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Oligoindole-Based Foldamers with a Helical Conformation Induced by Chloride

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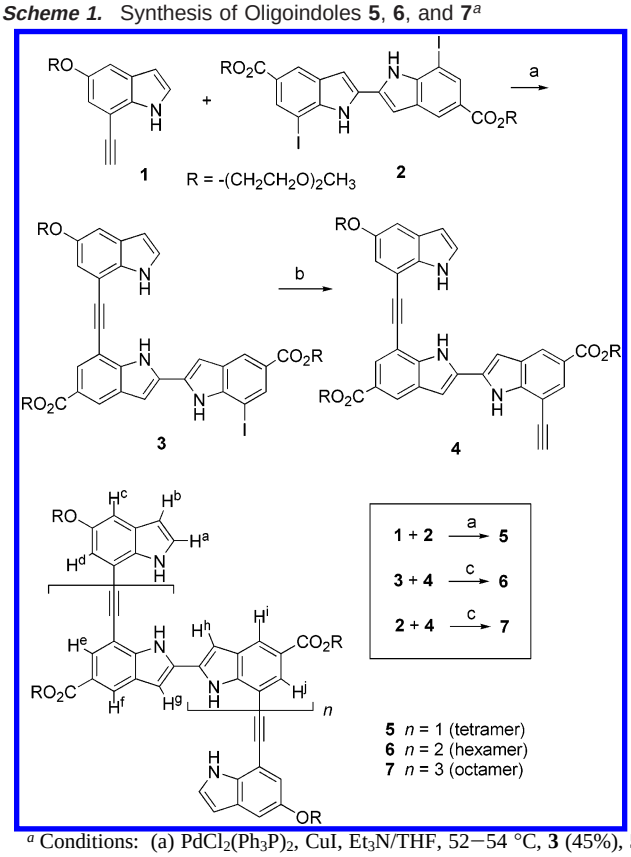
In recent years, much effort has been devoted to the synthesis and characterization of foldamers, synthetic molecules that fold into an ordered array by noncovalent interactions, to gain deeper insight on the folding principle of natural molecules and to create new bioinspired materials responsive to external stimulation.[1] A number of foldamers adopting ordered helical conformations have been reported to date,[2−4] and some of them have been demonstrated as synthetic receptors capable of accommodating small organic molecules in the internal cavities.[3] In addition, cations, such as transition metals and ammoniums, have been frequently used as templates to generate supramolecular helical structures.[4] However, examples of anion-induced foldamers with a helical conformation are extremely rare,[5] despite wide application of anions as templates to the supramolecular synthesis.[6] This is partly attributed to the lack of a molecular building block suitable to the construction of the foldamer bearing hydrogen-bond donors in the internal cavity. Herein, we report on a new type of foldamer based on oligoindoles, which can adopt a helical conformation stabilized by hydrogen-bonding interactions with chloride.

As molecular building blocks, a monoindole **1** and a biindole **2** were designed and synthesized from *p*-nitrophenol and *p*-aminobenzoic acid, respectively (see Supporting Information). The side chain of the diethylene glycol unit was introduced at the 5-position of the indole ring, outside of the cavity on the helical conformation, to modulate the solubility of the oligoindole in organic solvents. Oligoindoles **5**, **6**, and **7** were prepared by repeating Sonogashira coupling reaction:[7] tetramer **5** from **1** (2 equiv) and **2**, hexamer **6** from two trimers **3** and **4**, and octamer **7** from **2** and **4** (2 equiv).

According to computer modeling,[8] tetramer **5** exists in an extended structure where the biindole unit maintains *s-trans* conformation. When complexed with an anion, however, the biindole adopts a *s-cis* conformation and, consequently, four indole NHs of **5** become convergent to be simultaneously involved in hydrogen bonding. Moreover, hexamer **6** and octamer **7**, in the presence of an anion, give ordered helical conformations with one turn comprising four indole units; **6** and **7** yield 1.5 and 2 turns, respectively. Here, the folded structures generate an internal cavity surrounded by all of the existing NHs in a helical manner, and the size of the cavity matches well with that of chloride (see Supporting Information).

