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Helicity Control of an Indolocarbazole Foldamer by Chiral Organic Anions

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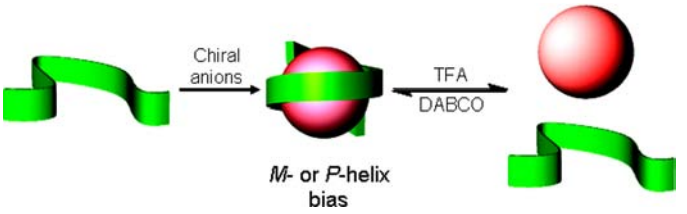
ABSTRACT



Chiral organic anions such as camphorsulfonates and cAMP give rise to the preferential formation of a one-handed helix of an indolocarbazole foldamer, thus inducing characteristic circular dichroic (CD) signals. Moreover, the on and off switching of the chiroptical signal can be operated by acid and base chemistry which efficiently controls the association and dissipation of the foldamer and cAMP.

Helical structures are unique features of proteins and DNAs wherein the chiral components such α-amino acids and 2-deoxyribose drive them to form one-handed helices. Many synthetic oligomers have been prepared that adopt helical structures by polar and nonpolar noncovalent interactions including hydrogen bond, dipole−dipole, van der Waals, and solvophobic interactions.[1,2] Unlike natural macromolecules, most of the synthetic oligomers give racemic mixtures of enantiomeric left- and right-handed helices because of the absence of any chiral constituent.[2] To induce the preferential formation of one-handed helices, two different approaches have been made to date. One is the covalent attachment of chiral segments to the backbones, side chains, or termini of oligomers and polymers.[3] The other is noncovalent interactions with chiral guests, which leads to the biased formation of two diastereomeric helical complexes.[4]

Indolocarbazoles possess two indole-type NH protons capable of forming strong hydrogen bonds with anions.[5] Using this scaffold as a repeating unit, we recently prepared an indolocarbazole foldamer **1** which consisted of three indolocarbazoles connected by ethynyl linkers and propargylic units at both ends.[6] The foldamer **1** was found to bind a sulfate ion strongly and selectively by eight hydrogen bonds, thus folding into a helical conformation. As shown in Figure 1, the sulfate ion was entrapped in the helical cavity in which each oxygen of the sulfate ion was held by two hydrogen bonds with NH and OH protons.

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In the crystal packing structure, two enantiomeric complexes of left- and right-handed helices stacked with one another to afford racemate crystals with tetrabutylammonium cations intercalated between layers. Herein, we have demonstrated for the first time that chiral organic anions **2**, **3**, and **4** efficiently induce one-handed helical folding of an indolocabazole foldamer **1** to generate characteristic circular dichroic (CD) signals. Furthermore, it is also demonstrated that the on and off state of the CD signal can be reversibly switched by addition of an acid (CF_3CO_2H) and a base (DABCO).

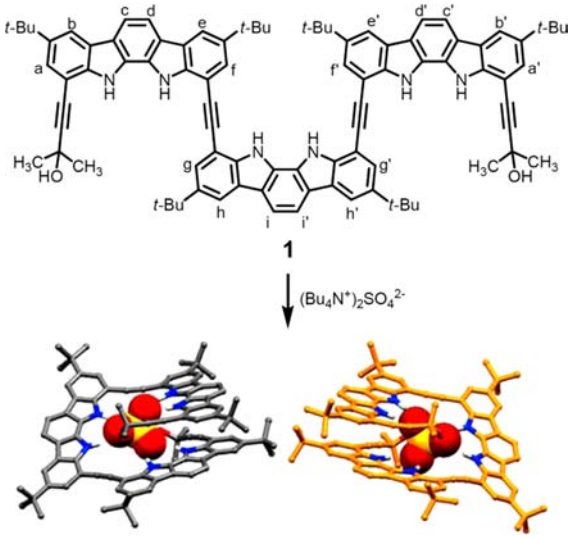

Figure 1. Molecular structure of trimer **1** (top) and its crystal structures when complexed with $(Bu_4N^+)_2SO_4^{2-}$, a left-handed helix (bottom, left) and a right-handed one (bottom, right).[6]

