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PAPER

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Hydrogen bonding-mediated oligobenzamide foldamer receptors that efficiently bind a triol and saccharides in chloroform

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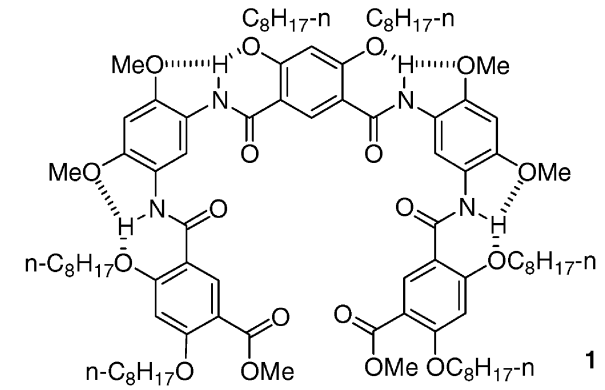
The self-assembly of two novel intramolecular hydrogen bonding-driven foldamers is described. Two linear symmetric aromatic amide oligomers, **1** and **2**, which are incorporated with benzene subunits, have been prepared by continuous amide-coupling reactions. The existence of three-centred hydrogen bonds in the oligomers and consequently the folding conformation of the oligomers in solution have been characterized by ^{1}H NMR experiments and by comparing them with the reported solid state structure of the identical structural skeleton. Molecular modeling reveals a rigid crescent conformation for **1** with a cavity of *ca.* 0.9 nm in diameter and a helical conformation for **2** with a cavity of *ca.* 0.8 nm in diameter. Due to the existence of intramolecular hydrogen bonding, all the C=O groups in both oligomers are located inwardly. The binding of **1** and **2** towards a trihydroxyl guest and four saccharide derivatives have been investigated with ^{1}H NMR, fluorescence, and circular dichroism spectroscopy. The association constants of the corresponding 1 : 1 complexes have been determined by fluorescence titration experiments.

Introduction

Non-covalent forces-induced folding or self-coiling is a common feature of biological macromolecules. The DNA double helices and protein folding represent the most typical examples of biomolecules.[1,2] In the past decade, there has been increasing interest in developing foldamers, artificial linear molecules that utilize non-covalent forces to modulate the folding or helical structures.[3–11] Among other non-covalent forces, hydrogen bonding has been widely utilized for this purpose. To date, a number of structurally elaborate aromatic amide folding and unfolding modes have been reported.[3,12–21]

We previously reported that hydrogen bonding-induced rigidified crescent and helical aromatic hydrazide oligomers can strongly complex mono- or disaccharide derivatives in less polar organic solvents like chloroform.[22] Recently, Huc *et al.* also found that hydrogen bonding-mediated oligopyridine-dicarboxamides can promote the *N*-oxidation of the peripheral pyridine units in oligopyridine-dicarboxamide-based foldamers[23] or encapsulate small molecules like water in chloroform.[24] Considering that the synthesis of unnatural folding receptors is obviously of higher efficiency than the synthesis of cyclophane or crown ether receptors of a comparable size, and that the cavity of the folding receptors could be readily tuned by modifying the structures of the assembling monomers,[25] these results suggest that rigid, folding structures may become a new generation of non-ring artificial receptors for molecular recognition or sensing after the covalently-bonded molecular tweezers.[26,27] In the search for new folding receptors for efficient molecular recognition, we had designed two new oligoamides **1** and **2**.[28] We herein report their synthesis, characterization and binding affinity towards triol and saccharide guests.[29–35]



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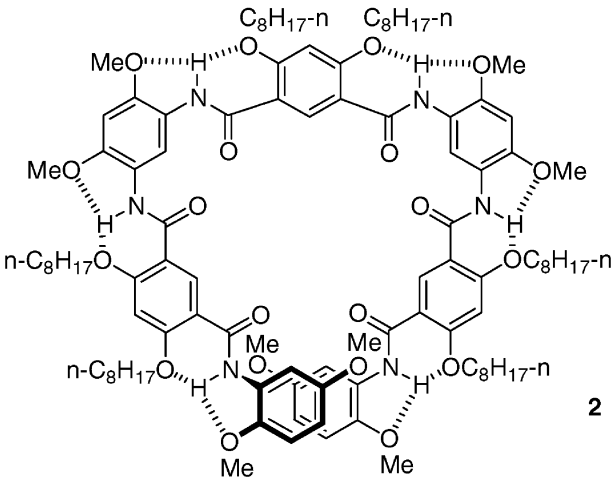

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Experimental

Melting points are uncorrected. All reactions were performed under an atmosphere of dry nitrogen. The ^{1}H NMR spectra were recorded on 400 or 300 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards. Chloroform (δ 7.26 ppm) was used as an internal standard for chloroform-*d* as solvent. Elemental analysis was carried out at the SIOC analytical center. Unless otherwise indicated, all starting materials obtained were of the best quality from commercial suppliers and used without further purification. All solvents were dried before use following standard procedures. Compound **15** was prepared according to the reported method.[36] The synthesis of compounds **16–19** has been reported in a previous paper.[22]

