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Hydrogen-Bonding-Mediated Anthranilamide Homoduplexes. Increasing Stability through Preorganization and Iterative Arrangement of a Simple Amide Binding Site

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Abstract: This paper describes the assembly of two new series of self-complementary duplexes by making use of amide units, the simplest assembling units of hydrogen bonding, as binding sites. All the new monomers possess a rigidified anthranilamide skeleton, which is stabilized by intramolecular hydrogen bonding. Amide units are iteratively introduced to one side of the preorganized skeletons to facilitate the formation of intermolecular hydrogen bonding. Compounds **2** and **3** bear two and three $CONH_2$ units, respectively, while **4**, **6**, and **7** are incorporated with two, three, and four AcNH units, respectively. For comparison, compound **5**, which is similar to **4** but contains one AcNH and one CF_3CONH unit, is also prepared. X-ray diffraction analysis of **2**, **4**, and **5** revealed homodimeric motifs in the solid state which are stabilized by two or more intermolecular hydrogen bonds. ^1H NMR investigations in $CDCl_3$ indicated that all the compounds form hydrogen-bonded homoduplexes. Duplexes **3·3**, **6·6**, and **7·7** are highly stable in $CDCl_3$, with a lower K_{assoc} limit of 2.3×10^5 M^{-1}. The K_{assoc} values of the three duplexes in more polar $CDCl_3/CD_3CN$ (9:1, v/v) were determined with the ^1H NMR dilution method. The result opens the way for the development of new polymeric duplexes of well-ordered structures.

Introduction

Self-assembly of linear oligomers into double- and multiple-stranded complexes is ubiquitous in biology and prerequisite for biomacromolecules to generate discrete higher structures and functions.[1] In addition to their utility for structural mimicking of biomacromolecules and development of abiotic self-replicating systems,[2] unnatural duplexes are of fundamental importance for the construction of multicomponent and polymeric architectures of functional properties.[3] Because of its great directionality and strength, hydrogen bonding is an ideal noncovalent force for this purpose.[4] Two general strategies have been developed for the design of hydrogen-bonding-mediated molecular building blocks. The first strategy is based on heterocyclic derivatives, in which hydrogen-bonding donors or acceptors are compactly arranged in a designed direction, as demonstrated by the recent self-assembly of various quadruply hydrogen-bonded binding modes.[5] The second strategy involves iteratively incorporating simple binding residues into linear backbones. Examples of this family of dimeric aggregates include sheetlike aromatic and aliphatic amide duplexes,[6,7] 3,6-diaminopyridazine-based homoduplexes,[8] and hydrazide-derived

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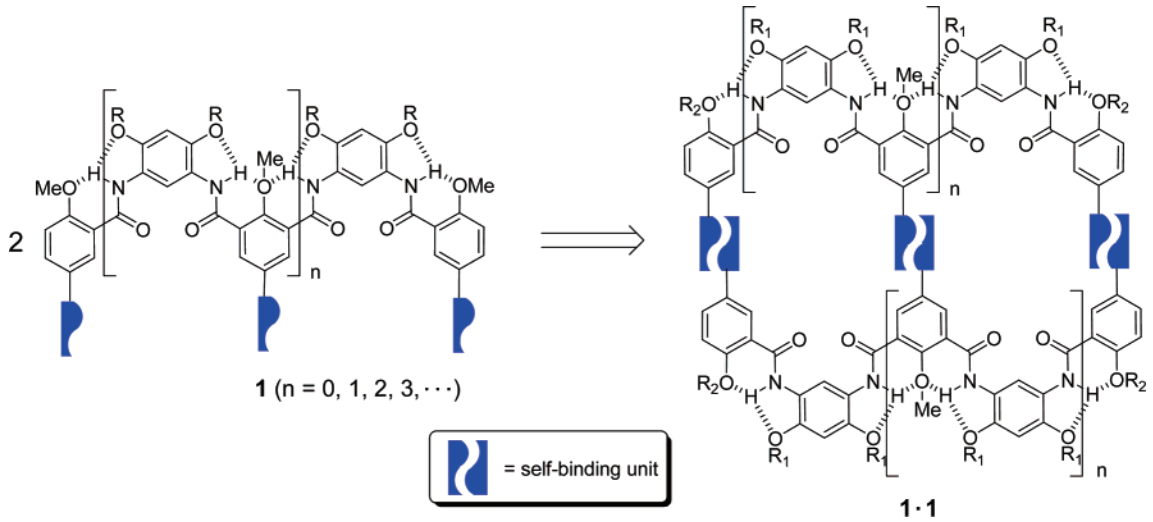

