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Induction of a Heterochiral Helix through the Covalent Chiral Domino Effect Originating in the "Schellman Motif"

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Helical structure originally promotes one-handed sense through chiral stimuli that are covalently or noncovalently incorporated there, even if the chiral/achiral ratio or enantiomeric bias is considerably small.[1] This chiral amplification readily creates homochiral nature in protein helices, which definitely choose a right-handed sense synchronized with the asymmetric conformation of most L-residues.[2] Despite the strong preference for right-handedness, a heterochiral nature is found in protein helices. The helix C-terminus (usually Gly) often favors a left-handed helical conformation, defined as the "Schellman motif".[3] This motif thus is regarded as a *local* heterochiral structure.

We report the formation of a heterochiral helix by increasing the chain length of single chirality, without using any L/D-sequences.[4,5] Peptides composed of L-sequences at the N-terminal side and the following achiral sequence are adopted here. A propensity for a left-handed helix sense in the achiral segment becomes more pronounced against increasing content of the L-residue favoring a right-handed sense. When the L-sequence reaches a sufficient length, the helical sense tends to be switched around the boundary of the chiral/achiral sequence. We propose a nucleation model of a heterochiral helix through the covalent chiral domino effect[6] derived from the Schellman motif[3] (Figure 1).[7]

We have demonstrated these issues with a series of chiral/achiral block-type peptides (**N1**[8]−**N5** and **NP**). The L-Leu sequence with a sufficient length will form a right-handed helix.[9] The achiral part is based on α-aminoisobutyric acid (Aib) and (*Z*)-α,β-dehydrophenylalanine (Δ^ZPhe) residues to form the optically inactive helix.[6e−g,10] Absorption band of the latter residue, free from those of usual solvents or peptide bonds, enables us to identify helix sense induced in the achiral segment.[4b,6d−g]

Boc-L-X*-(Aib-Δ^ZPhe)$_4$-Aib-OMe
(Boc, *t*-butoxycarbonyl; OMe, methoxy)
L-X* = Leu (**N1**),[8] Leu$_2$ (**N2**), Leu$_3$ (**N3**), Leu$_4$ (**N4**), and Leu$_5$ (**N5**).
(L-Leu)$_n$-(Aib-Δ^ZPhe)$_4$-Aib-OMe $n \sim 24$ (**NP**).

IR and NMR studies on peptides **N1**−**N5** suggested the presence of 3_{10}-helical conformation.[11] Amide I absorption of **NP** implied an α-helical conformation in the Leu segment.[11]

CD spectra of these peptides were acquired in several solvents. They mostly showed a split CD pattern around 280 nm based on the achiral Δ^ZPhe residue (Figure 2 and ref 11). The split profile has been interpreted as the helix sense of $-(\Delta^Z\text{Phe-X})_m-$ in a 3_{10}-helix.[6f] A split sign with positive signals (at longer wavelength) is assigned to a left-handed helix.[6f] In addition, the CD amplitude implies efficiency of chiral induction in the achiral sequence.

Figure 2A displays CD spectra of peptides **N1**−**NP** at room temperature. Peptide **N1** favored a left-handed helix in solution as reported previously.[6g,8] In contrast, the N-terminal homochiral doublets (**N2**) induced a right-handed helix, suggesting the reasonable tendency to promote a right-handed helicity by increasing the

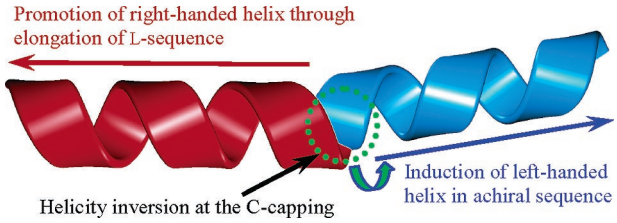

Figure 1. Induction of a heterochiral helix through the Schellman motif.[3]

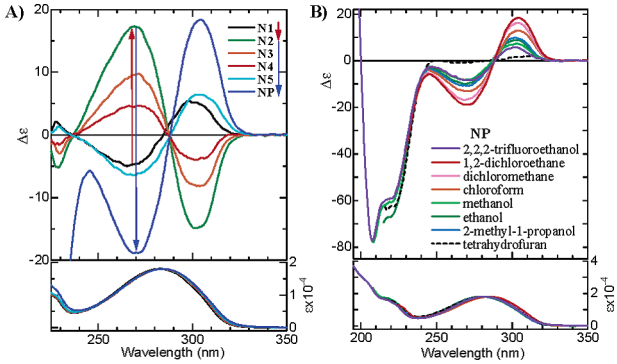

Figure 2. CD (upper) and absorption spectra of (A) peptides **N1**−**NP** in 1,2-dichloroethane, and (B) peptide **NP** in several solvents; $\Delta\epsilon$ and ϵ are expressed in terms of Δ^ZPhe residue concentration.