Syntheses

Compound 4. To a solution of compound **3**[22] (7.99 g, 17.7 mmol) in DMSO (50 mL), potassium hydroxide (0.99 g, 17.7 mmol) was added. The solution was stirred at 130 °C for 3 h and then poured onto ice–water (150 mL). Dilute hydrochloric acid (1 N) was added to adjust the pH of the solution to *ca.* 5. The resulting precipitate was filtered off and washed thoroughly with water. After recrystallization from *n*-hexane, compound **4** was obtained as a white solid (5.88 g, 76%). Mp 101–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (s, 1 H), 6.49 (s, 1 H), 4.27 (t, $J = 6.9$ Hz, 2 H), 4.09 (t, $J = 6.3$ Hz, 2 H), 3.86 (s, 3 H), 1.97–1.87 (m, 4 H), 1.70–1.45 (m, 4 H), 1.29 (m, 16 H), 0.89–0.87 (m, 6 H). MS (EI): *m*/*z* (%): 436 (18) $[M]^+$, 194 (100), 212 (49), 163 (25), 195 (22), 162 (21), 43 (19).

Compound 6. A solution of compound **4** (3.98 g, 9.10 mmol) and *N*-ethyl-*N*′-(3-dimethyl-aminopropyl) carbodiimide (EDCI, 1.51 g, 10.9 mmol) in dichloromethane was stirred at room temperature for 30 min and then a solution of diamine **5** (2.61 g, 15.5 mmol) in dichloromethane (30 mL) was added dropwise in 10 min. The solution was stirred at room temperature for 6 h and the solvent was removed under reduced pressure. The resulting residue was triturated in ether (100 mL) and the organic phase washed with water (30 mL × 2), dilute hydrochloric acid (1 N, 30 mL), saturated sodium bicarbonate (20 mL × 2), and brine (30 mL). After drying over sodium sulfate, the crude product was purified by column chromatography (dichloromethane–methanol 50 : 1) to afford **6** as a white solid (3.96 g, 74%). Mp 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.92 (s, 1 H), 8.84 (s, 1 H), 8.14 (s, 1 H), 6.50 (s, 1 H), 6.48 (s, 1 H), 4.21 (t, $J = 6.9$ Hz, 2 H), 4.08 (t, $J = 12$ Hz, 2 H), 3.86 (s, 9 H), 3.60–3.59 (br, 2 H), 2.00 (m, 2 H), 1.89 (m, 2 H), 1.51–1.29 (m, 40 H), 0.82–0.81 (m, 6 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 165.3, 162.9, 161.8, 160.8, 143.4, 137.2, 122.0, 114.5, 113.2, 109.5, 97.0, 69.9, 69.4, 56.5, 56.1, 51.6, 49.1, 34.0, 31.8, 31.7, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 25.9, 25.8, 25.6, 25.0, 22.7, 22.6, 14.1. MS (EI): *m*/*z* (%): 586 (50) $[M]^+$, 195 (35), 163 (100), 153 (22), 57 (25), 43 (36), 41 (20). IR (film): ν 3347, 2923, 2851, 1720, 1650, 1545, 1284, 1255, 1102, 1036 cm^{-1}. Anal. calcd. for $C_{33}H_{50}N_2O_7$: C, 67.55; H, 8.59; N, 4.77. Found: C, 67.39; H, 8.54; N, 4.71.

Compound 1. To a stirred solution of 4,6-bis-*n*-octyloxy-isophthalic acid[22] (1.06 g, 2.51 mmol) in dichloromethane, oxalyl chloride (0.2 mL, 2.33 mmol) and DMF (0.05 mL) were added. The solution was stirred at room temperature for 4 h and then concentrated *in vacuo* to afford crude compound **7** as a yellow solid. This product was dissolved in chloroform (20 mL) and the solution was added to a solution of compound **6** (2.95 g, 5.01 mmol) and triethylamine (2.0 mL, 14.0 mmol) in chloroform (50 mL). The solution was stirred at room temperature for 12 h and then concentrated under reduced pressure. The resulting residue was triturated with ether (100 mL) and the organic solution was washed with dilute hydrochloric acid (1 N, 15 mL × 2), saturated sodium bicarbonate (20 mL), water (30 mL) and brine (30 mL). After drying over sodium sulfate, the solvent was removed under reduced pressure. The resulting residue was subjected to column chromatography (dichloromethane–methanol 25 : 1) to afford compound **1** as a white powder (2.94 g, 75%). Mp 120–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.65 (s, 2 H), 1.59 (s, 2 H), 9.25 (s, 2 H), 9.15 (s, 1 H), 8.84 (s, 2 H), 6.44 (s, 2 H), 6.43 (s, 1 H), 6.40 (s, 1 H), 4.13 (t, $J = 8.7$ Hz, 8 H), 4.00 (t, $J = 6.9$ Hz, 4 H), 3.83 (s, 6 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 6 H), 1.94–1.79 (m, 12 H), 1.46–1.18 (m, 60 H), 0.82–0.76 (m, 18 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 165.4, 162.8, 162.0, 161.8, 160.8, 160., 146.2, 146.5, 137.6, 121.1, 120.5, 117.0, 115.6, 114.6, 113.0, 96.9, 95.0, 69.9, 69.8, 69.3, 55.9, 55.8, 51.6, 31.8, 31.8, 29.7, 29.5, 29.4, 29.4, 29.3, 29.2, 29.2, 29.1, 29.1, 25.9, 25.9, 22.7, 22.7, 22.6, 14.1, 14.1. MS (ESI): *m*/*z* (%): 1583 $[M + Na]^+$. IR (film): ν 3354, 2923, 2853, 1729, 1661, 1538, 1464, 1260, 1033, 804 cm^{-1}. Anal. Calcd. for $C_{90}H_{134}N_4O_{18}$: C, 69.29; H, 8.66; N, 3.59. Found: C, 69.04; H, 8.71; N, 3.56.

