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# A Foldamer-Based Chiroptical Molecular Switch That Displays Complete Inversion of the Helical Sense upon Anion Binding

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Supporting Information

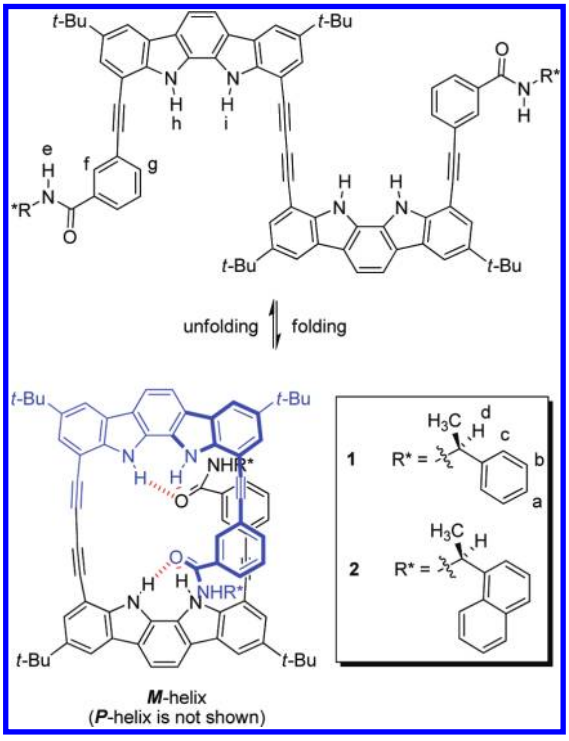
**ABSTRACT:** Chiral indolocarbazole dimers fold into a helical conformation by virtue of intramolecular hydrogen bonds, as demonstrated by $^1$H NMR and CD spectra and optical rotations. In particular, the optical properties of the dimers were found to be extremely sensitive to the nature of the solvent, depending on whether they are folded or not. The helical sense of the dimers can be reversibly switched by binding sulfate ion, which gives rise to complete inversion of the CD spectra. The binding mode and absolute stereochemistry of the sulfate complexes was unequivocally determined by single-crystal X-ray structures, which are all consistent with the CD and $^1$H NMR spectra in solution.

Much attention has been paid in recent years to the development of functional molecules capable of switching their conformations or structures in response to external stimuli. Molecular switches in general have two interchangeable stable states, each of which should have unique physical, optical or electrochemical properties.[1] Representative examples studied to date are diarylethenes, overcrowded olefins, organometallic complexes, and interlocked molecules that are responsive to light, temperature, pH, solvents, or other stimuli.[1,2]

Foldamers, which are acyclic oligomers that adopt ordered arrays stabilized by noncovalent interactions, have been prepared in order to understand underlying principles of protein folding and develop functional molecules and materials.[3] Among them, aromatic foldamers capable of folding into helical structures are useful candidates for molecular switches because the molecules exist either in an unfolded extended conformation or a folded compact conformation according to the environment.[4] Moreover, the foldamers may have an additional switching mode involving left- and right-handed helices, and control of the helical sense makes them useful as chiroptical molecular switches with characteristic optical signals.[5,6]

We previously prepared a series of oligoindoles and oligoindolocarbazoles that fold into a compact helical structure in the presence of an anion.[7] Herein we report on chiral indolocarbazole dimers **1** and **2** (Scheme 1) wherein intramolecular hydrogen bonds force the molecule to adopt a helical conformation even in the absence of an anion. The presence of chiral (*S*)-arylethylamido groups at both ends leads to the preferential formation of one helical isomer over the other, thus showing strong circular dichroism (CD) signals. Moreover, reversible and complete switching of the helical sense can be achieved by the addition and removal of anions such as sulfate, which enables the dimers to function as chiroptical molecular switches.

