Solid-State Conformation of a Hybrid Tripeptide between β-Amino Acid; 8-Aminocyclooct-4-enecarboxylic Acid and 2-Aminoisobutyric Acid

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An eight-membered cyclic β-amino acid, 8-aminocyclooct-4-enecarboxylic acid, was designed as a conformationally restricted non-proteinogenic amino acid. A hybrid tripeptide containing this eight-membered cyclic β-amino acid and 2-aminoisobutyric acids was synthesized by conventional solution methods. The conformation of the tripeptide was studied using X-ray analysis and was shown to form an eleven-membered hydrogen-bonded turn (3_{11}-helical structure) in the solid state.

Key words helical conformation; α,α-disubstituted amino acid; β-amino acid; 2-aminoisobutyric acid; hybrid peptide; conformational analysis

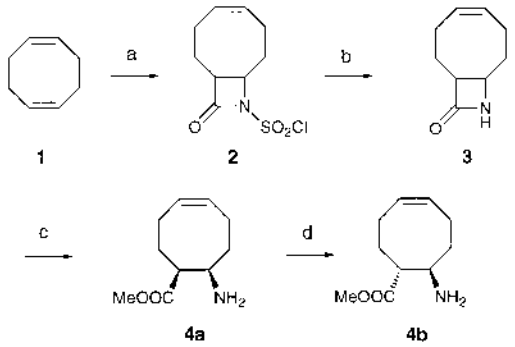
Recently, β-peptides capable of constructing unique secondary structures have been of great interest among organic, peptide, and protein chemists. The Seebach[1] and Gellman groups[2] independently reported that the secondary structures of β-peptides involved novel 3_{14}-helical and/or 2.5_{12}-helical structures in solution and in the solid state.[3] Such helical structures have not been found in natural proteins and peptides containing α-amino acids.[4] In order to obtain good crystals for X-ray diffraction studies, the Gellman group designed cyclic β-amino acids such as 2-aminocyclopentanecarboxylic acid and 2-aminocyclohexanecarboxylic acid. Employing cyclic β-amino acids restricts the freedom of conformation of peptides and good crystals for X-ray analysis were obtained. As a part of our ongoing research on non-proteinogenic amino acids and their peptides,[5,6] here we wish to report the conformation of a hybrid tripeptide containing eight-membered β-amino acid and an α,α-disubstituted α-amino acid,[7,8] that is to say, 8-aminocyclooct-4-enecarboxylic acid was used as a β-amino acid and 2-aminoisobutyric acid (Aib)[7] as an α,α-disubstituted amino acid. Both amino acid residues in the peptide are conformationally restricted.

Results and Discussion

Synthesis of *cis*-8-Aminocyclooct-4-enecarboxylic Acid and Its Peptide 1,5-Cyclooctadiene **1** was reacted with chlorosulfonyl isocyanate (CSI) to afford cycloadduct **2** in 43% yield based on CSI.[9] Deprotection of the *N*-chlorosulfonyl group by treatment with 15% aqueous Na_2SO_3 afforded β-lactam **3** in 92% yield.[10] Methanolysis of the β-lactam **3** with NaOMe in MeOH at room temperature gave methyl ester **4a** in 96% yield, and with NaOMe in refluxing MeOH afforded a mixture of *trans*-**4b** and *cis*-**4a**. The stereochemistry of product **4a** was determined to be *cis* because compound **4a** could be converted into **4b** by treatment with NaOMe in refluxing MeOH. The ^{1}H-NMR spectra of **4a** and **4b** also supported the proposed structures (Chart 1).

