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Hydrogen Bonded Oligohydrazide Foldamers and Their Recognition for Saccharides

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Abstract: This paper describes the synthesis and characterization of the first series of hydrogen bonding-driven hydrazide foldamers and their recognition for alkyl saccharides in chloroform. Oligomers **1**, **2**−**4**, **5**, **6**, and **7**, which contain one, two, four, six, or twelve repeated dibenzoyl hydrazide residues, respectively, have been prepared. The rigid and planar conformations of **1** and **2** or **4** have been established with X-ray analysis and ^{1}H NMR spectroscopy, whereas the folding and helical conformations of **5**−**7** have been evidenced by the 1D and 2D ^{1}H NMR and IR spectroscopy and molecular mechanics calculations. Molecular mechanics calculations also revealed that **5**, **6**, and **7** possess a rigid cavity with size of ca. 10.6 to 11.1 Å, and half of the carbonyl groups in the folding conformations are orientated inwardly inside the cavity. ^{1}H NMR and CD experiments revealed that **5**−**7** efficiently complex alkylated mono- and disaccharides **32**−**35** in chloroform. The association constants (K_{assoc}) of the complexes have been determined with the ^{1}H NMR and fluorescent titration methods. The energy-minimized conformation of **6**·**34** has been obtained with molecular mechanics calculation. The hydrazide-based folding structures described here represent novel examples of hydrogen bonding-driven foldamers that act as artificial receptors for selective molecular recognition.

Introduction

In recent years, there has been intense interest in developing unnatural oligomers (foldamers) that are induced by intramolecular noncovalent forces to fold into well-defined secondary structures.[1] Although studies on this kind of well-defined linear species have been initially inspired by the helical structures found in nature, it has been expected that progress in this field will eventually lead to unnatural macromolecules with sizes and functions of biomacromolecules such as proteins and DNAs.[1d] Among other noncovalent interactions such as metal−ligand coordination,[2] donor−acceptor interaction,[3,4] and solvophobic interaction,[5,6] the hydrogen bonding motif has proven itself to be a highly efficient tool for the formation of folding architectures. Examples of hydrogen (H) bonding-driven hairpin-styled foldamers include α-peptides,[7] β-peptides,[8] γ-peptides,[9] δ-peptides,[10] peptdoids,[11] heterocyclic ureas,[12] and various peptide analogues.[13−19] A number of H-bonding-induced aromatic

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(1) For review articles, see (a) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (c) Stigers, K. D.; Soth, M. J.; Nowick, J. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 714. (d) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893. (e) Sanford, A. R.; Gong, B. *Curr. Org. Chem.* **2003**, *7*, 1649. (f) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (g) Cubberley, M. S.; Iverson, B. L. *Curr. Opin. Chem. Biol.* **2001**, *5*, 650. (h) Patch, J. A.; Barron, A. E. *Curr. Opin. Chem. Biol.* **2002**, *6*, 872. (i) Schmuck, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2448. (j) Zhao, D.; Moore, J. S. *Chem. Commun.* **2003**, 807.
(2) Cuccia, L. A.; Lehn, J.-M.; Homo, J.-C.; Schmutz, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 233.
(3) (a) Lokey, R. S.; Iverson, B. L. *Nature* **1995**, *375*, 303. (b) Zych, A. J.; Iverson, B. L. *Helv. Chim. Acta* **2002**, *85*, 3294.
(4) Zhao, X.; Jia, M.-X.; Jiang, X.-K.; Wu, L.-Z.; Li, Z.-T.; Chen, G.-J. *J. Org. Chem.* **2004**, *69*, 270.
(5) (a) Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793. (b) Zhao, D.; Moore, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 9996.
(6) (a) Wang, W.; Li, L.-S.; Helms, G.; Zhou, H.-H.; Li, A. D. Q. *J. Am. Chem. Soc.* **2003**, *125*, 1120. (b) Li, A. D. Q.; Wang, W.; Wang, L.-Q. *Chem. Eur. J.* **2003**, *9*, 4594.
(7) (a) Nowick, J. S.; Lam, K. S.; Khasanova, T. V.; Kemnitzer, W. E.; Maitra, S.; Mee, H. T.; Liu, R. *J. Am. Chem. Soc.* **2002**, *124*, 4972. (b) Yang, X. W.; Martinovic, S.; Smith, R. D.; Gong, B. *J. Am. Chem. Soc.* **2003**, *125*, 9932. (c) Nowick, J. S.; Brower, J. O. *J. Am. Chem. Soc.* **2003**, *125*, 876.
(8) For recent examples, see: (a) Bruckner, A. M.; Chakraborty, P.; Gellman, S. H.; Diederichsen, U. *Angew. Chem., Int. Ed.* **2003**, *42*, 4395. (b) Park, J. S.; Lee, H. S.; Lai, J. R.; Kim, B. M.; Gellman, S. H. *J. Am. Chem. Soc.* **2003**, *125*, 8539. (c) Gademann, K.; Hane, A.; Rueping, M.; Jaun, B.; Seebach, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 1534. (d) Glattli, A.; Daura, X.; Seebach, D.; Gunsteren, W. E. *J. Am. Chem. Soc.* **2002**, *124*, 12972.
(9) (a) Hanessian, S.; Luo, X. H.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8569. (b) Seebach, D.; Brenner, M.; Rueping, M.; Jaun, B. *Chem. Eur. J.* **2002**, *8*, 573.
(10) (a) Szabo, L.; Smith, B. L.; McReynolds, K. D.; Parrill, A. L.; Morris, E. R.; Gervay, J. *J. Org. Chem.* **1998**, *63*, 1074. (b) Hungerford, N. L.; Claridge, T. D. W.; Watterson, M. P.; Aplin, R. T.; Moreno, A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3666.
(11) (a) Patch, J. A.; Barron, A. E. *J. Am. Chem. Soc.* **2003**, *125*, 12092. (b) Armand, P.; Kirshenbaum, K.; Goldsmith, R. A.; Farr-Jones, S.; Barron, A. E.; Truong, K. T.; Dill, K. A.; Mierke, D. F.; Cohen, F. E.; Zuckermann, R. N.; Bradley, E. K. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4309.
(12) Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10475.
(13) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568.
(14) Gennari, C.; Salom, B.; Potenza, D.; Williams, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2067.
(15) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088.
(16) Smith, A. B., III.; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672.

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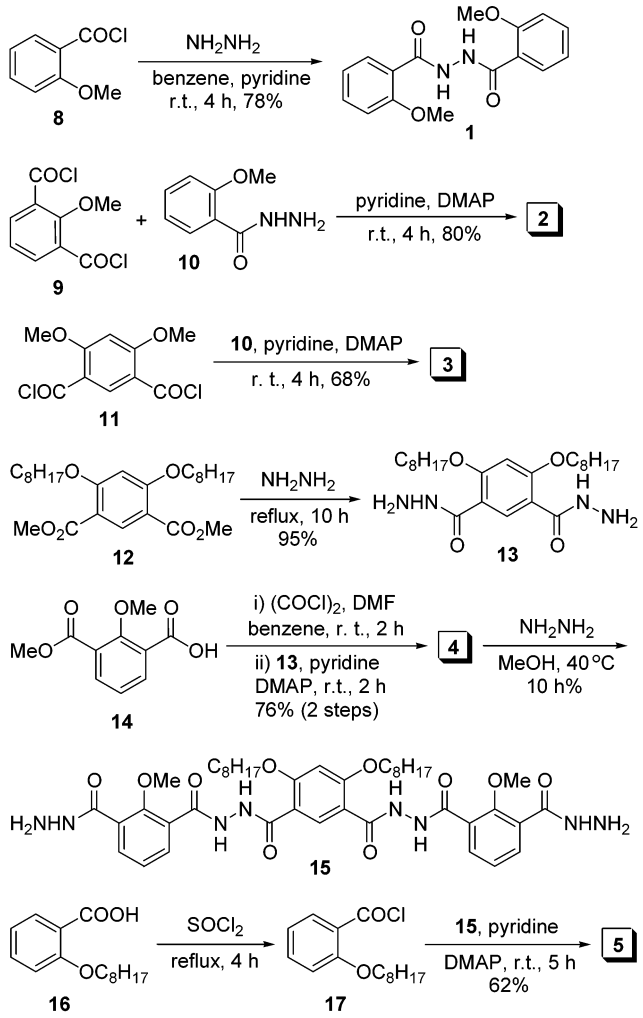
oligoamide and dendrimer foldamers have also been reported.[20,21] However, it is only recently that examples of folding architectures that display additional functions such as molecular recognition or catalysis have been reported.[22]

