Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2011, **9**, 8122

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PAPER

meta-Substituted benzamide oligomers that complex mono-, di- and tricarboxylates: folding-induced selectivity and chirality†‡

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Received 26th June 2011, Accepted 6th September 2011
DOI: 10.1039/c1ob06026k

meta-Substituted arylamide trimer, pentamer and heptamer have been prepared from simple benzene-1,3-diamine, benzene-1,3-dicarboxylic acid, and 3-aminobenzoic acid units. 2D NOESY ^{1}H NMR experiments reveal that these flexible oligomers form folded conformations to complex di- and tricarboxylate anions of varying sizes and shapes in DMSO of high polarity, which is driven by multiple intermolecular N–H···O═C and C–H···O═C hydrogen-bonds between the amide and aromatic hydrogens of the oligomers and the carboxylate oxygens of the anions. Generally, tricarboxylate anions display an increased binding affinity compared with the dicarboxylate anions and the complexes formed by 1,3-benzenedicarboxylate anion are more stable than those formed by 1,2- or 1,4-benzenedicarboxylate anions. Circular dichroism experiments show that chiral glutamic acid dianion can induce the oligomers to produce chiral bias, leading to the formation of chiral supramolecular complexes.

Introduction

Folded conformations are common for natural biopolymers such as proteins, nucleic acids and polysaccharides. With an original motivation to uncover the folding principles for these naturally occurring phenomena in a simplified way, chemists have created numerous artificial molecules, *i.e.*, foldamers,[1] that adopt folded conformations under certain conditions. In addition to the purpose of mimicking the secondary structures of biomolecules, in recent years great efforts have been devoted to the development of foldamers that are capable of undertaking specific functions such as molecular recognition[2] and catalysis.[3]

Currently, a variety of chemical structures have been designed as basic scaffolds to build foldamers. Typical examples include heterocycles,[4] amino acid derivatives,[5] arylamide,[6] oligo(*m*-phenylene ethynylene),[7] oligocholates,[8] and aliphatic oligoureas[9] whose folded conformations are stabilized by intramolecular hydrogen-bonding, π-stacking, or solvophobic interactions. Intrinsically flexible linear molecules can also be induced to fold into compact conformations through complexing size- and site-matched guests. In this context, a number of ionic species have been utilized as the guests to template the folding of several arylacetylene- and 1-aryl-1,2,3-triazole-based molecules.[10–12] We recently reported that naphthalene-2,7-diamine and benzene-1,3-dicarboxylic acid-derived arylamide oligomers bind benzene-1,3,5-tricarboxylate anions to form a folded or helical conformation driven by intermolecular N–H···O and C–H···O hydrogen bonds.[13] One notable feature of this system is that these hydrogen bonding-mediated complexes survive in DMSO, a highly competitive solvent. To further investigate the structure–binding relationship of this type of arylamide receptor, we have synthesized three new *meta*-substituted benzamide oligomers **T1–3**. In this paper, we describe a systematic investigation of their folding-based complexation to a variety of di- and tricarboxylate anions. We further demonstrate that chiral glutamic acid dianion can induce the longest molecule **T3**, a linear heptamer, to produce helical chirality.

Results and discussion

The synthesis of **T1–T3** is straightforward (Scheme 1). For the preparation of **T1**, succinic anhydride **1** was first reacted with di(n-octyl)amine **2** in toluene to afford acid **3** in 98% yield. The acid was then coupled with diamine **4** to give **T1** in 73% yield. Treatment of compound **3** with amine **5** produced compound **6** in 89% yield. The ester was further hydrolyzed with lithium hydroxide to give acid **7** in 95% yield. This acid was then coupled with diamine **4** to afford **T2** in 67% yield, while its coupling reaction with amine **5** afforded **8** in 85% yield. The ester **8** was hydrolyzed with lithium hydroxide to give **9** in 95% yield and the acid further coupled with diamine **4** to yield **T3** in 67% yield. Compounds **T1–T3** are soluble in organic solvents, including chloroform, dichloromethane and DMSO, due

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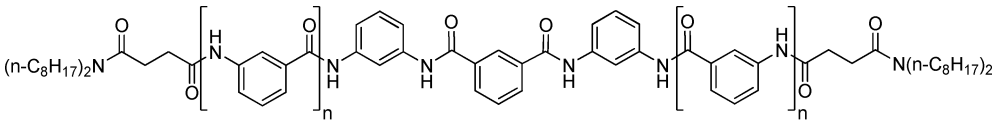
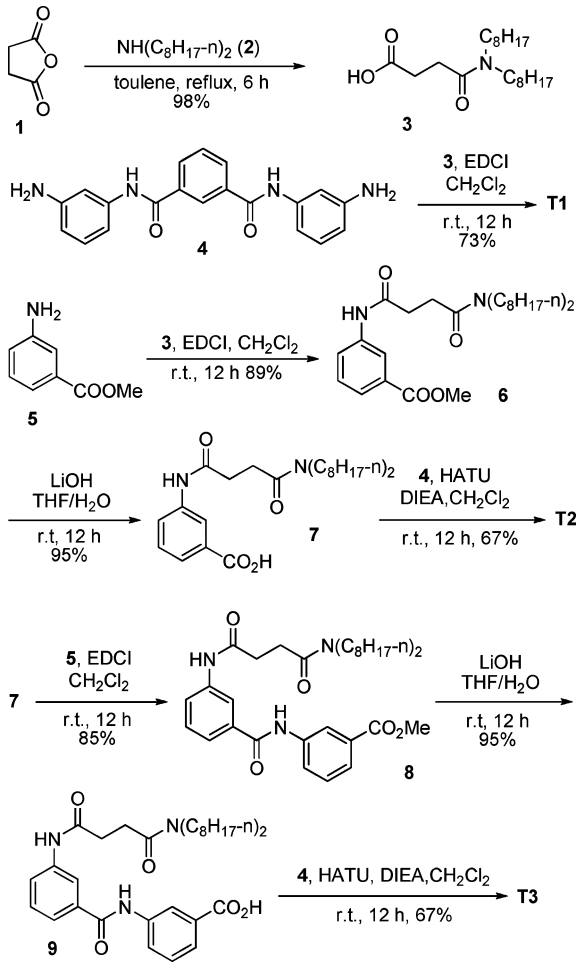
† This article is part of an *Organic & Biomolecular Chemistry* web theme issue on Foldamer Chemistry.

‡ Electronic supplementary information (ESI) available: Copies of additional ^{1}H NMR and 2D COSY and NOESY ^{1}H NMR spectra of the oligomers, the complexes and the guest molecules. Copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds. Benesi–Hildebrand (B–H) plots. See DOI: 10.1039/c1ob06026k



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



Scheme 1 Synthetic routes to compounds **T1–T3**.

to the introduction of the two side chains. Their structures have been characterized by the ^{1}H and ^{13}C NMR spectroscopy, and high resolution mass spectrometry, while the signals in the down-field area in the ^{1}H NMR spectra have been assigned on the basis of the 2D NOESY and COSY ^{1}H NMR experiments.