Figure 1. Intermolecular hydrogen-bonding-driven self-assembly of homoduplexes, directed by the backbone preorganization.

heteroduplexes.[9] To achieve high binding stability and selectivity, both strategies require preorganization and rigidity of the backbones and binding sites of monomers, which is usually realized by making use of intramolecular hydrogen bonding.[10]

Foldamers are linear molecules that are induced by noncovalent forces to adopt well-established secondary structures.[11] Also due to its directionality and strength, hydrogen bonding has proven itself to be highly efficient for constructing this family of structurally unique artificial secondary structures.[11] Particularly, a number of hydrogen-bonding-mediated aromatic amide foldamers of well-defined conformations have been assembled,[12−22] some of which represent a new generation of non-ring receptors for saccharides,[21b,c] alkylammoniums,[21d] or encapsulation of water.[22b] As part of a program in hydrogen-bonding-mediated self-assembly, we reported the construction of a new series of planar zigzag artificial secondary structures.[23] Recently we succeeded in utilizing them as rigidified backbones to develop assembled zinc porphyrin molecular tweezers that are able to efficiently complex fullerene and several fullerene derivatives.[24] One critical feature of the new assembled tweezers is the predictable preorganization of their aromatic oligoamide backbones, driven by consecutive intramolecular hydrogen bonds. In this paper, we report that this strategy has been successfully used to assemble two new classes of highly stable homoduplexes by making use of the cooperative interaction of amides, the simplest self-binding motif of hydrogen binding, as the driving force.

Results and Discussion

Previous investigations have demonstrated that the backbones of oligomers **1** adopt a rigidified zigzag conformation.[23] It was envisioned that iterative introduction of recognition residues at the 5-positions of the phthalic diamide moieties of the oligomers would produce rigidified, highly preorganized monomers which could self-assemble to generate new zipper-styled molecular duplexes as a result of cooperative intermolecular interactions (Figure 1). Compounds **2**−**7**, which possess two to four amide units, were therefore designed and

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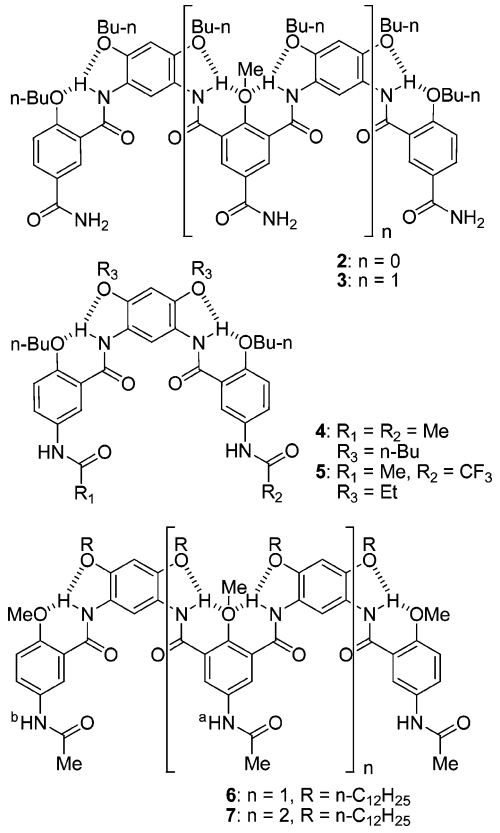
Chart 1



synthesized (Chart 1). The synthetic routes are provided in the Supporting Information.

A crystal of compound **2** suitable for X-ray crystallographic analysis was obtained from chloroform by slow evaporation. As expected, in the solid state compound **2** adopted a U-shaped planar conformation due to the formation of four intramolecular hydrogen bonds.[23,25] This preorganized conformation directed two molecules to form a self-complementary dimeric structure. The dimer was stabilized mainly by two intermolecular hydrogen bonds between the peripheral amides (NH···O distance = 2.039 Å, NH···O angle = 160.6°) (Figure 2). Interestingly, the exo amino proton (cis to the C═O oxygen) of one of its peripheral amides also forms two weak hydrogen bonds with the oxygen atoms of the central two amides of another molecule (NH···O distances = 2.454 and 2.691 Å, NH···O angles = 178.1 and 173.1°, respectively), which further rigidify the planarity of the dimeric structure. The dimeric units are further organized into an extended array through $R_2^2(8)$ dimerization of the unpaired amide sites.[26] Previously, it has been reported that benzamide exists in the $R_2^2(8)$ dimerizing pattern in the solid state.[27] For comparison, compound **8** (Chart 2) was also prepared (see the Supporting Information), and its solid-state structure is provided in Figure 3. As expected, **8** dimerizes in the $R_2^2(8)$ pattern, similar to that observed for benzamide. The different self-binding pattern exhibited by compound **2** in the solid state can be rationalized by considering two factors. First, the $R_2^2(8)$ mode would produce a large cavity in the center of the dimeric structure, which is unfavorable in the solid state in the absence of solvent molecules. Second, the observed dimerizing motif possesses six hydrogen bonds, while the $R_2^2(8)$ motif has only four.