Compound 9. A suspension of 1,4-dimethoxy-2-nitrobenzene (6.18 g, 33.7 mmol) and Pd–C (5%, 0.30 g) in tetrahydrofuran (50 mL) was stirred under 1 atmosphere of hydrogen gas at room temperature for 8 h. The solid was removed over celite and washed with dichloromethane. The combined filtrate was then concentrated with a rotavapor. The resulting crude product was subjected to flash chromatography (dichloromethane) to afford the desired product as a white solid (5.07 g, 98%). Mp 80–81 °C [81 °C].[37] ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (d, $J =$ 8.7 Hz, 1 H), 6.34 (d, $J = 3.0$ Hz, 1 H), 6.25 (q, $J = 9$, 3.0 Hz, 1 H), 3.81 (s, 3 H), 3.74 (s, 3 H). MS (EI): *m*/*z*: 153 (52) $[M]^+$, 154 (5), 139 (9), 138 (100), 111(5), 110 (28), 95 (20), 67 (6).

Compound 10. A solution of **4** (1.67 g, 3.83 mmol), oxalyl chloride (0.50 g) and DMF (0.05 mL) in dichloromethane was stirred at room temperature for 5 h and then concentrated under reduced pressure to afford **8** as a yellow solid. This solid was dissolved in chloroform (10 m) and the solution was added to a stirred solution of **9** (0.76 g, 4.97 mmol) and triethylamine (1.00 g, 10.0 mmol) in chloroform (30 mL). After stirring at room temperature for 10 h, the solution was worked up as described above for compound **1**. The crude product was subjected to column chromatography (petroleum ether–EtOAc 10 : 1) to produce **10** as a white solid (1.84 g, 84%). Mp 78–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.14 (s, 1 H), 8.85 (m, 1 H), 8.42 (d, $J = 2.7$ Hz, 1 H), 6.83 (d, $J = 8.7$ Hz, 1 H), 6.60 (d, d, $J_1 = 8.7$ Hz, $J_2 = 2.4$ Hz, 1 H), 6.49 (s, 1 H), 4.22 (t, $J = 7.2$ Hz, 2 H), 4.09 (t, $J = 6.3$ Hz, 2 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 3.83 (s, 3 H), 2.01 (t, $J = 6.9$ Hz, 2 H), 1.90 (t, $J = 6.9$ Hz, 2 H), 1.52–1.29 (m, 20 H), 0.89–0.84 (m, 6 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 165.1, 163.0, 162.3, 160.8, 153.8, 142.5, 137.3, 128.9, 114.1, 113.0, 110.5, 108.8, 106.5, 96.8, 69.9, 69.3, 55.9, 55.8, 51.7, 31.8, 31.7, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 25.9, 25.8, 22.7, 22.6, 14.1, 14.0. MS (EI): *m*/*z* (%): 571 (17) $[M]^+$, 419 (51), 195 (38), 163 (100), 69 (22), 57 (47), 55 (30), 43 (78), 41 (43). Anal. calcd. for $C_{33}H_{49}NO_7$: C, 69.32; H, 8.64; N, 2.45. Found: C, 69.50; H, 8.72; N, 2.39.

Compound 11. A solution of compound **10** (1.65 g, 2.89 mmol) and potassium hydroxide (0.20 g, 3.46 mmol) in a mixture of water (15 mL) and methanol (10 mL) was heated under reflux for 3 h. After workup, the crude product was recrystallized from ethanol to give **11** as a white solid (1.55 g, 96%). Mp 133–135 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.97 (s, 1 H), 9.10 (s, 1 H), 8.41 (d, $J = 2.7$ Hz, 1 H), 6.83 (d, $J = 9.3$ Hz, 1 H), 6.61 (d, $J = 9.3$ Hz, 1 H), 6.54 (s, 1 H), 4.26 (t, $J =$

