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Folding of Aromatic Amide-Based Oligomers Induced by Benzene-1,3,5-tricarboxylate Anion in DMSO

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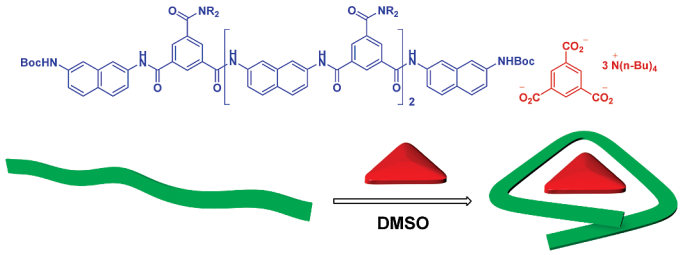

In this paper, we describe the folding of a series of linear arylamide oligomers in DMSO that is induced by benzene-1,3,5-tricarboxylate anion. The oligomers are comprised of naphthalene-2,7-diamine and 1,3,5-benzenetricarboxylic acid segments with two (*tert*-butoxycarbonylamino) groups at the ends and two to four hydrophilic *N*,*N*-bis(2-(2-(2-methoxyethoxy)ethoxy)ethyl)amino groups at one side of the backbones. (2D NOESY) ^{1}H NMR, fluorescence and UV−vis studies indicate that the oligomers do not adopt defined conformations in DMSO but fold into compact structures in the presence of the anion. It is revealed that the folded conformation is induced by intermolecular hydrogen bonds between the amide and aromatic hydrogen atoms of the oligomers and the oxygen atoms of the anion. ^{1}H NMR and UV−vis titrations support a 1:1 binding stoichiometry, and the associated constants are determined, which are found to increase with the elongation of the oligomers.

Introduction

Inspired by the helical or folded structures that are commonly found in proteins and nucleic acids, in the past decade there has been an increasing interest in developing foldamers, synthetic oligomers that spontaneously fold into well-defined secondary structures.[1] In most cases, the driving forces come from varying intramolecular interactions. Examples of the folded backbones that utilize this approach include linear heterocycles,[2] amino acid derivatives,[3] oligomeric arylamides,[4] and (*m*-phenylene ethynylene)s,[5] some of which have been reported to recognize small organic molecules[6] or serve as enzyme mimics to catalyze or promote

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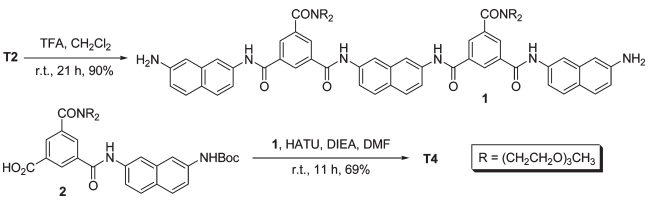
discrete reactions.[7] Another approach to create folded or helical structures makes use of an external interaction. In this case, the backbones themselves are structurally flexible but may fold to convergent conformations through binding a neutral or ionic template or undergoing photoisomerization.[8−14] In this context, chloride anion has recently been used as a template to induce structurally matched indole- and 1,2,3-triazole-based oligomers to fold through the intermolecular N−H···Cl^- or C−H···Cl^- hydrogen bonding.[13,14]

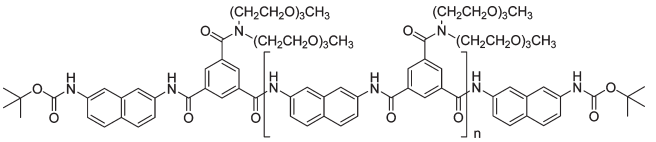
We have a long-standing interest in designing folded systems for molecular recognition.[15] In particular, we have constructed several series of arylamide oligomers-based artificial receptors whose folded conformations are stabilized by the intramolecular hydrogen bonding.[6a−c] One issue related to this series of arylamide backbones is whether they can form folded conformations without the induction of the intramolecular hydrogen bonding. To address this issue, we have designed a class of arylamide oligomers consisting of alternate benzene and naphthalene segments. Molecular mechanics calculations were performed on representative oligomer **T3** (without side chains). The result shows that its energy-minimized conformation forms a folded structure to host a 1,3,5-tricarboxylate anion (see Supporting Information). In this paper, we report that strong complexation did occur between them in DMSO, a highly polar solvent, which are driven by the intermolecular N−H···O^- and C−H···O^- hydrogen bonds, leading to the formation of folded structures. To the best of our knowledge, this research represents the first example using an organic anion to induce folded structures.

