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Folding and Anion-Binding Properties of Fluorescent Oligoindole Foldamers

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Abstract: A series of oligoindole foldamers **1a–d** that are highly fluorescent were prepared by using a biindole derivative as the repeating unit, and their folding and anion-binding properties were revealed by ^{1}H NMR and fluorescence spectroscopy. The oligoindoles exist in an extended conformation, but adopt a compact helical structure in the presence of an anion. The anion is entrapped inside the tubular cavity of the helical strand, comprising four aryl units per turn, by multiple hydrogen bonds with the indole NHs. These structural features were confirmed by ^{1}H NMR and fluorescence spectroscopy. When folded by anion binding, **1b–d** show characteristic downfield shifts of the NH signals and upfield shifts of the aromatic CH signals by $\Delta\delta = 0.1$–1.0 ppm. The average chemical shift for all the aromatic signals of **1a–d** is more upfield shifted as the chain lengthens, as anticipated from the degree of overlapped aromatic surfaces in the helical strand. Moreover, **1a–d** are strongly fluorescent in the absence of an anion. Upon binding an anion such as a chloride, the shorter oligoindoles **1a** and **b** lead to negligible change in the emission spectra, whereas the longer ones **1c** and **d** result in dramatic changes, that is, large hypochromic and bathochromic shifts ($\Delta\lambda =$ 65 and 70 nm) of the emission band, confirming the helical folding. The association constants (K_a) between oligoindoles and tetrabutylammonium chloride strongly depend on the chain length; $<1\,\text{M}^{-1}$ for **1a**, $630\,\text{M}^{-1}$ for **1b**, $1.1\times10^5\,\text{M}^{-1}$ for **1c**, and $2.9\times10^5\,\text{M}^{-1}$ for **1d** in 20% (v/v) MeOH/CH_2Cl_2 at 24 ± 1 °C. In addition, the association constants of **1c** and **1d** with other anions such as fluoride, bromide, iodide, azide, cyanide, acetate, and nitrate are determined to be in the order of 10^3–$10^6\,\text{M}^{-1}$ under the same conditions.

Keywords: anions · foldamers · helical structures · hydrogen bonding · receptors

Introduction

Despite high diversity and complexity, proteins and enzymes possess common structural motifs such as helices, sheets, and turns, which are stabilized by hydrogen bonds, dipole–dipole interactions, and other non-covalent forces. Over the last decade, chemists have prepared a variety of synthetic molecules capable of folding into an ordered array, so-called foldamers,[1] to gain insight into the fundamental principles for folding as well as to develop functional materials responsive to external stimulus. Examples include peptidomimetic foldamers derived from natural or unnatural amino acids,[2] aryl strand foldamers from rigid aromatic building blocks,[3–11] and others.[12] In recent years, more efforts have been made in the development of functional foldamers able to serve as synthetic receptors[13–15] or enzyme mimics.[16]

Indole, a key component of tryptophan, possesses a good hydrogen-bond donor of NH. It is, therefore, not surprising to find proteins and enzymes that utilize indole NHs for hydrogen bonding with anions, such as in sulfate-binding protein[17] and haloalkane dehalogenase.[18] We[19] and others[20–22] have demonstrated that indole can serve as a useful molecular building block for the construction of synthetic anion receptors. Among these, oligoindole foldamers have proven to adopt a helical structure upon binding a chloride, which leads to the conformational change of large amplitude.[15a] If this conformational variation results in absorption and or emission change, the foldamer would be highly attractive for possible applications as molecular sensors and smart materials responsive to external stimulation. With this in mind, we herein prepared a series of strongly fluorescent oligoindoles **1a–d** containing between two and eight indole rings, and their folding and anion-binding properties were characterized by ^{1}H NMR and fluorescence spectroscopy.

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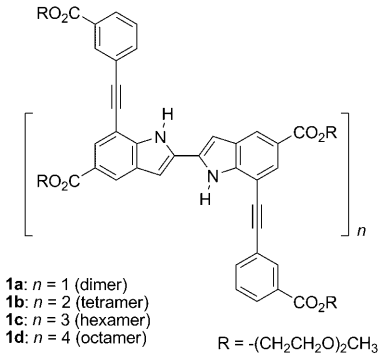


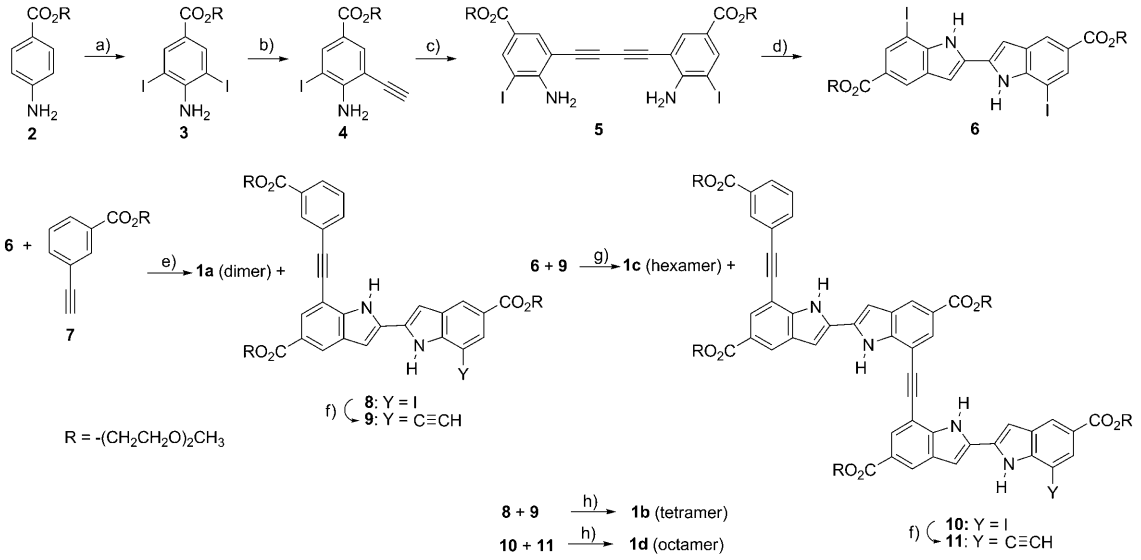
The longer sequences **1b–d** are able to fold into helical structures in the presence of an anion, as demonstrated by characteristic upfield shifts of the ^{1}H NMR aromatic signals and bathochromic ($\Delta\lambda = 65$–70 nm) and hypochromic shifts of the emission bands. In particular, the dramatic changes in the fluorescence spectra allow us to conveniently determine and compare the binding affinities between **1c**, **d** and anions in a competitive medium 20% (v/v) $MeOH/CH_2Cl_2$.

