

# 12/10-Helical $\beta$ -Peptide with Dynamic Folding Propensity: Coexistence of Right- and Left-Handed Helices in an Enantiomeric Foldamer

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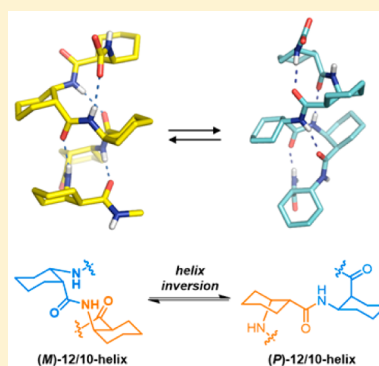
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**S** Supporting Information

**ABSTRACT:** We present the first examples of atomic-resolution crystal data for the  $\beta$ -peptide 12/10-helix from oligomers of *cis*-2-aminocyclohexane carboxylic acid (*cis*-ACHC) with alternating chirality. The local conformations of two enantiomeric *cis*-ACHC dimer units suggested that a chiral  $\beta$ -peptide may adopt both right-handed and left-handed helical conformations in solution. To probe the conformational behavior of 12/10-helical  $\beta$ -peptides, the two reference helices with a single handedness were synthesized with a more rigidified *cis*-ACHC derivative. Comparison with these reference helices at low temperature revealed that a chiral *cis*-ACHC oligomer with alternating chirality indeed displays 12/10-helical conformations with both handedness that equilibrate rapidly in solution. This is a very rare example of chiral oligomers with helix inversion ability. The 12/10-helical backbone should be a valuable addition to potential scaffolds for applications involving helices with dynamic folding propensity.



## INTRODUCTION

Helical structures of peptidic foldamers have been explored extensively for last two decades since Gellman and Seebach discovered unnatural  $\beta$ -peptide helices independently.<sup>1</sup> A helical structure is chiral with right or left handedness, which is usually dependent on the stereochemistry of building blocks. Conventional helices in proteins and most of peptidic foldamers are chiral with either handedness because of enantiomerically pure amino acid residues.<sup>2</sup> In contrast, helical foldamers that consist of achiral building blocks display both right- and left-handed conformations, which may interconvert in solution. Controlling the screw-sense preference of these helical foldamers with dynamic folding propensity recently has drawn much interest for potential applications such as molecular machines, molecular recognition, and asymmetric catalysis.<sup>3</sup> For example, oligomers of achiral  $\alpha$ -aminoisobutyric acid (Aib) strongly promote  $3_{10}$ -helical conformations.<sup>4</sup> Clayden and co-workers have recently reported several applications of Aib-rich oligomers by controlling the screw sense of the  $3_{10}$ -helix.<sup>5</sup> Inai and co-workers have reported that achiral peptides with Aib and  $\alpha,\beta$ -dehydrophenylalanine ( $\Delta^2$ Phe) residues adopt right- or left-handed  $3_{10}$ -helices by the interaction with chiral molecules.<sup>6</sup> Poly- $\beta$ -phenylalkyl-L-aspartates are rare examples of chiral peptides that switch helical handedness at different temperatures.<sup>7</sup> However, it is still hard to discover a chiral peptide backbone with reversible handedness among both natural and unnatural peptide helices.

A number of heterochiral  $\alpha$ -peptides that consist of alternating D- and L- $\alpha$ -amino acid residues are known to

display  $\beta$ -helical conformations with either handedness, which is dependent on various factors such as side chain groups, solvent polarity, hydrogen bonding patterns, and backbone constraints.<sup>8–10</sup> Lorenzi and co-workers have reported the crystal structures of two D,L-alternating peptide octamers, Boc-(L-Val-D-Val)<sub>4</sub>-OMe and Boc-(L-Phe-D-Phe)<sub>4</sub>-OMe, displaying double-stranded, antiparallel  $\beta$ -helical conformations with left and right handedness, respectively.<sup>8</sup> NMR analysis of related D,L-alternating peptides suggested that multiple forms of  $\beta$ -helices may exist in solution, although the major conformers are consistent with those in the crystal state.<sup>9</sup> In contrast, Clark and co-workers have reported that a cyclic analogue with two  $\beta$ -turn motifs and two alternating D,L-oligovaline fragments displays a single type of double-stranded, antiparallel  $\beta$ -helical conformations with right handedness.<sup>10</sup>