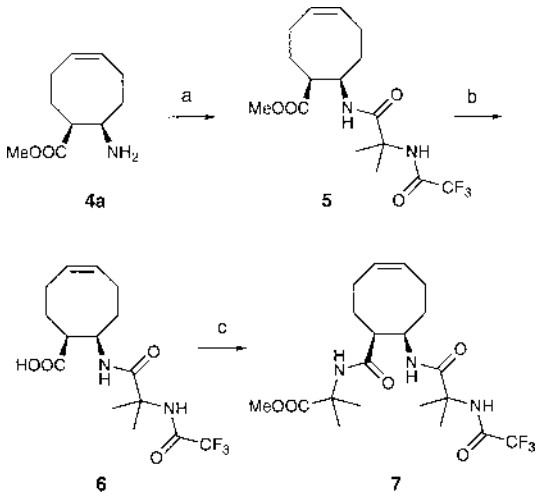
Tripeptide **7** was prepared by conventional solution methods. The amine **4a** was coupled with trifluoroacetyl-2-aminoisobutyric acid (CF_3CO-Aib)[7a] by using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) in CH_2Cl_2 to afford dipeptide **5** in 75% yield. Saponification of the methyl ester of **5** by KOH gave acid **6** in 69% yield. The coupling of the acid **6** and methyl 2-aminoisobutyrate (Aib-OMe)[7a] in the presence of EDC and HOBt afforded the tripeptide **7** in 87% yield. The spectroscopic data of **7** supported the structure (Chart 2).

Conformation of Tripeptide Good crystals for X-ray analysis were obtained by slow evaporation of a solution in



Reagents and conditions: (a) chlorosulfonyl isocyanate (CSI), benzene (43%); (b) Na_2SO_3, KOH, Et_2O–H_2O (92%); (c) NaOMe, MeOH (96%); (d) NaOMe, MeOH, reflux.

Chart 1



Reagents and conditions: (a) CF_3CO-Aib, EDC, HOBt (75%); (b) KOH, H_2O (69%); (c) Aib-OMe, EDC, HOBt (87%).

Chart 2

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$MeOH–CHCl_3$. Crystal and collection parameters are listed in Table 1. The molecular structures with atomic numbering schemes are shown in Figs. 1—3. Selected peptide main-chain torsion angles are given in Table 2. The intra- and intermolecular hydrogen bond parameters are listed in Table 3.

The structure of tripeptide **7** was solved in the $P2_1/a$ (No. 14) space group. Two independent molecules (A and B) occur in the asymmetric unit, and also two water molecules exist as a solvent. Rotational disorders typical of the trifluoroacetyl function at the *N*-terminal position were observed in molecule A. The major difference in the conformation of the two molecules, A and B, is the direction of the carbonyl function in the *C*-terminal methyl esters. The torsion angle O1–C2–C3–N3 in molecule A is 37.5(7)°, and the O6–C22–C23–N6 torsion angle in molecule B is 152.7(5)°. The enantiomers of both molecules also exist in the crystal because the centers of symmetry are present in the space group of $P2_1/a$ (No. 14). One intramolecular hydrogen bond was observed between the N3–H peptide donor and the C19=O5

Table 1. Crystallographic Data of Tripeptide **7**

Empirical formula	$C_{40}H_{64}O_{12}N_6F_6$
Formula weight	934.97
Crystal dimens (mm)	0.20×0.20×0.20
Crystal system	Monoclinic
Lattice parameters	
a, b, c (Å)	14.631(3), 17.796(4), 18.854(2)
α, β, γ (°)	90, 108.35(1), 90
V (Å^3)	4659(1)
Space group	$P2_1/a$ (No. 14)
Z value	4
D_{calc} (g/cm^3)	1.333
μ (Cu$K\alpha$, cm^{-1})	0.973
No. of observations	3895 ($I>2.0\ \sigma(I)$)
No. of variables	632
R, R_w	0.060, 0.060
Sol. of crystallization	$MeOH–CHCl_3$

Table 2. The Selected Peptide Main-Chain Torsion Angles

(a)	(b)	(c)	(d)		Angle (°)
Molecule A					
C16	N1	C19	C20	ω_{0a}	178.3(5)[a]
C15	C16	N1	C19	ϕ_{1a}	46.2(7)
N1	C16	C15	N2	ψ_{1a}	−135.7(5)
C14	N2	C15	C16	ω_{1a}	−177.3(5)
C7	C14	N2	C15	ϕ_{2a}	−72.3(6)
N2	C14	C7	C6	θ_{2a}	−72.7(5)
N3	C6	C7	C14	ψ_{2a}	83.8(6)
C3	N3	C6	C7	ω_{2a}	−175.5(5)
C2	C3	N3	C6	ϕ_{3a}	50.2(7)
O1	C2	C3	N3	ψ_{3a}	37.5(7)
C1	O1	C2	C3	ω_{3a}	−179.9(5)
Molecule B					
C36	N4	C39	C40	ω_{0b}	177.8(7)
C35	C36	N4	C39	ϕ_{1b}	−47.4(8)
N4	C36	C35	N5	ψ_{1b}	130.3(5)
C34	N5	C35	C36	ω_{1b}	−178.1(5)
C27	C34	N5	C35	ϕ_{2b}	84.5(6)
N5	C34	C27	C26	θ_{2b}	69.2(5)
N6	C26	C27	C34	ψ_{2b}	−93.7(6)
C23	N6	C26	C27	ω_{2b}	164.4(5)
C22	C23	N6	C26	ϕ_{3b}	−54.6(7)
O6	C22	C23	N6	ψ_{3b}	152.7(5)
C21	O6	C22	C23	ω_{3b}	170.3(7)