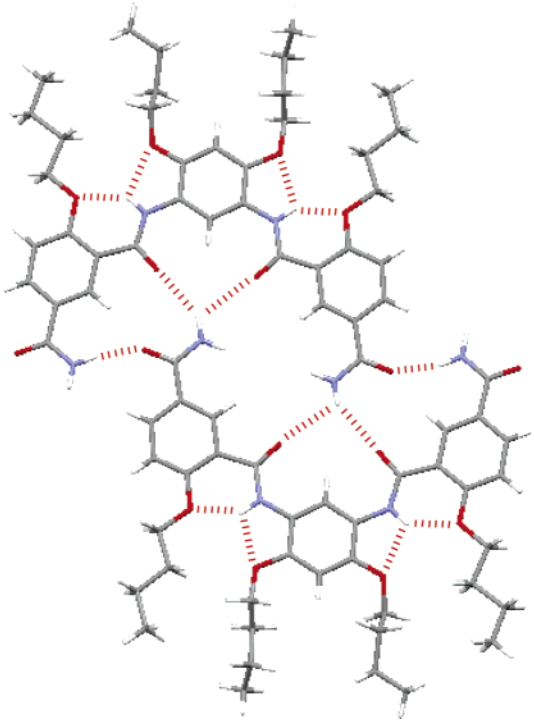
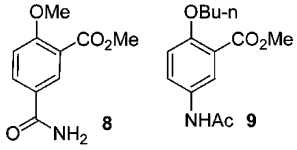


Figure 2. Solid-state structure of compound **2**, showing the dimeric binding motif which is stabilized by eight intramolecular and six intermolecular hydrogen bonds.

Chart 2



The ^{1}H NMR spectra of compounds **2** and **8** in $CDCl_3$ are provided in Figure 4. The NH signals of **2** have been assigned by the NOE and gradient experiments. The amide protons of **8** display two broad signals (5.70 and 6.01 ppm, respectively) as a result of the rotation of the amino group around the C−N bond. In contrast, the NH_2 protons of **2** exhibit two sharp signals in the downfield area (6.38 and 8.06 ppm, respectively). These results clearly indicate that the amide protons of **2** are involved in much stronger intermolecular hydrogen bonding, which decreases the rotation of the NH_2 groups around its N−CO bond.

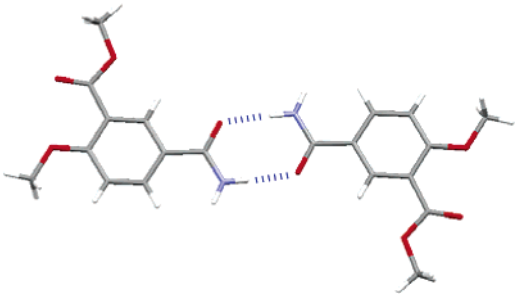


Figure 3. Solid-state structure of compound **8**, showing the $R_2^2(8)$ dimerizing mode. The crystal was grown by slow evaporation of a chloroform solution.

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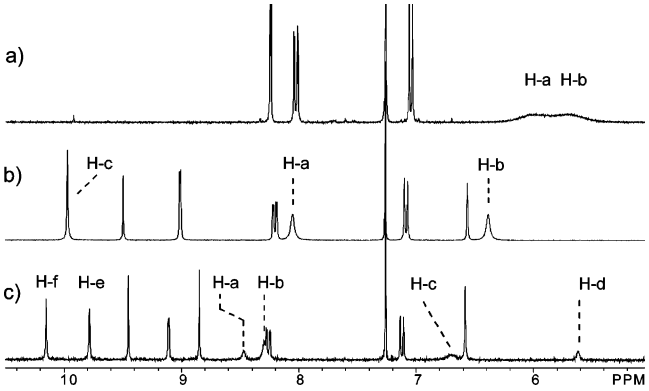


Figure 4. Partial ^{1}H NMR spectra (400 MHz) of (a) **8** (10 mM), (b) **2** (10 mM), and (c) **3** (3.8 mM) in $CDCl_3$ at 25 °C.

