Chiral Oligoindole Foldamers Showing Anion-Induced Helical Bias

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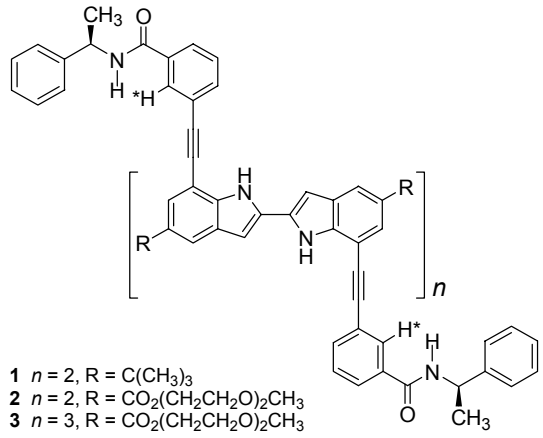
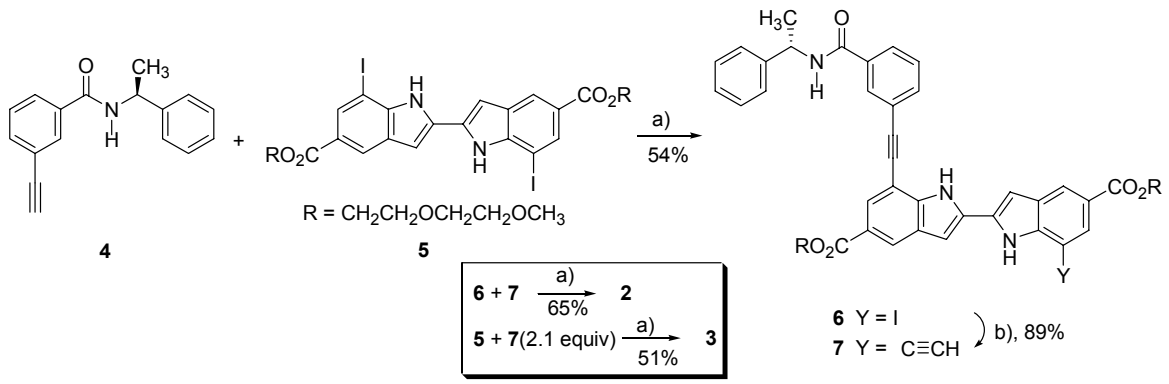
Synthetic oligomers capable of adopting helical conformations have recently attracted much attention because they can be served as artificial receptors for ions and organic molecules.[1,2] Moreover, the folding and unfolding of the oligomers may be reversibly controlled by environment, light, or chemical species, which is an essential property for functional organic materials responsive to external stimulation. Over the past decade, a variety of foldamers have been reported which fold to helical structures by conformational constraints, intramolecular hydrogen bonds, solvophobic interactions, or guest binding.[1,3] The helix is intrinsically chiral and can be either right-handed or left-handed. Biopolymers such as DNA and proteins exist in one particular type of two possible helices. For example, α -helix of proteins and double helix of DNA are right-handed while Z-DNA is left-handed. On the other hand, most of synthetic oligomers when folded give a racemic mixture of two helical isomers. In order to generate one-handed helix, two kinds of approaches have been described; noncovalent binding of chiral guests[4] and covalent attachment of chiral units to oligomers.[5]

In recent years, we described that oligoindoles were able to fold into a helical conformation in the presence of an anion.[6] The anion was entrapped in the internal cavity by forming multiple hydrogen bonds with indole NHs, which leads to the formation of left- and right-handed helices in an equal amount. In addition, we also prepared a chiral oligoindole **1** in which the chirality of phenylethylamido units was nicely transferred on the formation of the helix, thus resulting in the preferential formation of one isomer over another.[7] By modification of the side chain of *tert*-butyl groups into 2-methoxy-2-ethoxyethyl esters, we herein prepared new chiral oligoindoles **2** and **3** for the following reasons. First, as the foldamer chain grows, the bulky *tert*-butyl groups cause steric strain between turns, which make the resulting helix distorted and destabilized. This unfavorable strain for the helical folding can be greatly relieved by replacing them with sterically less-demanding, planar ester groups. Second, the electron-withdrawing ester groups are able to significantly increase the hydrogen- bonding ability of indole NHs through direct resonance. Finally, it has been known that the side chain affects not only the stability but also the orientation of the helix.[1,8]

