

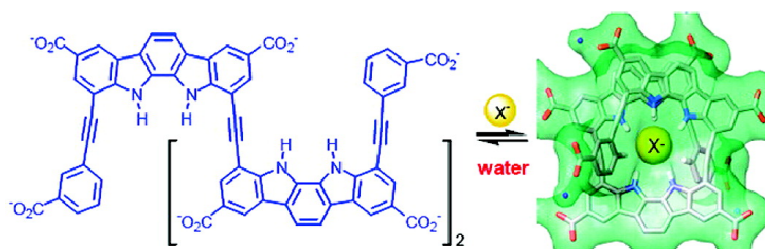
Communication

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## Indolocarbazole-Based Foldamers Capable of Binding Halides in Water

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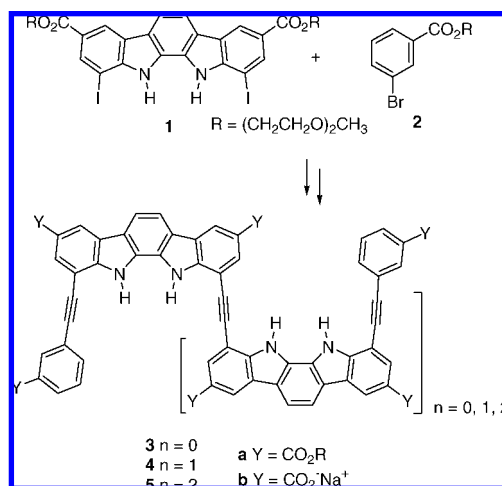
The structure and function of proteins and enzymes stem from folding of the primary sequences through various noncovalent interactions in water. The binding pocket, generated by the folding process, is surrounded by organic fragments and segregated from the bulk water. As a consequence, the hydrogen bond still plays a key role in binding and transporting an anion in aqueous media as seen in sulfate- and phosphate-binding proteins and a CIC chloride channel.<sup>1</sup> In contrast, most of the synthetic receptors based on the hydrogen bond are not able to bind an anion in water because the binding sites are completely exposed to the outside and strongly solvated by water molecules, which reduce the binding affinity between the receptor and the anion.<sup>2</sup>

Foldamers are synthetic molecules capable of folding into ordered arrays such as helical structures.<sup>3–5</sup> Some helical foldamers possess an internal cavity able to accommodate a complementary guest.<sup>4–6</sup> In particular, a water-soluble foldamer composed of the aromatic scaffold may fold to create a binding cavity shielded from the bulk water,<sup>7</sup> which would possibly allow anion binding to be studied in water. With this in mind, we here prepared a series of indolocarbazoles **3**, **4**, and **5** which can fold into a helical array to render an internal cavity with multiple indole NHs.<sup>8</sup> A water-soluble foldamer of the longest strand **5b** binds small halides such as fluoride, chloride, and bromide in water but does not bind larger anions such as iodide and perchlorate. Interestingly, the chloride ion binds in water slightly better than the fluoride ion, which is reverse to the binding trend ( $F^- > Cl^-$ ) of **5a** in an organic medium, 4:1 (v/v) DMSO/MeOH.

For the preparation of foldamers, indolocarbazole **1** with two indole NHs and an extended aromatic surface<sup>9</sup> was prepared as the repeating unit (Scheme 1). Using the Pd/CuI catalyzed reaction, **1** and **2** were coupled through ethynyl linkers to yield **3a**, **4a**, and **5a** with ester side chains which were subsequently hydrolyzed with KOH/DMSO–H<sub>2</sub>O to give the corresponding water-soluble derivatives, **3b**, **4b**, and **5b**. Details are described in the Supporting Information.