a) Estimated standard deviations are shown in the parentheses.

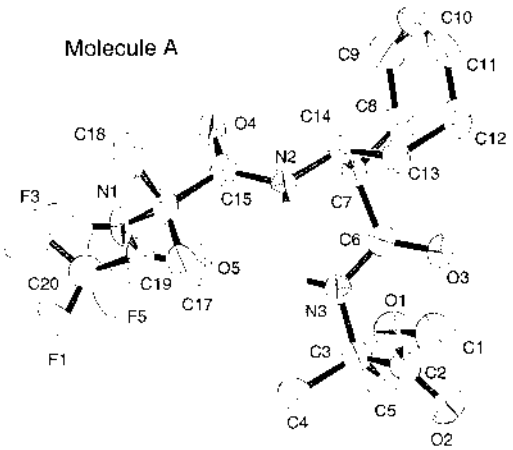

Fig. 1. ORTEP Drawing of the Crystal Structure of Tripeptide **7** (Molecule A) with Atom Numbering (Ellipsoids at 50% Probability)

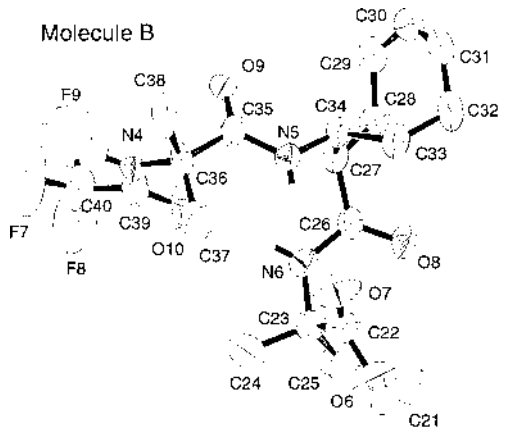

Fig. 2. ORTEP Drawing of the Crystal Structure of Tripeptide **7** (Molecule B) with Atom Numbering (Ellipsoids at 50% Probability)

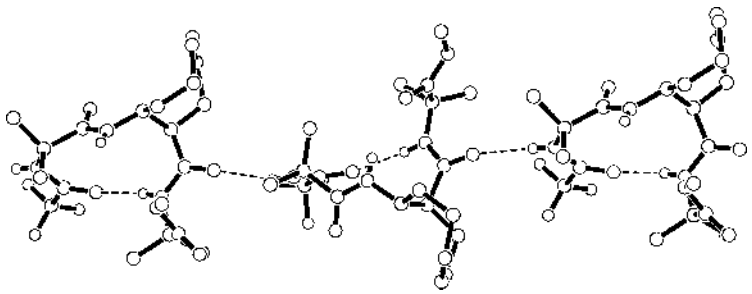

Fig. 3. View of the Crystal Structure of **7** (Molecules A and B)

The intramolecular and intermolecular hydrogen bonds are indicated as dashed lines.

Table 3. Intra- and Intermolecular Hydrogen Bonds for Tripeptide **7**

Donor D–H	Acceptor A	Distance (Å) D···A	Angle (°) D–H···A	Symmetry operation
Intramolecular hydrogen bonds				
N3–H	O5	2.959(7)[a)]	172(5)	x,y,z
N6–H	O10	3.000(7)	175(4)	x,y,z
Intermolecular hydrogen bonds				
N1–H	O8	2.879(6)	166(5)	x,y,z
N4–H	O3	2.854(6)	162(6)	$x,y,z-1$
N2–H	O11	3.273(6)	147(4)	x,y,z
O11–H	O4	2.796(6)	—	$x-1/2,-y+1/2,z$
O12–H	O10	2.94(3)	—	$x,y,z-1$

a) Estimated standard deviations are shown in the parentheses. *b*) The atoms O11 and O12 are oxygens of water solvents.