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6.6 Hz, 2 H), 4.24 (t, $J = 6.6$ Hz, 2 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 2.02 (t, $J = 7.5$ Hz, 2 H), 1.93 (t, $J = 6.6$ Hz, 2 H), 1.45–1.26 (m, 20 H), 0.98–0.92 (m, 6 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 213.0, 164.1, 161.6, 161.4, 160.9, 153.8, 142.6, 138.9, 128.8, 116.3, 110.8, 110.4, 108.5, 106.8, 96.5, 70.6, 70.4, 55.8, 31.8, 31.7, 29.3, 29.2, 29.1, 28.9, 28.8, 25.8, 22.6, 14.1. MS (EI): m/z (%): 557 (17) $[M]^+$, 163 (18), 153 (100), 138 (33), 57 (18), 44 (22), 43 (30), 41 (27). Anal. calcd. for $C_{32}H_{47}NO_7$: C, 68.91; H, 8.49; N, 2.52. Found: C, 68.70; H, 8.53; N, 2.47.

Compound 12. By using the experimental procedure described above for **6**, this compound was prepared as a white solid (67%) from the reaction of **11** and **5** (eluent for column chromatography: dichloromethane–ethanol 60 : 1). Mp 150–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.05 (s, 1 H), 9.83 (s, 1 H), 9.17 (d, $J = 1.5$ Hz, 1 H), 8.44 (d, d, $J_2 = 3.9$ Hz, $J_2 = 0.9$ Hz, 1 H), 8.17 (d, $J = 0.6$ Hz, 1 H), 6.81 (d, $J = 8.7$ Hz, 1 H), 6.60 (d, d, $J_1 = 9.0$ Hz, $J_2 = 3.6$ Hz, 1 H), 6.50 (d, $J = 6.6$ Hz, 2 H), 4.20 (t, $J = 6.9$ Hz, 4 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.61 (br, 2 H), 1.99 (t, $J = 6.9$ Hz, 4 H), 1.59–1.49 (m, 4 H), 1.39–1.26 (m, 20 H), 0.88–0.85 (m, 6 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 162.4, 161.8, 160.1, 160.0, 153.9, 143.0, 142.6, 141.7, 137.6, 129.3, 122.2, 115.4, 110.4, 109.2, 108.3, 108.2, 106.8, 96.7, 96.4, 70.0, 70.0, 56.2, 56.1, 55.8, 55.8, 55.8, 55.6, 31.9, 31.8, 31.7, 29.7, 29.5, 29.4, 29.3, 29.3, 29.2, 29.1, 25.8, 22.7, 22.6, 14.1. IR (film): ν 3359, 2925, 1660, 1536, 1281, 1223, 1198 cm^{-1}. MS (EI): m/z (%): 707 (46) $[M]^+$, 275 (52), 163 (100), 153 (67), 69 (38), 57 (46), 55 (40), 43 (64). Anal. calcd. for $C_{41}H_{57}N_3O_8$: C, 67.87; H, 8.12; N, 5.94. Found: C, 67.68; H, 8.06; N, 5.82.

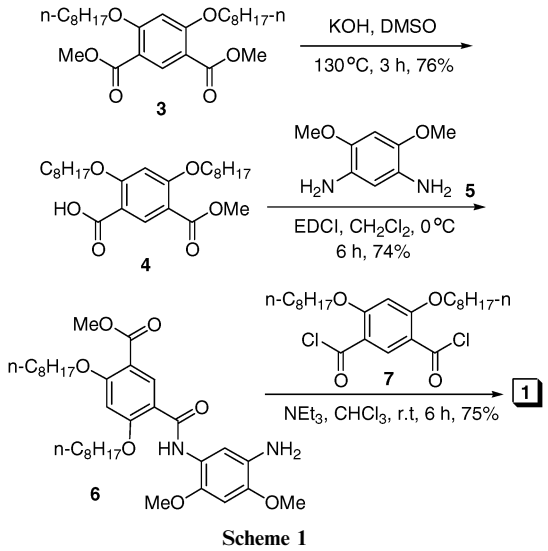
Compound 2. By using the experimental procedure described above for the preparation of **1**, this compound was prepared as a white solid (0.96 g, 60%) from the reaction of compounds **7** (0.37 g, 0.88 mmol) and **12** (1.25 g, 1.80 mmol) in chloroform (eluent for column chromatography: dichloromethane–ethanol 25 : 1). Mp 186–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.98 (s, 2 H), 9.64 (s, 2 H), 9.59 (s, 2 H), 9.25 (s, 2 H), 9.21 (s, 1 H), 9.19 (s, 2 H), 8.48 (d, $J = 2.4$ Hz, 2 H), 6.74 (d, $J = 9.0$ Hz, 2 H), 6.53 (d, d, $J_1 = 9.3$ Hz, $J_2 = 2.7$ Hz, 2 H), 6.46 (s, 3 H), 6.44 (s, 2 H), 4.15 (m, 12 H), 3.82 (s, 6 H), 3.81 (s, 6 H), 3.80 (s, 6 H), 3.78 (s, 6 H), 1.92 (m, 12 H), 1.46–1.22 (m, 60 H), 0.88–0.81 (m, 18 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 162.5, 161.9, 161.8, 160.3, 160.0, 159.9, 153.7, 146.4, 142.5, 137.7, 129.4, 128.5, 120.6, 120.3, 117.1, 115.4, 115.2, 115.1, 110.2, 108.2, 106.5, 96.5, 94.8, 55.8, 31.8, 29.5, 29.3, 29.2, 25.9, 25.8, 25.7, 14.1. IR (film): ν 3352, 2932, 2847, 1655, 1527, 1463, 1278, 1232, 1197, 710 cm^{-1}. MS (MALDI-TOF): m/z: 1825 $[M + Na]^+$. HRMS calcd. for $C_{104}H_{148}N_6O_{20}Na$: 1825.3063. Found: $C_{104}H_{148}N_6O_{20}Na^+$ 1825.3015.