The  $\beta$ -peptide 12/10-helix (or 10/12-helix) is a unique helical structure, in which two types of hydrogen bonds with opposite directionality alternate along the helical axis.<sup>11,12</sup> Unlike other unidirectional  $\beta$ -peptide helices, the 12/10-helix arises from a dimer unit that may consist of several combinations of  $\beta$ -amino acid residues. In particular, a number of dimer units that contain both enantiomers of a  $\beta$ -amino acid are known to promote stable 12/10-helical folding.<sup>12</sup> These 12/10-helical  $\beta$ -peptides with alternating chirality can be regarded as homologues of D,L-alternating  $\alpha$ -peptides and could serve as chiral peptide backbones with dynamic folding propensity, on

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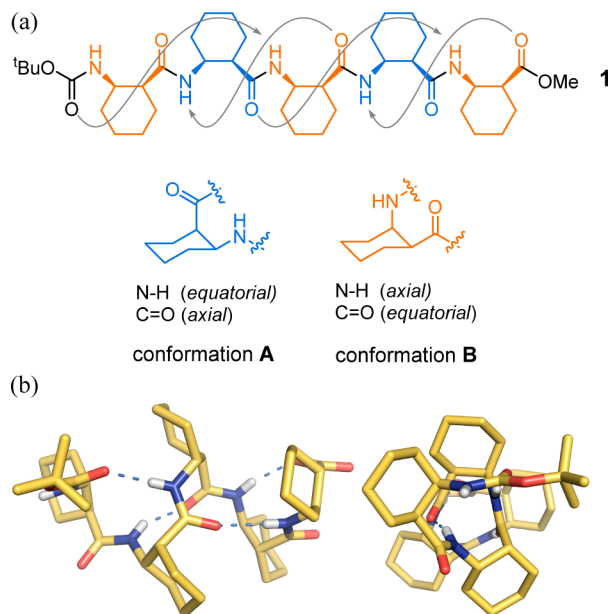
condition that the corresponding “pseudosymmetric” dimer units behave like achiral building blocks.

Although the 12/10-helix is among the most stable  $\beta$ -peptide helices and accessible from several combinations of  $\beta$ -residues,<sup>13</sup> no atomic-resolution structure for the  $\beta$ -peptide 12/10-helix has been known to date. The applications of a 12/10-helical backbone are extremely rare compared with those of other  $\beta$ -peptide helices.<sup>14</sup> The crystal structures for the 12/10-helix would provide the corresponding helical parameters, which should enable the precise disposition of functional groups along the helical axis for diverse applications.

Here we present the first examples of the crystal structures for the  $\beta$ -peptide 12/10-helix. More importantly, we report that a chiral 12/10-helical  $\beta$ -peptide shows dynamic folding propensity to adopt both right- and left-handed helical conformations in solution.

