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A chiral indolocarbazole foldamer displaying strong circular dichroism responsive to anion binding†

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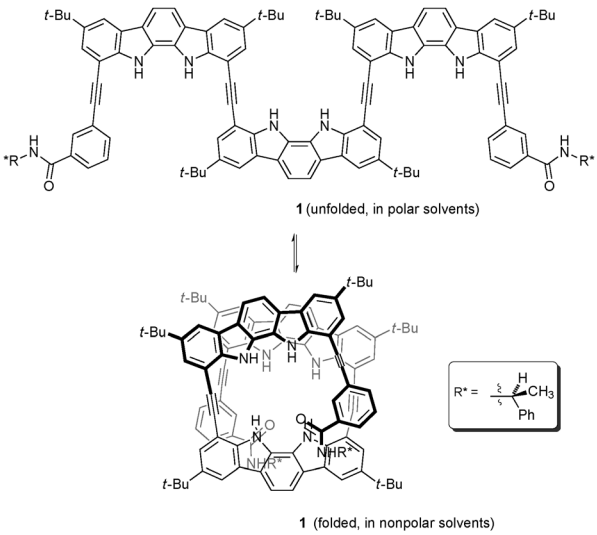
A chiral foldamer that consists of three indolocarbazoles and chiral amide residues folds into a helical conformation with the orientation bias, thus displaying characteristic CD signals. The X-ray crystal structure of its chloride complex was found to be a left-handed (M−) helix which stacks to give one-dimensional columnar arrays.

A number of synthetic oligomers, so-called foldamers, have been prepared by successive linking of building monomers that bear appropriate functional groups for elongation, folding, and other designed functions.[1] Some of them contain a binding cavity for ions and molecules, thus functioning as synthetic receptors.[2,3] Moreover, some are utilised as molecular switches based on the reversible control of folding and unfolding states or left- and right-handed helicity.[4] In this context, we prepared a series of biindoles and indolocarbazoles that existed in extended conformations but adopted compact helical conformations upon anion binding.[5] Herein, we describe the folding and chiroptical properties of a chiral indolocarbazole foldamer **1** which can fold into a helical conformation by intramolecular hydrogen bonds (Scheme 1). In particular, the local chirality of amide units at ends is effectively transferred to the folding process, rendering the biased formation of two diastereomeric helices to exhibit characteristic circular dichroism (CD) signals which are sensitive to the nature of solvents and anions.

Foldamer **1** was synthesized by repeating Sonogashira reaction[6] and the details are given in the ESI.† The folding properties of **1** were revealed by CD spectroscopy, known as a powerful method to provide valuable information on the helical array of the interacting chromophores.[7] The CD spectra of **1** (3.0×10^{-5} M) were recorded at 24 (±1) °C in several solvents (Fig. 1). In nonpolar solvents such as toluene and chlorinated solvents, strong CD signals are observed with negative Cotton effects maximised at 366 nm ($\Delta\varepsilon$ = −263, −129 and −117 M^{-1} cm^{-1} in toluene, $CHCl_3$ and CH_2Cl_2, respectively), suggesting that **1** exists in a helically folded conformation. In more polar solvents such as acetonitrile and dimethyl sulfoxide (DMSO), the CD signals are nearly negligible. In addition, the specific rotation ($[\alpha]_D$) of **1** was measured at 24 (±1) °C, and the magnitudes highly depend on the nature of solvents (Table S1, ESI†). The $[\alpha]_D$ values are large in toluene (−765°), CH_2Cl_2 (−514°) and $CHCl_3$ (−556°) while they are much smaller in more polar solvents, acetone (−0.3°) and DMSO (+6.5°). These results strongly support that **1** adopts a helically folded conformation and large magnitudes of the CD values and specific rotations in nonpolar solvents result from the global helical chirality, not from the local chirality of stereogenic amide appendages.



Scheme 1 Unfolded and folded structures of **1**.

Computer modeling studies (MacroModel 9.1,[8] Fig. S1, ESI†) afford additional evidence for the helical folding of **1**. An energy-minimised structure adopts a helical conformation which is stabilised by intramolecular hydrogen bonds between NH protons in the central indolocarbazole and the oxygen atoms of terminal amides and by π stacking between aromatic

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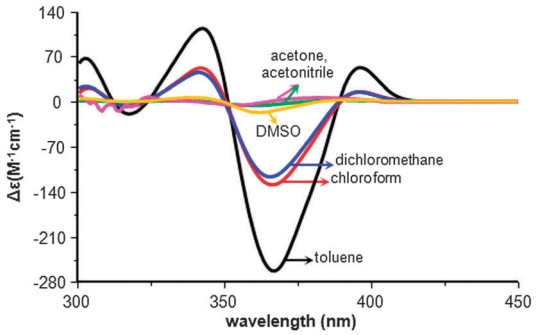

Fig. 1 CD spectra of **1** (3.0×10^{-5} M, 24 ± 1 °C) in organic solvents.

planes. The geometry of the hydrogen bonds is, however, far from ideal in the aspects of the angles (∠NH···O 89° and 117°) and distances (N···O 3.0 and 3.1 Å). As a result, the strengths of the hydrogen bonds are possibly too weak to be negligible in polar media.