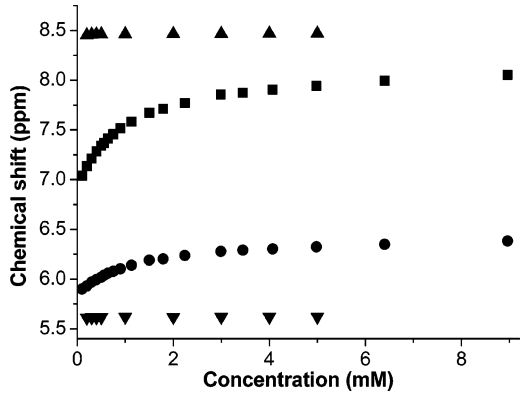


Figure 5. Plot of the chemical shifts of H-a (■) and H-b (●) of **2** and H-a (▲) and H-d (▼) of **3** in $CDCl_3$ at 25 °C.

^{1}H NMR dilution studies in $CDCl_3$ (from 12 to 0.2 mM) revealed important upfield shifting for the H-a signal (Figure 5). A fit of the chemical shift data to a 1:1 binding mode afforded an association constant K_{assoc} of $(3.0 \pm 0.2) \times 10^3$ M^{-1}.[28] The value is substantially larger than the reported value of 40 M^{-1} for benzamide, even in benzene of lower polarity,[29,30] and shows that important cooperativity exists for the peripheral amide units of **2** to induce the formation of the dimeric structure. Pronounced upfield shifting was also observed for the H-b signal upon dilution of the $CDCl_3$ solution (Figure 5), which corresponds to a K_{assoc} of $(3.0 \pm 0.3) \times 10^2$ M^{-1} obtained by fitting to the data to a 1:1 binding mode. The value is remarkably smaller than that derived from the H-a data. This discrepancy implies that, in addition to the compact chain-dimerizing motif **2·2** observed in the solid state (Figure 2, Chart 3), **2** may also self-associate through an $R_2^2(8)$ binding pattern, as revealed for benzamide.[27] In principle, at high concentrations, homodimer **2·2** may further self-assemble to more complicated supramolecular architectures through two $R_2^2(8)$-type hydrogen bonds.[31]

The ^{1}H NMR spectrum of compound **3** in $CDCl_3$ is also provided in Figure 4. The signals of the protons of the appended amides have been assigned by a combination of NOESY experiments and comparison of the integrated strength. Compared to the signals of the NH_2 protons of **8**, the H-a (8.47 ppm) and H-b (8.30 ppm) signals of compound **3** appeared in even more downfield ($\Delta\delta = 2.46$ and 2.29 ppm, respectively), even at the reduced concentration. This result implies that these protons are involved in stronger intermolecular hydrogen bonding than the corresponding amide protons of compound **2**. Dilution of the $CDCl_3$ solution of **3** from 5.0 to 0.2 mM did not lead to significant shifting of the H-a and H-d signals (<0.07 ppm, Figure 5). A conservative estimate of 90% self-association resulted in a lower K_{assoc} limit of 2.3×10^5 M^{-1} for homoduplex **3·3**.[5d,32] It is reasonable to propose that this homoduplex may also adopt a binding pattern similar to that of dimer **2·2** (Chart 4).

Increasing the polarity of the solvent should decrease the binding stability of the duplexes. Therefore, ^{1}H NMR dilution experiments were performed for both **2** and **3** in a more polar $CDCl_3/CD_3CN$ (9:1, v/v) mixture. Fitting the data of the chemical shift change against the concentration to a 1:1 binding mode gave rise to K_{assoc} values of $(8.0 \pm 1.0) \times 10^2$ and $(2.1 \pm 0.3) \times 10^4$ M^{-1} for duplexes **2·2** and **3·3**, respectively. The fact that **3·3** is remarkably more stable than **2·2** in both solvent systems strongly suggests an important cooperativity of the appended amide units in driving the formation of this series of duplex structures and demonstrates the high efficiency of the intramolecular hydrogen-bonding-driven preorganization of the oligomeric backbone.