We were interested in developing new folding systems, in which additional functional units could be orientated at specifically designed positions. We logically regarded this as the first step to develop new generation of noncyclic receptors for molecular recognition. Previously, we have reported the self-assembly of a novel series of highly stable quadruply H-bonded heterodimers from readily available, structurally complementary hydrazide monomers.[23] The X-ray and ^{1}H NMR studies demonstrated that the hydrazide skeleton of one series of monomers adopts rigid and planar conformation and the hydrazine amide units are arranged in the trans-orientated pattern. A recent X-ray investigation also revealed similar trans-arrangement of the amide units in 1,2-dibenzoyl hydrazine.[24] Following increased applications of hydrogen bonding in developing folding oligoamide architectures with well-defined cavity,[25] we had incorporated the 1,2-dibenzoyl hydrazide moiety and stable three-centered H-bonds into a novel series of oligohydrazides.[26,27] Intramolecular hydrogen bonding has induced the oligomers to adopt rigid crescent or helical conformations, depending on the length of the oligomers. In this paper, we report the design, synthesis and characterization of the novel series of H-bonding-induced hydrazide foldamers **2**−**7**. ^{1}H NMR and circular dichroism studies revealed that the longer folding pentamer **5**, heptamer **6**, and tridecamer **7** possesses a well-defined cavity with a size of ca. 10.6−11.1 Å,[25] in which half of the carbonyl groups are located inwardly, and can efficiently complex alkylated mono- and disaccharide guests in chloroform.[28,29]

Scheme 1



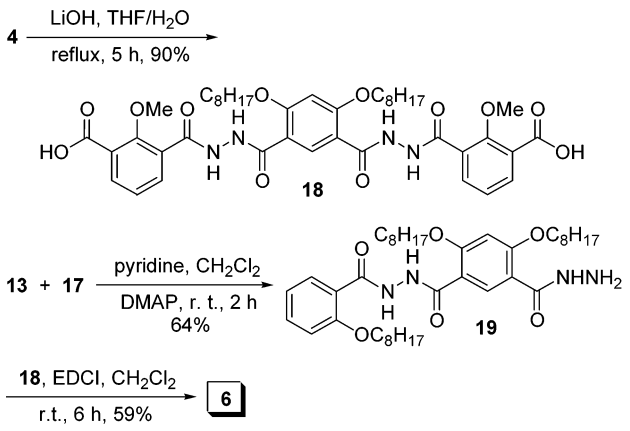
Results and Discussion

Design and Synthesis. Seven dibenzoyl hydrazide derivatives **1**, **2**−**4**, **5**, **6**, and **7** have been designed, which contain two, three, five, seven, and thirteen benzene rings, respectively. The short molecules **1**−**4** are used as models for the establishment of the folding pattern, whereas the longer molecules **5**−**7** are expected to give rise to crescent or helical structures. The *n*-octyl group has been used to improve the solubility of the longer oligomers **4**−**7** in common organic solvents such as chloroform and dichloromethane, while the methoxyl group was introduced to the isophthaloyl unit in order to minimize possible steric hindrance.

The syntheses of compounds **1**−**5** are shown in Scheme 1. Compound **8** was reacted with hydrazine in hot benzene to give dimer **1** in 78% yield, whereas the reaction of dichloride **9** with excessive amount of **10** in pyridine produced trimer **2** in 80%

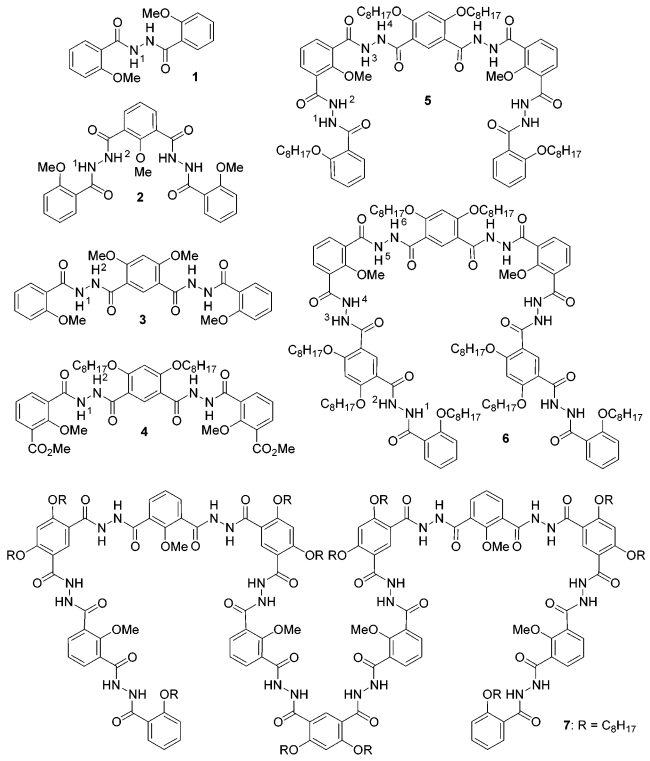
(17) Machetti, F.; Ferrali, A.; Menchi, G.; Occhiato, E. G.; Guarna, A. *Org. Lett.* **2000**, *2*, 3987.
(18) Winkler, J. D.; Piatnitski, E. L.; Mehlmann, J.; Kasparec, J.; Axelsen, P. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 743.
(19) Yang, D.; Li, W.; Qu, J.; Luo, S.-W.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 13018.
(20) (a) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529. (b) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587. (c) Ernst, J. T.; Becerril, J.; Park, H. S.; Yin, H.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2003**, *42*, 535. (d) Jiang, H.; Léger, J.-M.; Huc, I. *J. Am. Chem. Soc.* **2003**, *125*, 3448. (e) Jiang, H.; Dolain, C.; Léger, J.-M.; Gornitzka, H.; Huc, I. *J. Am. Chem. Soc.* **2004**, *126*, 1034.
(21) (a) Recker, J.; Tomcik, D.; Parquette, J. R. *J. Am. Chem. Soc.* **2000**, *122*, 10298. (b) Huang, B.; Parquette, J. R. *J. Am. Chem. Soc.* **2001**, *123*, 2689. (c) Huang, B.; Prantil, M. A.; Gustafson, T. L.; Parquette, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 14518.
(22) Moore et al. reported that solvophobically driven *m*-oligo(phenyleneethynylene) foldamers were able to recognize size-matching molecules and to promote the methylation of pyridine, see: (a) Prince, R. B.; Barnes, S. A.; Moore, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 2758. (b) Tanatani, A.; Mio, M. J.; Moore, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 1792. (c) Tanatani, A.; Hughes, T.; Moore, J. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 325. (d) Heemstra, J. M., Moore, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 1648.
(23) Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15128.
(24) Raj, S. S. S.; Yamin, B. M.; Boshaala, A. M. A.; Tarafder, M. T. H.; Crouse, K. A.; Fun, H.-K. *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **2000**, *56*, 1011.
(25) Several H-bonding-driven foldamers have been described, which have a defined cavity, see: (a) Gong, B.; Zeng, H.; Zhu, J.; Yuan, L.; Han, Y.; Cheng, S.; Furukawa, M.; Parra, R. D.; Kovalevsky, A. Y.; Mills, J. L.; Skrzypczak-Jankun, E.; Martinovic, S.; Smith, R. D.; Zheng, C.; Szyperski, T.; Zeng, X. C. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11583. (b) Dolain, C.; Maurizot, V.; Huc, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 2738. (c) Kolomiets, E.; Berl, V.; Odriozola, I.; Stadler, A.-M.; Kyritsakas, N.; Lehn, J.-M. *Chem. Commun.* **2003**, 2868. (d) Maurizot, V.; Linti, G.; Huc, I. *Chem. Commun.* **2004**, 924. (e) Yang, X.; Yuan, L.; Yamato, K.; Brown, A. L.; Feng, W.; Furukawa, M.; Zeng, X. C.; Gong, B. *J. Am. Chem. Soc.* **2004**, *126*, 3148.
(26) Gong, B. *Chem. Eur. J.* **2001**, *7*, 4337.
(27) Wu, Z.-Q.; Jiang, X.-K.; Zhu, S.-Z.; Li, Z.-T. *Org. Lett.* **2004**, *6*, 229.
(28) Several recognition-induced folding systems, driven by intermolecular hydrogen bonding, have been reported, see: (a) Yashima, E.; Maeda, K.; Okamoto, Y. *Nature* **1999**, *399*, 449. (b) Berl, V.; Krische, M. J.; Huc, I.; Lehn, J.-M.; Schmutz, M. *Chem. − Eur. J.* **2000**, *6*, 1938. (c) Onouchi, Maeda, K.; Yashima, E. *J. Am. Chem. Soc.* **2001**, *123*, 7441. (d) Inouye, M.; Waki, M.; Abe, H. *J. Am. Chem. Soc.* **2004**, *126*, 2022.
(29) Nowick et al. have utilized hydrazide moiety to promote the formation of the peptide β-sheets, see: (a) Nowick, J. S.; Smith, E. M.; Ziller, J. W.; Shaka, A. J. *Tetrahedron* **2002**, *58*, 727. (b) Nowick, J. S.; Chung, D. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1765. (c) Chung M.; Nowick, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3062.

