptide NH groups, and the strong bands at around 3350 cm^{-1} were assigned to peptide NH groups with N–H···O=C intramolecular hydrogen bonds (Figure 2). The difference in the spectra obtained at peptide concentrations of 1.0 mM and 0.1 mM was not significant (results not shown). These IR spectra are very similar to those of helical peptides in solution [12,21], but

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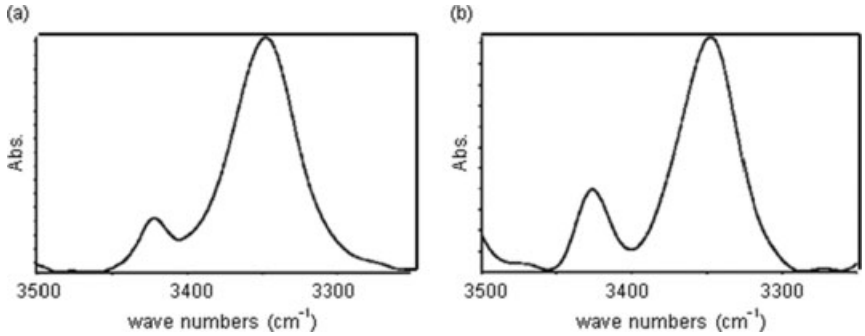

Figure 2. FT-IR spectra (3250–3500 cm^{-1} region) of peptides **1** (a) and **2** (b) in $CDCl_3$ solution. Peptide concentration: 1.0 mM.

different from those of peptides, which form the extended planar C_5 conformation [22].

^{1}H NMR Spectra

To obtain more detailed information on their preferred conformations, the ^{1}H NMR spectra of peptides **1** and **2** were measured in $CDCl_3$ solution. In the ^{1}H NMR spectra of **1** and **2**, N(1)H proton signals of the urethane type at the *N*-terminus were unambiguously determined by their high-field positions at δ 5.81 (br s, 1H) in **1** and δ 5.15 (br s, 1H) in **2**, but the remaining four peptide NH protons could not be assigned at this stage. Figure 3 shows solvent perturbation experiments involving the addition of the strong H-bond acceptor solvent DMSO [0–10% (*v*/*v*)] or the paramagnetic free radical TEMPO [0–5 $\times$ 10^{-2}% (*w*/*v*)]. Two NH chemical shifts in both **1** and **2** were sensitive to the addition of the perturbing reagent DMSO. Also, the addition of the TEMPO radical broadened the bandwidth of the two NH signals. These results demonstrate that the two NH protons are solvent-exposed, suggesting that they are not intramolecularly hydrogen bonded. These results are in accord with a 3_{10}-helical structure, in which two NH groups at the *N*-terminus of the peptide are freely solvated (not intramolecularly hydrogen bonded).

The NOESY ^{1}H NMR spectra of helical peptides show a series of strong sequential NH($i \rightarrow i+1$) dipolar interactions, which is often used to diagnose helical structures. Furthermore, in peptides and proteins based on coded α-amino acids, there are two NOE constraints, [d_{α_N} ($i \rightarrow i+2$)] and [d_{α_N} ($i \rightarrow i+4$)], which are believed to be characteristic of the 3_{10}- and the α-helical structure, respectively. Unfortunately, these latter interactions do not occur in peptides composed of α,α-disubstituted α-amino acids because their residues lack αCH protons. Figure 4 shows the 2D NOESY ^{1}H NMR spectra of **1**(Fig. 4a) and **2**(Fig. 4b) in $CDCl_3$ solution. The spectra of both **1**(Fig. 4a) and **2**(Fig. 4b) showed a complete series of sequential NH($i \rightarrow i+1$) dipolar interactions from the *N*-terminal N(1)H to the *C*-terminal N(5)H, which is characteristic of a helical secondary structure.

CD Spectra

The CD spectra of peptides **1** and **2** were measured in 2,2,2-trifluoroethanol solution to obtain information about their helical-screw senses. However, neither the spectra of **1** nor **2** showed maximum characteristic of a helical structure (208 and 222 nm) [23], suggesting the existence of roughly equivalent amounts of both right-handed (*P*) and left-handed (*M*) helices (data not shown).