Results and Discussion

Design principles and synthesis: For the construction of a foldamer, a key task is to select or design a proper monomer bearing all the information necessary for elongation and folding, such as proper functional groups, bending angle, and orientation. We chose an indole derivative functionalized at the 2- and 7-positions as a molecular building block because 1) it possesses a good hydrogen-bonding donor NH, and 2) the relative orientation between the 2- and 7-positions of indole is nearly perpendicular and, therefore, the elongation of the strand through these positions would afford a helical structure comprising four indole units per turn. The actual molecule we used as the repeating scaffold is a 2,2′-biindole derivative **6**. Here, the side chain of methoxyethoxyethyl esters at 5,5′-positions greatly increases the solubility of the oligomers in organic solvents, and the iodo groups at 7,7′-positions serve for the connection through Sonogashira coupling[23] under mild conditions. Finally, the fluorescent properties of oligoindoles have been found to be highly sensitive to the nature of terminal groups. Among those prepared in this laboratory, the benzoate group confers the strongest emission and, moreover, shows the largest change in intensity and wavelength of the band upon anion binding.

The synthesis began with 4-aminobenzoate **2**, which was reacted with I_2/Ag_2SO_4 to give 4-amino-3,5-diiodobenzoate (**3**, 91% yield).[24] The coupling reaction[23] of **3** and trimethylsilylethyne (1 equiv), followed by removal of the TMS group, gave compound **4** (51% yield for two steps), which was sequentially subjected to oxidative coupling[25] (95% yield) and indolization[26] (93% yield) in the presence of copper salts to give a biindole **6**. Then, 3-ethynylbenzoate **7** (1 equiv) was coupled to **6** to give **8** (49% yield) and dimer **1a** (22% yield). By similar procedures, tetramer **1b**, hexamer **1c**, and octamer **1d** were prepared from **6** and **8** as described in the Experimental Section (Scheme 1).

Computer modeling: The repeating biindole scaffold exists in the s-*trans* conformation between two indole rings; two NHs are in the opposite direction to minimize dipole–dipole repulsion according to computer modeling (MacroModel 9.1, MMFF force field).[28,29] Upon anion binding, the conformation switches to the s-*cis*, so that two indole NHs are able to simultaneously participate in hydrogen bonding with an anion.



Scheme 1. Synthesis of **1a–d**. a) I_2, Ag_2SO_4, EtOH, RT, 91%; b) $[Pd(PPh_3)_2Cl_2]$, CuI, trimethylsilylethyne, Et_3N/THF, 58–60°C, then TBAF, AcOH, THF, RT, 51% (2 steps); c) $Cu(OAc)_2{\cdot}H_2O$, pyridine, RT, 95%; d) CuI, DMF, 124–136°C, 93%; e) $[Pd(PPh_3)_2Cl_2]$, CuI, Et_3N/THF, 56–62°C, **8** (49%), **1a** (22%); f) $[Pd(PPh_3)_2Cl_2]$, CuI, trimethylsilylethyne, Et_3N/THF, 56–59°C, then TBAF, AcOH, THF, RT, **9** (74%), **11** (67%); g) $[Pd(PPh_3)_2Cl_2]$, CuI, Et_3N/THF, 56–62°C, **10** (55%), **1c** (18%); h) the same as g): **1b** (48%), **1d** (50%).

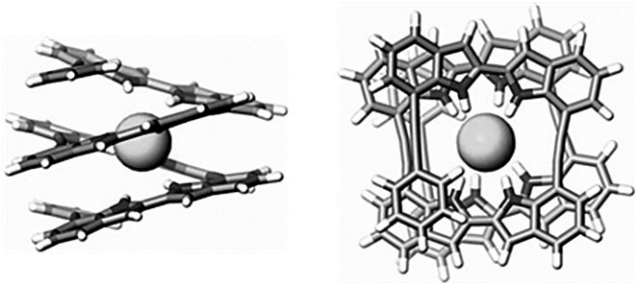


Figure 1. Side (left) and top (right) views of an energy-minimized structure[27] for complex **1d**-Cl$^-$ (MacroModel 9.1,[28] MMFF[29] force field, gas phase). The ester side chains of **1d** have been replaced with hydrogen atoms.

Oligoindoles **1a–d** exist in an extended conformation in the absence of an anion, but fold into a compact helical structure upon anion binding. The anion, for example, the chloride ion becomes entrapped inside the tubular cavity by multiple hydrogen bonds with the indole NHs (Figure 1). The relative orientation between *i* and *i*+2 residues of the sequence is nearly perpendicular, thus leading to one turn consisting of four aromatic components. As a consequence, **1b–d** are able to fold into a helical conformation of one-and-a-half, two, and two-and-a-half turns, respectively (Figure 1 for **1d** and also see Supporting Information).

Folding studies by ^{1}H NMR spectroscopy: Oligoindoles **1a–c** give well-resolved ^{1}H NMR spectra in [D$_6$]acetone at room temperature (Figure 2). In contrast, the ^{1}H NMR spectrum of the longest octamer **1d** is completely broadened out in the absence of an anion, but becomes sharp and nicely resolved upon addition of an anion, for example, a chloride (Figure 2g). In all cases, the NH signals for all the oligoindoles are shifted downfield in the presence of tetrabutylammonium chloride as a result of hydrogen bonding in [D$_6$]acetone. For example, the NH signal of **1a** is shifted from 11.50 to 14.27 ppm, and those of **1b** are shifted from 11.49 and 12.13 ppm to 11.56 and 13.57 ppm. Interestingly, among three NH signals in **1c** two are downfield shifted but one is slightly upfield shifted upon binding the chloride ion. This is possibly ascribed to the combination of hydrogen bonding, stacking, and desolvation associated with the conformational switching from an open extended arrangement to a compact helical one.

The aromatic CH signals provide clear evidence for the helical folding of oligoindoles in the presence of the chloride ion. The ^{1}H NMR data for the aromatic signals are summarized and compared in Table 1. The shortest strand **1a**, a reference without any stacking between aromatic surfaces, shows negligible changes in the chemical shifts of aromatic signals, except those for H^a and H^d involved in the CH···Cl$^-$ hydrogen bonds. On the other hand, the longer sequences **1b** and **1c** are able to fold into a helical conformation, thus