**Scheme 1. Molecular Structures of 1 and 2**




The syntheses of **1** and **2** are described in the Supporting Information (SI). A butadiynyl spacer between the two indolocarbazoles was chosen to attain intramolecular hydrogen bonds between the indolocarbazole NHs and amide oxygens, which in turn result in the helical folding of the dimers. Computer models[8] showed that each of the amide oxygens formed intramolecular hydrogen bonds with the NH protons of the opposite indolocarbazole ring. Because of the nature of a rigid aromatic strand, the C═O···H−N hydrogen bond cannot achieve an optimal geometry, which might be an advantage in facilitating the switching of the helical sense upon anion binding. $^1$H NMR spectra gave clear evidence for the intramolecular hydrogen bonding and helical folding. First, two NH signals of **1** were shifted downfield by $\Delta\delta$ = 1.1 and 0.2 ppm in 5% $CD_3CN/CD_2Cl_2$ and the CH

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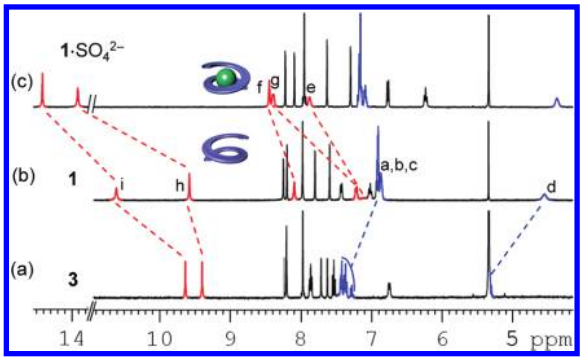
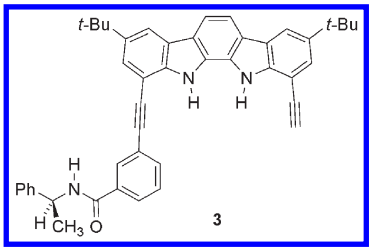



**Figure 1.** Partial $^1$H NMR spectra (400 MHz, 5% $CD_3CN/CD_2Cl_2$, 25 °C) of (a) reference molecule **3**, (b) dimer **1**, and (c) **1** in the presence of bis(tetrabutylammonium) sulfate (1 equiv).

signals of the phenylethyl moieties were shifted upfield by $\Delta\delta$ = 0.4−1.1 ppm (Figure 1b), in comparison with a reference **3** lacking such hydrogen bonds. Second, the magnitudes of the chemical shift differences ($\Delta\delta$) between **1** and **3** were noticeably smaller in polar solvents such as acetone and dimethyl sulfoxide (DMSO) (see the SI). This result suggests that the folded conformation is predominant in 5% $CD_3CN/CD_2Cl_2$ but the unfolded one prevails in DMSO because of the strong solvation of the NH protons by solvent molecules.[9] Third, nuclear Overhauser effect (NOE) cross-peaks were observed between indolocarbazole NHs and the terminal groups [e.g., the benzylic hydrogen ($H^d$) and the ortho hydrogen ($H^c$) in the phenyl ring], implying that the phenylethyl moieties are located close to the indolocarbazole plane as a result of the folding (see the SI).




The optical properties of **1** were characterized by CD spectroscopy and polarimetry in organic solvents. In the nonpolar solvent $CH_2Cl_2$, a strong CD signal with a negative Cotton effect ($\Delta\varepsilon$ = −104 $M^{-1}$ $cm^{-1}$; Table 1) was observed at 379 nm, corresponding to an absorption region of the indolocarbazole chromophore in the UV−vis spectrophotometer (Figure 2), but reference **3** was completely CD-silent. According to the exciton chirality method,[10] the negative Cotton effect of **1** implies the formation of a left-handed helix (*M*) at least preferentially. The CD intensity decreased in more polar solvents (−46, −38, and −6 $M^{-1}$ $cm^{-1}$ in acetonitrile, acetone, and DMSO, respectively; Table 1). The reduced intensities could be attributed to a decrease in the amount of the folded conformation in more polar solvents, as demonstrated by the $^1$H NMR studies. In addition, we prepared the enantiomer of **1** having the *R* configuration of the phenylethylamido moieties, which showed identical CD signals but opposite Cotton effects relative to **1** in the cases of both the unbound molecule and the sulfate complex (see the SI). This clearly demonstrates that the terminal chiral units determine the orientation of the helical sense.