The ^{1}H NMR spectra of **T1–3** in DMSO-d_6 were of high resolution, and diluting the solution from 50 mM to 0.78 mM (**T2** as representative, Fig. S1, ESI‡) did not cause shifting of the signals in the downfield area. These observations suggested that no important inter- and intramolecular aggregation took place. Their binding affinity to tetrabutylammonium benzene-1,3,5-tricarboxylate (**10**) was first investigated using the ^{1}H NMR spectroscopy. As can be seen in Fig. 1, upon addition of **10** (1.0 equiv), the NH signals of the oligomers all shifted downfield substantially ($\Delta\delta$ values provided in the spectra), suggesting that strong intermolecular N–H···O hydrogen bonds were formed between the amide hydrogens of the oligomers and the oxygens of **10**. The signals of the amide protons of **T2** and **T3** were also broadened, reflecting the dynamic feature of the binding, with a timescale comparable to that of the ^{1}H NMR technique, and also probably the intramolecular aromatic stacking. The signals of the H-1, H-10, and H-15 protons were also shifted downfield considerably, suggesting that these protons also formed intermolecular C–H···O hydrogen bonding. Since both the central and peripheral arylamide units were engaged in the intermolecular hydrogen bonding, it is reasonable to propose that longer oligomers **T2** and **T3** should adopt folded or helical conformations in the presence of the anion, as illustrated in Fig. 2, while short oligomer **T1** adopted a compact crescent conformation for binding **10**. Different from the signals of all other aromatic and amide protons, the H-5 signal of **T2** and **T3** was shifted upfield by about 0.1 ppm in the presence of **10**. This result indicated that these protons did not form intermolecular hydrogen bonding probably due to the strain generated by the formation of hydrogen-bonding between the oxygen of **10** and the amide H-4 and H-9 protons of the oligomers, which forced the benzene ring to twist out of the plane (Fig. 2).

To get more evidence for the complexation-induced folded structure of the oligomers, 2D NOESY ^{1}H NMR experiments were further carried out for the three 1 : 1 mixtures in DMSO-d_6. For all the complexes, important NOE connections related to the folded conformations were observed (Fig. S2-3‡). As shown in Fig. 3, strong NOE connections were displayed between H-1 and H-4, H-4 and H-5, H-5 and H-9, H9 and H-10, and H10 and H-14, and NOE cross peaks were also observed between H-1 and H-5, H-5 and H-10, and H9 and H-14. These observations all support the folded conformation of the oligomers. In addition to these intramolecular NOE correlations, intermolecular NOE connections were also observed between the hydrogen of **10** and the H-4, H-5, H-9, and H-10 of **T2**, further confirming that the oligomer folded to create a cavity to encapsulate the trianion.

Concerning the signals of the amide protons in the ^{1}H NMR spectra (Fig. 1), the downfield shifting caused by **10** also increased pronouncedly from **T1** to **T2**, and to **T3**, suggesting that the binding was strengthened with the elongation of the oligomers. ^{1}H NMR titration experiments were then performed in DMSO-d_6. By fitting the data to the Benesi–Hildebrand (B–H) equation (Fig. S4‡),[14] we determined the association constants (K_a) of the three complexes to be 213, 320 to 470 M^{-1}, respectively. These values are smaller than those of their naphthalene-1,3-diamine-based analogues.[13] Moreover, the values increased slightly, but all were of the same magnitude, reflecting a relatively low structural matching between the cavity of the folded **T2** and **T3** and the trianion. The CPK modeling shows that (Fig. 4), when the backbones of the longer oligomers fold into a co-planar conformation, they create a cavity of about 0.5 nm diameter. This small cavity cannot host the trianion, which has a diameter of 1.0 nm. Thus, the backbones must twist to expand its cavity for binding the trianion, which would lead to additional tension and weaken their binding affinity.