carbonyl oxygen of the trifluoroacetyl group at the *N*-terminus with a N3···O5 distance of 2.959(7) Å in molecule A, and also one hydrogen bond was observed between the N6–H peptide donor and the C39=O10 carbonyl oxygen of the trifluoroacetyl group at the *N*-terminus with a N6···O10 distance of 3.000(7) Å, in molecule B. Two intermolecular hydrogen bonds between tripeptides A and B were observed. One is a hydrogen bond between the N1–H peptide donor and the C26=O8 carbonyl oxygen acceptor with a N1···O8 distance of 2.879(6) Å, and the other is a hydrogen bond between the N4–H donor and the C6=O3 acceptor of a symmetry-related molecule ($x,y,z-1$) with a N4···O3 distance of 2.854(6) Å, as shown in Fig. 3. Intermolecular hydrogen bonds were also observed between the water molecules and tripeptides as summarized in Table 3. The solid-state conformation of tripeptide **7** was thus shown to be an eleven-membered hydrogen-bonded turn (3_{11}-helical structure).[11] The eleven-membered hydrogen-bonded turn may be formed because the tripeptide **7** is a hybrid peptide between β-amino acid and α,α-disubstituted amino acids.[12]

Conclusion

The hybrid tripeptide **7** was prepared from the eight-membered β-amino acid **4a** and Aib. The solid-state conformation of **7** was unambigously determined to be an eleven-membered hydrogen-bonded turn conformation (3_{11}-helical structure). The turn structure observed in the solid state should be analogous with the β-turn structure with proteinogenic α-amino acids. The olefin function in the β-amino acid may be converted to various functional groups, such as epoxide, diol and dicarboxylic acid, therefore modification of peptides containing this moiety may be easily made.

In summary, hybridization between β-amino acids and α,α-disubstituted amino acids may provide conformationally rigid, new secondary structures for peptides.

Experimental

General Methods ^{1}H-NMR spectra were determined at 270 MHz (JEOL GX-270) or 500 MHz (VARIAN UNITY-500P) and ^{13}C-NMR spectra were measured at 68 MHz (JEOL GX-270). Infrared spectra (IR) were recorded on a JASCO A-100 spectrometer. EI-MS and FAB-MS spectra were taken on a JEOL JMS 610H or JEOL JMS-SX 102 spectrometer. Elemental analyses were performed in the Analytical Center of the Faculty of Sciences at Kyushu University. General procedures used for syntheses followed those in the previous reports.[5]

10-Aza-10-(chlorosulfonyl)bicyclo[6.2.0]dec-4-en-9-one (2) A mixture of 1,5-cyclooctadiene (150 ml) and chlorosulfonyl isocyanate (CSI, 25 g, 176 mmol) in benzene (300 ml) was stirred at 50 °C for 24 h. After being cooled to room temperature, the mixture was diluted with H_2O, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (20% EtOAc in hexane) to give the adduct **2** (18.4 g, 43% based on CSI) as a yellowish oil: IR (neat) cm^{-1}: 3025, 1820, 1400, 1180, 1110, 1090. ^{1}H-NMR ($CDCl_3$; 270 MHz) δ: 5.65—5.85 (2H, m), 4.45 (1H, ddd, J=4.0, 5.3, 6.9 Hz), 3.60 (1H, q, J=7.0 Hz), 2.10—2.60 (8H, m). EI-MS *m/z*: 249.0 (M^+, 4), 214.0 (3), 166.0 (16), 150.1 (27), 122.1 (30), 79.1 (66), 67.1 (100). HR-MS *m/z*: 249.0026 (Calcd for $C_9H_{12}N_1O_3C_{11}S_1$ (M^+): 249.0226). This compound was not stable at room temperature, and was used immediately in the next reaction.