Molecular mechanics calculation

The folding patterns of the oligomers were constructed by using the Builder program within the package HyperChem. Then they were optimized by the conjugate gradient with AccuModel software 2.1 using the MM3 force field. To explore lower energy conformation, molecular dynamics calculations were performed without constraints for the oligomers.

Binding studies

For fluorescent titration experiments, typically a solution of the receptor in chloroform was prepared at about 2.0–6.0 mM, and a solution of the guest in chloroform was prepared at 5–50 mM. A mixture of the solutions with a fixed host concentration and a changing guest concentration was placed in a cuvette and the fluorescent spectra were sequentially recorded. Usually 15–20 spectra were recorded for one case. The values of the



Scheme 1

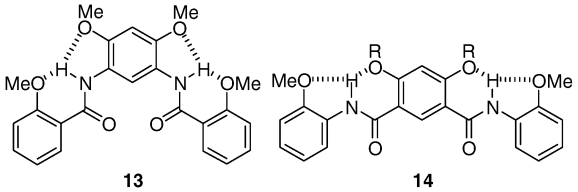
emission, I, at a fixed wavelength were collected and Origin 6.0 software was used to fit a 1 : 1 binding isotherm to the data: $\Delta I = (\Delta I_{max}/[A]) \times \{0.5[G] + 0.5([A] + K_d) - 0.5([G]^2 + \{2[G](K_d - [A]) + (K_d + [A])^2\}^{1/2})\}$, where [A] is the concentration of **1** or **2**, [G] is the concentration of the guest, $K_d = (K_{assoc})^{-1}$. Association constants reported are the average values of two or three experiments.[22]

Results and discussion

The synthesis of 5-mer **1** is shown in Scheme 1. Compound **3** was first hydrolysed in DMSO, with potassium hydroxide as base, to give acid **4** in 76% yield. The latter was treated with diamine **5** in dichloromethane in the presence of *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDCI) to afford compound **6** in 74% yield. Finally, **6** was reacted with diacyl chloride **7** in chloroform with triethylamine as base to produce compound **1** in 75% yield.

For the synthesis of 7-mer **2** (Scheme 2), compound **4** was first converted into acyl chloride **8** by oxalyl chloride in dichloromethane. The latter was then reacted with aniline **9** to produce **10** in 84% yield (two steps). Compound **10** was hydrolysed with potassium hydroxide in refluxing aqueous methanol to afford intermediate **11** in 96% yield and the acid was then coupled with 1 equivalent of diamine **5** to give aniline **12** in 67% yield. Finally, **12** was reacted with **7** in chloroform and produced compound **2** in 60% yield. Compounds **1** and **2** are well soluble in common organic solvents like dichloromethane and chloroform and have been characterized by the ^{1}H and ^{13}C NMR and mass spectroscopy and microanalysis.

Previously, the localized three-centred intramolecular hydrogen bonding mode consisting of the S(6) and S(5) type[38] has been well-established and utilized to assemble a number of folded and unfolded secondary structures.[19–22,39,40] In addition, the three-centred hydrogen bonds in model compounds **13**[20,21] and **14**[14] have been established by X-ray analysis. Because the backbones of longer oligomers **1** and **2** can be regarded as



a repeating combination of one or more **13** and **14**, it is reasonable to assume that, without additional important steric

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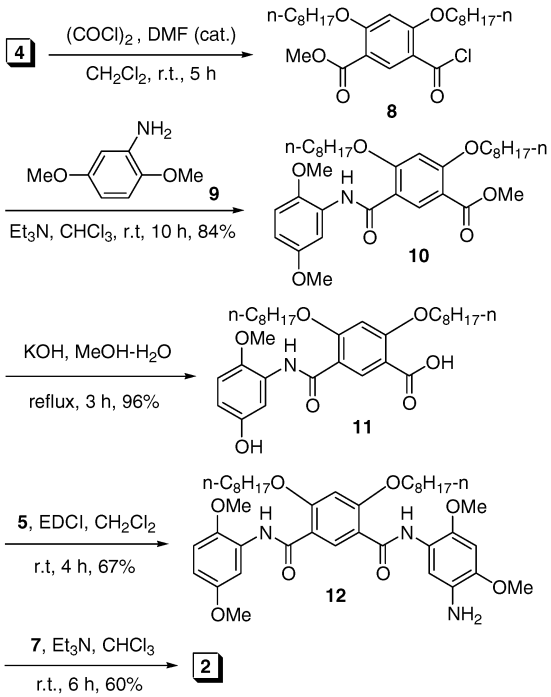


Scheme 2

hindrance, similar three-centred hydrogen bonds should also exist in the longer oligomers, which would lead to a rigidified, folded conformation for both oligomers.