Scheme 2



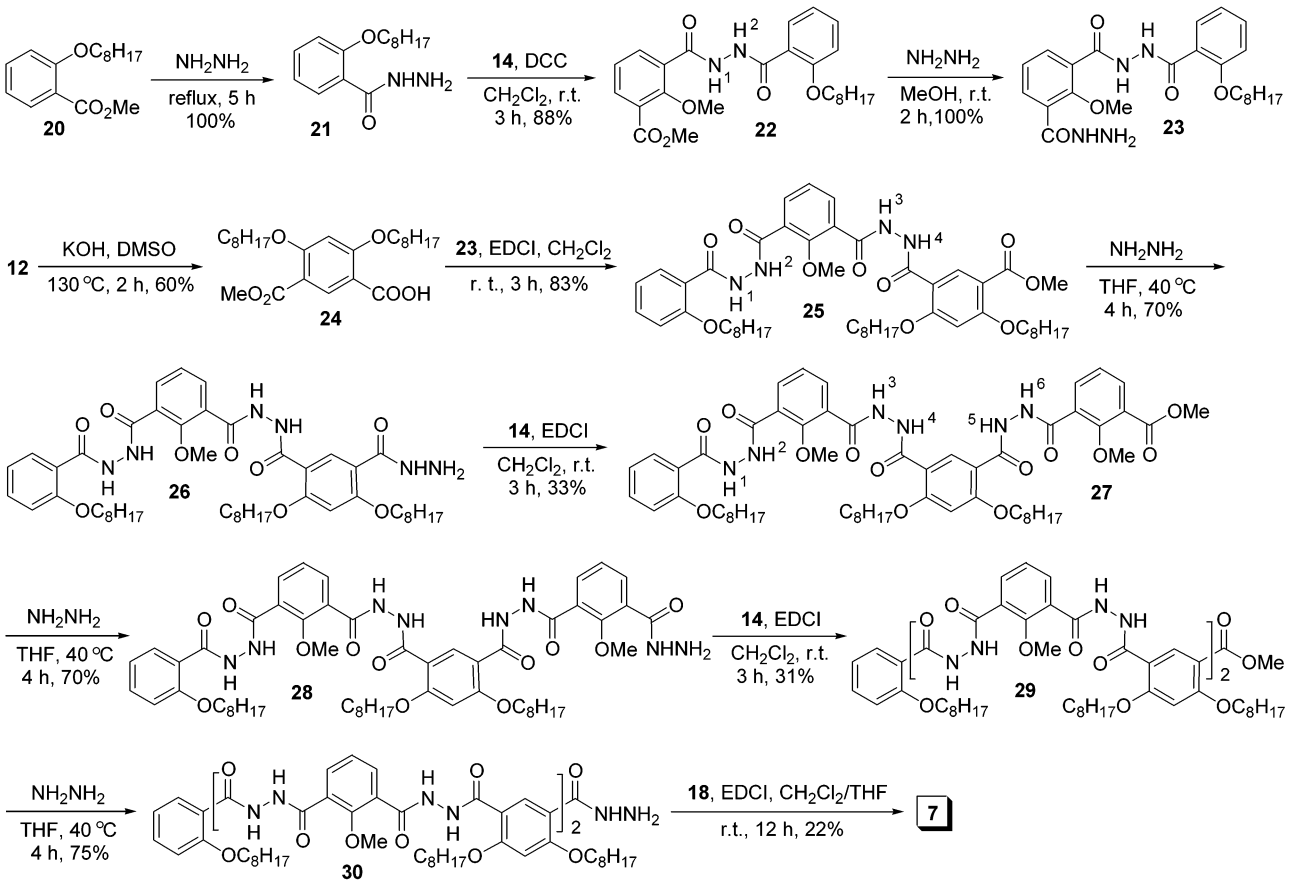
yield. In a similar way, diester **12** was reacted with **10** to afford trimer **3** in 68% yield. For the preparation of trimer **4** and pentamer **5**, compound **12** was first refluxed in hydrazine to yield **13** quantitatively. Compound **14** was then converted into the corresponding acyl chloride, which was treated with **13** to produce **4** in overall 76% yield. Trimer **4** was then reacted with excessive hydrazine to afford **15** in 90% yield. Finally, the reaction of **15** with **17** afforded pentamer **5** in 62% yield.

The synthesis of heptamer **6** is provided in Scheme 2. Thus, compound **4** was first hydrolyzed with lithium hydroxide in aqueous THF to diacid **18** in 90% yield. Then, compound **13** was reacted with acyl chloride **17** in dichloromethane to afford **19** in 64% yield. Finally, **19** coupled with **18** in dichloromethane in the presence of EDCI to produce **6** in 59% yield.



Scheme 3 shows the synthesis of tridecamer **7**. Treatment of compound **20** with excessive hydrazine generated hydrazide **21** in quantitative yield. Compound **21** coupled with **14** in dichloromethane in the presence of DCC to give **22** in 88% yield.