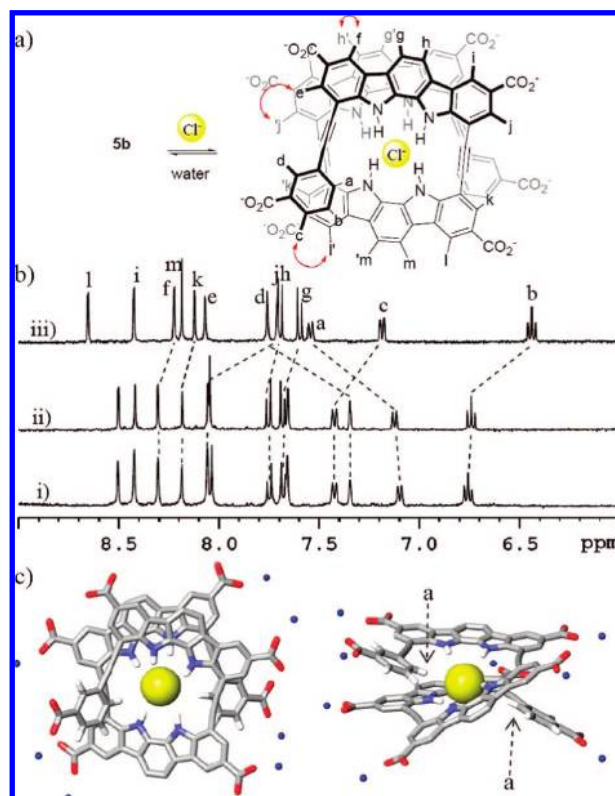
The folding properties of **3a**, **4a**, and **5a** were first investigated in organic media. The <sup>1</sup>H NMR spectra of the short strands **3a** and **4a** are sharp and well-resolved in acetone-*d*<sub>6</sub>. On the other hand, the <sup>1</sup>H NMR spectrum of the longer one **5a** is completely broadened out on the baseline but becomes sharpened upon addition of tetrabutylammonium chloride (see Supporting Information). Three NH signals of **5a** are clearly resolved, and all appear at far downfield regions (12.82, 11.64, and 11.01 ppm) as a result of hydrogen bonding with the chloride ion. The aromatic CH signals are upfield shifted relative to the corresponding signals of **3a**. The average chemical shifts for the aromatic signals of **3a**, **4a**, and **5a** in the presence of chloride are more upfield shifted as the chain length grows. The computer modeling<sup>10</sup> shows that **4a** and **5a** are capable of folding into a helical structure of approximately one and one-half turns and two turns, respectively. In addition, the 2D <sup>1</sup>H NMR ROESY experiment with a 1:1 mixture of **5a** and tetrabutylammonium chloride shows characteristic NOE cross-peaks which can

**Scheme 1.** Synthesis of Foldamers **3**, **4**, and **5**



be observed only in the helically folded conformation (see Supporting Information). These observations suggest consistently that **5a** adopts a compact helical conformation upon binding a chloride. Finally, the association constant of **5a** with tetrabutylammonium chloride is determined to be 36 800 M<sup>-1</sup> in a highly polar medium 4:1 (v/v) DMSO/MeOH at 24 ± 1 °C, while those of **3a** and **4a** are only 11 and 560 M<sup>-1</sup>, respectively.<sup>11</sup> The magnitude of the association constants reflects the number of possible hydrogen bonds in complexes. It should be noted that the helical folding of **5a** is the only way for all the existing NHs able to participate in hydrogen bonding with a chloride, thus forming a 1:1 complex.<sup>12</sup>

Next, the folding and binding properties in water were revealed with water-soluble derivatives, **3b**, **4b**, and **5b**. Regardless of the chain length, the foldamers display concentration-independent (<1.0 × 10<sup>-3</sup> M) and well resolved <sup>1</sup>H NMR signals in D<sub>2</sub>O at room temperature. In addition, signals for the terminal benzoate of **5b** are noticeably upfield shift ( $\Delta\delta = 0.4$ –1 ppm) relative to those of **3b**. These observations imply that **5b** exists in a nonaggregated, compact form, unlike the ester derivative **5a** in organic solvents. The binding properties of **3b**, **4b**, and **5b** with sodium salts were qualitatively compared in water. The <sup>1</sup>H NMR spectra of the shorter chains **3b** and **4b** remained unchanged when a large excess (~400 equiv) of any kind of sodium halides was added. On the other hand, the spectral behavior of **5b** depends on the kind of sodium salts; the spectral changes are apparent with small anions (NaF, NaCl, and NaBr) but negligible with large anions (NaI and NaClO<sub>4</sub>) as shown in Figure 1b. The 2D <sup>1</sup>H NMR ROESY spectrum of complex **5b**·Cl<sup>-</sup> confirms the helical folding in water, showing the NOE cross-peaks between H<sup>c</sup> and H<sup>i</sup>, H<sup>c</sup> and H<sup>j</sup>, H<sup>f</sup> and H<sup>h</sup> (Figure 1a and Supporting Information).<sup>13</sup> The <sup>1</sup>H NMR titration experiments were carried out at a constant concentration of **5b** (2.0 × 10<sup>-4</sup> M) by increasing the amount of a salt in D<sub>2</sub>O at 24 ± 1 °C, showing



