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Helical-Screw Directions of Diastereoisomeric Cyclic α-Amino Acid Oligomers

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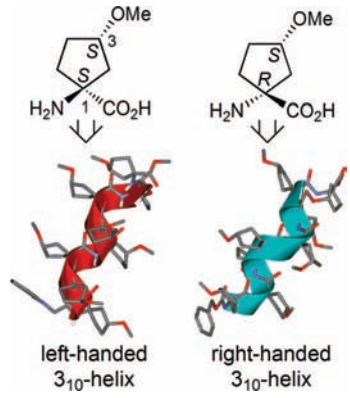
ABSTRACT



Two series of homooligomers composed of diastereoisomeric cyclic α-amino acids having two chiral centers at the α-carbon and the side chain were synthesized, and their preferred secondary structures were studied in solution and in the crystal state. The oligomers are a new class of helical-foldamers possessing two kinds of chiral centers on the helical backbone and at the lateral surface of the helix.

Right-handed α-helical-screw structures in proteins are believed to result from the L-(*S*)-chiral α-carbon atoms on the peptide backbone.[1] Recently, Toniolo's group and we independently reported that the helical-screw sense of peptide-oligomers can be controlled without a chiral center on the peptide backbone, but by chiral centers at the side chain.[2] However, so far, little attention has been paid to how both chiral centers on the peptide backbone and at the side chain influence the secondary structures of their oligomers.[3] Herein, we designed two diastereoisomeric cyclic amino

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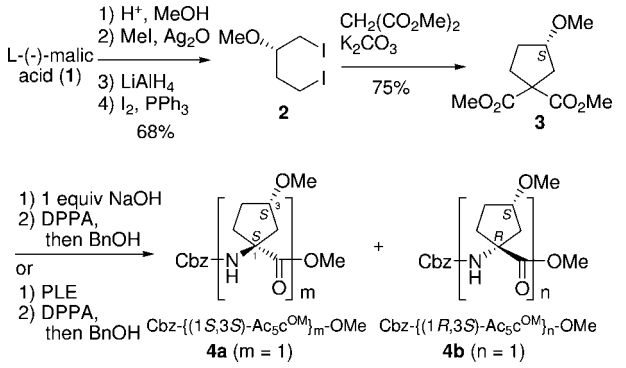
acids,[4] (1*S*,3*S*)- and (1*R*,3*S*)-1-amino-3-(methoxy)cyclopentanecarboxylic acids (Ac_5c^{OM}), constructed their homooligomers having chiral centers both on the peptide-backbone and at the side chain, and revealed their unique helical structures with high resolution analyses.

Two cyclic amino acids (1*S*,3*S*)-Ac_5c^{OM} and (1*R*,3*S*)-Ac_5c^{OM} were synthesized starting from L-(−)-malic acid **1** (Scheme 1). After esterification of **1**, the secondary alcohol

Scheme 1. Synthesis of (1*S*,3*S*)- and (1*R*,3*S*)-Ac_5c^{OM}



was converted to a methyl ether. Then, reduction of diester followed by iodination of alcohol gave a diiodide **2**. Dialkylation of dimethyl malonate with **2** afforded a cyclopentane diester **3**. Monohydrolysis of **3** with an alkaline solution, followed by Curtius rearrangement with diphenylphosphoryl azide (DPPA), produced two separable diastereoisomers (1*S*,3*S*)-Ac_5c^{OM} (**4a**) and (1*R*,3*S*)-Ac_5c^{OM} (**4b**) in a ratio of 3:1 in 85% yield.[5] Meanwhile, hydrolysis of **3** with pig liver esterase (PLE) followed by Curtius rearrangement could change the diastereoselectiviy (**4a**:**4b** = 1:2; 84% yield). The stereochemistry of products was unambiguously assigned by the X-ray crystallographic analyses of their oligomers.[6]

Oligomers Cbz-{(1*S*,3*S*)-Ac_5c^{OM}}$_m$-OMe {m = 2 (**5a**), 4 (**7a**), 6 (**8a**), 8 (**9a**), 10 (**10a**)} and Cbz-{(1*R*,3*S*)-Ac_5c^{OM}}$_n$-OMe {n = 2 (**5b**), 3 (**6b**), 4 (**7b**), 6 (**8b**), 8 (**9b**), 10 (**10b**)} were generally prepared by the coupling between N-terminal-free oligomers and N-protected dipeptide acid via solution-phase methods. It should be noted that elongation of N-terminal-free (1*R*,3*S*)-Ac_5c^{OM} dimer to a tetramer **7b** did not work well because diketopiperazine was formed as a byproduct. Thus, the (1*R*,3*S*)-tetramer was prepared via a trimer **6b**, which was derived from an N-terminal-free amino acid and the dipeptide acid.[6]