Scheme 3



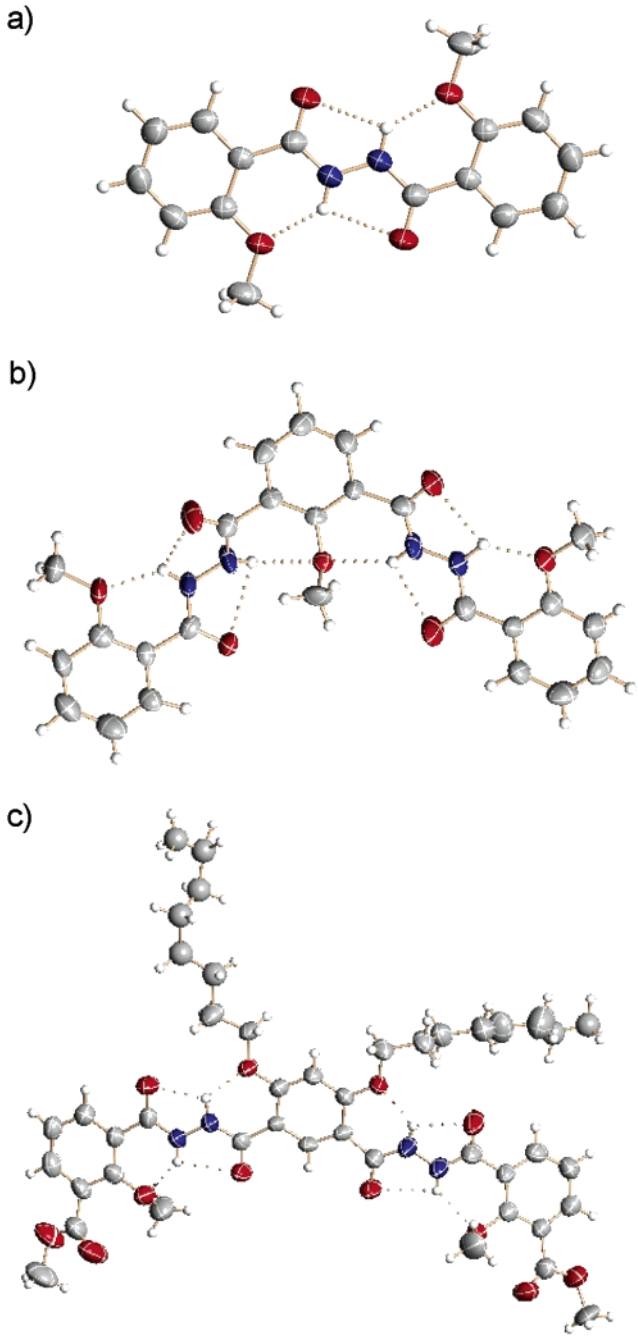


Figure 1. Crystal structures of dimer **1** and trimers **2** and **4**. All of the molecules adopt planar conformations due to the presence of two or four three-centered H-bonds.

The latter was then converted into hydrazide **23** quantitatively in refluxing hydrazine. Acid **24** was then prepared from the mono-hydrolysis of diester **12** with potassium hydroxide in hot DMSO. An EDCI-mediated coupling reaction of **24** with compound **23** in dichloromethane produced trimer **25** in 83% yield. The latter was then converted into **26** in hot hydrazine. Hydrazide **26** was then coupled with **14** to produce tetramer **27**. Treatment of **27** with hydrazine produced **28** in 70% yield, which then reacted with **14** in dichloromethane in the presence of EDCI to afford pentamer **29** in 31% yield. Compound **29** was treated with hydrazine to give pentamer **30** in 75% yield. Finally, the convergent coupling reaction of **30** with **18** in the presence of EDCI produced tridecamer **7** in 22% yield.

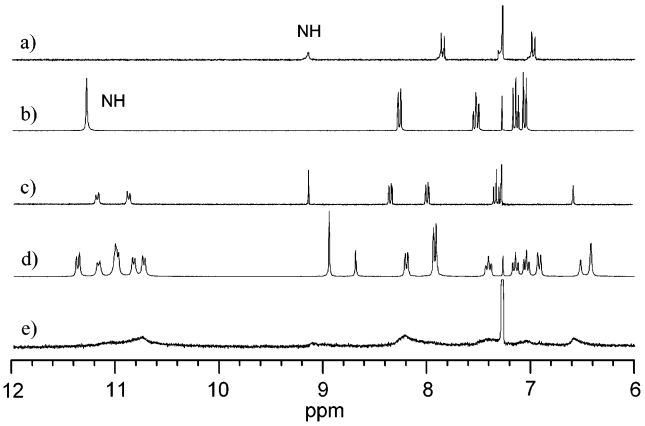


Figure 2. Partial ^{1}H NMR spectrum (400 MHz) of (a) **31**, (b) **1**, (c) **4**, (d) **6**, and (e) **7** (2.0 mM) in $CDCl_3$ at room temperature, highlighting hydrogen bonding-induced downfield shifting of **1**, **4**, **6**, and **7**.

X-ray Structures. Single crystals of dimer **1** were obtained by slow evaporation of the solution in dichloromethane and methanol at room temperature. The crystal structure was determined by the X-ray analysis and is provided in Figure 1. It can be found that the compound adopts a well-defined planar conformation, which is rigidified by two six-numbered ring H-bonds (NH···O distance = 2.08 Å) and two five-numbered ring H-bonds (NH···O distance = 2.32 Å). As expected, the two carbonyl groups point away from the central backbone. The crystals of trimers **2** and **4** suitable for the X-ray analysis were also grown by slow evaporation of a chloroform solution of **2** or **4** at room temperature. The solid-state structures of these compounds also show that all the benzene and hydrazine units share one plane completely due to the existence of four six-numbered ring H-bonds (**2**: NH···O distance = 2.07 Å, **4**: NH···O distance = 2.08 Å) and four five-numbered ring H-bonds (**2**: NH···O distance = 2.31 Å, **4**: NH···O distance = 2.32 Å) (Figure 1). In addition, the benzene rings and hydrazide moieties (joining together with the two terminal methyl ester groups in the case of **4**) give rise to a folding conformation for both of them. Because the backbones of longer oligomers **5**−**7** can be regarded as the combination of one or more backbones of **2** and **4**, it is reasonable to assume that, in the absence of important steric hindrance, the longer oligomers should also adopt similar rigidified folding conformation.

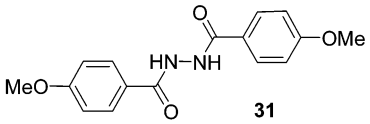
^{1}H NMR Spectroscopy. The peaks of the ^{1}H NMR spectrum of compounds **1**−**6** in chloroform-*d* are sharp, and the spectra of **1**, **4**, and **6** are provided in Figure 2 as examples. In contrast, tridecamer **7** dispalys a ^{1}H NMR spectrum of low resolution (Figure 2e). This result suggests that extensive aromatic stacking exists in **7**. The chemical shifts of the hydrazide protons of oligomers **1**−**6** in chloroform-*d*, together with those of compounds **22**, **25**, and **27**, are listed in Table 1. The signals have been assigned based on the 2D-NOESY and COSY ^{1}H NMR experiments. Compared to that of **31** (Figure 2a), which cannot form any intramolecular six-numbered ring H-bonds, all the signals of the hydrazide protons of the new series of oligomers shifted substantially downfield (1.58−2.29 ppm). The results are well consistent with the expectation that stable six-numbered ring H-bonds are formed in the oligomers,[23] which combine with the five-numbered ring H-bonds of the hydrazide unit to rigidify the planar conformation. Compared to those of the shorter oligomers, the resolution of the ^{1}H NMR spectrum of **7**