Syntheses of **4** and **5** were prepared according to the procedures previously described.[6a,7] Sonogashira coupling reaction[9] of **4** and **5** gave compound **6** in 54% yield. Here, approximately 0.8 equivalent of **4** was used to reduce the side product resulted from both iodides of **5** substituted by **4**. Then, Pd(0)/CuI-catalyzed reaction of **6** with trimethylsilyl (TMS)-ethyne, followed by removal of the TMS group with tetra-





Scheme 1. Synthesis of Chiral Oligoindole Foldamers **2** and **3**. a) Pd(dba), CuI, PPh_3/Et_3N-THF, b)Trimethylsilyl(TMS)-ethyne, $Pd(dba)_2$, CuI, PPh_3/Et_3N-THF, then $TBAF/CH_3CO_2H$-THF

butylammonium fluoride (TBAF) in the presence of acetic acid, gave **7** in 89% yield (two steps). Finally, **6** and **7** were coupled to give tetraindole **2** (65%) and **5** and **7** (2.1 equiv) provided hexaindole **3** in 51% yield. Foldamers **2** and **3** were unambiguously characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.

The biindole unit adopts *s*-trans conformation between two indole rings to minimize dipole-dipole repulsions, thus imparting extended zig-zag conformations of oligoindoles. In the presence of an anion such as chloride, however, **2** and **3** fold into a helical conformation with four indoles per turn, in which all of the indole NHs and amide NHs are inward directed in order to simultaneously participate hydrogen bonding with the chloride ion (Figure 2a). The folding into a helical conformation was first confirmed by circular dichroism (CD) spectroscopy which has been widely used for the characterization of helical architectures. As anticipated from the extended conformation, tetraindole foldamer **2** shows no CD signal in the absence of an anion in 1:1 (v/v) CH_3CN/CH_2Cl_2 (5×10^{-5} M) at room temperature (Figure 1a). Upon addition of TBA^+Cl^-,[10] **2** display strong induced CD signal centered at 309 and 389 nm, diagnostic of helical folding as well as prevalent formation of one helix. For comparison, we prepared **ent-2**, enantiomer of **2**, with the (*R,R*)-configuration of the 1-phenylethylamido moiety at both ends. **Ent-2** shows CD spectra with the opposite Cotton effect (Figure 1b), confirming that the induced CD signal originates from helical folding. In addition, hexaindole foldamer **3** with the longer strand shows similar behaviors of the CD spectrum but the relative intensity is slightly weaker than that of **2** (Figure 1c). This result implies that the CD intensity is not simply proportional to the number of the turn in the helix. It should be noted that the (*P*)-helix of **1** is energetically more favorable than the corresponding (*M*)-helix according to theoretical calculations as described previously.[7] Upon binding a chloride, **2** and **3** display the same pattern of the induced CD spectra as that of **1**. More studies and high-level calculations are needed to give an answer for which helix is energetically more stable in **2** and **3** and how much.

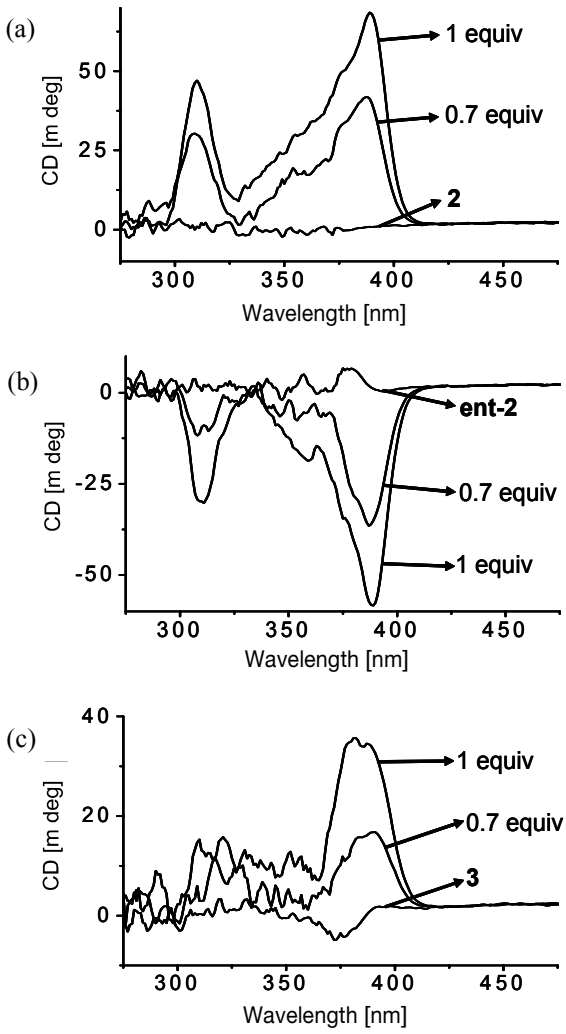


Figure 1. Induced CD spectra of a) **2** (5×10^{-5}), b) **ent-2** (5×10^{-5}) and c) **3** (5×10^{-5}) upon addition of nBu$_4$N$^+$Cl$^-$ in 1:1 (v/v) CH_3CN/CH_2Cl_2 at 24°C.