10-Azabicyclo[6.2.0]dec-4-en-9-one (3) Fifteen percent aqueous Na_2SO_3 (200 ml) was added to the stirred solution of **2** (2.40 g, 9.64 mmol) in ether (100 ml). The mixture was neutralized with 5% aqueous KOH until the pH of solution become 7 to 8, and the mixture was stirred for 20 min. The etheral layer was separated, and dried over $MgSO_4$. Removal of the solvent gave a white solid, which was purified by column chromatography on silica gel. The fraction eluted with 10% MeOH in $CHCl_3$ afforded **3** (1.40 g, 92%) as colorless crystals: mp 112.0—113.0 °C (MeOH–$CHCl_3$). IR (KBr) cm^{-1}: 3200 (br), 1730 (br), 1700 (br). ^{1}H-NMR ($CDCl_3$; 270 MHz) δ: 5.90 (1H, br s), 5.62—5.80 (2H, m), 3.85 (1H, m), 3.31 (1H, m), 2.32—2.53 (2H, m), 1.80—2.20 (6H, m). FAB-MS *m/z*: 152.1 (M^++1); *Anal*. Calcd for $C_9H_{13}N_1O_1$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.12; H, 8.65; N, 9.11.

Methyl (1*RS*,8*SR*)-8-Aminocyclooct-4-enecarboxylate (4a) A mixture of NaOMe (1 g) and **3** (1.00 g, 6.57 mmol) in MeOH (100 ml) was stirred at room temperature for 24 h. The mixture was neutralized with 10% aqueous HCl and the MeOH was evaporated. The residue was diluted with water, extracted with $CHCl_3$, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (10% MeOH in $CHCl_3$) to leave **4a** (1.20 g, 96%) as a colorless oil: IR (neat) cm^{-1}: 3400 (br), 1725. ^{1}H-NMR δ: ($CDCl_3$; 270 MHz) 5.55—5.76 (2H, m), 3.69 (3H, s), 3.45 (1H, m), 2.82 (1H, ddd, J=1.3, 4.3, 5.6 Hz), 2.60 (1H, m), 2.46 (1H, m), 1.65—2.20 (8H, m). ^{13}C-NMR δ: ($CDCl_3$) 176.4, 130.9, 128.1, 51.6, 51.3, 46.5, 35.0, 26.3, 24.1, 23.9. EI-MS *m/z*: 184.1 (13), 183.1 (M^+, 11), 167.0 (44), 149 (100); HR-MS *m/z*: 183.1184 (Calcd for $C_{10}H_{17}N_1O_2$ (M^+): 183.1259).

Methyl (1*RS*,8*RS*)-8-Aminocyclooct-4-enecarboxylate (4b) IR (neat) cm^{-1}: 3400, 1725. ^{1}H-NMR ($CDCl_3$; 270 MHz) δ: 5.54—5.82 (2H, m), 3.68 (3H, s), 3.41 (1H, br t, J=6.5 Hz), 2.80 (1H, ddd, J=1.6, 4.3, 5.9 Hz), 2.60 (1H, m), 2.40 (1H, m), 1.60—2.20 (8H, m).

Methyl (1*RS*,8*SR*)-8-[2-Methyl-2-(trifluoroacetylamino)propanoylamino]cyclooct-4-enecarboxylate (5) A mixture of **4a** (940 mg, 5.14 mmol), CF_3CO-Aib (1.55 g, 13.0 mmol),[7a)] EDC (1.15 g, 6.00 mmol) and HOBt (810 mg, 6.00 mmol) in CH_2Cl_2 (50 ml) was stirred overnight at room temperature. The mixture was diluted with $CHCl_3$, washed with 2% aqueous HCl, 5% aqueous $NaHCO_3$, brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel to give **5** (2.30 g, 75%) as a colorless oil: IR (neat) cm^{-1}: 3340 (br), 1720, 1640, 1510. ^{1}H-NMR ($CDCl_3$; 270 MHz) δ: 7.75 (1H, br s), 6.49 (1H, br d, J=9.2 Hz), 5.64—5.81 (2H, m), 4.50 (1H, m), 3.74 (3H, s), 2.81 (1H, m), 1.64 (3H, s), 1.63 (3H, s), 1.60—2.55 (8H, m). ^{13}C-NMR ($CDCl_3$) δ: 174.4, 171.9, 155.9 (J=37 Hz), 130.8, 129.0, 115.5 (J=288 Hz), 57.4, 51.7, 49.1, 47.5, 32.4, 27.0, 24.8, 24.1, 23.8, 22.9. EI-MS *m/z*: 364.1 (M^++1), 332.1 (41), 304.1 (30), 210.1 (61), 182.1 (62), 155.0 (100). HR-MS *m/z*: 364.1619 (Calcd for $C_{16}H_{23}F_3N_2O_4$ (M^++1): 364.1610).