## RESULTS AND DISCUSSION

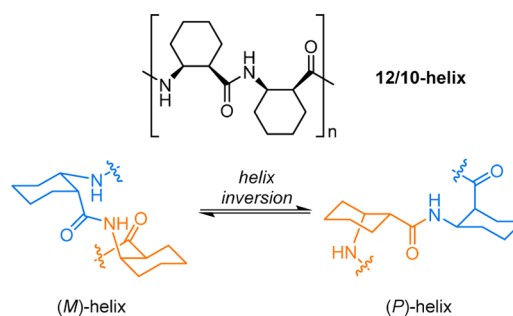
**Crystal Structure of a 12/10-Helical *cis*-ACHC Oligomer with Alternating Chirality.** *cis*-2-Aminocyclohexane carboxylic acid (*cis*-ACHC)<sup>15</sup> is a ring-constrained  $\beta$ -amino acid that promotes mixed helices in different foldamer backbones. Martinek and co-workers have reported that oligomers of *cis*-ACHC with alternating chirality adopt 12/10-helical conformations in solution.<sup>12c</sup> We have shown that *cis*-ACHC residues in  $\alpha/\beta$ -peptides promote homologous 11/9-helices both in solution and in crystal state.<sup>16</sup> X-ray quality crystals for the 11/9-helix have been grown by a racemic crystallization method.<sup>17</sup> In light of these, we chose oligomers of *cis*-ACHC with alternating chirality for growing crystals of 12/10-helical structures and prepared  $\beta$ -peptide pentamer **1** and its enantiomer (*ent*-**1**) (Figure 1a). X-ray quality crystals for the 12/10-helix were successfully grown from a racemic mixture of **1** and *ent*-**1** (*rac*-**1**) in chloroform and *n*-pentane. The crystal structure of *rac*-**1** has a  $P\bar{1}$  space group and displays two symmetry-independent conformations, both of which are



**Figure 1.** Crystal structure of **1**: (a) local conformations of *cis*-ACHC residue; (b) side view (left) and top view (right). Arrows and dashed lines indicate hydrogen bonds. Only one symmetry-independent conformation is shown.

almost identical and fully folded 12/10-helices (Figure 1b). Pentamers **1** and *ent*-**1** adopt left-handed and right-handed helices, respectively. Two enantiomeric *cis*-ACHC residues adopt different local conformations. In the left-handed 12/10-helical structure of **1**, (1*R*,2*S*)-ACHC adopts the equatorial NH group and the axial CO group (conformation A), while (1*S*,2*R*)-ACHC adopts the axial NH group and the equatorial CO group (conformation B). It is noteworthy that the  $\alpha/\beta$ -peptide 11/9-helix requires only the conformation A,<sup>18</sup> but the  $\beta$ -peptide 12/10-helix requires both local conformations of *cis*-ACHC. The two sets of average backbone torsion angles for two enantiomeric *cis*-ACHC residues were derived from **1**:  $\phi = 103^\circ$ ,  $\theta = -52^\circ$ ,  $\psi = -87^\circ$  for (1*S*,2*R*)-ACHCs (ACHC1, ACHC3, and ACHC5);  $\phi = -110^\circ$ ,  $\theta = -58^\circ$ ,  $\psi = 98^\circ$  for (1*R*,2*S*)-ACHCs (ACHC2 and ACHC4). These backbone torsion angles are consistent with those calculated for the left-handed 12/10-helix by quantum mechanical studies.<sup>13</sup>

**Design and Characterization of a 12/10-Helical *cis*-ACHC Oligomer with Dynamic Folding Propensity.** Two enantiomeric peptides **1** and *ent*-**1** share a dimer fragment of (1*R*,2*S*)-ACHC and (1*S*,2*R*)-ACHC. However, the dimer fragment adopts different local conformations in the crystal structures of **1** and *ent*-**1** (Figure 2). The two local

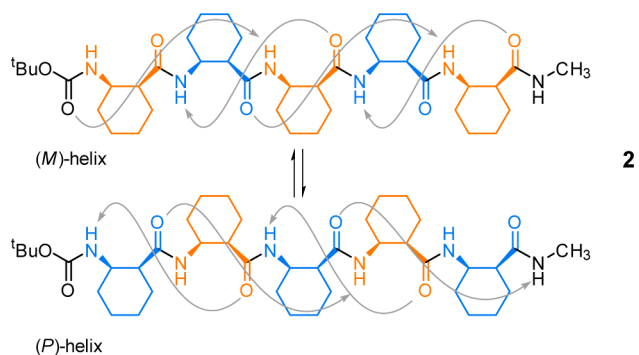


**Figure 2.** Helix inversion between  $\beta$ -peptide 12/10-helices with opposite handedness.

conformations are interconvertible by ring flipping of the cyclohexane ring moieties. These results led us to hypothesize that an oligomer of *cis*-ACHC with alternating chirality could adopt both right- and left-handed 12/10-helical conformations in solution. Helix inversion may be achieved by cooperative ring flipping of the cyclohexane moieties in both enantiomeric *cis*-ACHC residues.

