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Solid-state conformation of diastereomeric -Pro-Pro-(Aib)$_4$ sequences

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ABSTRACT

The crystal structures of two diastereomeric -Pro-Pro-(Aib)$_4$- sequences, Cbz-L-Pro-L-Pro-(Aib)$_4$-OMe (**1**) and Cbz-D-Pro-L-Pro-(Aib)$_4$-OMe (**2**), have been determined by X-ray crystallographic analysis. The crystals of the two compounds were characterized by the following parameters: (**1**) monoclinic, $P2_1$, a=10.543 Å, b=8.103 Å, c=22.642 Å, β=97.679, Z=2, R_1=0.104, and R_w=0.327; (**2**) orthorhombic, $P2_12_12_1$, a=10.470 Å, b=10.953 Å, c=32.405 Å, Z=4, R_1=0.040, and R_w=0.046. In the asymmetric unit of **1**, the homochiral L-Pro^1-L-Pro^2 adopts a polyproline II structure, which induces a left-handed (M) 3_{10}-helical structure in the following -(Aib)$_4$- sequence. The preferred conformation of diastereomeric **2**, which contains heterochiral D-Pro^1-L-Pro^2 segments, was similar to that of **1** with differences at the N-terminal D-Pro residue.

1. Introduction

The development of a template for controlling the secondary structure of peptides is important for creating a variety of artificial peptides, proteins, and macromolecules.[1] To date, we have studied the conformation of peptides composed of various α,α-disubstituted α-amino acids.[2] L-Proline (L-Pro), one of the 20 naturally occurring amino acids, has a propensity to induce a turn structure in peptide sequences because of the constraint of its pyrrolidine ring skeleton, and L-Pro and its derivatives (including some specially designed derivatives) have been synthesized to control peptide secondary structures.[3] Furthermore, homochiral diproline (L-Pro-L-Pro) segments have been used as templates for the induction and stabilization of helical structures,[4] and heterochiral D-Pro-L-Pro segments have been used as templates for β-hairpin structures.[5] As part of our ongoing research, we wish herein to report the conformation of two diastereomeric hybrid peptides containing diproline segments and an α,α-disubstituted α-amino acid. That is to say, L-Pro-L-Pro and D-Pro-L-Pro were used as diproline segments, and 2-aminoisobutyric acid (Aib) was used as an α,α-disubstituted α-amino acid. Aib is widely used to construct helical structures and does not show helical-screw handedness bias because of its achiral amino acid.[6] We have designed and synthesized two hexapeptides, Cbz-L-Pro-L-Pro-(Aib)$_4$-OMe (**1**) and Cbz-D-Pro-L-Pro-(Aib)$_4$-OMe (**2**), and studied their preferred conformations in the crystalline state.

2. Results and discussion

2.1. Synthesis of two diastereomeric peptides 1 and 2

The synthesis of peptides **1** and **2** was performed by the coupling of Cbz-(Pro)$_2$-OH and H-(Aib)$_4$-OMe using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole hydrate (HOBt) as coupling reagents by the solution-phase method (Scheme 1). The spectroscopic data of **1** and **2** supported the structures in Scheme 1.

2.2. Conformation of peptides 1 and 2

Single crystals of peptides **1** and **2** were grown from MeOH/H_2O and EtOH, respectively. Data collection was performed using Bruker Smart 1000 imaging plate diffractometers and graphite-monochromated Mo $K\alpha$ radiation. All crystals remained stable during the X-ray-data collection. The structures were solved using the SHELEX-97[7] and SIR-97[8] direct methods and expanded by the Fourier technique.[9] All non-H-atoms were given anisotropic thermal parameters, some H-atoms were refined isotropically, and the