SCHEME 1. Synthetic Route for Compound T4

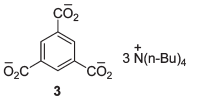


Results and Discussion

Synthesis. Compounds **T1**−**T4** have been designed for binding benzene-1,3,5-tricarboxylate anion (**3**). Compounds **T1**−**T3** were prepared according to reported methods.[16] The synthetic route for longer oligomer **T4** is provided in Scheme 1. Thus, compound **T2** was first treated with an excess of trifluoroacetic acid in dichloromethane to afford diamine **1**, which was then coupled with acid **2**[16] in DMF in the presence of HATU and DIEA to afford **T4** in 69% yield. Compound **T4** has been characterized by ^{1}H and ^{13}C NMR spectroscopy and (high-resolution) mass spectrometry.



T1: n = 0, **T2**: n = 1, **T3**: n = 2, **T4**: n = 3



3

^{1}H NMR Studies. Since the guest molecule tetrabutylamonium benzene-1,3,5-tricarboxylate (**3**) was insoluble in organic solvents of low polarity such as chloroform, dichloromethane, or acetonitrile, we chose to use DMSO-d_6 as the solvent. The binding behavior of **T3** was first investigated. The formation of a folded structure for **T3** to bind the benzene-1,3,5-tricarboxylate anion was first evidenced by ^{1}H NMR titration experiments. As can be seen in Figure 1, **T3** itself gave rise to a set of signals of high resolution. However, upon incremental introduction of **3**, a new set of signals appeared, while the signals of **T3** itself were weakened gradually (Figures 1c−e). The new set of signals could be rationally assigned to a complex formed between **T3** and **3** as a result of a slow exchange between the complexed and free **T3** on the NMR time scale. The signals of free **T3**

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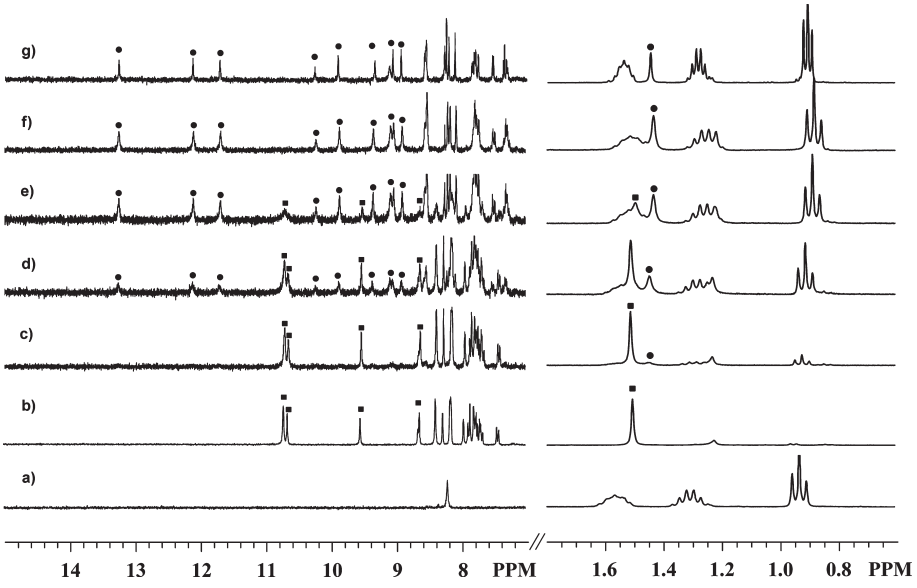

FIGURE 1. Partial ^{1}H NMR spectra (300 MHz) of (a) **3** (0.77 mM), (b) **T3**, (c) **T3** + **3** (0.13 equiv), (d) **T3** + **3** (0.42 equiv), (e) **T3** + **3** (0.75 equiv), (f) **T3** + **3** (1.06 equiv), and (g) **T3** + **3** (2.72 equiv) in DMSO-d_6) at 25 °C, highlighting the signals of free **T3** (■) and the complexed **T3** (●). [T3] = 0.77 mM.