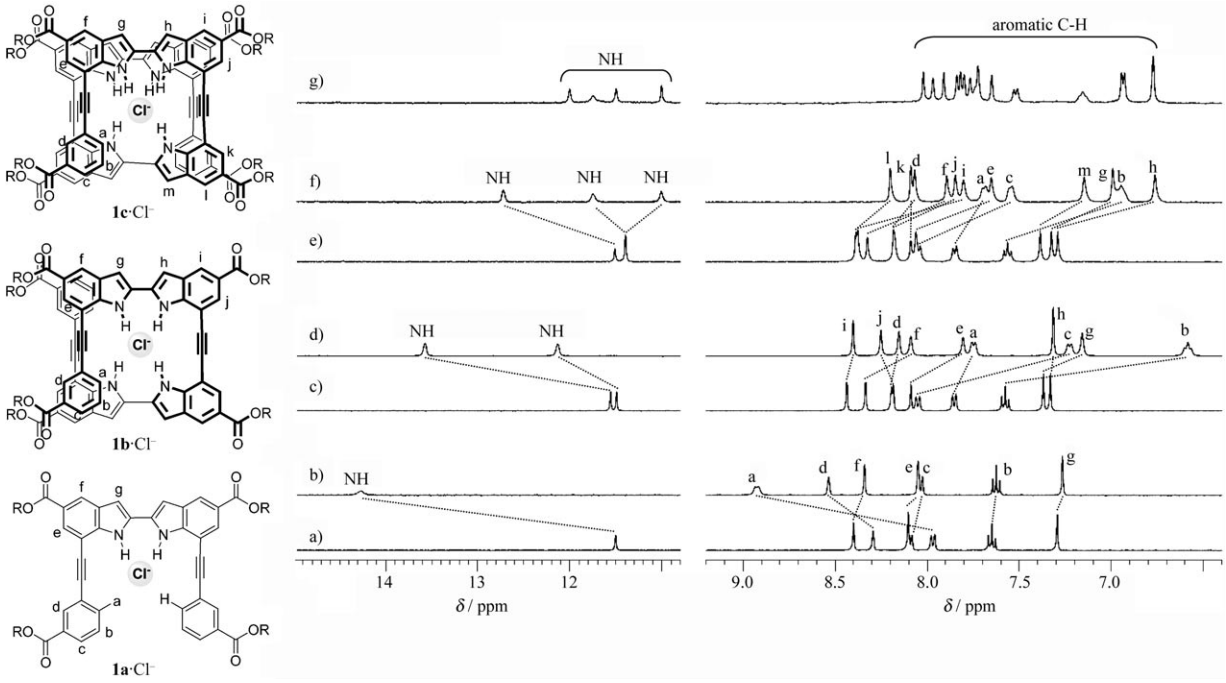


Figure 2. Partial ^{1}H NMR spectra (400 MHz, [D$_6$]acetone, 25 °C) of a) **1a** (0.5 mM), b) **1a** (0.5 mM)+nBu$_4$N$^+$Cl$^-$ (1 equiv), c) **1b** (0.5 mM), d) **1b** (0.5 mM)+nBu$_4$N$^+$Cl$^-$ (1 equiv), e) **1c** (0.3 mM), f) **1c** (0.3 mM)+nBu$_4$N$^+$Cl$^-$ (1 equiv), and g) **1d** (0.1 mM)+nBu$_4$N$^+$Cl$^-$ (1 equiv).

allowing for intramolecular aromatic stacking. In the presence of the chloride ion (<1 equiv), **1b** and **1c** show two separate sets of ^{1}H NMR signals, one for the free and another for its complex, due to slow exchange on the NMR (400 MHz) timescale in [D$_6$]acetone at room temperature (see Supporting Information). When more than one equivalent of the chloride ion is added, the signals for the complex can be only seen in the expense of the free. The trend and magnitude of the chemical-shift changes in Table 1 are consistent with the energy-minimized structures of **1b** and **1c** that afford helical structures of one-and-a-half turns and two turns, respectively. In the presence of excess TBA$^+$Cl$^-$ (5 equiv), the ^{1}H NMR spectrum of **1b** and **1c** became broadened without changing the chemical shifts of the signals, but the longer oligoindole **1d** afforded broad ^{1}H NMR signals with different chemical shifts, possibly attributed to the formation of a 2:1 Cl$^-$/**1d** complex under these conditions. Additional evidence for the helical conformation was obtained from 2D ^{1}H ROESY experiments with a 1:1 mixture of **1c** and tetrabutylammonium chloride (Figure 3). Nuclear Overhauser effect (NOE) correlations are clearly observed between H^h and H^f, H^j and H^e, and H^m and H^c, which are not detectable without the anion, confirming the anion-induced helical conformation. Finally, the average chemical shift for the aromatic signals of **1a–d** in the presence of the chloride ion is plotted against the chain length (Figure 4). More upfield shift is observed as the chain grows, which is consistent with the degree of stacked aromatic surfaces in the helically folded strand. All of the observations described above consistently support that oligoindoles **1b–d** fold into a compact, helical conformation in the presence of the chloride ion.

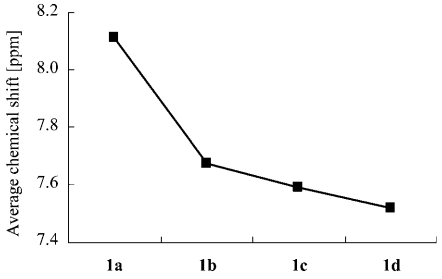


Figure 4. Average chemical shifts of aromatic proton signals of **1a–d** when complexed with tetrabutylammonium chloride in [D$_6$]acetone at 25 °C.

Table 1. Changes in the chemical shift of ^{1}H NMR aromatic signals of oligoindoles **1a–c** upon addition of tetrabutylammonium chloride (1 equiv) in [D$_6$]acetone at 25 °C.

Aromatic proton	Induced chemical-shift change [ppm, $\Delta\delta=\delta_{complex}-\delta_{free}$]		
	1a	**1b**	**1c**
H^a	+0.95	−0.11	−0.16
H^b	−0.03	−1.00	−0.61
H^c	−0.05	−0.82	−0.50
H^d	+0.24	−0.04	−0.11
H^e	−0.05	−0.28	−0.41
H^f	−0.06	−0.24	−0.44
H^g	−0.02	−0.21	−0.34
H^h		−0.02	−0.53
H^i		−0.04	−0.59
H^j		+0.07	−0.33
H^k			0.00
H^l			−0.19
H^m			−0.24

Folding studies by fluorescence spectroscopy: Fluorescence spectroscopy has been widely used to characterize the folding of aromatic strand foldamers.[4,8,11] The helical folding often leads to the bathochromic and/or hypochromic shifts of the emission spectra because of the intramolecular excimer formation in the stacked aromatic array. The fluorescence spectra of **1a–d** were taken with excitation at 310 nm in 20% (v/v) MeOH/CH_2Cl_2 at room temperature. Under these conditions, oligoindoles **1a–d** showed strong emission bands with the highest intensities at wavelengths 418, 427, 428, and 433 nm, respectively. The quantum yields[30] were measured to be 0.82 (**1a**), 0.70 (**1b**), 0.49 (**1c**), and 0.39 (**1d**) by using quinine sulfate as a reference.[31] Upon addition of tetrabutylammonium chloride up to 1000 equivalents, the emission spectrum of **1a** remained unchanged, whereas that of **1b** showed slight red shift (≈10 nm) without any noticeable hypochromic shift. In contrast, the longer strands **1c** and **d**