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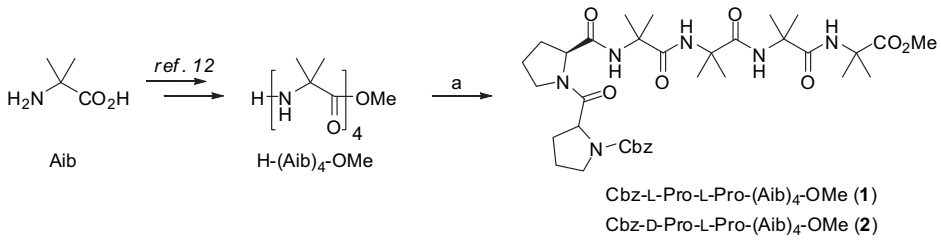

Scheme 1. Reagents and conditions: (a) EDC, HOBt, Cbz-L-Pro-L-Pro-OH, or Cbz-D-Pro-L-Pro-OH, MeCN.

remaining H-atoms were given at the calculated positions. The final cycle of full-matrix least-squares refinement of **1** gave an R_1 factor of 0.104 based on 4908 ($I>2\sigma(I)$) reflections and an R_w factor of 0.327 for all data. The R_1 factor of **2** was 0.040 based on 2951 ($I>2\sigma(I)$) reflections and an R_w factor of 0.046 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-757487 and -757488, respectively.[10] The crystal and diffraction parameters of **1** and **2** are summarized in Table 1. The relevant backbone torsion angles and the intra- and intermolecular hydrogen-bond parameters are listed in Tables 2 and 3.

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

	1	**2**
Empirical formula	$C_{35}H_{52}O_9N_6$, $2H_2O$	$C_{35}H_{52}O_9N_6$, H_2O
Mr	736.85	718.85
Crystal dimensions [mm]	0.30×0.20×0.10	0.35×0.25×0.25
Crystal system	Monoclinic	Orthorhombic
Lattice parameters:		
a, *b*, *c* [Å]	10.543, 8.103, 22.642	10.470, 10.953, 32.405
α,β,γ [°]	90, 97.679, 90	90, 90, 90
V [Å^3]	1917.0	3716.3
Space group	$P2_1$	$P2_12_12_1$
Z value	2	4
D_{calcd} [g/cm^3]	1.270	1.285
μ (Mo K_α) [cm^{-1}]	0.95	0.94
No. of observations	4908 ($I>2\sigma(I)$)	2951 ($I>2\sigma(I)$)
No. of variables	469	462
R_1, R_w	0.104, 0.327	0.040, 0.046
Solvent	MeOH/H_2O	EtOH

Table 2
Selected torsion angles ω, ϕ, and φ [°] for **1** and **2** as determined by X-ray crystallographic analysis

Torsion angles	**1**	**2**
ω_0	−0.6	176.9
ϕ_1	−60.3	62.8
φ_1	159.8	−136.8
ω_1	176.4	−163.6
ϕ_2	−57.9	−59.0
φ_2	145.2	125.2
ω_2	173.8	174.7
ϕ_3	51.1	63.8
φ_3	35.3	19.7
ω_3	172.2	156.1
ϕ_4	53.7	51.7
φ_4	34.4	49.3
ω_4	178.8	172.2
ϕ_5	52.8	66.6
φ_5	41.6	17.4
ω_5	172.2	179.7
ϕ_6	−47.4	−51.0
φ_6	−46.2	−41.2
ω_6	−172.2	−179.5

Table 3
Intra- and intermolecular H-bond parameters for **1** and **2**[a]

Donor D–H	Acceptor A	Distance [Å] D···A	Angle [°] D–H···A	Symmetry operations
Cbz-L-Pro-L-Pro-(Aib)$_4$-OMe (**1**)				
N_4–H	O_1	3.31[b]	138.3	*x*, *y*, *z*
N_5–H	O_2	3.08	153.0	*x*, *y*, *z*
N_6–H	O_3	2.91	141.9	*x*, *y*, *z*
O_{wa}–H[c]	O_1	2.79	174.3	*x*, *y*, *z*
O_{wb}–H	O_{wa}	2.81	168.5	*x*, *y*, *z*
N_3–H	$O_{5'}$	3.04	160.6	*x*−1, *y*, *z*
O_{wb}–H	$O_{4'}$	2.84	171.3	*x*−1, *y*, *z*
Cbz-D-Pro-L-Pro-(Aib)$_4$-OMe (**2**)				
N_4–H	O_1	3.12	162.3	*x*, *y*, *z*
N_5–H	O_w[c]	2.90	160.8	*x*, *y*, *z*
N_6–H	O_3	2.95	150.5	*x*, *y*, *z*
O_w–H	O_0	2.78	172.2	*x*, *y*, *z*
O_w–H	O_1	2.74	163.4	*x*, *y*, *z*
N_3–H	$O_{5'}$	2.99	171.0	*x*, *y*−1, *z*