^{1}H NMR spectroscopy evidently supports the helical folding of **2** and **3** (Figure 2b). When tetrabutylammonium chloride was added, ^{1}H NMR spectra of **2** and **3** were significantly changed. For example, the indole NH signals of **2** were largely downfield shifted from 11.4 and 11.5 ppm to 12.2 and 13.5 ppm as the result of hydrogen bonding with the anion. In the longer foldamers **3**, two of three indole NH signals were shifted downfield ($\Delta\delta$ = 2.5 and 0.4 ppm) but one is upfield shifted upfield ($\Delta\delta$ = – 0.4 ppm) upon addition of the chloride ion. This observation indicates that the terminal indole NHs are not or weakly involved in hydrogen bonding with the anion due to remote distance. However, the terminal indole rings seem to adopt a stacked helical array, thus giving rise to the upfield shift of the indole NH signal. The helical folding of **2** and **3** was further confirmed by changes in the chemical shifts of the aromatic CH signals which were considerably shifted upfield up to approximately 1 ppm upon binding a chloride, strongly supporting a stacked array exerting the ring current of aromatic planes to the above or below hydrogen atoms. Finally, the 2D ^{1}H-^{1}H ROESY experiment of a 1:1 mixture of **2** and TBA^+Cl^- in acetone-d_6 gave an additional evidence for helical folding, showing characteristic long-distance NOE cross peaks between H^g and H^k, H^l and NH^e, and H^f and NH^e (Figure 2a).

In conclusion, chiral oligoindole foldamers **2** and **3** with ester side chains have been synthesized which fold to generate the helical structure in the presence of a chloride. ^{1}H NMR and CD spectroscopy have clearly demonstrated that the chirality of the phenylethylamido unit at both ends is effectively transferred on the folding in a helix, thus leading to the preferred formation of one helical isomer over another. We are currently pursuing whether the folding or unfolding, and the right-handed or left-handed of chiral foldamers can be reversibly controlled by external chemical stimulus.

Experimental Section

Compound 6: The synthesis of **4** and **5** were described previously.[6a,7] **5** (4.0 g, 5.15 mmol), PPh_3 (103 mg, 0.396 mmol), CuI (19 mg, 0.10 mmol), and $Pd(dba)_2$ (57 mg, 0.10 mmol) were added to a Schlenk flask under nitrogen and dissolved in degassed anhydrous Et_3N (20 mL) and THF (25