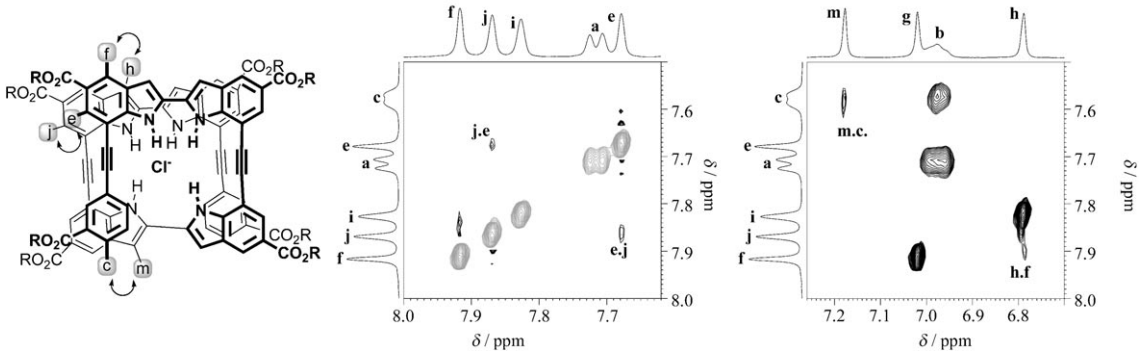


Figure 3. 2D ^{1}H NMR ROESY spectrum of **1c** in the presence of tetrabutylammonium chloride (1 equiv) in [D$_6$]acetone at 25 °C. The NOE cross-peaks, diagnostic signals for helical folding, are observed between H^h and H^f, H^j and H^e, and H^m and H^c.

capable of folding into helical structures showed dramatic changes. That is, the emission band at 428 (**1c**) or 433 nm (**1d**) were significantly quenched and a new broad band appeared at 493 nm (**1c**) or 503 nm (**1d**) (Figure 5). This result must be attributed to excimer formation between overlapped indole surfaces, which strongly supports the helical folding of **1c** and **d**. As demonstrated in Figure 5, a solution of **1c** (or **1d**) turns from bright blue to dim bluish-green upon addition of tetrabutylammonium chloride (>1 equiv) in acetone.

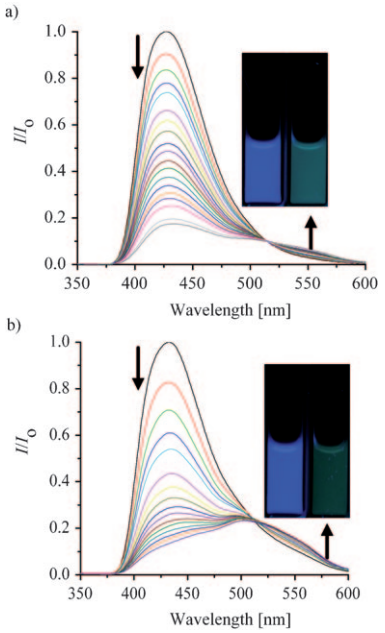


Figure 5. Fluorescence spectral changes of **1c** (left) and **1d** (right) upon addition of tetrabutylammonium chloride in 20% (v/v) $MeOH/CH_2Cl_2$ at 24±1°C. The fluorescence color of each solution (2×10^{-6} M) changes from blue to bluish-green upon addition of tetrabutylammonium chloride (5 equiv) in acetone.

Binding studies: To quantitatively reveal and compare the binding affinities, titrations were performed in a hydrogen-bond-competitive medium 20% (v/v) $MeOH/CH_2Cl_2$ at 24±1°C using ^{1}H NMR spectroscopy for **1a** and **b** and fluorescence spectroscopy for **1c** and **d**. As mentioned above, the NH signal of **1a** was largely downfield shifted ($\Delta\lambda$ = 2.8 ppm) in [D_6]acetone upon addition of tetrabutylammonium chloride (1 equiv). However, in a more competitive medium 20% (v/v) [D_3]CH_3OH/[D_2]CH_2Cl_2, the induced shift is negligible ($\Delta\delta<0.05$ ppm), even in the presence of excess (≈10 equiv) tetrabutylammonium chloride due to a weak binding constant ($K_a<1\,M^{-1}$). On the other hand, two NH signals of **1b** were significantly downfield shifted from 11.30 and 11.47 ppm to 11.72 and 12.92 ppm during the titration in 20% (v/v) [D_3]CH_3OH/[D_2]CH_2Cl_2 at 24±1°C. The time-averaged ^{1}H NMR signals of the free and complex were observed in this medium, unlike in acetone. The nonlinear least-squares fitting[32] of two NH titration curves yielded an identical association constant (K_a) of 625±15 M^{-1}, indicative of two NHs participating in the same binding event. The association constants of the longer strands **1c** and **d** with the chloride ion could not be determined by the ^{1}H NMR titration because of high affinities and severe aggregation at the concentration for the ^{1}H NMR spectroscopy.

Fluorescence spectroscopy was used to quantify the association constants between **1c** and **d** and anions. Prior to the titration, we demonstrated that the fluorescence intensity of **1c** and **d** is linearly proportional to the concentration ranging from 0.2×10^{-6} M to 4×10^{-6} M in 20% (v/v) [D_3]CH_3OH/[D_2]CH_2Cl_2. The titration experiments were conducted at the constant concentration (1.0×10^{-6} M) of **1c** (or **1d**) by gradually increasing the concentration of an anion, which resulted in significant quenching of the emission band at 428 nm (**1c**) or 433 nm (**1d**) and arising of a new broad band at 493 nm (**1c**) or 503 nm (**1d**). The association constants, analyzed by nonlinear least-squares fitting,[32] are summarized in Table 2. First, the association constants of **1c** and **1d** with the chloride ion are estimated to be $1.1\times10^5\,M^{-1}$ and $2.9\times10^5\,M^{-1}$, respectively, which are much higher than that of tetramer **1b** ($625\,M^{-1}$). The difference in the association constants of **1b** and **1c** is approximately 180-fold, but only threefold between **1c** and **1d**, although the indole NHs increase by the same number upon going from **1b** to **1c** to **1d**. Job's plots[32b,33] show that **1b**, **1c**, and **1d** form 1:1 complexes with anions.[34] These results imply that the chloride ion is effectively wrapped up by **1c** with six indole units and, therefore, two additional indole NHs in **1d** contribute little to the stability of the complex. Finally, the binding affinities of **1c** and **1d** with other anions are compared with each other. In a series of halides, the binding affinity parallels with the hydrogen-bonding ability of a halide. Considering the basicities, halides bind more strongly relative to polyatomic anions. According to computer modeling, spherical halides are better entrapped in a sandwiched manner in between two turns of the helical conformation.

Table 2. Association constants (K_a±20%, M^{-1}) of oligoindoles **1c** and **d** with anions in 20% (v/v) $MeOH/CH_2Cl_2$ at 24±1°C.