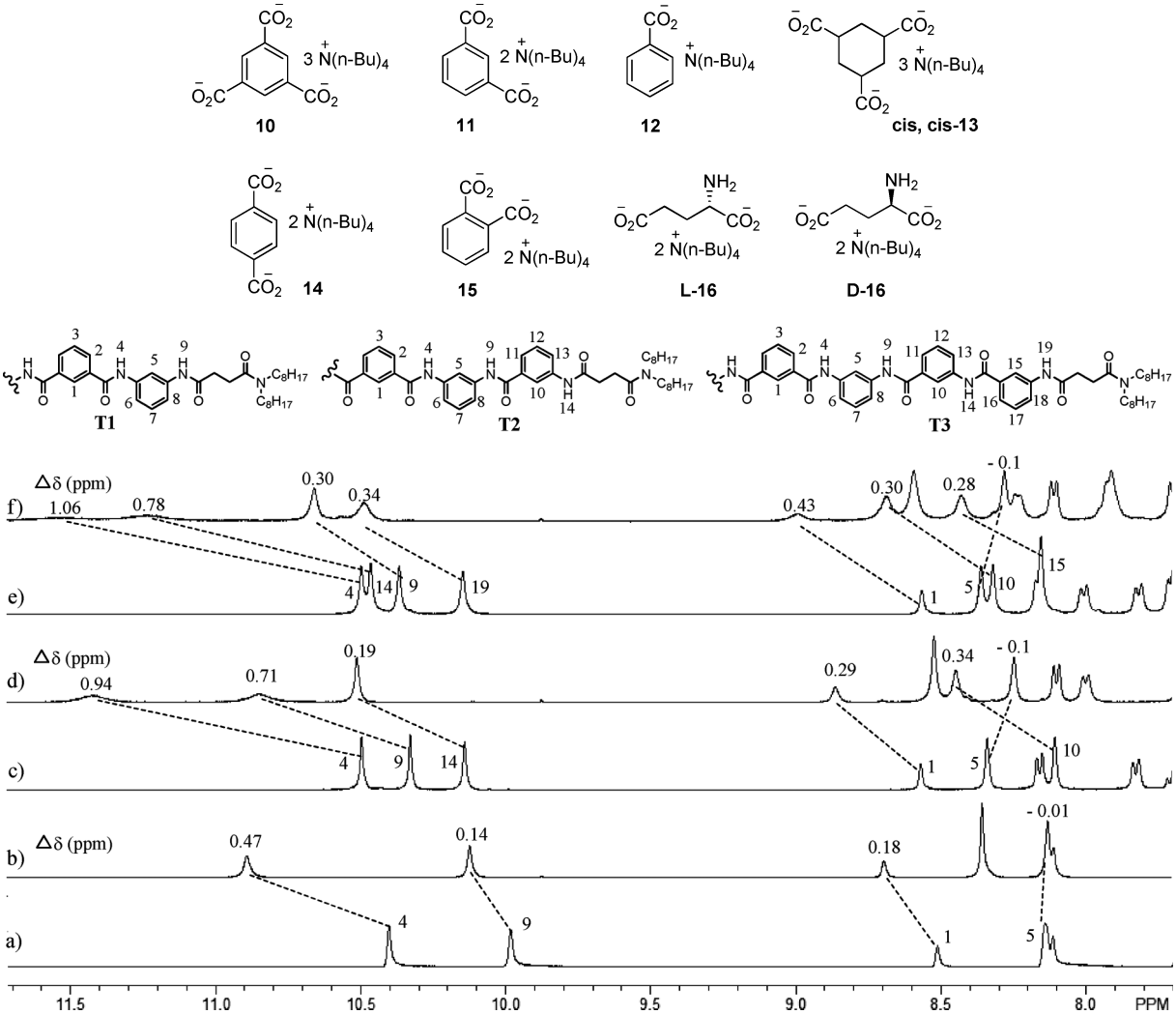


Fig. 1 Partial ^{1}H NMR (300 MHz) spectra of (a) **T1**, (b) **T1**+ **10** (1 : 1), (c) **T2**, (d) **T2**+ **10** (1 : 1), (e) **T3**, and (f) **T3**+ **10** (1 : 1), in DMSO-d_6 at 25 °C. The concentration was 5.0 mM.

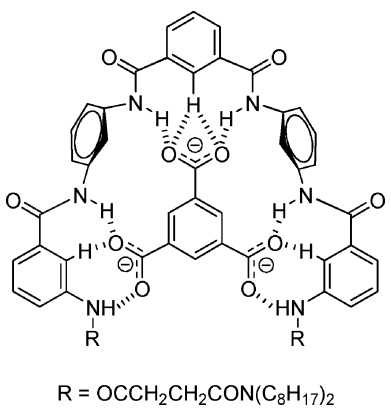


Fig. 2 Proposed folding-based binding pattern for **T2** and the benzene-1,3,5-tricarboxylate anion, highlighting the multiple intermolecular N–H···O and C–H···O hydrogen bonds. The counter cations were omitted for clarity.

Since heptamer **T3** exhibited the highest binding affinity for the trianion, we further investigated its binding capacity to anions **11**–**15**. Also using the ^{1}H NMR titration method, we determined the K_a values of the complexes between **T3** and **11**–**15** in DMSO-d_6 to be 302, 80, 282, 177, and 130 M^{-1}, respectively. Checking the data of **10**, **11** and **12** shows that the increase of the carboxylate unit in the guests pronouncedly enhanced the binding stability due to the increase of the intermolecular hydrogen bonds. This trend is consistent with the ^{1}H NMR results (Fig. 5), which reveal that the downfield shifting of the N*H* signals of the oligomers caused by the anions was increased considerably from **12** to **11** and to **10**. A comparison of the data of **11**, **14** and **15** reveals that the *meta*-substituted dianion matched the folded oligomer in the best way. Compound **13** also bears three carboxyl groups. However, its K_a is a little smaller than that of **10**. Probably the nonplanar conformation of its cyclohexane ring makes the hydrogen-bonding orientation of the carboxyl groups not as well-matched as that of the planar benzene ring to the structure of **T3**.

Since the binding model for the complexes of the oligomers and the anions has been established, we anticipated that chiral folded structures might be built if proper chiral anions were encapsulated inside by the oligomers. The complexation of **T3** to chiral glutamic acid dianion **16** was further investigated. The

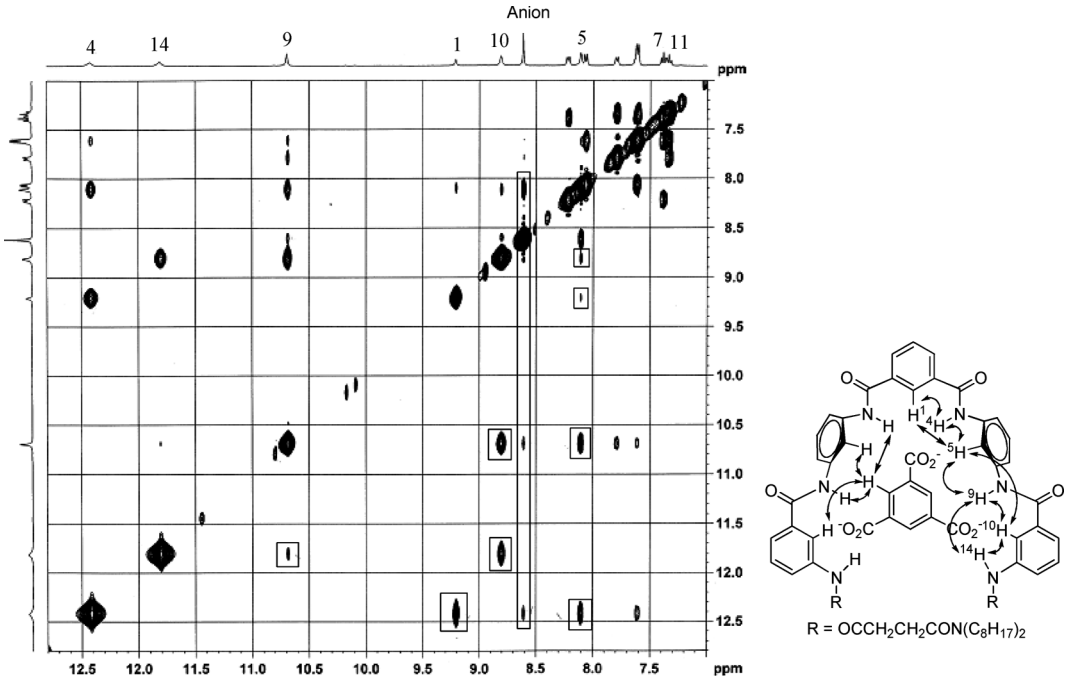


Fig. 3 Partial NOESY spectrum (400 MHz) of the mixture of **T2** (10 mM) + **10** (10 mM) in DMSO-d_6 at 25 °C (mixing time = 0.3 s).

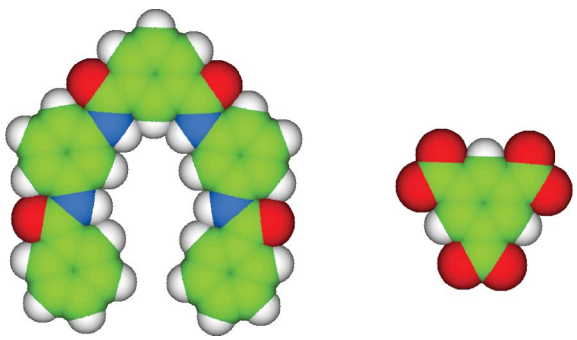


Fig. 4 The CPK model of the co-planar aromatic backbone of **T2** (left) and benzene-1,3,5-tricarboxylate (right), revealing that the binding between the longer oligomers and the trianion would require the oligomers to twist their folding structures to create a larger cavity for the trianion.