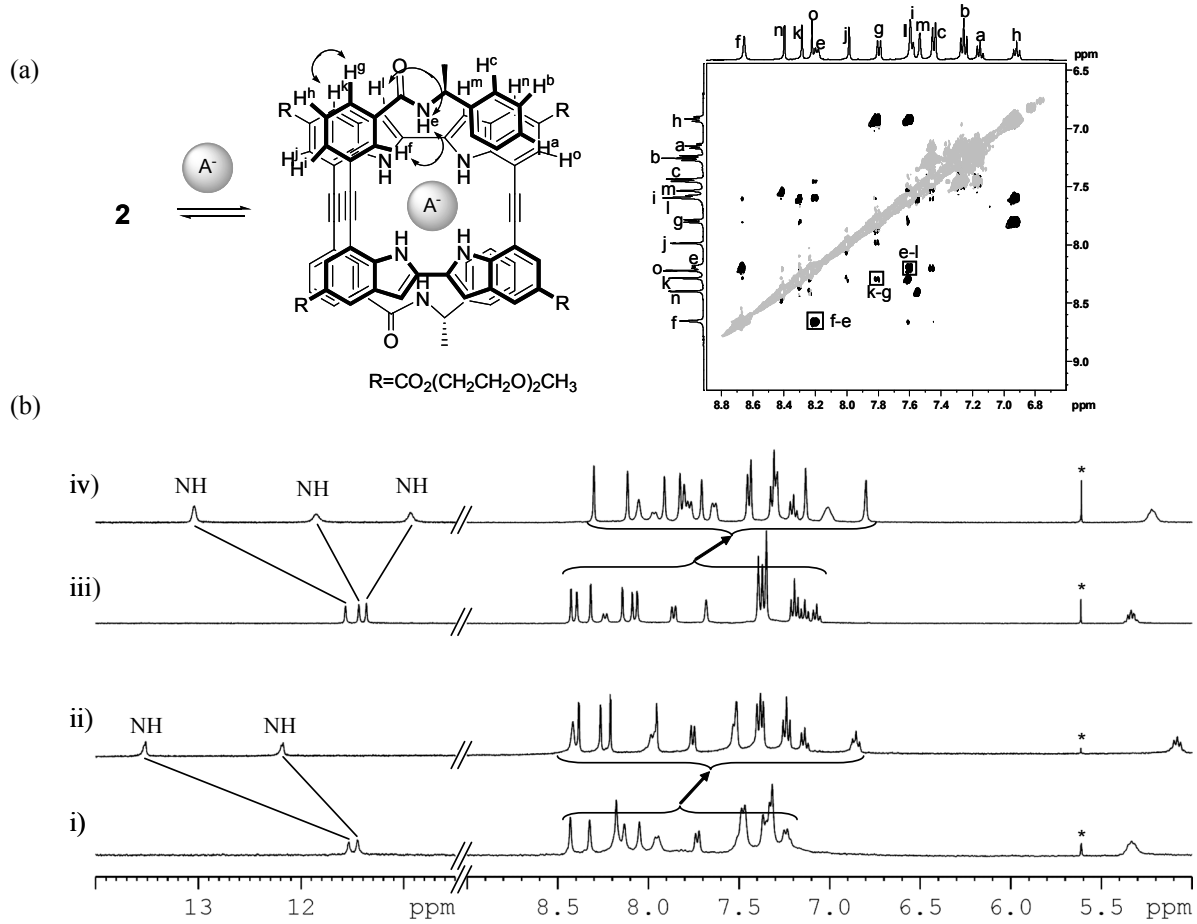


Figure 2. a) Partial 2D ^{1}H-^{1}H ROESY spectrum of **2** + nBu$_4$N$^+$Cl$^-$ in acetone-d_6 at 25°C. b) partial ^{1}H NMR spectra (400 MHz, acetone-d_6, 25°C) of i) **2** (0.5 mM), ii) **2** (0.5 mM) + nBu$_4$N$^+$Cl$^-$ (1 equiv), iii) **3** (0.5 mM) and iv) **3** (0.5 mM) + nBu$_4$N$^+$Cl$^-$ (1 equiv). The marked peak (*) is attributed to residual CH_2Cl_2.

mL). After degassing and back-filled the flask with nitrogen, **4** (103 mg, 0.396 mmol) was added. Then, the reaction mixture was stirred at 55-58 ºC for 20 h. The mixture was cooled to room temperature and filtered through Celite pad and concentrated. The residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, EtOAc/hexanes = 1:2) to give **6** (1.9 g, 54 %) as a white solid, together with di-coupled side product (0.6 g, 18 %): Mp 223-225 ºC; ^{1}H NMR (400 MHz, acetone-d_6) δ 11.48 (s, 1H), 10.66 (s, 1H), 8.38-8.32 (m, 3H), 8.24-8.22 (m, 2H), 8.18-8.17 (m, 1H), 8.05 (d, J = 1.6 Hz, 1H), 8.0-7.77 (m, 2H), 7.57-7.53 (t, J = 7.8 Hz, 1H), 7.39-7.37 (m, 4H), 7.32 (t, J = 7.8 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 5.39-5.33 (m, 1H), 4.48-4.43 (m, 4H), 3.87-3.82 (m, 4H), 3.70-3.66, (m, 4H), 3.54-3.50 (m, 4H), 3.30 (m, 4H), 1.60 (d, J = 7.16 Hz, 3H); ESI-MASS *m/z* 920 (MNa^+).