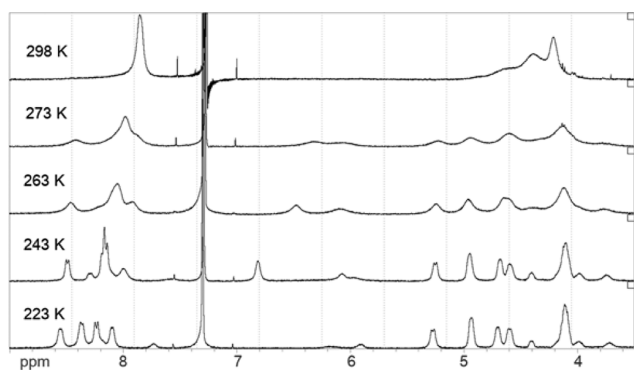
The preference for a left-handed 12/10-helix in **1** can be elucidated in terms of an additional intramolecular hydrogen bond compared with those for a right-handed 12/10-helix. We therefore designed pentamer **2** with the C-terminal methyl amide group, so that both right- and left-handed 12/10-helices in **2** involve the same sets of 12- and 10-membered hydrogen bonds (Figure 3).

X-ray quality crystals of **2** were grown as a single enantiomer unlike racemic crystals of *rac*-**1**. The crystal structure of **2**, however, displayed a left-handed 12/10-helical conformation very similar to that of **1** (see Figure S8 in the Supporting Information). The circular dichroism spectra of **1** and **2** showed a negative Cotton effect at 205 nm, which is consistent with left-handed 12/10-helical conformations. Interestingly, most of the NH peaks in the H NMR spectrum of **2** were very poorly resolved and impossible to be assigned, suggesting that these NH groups may be in rapid equilibrium between multiple



**Figure 3.** Two 12/10-helices of **2** with opposite handedness. Curved arrows indicate intramolecular hydrogen bonds.

conformations in solution. The variable temperature H NMR spectra of **2** supported this hypothesis (Figure 4).

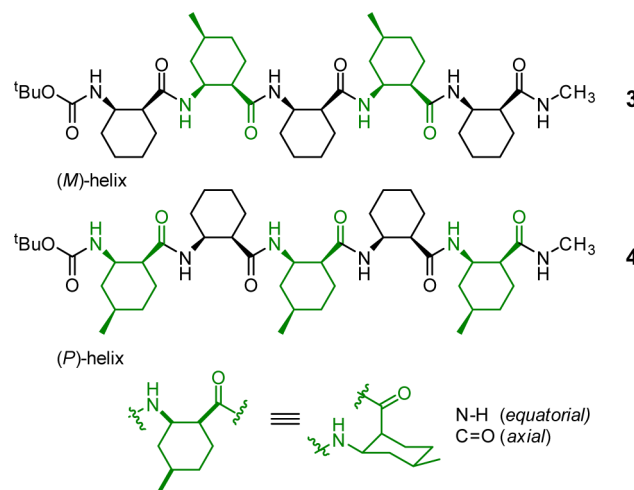


**Figure 4.** Variable temperature H NMR spectra of **2**.

As the temperature decreased gradually, the NH peaks in the H NMR spectrum of **2** started dispersing as narrower peaks and an additional set of small peaks emerged. The H NMR spectrum at 223 K showed two sets of chemical shifts by the ratio of 4:1, suggesting that two distinct conformations of **2** equilibrate in solution. These results are similar to those observed previously by Martinek and co-workers for an analogous *cis*-ACHC hexamer with alternating chirality, of which H NMR spectra showed an additional set of small signals at 245 K.<sup>12c</sup> They have proposed an 18/20-helical conformation as the minor conformer based on DFT calculations. In contrast, we speculated that the minor conformer is more likely a right-handed 12/10-helical conformation based on the interconversion of two opposite-handed helices as proposed in Figures 2 and 3.