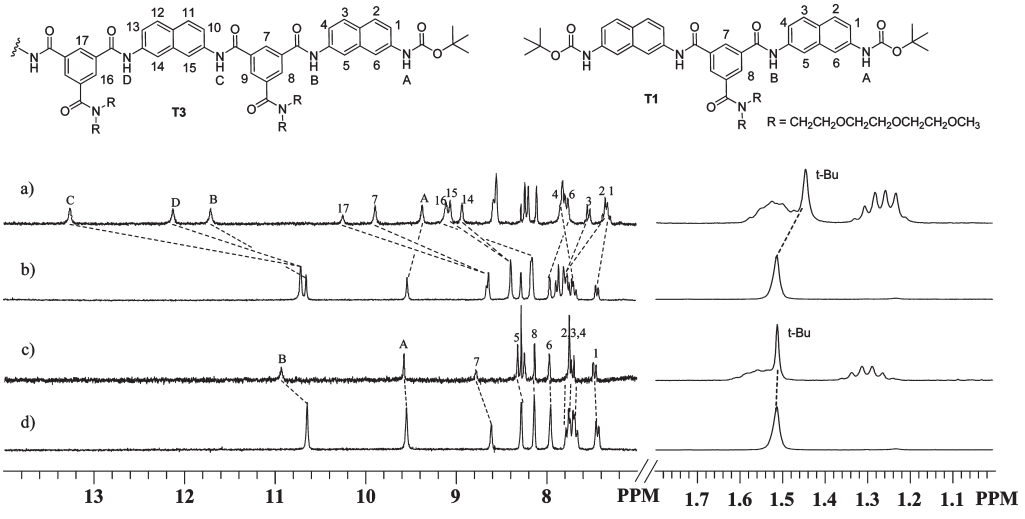

FIGURE 2. Partial ^{1}HNMR (300 MHz) spectra of (a) **T3** + **3**, (b) **T3**, (c) **T1** + **3**, and (d) **T1** in DMSO-d_6 at 25 °C. The concentration was 0.77 mM.

disappeared after ~1 equiv of **3** was added (Figure 1f). Addition of an excess of **3** (up to 2.72 equiv) did not cause the signals in the downfield area to shift anymore, suggesting that **T3** has been saturated by just 1 equiv of **3** and also a 1:1 binding model.

The ^{1}H NMR spectra of free **T3** and the 1:1 mixture of **T3** and **3** in DMSO-d_6 are provided in Figure 2 for further analysis. The marked signals of **T3** have been assigned on the basis of the 2D NOESY and COSY ^{1}H NMR experiments. It can be found that, upon addition of **3**, the B, C, and D NH signals of **T3** were shifted downfield substantially ($\Delta\delta$ = 1.06, 2.56, and 1.42 ppm, respectively) (Figure 2a,b), suggesting the formation of strong intermolecular N−H···O hydrogen bonds between these hydrogen atoms and the oxygen atoms of **3**. The signals of H-7 and H-17 of **T3** were also shifted downfield dramatically ($\Delta\delta$ = 1.24 and 1.60 ppm, respectively), suggesting that these hydrogen atoms also formed intermolecular C−H···O hydrogen bonds to induce the formation of a folded conformation for **T3**, as shown in Figure 3a.[17,18] Similar chloride-induced folding of linear 1,2,3-triazole-based oligomers have been reported, which utilized the intermolecular C−H···Cl$^-$ hydrogen bonding as the driving force.[19] The signals of the H-14 and H-15 hydrogen atoms were also shifted downfield pronouncedly ($\Delta\delta$ = 0.54 and 0.67 ppm, respectively), which was also consistent with the folded conformation and indicated short C−H···O contacts (Figure 3a). Interestingly, the signal of

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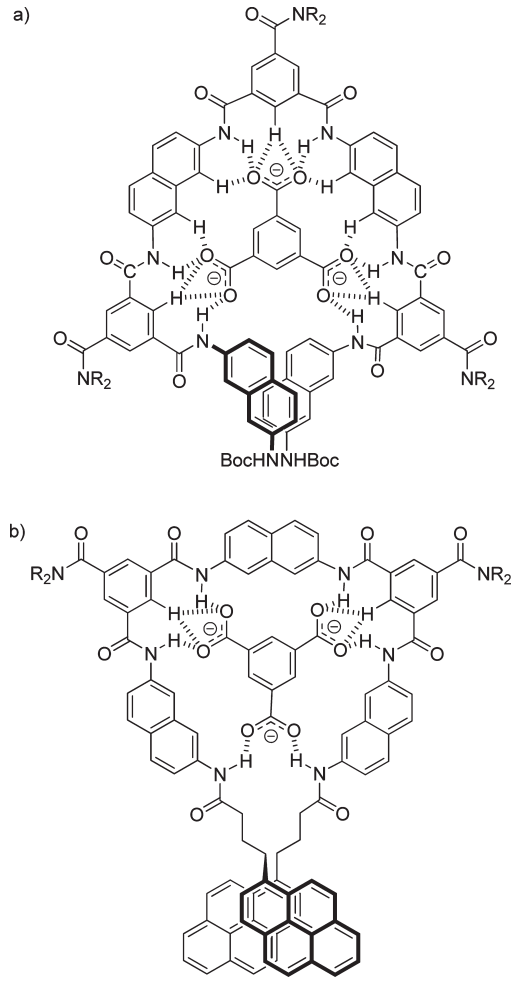