The folding properties of the oligoindoles in solution were first revealed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of **5**, **6**, and **7** were considerably changed when chloride was added as tetrabutylammonium salt at room temperature (Figure 1). For example, the NH signals (two for **5**, three for **6**, and four for **7**) were downfield shifted as a result of hydrogen-bonding formation. In addition, the aromatic CH signals of longer oligoindoles **6** and **7** are characteristically upfield shifted in the presence of chloride ($\Delta\delta$ 0.3−0.5 ppm), while those of tetramer **5** remain unchanged ($\Delta\delta$ < 0.05 ppm). The upfield shifts must, therefore, be attributed to the aromatic stacking induced by the helical folding of **6** and **7**.

Scheme 1. Synthesis of Oligoindoles **5**, **6**, and **7**[a]



[a] Conditions: (a) $PdCl_2(Ph_3P)_2$, CuI, Et_3N/THF, 52−54 °C, **3** (45%), **5** (15%). (b) $Pd(dba)_2$, CuI, Ph_3P, trimethylsilylethyne, Et_3N/THF, 52−54 °C, 75%, then TBAF−AcOH, rt, 92%. (c) $PdCl_2(Ph_3P)_2$, CuI, Et_3N/THF, 52−54 °C, 70%.

It should be also mentioned that the ^{1}H NMR spectral changes were saturated when 1 equiv of chloride was added, implying that each of the oligoindoles binds 1 equiv of chloride.

As mentioned above, hexamer **6** can fold into a helical conformation with 1.5 turns, thus making a half of the internal biindole moieties stacked with terminal indole units but the other half not stacked (Figure 2). This is probably responsible for the sharp and well-resolved ^{1}H NMR spectrum (Figure 1d), and therefore, we carried out further the ^{1}H NMR studies with **6**. The ^{1}H NMR signals were unambiguously assigned by a combination of 2D NMR experiments, TOCSY, NOESY, and ROESY (see Supporting Information). The aromatic signals (H^a, H^b, and H^c) for the terminal indoles were upfield shifted ($\Delta\delta$ 0.40−0.49 ppm) upon addition of chloride. More importantly, the signals (H^e and H^f) for the stacked portion of the internal biindole in the helical conformation were greatly upfield shifted ($\Delta\delta$ 0.34 ppm) relative to the aryl signals, H^i and H^j, without being stacked ($\Delta\delta$ 0.02−0.04 ppm). Furthermore, the 2D ROESY experiment illustrated nicely that the NOE cross-peaks between H^b and H^g, H^c and H^f, and H^d and H^e

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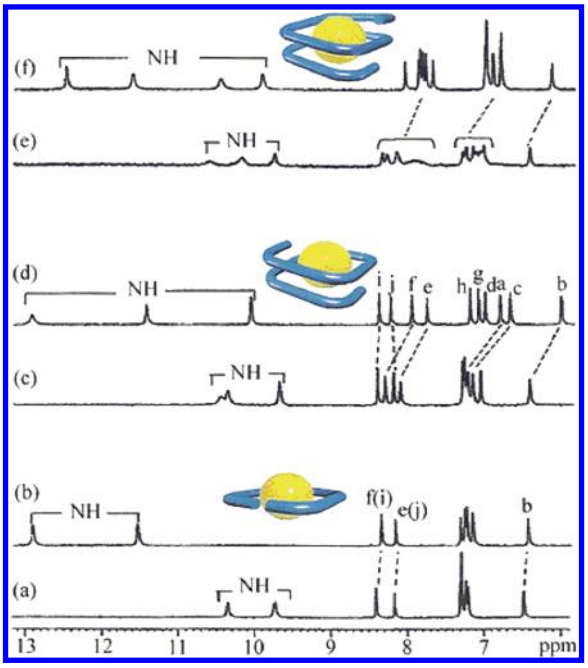

Figure 1. ^{1}H NMR (500 MHz, CD_3CN) spectral changes of oligoindoles ($2-5 \times 10^{-4}$ M) upon addition of chloride (1 equiv) at 25 °C: (a) **5**, (b) **5** + Cl^-, (c) **6**, (d) **6** + Cl^-, (e) **7**, and (f) **7** + Cl^-. Herein, magnitudes of chloride-induced changes ($\Delta\delta$) in the NH chemical shifts are 2.5 and 1.8 ppm for **5**, 2.4, 1.1, and 0.3 ppm for **6**, and 1.9, 1.5, 0.3, and 0.1 ppm for **7**.