**Design and Characterization of 12/10-Helical  $\beta$ -Peptides with a Single Handedness Containing *cis,cis*-mACHC.** To characterize the minor conformer of **2** in solution, we designed and synthesized two reference peptides that would exclusively adopt a right-handed (*P*-helix) or left-handed (*M*-helix) 12/10-helical conformation. In light of the assumption that helix inversion may occur via ring flipping of the cyclohexane moiety in each residue, we reasoned that helical handedness can be fixed by locking the cyclohexane moieties of *cis*-ACHCs to adopt the conformation A or the conformation B exclusively. We have recently reported a more rigidified *cis*-ACHC derivative, *cis*-2-amino-*cis*-4-methylcyclohexane carboxylic acid (*cis,cis*-mACHC), which adopts the conformation A predominantly.<sup>18</sup> Incorporation of *cis,cis*-mACHC into a 12/10-

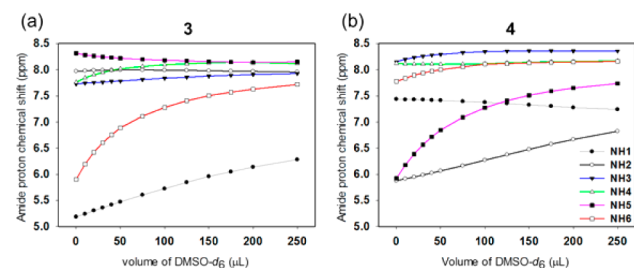
helical *cis*-ACHC oligomer would inhibit cooperative ring flipping of the cyclohexane moieties. Figure 5 shows two



**Figure 5.** Helical  $\beta$ -peptides with a single handedness: **3** for (*M*)-helix and **4** for (*P*)-helix.

reference peptides **3** and **4** designed for left-handed and right-handed 12/10-helices, respectively. *cis,cis*-mACHC residues in **3** and **4** adopt the conformation A and would force adjacent *cis*-ACHC residues to adopt the conformation B for 12/10-helical folding. The handedness of each reference peptide is thus dependent on the stereochemistry of *cis,cis*-mACHC residues.

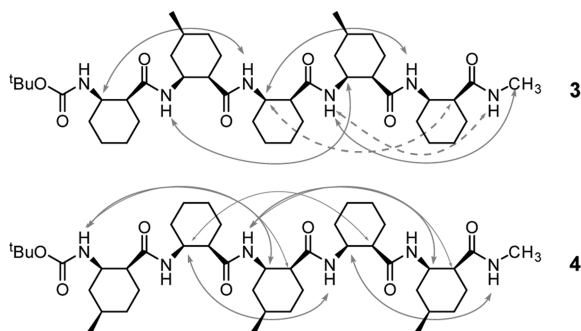
The H NMR spectra of **3** and **4** at room temperature showed well-resolved amide proton peaks, which allowed us to perform the solvent titration study with DMSO-*d*<sub>6</sub> and two-dimensional NMR analysis (TOCSY and ROESY). The dependence of  $\delta$ NHs for **3** and **4** in CDCl<sub>3</sub> by the addition of DMSO-*d*<sub>6</sub> was fully consistent with intramolecular hydrogen bonding patterns for left- and right-handed 12/10-helices, respectively (Figure 6).



**Figure 6.** DMSO-*d*<sub>6</sub> dependence of  $\delta$ NHs in CDCl<sub>3</sub> solution: (a) **3** and (b) **4**.

Figure 3 indicates that a 12/10-helical conformation with a single handedness leaves two NH groups not involved in intramolecular hydrogen bonding: the NH1 and the NH6 in **3** (*M*-helix) and the NH2 and the NH5 in **4** (*P*-helix). The chemical shifts of these NH groups are below 6 ppm in CDCl<sub>3</sub> and were shifted downfield substantially as DMSO-*d*<sub>6</sub> was added to CDCl<sub>3</sub> solution. In contrast, the other NH groups showed small changes in chemical shifts despite addition of DMSO-*d*<sub>6</sub>.