**Figure 1.** (a) NOE cross-peaks are marked by double-headed arrows, observed from 2D  $^1\text{H}$  NMR ROESY spectrum. (b)  $^1\text{H}$  NMR spectra (400 MHz,  $\text{D}_2\text{O}$ , 25  $^\circ\text{C}$ ) of **5b** ( $2.0 \times 10^{-4}$  M) in the presence of (i) none, (ii)  $\text{NaClO}_4$  (100 equiv), and (iii)  $\text{NaCl}$  (100 equiv). (c) Top (left) and side (right) views of an energy-minimized structure (MacroModel 9.1, MMFFs force field, in water). The  $\text{C}-\text{H}_a$  hydrogen atoms, hydrogen bonded with the chloride ion, are marked by dotted arrows in the side view.

the induced chemical shift changes of  $\Delta\delta = \pm 0.1\text{--}0.7$  ppm for the aromatic signals. According to computer modeling (Figure 1c), the chloride ion is stabilized by a total of eight hydrogen bonds: six with indole NHs and two with  $\text{CH}^a$  hydrogens on the benzoate termini. The latter  $\text{CH}^a \cdots \text{Cl}^-$  hydrogen bonds make both benzoate termini inclined toward the indolocarbazole surface, thus allowing for a tilted T-shape stacking. As a result,  $\text{H}^b$  and  $\text{H}^c$  are directed on the aromatic plane but  $\text{H}^d$  is further away. This conformational variation as well as polarization by the anion is possibly responsible for noticeable upfield shifts of the  $\text{H}^b$  and  $\text{H}^c$  signals and downfield shifts of the  $\text{H}^a$  and  $\text{H}^d$  signals.

Nonlinear squares fitting of the titration curves, plotted for all of the aromatic protons, provided an identical association constant of  $65 \pm 2 \text{ M}^{-1}$ , meaning that all of the chemical shift changes are associated with the same binding event. Moreover, the binding affinity with the chloride ion was found to be independent of the counterion;  $\text{LiCl}$ ,  $\text{NaCl}$ , and  $\text{KCl}$  gave an identical binding constant. Finally, the binding selectivity between anions was revealed in water using sodium salts. **5b** binds fluoride ( $46 \pm 2 \text{ M}^{-1}$ ) and bromide ( $19 \pm 2 \text{ M}^{-1}$ ) but negligibly binds iodide and perchlorate ( $<1 \text{ M}^{-1}$ ). It is unexpected that the fluoride ion shows lower affinity than chloride. The fluoride ion solvates much more strongly in water than the chloride ion, and consequently the former requires higher desolvation energy for binding,<sup>14</sup> which is possibly attributed to the reduced affinity. For comparison, the association constants between **5a** with tetrabutylammonium halides were

determined in an organic medium, 4:1 (v/v)  $\text{DMSO}/\text{MeOH}$ . As anticipated based on the hydrogen-bonding capability, the association constants decrease in the order  $\text{F}^-$  ( $183\,000 \text{ M}^{-1}$ )  $>$   $\text{Cl}^-$  ( $36\,800 \text{ M}^{-1}$ )  $>$   $\text{Br}^-$  ( $1350 \text{ M}^{-1}$ )  $>$   $\text{I}^-$  ( $86 \text{ M}^{-1}$ ).

In conclusion, we have prepared indolocarbazole-based foldamers which can adopt a helical conformation affording a tubular cavity functionalized by multiple indole NHs. In particular, a water-soluble derivative of the longest strand **5b** binds smaller halides by multiple hydrogen bonds in the order  $\text{Cl}^- > \text{F}^- > \text{Br}^-$  in water, different from the binding trend in organic media due to the competing solvation energy. We are currently pursuing development of a water-soluble foldamer which not only imparts the enhanced affinity and selectivity toward an anion but also functions as a synthetic anion carrier or channel through lipid membranes.

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**Supporting Information Available:** Synthetic procedures, characterization of compounds, computer modeling, and all of the binding studies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (11) Titrations were carried out in the  $^1\text{H}$  NMR (**3a** and **4a**) or fluorescence spectroscopy (**5a**), and the binding constants ( $K_a \pm 10\%$ ,  $\text{M}^{-1}$ ) were evaluated by nonlinear squares fitting analyses.
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