Table 1. Chemical Shifts (ppm) of Hydrazide NH Signals in $CDCl_3$ (2.0 mM) at 25 °C[a]

compound	H^1	H^2	H^3	H^4	H^5	H^6
1	11.28					
2	10.72	10.94				
3	10.98	11.25				
4	11.20	10.88				
5	10.70	11.09	10.83	10.72		
6	10.76	10.81	11.43	11.09	10.76	10.81
22	11.23	11.21				
25	10.75	11.14	10.82	10.74		
27	10.90	11.11	11.21	10.83	10.71	10.71
31	9.14					

[a] The numbering is shown in the text.

in chloroform-*d* is lowered substantially. Reducing the concentration (to 1.0×10^{-4} M) does not obviously improve the resolution. In contrast, the ^{1}H NMR spectrum of **7** in DMSO-d_6 at the identical concentration is of relatively high resolution (see the Supporting Information). The solubility of compound **6** is low in DMSO. Nevertheless, its ^{1}H NMR spectrum in the mixture of DMSO-d_6 and $CDCl_3$ (v/v 9:1) is also of good resolution (see the Supporting Information). These observations suggest that the extensive signal overlapping in the ^{1}H NMR spectrum of **7** in chloroform-*d* is resulted from intramolecular aromatic stacking due to a rigid helical conformation. Such a helical conformation is de-stabilized in highly competitive DMSO, which remarkably weakens the intramolecular hydrogen bonding.



31

Upon dilution from 40 mM to 0.5 mM, the signals of the NH and aromatic protons in the ^{1}H NMR spectrum of these hydrazide oligomers in chloroform-*d* shift downfield slightly. The largest change of the chemical shift was observed for trimer **2** ($\Delta\delta$ = 0.019 ppm for H-3). Because intermolecularly H-bonded NH signals usually shift upfield due to the H-bonding weakening when the concentration of the solution is decreased, this small downfield shifting reflects that weak intermolecular aromatic stacking exists at high concentration, which becomes even weaker at reduced concentration. Such intermolecular aggregation has been observed for *m*-oligo(phenylene-ethynylene)-based foldamers.[5a] By fitting the ^{1}H NMR dilution data of **2** to a 1:1 binding mode with H-3 signal as probe, a K_{assoc} of ca. 8 M^{-1} was determined.[30,31] Variable-temperature ^{1}H NMR experiments of trimer **4** in chloroform-*d* (3.0 mM) from −20 to 55 °C revealed small upfield shifting for the signals of the hydrazide protons ($\leq -3.42 \times 10^{-3}$ ppm/K), which also support the formation of the intramolecular H-bonds in the hydrazide oligomers.[32,33]

(30) The analysis is based on the assumption that monomer−dimer equilibrium is the predominant process of the self-aggregation, see: Tobe, Y.; Utsumi, N.; Kawabata, K.; Nagano, A.; Adachi, K. Araki, S.; Sonoda, M.; Hirose, K.; Naemura, K. *J. Am. Chem. Soc.* **2002**, *124*, 5350.
(31) (a) Conners, K. A. *Binding Constants: The Measurement of Molecular Complex Stability*; Wiley: New York, 1987. (b) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry;* Schneider, H.-J., Dürr, H. Eds., VCH: New York, 1991; p 123.
(32) Kesseler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512.
(33) Parra, R. D.; Zeng, H. Q.; Zhu, J.; Zheng, C.; Zeng, X. C.; Gong, B. *Chem.-Eur. J.* **2001**, *7*, 4352.

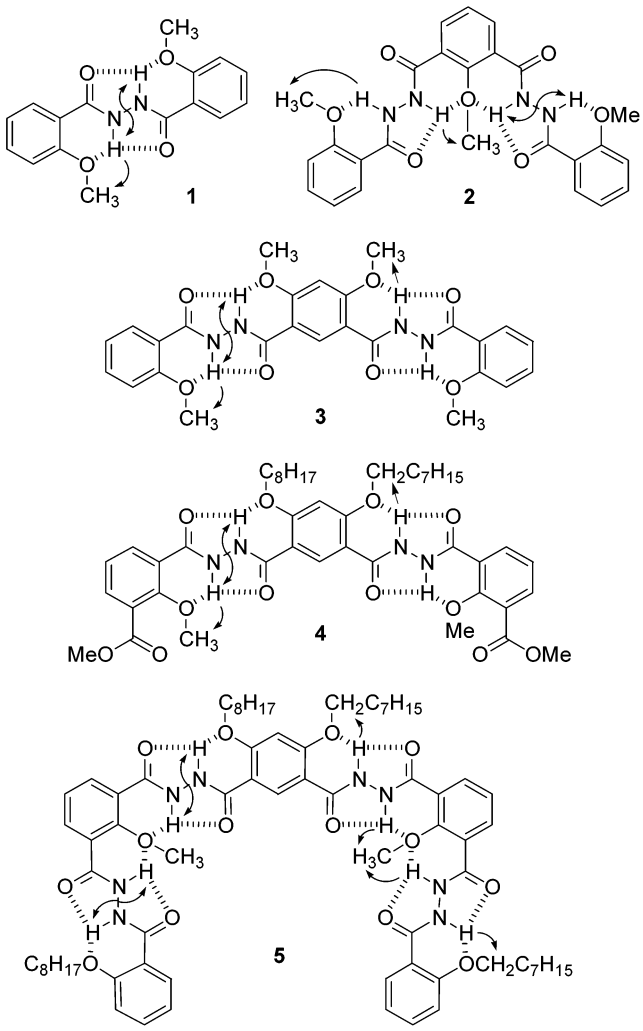


Figure 3. Partial NOE connections observed for oligomers **1**−**5** (5 mM in $CDCl_3$, 400 MHz) at 23 °C (mixing time: 1 s).

NOESY experiments were also carried out for oligomers **1**−**5** in chloroform-*d*. Important NOE connections were observed between the NH signal and all their neighboring CH_3 or OCH_2 signals, which are provided in Figure 3. The intensity of these NOEs is comparable for all the compounds, indicating that the intramolecular H-bonds in the oligomers have similar binding strength. As expected, NOEs were also observed between the two NH signals of one hydrazide unit.[23]

Similar NOE connections were also displayed in the NOESY spectrum of heptamer **6**. Especially, NOE between H−a and H−b of the ending benzene unit was observed (Figure 4, see the Supporting Information for the spectra at the mixing time of 0.5 and 0.25 s). ^{1}H NMR diluting experiments from 30 mM to 0.8 mM in chloroform-*d* revealed no important shifting of the NH or Ar proton signals ($\Delta\delta_{max}$ = 0.016 ppm), indicating that intermolecular stacking is very weak for **6** in chloroform. Because this NOE was absent in the NOESY spectrum of all the short oligomers **1**−**5** even at higher concentration (12 mM), the observed NOE between H−a and H−b of **6** can only be attributed to that generated in a cross-ring manner, as shown in Figure 4. This end-to-end NOE connect clearly proved the rigidified helical conformation of this oligomer. The backbone of pentamer **5** is not long enough for its two ending benzene units to stack or even to be in