^{1}H NMR spectrum of **T3** and L-**16** in $CDCl_3$ was first recorded. The ^{1}H NMR spectrum of pure **T3** in $CDCl_3$ was of extremely low resolution, reflecting significant aggregation due to the formation of strong intermolecular hydrogen-bonding.[15] Upon addition of L-**16**, however, the spectra became of clear resolution, indicating they had formed a well-defined complex. Furthermore, downfield shifts were observed for the NH signals of **T3** with the increase of L-**16**, suggesting that these protons were involved in the formation of hydrogen bonds (Fig. 6). The circular dichroism (CD) spectra of the mixture of **T3** with both L- and D-**16** were then recorded in chloroform, which displayed a CD signal of mirror-symmetry centered around 300 nm (Fig. 7). Since both species themselves did not exhibit any CD signal in the same wavelength region (**T3** is achiral and obviously it has no CD spectrum, and the CD of L-**16** appears below 270 nm (Fig. S5‡)), this CD signal should be

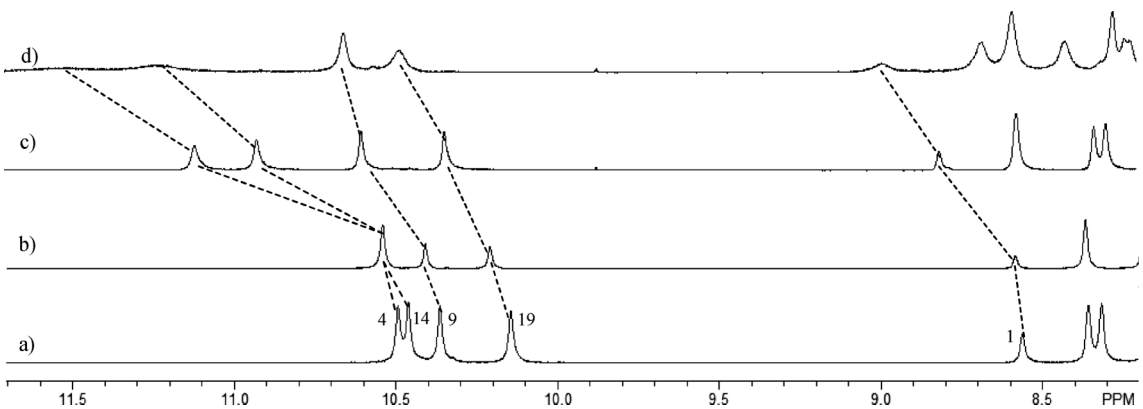


Fig. 5 Partial ^{1}H NMR (300 MHz) spectra of (a) **T3**, (b) **T3** + **12** (1 : 1), (c) **T3** + **11** (1 : 1), and (d) **T3** + **10** (1 : 1) in DMSO-d_6 at 25 °C. The concentration was 5.0 mM.

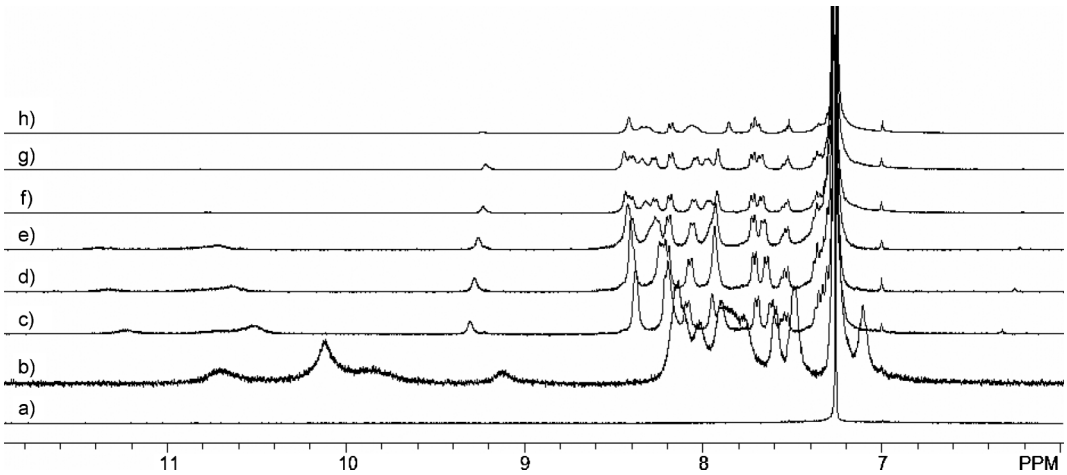


Fig. 6 ^{1}H NMR (400 MHz) spectra of (a) **T3**, (b) **T3** + L-**16** (1 : 0.38), (c) **T3** + L-**16** (1 : 0.75), (d) **T3** + L-**16** (1 : 1.12), (e) **T3** + L-**16** (1 : 1.5), (f) **T3** + L-**16** (1 : 1.88), (g) **T3** + L-**16** (1 : 3.5), and (h) **T3** + L-**16** (1 : 6) in $CDCl_3$ at 25 °C. The concentration of **T3** was 2.7 mM.

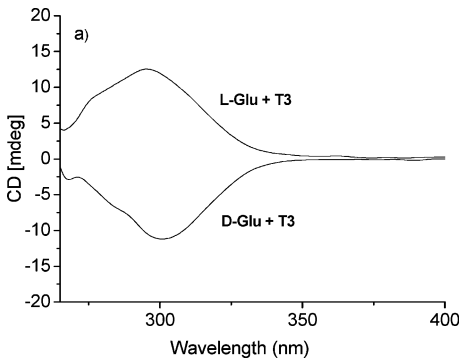


Fig. 7 CD spectra of **T3** (1.0 mM) upon mixing with L-**16** and D-**16** (20 mM) in $CHCl_3$ at 25 °C.

attributed to that of the chiral folded structure of **T3** induced by the chiral guest, as shown in Fig. 8.

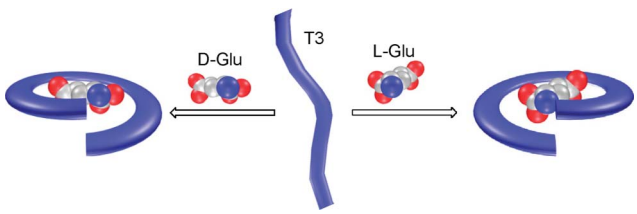


Fig. 8 Cartoon representation for the formation of the chiral folded structures of **T3** induced by L-**16** and D-**16**. The counter cations were omitted for clarity.