The ^{1}H NMR spectra of compounds **1**, **2**, and **10** in chloroform-*d* are presented in Fig. 1. As expected, all the amide protons of the oligomers appeared in the downfield area (10.14 to 9.59 ppm), clearly indicating that three-centred hydrogen bonding also exists in these molecules in solution. The resolution of the spectrum of 7-mer **2** (Fig. 1c) is not reduced compared to that of **10** and 5-mer **1**, implying that there is no important intermolecular π–π stacking in **2**. The ^{1}H NMR dilution experiments in chloroform-*d* (from 15 mM to 0.5 mM) revealed only very small shifting (<0.03 ppm) of the signals for both **1** and **2** ($K_{\text{self-assoc}} < 5\ M^{-1}$), which is consistent with the above observation.

A molecular modelling study revealed that 5-mer **1** possesses a crescent conformation, whereas 7-mer **2** is long enough to produce a helical conformation with the two peripheral benzene subunits stacking with each other.[14,22] In addition, all the C=O oxygen atoms point into the cavity as a result of the intramolecular hydrogen bonding, producing a polar cavity of *ca*. 0.9 and 0.8 nm in diameter, respectively. Such a polar cavity provides enough large space to complex multi-hydroxyl guests through intermolecular hydrogen bonding.[20,22] Therefore, their binding affinity towards guest **15** was first investigated in chloroform.

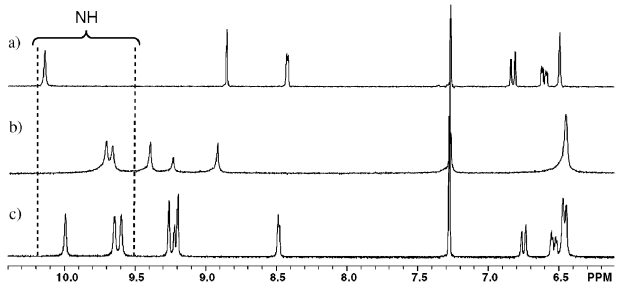


Fig. 1 Partial ^{1}H NMR spectra (400 MHz, 5 mM) of **10** (a), **1** (b), and **2** (c) in chloroform-*d* at 298 K.

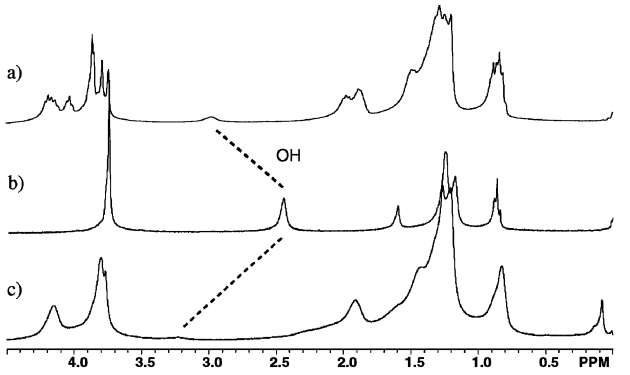
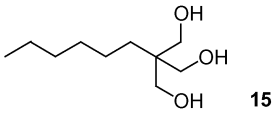


Fig. 2 Partial ^{1}H NMR spectra (400 MHz, 5 mM) of **15** + **1** (1 : 1) (a), **15** (b), and **15** + **2** (1 : 1) (c) in chloroform-*d* at 298 K, highlighting the downfield shifting of the OH signal of **15** upon complexation with **1** and **2**.



Mixing 1 equiv. of **1** or **2** with **15** in chloroform-*d* caused the OH signal of **15** to move downfield ($\Delta\delta$: 0.54 and 0.73 ppm, respectively) substantially (Fig. 2), indicating that strong complexation occurs between **1** or **2** and **15**. Because intermolecular hydrogen binding also exists between different molecules of **15**, a Job's plot investigation could not be utilized to evaluate the binding stoichiometry of the complex.[41] To estimate the stoichiometry between **15** and the hosts, ^{1}H NMR spectra for [**2**] : [**15**] = 0 : 1–2.5 : 1 in chloroform-*d* were measured. The OH signal of **15** moved downfield and the plot of the change *versus* the concentration ratio gave rise to an inflexion at [**2**] : [**15**] = 1 : 1 (Fig. 3), supporting a 1 : 1 binding mode for the complex. A quantitative study of the complexing behaviour by the ^{1}H NMR titration method was found to be impossible due to lack of a suitable probe (the HO signal of **15** was buried at high concentrations of **1** or **2**). It was also found that the fluorescence intensity of **1** and **2** in chloroform was increased significantly upon addition of **15**; the titration spectra of **2** with **15** in chloroform are presented in Fig. 4 as an example. The titration results were utilized to derive the association constants by fitting a 1 : 1 regression equation to the data (Table 1).[22,42] Both complexes display comparable stabilities, which may be rationalized by considering that receptors **1** and **2** possess an identical number of C=O groups.