The binding properties of **1** with tetrabutylammonium anions were examined. First, addition of anions gave rise to remarkable changes in the CD spectrum of **1** (3.0×10^{-5} M) in CH_2Cl_2 at 24 ± 1 °C (Fig. 2a). For example, when anions such as chloride, bromide and acetate were added, the CD spectra were inverted with opposite Cotton effects. It is worthwhile mentioning that the patterns and intensities of the CD spectra of the complexes depend on the nature of solvents (Fig. S3, ESI†), possibly due to changes in the degree of helicity bias and in the geometrical array of interacting chromophores, indolocarbazole and ethynylbenzamide planes in different environments.

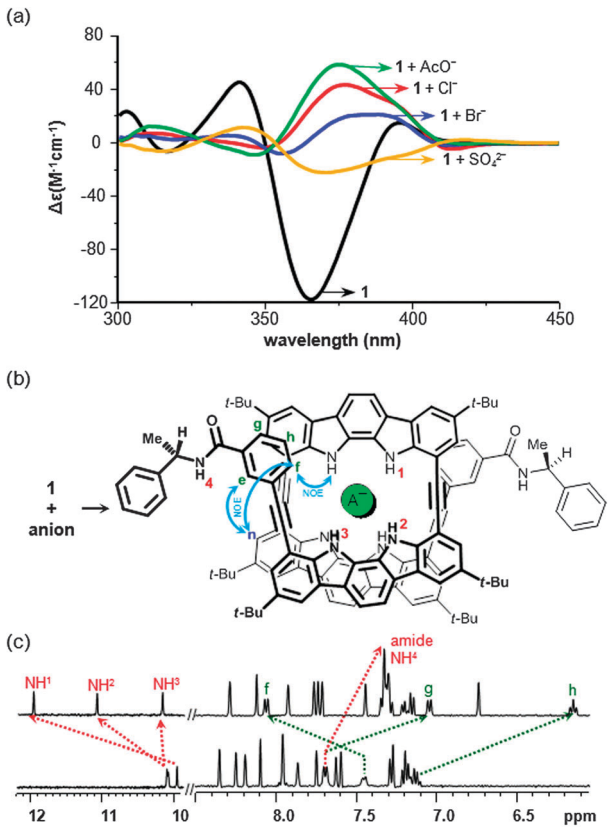

Fig. 2 (a) CD spectra of **1** (3.0×10^{-5} M, CH_2Cl_2, 24 ± 1 °C) in the absence (black) and presence of the tetrabutylammonium (TBA) anions (1 equiv.), (b) molecular structures of a complex between **1** and an anion with the NOE correlations marked with curved double-headed arrows, and (c) partial ^{1}H NMR spectra (400 MHz, 1/1 (v/v) acetone-d_6–CD_3CN, 25 °C) of free **1** (bottom) and in the presence of TBA chloride (1.1 equiv.) (top).

Table 1 Binding affinities of **1** with anions in 10% (v/v) MeOH–CH_3CN at 23 ± 1 °C

Anion[a]	K_a (±10%, M^{-1})	$-\Delta G$ (kcal mol^{-1})
Cl^-	1.2×10^6	8.23
Br^-	5.6×10^4	6.43
AcO^-	1.3×10^4	5.57
SO_4^{2-}	2.3×10^6	8.62

[a] Anions used as tetrabutylammonium salts.

Next, the ^{1}H NMR signals are somewhat broadened in the chlorinated solvents such as CD_2Cl_2 and $CDCl_3$ due to slow exchange between **1** and its aggregates, but they are sharp and well resolved in more polar media such as deuterated acetone and DMSO. Anion binding causes characteristic changes in the ^{1}H NMR spectrum of **1** (Fig. 2c). Three NH signals of the indolocarbazoles are shifted downfield by $\Delta\delta$ = 1.86, 0.98, and 0.22 ppm when tetrabutylammonium chloride is added in 1/1 (v/v) acetone-d_6–CD_3CN, as a result of hydrogen bonding. It should be noted that the amide NH signal is not downfield shifted but rather upfield shifted by $\Delta\delta = -0.38$ ppm, suggesting that the amide proton does not participate in the hydrogen bonding with the anion. In addition, the aromatic CH^h in the benzoate plane is noticeably upfield shifted by $\Delta\delta = -0.97$ ppm, indicative of this proton located just on the strong shielding region of the indolocarbazole ring current. The UV-visible titrations afford quantitative binding affinities between **1** and tetrabutylammonium anions in 10% (v/v) MeOH–CH_3CN at 23 ± 1 °C (Fig. S7, ESI†). As summarized in Table 1, **1** binds anions very strongly in the order $SO_4^{2-} > Cl^- > Br^- > AcO^-$. This trend implies that the binding affinity depends more on how well the anions fit into the helical cavity by forming complementary hydrogen bonds, simply than on the basicity of the anions.