[a] The number of amino acid residues begins from the N-terminus of the peptide chain.
[b] The D···A distance is somewhat long for a hydrogen bond.
[c] O_w: Water.

In the asymmetric unit of **1**, only one conformer of the peptide molecule was found together with two water molecules, and the -L-Pro^1-L-Pro^2 adopted a polyproline type II (P_{II}) structure, which induced a left-handed (*M*) 3_{10}-helical structure in the following -(Aib)$_4$- sequence (Fig. 1). The ϕ and φ torsion angles of L-Pro^1 were −60.3° and +159.8°, and those of L-Pro^2 were −57.9° and +145.2°, which are close to those of the P_{II} structure (−78° and +149°). The mean values of the ϕ and φ torsion angles of the Aib residues (Aib^3 to Aib^5) were +52.5° and +37.1°, which are close to those for an ideal left-handed (*M*) 3_{10}-helical structure (+57° and +30°). Flipping of the torsion angles at the C-terminus occurred, that is, the values of the ϕ and φ torsion angles (−47.4°, and −46.2°) of the Aib^6 residue were negative while those of the preceding residues, Aib^3, Aib^4, and Aib^5, were positive.

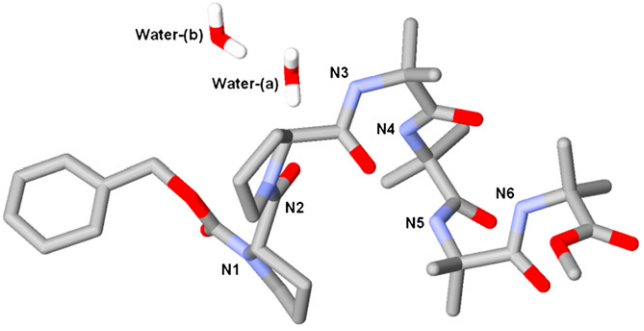

Figure 1. X-ray diffraction structure of **1**.

Two intramolecular hydrogen bonds, in which each hydrogen bond formed a 10-membered (atoms) pseudo ring of the $i \leftarrow i+3$ type, were present in the 3_{10}-helical molecule of **1**. That is, they were present between the H–N(5) and C(2)=O(2) [N(5)···

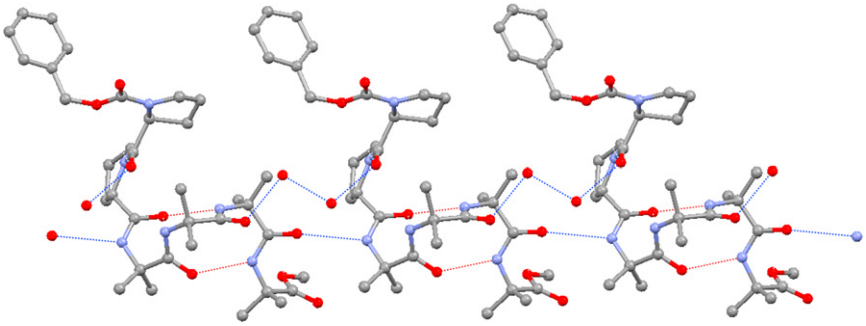

Figure 2. Packing of **1** in the crystalline state. Intramolecular (red) and intermolecular (blue) hydrogen bonds are indicated as dashed lines.