FIGURE 3. (a) Proposed folded conformation of **T3**, upon binding with the benzene-1,3,5-tricarboxylate anion, stabilized by the intermolecular N−H···O and C−H···O hydrogen bonds. The counter cations were omitted for clarity. (b) Folding-induced formation of the excimer of the appended pyrene units of **4**.

the H-16 hydrogen was also shifted downfield by 0.95 ppm. This result may be explained by considering that the formation of the folded conformation forced the oxygen atoms of the two carbonyl groups at the 1- and 3-positions to orientate toward this hydrogen and thus to impose a strong deshielding effect.[20]

The signals of the H-1, H-2, H-3, and H-6 atoms of the terminal naphthalene units and the *tert*-butyl hydrogen atoms were shifted upfield notably, further supporting that stacking of these two naphthalene rings occurred due to the formation of a folded conformation. Different from the B, C, and D NH signals, the signal of the Boc-bearing NH (A) was shifted upfield by 0.07 ppm, which should be attributed to the shielding of another terminal naphthalene unit due to the above stacking.

The formation of the above N−H···O and C−H···O hydrogen bonding was further supported by the ^{1}H NMR binding experiments between **T1** and **3** (Figures 2c and 2d). Upon addition of 1 equiv of **3** to a DMSO-d_6 solution of **T1**, the signals of the B and H-7 hydrogen atoms of **T1** were shifted downfield pronouncedly ($\Delta\delta$ = 0.27 and 0.16 ppm, respectively), suggesting that hydrogen bonds formed between B and H-7 and the oxygen of 1, 3, 5-benzenetricarboxylate anion. However, different from that of **T3**, the signals of the H-5, H-6, H-8, and A hydrogens of **T1** showed very little downfield shift (< 0.03 ppm), which was consistent with the minimal binding of these hydrogen atoms and implied that **T1** did not fold to host **3**.

Figure 4 provides the ^{1}H NMR spectra of **T2** and **T4** in the absence and presence of **3**. Two distinct sets of signals could still be observed after addition of **3**. The changes of the chemical shifts after 1 equiv of **3** was added are also provided in Figure 4. Just like that of **T3**, the B and C NH signals as well as H-7 of **T2** were shifted downfield notably, which should result from strong intermolecular hydrogen binding between these hydrogen atoms and the oxygen atoms of **3**. Different from that of **T3**, the signal of carbamate hydrogen A of **T2** was shifted downfield, suggesting the participation of intermolecular hydrogen bonding of this hydrogen. As expected, the hydrogen atoms of the *tert*-butyl group of **T2** showed very little upfield shifting, which is consistent with the fact that the two terminal naphthalene units did not stack due to its shorter chain length. These results indicated that, although **T2** has fewer hydrogen-bonding sites than **T3**, it can still form a stable complex with **3**. The resolution of ^{1}H NMR of oligomer **T4** was lower than that of its analogues **T2** and **T3**, and the peaks could not be assigned completely according to the 2D NOESY and COSY experiments due to significant overlapping of the signals. However, remarkable downfield shifts can still be observed for the signals of amide hydrogens D and C as well as H-14, H-15, H-17, and H-21, characteristic of strong intermolecular hydrogen-binding interactions. Meanwhile, upfield shifting was also displayed for the signals of the *tert*-butyl hydrogen atoms. All of these results support that oligomer **T4** should also adopt similar folded conformation as **T3**. Furthermore, ^{1}H NMR titration experiments of **T2** and **T4** with **3** also showed a saturation of complexation after the addition of 1 equiv of **3**, reflecting a 1:1 binding model and the high stability of the complexes.

To obtain deeper insight for the anion-induced folding, the 2D NOESY ^{1}H NMR experiment was further carried out for the mixture of **T3** and **3** in DMSO-d_6. The result is provided in Figure 5. A NOE connection was clearly observed between the signals of H-2 and H-4 of the terminal naphthalene units. Since such NOE connections were not detected for **T3** in the absence of **3** (see the Supporting Information), this NOE can only be reasonably attributed to a cross-ring contact of the folding of **T3**. Similar NOE connection was not observed for **T2** in the presence of **3**, which reflected the fact that this oligomer is not longer enough for its two ending naphthalene units to stack or even to be in close proximity.[6a] Strong NOE connections were also exhibited between the H-4 and H-7, H-7 and H-15, H-14 and H-17, and B and C hydrogen atoms of **T3** in the mixture, which also supported the formation of the folded conformation. In addition to the above intramolecular NOE connections, intermolecular NOEs were also observed between the signal of **3** and the signals of the H-4, H-7, H-14, H-15, H-17, B, and D hydrogen atoms of **T3**, indicating that **T3** did fold to host **3** and the resulting complex was stable enough. These NOE connections can still be observed in the spectrum acquired by using mixing time of 0.5 s, which is consistent with that predicted by the