Anion	K_a [M^{-1}]	
	1c	**1d**
F^-	5.1×10^5	1.2×10^6
Cl^-	1.1×10^5	2.9×10^5
Br^-	1.6×10^4	5.0×10^4
I^-	4.0×10^3	2.1×10^4
CN^-	8.5×10^4	1.1×10^5
N_3^-	6.0×10^4	1.2×10^5
NO_3^-	4.8×10^3	8.0×10^4
AcO^-	2.9×10^4	9.4×10^4

Conclusions

We have described a series of oligoindoles **1a–d** that adopt a compact helical structure induced by an anion entrapped

in the tubular cavity through multiple hydrogen bonds with the indole NHs. Helical folding was unambiguously proven by results of ^{1}H NMR spectroscopy, which shows characteristic upfield shifts of the aromatic CH signals, together with downfield shifts of the NH signals as a result of the hydrogen bonding. Oligoindoles **1a** and **d** bind anions, and the binding strengths depend on the number of hydrogen bonds and the nature of anions. Upon binding an anion, the longer oligoindoles **1c** and **d** display large hypochromic and bathochromic shifts of the emission bands, along with the fluorescence color change from blue to bluish-green. This color change informs us of the folded or unfolded state of oligoindoles, as well as the anion-binding event. Consequently, the foldamer described here not only functions as a synthetic receptor or sensor for anions but also has potential to be utilized for external stimuli-responsive materials with fluorescence signaling.

Experimental Section

General: Air- or moisture-sensitive reactions were carried out under nitrogen or argon. All chemicals were used as purchased unless noted. Triethylamine was distilled over CaH_2, and THF was distilled from sodium/benzophenone. Column chromatography was performed on silica gel 60 (230–240 mesh). ^{1}H NMR spectra were recorded by using Bruker DRX 400 and DRX 500 instruments, and chemical shifts were reported in ppm relative to the residual protonated peaks ($CHCl_3$: $\delta = 7.26$ ppm for ^{1}H, $\delta = 77.16$ ppm for ^{13}C; DMSO: $\delta = 2.50$ ppm for ^{1}H, $\delta = 39.52$ ppm for ^{13}C; acetone: $\delta = 2.05$ ppm for ^{1}H). Melting points were measured by using a Barnstead Electrothermal (IA9100) apparatus and are uncorrected. The UV/Vis spectra were recorded by using an Agilent 8453 UV-visible spectrophotometer, fluorescence spectra by using a F-4500 fluorescence spectrophotometer, and FTIR spectra by using a Nicolet Impact-400 FTIR spectrometer. Elemental analyses were obtained from the National Center for Inter-University Research Facilities at the Seoul National University.

2-(2-Methoxyethoxy)ethyl 4-amino-3,5-diiodobenzoate (3): I_2 (60 g, 0.24 mol, 2.2 equiv) and Ag_2SO_4 (74 g, 0.24 mol, 2.2 equiv) were added to a solution of **2** (27.0 g, 113 mmol) in EtOH (1.4 L).[24] The mixture was mechanically stirred for 1 h at RT, then filtered through Celite and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (500 mL). The solution was washed with 1 N NaOH aqueous solution, saturated aqueous $NaHCO_3$ solution, brine and water, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography (CH_2Cl_2/EtOAc 1:3) to give **3** as a white floppy solid (50.6 g, 91 %). M.p. 80–81 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, $CHCl_3$): $\delta = 8.28$ (s, 2H), 5.06 (s, 2H; NH_2), 4.40 (m, 2H), 3.78 (m, 2H), 3.65 (m, 2H), 3.54 (m, 2H), 3.37 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C, $CHCl_3$): $\delta = 163.8$, 149.8, 141.1, 122.4, 79.4, 72.8, 70.6, 69.3, 64.1, 59.2 ppm; IR (KBr): $\tilde{\nu} = 3428$ (NH_2), 1705 (C=O) cm^{-1}; ESI-MS: m/z: 513.8 $[M+Na]^+$.

2-(2-Methoxyethoxy)ethyl 4-amino-3-ethynyl-5-diiodobenzoate (4): Compound **3** (18.0 g, 36.7 mmol), $[Pd(PPh_3)_2Cl_2]$ (0.52 g, 0.02 equiv), and CuI (0.18 g, 0.025 equiv) were placed in a Schlenk flask. The flask was degassed under high vacuum and back-filled with nitrogen. This process was repeated three times. Dried THF (50 mL), Et_3N (300 mL), and trimethylsilylethyne (5.2 mL, 1.0 equiv) were added, and the solution was stirred at 58–60 °C for 18 h. The mixture was filtered through Celite, the organic solution was concentrated, and the residue was dissolved in CH_2Cl_2. The organic solution was washed with saturated aqueous $NaHCO_3$ solution, brine and water, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography (EtOAc/hexane 1:3) to give a TMS-protected precursor ($\approx$8.0 g). This intermediate was dissolved in THF (40 mL) and the solution was cooled to 0 °C (iced-water bath), to which acetic acid (1.1 equiv) and tetrabutylammonium fluoride (TBAF) (1 M in THF, 1.1 equiv) were sequentially added and the solution was stirred for 30 min at RT. After concentration, the reaction mixture was dissolved in EtOAc, washed with saturated $NaHCO_3$ solution, brine and water. The crude product was purified by flash column chromatography (EtOAc/hexane 1:2) to give **4** (7.3 g, 51 %) as a white solid. M.p. 73–74 °C; ^{1}H NMR (500 MHz, $[D_6]$DMSO, 25 °C, DMSO): $\delta = 8.19$ (s, 1H), 7.82 (s, 1H), 6.08 (s, 2H; NH_2), 4.64 (s, 1H), 4.34 (m, 2H), 3.75 (m, 2H), 3.61 (m, 2H), 3.49 (m, 2H), 3.29 ppm (s, 3H); ^{13}C NMR (126 MHz, $[D_6]$DMSO, 25 °C, DMSO): $\delta = 163.8$, 153.0, 140.7, 133.7, 118.6, 104.7, 87.0, 81.4, 79.2, 71.3, 69.6, 68.3, 63.8, 58.1 ppm; IR (KBr): $\tilde{\nu} = 3429$ (NH_2), 2101(C≡C), 1706 (C=O) cm^{-1}; ESI-MS: m/z: 411.8 $[M+Na]^+$.

Compound 5: Compound **4** (6.0 g, 15 mmol) was dissolved in pyridine (60 mL) and $Cu(OAc)_2 \cdot H_2O$ (3.4 g, 17 mmol) was added.[25] After stirring at RT for 16 h, the mixture was filtered through Celite and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2, and the organic solution was washed with saturated aqueous $NaHCO_3$ solution, brine and water, and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by column chromatography (EtOAc/hexane 2:1) to give **5** as a yellow solid (5.7 g, 95 %). M.p. 112–113 °C; ^{1}H NMR (500 MHz, $[D_6]$DMSO, 25 °C, DMSO): $\delta = 8.18$ (s, 1H), 7.88 (s, 1H), 6.42 (s, 2H; NH_2), 4.40 (m, 2H), 3.78 (m, 2H), 3.65 (m, 2H), 3.54 (m, 2H), 3.37 ppm (s, 3H); ^{13}C NMR (126 MHz, $[D_6]$DMSO, 25 °C, DMSO): $\delta = 163.6$, 153.8, 141.5, 134.4, 118.6, 103.1, 82.0, 79.2, 71.2, 70.0, 68.3, 64.0, 58.1 ppm; IR (KBr): $\tilde{\nu} = 3470$ (NH_2), 2128 (C≡C), 1704 (C=O) cm^{-1}; ESI-MS: m/z: 799.1 $[M+Na]^+$.