Table 2. Selected torsion angles [ω, ϕ, ψ and x (°)] for pentapeptides **1** and **2** as determined by X-ray crystallographic analysis

Torsion angle	1	2
ω_0	179.7	−176.7
ϕ_1	57.8	−57.4
ψ_1	27.1	−32.4
ω_1	176.2	−178.2
ϕ_2	59.0	−53.1
ψ_2	32.4	−34.3
ω_2	175.1	−176.1
ϕ_3	56.6	−53.3
ψ_3	23.8	−38.6
ω_3	−177.3	−174.5
ϕ_4	52.1	−62.6
ψ_4	35.3	−20.8
ω_4	−170.4	−170.7
ϕ_5	−49.1	51.9
ψ_5	−50.4	35.6
ω_5	−175.9	−174.2
χ_1	84.6	–
χ_1'	−104.9	–
χ_5	–	92.2
χ_5'	–	−117.7

X-ray Diffraction

X-ray crystallographic analysis unambiguously revealed the molecular structural conformations of the peptides in the crystal state. The pentapeptides **1** and **2** were turned into suitable crystals for X-ray crystallographic analysis by slow evaporation of the solvent (MeOH/H_2O or EtOH/H_2O) at room temperature. The crystal and diffraction parameters of **1** and **2** are summarized in Table 1, and their molecular structures are given in Figures 5 and 6. Relevant backbone and side-chain torsion angles and the intra- and intermolecular hydrogen-bond parameters are listed in Tables 2 and 3, respectively.

In the asymmetric unit of pentapeptide **1**, only one conformer of the peptide molecule existed, and it is folded into a left-handed (*M*) 3_{10}-helix. The mean values of the ϕ and ψ torsion angles of the amino-acid residues (1–4) were +56.4° and +29.7°, respectively, which are close to those for an ideal left-handed (*M*) 3_{10}-helical structure (+60° and +30°) [24]. Reversal of the torsion angle signs at the *C*-terminus occurred; i.e. the signs of the ϕ and ψ torsion angles (−49.1° and −50.4°) of the Aib^5 residue were negative.