L-residue number. Peptides **N3** and **N4** also adopted a right-handed helix. However, the CD intensity around 280 nm decreased with the chiral length, indicating that the right-handed helicity of the achiral sequence becomes less prominent in elongation of the L-Leu length. Intriguingly, peptides **N5** and **NP** having longer L-sequences produced a split pattern opposite to the case of **N2**−**N4**. Obviously, the left-handed helicity appears in the achiral segment of **N5** and **NP**. In Figure 2A, an isodichroic point[12] among **N2**−**NP** seems to appear at ca. 288 nm, suggesting varying ratios of two common conformers in the achiral sequence. Increasing the L-sequence length shifts dynamic equilibrium of the two helical populations toward a left-handed helicity.

In 2,2,2-trifluoroethanol (Figure 2B), peptide **NP** yielded a pattern at the amide region, typically assigned to a right-handed α-helix,[13] in which the L-Leu sequence reasonably adopts a right-handed helix. In contrast, a split pattern for the left-handed helicity was found at the Δ^ZPhe chromophores of the achiral segment. Consequently, the helical inversion occurs around the chiral/achiral boundary on a single chain of peptide **NP** as proposed in Figure 1.

Helix sense induction through the covalent domino effect has been widely proposed in other unique molecules, in which the chiral sign of a chain-terminal moiety plays a key role.[6,14] In contrast, the present induction of helicity in the achiral segment varies with the preceding homochiral length, whereas the L-Leu residue is commonly located at the chiral/achiral boundary of **N1**−**NP**. This

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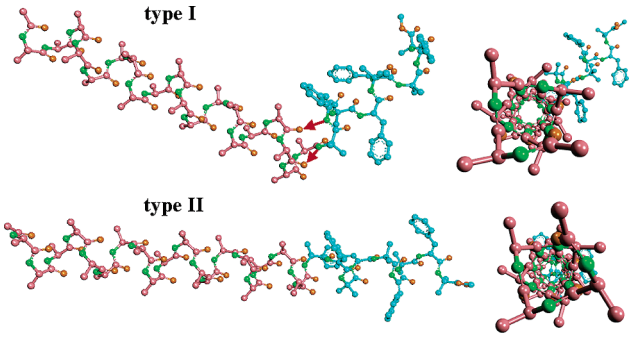

Figure 3. Heterochiral helix (type I) and homochiral helix (type II) simulated in acetyl-L-Ala$_{20}$-(Aib-Δ^ZPhe)$_4$-Aib-OMe.[18] The chiral segment (light-red carbon) adopts an essentially right-handed α-helix. In type I, the achiral segment (blue carbon) takes a left-handed 3_{10}-helix, in which the red arrow indicates 6 → 1 and 5 → 2 hydrogen bonds for the Schellman motif.[3,4c,5a,7a]

chiral length effect originates from not only chirality of the boundary L-Leu but also conformational asymmetry of the preceding L-sequence. Thus, left-handed helicity in **NP** is induced through the C-terminal inversion of the right-handed α-helix.

CD data in other solvents are summarized in ref 11. Dichloromethane and chloroform showed a similar tendency: elongation of the L-sequence weakens the preference for a right-handed helicity, commonly inducing a left-handed helicity in **NP**. Acetonitrile or alcohols led to induction of left-handed helicity in **N1**−**N5**. **NP** also underwent induction of the left-handed helix in methanol, ethanol, and 2-methyl-1-propanol, while the split pattern was somewhat distorted in tetrahydrofuran. In the three alcohols, left-handed helical tendency in **N4**, **N5**, and **NP** seems to be promoted with the L-sequence length. In most solvents (Figure 2B), the achiral sequence of **NP** prefers a left-handed helicity. This solvent-insensitive formation of a heterochiral helix might be consistent with the view that conformational inversion at the C-terminal Gly of an α-helix is based on stereochemical origin rather than solvent effect.[3d]

Such a heterochiral helical structure was simulated by semiempirical MO (AM1)[11,15] computation. A stable structure found (type I, Figure 3) involves 6 → 1 and 5 → 2 hydrogen bonds for the Schellman motif at the boundary, favoring a bending form.[3,4c,5a,7a] In contrast, the homochiral helix (type II, Figure 3) preferred a more straight form.[16] Here the type I was predicted to be slightly more preferential in solution.[17] Thus the heterochiral helix might be stabilized in solution through local inversion in helix sense and molecular shape advantageous to solvent effects.[17]

Consequently, we have demonstrated that a heterochiral helix can be induced through the chiral switch generated by the L-sequence length. In other words, the local inversion derived from the Schellman motif is proven to nucleate the helix sense in the following achiral segment to function as the domino effect, when the segment is composed of strong helical inducers. These findings not only provide novel insights into peptide design of a heterochiral helix but also support an elementary model for homochiral−heterochiral origins in the evolution of hierarchical structures from primitive chiral/achiral sequences.[5]

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Supporting Information Available: Theoretical energy calculation, characterization, spectroscopic data, and discussion. This material is available free of charge via the Internet at http://pubs.acs.org.

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