O(2)=3.08 Å] and between the H–N(6) and C(3)=O(3) [N(6)···O(3)=2.91 Å]. Furthermore, one weak intramolecular hydrogen bond was observed between the H–N(4) and C(1)=O(1) [N(6)···O(1)=3.31 Å]. Two water molecules (a, b) formed intermolecular hydrogen bonds between the H–O_w(a) of the water (a) donor and the C(1)=O(1) [O_w(a)···O(1)=2.79 Å] and between the H–O_w(b) of the water (b) donor and the O_w(a) of the water (a) acceptor [O_w(b)···O_w(a)=2.81 Å]. In the packing mode, two intermolecular hydrogen bonds were observed between the H–N(3) peptide donor and the C(5′)=O(5′) acceptor [N(3)···O(5′)=3.04 Å] of a symmetry-related molecule ($x-1$, y, z) and between the H–O_w(b) of the water (b) donor and the C(4′)=O(4′) acceptor [O_w(b)···O (4′)=2.84 Å] of a symmetry-related molecule ($x-1$, y, z), as shown in Figure 2.

In the asymmetric unit of **2**, only one conformer of the peptide molecule was present together with one water molecule (Fig. 3). The ϕ and φ torsion angles of D-Pro[1] were +62.8° and −136.8°, and those of L-Pro[2] were −59.0° and +125.2°. Thus, the D-Pro[1]-L-Pro[2] segment did not form a type-II′ β-turn conformation[11] because of the presence of the water molecule. The mean values of the ϕ and φ torsion angles of the Aib residues (Aib[3] to Aib[5]) were +60.7° and +28.8°, which are close to those of an ideal left-handed (*M*) 3_{10}-helical structure. The flipping of the torsion angles occurred at the C-terminus, and the ϕ and φ torsion angles (−51.0° and −41.2°, respectively) of the Aib[6] residue were negative while those of the Aib[3], Aib[4], and Aib[5] residues were positive.

Two intramolecular hydrogen bonds, in which each hydrogen bond formed a 10-membered (atoms) pseudo ring of the $i \leftarrow i+3$ type, were present in the 3_{10}-helical molecule of **2**. These bonds were found between the H–N(4) and C(1)=O(1) [N(4)···O(1)=3.12 Å] and the H–N(6) and C(3)=O(3) [N(6)···O(3)=2.95 Å]. The water molecule was fixed by three hydrogen bonds between H–N(5) and O_w [N(5)···O_w=2.90 Å], H–O_w and C(0)=O(0) [O_w···O(0)=2.78 Å], and between H–O_w and C(1)=O(1) [O_w···O(1)=2.74 Å]. In the packing mode, one intermolecular hydrogen bond was observed between the H–N(3) peptide donor and the C(5′)=O(5′) acceptor [N(3)···O(5′)=2.99 Å] of a symmetry-related molecule (x, y−1, z), as shown in Figure 4.

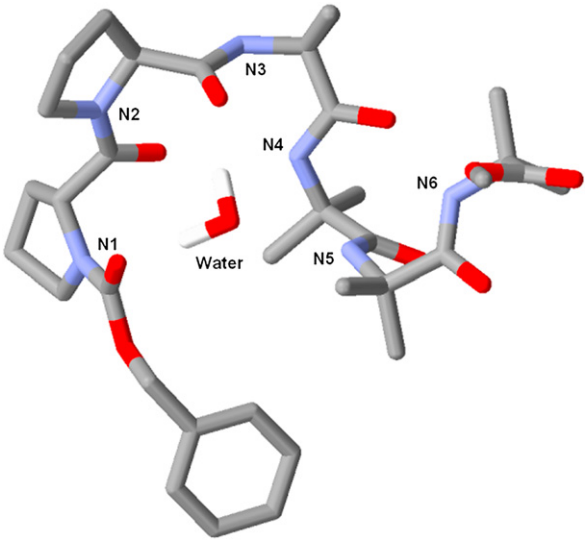

Figure 3. X-ray diffraction structure of **2**.