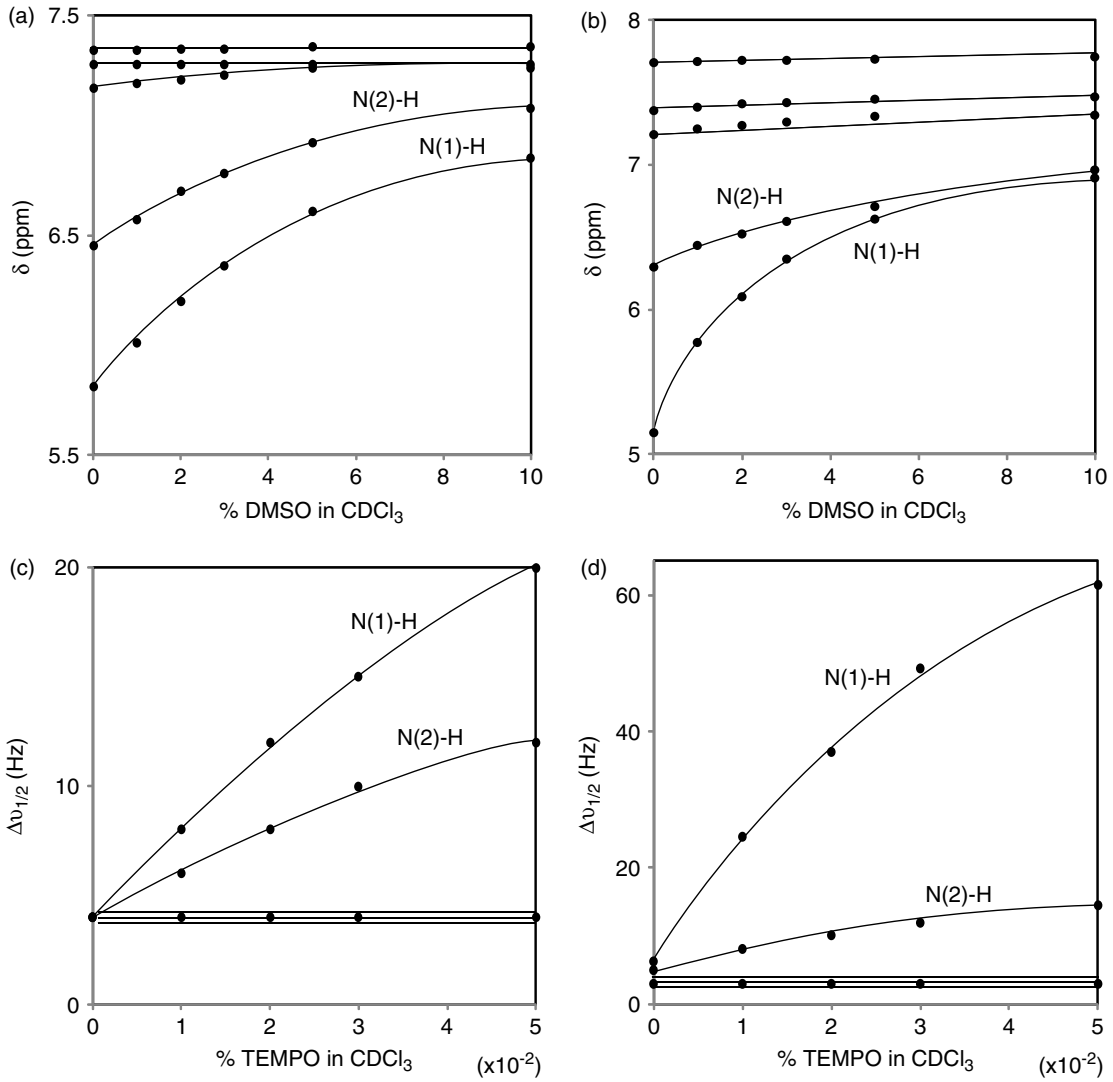

Figure 3. ^{1}H NMR experiments involving the addition of DMSO and the radical TEMPO to the $CDCl_3$ solutions of peptides **1** and **2**. Plots of NH chemical shifts in the ^{1}H NMR spectra of **1** (a) and **2** (b) as a function of increasing concentrations of DMSO (*v*/*v*) being added to the $CDCl_3$ solution. Plots of the bandwidths of the NH protons in the ^{1}H NMR spectra of **1** (c) and **2** (d) as a function of increasing concentrations of TEMPO (*w*/*v*) being added to the $CDCl_3$ solution. Peptide concentration: 1.0 mM.

Table 3. Intra- and intermolecular H-bond parameters for pentapeptides **1** and **2**

Peptide[a]	Donor D–H	Acceptor A	Distance (Å) D···A	Angle (°) D—H···A	Symmetry operations
Cbz-[(*S*,*S*)-Ac_5c^{dOM}]-$(Aib)_4$-OEt (**1**)	N_3-H	O_0	3.15	164.2	*x*, *y*, *z*
	N_4-H	O_1	3.00	161.8	*x*, *y*, *z*
	N_5-H	O_2	3.02	145.8	*x*, *y*, *z*
	N_1-H	O_4'	2.83	160.6	*x*, *y*, *z* + 1
	N_2-H	O_5'	3.15	115.7	*x*, *y*, *z* + 1
Cbz-$(Aib)_4$-[(*S*,*S*)-Ac_5c^{dOM}]-OMe (**2**)	N_3-H	O_0	3.01	152.0	*x*, *y*, *z*
	N_4-H	O_1	3.04	145.6	*x*, *y*, *z*
	N_5-H	O_2	3.00	161.5	*x*, *y*, *z*
	N_1-H	O_4'	2.86	164.1	*x* − 1, *y*, *z*
	N_2-H[b]	–	–	–	–

[a] The amino-acid numbering begins at the *N*-terminus of the peptide chain.
[b] No intermolecular hydrogen bond was observed at N_2-H in the packing mode.