The chiroptical properties of **1** were first revealed by CD spectroscopy at room temperature (Figure 2). A CH_2Cl_2 solution (2.0×10^{-5} M) of **1** was completely CD-silent because it exists in an extended conformation. However, **1** folded into a helical structure when complexed with bis(tetrabutylammonium) sulfate although no CD signal was shown because the 1:1 mixture of left- and right-handed helices was formed as mentioned above. In contrast, addition of (*R*)-10-camphorsulfonate **2** as a chiral guest gave rise to characteristic CD signals with a strong positive Cotton effect ($\Delta\varepsilon = 37\ M^{-1}\cdot cm^{-1}$ at 362 nm) attributed to the exciton coupling of indolocarbazole chromophores. The CD spectrum was completely inverted with the opposite Cotton effect when the enantiomer (*S*)-10-camphorsulfonate **3** was used as a chiral guest. This observation supports that the induced CD signals result from the biased formation of two diastereomeric helical complexes. It should be also noted that the specific rotation of chiral guest **2** was measured to be $-32°$ in CH_2Cl_2 ($c = 1.0\ mg\cdot mL^{-1}$) at 21 °C, which dramatically changed to $+224°$ upon addition of **1** ($\sim$3 equiv), indicative of the formation of a helical structure.[7]

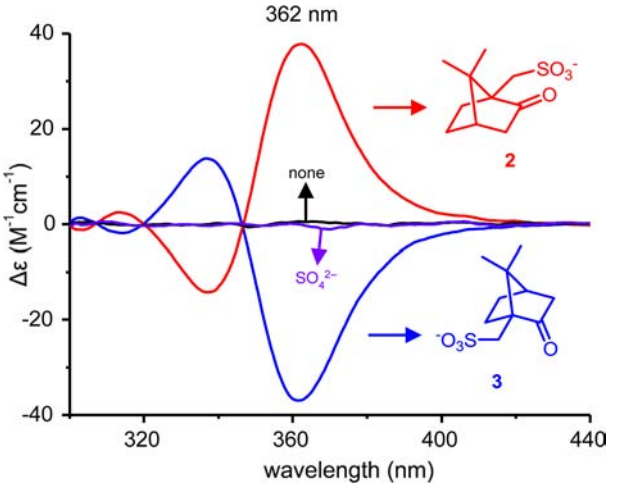

Figure 2. CD spectra of foldamer **1** (CH_2Cl_2, rt) in the absence (none, black) and presence of the tetrabutylammonium salts of sulfate (violet), **2** (red), and **3** (blue).

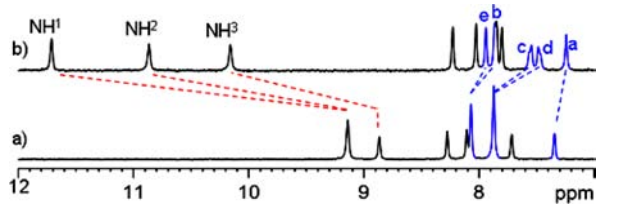

Figure 3. Partial ^1H NMR spectra (400 MHz, 25 °C) of (a) foldamer **1** and (b) in the presence of Bu_4N^+(*R*)-10-camphorsulfonate (1 equiv) in CD_2Cl_2. For the designation of each peak in the spectra, see the molecular structure of **1** in Figure 1.