Biindole 6: A solution containing **5** (4.0 g, 5.2 mmol) and CuI (2.0 g, 10 mmol, 2.1 equiv) in DMF (50 mL) was heated at 124–136 °C for 8.5 h.[26] The reaction mixture was cooled to ambient temperature, filtered through Celite, and concentrated. The residue was dissolved in CH_2Cl_2 and the organic solution was washed with saturated aqueous $NaHCO_3$ solution, brine and water, dried over anhydrous $MgSO_4$, and concentrated. The residue was washed with a small amount of EtOAc (slightly soluble) to give **6** as a white solid (3.7 g, 93 %). M.p. 161–162 °C; ^{1}H NMR (500 MHz, $[D_6]$DMSO, 25 °C, DMSO): $\delta = 11.66$ (s, 2H; NH), 8.24 (s, 2H), 8.10 (s, 2H), 7.48 (s, 2H), 4.39 (m, 4H), 3.77 (m, 4H), 3.61 (m, 4H), 3.47 (m, 4H), 3.26 ppm (s, 6H); ^{13}C NMR (126 MHz, $[D_6]$DMSO, 25 °C, DMSO): $\delta = 165.2$, 141.3, 132.3, 132.0, 128.0, 123.2, 122.4, 104.0, 76.2, 71.2, 70.0, 68.4, 64.0, 58.1 ppm; IR (KBr): $\tilde{\nu} = 3437$ (NH), 1711 (C=O) cm^{-1}; ESI-MS: m/z: 799.1 $[M+Na]^+$.

2-(2-Methoxyethoxy)ethyl-3-ethynylbenzoate (7): 3-Bromobenzoate (3.16 g, 10 mmol), $[Pd(dba)_2]$ (dba = (*E*,*E*)-dibenzylideneacetone) (60 mg, 0.1 mmol, 0.01 equiv), PPh_3 (140 mg, 0.5 mmol, 0.05 equiv), and CuI (20 mg, 0.1 mmol, 0.01 equiv) were placed in a Schlenk flask. The flask was degassed under high vacuum and back-filled with nitrogen. This process was repeated three times. Dried THF (20 mL), Et_3N (30 mL), and trimethylsilylethyne (2.3 mL, 15 mmol, 1.5 equiv) were added. The solution was stirred under nitrogen at 82–87 °C for 19 h, and cooled to ambient temperature. The mixture was filtered through Celite and the filtrate was concentrated. The residue was dissolved in EtOAc, and washed with saturated $NaHCO_3$ solution, brine and water. The organic layer was dried over anhydrous $MgSO_4$. Without further purification, the crude product was dissolved in THF (30 mL) to which acetic acid (1 M in THF, 10 mL) and TBAF (1 M in THF, 10 mL) were sequentially added at 0 °C, and the solution was stirred for 30 min at RT. After concentration, the reaction mixture was dissolved in EtOAc, washed with saturated $NaHCO_3$ solution, brine and water. The organic layer was dried through anhydrous $MgSO_4$. The crude product was purified by flash column chromatography (CH_2Cl_2) to give **7** as an oily liquid (2.38 g, 92 %). ^{1}H NMR (400 MHz, $[D_6]$DMSO, 25 °C, DMSO): $\delta = 7.96$–7.94 (2H, two peaks overlapped), 7.74 (d, $J = 7.6$ Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 1H), 4.37 (t, $J = 4.4$ Hz, 2H), 4.31 (s, 1H), 3.72 (t, $J = 4.4$ Hz, 2H), 3.56 (t, $J = 4.8$ Hz, 2H), 3.42 (t, $J = 4.4$ Hz, 2H), 3.21 ppm (s, 3H); ^{13}C NMR (100 MHz, $[D_6]$DMSO, 25 °C, DMSO): $\delta = 164.9$, 136.3, 132.1, 130.3, 129.6, 129.5, 122.3, 82.3, 82.02, 81.99, 71.3, 69.7, 68.3, 64.4, 58.1 ppm; IR (thin film): $\tilde{\nu} = 2251$ (C≡C), 1720 (C=O) cm^{-1}; ESI-MS: m/z: 271.1 $[M+Na]^+$.

Compound 8: Compound **6** (2.41 g, 3.10 mmol, 1.1 equiv), CuI (10 mg, 0.06 mmol, 0.02 equiv), and $[Pd(PPh_3)_2Cl_2]$ (20 mg, 0.03 mmol, 0.01 equiv) were placed in a Schlenk flask. The flask was degassed under high vacuum and back-filled with nitrogen. This process was repeated three times. Dried THF (20 mL) and Et_3N (70 mL) were added. Then, a degassed THF solution (10 mL) of **7** (0.7 g, 2.82 mmol, 1.0 equiv) was added under a cannula. The resulting solution was stirred under nitrogen at 56–62 °C for 15 h, and cooled to ambient temperature. The mixture was filtered through Celite and the filtrate was concentrated. The residue was dissolved in EtOAc, and washed with saturated $NaHCO_3$ solution, brine and water. The organic layer was dried over anhydrous $MgSO_4$. After concentration, the residue was purified by column chromatography (EtOAc/hexane 4:1) to give **8** as a slightly yellowish solid (1.23 g, 49%), together with **1a** (0.57 g, 22%). Compound **8**: M.p. 111–112 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 12.20 (s, 1H; NH), 11.71 (s, 1H; NH), 8.35 (m, 2H), 8.30 (d, J = 1.2 Hz, 1H), 8.13 (d, J = 1.2 Hz, 1H), 8.06 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 7.99 (d, J = 1.6 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.53 (s, 2H), 4.43 (m, 6H), 3.79 (m, 6H), 3.63 (m, 6H), 3.48 (m, 6H), 3.27 (s, 3H), 3.26 (s, 3H), 3.23 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 165.8, 165.3, 165.1, 141.5, 139.2, 136.3, 132.72, 132.68, 132.2, 131.9, 130.3, 129.6, 129.5, 128.4, 128.0, 126.9, 123.6, 123.2, 123.1, 122.5, 121.8, 105.3, 103.7, 103.3, 92.34, 86.4, 76.2, 71.3, 69.69, 69.67, 68.5, 68.4, 68.3, 64.4, 64.0, 58.1, 58.08 ppm; IR (thin film): $\tilde{\nu}$ = 3312 (NH), 2202 (C≡C), 1713 (C=O), 1597 (C=C) cm^{-1}; elemental analysis calcd (%) for $C_{42}H_{45}IN_2O_{12}$: C 56.26, H 5.06, N 3.12; found: C 56.22, H 5.02, N 3.11.