Crystals of compound **4** suitable for X-ray analysis were grown from methanol, chloroform, and benzene, respectively,

Chart 3

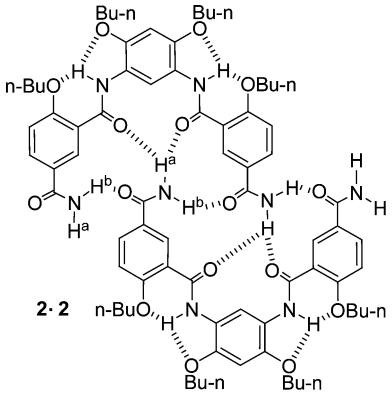
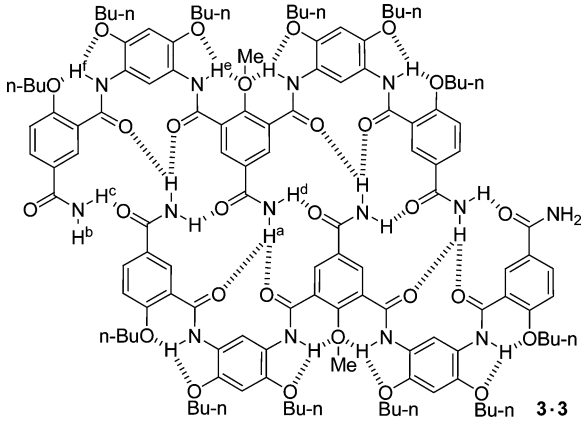


Chart 4



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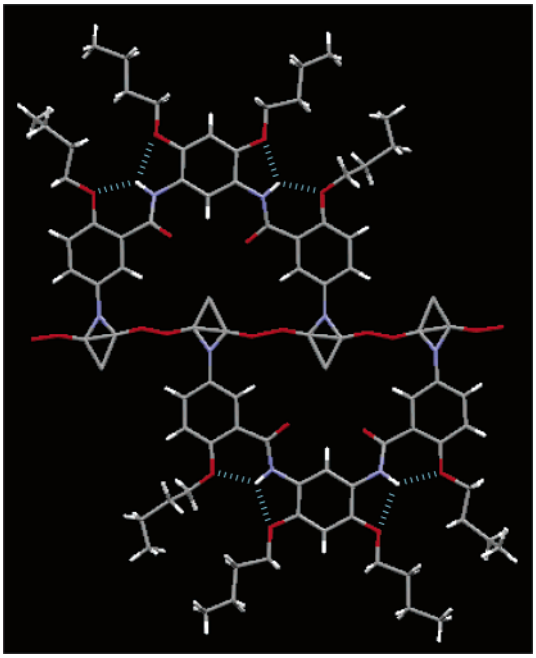


Figure 6. Solid-state structure of the crystal of **4** grown by slow evaporation of a chloroform solution. The crystal obtained from benzene exhibits the identical structural pattern.

by slow evaporation. The solid-state structure of the crystal of **4** obtained from polar methanol (see the Supporting Information) revealed a linear staggered stacking pattern. The backbone of the molecule remains planar due to the intramolecular hydrogen bonding. Neighboring molecules are connected by one hydrogen bond between the end amide units. The solid-state structure of the crystal produced from chloroform of lower polarity is shown in Figure 6, which reveals a centrosymmetric dimeric motif. Surprisingly, the appended acetamide units adopt opposite orientations in the solid state.[33] The fact that all the acetamide units are arranged in a straight line with identical separation distance suggests that the structure of the monomer is perfect for the formation of dimeric structure through consecutive intermolecular hydrogen bonding. Single crystals of **4** were also grown from dichloromethane of decreased size. X-ray analysis did reveal a dimeric structure, stabilized by two intermolecular hydrogen bonds (see the Supporting Information). What is different for this solid structure is that the cavity of the U-shaped monomer is filled with a dichloromethane molecule.[34]

The solid-state structure of compound **4** shown in Figure 6 is intriguing. To explore whether the dimeric motif is general for this series of diamide monomers, a crystal of compound **5**, which is incorporated with one trifluoroacetamide unit, was also grown from chloroform, and its X-ray solid-state structure is provided in Figure 7. It can be seen that this asymmetric molecule also self-assembled to a dimeric structure, which is stabilized by two intermolecular hydrogen bonds. Obviously due to the increased steric hindrance, in the dimeric structure the two CF_3 groups are located on the outside. Also notably, both protons of the trifluoroacetamide units served as hydrogen-bonding donors, which may be ascribed to their stronger acidity relative to that of their fluorine-free counterparts.