Compound 7: 6 (1.25 g, 1.39 mmol), PPh_3 (36 mg, 0.14 mmol), CuI (4 mg, 0.023 mmol) and $Pd(dba)_2$ (20 mg, 0.035 mmol) were mixed in a Schlenk flask. Then, the mixture was degassed and backfilled with nitrogen and dissolved in dry Et_3N (20 mL) and THF (25 mL). After addition of (trimethylsilyl) ethyne (0.27g, 2.78 mmol), the mixture was degassed and heated to 50-53 ºC for 13 h. The solution was cooled to room temperature and filtered through Celite pad and concentrated. The crude residue was dissolved in THF, and AcOH (1 M in THF, 2.35 mL, 2 equiv) and TBAF (1 M in THF, 2.35 mL, 2 equiv) were sequentially added at 0 ºC (iced water bath). The solution was stirred at room temperature for 30 min, and the residue was dissolved in CH_2Cl_2 and washed with H_2O and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, EtOAc/hexanes = 1:3) to give **7** (0.85 g, 89 % two steps): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 2H), 9.0 (d, J = 8.0 Hz, 1H), 8.33-8.30 (m, 3H), 7.96-7.86 (m, 3H), 7.60 (t, J = 7.7 Hz, 1H), 7.50-7.41 (m, 5H), 7.34 (t, J = 7.9 Hz, 2H), 7.23 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.48-7.46 (m, 3H), 7.36-7.31 (m, 4H), 7.24 (t, J = 7.4 Hz, 1H), 5.20 (m, 1H), 4.64 (s, 1H), 3.79-3.75 (m, 4H), 3.62-3.46 (m, 8H), 3.24 (s, 6H), 3.26 (s, 3H), 1.50 (d, J = 7.4 Hz, 1H); ESI-MASS *m/z* 818 (MNa^+).

Compound 2: 6 (0.69 g, 0.774 mmol), PPh_3 (20 mg, 0.077 mmol), CuI (3 mg, 0.015 mmol), and $Pd(dba)_2$ (11 mg, 0.019 mmol) were added to a 50 mL Schlenk flask. The mixture was dissolved in degassed anhydrous Et_3N (20 mL) and THF (25 mL). After addition of **7** (0.62 g, 0.774 mmol) the mixture was degassed and heated to 50-53 ºC for 28 h. The work-up procedure is the same as that for **6**. The product was purified by column chromatography (silica gel, MeOH/CH_2Cl_2 =

2:98) to give **2** (0.7 g, 65 %) as a white solid. Ent-**2** was prepared by the same procedure from ent-**6** and ent-**7** in 62% yield: Mp 279-282 ºC ° (decomp); ^{1}H NMR (400 MHz, Acetone-d_6) δ 11.53 (s, 1H) 11.45 (s, 1H), 8.43 (s, 1H), 8.32, (s, 1H), 8.17-8.13 (m, 3H), 8.0 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.48-7.46 (m, 3H), 7.36-7.31 (m, 4H), 7.24(t, J = 7.4 Hz, 1H), 4.50-4.44 (m, 4H), 3.88-3.82 (m, 4H), 3.73-3.63 (m, 4H),3.54-3.48 (m, 4H), 3.33 (s, 3H), 3.26 (s, 3H), 1.58 (s, 3H); ESI-MASS *m/z* 1589 (MNa^+).

Compound 3: 5 (0.232 g, 0.3 mmol), PPh_3 (8 mg, 0.396 mmol), CuI (2 mg, 0.006 mmol) and $Pd(dba)_2$ (57 mg, 0.10 mmol) were mixed in a Schlenk flask. The mixture was dissolved in degassed anhydrous Et_3N (20 mL) and THF (25 mL). After addition of **7** (0.50 g, 0.628 mmol)**,** the mixture was degassed and heated to 50-53 ºC for 16 h. The work up is the same as that for **6**. The product was purified by column chromatography (silica gel, MeOH/CH_2Cl_2 = 2:98) to give **3** (0.32 g, 51%) as a white solid: ; Mp 248-250 ºC (decomp); ^{1}H NMR (400 MHz, acetone-d_6) δ 11.57 (s, 1H) 11.44 (s, 1H), 11.37 (s, 1H), 8.43 (s, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.14 (s, 1H), 8.08 (s, 1H), 8.06 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.37 (m, 6H), 7.19 (t, J = 7.4 Hz, 2H), 7.13 (t, J = 7.8 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 5.34 (m, 1H), 4.50-4.46 (m, 6H), 3.87-3.81 (m, 6H), 3.69-3.61 (m, 6H), 3.53-3.44 (m, 6H), 3.30 (s, 3H), 3.29 (s, 3H), 3.29 (s, 3H), 3.24 (s, 3H), 1.59 (s, 3H); ESI-MASS *m/z* 2135 (MNa^+).

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10. The chloride ion strongly binds to **2** and **3** with the association constant of K_a (M^{-1}) > 10^6 M^{-1} in 1:1 (v/v) CH_3CN/CH_2Cl_2.