More detailed information on the complex formation was obtained by ^1H NMR spectroscopy. Addition (1 equiv) of **2** as the tetrabutylammonium salt to a CD_2Cl_2 solution (1.0×10^{-3} M) of **1** led to large downfield shifts of ^1H NMR signals of three NH protons by $\Delta\delta = 1.29, 1.73,$

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and 2.57 ppm due to the formation of hydrogen bonds (Figure 3). In addition, the aromatic CH signals in two terminal indolocarbazoles were upfield shifted by $\Delta\delta$ = 0.1−0.4 ppm, but those in the central indolocarbazole were shifted negligibly ($\Delta\delta$ < 0.1 ppm). This result implies that two indolocarbazole planes at both ends stack to give a helical conformation upon binding of a chiral sulfonate, **2**. The OH signal of **1** could not be seen only in CD_2Cl_2 but appeared at 3.52 ppm in 1:9 (v/v) CD_2Cl_2/CD_3CN (containing 1% H_2O), which was also shifted downfield by $\Delta\delta$ = 0.91 ppm upon addition of **2** (~10 equiv) due to hydrogen bonding with guest **2** (Figure S1, Supporting Information (SI)). The UV−visible titration gave an association constant of 1.3×10^6 M^{-1} between **1** and **2** in 1% (v/v) MeOH/CH_2Cl_2.

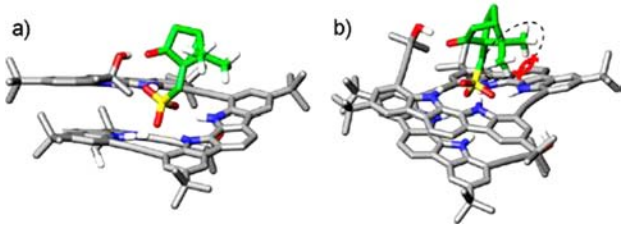

Figure 4. Energy-minimized structures (Macromodel 9.1, AMBER) of complex between **1** and **2** (shown as a green). The *P*-helix (a, left) was calculated to be more stable by 11 kJ/mol in the gas phase than the corresponding *M*-helix (b, right).

According to computer modeling studies (Macromodel 9.1,[8] AMBER,[9] gas phase), foldamer **1** coiled to a right-handed helix (*P*-helix) when complexed with (*R*)-10-camphorsulfonate **2** (Figure 4a). The corresponding *M*-helix was found to be unstable by 11 kJ·mol^{-1} because of steric repulsions between methyl groups of **2** and indolocarbazole planes (Figure 4b). The exciton chirality method[10] has been well-known to predict the absolute stereochemistry of helices; a positive Cotton effect at a longer wavelength is attributed to the *P*-helix while a negative Cotton effect is attributed to the *M*-helix. Accordingly, (*R*)-10-camphorsulfonate **2** forms the complex of *P*-helix at least preferentially in solution, consistent with the theoretical calculations. The helical folding was also confirmed by a $^1H-^1H$ 2D ROESY experiment, clearly showing characteristic NOE cross peaks between the central indolocarbazole protons, H^h and H^g, of **1** and the methyl protons of **3** (Figure S3, SI).

To determine the ratio of *M*- and *P*-helix in the complex between **1** and **3**, low temperature experiments were performed in CD_2Cl_2 (Figure S4, SI). At room temperature, a mixture of **1** and **3** showed one set of ^1H NMR signals due