Complexation driven by intermolecular hydrogen bonding is a dynamic, reversible process. In order to obtain more insight

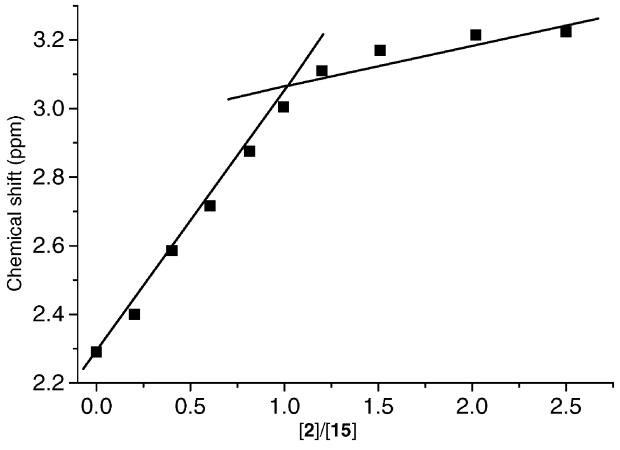


Fig. 3 Plot of the chemical shift change of the OH signal of **15** *versus* [**2**] : [**15**] (in chloroform-*d* at 298 K).

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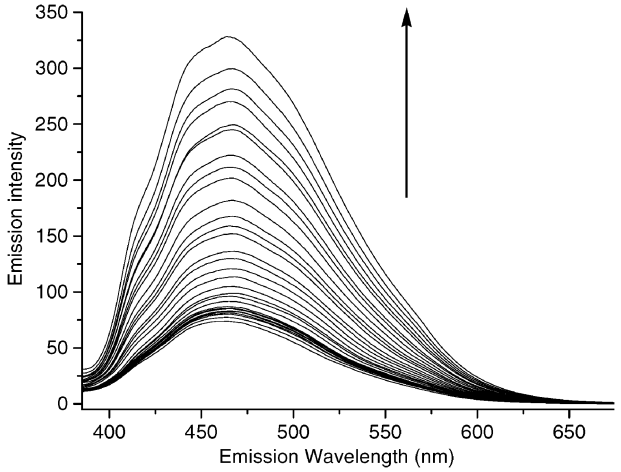


Fig. 4 The fluorescence spectra of **2** (3.0×10^{-5} M, excitation wavelength = 350 nm) in chloroform at 298 K, increasing with incremental addition of **15** (0–500 times).

into the structure of the complexes, ^{1}H NMR NOESY experiments were performed for the 1 : 1 solutions of both systems in chloroform-*d*, which revealed an intermolecular NOE connection between the H-a signal of **2** and the OH signal of **15** (Fig. 5). No other intermolecular NOEs were observed for both complexes.

As a previous study had revealed that aromatic hydrazide-based folding oligomers, which have a slightly larger cavity of *ca.* 1.0 nm in diameter, are good non-cycle receptors for saccharide guests in chloroform,[22,43–46] the present foldamers were also envisioned to be able to bind saccharides. To explore this complexing possibility, saccharide derivatives **16–19** were chosen as guests. The ^{1}H NMR investigation in chloroform-*d* revealed significant changes of the chemical shift of the OH signals of the guests. Due to overlapping of signals, a quantitative study could not be carried out with ^{1}H NMR spectroscopy. Addition of the guest to the solution of **1** or **2** in chloroform also resulted in remarkable enhancement of the fluorescent emission of the oligomers. Association constants in chloroform were therefore determined from the fluorescence titration data of the oligomers with the guests by assuming a 1 : 1 binding mode. The corresponding results are listed in Table 1. It can be found thatthe complexes of saccharides with more hydroxyl groups exhibit higher binding stabilities. As expected, 7-mer receptor **2** did not display increased binding affinity compared to 5-mer **1**. This result is similar to the observation for the complex of guest **15**.