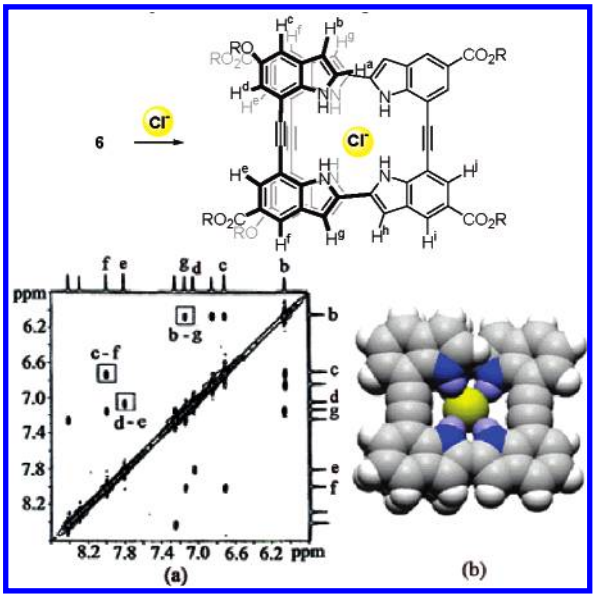

Figure 2. (a) ^{1}H−^{1}H ROESY spectrum of **6** + Cl^- (1 equiv) and (b) the energy-minimized structure (MacroModel 7.1, Amber* force field), where side chains were replaced by hydrogens. The structure is arbitrarily drawn in a *M*-helix.

exist in the presence of chloride (1 equiv), diagnostic of stacking between two indoles. In the absence of chloride, however, these NOE correlations could not be seen under the same experimental conditions. This is definitive evidence for a helically stacked conformation of **6** upon complexation with chloride.

The binding studies of the oligoindoles with chloride provided additional evidence for the helical conformation of oligoindoles. The UV/visible absorption spectra of **5**, **6**, and **7** (1.0×10^{-5} M in CH_3CN) were gradually changed as a solution of chloride was added while keeping the oligoindole concentration constant at 22 ± 1 °C. Nonlinear least-squares fitting analyses[9] of the titration curves gave association constants (K_a) of $1.3(\pm0.1) \times 10^5$ M^{-1} for **5**, $1.2(\pm0.1) \times 10^6$ M^{-1} for **6**, and $>10^7$ M^{-1} for **7**. Here, the association constants of **6** and **7** were too high to determine accurately in CH_3CN, and therefore, the magnitudes were compared in a more competitive medium, 10% (v/v) H_2O/CH_3CN. Under these conditions, the association constants were determined to be $2.1(\pm0.1) \times 10^2$ M^{-1} for **6** and $2.3(\pm0.2) \times 10^4$ M^{-1} for **7**. The latter value is unexpectedly high in a polar aqueous solution, considering that hydrogen bonds are a main driving force for the association. As anticipated, the association constants increase greatly with increasing number of the hydrogen-bond donors, indole NHs. In addition, Job's plots demonstrated that the oligoindoles formed 1:1 complexes with chloride (see Supporting Information). Again, these results are all consistent with the helical folding of the oligoindoles.[10]

In conclusion, a series of oligoindoles described here fold into a helical conformation by entrapping chloride inside the tubular cavity through hydrogen-bonding interactions. Modification of the oligomer length and the side chain may produce an oligoindole-based foldamer that gives a more stable helical conformation with a longer cavity, thus serving as an artificial chloride channel.[11]

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Supporting Information Available: Synthesis, modeling structures, 2D NMR spectra, and UV/visible binding studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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