Compound 9: Compound **8** (1.19 g, 1.33 mmol), CuI (10 mg, 0.025 equiv) and $[Pd(PPh_3)_2Cl_2]$ (20 mg, 0.02 equiv) were placed in a Schlenk flask. The flask was degassed under high vacuum and back-filled with nitrogen. This process was repeated three times. Dried THF (5 mL), Et_3N (10 mL), and trimethylsilylethyne (0.30 mL, 1.0 mmol, 1.5 equiv) were added. The solution was stirred under nitrogen at 56–59 °C for 19 h, and then cooled to ambient temperature. The mixture was filtered through Celite and the filtrate was concentrated. The residue was dissolved in EtOAc, and washed with saturated $NaHCO_3$, brine and water. The organic layer was dried over anhydrous $MgSO_4$. After concentration, the residue was purified by column chromatography (EtOAc/hexane 3:1) to give a TMS-protected precursor (0.89 g). The TMS group (0.89 g, 1.03 mmol) was carefully removed with acetic acid (1.1 equiv) and TBAF (2.0 equiv) in THF (10 mL) to give **9** as a slightly yellowish solid (0.78 g, 74%). M.p. 109–110 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 12.16 (s, 2H; NH), 8.35 (s, 2H), 8.33 (s, 1H), 8.06 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 1.6 Hz, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.52 (s.1H), 7.45 (s, 1H), 4.68 (s, 1H), 4.43 (m, 6H), 3.79 (m, 6H), 3.63 (m, 6H), 3.48 (m, 6H), 3.27 (s, 3H), 3.26 (s, 3H), 3.23 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 165.84, 165.79, 165.1, 139.8, 139.3, 136.3, 132.9, 132.2, 131.54, 131.45, 130.3, 129.6, 129.5, 128.5, 128.3, 127.05, 126.8, 123.6, 123.5, 123.1, 121.8, 121.6, 105.3, 105.1, 103.1, 103.0, 92.3, 86.3, 85.6, 79.6, 71.3, 69.68, 69.66, 68.4, 68.3, 64.4, 63.9, 58.11, 58.07 ppm; IR (thin film): $\tilde{\nu}$ = 3282 (NH), 2206 (C≡C), 1713 (C=O), 1597 (C=C) cm^{-1}; elemental analysis calcd (%) for $C_{44}H_{46}N_2O_{12}$: C 66.49, H 5.83, N 3.52; found: C 66.51, H 5.83, N 3.50.

Compound 10: Using **6** (1.89 g, 2.43 mmol, 1.1 equiv) and **9** (1.76 g, 2.21 mmol, 1.0 equiv), **10** was prepared following the same procedure described for the preparation of **8**. The product was purified by column chromatography (MeOH/CH_2Cl_2 1:49) to give **10** as a white solid (1.76 g, 55%), together with **1c** as a white solid (0.84 g, 18%). Compound **10**: M.p. 218–220 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 12.30 (s, 2H; NH), 12.23 (s, 1H; NH), 11.74 (s, 1H; NH), 8.42 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 8.24 (m, 4H), 8.10 (s, 1H), 7.99 (m, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.56 (m, 5H), 4.43 (m, 10H), 3.79 (m, 10H), 3.62 (m, 10H), 3.47 (m, 10H), 3.26 (s, 3H), 3.25 (s, 3H), 3.24 (s, 3H), 3.23 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 166.0, 165.8, 165.3, 165.1, 141.5, 139.5, 139.4, 139.3, 136.1, 133.0, 132.9, 132.8, 132.6, 132.1, 131.9, 130.1, 129.4, 129.2, 128.4, 128.0, 127.1, 126.9, 123.63, 123.55, 123.2, 123.0, 122.5, 121.8, 106.02, 105.96, 105.5, 103.8, 103.3, 103.2, 103.18, 103.13, 92.4, 89.7, 89.6, 86.4, 76.1, 71.33, 71.27, 69.7, 69.8, 68.5, 68.4, 68.3, 64.4, 64.0, 63.9, 58.1 ppm; IR (thin film): $\tilde{\nu}$ = 3308 (NH), 2210 (C≡C), 1709 (C=O), 1601 (C=C) cm^{-1}; elemental analysis calcd (%) for $C_{72}H_{75}IN_4O_{20}$: C 59.92, H 5.24, N 3.88; found: C 59.24, H 5.21, N 3.84.

Compound 11: This compound was obtained from **10** as a white solid (67% yield) according to the same procedure for the preparation of **9** from **8**. M.p. 198–200 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 12.29 (s, 2H; NH), 12.18 (s, 2H; NH), 8.42 (s, 1H), 8.38 (s, 1H), 8.35 (s, 1H), 8.26 (m, 4H), 7.99 (m, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 7.55 (m, 5H), 4.58 (s, 1H), 4.43 (m, 10H), 3.79 (m, 10H), 3.63 (m, 10H), 3.47 (m, 10H), 3.24 ppm (m, 15H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 166.0, 165.81, 165.75, 165.1, 139.8, 139.42, 139.37, 139.3, 136.1, 133.0, 132.87, 132.86, 132.79, 132.0, 130.1, 129.41, 129.38, 129.2, 128.42, 128.41, 128.2, 127.2, 127.1, 127.0, 126.89, 126.9, 123.61, 123.55, 123.48, 123.43, 123.0, 121.8, 121.7, 121.6, 105.5, 105.1, 103.27, 103.25, 103.1, 102.92, 102.90, 85.5, 79.5, 78.7, 69.68, 69.65, 69.62, 68.5, 68.4, 68.2, 64.3, 64.0, 63.95, 63.91, 63.88, 58.05, 58.04 ppm; IR (thin film): $\tilde{\nu}$ = 3429 (NH), 2115 (C≡C), 1718 (C=O), 1648 (C=C) cm^{-1}; elemental analysis calcd (%) for $C_{74}H_{76}N_4O_{20}$: C 66.26, H 5.71, N 4.18; found: C 65.68, H 5.97, N 3.93.

Dimer 1a: See procedure for **8** described above. M.p. 116–117 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 12.30 (s, 2H; NH), 8.37 (d, J = 8.8 Hz, 3H), 8.05 (t, J = 7.2 Hz, 4H), 7.99 (s, 2H), 7.67 (t, J = 8.0 Hz, 3H), 7.45 (s, 2H), 4.43 (m, 8H), 3.79 (m, 8H), 3.62 (m, 8H), 3.47 (m, 8H), 3.266 (s, 3H), 3.264 (s, 3H), 3.233 (s, 3H), 3.231 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 165.8, 165.1, 139.4, 136.3, 132.9, 132.2, 130.3, 129.5, 129.4, 128.4, 126.8, 123.6, 123.1, 121.8, 105.4, 103.2, 92.4, 86.3, 71.3, 69.7, 68.4, 68.3, 64.4, 63.9, 58.08, 58.05 ppm; IR (thin film): $\tilde{\nu}$ = 3330 (NH), 1709 (C=O) cm^{-1}; elemental analysis calcd (%) for $C_{56}H_{60}N_2O_{16}$: C 66.13, H 5.95, N 2.75; found: C 66.18, H 6.00, N 2.71.