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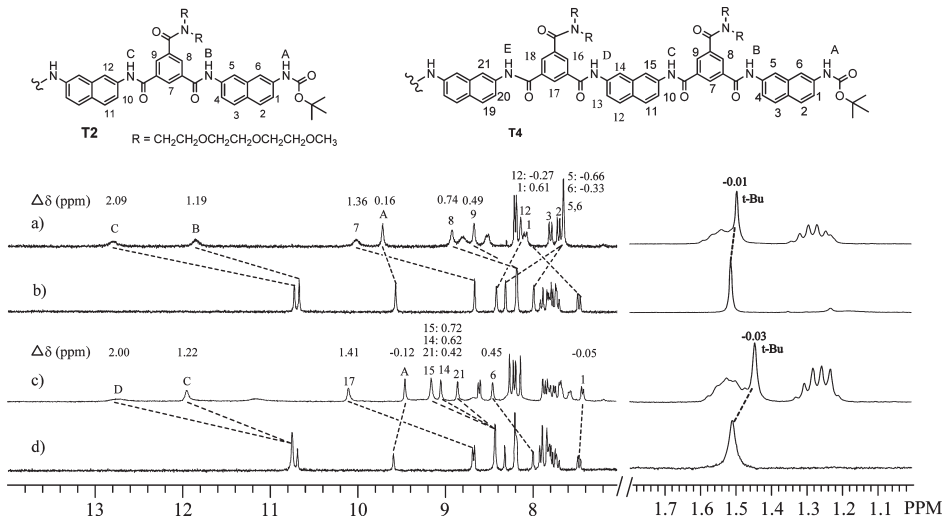

FIGURE 4. Partial ^{1}H NMR (300 MHz) spectra of (a) **T2** + **3** (1:1), (b) **T2**, and (c) **T4** + **3** (1:1), (d) **T4** in DMSO-d_6 at 25 °C. The concentration was 0.77 mM.

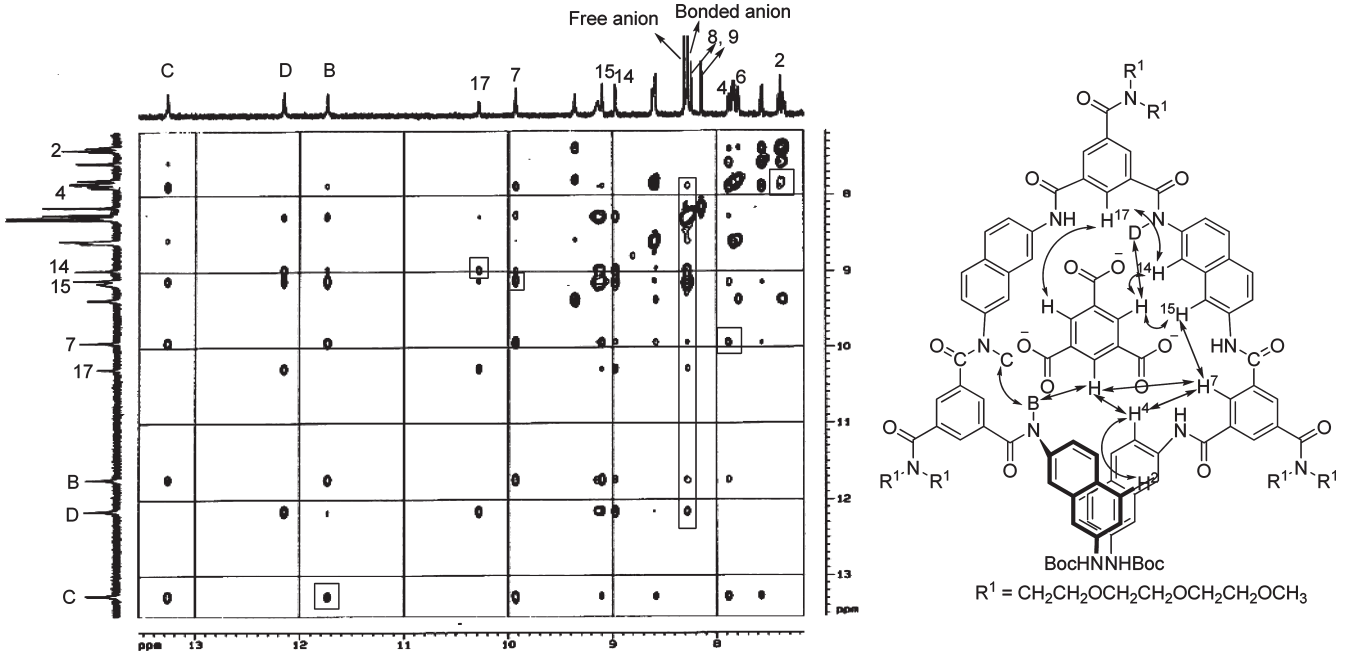

FIGURE 5. Partial NOESY spectrum (500 MHz) of the mixture of **T3** (0.77 mM) + **3** (2.1 mM) in DMSO-d_6 at 25 °C (mixing time = 1 s).