Conclusion

In summary, we have demonstrated that *meta*-substituted benzamide oligomers can fold to complex di- and tricarboxylate anions in DMSO. The association stability is modest. Considering the high polarity of the solvent, it is still impressive, illustrating the efficiency of multivalence in designing hydrogen bonding-based hosts for molecular recognition in competitive media. The fact that the arylamide oligomers can fold to bind carboxylate anions of different sizes and shapes bodes well for further applications for binding phosphate or sulfate anions. Because the all-benzene-based amide oligomers have to adopt strained conformations to maximize the intermolecular hydrogen bonding, partially replacing the benzene rings with flexible aliphatic chains of different length may lead to the construction of new modular receptors for anion guests.

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. Silica gel (10–40 μ) was used for all column chromatography. The NMR spectra were recorded on Bruker Avance 300 or 400 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual proton resonances of the deuterated solvents as the internal standards. Compound **10**[13] and compound **4**[16] were prepared according to the reported procedures.

Compound 3

A mixture of succinic anhydride **1** (10.0 g, 0.10 mol) and dioctylamine **2** (24.1 g, 0.10 mol) in toluene (150 mL) was refluxed for 5 h. After being cooled to room temperature, the mixture was washed with hydrochloric acid (6 M, 100 mL) and brine (2 × 100 mL), and then dried over anhydrous sodium sulfate. Upon removal of the solvent with a rotavapor, the resulting residual was purified by flash chromatography (petroleum ether/EtOAc 1 : 1) to afford compound **3** as a yellow oil (33.5 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.28 (t, J = 8.1 Hz, 2H), 3.22 (t, J = 8.1 Hz, 2H), 2.66 (s, 4H), 1.55–1.52 (m, 4H), 1.25 (br, 20H), 0.86 (br, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 171.6, 48.1, 46.4, 31.7(d), 30.1, 29.3 (d), 29.2 (d), 28.8, 28.1, 27.6, 27.0, 26.9, 22.6 (d), 14.0. MS (ESI) m/z: 342.3 $[M + H]^+$. HRMS (MALDI-TOF): Calcd for $C_{20}H_{40}NO_3$ $[M + H]^+$: 342.3008. Found: 342.30027.

Compound T1

To a solution of compounds **3** (1.50 g, 2.20 mmol) and **4** (0.69 g, 2.00 mmol) in dichloromethane (50 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (0.93 g, 2.40 mmol). The mixture was stirred at room temperature for 12 h and then saturated NH_4Cl solution (50 mL) was added. The separated organic phase was washed with brine (2 × 30 mL) and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting residue was purified by column chromatography (petroleum ether/EtOAc 1 : 2) to give compound **T1** as a white solid (1.45 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 2H), 9.27 (s, 2H), 8.47 (s, 1H), 8.05 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 2H), 7.90 (s, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.49 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 2H), 7.29 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 2H), 7.11 (t, J = 8.0 Hz, 1H), 3.22 (t, J = 8.0 Hz, 4H), 3.15 (t, J = 8.0 Hz, 4H), 2.59–2.57 (m, 8H), 1.55–1.52 (m, 4H), 1.39–1.36 (m, 4H), 1.25 (br, 40H), 0.86 (br, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 171.6 (d), 165.4, 138.7, 138.6, 134.7, 131.4, 129.0, 128.9, 124.6, 116.0, 112.1, 48.1, 46.4, 32.3, 31.8 (t), 29.4, 29.3 (t), 29.2, 29.1, 29.0, 28.8, 27.7, 27.0, 26.9 (d), 22.6 (d), 14.1. MS (ESI) m/z: 994.2 $[M + H]^+$. HRMS (MALDI-TOF): Calcd for $C_{60}H_{92}N_6NaO_6$ $[M + Na]^+$: 1015.6976. Found: 1015.6970.

Compound 6 was prepared in 89% yield as an oil from the reaction of acid **3** and amine **5** according to a procedure similar to that described for compound **T1**. ^{1}H NMR (400 MHz, acetone-d_6): δ 9.48 (s, 1H), 8. 35 (t, J_1 = 2.0 Hz, 1H), 7.91 (ddd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, J_3 = 0.8 Hz, 1H), 7.68 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7. 42 (t, J = 7.6 Hz, 1H), 3.89 (s, 3H), 3.35–3.32 (m, 4H), 2.78–2.74 (m, 4 H), 1.68–1.65 (m, 2 H), 1.52–1.49 (m, 4 H), 1.40–1.20 (m, 20 H), 0.91–0.89 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 171.2, 161.6, 139.8, 129.3, 128.8, 125.3, 124.6, 120.3, 48.0, 46.4, 46.2, 31.8(t), 29.4(d), 29.1(d), 29.0, 28.8, 28.4, 28.3, 27.8, 27.7, 27.0, 26.9 (d), 22.6 (d), 14.1. MS (ESI) m/z: 475.5 $[M + H]^+$. HRMS (MALDI-TOF): Calcd. for $C_{28}H_{46}N_2NaO_4$ $[M + Na]^+$: 497.3355. Found: 497.3342.

Compound 7

A mixture of **6** (4.74 g, 10 mmol) and lithium hydroxide monohydrate (1.05 g, 25 mmol) in THF (10 mL) and water (10 mL) was stirred at 50 °C for 12 h and then concentrated with a rotavapor to about 10 mL. Concentrated hydrochloric acid was added dropwise to pH = 4. The formed precipitate was filtered, washed with water, and dried *in vacuo* to give compound **7** as a white solid (4.46 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 8.50 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 8.14 (s, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 3.34–3.32 (m, 4H), 2.83–2.80 (m, 4H), 1.62–1.59 (m, 2H), 1.53–1.50 (m, 4H), 1.40–1.20 (m, 20H), 0.91–0.88 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.8, 170.4, 167.2, 139.6, 131.2, 128.7, 123.5, 122.8, 119.6, 47.0, 45.1, 31.6, 31.2, 28.8, 28.7, 28.6, 28.5, 27.3, 26.4, 26.3, 22.0, 13.8. MS (ESI) m/z: 461.5 $[M + H]^+$. HRMS (MALDI-TOF): Calcd. for $C_{27}H_{44}N_2NaO_4$ $[M + Na]^+$: 483.3199. Found: 483.3198.