**Table 1. Magnitudes of Molar CD Values ($\Delta\varepsilon$) at 379 nm and Optical Rotations ($[\alpha]_D$) of 1 in Organic Solvents**

| solvent | $\Delta\varepsilon$ ($M^{-1}$ $cm^{-1}$) | $[\alpha]_D$ (deg) |
|---|---|---|
| dichloromethane | −104 | −913 |
| acetonitrile | −46 | −429 |
| acetone | −38 | −235 |
| DMSO | −6 | −31 |

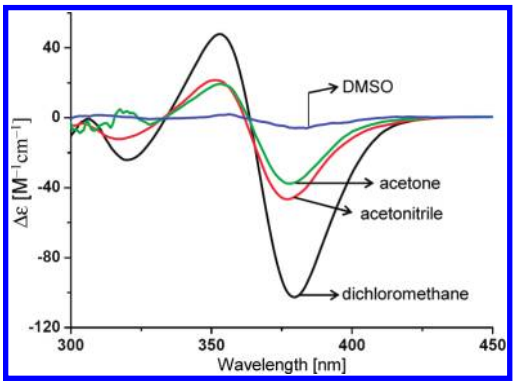



**Figure 2.** CD spectra of **1** in organic solvents with different polarities. The relative intensity of the CD spectrum strongly depends on the nature of the solvent.

The optical rotation of **1** was measured in dilute organic solutions ($c$ = 1.0 mg/mL) at 21 °C, and the magnitude of the specific rotation ($[\alpha]_D$) was found to be extremely sensitive to the nature of the solvent (Table 1). For example, the $[\alpha]_D$ value was only −31° in DMSO but dramatically increased to −913° in the nonpolar solvent $CH_2Cl_2$. The optical rotations of helicenes have been known to be very high.[11] Accordingly, the large-amplitude optical rotation observed here in nonpolar solvents originates mainly from the helical chirality of the folding structure, not from the local stereocenters.

The chiral dimer **1** possesses multiple hydrogen-bond donors and therefore can strongly bind anions. For example, the UV−vis titration of **1** with bis(tetrabutylammonium) sulfate yielded an association constant of 2.2 × $10^5$ $M^{-1}$ in 5% (v/v) MeOH/$CH_3CN$ at 24 ± 1 °C. Of great interest is the fact that the CD spectrum of **1** was completely inverted upon binding of a sulfate ion (Figure 3), indicating that the helical sense switched from left-handed (unbound) to right-handed (complex). The pattern of the CD spectrum changed gradually in proportion to the amount of sulfate ion and was completely reversed when ∼1 equiv of the anion had been added in $CH_2Cl_2$. The $\lambda_{max}$ value of the sulfate complex was red-shifted from 379 to 386 nm, and the magnitude of the $\Delta\varepsilon$ value was identical to that of unbound **1** but had the opposite Cotton effect ($\Delta\varepsilon$ = +104 $M^{-1}$ $cm^{-1}$).[12] As in the CD results, the optical rotation ($[\alpha]_D$, 21 °C) of **1** was also changed into the opposite direction from −913° to +1247° upon binding of sulfate ion in $CH_2Cl_2$. In addition, the reversibility of the CD spectral change was examined using the sulfate-sequestering agent **4**, which binds the anion ∼34-fold more strongly than **1** under the same conditions.[13] The original CD spectrum of unbound **1** was restored when **4** (∼1 equiv) was added to a $CH_2Cl_2$ solution of the sulfate complex. Addition of