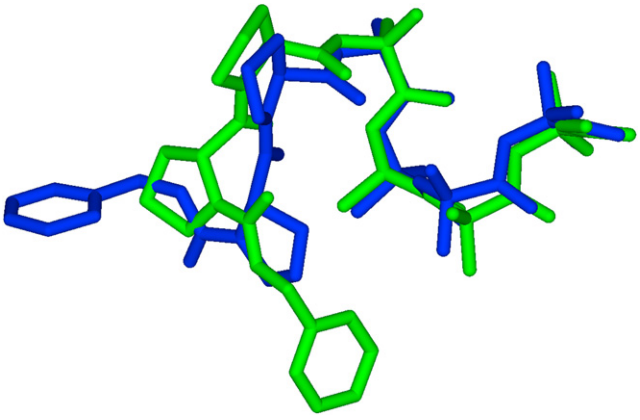

Figure 5. Overlay of the structures of peptides **1** (blue) and **2** (green).

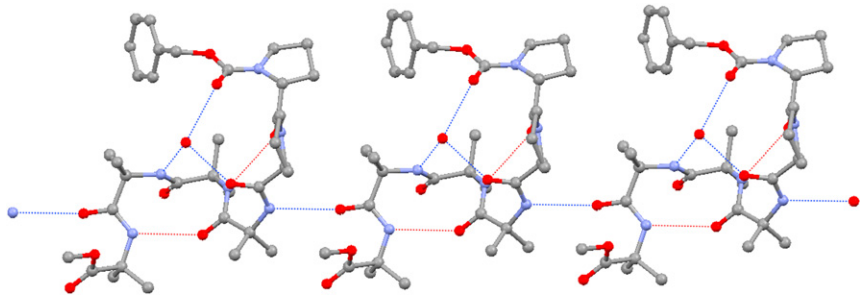

Figure 4. Packing of **2** in the crystalline state. Intramolecular (red) and intermolecular (blue) hydrogen bonds are indicated as dashed lines.

The structure of **2** is well matched with that of **1** except for the N-terminal D-Pro residue, as shown by their superimposition in Figure 5.

3. Conclusion

Two diastereomeric diproline (L-Pro-L-Pro and D-Pro-L-Pro) segments were attached on the N-terminus of H-(Aib)$_4$-OMe segment. X-ray crystallographic analysis revealed the preferred conformations of hexapeptides **1** and **2** in the crystalline state. In the crystal state of **1**, the homochiral L-Pro^1-L-Pro^2 segment adopted a polyproline type II structure, which induced a left-handed (*M*) 3_{10}-helical structure in the following -(Aib)$_4$- sequence. On the other hand, in the crystal state of **2**, the heterochiral D-Pro^1-L-Pro^2 segment did not form a type-II′ β-turn conformation because of the presence of a fixed water molecule. Thus, the L-Pro^2-Aib^3 segment bestowed a left-handed (*M*) screw sense[3c] on the following Aib sequence. That is to say, the two diastereomeric Cbz-Pro-L-Pro-(Aib)$_4$-OMe peptides formed similar structures with different N-terminal Pro residues. These results will be valuable for researchers investigating the control of secondary structures and may be also relevant for the *de novo* design of peptides/proteins.

4. Experimental

4.1. General methods

Optical rotations $[\alpha]_D$ were measured with a *Jasco DIP*-316 polarimeter using a 0.5 or 1.0 dm cell. ^{1}H NMR and ^{13}C spectra were recorded on a *Varian AS* 400 spectrometer, and measurements were carried out in $CDCl_3$ with tetramethylsilane used as an internal standard. FTIR spectra were recorded on a *JASCO FT/IR*-4100 spectrometer at 1 cm^{-1} resolution, with a mean of 32 scans used for the solution ($CDCl_3$) method and a 0.1 mm path length adopted for NaCl cells. FABMS spectra were measured on a JEOL JMS-SX 102 spectrometer. Elemental analysis was performed at the Analytical Center of the Faculty of Sciences at Kyushu University.