Compound T2

To a stirred solution of compound **7** (0.46 g, 1.0 mmol) in DMF (10 mL), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) (0.13 g, 1.0 mmol), and *N*,*N*-diisopropylethylamine (DIEA) (0.2 mL) was added. The mixture was stirred at room temperature for 0.5 h and then diamine **4** (0.17 g, 0.45 mmol) added. The mixture was stirred at 50 °C for 12 h and then concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (100 mL). The solution was successively washed with saturated NH_4Cl solution (2 × 100 mL) and brine (2 × 100 mL), and dried over sodium sulfate. After workup, the crude product was recrystallized from methanol and dichloromethane to afford **T2** as a white solid (0.41 g, 67%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 2H), 10.32 (s, 2H), 10.13 (s, 2H), 8.56 (s, 2H), 8.33 (t, J = 1.6 Hz, 2H), 8. 15 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 8.10 (t, J = 2.0 Hz, 2H), 7.83 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 7.70 (t, J = 7.6 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 3.20 (t, J = 7.6 Hz, 2H), 2.60 (s, 4H), 1.54–1.51 (m, 2H), 1.42–1.40 (m, 2H), 1.40–1.20 (m, 40H), 0.86–0.83 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.9, 170.4, 165.6, 165.0, 139.6, 139.4, 139.3, 135.7, 135.0, 130.7, 128.5, 127.0, 121.7, 118.4, 116.0, 115.9, 112.8, 47.0, 45.0, 31.6, 31.2, 28.8(d), 28.6, 28.5, 27.3, 26.4, 26.3, 22.0, 13.9. MS (ESI) m/z: 1232.0 $[M + H]^+$. HRMS (MALDI-TOF): Calcd for $C_{74}H_{102}N_8NaO_8$ $[M + Na]^+$: 1253.7718. Found: 1253.7715.

Compound 8 was prepared in 85% yield as a white solid from the reaction of acid **7** and amine **5** according to a procedure similar to that described for compound **6**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.25 (s, 1H), 9.63 (s, 1H), 8.67 (s, 1H), 8. 38 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.46 (t, J = 8.4 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.00 (t, J = 8.4 Hz, 1H), 6.87 (s, 1H), 3.94 (s, 3H), 3.26–3.24 (m, 4H), 2.99–2.97 (m, 4H), 1.47–1.44 (m, 2H), 1.37–1.34 (m, 2H), 1.30–1.00 (m, 20H), 0.90 (t, J = 6.9 Hz, 6H), 0.80 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 170.8, 166.0, 165.0, 139.1, 137.1, 134.1, 129.6, 127.8, 123.5, 123.4, 122.6, 121.5, 120.2, 116.6, 51.0, 47.0, 45.2, 30.7 (d), 30.6, 30.4, 28.3 (d), 28.2, 28.0 (d), 27.9, 27.6, 26.7 (d), 26.6 (d), 25.9, 25.8, 21.6, 21.5, 13.0 (d). MS (ESI) m/z: 616.6 $[M + Na]^+$. HRMS (MALDI-TOF): Calcd for $C_{35}H_{51}N_3NaO_5$ $[M + Na]^+$: 616.3726. Found: 616.3716.

Compound 9 was prepared in 95% yield as a white solid starting from ester **8** according to a procedure similar to that described for compound **7**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.99 (s, 1H), 10.45 (s, 1H), 10.16 (s, 1H), 8.42 (s, 1H), 8.13 (s, 1H), 8. 02 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 3.22–3.19 (m, 4H), 2.60 (s, 4H), 1.54–1.51 (m, 2H), 1.42–1.40 (m, 2H), 1.35–1.15 (m, 20H), 0.86–0.83 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.9, 170.4, 167.2, 165.7, 139.6, 139.4, 135.4, 131.2, 128.7, 128.6, 124.4, 124.3, 121.9, 121.7, 121.0, 118.4, 47.0, 45.1, 31.6, 31.2, 28.7(d), 28.6, 28.5, 27.3, 26.4, 26.3, 22.0, 13.9. MS (ESI) m/z: 578.3 $[M - H]^-$. HRMS (MALDI-TOF): Calcd. for $C_{34}H_{49}N_3NaO_5$ $[M + Na]^+$: 602.3570. Found: 602.3563.

Compound T3 was prepared in 67% yield as a white solid from the reaction of acid **9** and diamine **4** according to a procedure similar to that described for compound **T2**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 2H), 10.46 (s, 2H), 10.36 (s, 2H), 10.1 (s, 2H), 8.56 (s, 2H), 8.35 (s, 2H), 8.32 (s, 2H), 8.17 (d, J = 8.0 Hz, 2H), 8.15 (s, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.56–7.49 (m, 6H), 7.44 (t, J = 8.4 Hz, 2H), 7.34 (t, J = 8.4 Hz, 2H), 3.25 (t,

J = 7.6 Hz, 2H), 3.20 (t, J = 7.6 Hz, 2H), 2.60 (s, 4H), 1.54–1.51 (m, 4H), 1.43–1.40 (m, 4H), 1.40–1.20 (m, 40H), 0.86–0.83 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.9, 170.4, 165.7, 165.6, 165.0, 139.6, 139.4, 139.3, 139.2, 135.7, 135.4, 135.2, 130.6, 128.6(d), 127.0, 123.2, 122.6, 121.9, 121.7, 119.9, 118.4, 116.1, 116.0, 112.8, 47.0, 45.1, 31.6, 31.2, 28.7(d), 28.6, 28.5, 27.3 (d), 26.4, 26.3, 22.0, 13.9. MS (ESI) m/z: 1492.8 [M + Na]$^+$. HRMS (MALDI-TOF): Calcd. for $C_{88}H_{112}N_{10}NaO_{10}$ [M + Na]$^+$: 1491.8461. Found: 1491.8450.

Compound 11

To a stirred solution of benzene-1,3-dicarboxylic acid (0.17 g, 1.0 mmol) in methanol (5 mL) was added aqueous tetrabutylammonium hydroxide solution (5 mL, 25%). The reaction mixture was stirred at room temperature overnight. After removal of the solvent, the resulting residue was dried under vacuum at 80 °C to give **11** quantitatively as a sticky white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (s, 1H), 7.64 (d, J = 7.6 Hz, 2H), 7.00 (t, J = 7.6 Hz, 1H), 3.17 (t, J = 8.0 Hz, 16H), 1.55 (m, 16H),1.35–1.27 (m, 16H), 0.93 (t, J = 7.2 Hz, 24H).

Compound 12 was prepared from the reaction of benzoic acid and tetrabutylammonium hydroxide according to a procedure similar to that described for compound **11**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (m, 2H), 7.20 (m, 3H), 3.17 (t, J = 8.0 Hz, 16H), 1.55 (m, 16H),1.35–1.27 (m, 16H), 0.93 (t, J = 7.2 Hz, 24H).

Compound 13 was prepared from the reaction of *cis*,*cis*-1,3,5-cyclohexanetricarboxylic acid and tetrabutylammonium hydroxide according to a procedure similar to that described for compound **11**.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.18 (t, J = 8.4 Hz, 24H), 1.69 (m, 3H), 1.57 (m, 27H),1.35–1.27 (m, 24H), 1.01 (m, 3H), 0.93 (t, J = 7.2 Hz, 36H).