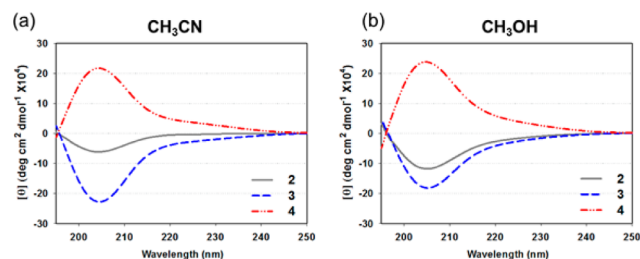
Figure 7 shows medium-range NOEs between backbone hydrogen atoms attached to nonadjacent residues in **3** and **4**. Several (*i,i*+2) NOEs are indicative of stable 12/10-helical conformations for both **3** and **4**. However, none of these



**Figure 7.** Medium-range NOEs observed for 3 and 4. Dashed arrows indicate ambiguous NOEs.

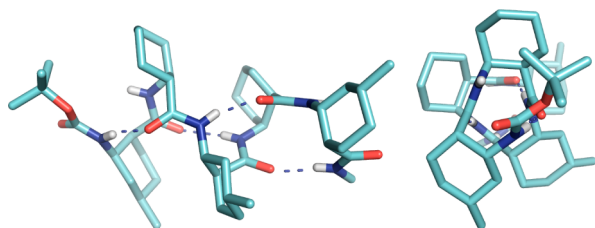
nonsequential NOEs was observed for both 3 and 4, suggesting that there is no structural overlap between the backbone conformations of 3 and 4.

The CD spectra of 3 and 4 were consistent with 12/10-helical conformations with expected handedness: a negative maximum for 3 (*M*-helix) and a positive maximum for 4 (*P*-helix) at 205 nm (Figure 8). All of these results suggested that the two reference peptides display 12/10-helical conformations with a single handedness in solution.



**Figure 8.** CD spectra of 2–4 in (a) CH<sub>3</sub>CN and (b) CH<sub>3</sub>OH.

Several crystallization attempts of 3 were not successful. *P*-helical reference peptide 4 was crystallized as an enantiomer from a chloroform/ether/*n*-pentane mixture, displaying right-handed 12/10-helical conformations (Figure 9). The intramolecular hydrogen bonds and the local conformations of *cis,cis*-mACHC and *cis*-ACHC residues in 4 are consistent with those proposed for the (*P*)-12/10-helix in Figure 3.

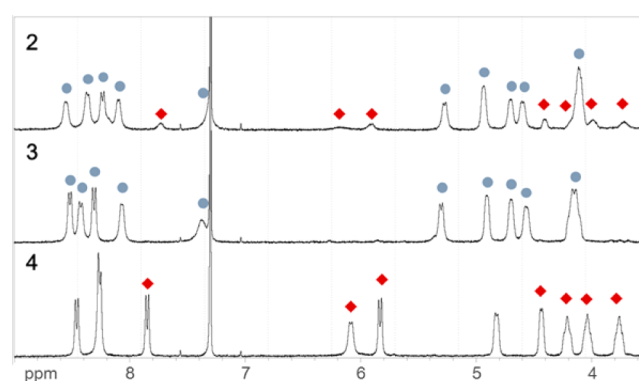


**Figure 9.** Crystal structure of 4: side view (left) and top view (right). Only one symmetry-independent conformation is shown.