*4.1.1. Cbz-L-Pro-L-Pro-(Aib)$_4$-OMe (**1**).* A mixture of Cbz-L-Pro-L-Pro-OH (173 mg, 0.5 mmol), H-(Aib)$_4$-OMe (186 mg, 0.5 mmol),[12] EDC (115 mg, 0.6 mmol), and HOBt (81 mg, 0.6 mmol) in MeCN was stirred at room temperature for 48 h. The solution was then evaporated; diluted with AcOEt (30 mL); washed with 3% aqueous HCl, 5% $NaHCO_3$, and brine; and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a white solid, which was purified by column chromatography on silica gel (*n*-hexane/AcOEt=1:9) to give **1** (164 mg, 47%) as colorless crystals. Mp 193–194 °C (recryst from MeOH/H_2O); $[\alpha]_D^{24}$ −51.2 (*c*1.7, $CHCl_3$); IR (in $CDCl_3$ solution) 3317, 1741, 1698, 1645 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (br s, 1H), 7.30–7.36 (m, 5H), 7.21 (br s, 1H), 7.19 (br s, 1H), 6.76 (br s, 1H), 5.14 (ABX, J_{AX}=13.0 Hz, J_{BX}=13.0 Hz, J_{AB}=37.0 Hz, 2H), 4.50 (t, *J*=7.5 Hz, 1H), 4.25 (t, *J*=7.5 Hz, 1H), 3.62–3.73 (m, 2H), 3.68 (s, 3H), 3.44 (m, 1H), 3.34 (m, 1H), 2.19–2.37 (m, 2H), 1.79–2.04 (m, 6H), 1.44–1.52 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 174.6, 174.2, 173.6, 172.0, 171.3, 154.9, 136.4, 128.5, 128.2, 128.0, 67.2, 61.8, 59.8, 56.9, 56.8, 56.5, 55.7, 52.0, 47.2, 46.7, 29.0, 28.8, 25.8, 25.6, 25.5, 25.2, 25.0, 24.9, 24.7, 24.5, 23.9; FAB(+)-MS: 701 (M+H); Anal. Calcd for $C_{35}H_{52}N_6O_9$: C, 59.98; H, 7.48; N, 11.99. Found: C, 59.73; H, 7.40; N, 11.91.

*4.1.2. Cbz-D-Pro-L-Pro-(Aib)$_4$-OMe (**2**).* Peptide **2** was prepared using a similar method to that described for the preparation of **1** (0.5 mmol scale). 137 mg, 39% yield; colorless crystals; mp 175–177 °C (recryst from EtOH); $[\alpha]_D^{24}$ −20.1 (*c*1.1, $CHCl_3$). IR (in $CDCl_3$ solution) 3327, 1740, 1666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (br s, 1H), 7.29–7.39 (m, 5H), 7.25 (br s, 1H), 7.24 (br s, 1H), 7.09 (br s, 1H), 5.19 (d, *J*=13.0 Hz, 1H), 4.99 (d, *J*=13.0 Hz, 1H), 4.46 (t, *J*=6.7 Hz, 1H), 4.41 (t, *J*=6.2 Hz, 1H), 3.97 (m, 1H), 3.68 (s, 3H), 3.55–3.64 (m, 3H), 1.91–2.27 (m, 8H), 1.52 (s, 3H), 1.50 (s, 6H), 1.48 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 174.6, 173.4, 172.7, 171.4, 155.1, 135.9, 128.6, 128.2, 127.3, 67.2, 61.5, 58.2, 56.8, 56.6, 56.5, 55.6, 51.9, 47.5, 47.0, 29.7, 29.2, 28.4, 26.3, 25.8, 25.7, 25.2, 25.0, 24.9, 24.5, 24.4, 24.3, 24.0, 19.3; FAB(+)-MS: 701 (M+H).

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10. CCDC-757487 and -757488 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).
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