Compound 14 was prepared from the reaction of benzene-1,4-dicarboxylic acid and tetrabutylammonium hydroxide according to a procedure similar to that described for compound **11**.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.61 (s, 4H), 3.17 (t, J = 8.0 Hz, 16H), 1.55 (m, 16H),1.35–1.27 (m, 16H), 0.93 (t, J = 7.2 Hz, 24H).

Compound 15 was prepared from the reaction of benzene-1,2-dicarboxylic acid and tetrabutylammonium hydroxide according to a procedure similar to that described for compound **11**.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.06 (m, 2H), 6.80 (m, 2H), 3.17 (t, J = 8.0 Hz, 16H), 1.55 (m, 16H),1.35–1.27 (m, 16H), 0.93 (t, J = 7.2 Hz, 24H).

Compounds L-**16** and D-**16** were prepared from the reaction of L-glumatic acid and D-glumatic acid and tetrabutylammonium hydroxide according to a procedure similar to that described for compound **11**, respectively. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.17 (t, J = 8.0 Hz, 16H), 1.99 (m, 1H), 1.86 (m, 1H), 1.74 (m, 1H), 1.55 (m, 16H),1.35–1.27 (m, 17H), 0.93 (t, J = 7.2 Hz, 24H).

Acknowledgements

We thank MOST (2007CB808001), NSFC (20732007, 20921091, 20872167, 20974118, 20972180), and STCSM (09XD1405300, 10PJ1412200) for financial support.

References

1 (*a*) S. Hecht and I. Huc, (eds) *Foldamers: Structure Properties and Applications*, Wiley-VCH, Weinheim, 2007; (*b*) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes and J. S. Moore, *Chem. Rev.*, 2001, **101**, 3893–4011.

2 For examples, see: (*a*) J.-L. Hou, X.-B. Shao, G.-J. Chen, Y.-X. Zhou, X.-K. Jiang and Z.-T. Li, *J. Am. Chem. Soc.*, 2004, **126**, 12386–12394; (*b*) C. Li, S.-F. Ren, J.-L. Hou, H.-P. Yi, S.-Z. Zhu, X.-K. Jiang and Z.-T. Li, *Angew. Chem., Int. Ed.*, 2005, **44**, 5725–5729; (*c*) J. J.-M. Leger Garric and I. Huc, *Angew. Chem., Int. Ed.*, 2005, **44**, 1954–1958; (*d*) C. Li, G.-T. Wang, H.-P. Yi, X.-K. Jiang, Z.-T. Li and R.-X. Wang, *Org. Lett.*, 2007, **9**, 1797–1800; (*e*) V. J. Chebny and R. Rathore, *J. Am. Chem. Soc.*, 2007, **129**, 8458–8465; (*f*) H. Abe, H. Machiguchi, S. Matsumoto and M. Inouye, *J. Org. Chem.*, 2008, **73**, 4650–4661.

3 For recent examples, see: (*a*) R. A. Smaldone and J. S. Moore, *J. Am. Chem. Soc.*, 2007, **129**, 5444–5450; (*b*) H.-P. Yi, J. Wu, K.-L. Ding, X.-K. Jiang and Z.-T. Li, *J. Org. Chem.*, 2007, **72**, 870–877; (*c*) W. S. Horne, M. D. Boersma, M. A. Windsor and S. H. Gellman, *Angew. Chem., Int. Ed.*, 2008, **47**, 2853–2856; (*d*) R. A. Smaldone and J. S. Moore, *Chem.–Eur. J.*, 2008, **14**, 2650–2657; (*e*) M. M. Muller, M. A. Windsor, W. C. Pomerantz, S. H. Gellman and D. Hilvert, *Angew. Chem., Int. Ed.*, 2009, **48**, 922–925.

4 For examples, see: (*a*) Q. Gan, Y. Ferrand, C. Bao, B. Kauffmann, A. Glelard, H. Jiang and I. Huc, *Science*, 2011, **331**, 1172–1175; (*b*) Z. Merican, K. D. Johnstone and M. J. Gunter, *Org. Biomol. Chem.*, 2008, **6**, 2534–2543; (*c*) L. A. Cuccia, J.-M. Lehn, J.-C. Homo and M. Schmutz, *Angew. Chem., Int. Ed.*, 2000, **39**, 233–237; (*d*) P. S. Corbin, S. C. Zimmerman, P. A. Thiessen, N. A. Hawryluk and T. J. Murray, *J. Am. Chem. Soc.*, 2001, **123**, 10475–10488; (*e*) C. Dolain, V. Maurizot and I. Huc, *Angew. Chem., Int. Ed.*, 2003, **42**, 2738–2740; (*f*) E. Kolomiets, V. Berl, I. Odriozola, A.-M. Stadler, N. Kyritsakas and J.-M. Lehn, *Chem. Commun.*, 2003, 2868–2869; (*g*) A. Petitjean, L. A. Cuccia, M. Schmutz and J.-M. Lehn, *J. Org. Chem.*, 2008, **73**, 2481–2495.

5 For examples, see: (*a*) A. S. Norgren and P. I. Arvidsson, *Org. Biomol. Chem.*, 2005, **3**, 1359–1361; (*b*) G. Luppi, R. Galeazzi, M. Garavelli, F. Formaggio and C. Tomasini, *Org. Biomol. Chem.*, 2004, **2**, 2181–2187; (*c*) A. Hayen, M. A. Schmitt, F. N. Ngassa, K. A. Thomasson and S. H. Gellman, *Angew. Chem., Int. Ed.*, 2004, **43**, 505–510; (*d*) L. Xiang, Y.-D. Wu and D. Yang, *Acc. Chem. Res.*, 2008, **41**, 1428–1438; (*e*) S. H. Choi, I. A. Guzei, L. C. Spencer and S. H. Gellman, *J. Am. Chem. Soc.*, 2009, **131**, 2917–2924; (*f*) J. P. Saludes, J. B. Ames and J. Gervay-Hague, *J. Am. Chem. Soc.*, 2009, **131**, 5495–5405; (*g*) I. M. Mándity, E. Wéber, T. A. Martinek, G. Olajos, G. K. Tóth, E. Vass and F. Fülöp, *Angew. Chem., Int. Ed.*, 2009, **48**, 2171–2175; (*h*) X. Zhao, M.-X. Jia, X.-K. Jiang, L.-Z. Wu, Z.-T. Li and G.-J. Chen, *J. Org. Chem.*, 2004, **69**, 270–279.