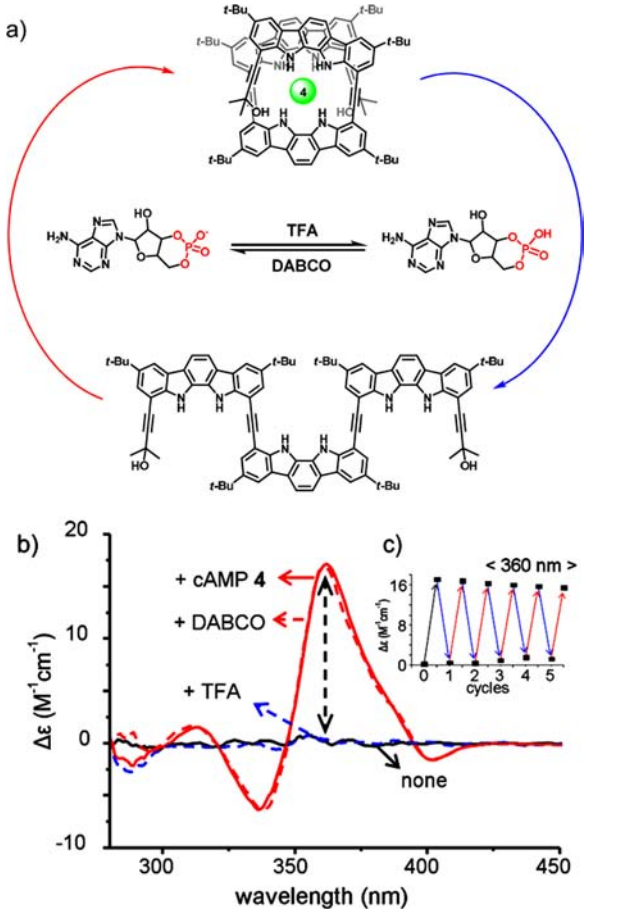

Figure 5. (a) Schematic representation of association and dissipation between **1** and **4** in the presence of TFA and DABCO; (b) CD spectra of **1** (black, solid line) and sequential addition of **4** (red, solid line), TFA (blue, dotted line), and DABCO (red, dotted line), and (c) a repetitive CD intensity ($\Delta\varepsilon$) cycle upon alternating additions of TFA and DABCO.

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to fast exchange between the free and complex on the ^{1}H NMR (400 MHz) time scale. When the temperature was lowered down to −50 °C, the signals of the ^{1}H NMR spectrum broadened and some disappeared. Then, further lowering of the temperature to −80 °C provided a more complex but well resolved ^{1}H NMR spectrum of **1**. For example, six NH protons of a symmetrical foldamer **1** appeared as three separate signals at room temperature but they split into six signals at −80 °C. This is because the original symmetry was destroyed at −80 °C by binding of a chiral guest as well as exchange between the free and complex was slowed down enough to resolve all six NH signals. Even at this temperature, however, ^{1}H NMR signals corresponding to minor components could not be detected, indicating that the one-handed helix of complex is formed predominantly (> 90%) in solution.

Next, to demonstrate the on and off switching of CD signals, we chose another chiral guest, adenosine 3′,5′-cyclic monophosphate (**4**, cAMP) with a more basic phosphate group which allows us to control the protonated and deprotonated states by acid and base chemistry. It is hypothesized that the deprotonated form (**4**-phosphate) of cAMP strongly binds to **1** while the protonated neutral one (**4**-phosphoric acid) does so negligibly. The binding properties were first examined by the ^{1}H NMR spectroscopy in 1:9:90 (v/v/v) $H_2O/CD_2Cl_2/CD_3CN$ at 24 ± 1 °C for solubility. As in the case of the binding of chiral sulfonates **2** and **3**, the NH and OH signals were all shifted downfield as a result of the hydrogen bond formation (Figures S5 and S6, SI). The binding constant was determined to be $1.1 \times 10^4\ M^{-1}$, which was much higher than that of a chiral sulfonate **2** ($9.4 \times 10^2\ M^{-1}$) under the same conditions.

As anticipated, addition of **4**-phosphate (3 equiv) induced a strong CD signal of **1** with a positive Cotton effect between 350 and 400 nm in CH_3CN (containing 1% H_2O) at room temperature (Figure 5). Then, trifluoroacetic acid (TFA, 1 equiv to **4**) was added to convert **4**-phosphate to **4**-phosphoric acid. As a result, the complex became dissociated and the CD signal disappeared. To this solution, addition of amine base 1,4-diazabicyclo[2.2.2]octane (DABCO, 1 equiv to TFA) allowed **4**-phosphate to be regenerated which in turn formed the complex to give the CD signal again. This process can be repeated several times as shown in Figure 5c. It should be noted that this is a rare example, showing reversible switching between folding and unfolding states with characteristic chiroptical signals.[11]

In summary, we have demonstrated that the helical sense of a foldamer can be effectively controlled by the binding of chiral organic anions. Moreover, the on and off switching of CD signals can be reversibly operated by acid and base chemistry, which is a key prerequisite to development of a chiroptical molecular switch.

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Supporting Information Available. Titration data, low temp NMR data, ^{1}H−^{1}H 2D NMR data, and Job plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.