molecular mechanics calculations (see the Supporting Information). Despite the strong binding, bonded **3** gave rise to only one singlet, which implied that it could rotate quickly in the cavity of the folded **T3**, well reflecting its high structural symmetry. The NOESY ^{1}H NMR spectrum of the 1:1 solution of longer oligomer **T4** and **3** in DMSO-d_6 was also recorded, which displayed similar intermolecular NOE cross-peaks, again supporting that **T4** complexed **3** also through the formation of a folded conformation (see the Supporting Information).

Fluorescence Spectroscopy. Because of its strong excimer emission, pyrene has been used as an indicator for detecting the folding of linear molecules.[8d,21] Therefore, we designed **4**,[16] analogue of **T2**, to investigate the pyrene interactions induced by **3**. Its fluorescence spectra in the presence of varying amounts of **3** were recorded in DMSO and are shown in Figure 6. With the increase of **3**, the excimer emission of the pyrene unit, centered at ca. 490 nm, was increased pronouncedly at the expense of a decrease of its monomer emission at ca. 400 nm. The result clearly indicated that the oligomer was induced by **3** to adopt a folded conformation and consequently forced the two terminal pyrene units to approach each other to form an excimer (Figure 3b), which is consistent with the above ^{1}H NMR result for the mixture of **T2** and **3**.

UV−vis Spectroscopy. UV−vis experiments were carried out in DMSO to quantitatively evaluate the binding properties of the oligomers toward **3**. The representative results are

(21) (a) Zhou, W.; Li, Y.; Li, Y.; Liu, H.; Wang, S.; Li, C.; Yuan, M.; Liu, X.; Zhu, D. *Chem.−Asian. J.* **2006**, *1*, 224–230. (b) Pan, X.; Zhao, Y. *Org. Lett.* **2009**, *11*, 69–72.

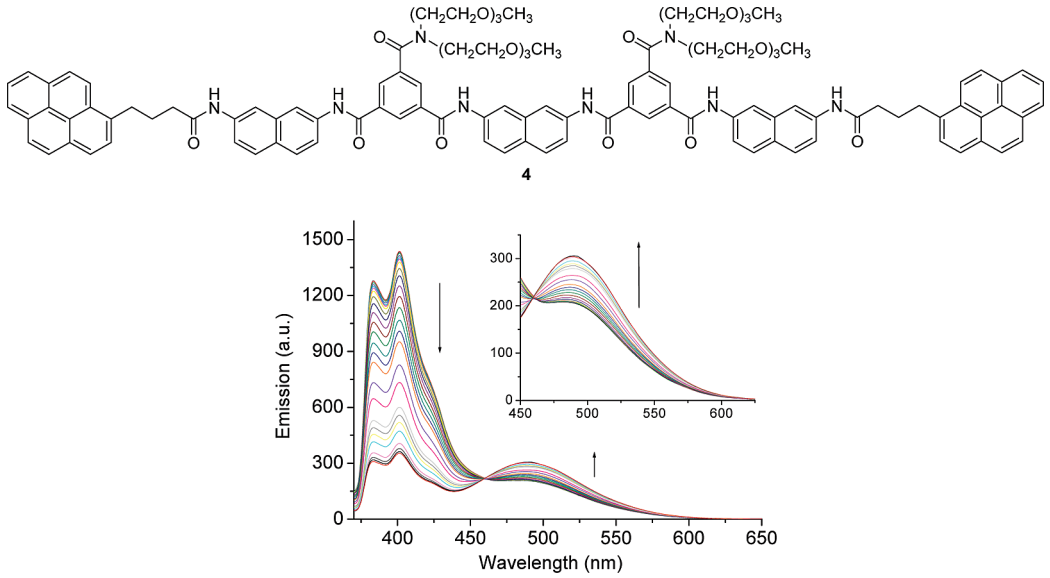

FIGURE 6. Fluorescence spectra of **4** (0.5 μM) with the addition of **3** (0−28 μM) in DMSO at 25 °C (λ_{ex} = 349 nm). Inset: the fluorescence emission in the 450−625 nm region.