6 For representative examples, see: (*a*) Y. Hamuro, S. J. Geib and A. D. Hamilton, *J. Am. Chem. Soc.*, 1996, **118**, 7529–7541; (*b*) L. Yuan, H. Q. Zeng, K. Yamato, A. R. Sanford, W. Feng, H. Atreya, D. K. Sukumaran, T. Szyperski and B. Gong, *J. Am. Chem. Soc.*, 2004, **126**, 16528–16537; (*c*) H. Jiang, J.-M. Leger and I. Huc, *J. Am. Chem. Soc.*, 2003, **125**, 3448–3449; (*d*) V. Maurizot, C. Dolain, Y. Leydet, J.-M. Leger, P. Guionneau and I. Huc, *J. Am. Chem. Soc.*, 2004, **126**, 10049–10052; (*e*) E. R. Gillies, F. Deiss, C. Staedel, J.-M. Schmitter and I. Huc, *Angew. Chem., Int. Ed.*, 2007, **46**, 4081–4084; (*f*) Z.-Q. Hu, H.-Y. Hu and C.-F. Chen, *J. Org. Chem.*, 2006, **71**, 1131–1138; (*g*) H.-Y. Hu, J.-F. Xiang and C.-F. Chen, *Org. Biomol. Chem.*, 2009, **7**, 2534–2539.

7 (*a*) Z. Yu and S. Hecht, *Angew. Chem., Int. Ed.*, 2011, **50**, 1640–1643; (*b*) N. Zhu, W. Hu, S. Han, Q. Wang and D. Zhao, *Org. Lett.*, 2008, **10**, 4283–4286; (*c*) J. C. Nelson, J. G. Saven, J. S. Moore and P. G. Wolynes, *Science*, 1997, **277**, 1793–1796; (*d*) K. Oh, K.-S. Jeong and J. S. Moore, *Nature*, 2001, **414**, 889–893; (*e*) M. T. Stone, J. M. Heemstra and J. S. Moore, *Acc. Chem. Res.*, 2006, **39**, 11–20; (*f*) X. Yang, A. L. Brown, M. Furukawa, S. Li, W. E. Gardinier, E. J. Bukowski, F. V. Bright, C. Zheng, X. C. Zeng and B. Gong, *Chem. Commun.*, 2003, 56–57.

8 (*a*) X. Pan and Y. Zhao, *Org. Lett.*, 2009, **11**, 69–72; (*b*) Z. Zhong and Y. Zhao, *Org. Lett.*, 2007, **9**, 2891–2894; (*c*) Z. Zhong and Y. Zhao, *J. Am. Chem. Soc.*, 2006, **128**, 9988–9989; (*d*) Y. Zhao, Z. Zheng and E.-H. Ryu, *J. Am. Chem. Soc.*, 2007, **129**, 218–225.

9 (*a*) L. Fischer, P. Claudon, N. Pendem, E. Miclet, C. Didierjean, E. Ennifar and G. Guichard, *Angew. Chem., Int. Ed.*, 2010, **49**, 1067–1070; (*b*) L. Fischer, C. Didierjean, F. Jolibois, V. Semetey, J. M. Lozano, J.-P. Briand, M. Marraud, R. Poteau and G. Guichard, *Org. Biomol. Chem.*, 2008, **6**, 2596–2610; (*c*) A. Violette, M. C. Averlant-Petit, V. Semetey,

C. Hemmerlin, R. Casimir, R. Graff, M. Marraud, J.-P. Briand, D. Rognan and G. Guichard, *J. Am. Chem. Soc.*, 2005, **127**, 2156–2164.
10 (*a*) H. Juwarker and K.-S. Jeong, *Chem. Soc. Rev.*, 2010, **39**, 3664–3674; (*b*) Y.-Y. Zhu, G.-T. Wang and Z.-T. Li, *Curr. Org. Chem.*, 2011, **15**, 1266–1292.
11 (*a*) K.-J. Chang, B.-N. Kang, M.-H. Lee and K.-S. Jeong, *J. Am. Chem. Soc.*, 2005, **127**, 12214–12215; (*b*) V. R. Naidu, M. C. Kim, J.-m. Suk, H.-J. Kim, M. Lee, E. Sim and K.-S. Jeong, *Org. Lett.*, 2008, **10**, 5373–5376; (*c*) J.-m. Suk and K.-S. Jeong, *J. Am. Chem. Soc.*, 2008, **130**, 11868–11869.
12 (*a*) H. Juwarker, J. M. Lenhardt, D. M. Pham and S. L. Craig, *Angew. Chem., Int. Ed.*, 2008, **47**, 3740–3743; (*b*) R. M. Meudtner and S. Hecht, *Angew. Chem., Int. Ed.*, 2008, **47**, 4926–4930; (*c*) J. Sanchez-Quesada, C. Seel, P. Prados and J. De Mendoza, *J. Am. Chem. Soc.*, 1996, **118**, 277–278; (*d*) Y. Wang, J. Xiang and H. Jiang, *Chem.–Eur. J.*, 2011, **17**, 613–619; (*e*) Y. Wang, F. Bie and H. Jiang, *Org. Lett.*, 2010, **12**, 3630–3633; (*f*) A. Khan, C. Kaiser and S. Hecht, *Angew. Chem., Int. Ed.*, 2006, **45**, 1878–1881; (*g*) A. Khan and S. Hecht, *Chem.–Eur. J.*, 2006, **12**, 4764–4774; (*h*) C. Tie, J. C. Gallucci and J. R. Parquette, *J. Am. Chem. Soc.*, 2006, **128**, 1162–1171; (*i*) Y. Li and A. H. Flood, *J. Am. Chem. Soc.*, 2008, **130**, 12111–12122; (*j*) Y. Hua and A. H. Flood, *J. Am. Chem. Soc.*, 2010, **132**, 12838–12840.
13 Y.-X. Xu, G.-T. Wang, X. Zhao, X.-K. Jiang and Z.-T. Li, *J. Org. Chem.*, 2009, **74**, 7267–7272.
14 Applying the titrating data to a 1 : 1 stoichiometry gave rise to good results, while adopting a 1 : 2 or 2 : 1 stoichiometry yielded poor results, see: (*a*) A. H. Benesi and J. H. J. Hildebrand, *J. Am. Chem. Soc.*, 1949, **71**, 2703–2707; (*b*) O. S. Abou-Zied, *Spectrochim. Acta, Part A*, 2005, **62**, 245–251.
15 The binding constant and stoichiometry for **T3** and the dianion of glutamic acid (Glu) in $CDCl_3$ could not be estimated through titration of **T3** with the dianion of L-Glu acid because the low resolution of the spectra under the experimental condition, especially the very low intensities of NH signals. Instead, the stoichiometry was confirmed to be 1 : 1 for **T3** and dianion of L-Glu in DMSO-d_6 by fitting the ^{1}H NMR titration data to the Benesi–Hildebrand (B–H) equation, and the binding constant was estimated to be 411 M^{-1}.
16 A. Ben-Haida, P. Hodge and H. M. Colquhoun, *Macromolecules*, 2005, **38**, 722–729.