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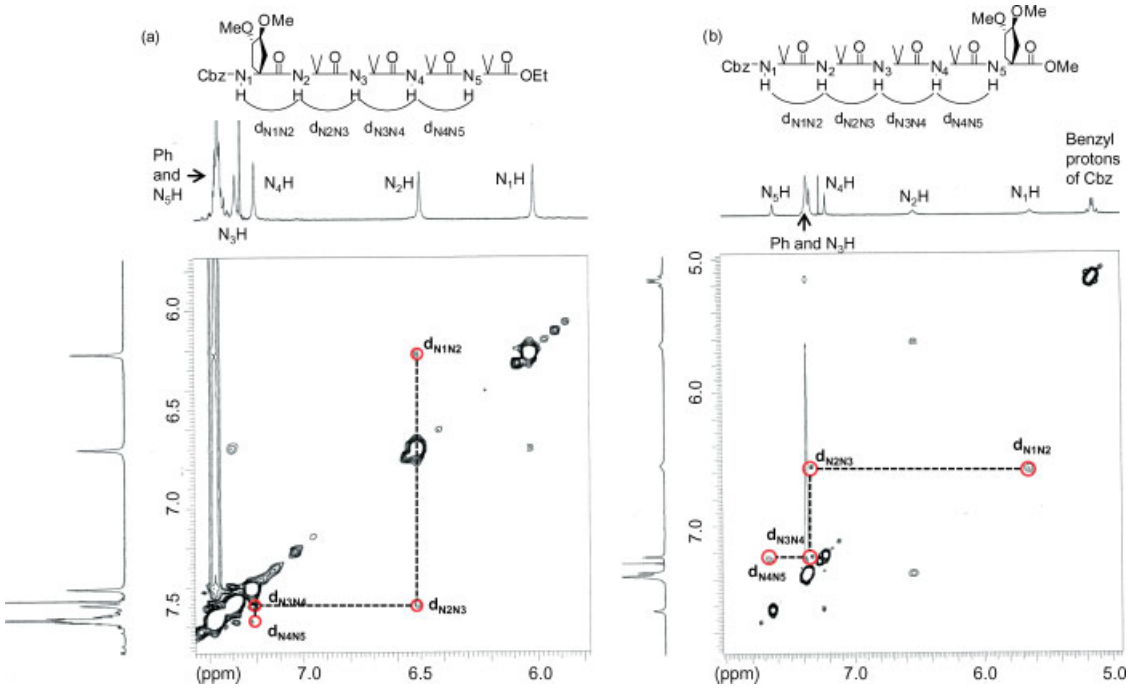

Figure 4. The NOESY ^{1}H NMR ($CDCl_3$) spectra of peptides **1** (a) and **2** (b). Peptide concentration: 5.0 mM; mixing time: 200 ms; sample temperature; 24 °C.

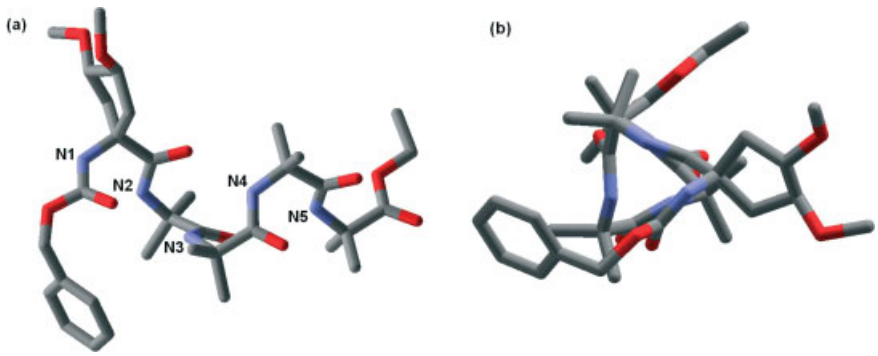

Figure 5. X-ray diffraction structure of **1** as viewed (a) perpendicular to and (b) along the helical axis.

Figure 5 shows the X-ray structures of the (*M*) 3_{10}-helical triangle (Fig. 5a) perpendicular to and (Fig. 5b) along the helical axis.

Three intramolecular hydrogen bonds, each of which form a ten-membered (atoms) pseudo ring of the $i \leftarrow i+3$ type, exist in the 3_{10}-helical molecule of **1**. The three intramolecular hydrogen bonds are present between the H-N(3) and C(0)═O(0) O atom of the Cbz group with an N(3)···O(0) distance of 3.15 Å, between the H-N(4) and C(1)═O(1) [N(4)···O(1) = 3.00 Å], and between the H-N(5) and C(2)═O(2) [N(5)···O(2) = 3.04 Å]. In the packing mode, two intermolecular hydrogen bonds were observed between the 3_{10}-helical conformers; i.e. between the H-N(1) urethane donor and the C(4′)═O(4′) O atom of a symmetry-related molecule (x, y, $z+1$) [N(1)···O(4′) = 2.83 Å] and between the H-N(2) peptide donor and the C(5′)═O(5′) O atom of a symmetry-related molecule (x, y, $z+1$) [N(2)···O(5′) = 3.15 Å].