The FT-IR absorption spectra of both (1*S*,3*S*)- and (1*R*,3*S*)-Ac_5c^{OM} oligomers in $CDCl_3$ solution showed weak bands in the region 3420−3430 cm^{-1} [free (solvated) peptide NH groups] and strong bands at 3320−3380 cm^{-1} (intramolecularly H-bonded peptide NH groups). The latter bands observed at 3380 cm^{-1} in **5a** and at 3376 cm^{-1} in **5b** shift to lower wavenumbers (3320 cm^{-1} in **10a** and 3320 cm^{-1} in **10b**), respectively, and the relative intensities increase with elongation of the peptide length. These IR spectra are very similar to those of helical $Ac_{(n)}c$ oligomers.[7]

In the ROESY ^{1}H NMR spectra, the hexamers **8a** and **8b** showed a complete series of sequential d_{NN} cross-peaks of NOEs from the N-terminal NH(1) to the C-terminal NH(6), respectively.[6] These correlations are characteristic for the helical structure, albeit that those of longer oligomers only gave a partial series of sequential d_{NN} cross-peaks. Addition of DMSO or the free-radical TEMPO in the ^{1}H NMR spectroscopy indicated that the two NH signals [NH(1) and NH(2)] at the N-terminus of (1*R*,3*S*)-oligomers **8b** and **9b** are sensitive (solvent-exposed NH group), respectively, suggesting that the two NH groups are not intramolecularly H-bonded, and formation of a helical structure.[2,6,7] The experiments of (1*S*,3*S*)-oligomers **8a** and **9a** did not give clear results because the relevant NH peaks overlapped.[6]

The CD spectra of tetramers **7** and hexamers **8** in 2,2,2-trifluoroethanol (TFE) solution, both (1*S*,3*S*)- and (1*R*,3*S*)-Ac_5c^{OM}, did not show characteristic maxima (208 and 222 nm) for the helical structure. These spectra may suggest the presence of both right-handed (*P*) and left-handed (*M*) helices or disordered structures. Elongation of oligomer length changed the shapes of CD spectra, and positive maxima at 208 and 222 nm were observed in the (1*S*,3*S*)-octamer **9a** and decamer **10a** while negative maxima were seen in the (1*R*,3*S*)-**9b** and **10b**. These CD spectra suggest that the dominant conformation of (1*S*,3*S*)-**9a** and **10a** is a left-handed (*M*) helix and that of (1*R*,3*S*)-**9b** and **10b** is a right-handed (*P*) helix. The CD spectra of (1*S*,3*S*)- and (1*R*,3*S*)-oligomers showed a pseudosymmetric shape, strongly indicating that the CD curves are the result of approximately enantiomeric global chain helicity (Figure 1).

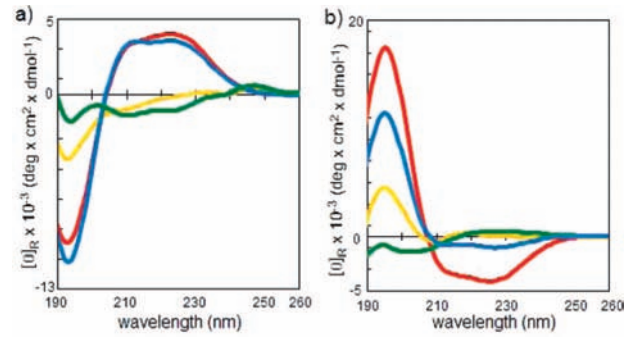


Figure 1. CD spectra of (1*S*,3*S*)- and (1*R*,3*S*)-oligomers in TFE solution (100 μM). (a) **7**−**10a**: Cbz-{(1*S*,3*S*)-Ac_5c^{OM}}$_m$-OMe (m = 4, 6, 8, 10). (b) **7**−**10b**: Cbz-{(1*R*,3*S*)-Ac_5c^{OM}}$_n$-OMe (n = 4, 6, 8, 10). Tetramer **7** (green), hexamer **8** (yellow), octamer **9** (blue), and decamer **10** (red).

The X-ray analysis of (1*S*,3*S*)-Ac_5c^{OM} hexamer **8a** having 12 chiral centers showed both diastereomeric right-handed

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(6) See the Supporting Information.

(*P*) and left-handed (*M*) 3_{10}-helices (Figure 2). In contrast, (1*S*,3*S*)-octamer **9a** crystallized exclusively to left-handed

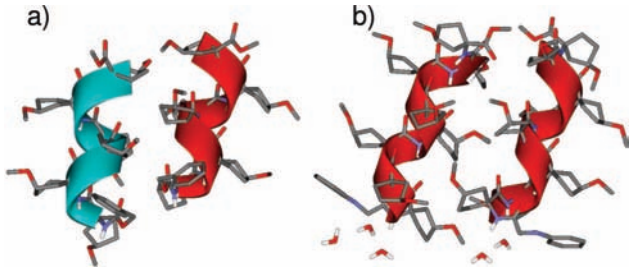

Figure 2. X-ray crystallographic analysis of Cbz-{(1*S*,3*S*)-Ac_5c^{OM}}$_m$-OMe {(a) **8a**: $m = 6$, (b) **9a**: $m = 8$}. Red: left-handedness (*M*), blue: right-handedness (*P*).