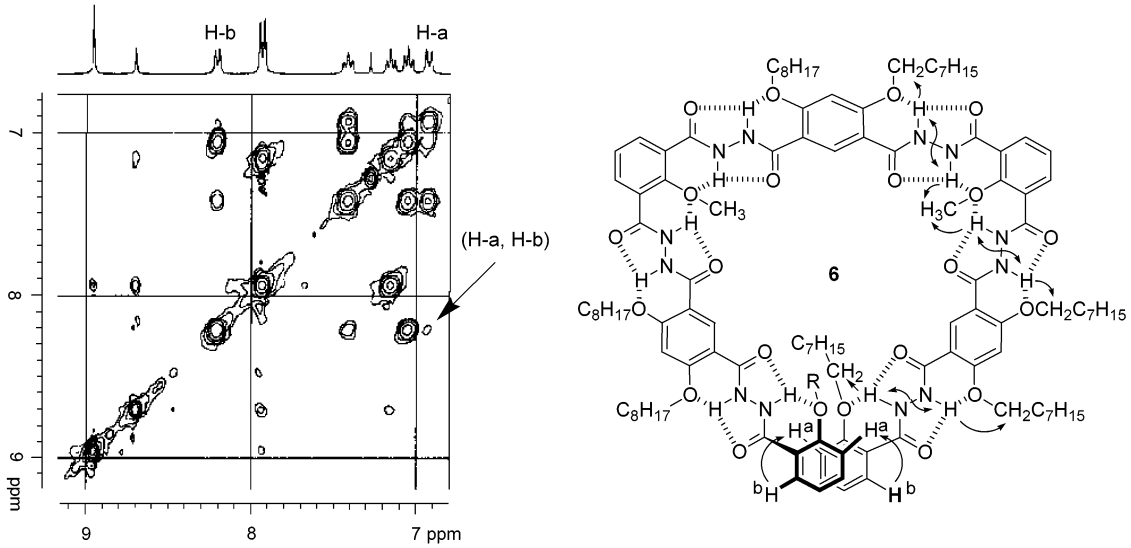


Figure 4. Partial NOESY spectrum of heptamer **6** (8.0 mM in chloroform-*d*, 400 MHz, mixing time: 1 s) at 23 °C, revealing the folding-induced end-to-end NOE between H−a and H−b. Such NOE connection is absent in the spectrum of all shorter oligomers **2**−**5**.

close proximity. The NOESY spectrum of tridecamer **7** in chloroform-*d* did not provide useful information due to important overlapping of the signals. However, considering the structural similarity of the backbones of **6** and **7**, it is reasonable to assume that tridecamer **7** should also adopt a helical conformation.

IR spectroscopy. The NH stretching frequencies (ν) of oligomers **1**−**7** were measured in chloroform (3 mM) and with KBr disk method by the IR spectroscopy, which provide additional evidence for the formation of intramolecular hydrogen bonds in both solution and solid state. For all molecules, typical intramolecularly hydrogen bonded N−H stretch peaks were observed (<3365 cm^{-1}). No peaks were displayed in the free N−H stretch region (3400−3500 cm^{-1}).[34] In addition, the NH stretching frequencies in chloroform is independent of concentration changes. These observations are consistent with the above ^{1}H NMR results, supporting that oligomers **2**−**7** adopt folding conformations.

Computer Modeling. Molecular mechanics calculations were performed on the methyl-substituted analogues of the longer oligomers **5**, **6**, and **7**. The energy-minimized conformations are provided in Figure 5. As expected, pentamer **5** adopts a crescent planar conformation, which can be regarded as a result of the combination of trimer **2** and **3**. On the other hand, both heptamer **6** and tridecamer **7** adopt a helical conformation with one and two turns, respectively. The results are fully consistent with the above 2D NMR investigations. The cavity of **6** and **7** (ca. 10.8 and 10.6 Å) is slightly smaller than that of **5** (ca. 11.1 Å) due to the torsion of their backbones. The pitch of both helicates is approximately 3.4 Å. For all the folding conformations, half of the carbonyl groups are arranged inwardly with the oxygen atoms pointing to the inner of the cavity. Such arrangement is very favorable for binding guest molecules through intermolecular hydrogen bonds.

Saccharide Recognition. The binding ability of oligomers **2**−**7** for typical organic soluble mono- and disaccharides **32**−**35** was investigated in chloroform.[35,36] Induced circular dichroism (CD) spectroscopy is an efficient tool for probing the interaction of an achiral molecule with a chiral molecule.[22,36] As expected, oligomers **2**−**7** exhibit no CD signals in the absence of saccharides. The addition of saccharides **32**−**35** to the solution of oligomers **5**−**7** in chloroform induces Cotton effect of moderate strength. The representative CD results and the UV−vis spectra of oligomers **5**−**7** are provided in Figure 6. Two mirror image spectra were obtained for the mixtures of **5**−**7** with enantiomerical isomers **32** and **33**, indicating that the

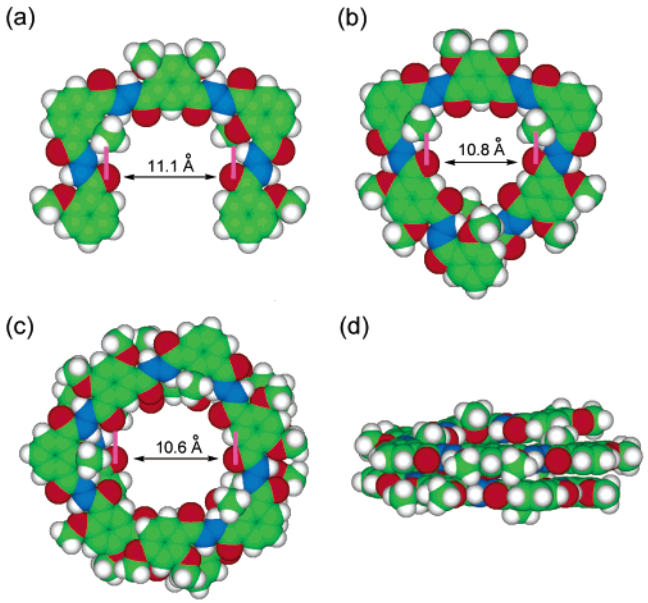


Figure 5. Energy-minimized (MM3 force field) crescent or helical conformations of (a) **5**, (b) **6**, and (c) **7** (top view), and (d) **7** (side view). All the octyl groups are replaced with methyl groups for clarity.

(34) (a) Legon, A. C. *Chem. Soc. Rev.* **1990**, *19*, 197. (b) Nowick, J. S.; Powell, N. A.; Martinez, E. J.; Smith, E. M.; Noronha, G. *J. Org. Chem.* **1992**, *57*, 3763. (c) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 1054.

(35) For recent reviews of saccharide recognition, see: (a) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2979. (b) James, T. D.; Shinkai, S. *Top. Curr. Chem.* **2002**, *218*, 159. (c) Striegler, S. *Curr. Org. Chem.* **2003**, *7*, 81.

(36) Covalently fused-pyridine folding receptors for monosaccharides have been reported, see: (a) Tamaru, S.-I.; Yamamoto, M.; Shinkai, S.; Khasanov, A. B.; Bell, T. W. *Chem. −Eur. J.* **2001**, *7*, 5270. (b) Tamaru, S.-I.; Shinkai, S.; Khasanov, A. B.; Bell, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4972.