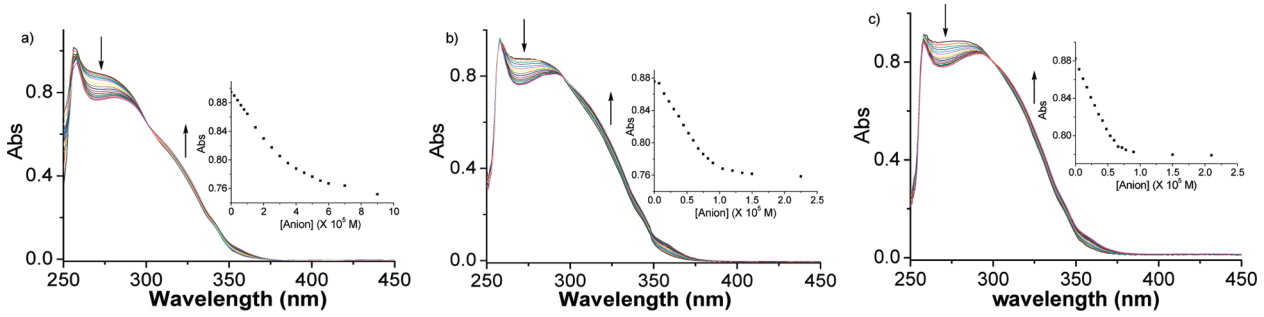

FIGURE 7. UV−vis absorption spectra of (a) **T2** (10 μM), (b) **T3** (7.5 μM), and (c) **T4** (6.0 μM) upon addition of **3** (from 0 to 90, 22.5, and 21 μM for **T2**, **T3**, and **T4**, respectively) in DMSO at 25 °C. Inset: the plot of the absorbance at 269 nm vs [**3**].

presented in Figure 7. Upon addition of **3**, the spectra of **T2**−**T4** were all changed gradually, reflecting their structural reorganization due to binding the anion. The absorption change of all three samples displayed an isosbestic point at around 300 nm, indicating that just two states existed in the system.[22,23] That is, one for the free oligomers and another for their complexes with the anion, which is consistent with the above ^{1}H NMR results. A Job's plot analysis of **T3** and **3** reconfirmed the 1:1 binding stoichiometry for the complex (see the Supporting Information).[24] On the basis of the titration results, their association constants were estimated to be 2.5 (±0.29) × 10^4, 8.6 (±3.0) × 10^5, and 5.5 (±0.64) × 10^6 M^{-1}.[25] The values were increased substantially with the elongation of the backbones, reflecting that longer oligomers can provide more amide units for the formation of more intermolecular hydrogen bonds. Considering the high polarity of the solvent, the values are impressive, suggesting that the multiple intermolecular hydrogen bonds are highly effective in stabilizing the resulting complexes. The UV−vis titration of **T1** with **3** was also carried out (see the Supporting Information). In contrast to that of **T2**−**T4**, the addition of **3** caused a slight decrease of UV absorption of **T1**, and no saturation or isosbestic point was observed, suggesting that **T1** and **3** did not form a well-defined complex, which is consistent with the above ^{1}H NMR result. Other anions such as chloride, bromide, nitrate, acetate, and isophthalate were also tested on their abilities to induce the formation of a folded conformation for **T3**. The ^{1}H NMR studies revealed that they did not induce the folded structure of the oligomer, although weak binding might exist between **T3** and these anions (see the Supporting Information). This result shows that the binding between **T3** and benzene-1,3,5-tricarboxylate anion is specific.

Conclusion

In recent years, intramolecularly hydrogen bonding-induced oligomeric arylamide-based foldamers have been extensively investigated. In this paper, we have demonstrated that similar backbones can be forced by structurally matched guest to form a folded conformation through the formation of strong intermolecular multiple hydrogen bonds. One notable feature of the present study is the very

(22) Groger, G.; Stepanenko, V.; Wurthner, F.; Schmuck, C. *Chem. Commun.* **2009**, 698–700.
(23) Schneider, H.-J.; Yatsimirsky, A. *Principles and Methods in Supramolecular Chemistry*; Wiley: Chichester, 2000; p 177.
(24) Job, P. *Ann. Chim. Ser.* 10, **1928**, *9*, 113−134.
(25) Conners, K. A. *Binding Constants: The Measurement of Molecular Complex Stability*; Wiley: New York, 1987.

high binding ability of the new arylamide oligomers toward the trianion guest that occurs in DMSO, a highly polar and hydrogen-binding competitive solvent. The result raises the possibility of designing other oligomers that possess a smaller or larger cavity to bind other anionic guests. If chiral units are introduced to the oligomeric hosts and/or guests, we may expect that new chiral supramolecular systems would be produced due to the great binding stability.