(*M*) 3_{10}-helices, while in the asymmetric unit there were two crystallographically independent (*M*) 3_{10}-helical conformers. The diastereomeric (1*R*,3*S*)-Ac_5c^{OM} hexamer **8b** showed two crystallographically independent right-handed (*P*) 3_{10}-helices. The (1*R*,3*S*)-octamer **9b** also showed two conformers, both (*P*) 3_{10}-helices but in the one conformer the signs of ϕ, ψ torsion angles at the C-terminal residue were opposite. There, six consecutive intramolecular H-bonds of the $i \leftarrow i+3$ type ($i = 0 \sim 5$) were found, respectively.[6,8]

In the crystal state, the (1*S*,3*S*)-hexamer **8a** having 12 chiral centers at the α-carbon and the side chain assumed both (*P*) and (*M*) 3_{10}-helices,[2b] while the (1*R*,3*S*)-hexamer **8b** formed only (*P*) helices, probably influenced by the crystal packing force. By the elongation of peptide length, i.e., by the increase of chiral centers, both (1*S*,3*S*)- and (1*R*,3*S*)-oligomers were controlled to form one-handed helical-screw structures in solution and in the crystal state; i.e., the (1*S*,3*S*)-octamer **9a** formed (*M*) helices and the (1*R*,3*S*)-octamer **9b** formed (*P*) helices. Molecular mechanics/ab initio (RHF/3-21G*) calculations of (1*S*,3*S*)-**9a** produced a (*M*) 3_{10}-helix as a global minimum-energy (GME) conformation, and those of (1*R*,3*S*)-**9b** gave a (*P*) 3_{10}-helix as a GME conformation.[6]

At first, we considered each effect of the α-carbon and the side-chain chiral centers or match/mismatch of chiral centers on one-handed helical-screw direction. However, the

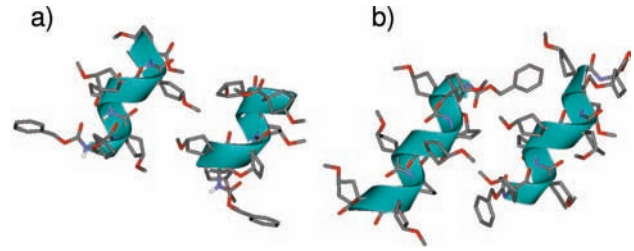

Figure 3. X-ray crystallographic analysis of Cbz-{(1*R*,3*S*)-Ac_5c^{OM}}$_n$-OMe [(a) **8b**: $n = 6$, (b) **9b**: $m = 8$].

Ac_5c^{OM} possess a unique chiral structure; i.e., transfer of the MeO-substituent on the γ-positions of cyclopentane in (1*S*,3*S*)-**4a** results in formation of enantiomer (1*R*,3*R*) or diastereomer (1*R*,3*S*) because the chirality of the α-carbon (C1) is changed (Figure 4). Thus, the helical-screw structures

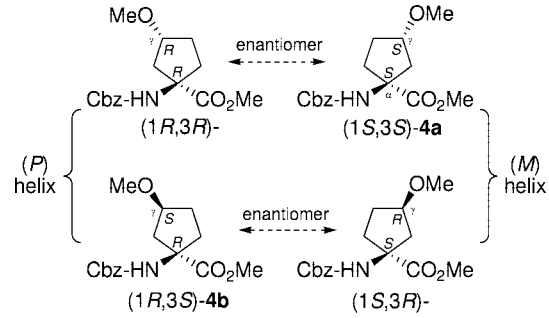

Figure 4. Unique chiral structure of Ac_5c^{OM} and helical-screw direction of their oligomers.

might be controlled by the whole chiral cyclopentane amino acid structure.

In summary, we synthesized two series of the diastereomeric Ac_5c^{OM} oligomers that are a new class of helical-foldamers possessing two kinds of chiral centers on the helical backbone and at the lateral surface of the helix[9] and revealed their preferred helical conformations in solution and in the crystal state. These results might be useful for design of foldamer catalysts and lead compounds, which are currently under investigation in our group.

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Supporting Information Available: Experimental section, spectroscopic data of new compounds, crystallographic details (CIF), and molecular calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) In some oligomers, inversions of signs or distortions of ϕ, ψ torsion angles at the C-terminal residue are observed. See the Supporting Information.

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