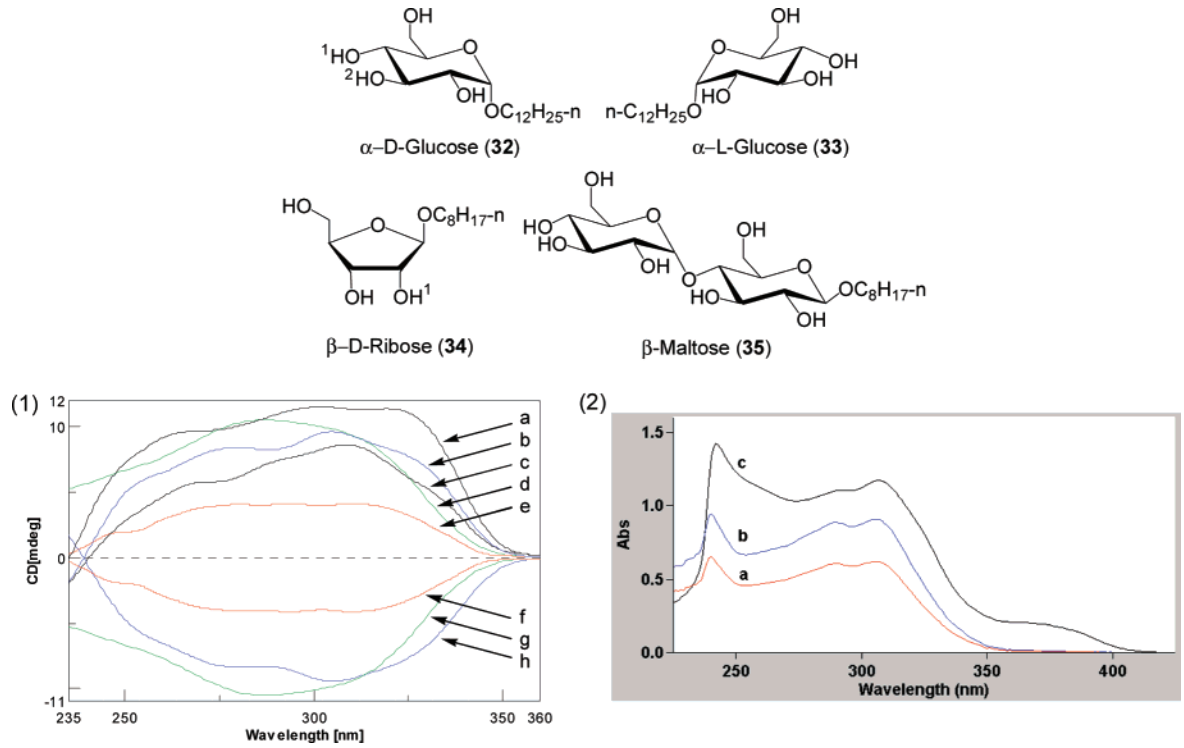


Figure 6. (1) Induced CD spectra of complexes of **5** with **32** (e) and **33** (f), **6** with **32** (b), **33** (h), **34** (c), and **35** (a), and **7** with **32** (d) and **33** (g) in chloroform at 25 °C ([**5**] = [**6**] = [**7**] = 2.0 × 10^{-4} M, [**32**] = [**33**] = [**34**] = [**35**] = 4.0 × 10^{-3} M). (2) UV−vis spectra of **5** (a), **6** (b), and **7** (c) in chloroform (2.0 × 10^{-4} M) at 25 °C.

induced CD signals are generated as a result of association of the oligomers with saccharides. The CD intensity was efficiently weakened by the addition of methanol and disappeared finally when enough amount of methanol was added (15% for the mixture of **6** and **32**). These results clearly indicate that the CD-active complexes between the oligomers and the alkyl saccharides are stabilized by intermolecular hydrogen bonding, which is weakened by competition with methanol solvation. No similar Cotton effect was observed for the shorter oligomers **2**−**4** under similar conditions, implying that their interaction with the alkyl saccharides is weak. A new band at ca. 370 nm appears in the UV−vis spectrum of **7** (Figure 6), which are not observed in the spectra of the shorter oligomers. Dilution experiments indicates that there is no substantial intermolecular aromatic stacking occurring at the concentration investigated (see the Supporting Information), therefore this new shoulder for **7** might be ascribed to exciton coupling due to intramolecular aromatic stacking in the helical conformation.[25e] The fact that no similar shoulder is observed for **6** might suggest that the stacking between only two ending aromatic units is not strong enough to produce an observable band.

Adding **2**−**4** (up to 15 mM) to the solution of **32**−**35** (2.5 mM) in chloroform-*d* only induced the OH signals to shift downfield slightly (<0.08 ppm). In contrast, remarkable downfield shifting was displayed upon addition of 1 equiv of oligomers **5**−**7** to the solution of **32**−**35** (8 mM) in chloroform-*d*, suggesting a strong complexation between them. The 1:1 stoichiometry of the complexes was estimated according to Job's plots (Figure 7),[37] which showed the largest chemical shifting change at 1:1 ratio when the overall concentration of two components was fixed. The association constants of several

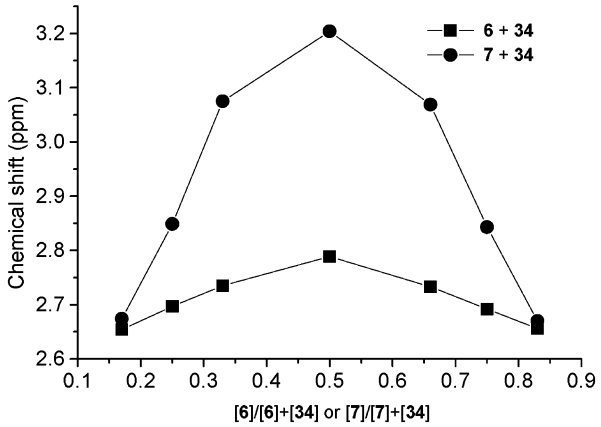


Figure 7. Job's plots in $CDCl_3$ at 23 °C ([**6**] + [**34**] = [**7**] + [**34**] = 2.4 mM) with H-1 of **34** as probe.

Table 2. Association Constants of Complexes between Hydrazides and Saccharides in $CDCl_3$ at 25 °C.

complex	K_{assoc} (M^{-1})[a]	ΔG (kcal/mol)	complex	K_{assoc} (M^{-1})[b]	ΔG (kcal/mol)
5·32	2.1 (±0.2) × 10^3	4.5	**5·35**	1.3 (±0.2) × 10^4	5.6
5·34	8.6 (±0.7) × 10^2	4.0	**6·32**	1.3 (±0.2) × 10^4	5.6
6·32	9.3 (±0.7) × 10^3	5.4	**6·34**	3.1 (±0.4) × 10^3	4.8
6·34	2.9 (±0.3) × 10^3	4.7	**6·35**	3.0 (±0.5) × 10^4	6.1
			7·32	2.6 (±0.3) × 10^5	7.4
			7·34	5.6 (±0.6) × 10^4	7.8
			7·35	6.9 (±0.8) × 10^6	9.3

[a] Determined with ^{1}H NMR titration method. [b] Determined with fluorescent titration method.

complexes (see Table 2) were determined based on the plots of the chemical shift change of suitable OH probe of the saccharides vs hydrazide concentration by titration of the saccharides in chloroform-*d* (Figure 8) and listed in Table 2.[23] The associa-

(37) Job, P. *Ann. Chim. Ser. 10* **1928**, *9*, 113.

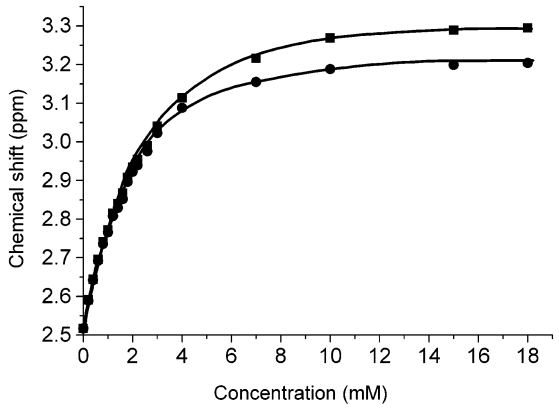


Figure 8. Plot of the chemical shifts of H-1 of **32** (1.2 mM, ■) and **34** (1.2 mM, ●) versus **6** (0−17.5 mM) in $CDCl_3$ at 23 °C.