Table 1 Association constants and the associated free-energy change of complexes between the novel aromatic amide receptors and multi-hydroxyl guests in chloroform-*d* at 298 K[a]

Complex	K_{assoc}/M^{-1}	ΔG/kcal mol^{-1}
1·**15**	$1.8 (\pm 0.2) \times 10^3$	4.4
2·**15**	$1.5 (\pm 0.2) \times 10^3$	4.3
1·**16**	$5.5 (\pm 0.6) \times 10^2$	3.8
1·**17**	$1.6 (\pm 0.2) \times 10^3$	4.4
1·**18**	$1.7 (\pm 0.3) \times 10^3$	4.4
1·**19**	$5.5 (\pm 0.7) \times 10^3$	5.2
2·**16**	$7.8 (\pm 0.9) \times 10^2$	4.0
2·**17**	$2.3 (\pm 0.3) \times 10^3$	4.6
2·**18**	$2.4 (\pm 0.2) \times 10^3$	4.7
2·**19**	$7.2 (\pm 0.8) \times 10^3$	5.3

[a] Obtained based on emission at 455 nm (excitation wavelength = 350 nm).

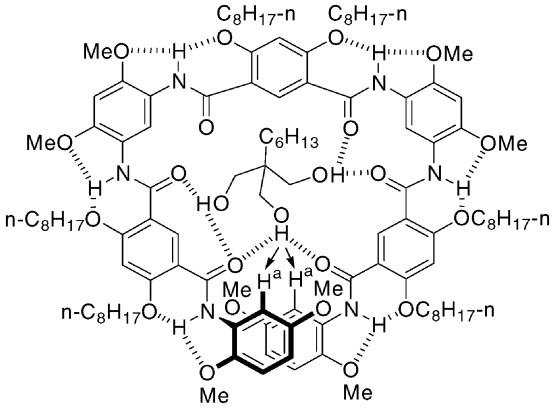
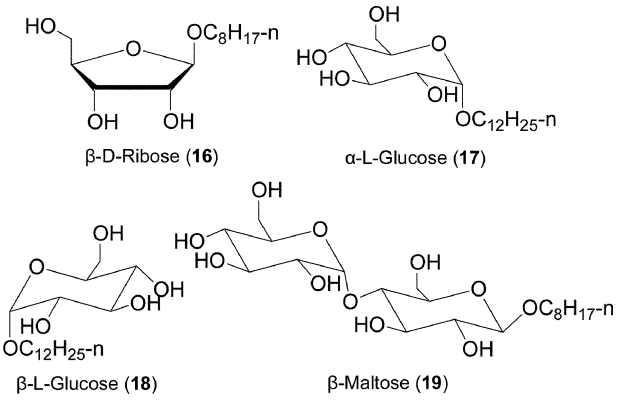


Fig. 5 Intermolecular NOE connection observed in complex **2**·**15** (6 mM) in chloroform-*d* (400 MHz) at 298 K (the mixing time is 0.5 s).



Related to the relatively strong binding feature of **1** and **2** to the saccharide guests, chiral induction in chloroform through complexation of the foldamer receptors for saccharides was also investigated.[22,31,47] For example, addition of saccharides **16** or **17** to a solution of **2** induces a negative Cotton effect of moderate strength at *ca.* 269 nm, which is due to the foldamer's aromatic chromophore (Fig. 6). The induced CDs increased with an increase of the concentration of the guest, and decreased and eventually vanished with addition of polar methanol in the solvent, indicating that the signals were generated through intermolecular hydrogen bonding. In principle, the helical **2** should give rise to two chiral conformational isomers of the 1 : 1 ratio, upon complexation with chiral saccharide guest, and the content of one isomer was increased resulting in the formation of the new CD signal. Under similar conditions, no induced CD signals were observed for 5-mer **1**

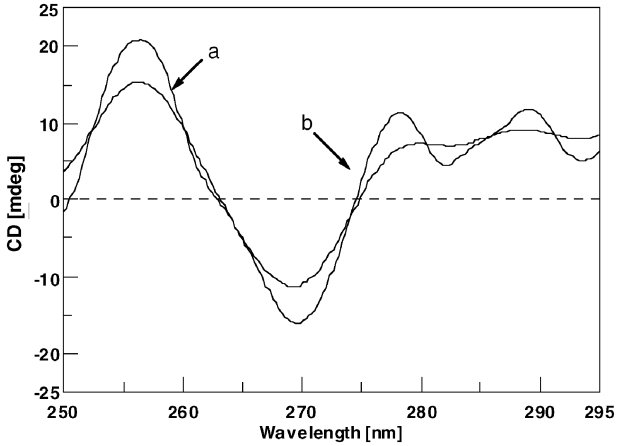


Fig. 6 Induced CD spectrum of complexes of **2** (0.52 mM) with **16** (0.10 mM) (a) and **17** (0.10 mM) (b) in chloroform at 298 K.

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when the saccharide guest was added probably due to a smaller conformational change of this shorter folding oligomer upon complexation.

Conclusion

We have reported the synthesis and characterization of two new hydrogen bonding-induced aromatic amide foldamers. The new folding structures can efficiently complex multi-hydroxyl molecules and saccharide derivatives in chloroform through intermolecular multiple hydrogen bonding. The complexation for disaccharide guest is remarkably stronger, which bodes well for the development of longer oligomers or polymers of an identical skeleton for enhanced binding of saccharide molecules. Progress along this line might lead to the development of unnatural systems of the nanoscale for macromolecular transportation or encapsulation.

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