Tetramer 1b: Using **8** (0.21 g, 0.23 mmol) and **9** (0.18 mg, 0.23 mmol, 1 equiv), **1b** was prepared as a slightly greenish solid (0.12 g, 48% yield) by the same procedure described for the preparation of **1a**. The product was first purified by column chromatography (MeOH/CH_2Cl_2 1:49), then washed with water to remove any inorganic salt possibly contaminated during the column chromatography. M.p. 171–173 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 12.25 (s, 4H; NH), 8.41 (s, 2H), 8.31 (s, 2H), 8.24 (s, 4H), 7.99 (s, 4H), 7.97 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.57 (t, J = 8.0 Hz, 2H), 7.50 (s, 4H), 4.42 (m, 12H), 3.78 (m, 12H), 3.62 (m, 12H), 3.47 (m, 12H), 3.26 (s, 6H), 3.24 (s, 6H), 3.22 ppm (s, 6H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 166.0, 165.8, 165.0, 139.4, 136.1, 132.92, 132.85, 132.0, 130.1, 129.4, 129.2, 128.4, 127.1, 126.9, 123.7, 123.6, 123.5, 123.0, 121.80, 121.76, 106.0, 105.4, 103.2, 103.1, 103.0, 92.4, 89.6, 86.3, 71.3, 71.2, 69.70, 69.66, 69.54, 68.50, 68.4, 68.2, 64.3, 64.0, 63.9, 58.1 ppm; IR (thin film): $\tilde{\nu}$ = 3360 (NH), 1722 (C=O) cm^{-1}; elemental analysis calcd (%) for $C_{86}H_{90}N_4O_{24}$: C 66.06, H 5.80, N 3.58; found: C 65.74, H 5.82, N 3.58.

Hexamer 1c: See the procedure for **10** described above. After column chromatography (MeOH/CH_2Cl_2 1:39), the product was washed with ethyl acetate to remove unknown organic impurities, then with water to remove any inorganic salt contaminated during the column chromatography. M.p. 236–238 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 12.33 (s, 2H; NH), 12.15 (s, 4H; NH), 8.37 (s, 2H), 8.28 (m, 7H), 8.08 (s, 2H), 7.96 (m, 7H), 7.56 (m, 4H), 7.43 (s, 4H), 4.43 (m, 16H), 3.76 (m, 16H), 3.61 (m, 16H), 3.47 (m, 16H), 3.23 ppm (m, 18H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 166.0, 165.9, 165.8, 165.1, 139.31, 139.29, 139.24, 136.1, 132.8, 132.7, 132.1, 130.1, 129.3, 129.2, 128.4, 128.28, 128.25, 127.2, 126.9, 123.54, 123.48, 123.45, 123.29, 123.27, 123.1, 121.9, 121.6, 106.1, 105.8, 105.3, 103.2, 102.9, 92.3, 89.8, 89.6, 86.5, 71.28, 71.26, 71.25, 71.23, 69.69, 69.67, 69.63, 68.5, 68.3, 64.3, 63.94, 63.86, 58.07, 58.05, 58.03 ppm; IR (thin film): $\tilde{\nu}$ = 3338 (NH), 2279 (C≡C), 1709 (C=O), 1661 (C=C) cm^{-1}; elemental analysis calcd (%) for $C_{116}H_{120}N_6O_{32}$: C 66.02, H 5.73, N 3.98; found: C 65.39, H 5.70, N 3.51.

Octamer 1d: This compound was prepared as a white solid (0.32 g, 50% yield) from **10** (0.24 g, 0.17 mmol) and **11** (0.23 g, 0.17 mmol) by the same procedure described for the preparation of **1b**. After column chromatography (MeOH/CH_2Cl_2 1:24), the product was washed with ethyl acetate to remove unknown organic impurities, then with water to remove any inorganic salt contaminated during the column chromatography. M.p.

280–282 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 12.22 (m, 8H; NH), 8.26 (m, 12H), 8.12 (m, 4H), 7.95 (m, 6H), 7.50 (m, 10H), 4.41 (m, 20H), 3.76 (m, 20H), 3.61 (m, 20H), 3.46 (m, 20H), 3.23 ppm (m, 30H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C, DMSO): δ = 166.54, 166.50, 166.46, 166.4, 165.6, 139.9, 139.80, 139.78, 136.7, 133.4, 133.32, 133.28, 132.6, 130.7, 129.9, 129.7, 128.8, 127.87, 127.85, 127.83, 127.79, 127.72, 127.70, 127.41, 127.40, 127.38, 127.35, 123.7, 122.24, 122.17, 106.54, 106.52, 105.8, 103.58, 103.52, 103.49, 103.46, 103.45, 103.42, 92.8, 90.3, 87.0, 71.86, 71.83, 71.82, 70.28, 70.24, 70.20, 69.1, 68.8, 64.9, 64.47, 64.43, 64.38, 58.63, 58.60 ppm; IR (thin film): $\tilde{\nu}$ = 3468 (NH), 1718 (C=O), 1631 (C=C) cm^{-1}; elemental analysis calcd (%) for $C_{146}H_{150}N_8O_{40}$: C 66.00, H 5.69, N 4.22; found: C 65.45, H 5.70, N 4.12.

^{1}H NMR titration: Stock solutions of **1b** (1.00×10^{-3} M) and tetrabutylammonium chloride (1.0×10^{-2} M) in 4:1 (v/v) [D$_2$]CH$_2$Cl$_2$/[D$_3$]CH$_3$OH were separately prepared. An amount, 450 μL, of **1b** was transferred to an NMR tube, and an initial spectrum was taken at 25 °C. Small portions of the tetrabutylammonium chloride solution were added, the spectrum was recorded after each addition, and 17 data points were obtained. The association constant (K_a, M^{-1}) was determined by nonlinear least-squares fitting of the titration curves.

Fluorescence titration: Dichloromethane and methanol of a spectroscopic grade were degassed prior to use. A stock solution (1.0×10^{-6} M, 10 mL) of **1c** (or **1d**) was prepared in 4:1 (v/v) CH$_2$Cl$_2$/methanol. Using this solution, each stock solution (2.0–3.0 mL) of tetrabutylammonium anions was prepared and the concentrations were between 3.0×10^{-5} and 2.0×10^{-3} M, depending on the magnitude of the association constant. A solution of **1c** (or **1d**) (1.0 mL) was transferred to a fluorescence cell, and an initial fluorescence spectrum was taken. Then, the anion solution (5–10 μL initially, then 20–100 μL, and finally 200–700 μL) was added and the spectrum was recorded after each addition, thus affording 12–19 data points overall at 24 ± 1 °C. The association constant (K_a, M^{-1}) was determined by nonlinear least-squares fitting of the titration curves.

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