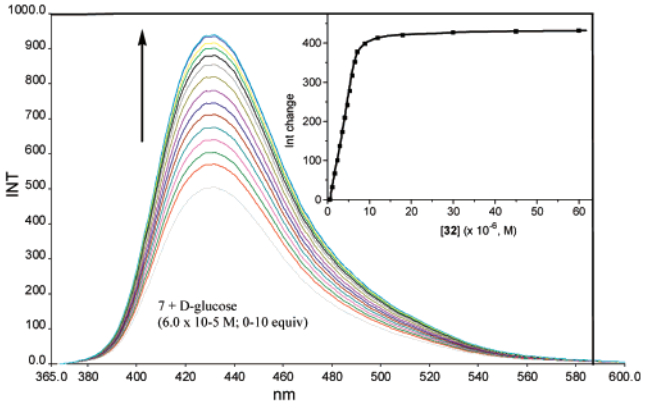


Figure 9. Fluorescent spectra of **7** (3.0×10^{-6} M, excitation wavelength = 350 nm) in chloroform at 23 °C, increased gradually with the addition of saccharide **32** (0 to 6.0×10^{-5} M).

tion constants of other complexes could not be obtained with the ^{1}H NMR titration method due to overlapping of the probe signal at high concentration of oligomers. Fluorescent spectroscopy was then utilized for quantitative investigation of the stability of other complexes (Table 2).[38] On excitation at 350 nm, oligomers **5**−**7** emitted fluorescence between 365 and 580 nm (λ_{max} = 432 nm). Addition of saccharides **32**−**35** remarkably increased the intensity of the emission. Association constants were then derived from the titration data of the oligomers with saccharides, which are listed in Table 1. The fluorescent spectra of **7** with **32** are provided in Figure 9 as an example.

It can be found that the association constants increase with the increase of the number of the hydroxyl groups in saccharides and the longer oligomers display greater binding ability to the identical saccharide. These results also indicate that intermolecular hydrogen bonds are the major driving force for the formation of the complexes and more hydrogen bonds generates greater stability. The binding ability of tridecamer **7** to disaccharide **35** is very impressive, showing that this kind of hydrazide receptors may also recognize polysaccharide through multiple hydrogen bonds.

Because trimers **2**−**4** did not efficiently bind saccharides and a 1:1 stoichiometry was observed for the complex of longer oligomers and saccharides, the binding of the saccharides on the surface of the oligomers can be ruled out. Therefore, the binding should take place within the cavity of the longer oligomers. NOESY spectrum revealed intermolecular NOEs for the 1:1 solution of **6** and **34** in chloroform-*d* (8 mM) (Figure 10). The signals have been assigned based on the COSY and NOESY experiments. On the basis of the ^{1}H NMR results, molecular mechanics calculation produced a binding mode for the complex of **6** and **34**, which is shown in Figure 10.[39] Similar assignable NOEs have also been observed between **5** and **32** but not **34**, which is consistent with the reduced stability of complex **5**·**34**. The NOESY spectra of other complexes could not provide useful information due to substantial signal overlapping.

Conclusions

A new series of hydrogen bonding-driven hydrazide-based folding, crescent, and helical architectures have been developed in chloroform and their structures have been investigated in solid state and solution. The longer hadrazide foldamers can efficiently complex mono- and disaccharides in chloroform. The work represents new examples of hydrogen bonding-driven foldamers that can serve as artificial receptors for molecular recognition. The fact that a binding cavity can be created from the folded hydrazide oligomers runs parallel to concepts in biomacromolecular recognition. The elaborate arrangement of the carbonyl units in the cavity of the new generation of foldamers also make them, to some extent, resemble rigid, but covalently bonded spherands developed thirty years ago by Cram et al.[40] The very high binding affinity displayed by tridecamer **7** toward β-maltose **35** suggests that longer oligomers

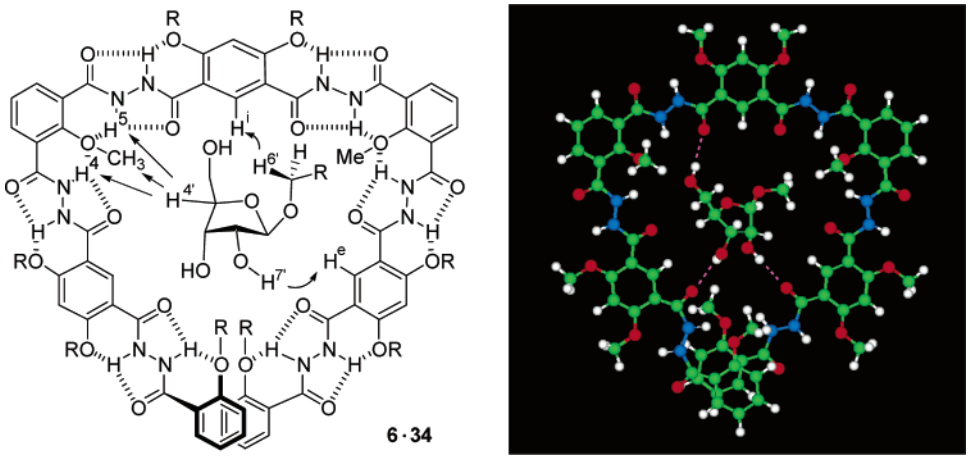


Figure 10. Assigned intermolecular NOEs and the possible binding mode produced from molecular mechanics calculation for complex **6**·**34**. The position and orientation of **34** in the helical cavity of **6** were actually varied. All octyl groups are replaced with methyl groups for clarity.

or polymers may bind more than one single substrate. Therefore, an obvious next step will be extending the design principle to longer polymers to produce long cavity of nanoscale. In addition, incorporating suitably designed pyridine building blocks can, in principle, also generate reversible acid−base-regulated folding and unfolding switching device, which is being investigated.

Acknowledgment. We are grateful to the Ministry of Science and Technology, the National Natural Science Foundation, the State Laboratory of Bioorganic and Natural Products Chemistry of China, and the Chinese Academy of Sciences for financial support.

Supporting Information Available: The entire Exprimental Section, NOESY and/or COSY spectra of **1**, **2**, **3**, **4**, **5**, **6**, **7**, and **34** in $CDCl_3$ or DMSO-d_6 (for **3** and **7**) or DMSO-d_6−$CDCl_3$ (9:1 v/v, for **6**), NOESY spectrum of complex between **6** and **34** in $CDCl_3$, concentration-dependent CD spectra of complexes between **6** and **34** (1:1) in $CHCl_3$, concentration-dependent UV−vis spectra of **7** in $CHCl_3$, X-ray crystallographic data for **1**, **2**, and **4** (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

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(38) For examples of utilizing fluorescent spectroscopy to study the binding affinity of synthetic receptors for saccharides, see: (a) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2270. (b) Gunnlaugsson, T.; Davis, A. P.; O'Brien, J. E.; Glynn, M. *Org. Lett.* **2002**, *4*, 2449.
(39) Since the carbonyl groups in the cavity of the oligimers are orientated in a highly symmetric pattern, other binding modes were not excluded.
(40) Marverick, E.; Cram, D. J. in *Comprehensive Supramolecular Chemistry* Vol. 1, Ed. Gokel, G. W. Elsevier, New York, 1996.