The observations in solution are consistent with the crystal structure of the chloride complex of **1** (Fig. 3 and Fig. S6, ESI†). Single crystals† were obtained by slow diffusion of hexane into a 1/2 (v/v) ethyl acetate–CH_2Cl_2 solution of **1** and tetrabutylammonium chloride (2 equiv.). Several features are apparent in the crystal structure. First, **1** folds into a left-handed (M−) helix when complexed with chloride ions. Two indolocarbazole planes stack each other in a parallel-displaced manner,[9] and terminal benzoates partially stack with the central indolocarbazole ring. As a result, the CH^h in the benzoate is placed directly above and below the indolocarbazole plane, which agrees well with the large upfield shift ($\Delta\delta = -0.97$ ppm) of the ^{1}H NMR signal as mentioned earlier, together with the ^{1}H–^{1}H NOESY experiment showing characteristic cross peaks between NH^1 and H^f and between H^e and H^n (Fig. 2b and Fig. S6, ESI†). Second, the chloride ion is located in the middle of the helical cavity, stabilised by hydrogen bonds with all six NH protons in the indolocarbazoles ($N\cdots Cl^-$ distances 3.22–3.43 Å). However, two amide NH protons

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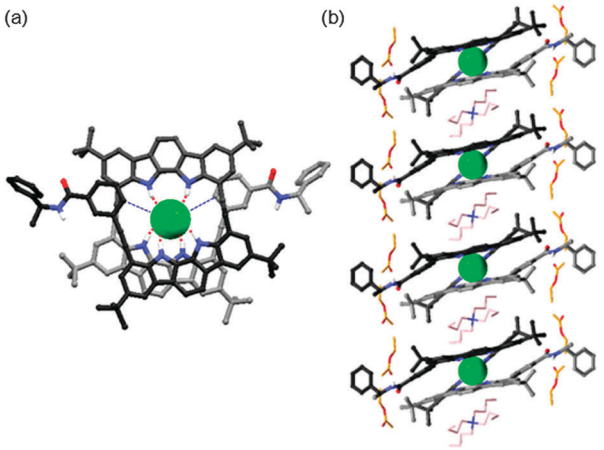

Fig. 3 (a) X-ray crystal structure of the complex between **1** and tetrabutylammonium (TBA) chloride, showing a left-handed (M−) helix. The helical structure is obtained by crystallographically imposing twofold symmetry operation of asymmetric units. The chloride ion (green) is in the middle of the cavity by hydrogen bonding with six NH protons and two CH protons. Here, TBA and hydrogen atoms except for NH protons are omitted for clarity. (b) 1D-columnar packing array of the complex wherein TBA's are intercalated between complexes and solvent molecules, ethyl acetate, are bound to the amide oxygen atoms.

are pointed away from the cavity, not hydrogen bonded with the chloride but with solvent molecules, ethyl acetate. Instead, two CH^f protons at the *para* position of carbonyls in benzoates also participate in weak hydrogen bonds (4.63 Å for C···Cl^-), which is consistent with large downfield shift ($\Delta\delta$ = 0.6 ppm) of the CH^f signal upon chloride binding (Fig. 2c). Third, in the packing structure, the helically folded complex stacks to afford one-dimensional (1D) columnar arrays[10] with tetrabutylammonium cations intercalated between the anionic complexes alternatively. This 1D columnar structure is stabilised mainly by electrostatic forces between chloride and tetrabutylammonium ions, and the N^+···Cl^- distances are equally 5.58 Å for upper and lower ion pairs. Noticeably, the CH protons in the γ and δ carbons of the tetrabutylammoniums directly come into contact with indolocarbazole surfaces. In addition, two of four butyl chains interact with the aryl plane in the upper complex and the remaining two chains come into contact with that in the lower one. This observation indicates that the CH···π interaction is an additional force stabilising the 1D columnar array.

In conclusion, it is demonstrated that the helicity direction of a foldamer can be effectively controlled by incorporation of chiral segments at ends. The foldamer described here displays characteristic CD signals responsive to the solvent polarity as well as anion binding, which might be further applied to the development of molecular sensors and switches based on the chiroptical signal.

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