The crystal structures of the 12/10-helical backbones with both handedness (*M*-helix for 2 and *P*-helix for 4) allowed us to compare the conformational behaviors of 3 and 4 in solution with those in the crystal state. All but one of the interproton distances that correspond to the medium-range NOEs were within 5 Å for the crystal structure with expected handedness and over 5 Å for that with the opposite handedness (see Figure

S3 in the Supporting Information). The NOEs for 3 were consistent with the corresponding interproton distances measured from the *M*-helical structure of 2. The NOEs for 4 were consistent with the corresponding interproton distances measured from the *P*-helical structure of 4. These results provide additional evidence for left- and right-handed 12/10-helical conformations of 3 and 4, respectively.

**Coexistence of Right- and Left-Handed 12/10-Helices in a Chiral  $\beta$ -Peptide.** The variable-temperature H NMR spectra of 3 and 4 showed only small changes in chemical shifts and little signal broadening at low temperatures. Figure 10



**Figure 10.** H NMR spectra of 2–4 at 223 K.

shows the comparison of the H NMR spectra of 2–4 at 223 K. Each of the two sets of chemical shifts for 2 matches quite well those for 3 or 4. The chemical shifts for the major conformation of 2 match those for 3 (*M*-helix), and most of the chemical shifts for the minor conformation of 2 match those for 4 (*P*-helix) except a few signals overlapped with major peaks. These results are strong evidence that chiral  $\beta$ -peptide 2 indeed adopts 12/10-helical conformations with right- and left-handedness that equilibrate in CDCl<sub>3</sub> by the ratio of 1:4.

The ratio of the two opposite-handed 12/10-helices in acetonitrile or in methanol was also derived from the CD spectra of 2–4 in Figure 8, based on the assumption that the three  $\beta$ -peptide pentamers have virtually the same extinction coefficient for UV absorption and solely adopt 12/10-helical conformations. The intensities of a negative and a positive maxima for 3 and 4 would correspond to fully folded 12/10-helical conformations with left- and right-handedness, respectively. The maximum intensity for 2 then would be regarded as a weighted average by relative population of the two opposite-handed helices.

Table 1 lists relative populations of the two 12/10-helices with opposite handedness for 2 derived from experiments and

**Table 1. Populations (%) of Two Helices with Opposite Handedness in 2**

solvent	helical ratio ( <i>M</i> : <i>P</i> )	
	experiment	DFT <sup>a</sup>
gas phase	–	98:2
CHCl <sub>3</sub>	80:20 <sup>b</sup>	81:19
CH <sub>3</sub> CN	63:37 <sup>c</sup>	63:37
CH <sub>3</sub> OH	85:15 <sup>c</sup>	64:36

<sup>a</sup>Calculated at the M06-2X/cc-pVTZ//M06-2X/6-31G(d) level of theory with the PCM solvation model. <sup>b</sup>Derived from the VT H NMR spectra. <sup>c</sup>Derived from the CD spectra.

by DFT calculations at the M06-2X/cc-pVTZ//M06-2X/6-31G(d) level of theory with the PCM solvation model using Gaussian 09<sup>19</sup> (see the Supporting Information). The uneven helical ratio is attributed in part to the terminal groups, which may cause different environments for the two helices. The results of molecular modeling study are mostly consistent with those derived from experiments. The observed helical ratios in CDCl<sub>3</sub> and in CH<sub>3</sub>CN are very similar to those estimated by DFT calculations. The (*M*)-12/10-helix was predicted to be more stable than the (*P*)-12/10-helix in the gas phase, and the helical ratio varies depending on solvent polarity. The (*M*)-18/20-helix, a possible alternative folded conformation, was found to have the relative energy higher than 9 kcal mol<sup>-1</sup> and would be negligibly populated.