Experimental Section

General Methods. All reagents and chemicals were obtained from commercial sources and used without further purification unless otherwise noted. The solvents have been purified by standard procedures before use. Chemical shifts are expressed in parts per million (δ) using residual proton resonances of the deuterated solvents as the internal standards. The synthetic procedures and characterizations of compound **T1**, **T2**, **T3**, and **4** have been reported previously.[16]

Compound 1. Compound **T2** (0.51 g, 0.32 mmol) was dissolved in dichloromethane (10 mL), and trifluoroacetic acid (0.97 mL, 12.6 mmol) was then added. The resulting mixture was stirred at room temperature for 21 h. After removal of the solvent, the residue was redissolved in dichloromethane (200 mL), washed with saturated sodium bicarbonate solution and brine, and then dried over anhydrous sodium sulfate. The organic solvent was removed with a rotavapor, and the resulting residual was purified by column chromatography (CH_2Cl_2/EtOAc/MeOH 2:8:1 then 5:5:1) to afford compound **1** as an oil (0.40 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.64 (s, 4 H), 8.48 (s, 2 H), 8.04−7.98 (m, 8 H), 7.69−7.43 (m, 10 H), 6.80 (d, J = 9.0 Hz, 2 H), 6.69 (s, 2 H), 3.97 (s, 4 H), 3.70−3.15 (m, 60 H). ^{13}C NMR (125 MHz, $CDCl_3$):δ 171.1, 165.1, 165.0, 145.0, 137.1, 136.2, 135.6, 135.3, 133.9, 129.2, 128.7, 128.4, 128.2, 127.2, 125.2, 120.1, 117.6, 116.9, 115.6, 108.3, 71.8, 71.7, 70.4, 70.3, 70.2, 70.0, 69.0, 68.2, 58.8, 58.7, 49.8, 45.1. MS (MALDI-TOF): m/z 1428.9 $[M + Na]^+$. HRMS: calcd for $C_{76}H_{92}N_8O_{18}Na$ $[M + Na]^+$ 1427.6436, found 1427.6422.

Compound T4. A mixture of diamine **1** (0.21 g, 0.15 mmol), acid **2** (0.25 g, 0.34 mmol), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) (0.17 g, 0.44 mmol), and *N*,*N*-diisopropylethylamine (0.18 mL, 1.0 mmol) in DMF (5 mL) was stirred at room temperature for 11 h. After removal of the solvent with a rotavapor, the resulting residue was subjected to flash column chromatography (CH_2Cl_2/EtOAc/MeOH 5:5:1) to give **T4** as a pale yellow solid (0.29 g, 69%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.73 (s, 6 H), 10.67 (s, 2 H), 9.54 (s, 2 H), 8.72−8.69 (m, 4 H), 8.44 (s, 6 H), 8.33 (s, 2 H), 8.22−8.20 (m, 8 H), 8.01 (s, 2 H), 7.92−7.75 (m, 18 H), 7.50 (d, J = 9.0 Hz, 2 H), 3.72 (s, 16 H), 3.61−3.31 (m, 80 H), 3.22 (s, 12 H), 3.14 (s, 12 H), 1.52 (s, 18 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.84, 164.68, 152.85, 137.70, 137.42, 137.13, 136.98, 135.30, 135.24, 133.87, 133.65, 128.90, 128.00, 127.88, 127.53, 127.19, 126.23, 119.74, 118.87, 116.31, 115.92, 113.07, 79.20, 71.25, 71.10, 69.74, 69.56, 67.95, 67.81, 57.96, 57.89, 49.12, 44.27, 28.11. MS (MALDI-TOF): m/z 2874.3 $[M + Na]^+$. HRMS: calcd for $C_{152}H_{190}N_{14}O_{40}$ Na $[M + Na]^+$ 2874.3096, found 2874.3156.

Tetrabutylamonium Benzene-1,3,5-tricarboxylate (3). To a stirred solution of benzene-1,3,5-tricarboxylic acid (0.43 g, 2.0 mmol) in methanol (7 mL) was added aqueous tetrabutylammonium hydroxide solution (15.6 g, 6.0 mM). The reaction mixture was stirred at room temperature overnight. After removal of the solvent, the resulting residue was dried over P_2O_5 under vacuum at 80 °C to give **3** quantitatively as a sticky white solid. ^{1}H NMR (300 MHz, DMSO-d_6): 8.19 (s, 3 H), 3.19−3.13 (m, 24 H), 1.56−1.51 (m, 24 H), 1.36−1.24 (m, 24 H), 0.93 (t, J = 7.5 Hz, 36 H). MS (ESI): m/z 242.3 $[Bu_4N]^+$, 208.9 $[M - 3Bu_4N + 2H]^-$.

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Supporting Information Available: The energy-minimized conformation of the complex, the method for evaluating the association constants, additional ^{1}H NMR COSY and NOESY spectra, and ^{1}H and/or ^{13}C NMR spectra of compound **1**, **3**, and **T4**. This material is available free of charge via the Internet at http://pubs.acs.org.