The pentapeptide **2** exclusively crystallized into a right-handed (*P*) 3_{10}-helical conformer (Figure 6). The helical screw handedness (*P*) of **2** was opposite to that of **1** (*M*). The mean values of the ϕ and ψ torsion angles of the amino-acid residues (1–4) were −56.6° and −31.5°, and reversal of the torsion angle signs at the *C*-terminus occurred at the Ac_5c^{dOM} residue ($\phi = +51.9°$, $\psi = +35.6°$).

Three consecutive intramolecular hydrogen bonds of the $i \leftarrow i+3$ type, between the H-N(3) and C(0)═O(0) [N(3)···O(0) = 3.01 Å], the H-N(4) and C(1)═O(1) [N(4)···O(1) = 3.04 Å], and the H-N(5) and C(2)═O(2) [N(5)···O(2) = 3.00 Å] were observed. In the packing mode, one intermolecular hydrogen bond was observed between the H–N(1) donor and the C(4′)═O(4′) acceptor [N(1)···O(4′) = 2.86 Å] of a symmetry-related molecule (x, y, $z-1$).

Conclusions

A single chiral cyclic α,α-disubstituted amino acid, (*S*,*S*)-Ac_5c^{dOM}, was attached to the *N*-terminal or *C*-terminal positions of achiral Aib-based peptide segments. The dominant conformations of peptides **1** and **2** in solution were both found to be 3_{10}-helical structures by IR, ^{1}H NMR, and 2D NOESY spectra. Furthermore, the CD spectra of **1** and **2** suggested the existence of roughly equivalent amounts of both right-handed (*P*) and left-handed (*M*) helices. The conformations of **1** and **2** in the crystalline state

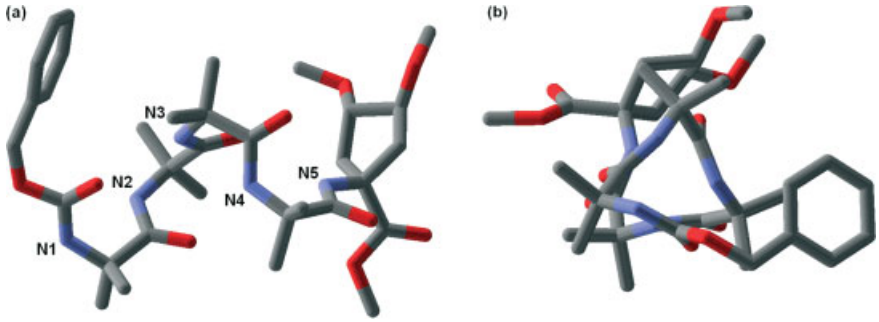

Figure 6. X-ray diffraction structure of **2** as viewed (a) perpendicular to and (b) along the helical axis.

were analyzed by X-ray diffraction. A left-handed (*M*) 3_{10}-helical structure was present in **1**, whereas a right-handed (*P*) 3_{10}-helical structure was present in **2** in their crystalline states. The attachment of (*S*,*S*)-Ac_5c^{dOM} to the *N*-terminal position of an achiral Aib-based peptide segment induced a left-handed helical screw sense, as (*S*,*S*)-Ac_5c^{dOM} homopeptides did [12], whereas its attachment at the *C*-terminal position gave a right-handed helical structure. Considering these results, both right-handed and left-handed helices are present in the equilibrium mixtures of these peptides in solution, and a slightly energetically favorable conformer is preferentially packed in the crystalline state. We conclude that the preference for a given helical handedness governed by side-chain chiral centers, which affects achiral Aib-based peptide segments is lower than that of L-amino acids with an α-chiral center [4].

Acknowledgements

This work was supported in part by a Grant-in-Aid for Young Scientists (B) (21790018); a Grant-in-Aid for Scientific Research on Priority Areas (No. 20037054, 'Chemistry of Concerto Catalysis') from the Ministry of Education, Science, Sports, and Culture of Japan; and a Grant-in-Aid from the ASAHI GLASS Foundation.

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