#### Helical Parameters for the $\beta$ -Peptide 12/10-Helix.

Application of a helical backbone requires the corresponding structural parameters that provide spatial disposition of each residue along the helical axis. Average structural parameters of the  $\beta$ -peptide 12/10-helix were derived from the three crystal structures of **1**, **2**, and **4**: 2.6 residues per turn, 5.7 Å rise per turn (pitch), and 2.0 Å radius. These parameters are very similar to those calculated by Wu and co-workers.<sup>13b</sup> In addition, the helical parameters revealed that 12/10- and 12-helical  $\beta$ -peptide backbones are structurally very similar despite different hydrogen bonding patterns.<sup>20</sup> This relationship between the 12/10-helix and the 12-helix in  $\beta$ -peptides is analogous to the structural similarity between the 11/9-helix and the 3<sub>10</sub>-helix.<sup>16</sup>

**Characteristics of Two 12/10-Helices with Opposite Handedness.** The crystal structures of **2** and **4** clearly show that each enantiomeric *cis*-ACHC residue adopts either of the two different local conformations, the conformation A or the conformation B, depending on the handedness of the 12/10-helix as proposed in Figure 2. Two (1*R*,2*S*)-ACHC residues (ACHC2 and ACHC4) adopt the conformation A in an *M*-helical crystal structure of **2**, but adopt the conformation B in a *P*-helical crystal structure of **4**. In contrast, three (1*S*,2*R*)-ACHC residues in **2** adopt the conformation B, while isochiral (1*R*,2*S*,4*R*)-*m*ACHC residues in **4** adopt the conformation A. The conformation A has been known to be more stable than the conformation B based on a number of crystal structures containing *cis*-ACHC.<sup>15,18,21</sup> However, the relative population of two 12/10-helices in Table 1 shows the opposite trend; a more stable (*M*)-12/10-helical conformation of **2** contains two *cis*-ACHCs adopting the conformation A, while a less stable (*P*)-12/10-helical conformation contains three *cis*-ACHCs adopting the conformation A. In light of the same sets of hydrogen bonds and enantiomeric relationship between the two 12/10-helical conformations of **2**, the terminal groups are therefore more likely main factors in determining the helical ratio.

The two local conformations of *cis*-ACHC are reminiscent of the conformational behavior of a series of C-linked carbo- $\beta$ -amino acid ( $\beta$ -Caa) residues reported by Sharma and co-workers.<sup>11d,12a,e</sup> A chiral  $\beta$ -Caa residue can adopt two different local conformations that promote right- and left-handed 12/10-helices, respectively. Oligomers of a  $\beta$ -Caa with alternating chirality display right-handed 12/10-helices, while oligomers that consist of the same  $\beta$ -Caa and  $\beta$ -alanine with residue alternation display left-handed helices. These  $\beta$ -Caa-containing oligomers display 12/10-helices with a single handedness, because the  $\beta$ -Caa residue adopts only one of the two available local conformations depending on adjacent residues, as in the

case for the *cis*-ACHC residue of **3** and **4** in this study. In contrast, each enantiomeric *cis*-ACHC residue of **2** adopts both local conformations that interconvert rapidly in solution, resulting in coexistence of both right- and left-handed 12/10-helical conformations in a chiral  $\beta$ -peptide.

## CONCLUSION

We have shown that a chiral oligomer of *cis*-ACHC with alternating chirality adopts 12/10-helical conformations with both handedness that rapidly interconvert in solution. The interconversion of two opposite-handed helices in chiral  $\beta$ -peptide **2** is achieved via cooperative ring flipping of the cyclohexane moieties. Helical handedness can be locked by incorporation of more rigidly preorganized residues, such as *cis*,*cis*-*m*ACHC. The effect of terminal groups on the handedness could be utilized to develop dynamic helical backbones that can reversibly switch the handedness by interaction with diverse chemical species at each terminus. The unique conformational behavior and the crystal structures of these 12/10-helical  $\beta$ -peptides should be a valuable addition to potential scaffolds for applications of dynamic foldamer helices.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08235.

Crystallographic data (CIF)

Detailed experimental procedures and characterization data; 2D NMR data; crystallographic structure data CCDC 1486358 (*rac*-**1**), 1486359 (**2**), and 1486360 (**4**); backbone torsion angles and helical parameters; results of DFT calculations (PDF)

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### Notes

The authors declare no competing financial interest.

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