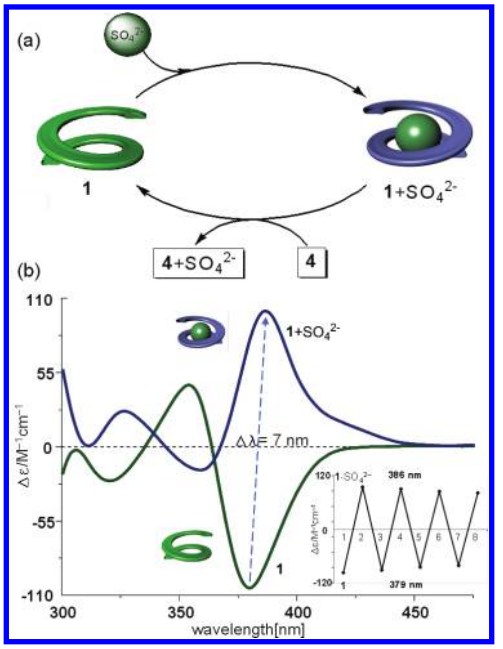
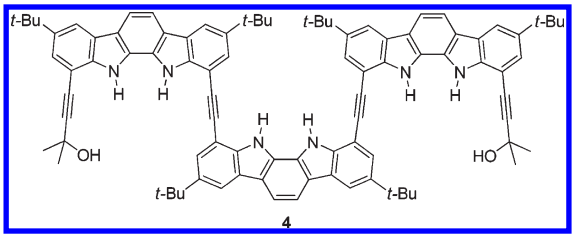



**Figure 3.** (a) Schematic representation of the reversible switching of the helical sense of **1** upon addition and removal of sulfate ion. (b) CD spectra of unbound **1** (green) and its sulfate complex (blue) and (inset) a repetitive CD cycle upon addition of sulfate or the sulfate-sequestering agent **4**.

more sulfate ion then led to the reappearance of the CD spectrum corresponding to the sulfate complex (Figure 3 inset).




We prepared another chiral dimer **2** by changing the chiral segment into the (*S*)-1-naphthylethylamido group, which may alter the relative ratio of the two helical diastereomers (the *M* and *P* helices). The CD spectra of both unbound **2** and its sulfate complex were almost identical to the corresponding spectra of **1**. In particular, the CD signals attributed to the indolocarbazole chromophore overlapped each other exactly (see the SI). This result reflects the fact that one helical isomer, an *M* helix (unbound) or a *P* helix (complex), is predominantly formed in both **1** and **2**, providing the indistinguishable CD spectra. Less likely is the possibility that the relative intensity of the CD spectra may be accidently independent of the kind of chiral units that determine the bias of the relative population of *M* and *P* isomers.

The absolute stereochemistry of the helical conformation was confirmed by the X-ray structures of the sulfate complexes of **1** and **2** (Figure 4). Heptane was slowly diffused into a heptane/acetone solution containing **1** or **2** and bis(tetrabutylammonium) sulfate (~1.5 equiv) to give single crystals of the corresponding sulfate complex that were suitable for X-ray diffraction analysis. First, the sulfate complex of **1** was found to be a *P* helix, as anticipated from the positive Cotton effect at the longer

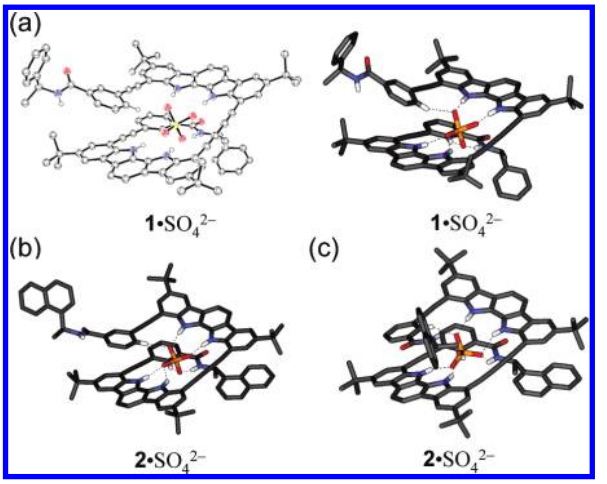



**Figure 4.** (a) ORTEP (left) and stick (right) views of the X-ray crystal structure of complex **1**·(*n*-$Bu_4N^+$)$_2SO_4^{2-}$. (b, c) Two independent X-ray crystal structures of complex **2**·(*n*-$Bu_4N^+$)$_2SO_4^{2-}$. Countercations and hydrogen atoms except hydrogen-bonded ones have been omitted for clarity. All of the structures were found to be *P* helices.