(1*RS*,8*SR*)-8-[2-Methyl-2-(trifluoroacetylamino)propanoylamino]cyclooct-4-enecarboxylic Acid (6) A solution of **5** (400 mg, 1.10 mmol) and KOH (400 mg, 7.13 mmol) in MeOH (5 ml) and H_2O (5 ml) was stirred at room temperature for 2 h. The solution was neutralized with 5% aqueous HCl and the MeOH was evaporated. The residue was diluted with 2% aqueous HCl, extracted with $CHCl_3$ and dried over $MgSO_4$. Removal of the solvent afforded the acid **6** (265 mg, 69%) as a colorless solid, which was used in the next reaction without purification.

Methyl 2-({(1*RS*,8*SR*)-8-[2-Methyl-2-(trifluoroacetylamino)propanoylamino]-cyclooct-4-enyl}carbonylamino)-2-methylpropanoate (7) A mixture of **6** (77 mg, 0.220 mmol), Aib-OMe (38 mg, 0.325 mmol),[7a)] EDC (63 mg, 0.329 mmol), and HOBt (44 mg, 0.326 mmol) was stirred at room temperature for 2 d. The solution was diluted with $CHCl_3$, washed with 2% aqueous HCl, 5% aqueous $NaHCO_3$, brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel to give **7** (89 mg, 87%) as colorless crystals: mp 99.0—100.0 °C. IR (KBr) cm^{-1}: 3600, 3360, 3250, 2950, 1730, 1715, 1640, 1530, 1180, 1155. ^{1}H-NMR ($CDCl_3$; 500 MHz) δ: 7.24 (1H, br s), 6.91 (1H, br d, J=9.1 Hz), 6.73 (1H, br s), 5.62—5.73 (2H, m), 4.52 (1H, m), 3.73 (3H, s), 2.71

(1H, m), 2.60 (1H, m), 2.47 (1H, m), 2.22—2.38 (2H, m), 2.03 (1H, m), 1.89 (1H, m), 1.82 (1H, m), 1.65 (1H, m), 1.63 (3H, s), 1.60 (3H, s), 1.58 (3H, s), 1.43 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 175.8, 173.5, 171.6, 155.9 (J=37 Hz), 131.6, 127.8, 115.5 (J=288 Hz), 57.5, 56.7, 52.6, 50.1, 48.6, 32.0, 27.5, 26.9, 25.7, 25.3, 24.3, 23.2, 22.9. EI-MS m/z: 449.0 (M^+, 13), 421.1 (6), 390.1 (7), 295.1 (24), 154.0 (72), 58.1 (100). HR-MS m/z: 449.2183 (Calcd for $C_{20}H_{30}F_3N_3O_5$ (M^+): 449.2137).

X-Ray Diffraction Crystals were grown from $CHCl_3$–MeOH. Data collection was performed on a Rigaku AFC5R diffractometer, using Ni foil filtered Cu$K\alpha$ radiation. The crystal remained stable at room temperature during the X-ray data collection. The structure was solved by direct methods using SIR92 and expanded using Fourier techniques. All non-hydrogen atoms were given anisotropic thermal parameters and hydrogen atoms included in calculated positions given isotropic thermal parameters. The final cycle of full-matrix least-squares refinement of tripeptide **7** gave a conventional R factor of 0.060 (R_w=0.060) based on 3895 ($I>2.0\sigma(I)$) reflections, and the largest peak and hole in the final difference Fourier map were 0.33 and -0.40 e Å^{-3}. All calculations were performed using the teXsan[13] crystallographic package of Molecular Structure Corporation.

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11) The 3_{11}-helical structure means the hydrogen bond forming an eleven-membered ring and three amino acid residues per one turn.
12) The additional effects of the strong hydrogen-bonding acceptor solvent DMSO or the paramagnetic free radical 2,2,6,6-tetramethyl-1-piperidyloxyl (TEMPO) were measured in the ^{1}H-NMR spectrum of **7**. The measurement suggests that two NH protons are solvent-exposed, but shows no evidence for 3_{11}-turn conformation in $CDCl_3$ solution.
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