wavelength of the CD spectrum in $CH_2Cl_2$. The sulfate ion is entrapped in the middle of the cavity by multiple hydrogen bonds (Figure 4a). It is interesting that one of two amide NH protons is rotated away from the binding cavity and thus does not form the hydrogen bond. Instead, the aromatic CH hydrogen at the para position of the carbonyl group is involved in the hydrogen bonding with the sulfate ion. On the other hand, the sulfate complex of **2** yielded two independent single crystals (Figure 4b,c). Both of the crystal structures are *P* helices, consistent with the CD spectra in $CH_2Cl_2$. One is identical to that described above for **1** except that it contains naphthyl instead of phenyl substituents (Figure 4b). The other one shows that all of the existing six NHs are directed to the cavity of the helix to participate in hydrogen bonding with the sulfate ion (Figure 4c). In all three crystal structures, the distances of the N(indole)···O(sulfate) hydrogen bonds are in the range 2.58−2.71 Å, while those of the N(amide)···O(sulfate) bonds are 2.83−2.96 Å (see the SI), suggesting that the former form strong hydrogen bonds but the latter make very weak hydrogen bonds. This is possibly responsible for the formation of two different crystals with the comparable stability of the CH···O and NH(amide)···O hydrogen bonds. The observations in the crystal structures are in good agreement with the $^1$H NMR spectrum of the sulfate complex in $CD_2Cl_2$. When a sulfate ion was bound, the indole NH signals of **1** and **2** were shifted significantly downfield by $\Delta\delta$ = 3.8−4.6 ppm, but the amide NHs showed shifts of only $\Delta\delta$ = 0.66−0.78 ppm (Figure 1c). In addition, the aromatic CH$^g$ signal, which was hydrogen-bonded in the crystal structure, was shifted noticeably downfield from 7.20 to 8.39 ppm for **1** and 7.53 to 8.43 ppm for **2**.

In conclusion, we for the first time have prepared new chiral indolocarbazole dimers **1** and **2** that show complete inversion of the helical sense upon anion stimulus and can function as a new class of chiroptical molecular switches based on the helical foldamer. The optical readouts of these molecules were found to be quite sensitive to and tunable by the kind of solvent and anion. Further studies to reveal the origin of helical bias and switching of this molecular system are underway.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental procedures; physical and spectroscopic data for new compounds; $^1$H NMR, 2D NOESY, and CD spectra; X-ray details; and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) MacroModel 9.1 (MMFFs force field) was used for the modeling study.

(9) The NH and CH signals of **1** were further shifted when the temperature was decreased to −45 °C in $CD_2Cl_2$, implying that tighter intramolecular hydrogen bonds possibly form at low temperatures, thus possibly creating a more compact structure of folding. Another possibility is that the relative population of the folded conformation increases at lower temperatures.

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(12) Addition of other anions (fluoride, chloride, bromide, iodide, azide, and acetate) also gave rise to the inversion of CD spectra but with less intense signals than for sulfate ion. Dihydrogen phosphate (∼5 equiv) displayed a CD intensity ($\Delta\varepsilon$ = +113 $M^{-1}$ $cm^{-1}$) comparable to that for the sulfate ion (see the SI), suggesting that two tetrahedral anions form similar structures of complexes.

(13) The binding constants of **1** and **4** with sulfate were determined to be $1.9 \times 10^4$ and $6.4 \times 10^5$ $M^{-1}$, respectively, in 10% (v/v) MeOH/$CH_3CN$. For the synthesis and anion-binding properties of **4**, see ref 7d.