(33) This result was originally ascribed to the low quality of the crystal. However, crystals of different sizes grown from chloroform or toluene gave the identical structural pattern. Therefore, we attribute this unexpected structural pattern to the possibility that the opposite orientation of the ending amide units is very similar in energy and occurs with identical probability.

(34) The two methylene units connected to the central benzenes are not resolved in the solid structure.

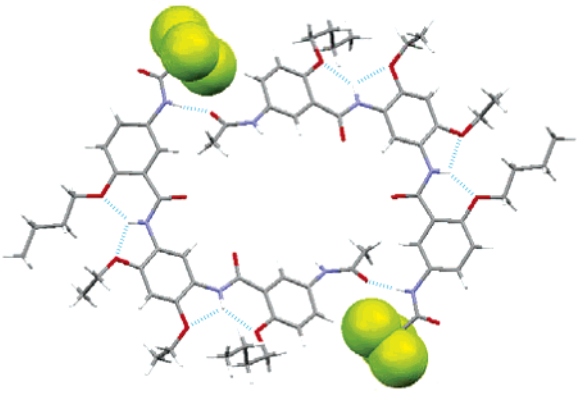


Figure 7. Solid-state structure of compound **5**.

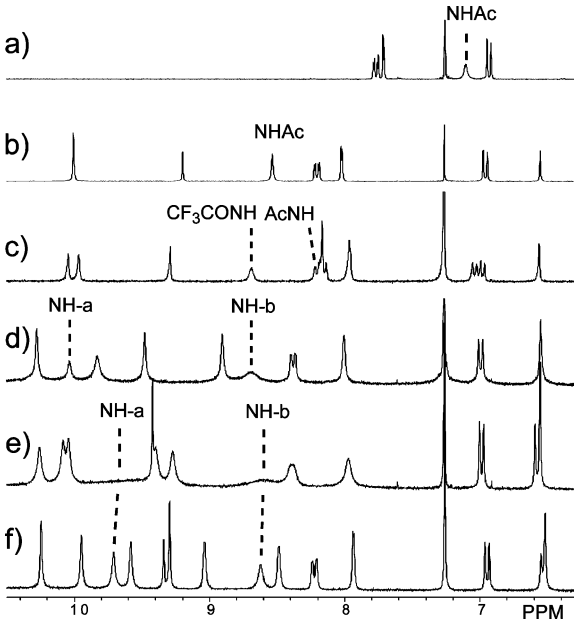
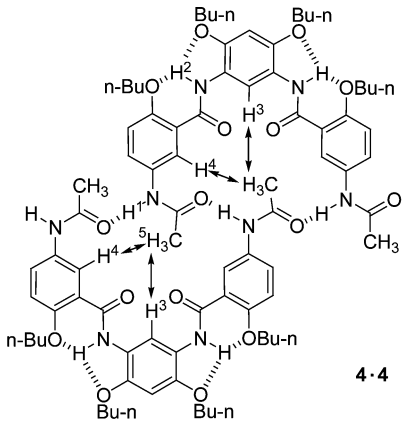


Figure 8. Partial ^{1}H NMR spectra (400 MHz) of (a) **9** (5 mM), (b) **4** (5.0 mM), (c) **5** (5.0 mM), (d) **6** (3.5 mM), (e) **7** (3.5 mM) in $CDCl_3$, and (f) **7** (3.5 mM) in $CD_3CN/CDCl_3$ (1:9, v/v) at 25 °C.

The self-assembling behaviors of compounds **4**−**7** in solution were then investigated. Their ^{1}H NMR spectra in $CDCl_3$ are provided in Figure 8. The signals of all the compounds in the downfield area have been assigned on the basis of NOESY experiments, together with their integrated strength (for **6**). Due to the feature of structural symmetry, all the compounds displayed relatively simple spectra. Compared to the signal of the amide proton of **9** (7.11 ppm), the signals of all the protons of the appended amides of **4**−**7** shifted substantially downfield ($\Delta\delta \approx 1.09-2.93$ ppm), indicating that all these protons were involved in much stronger intermolecular hydrogen bonding. Important intermolecular NOE connections were also observed for **4**, **6**, and **7** (Charts 5, 6, and 7, vide infra). Under identical experimental conditions, no similar connections were observed for compound **9**. All these results support that stable homoduplexes were formed in solution for these oligomers. Charts 5 and 6 provide the proposed structures for these duplexes. With the elongation of the oligomers, the resolution of their ^{1}H NMR spectrum became lower and the protons of the appended amides of **7** displayed only two broadened signals. This result may be

Chart 5



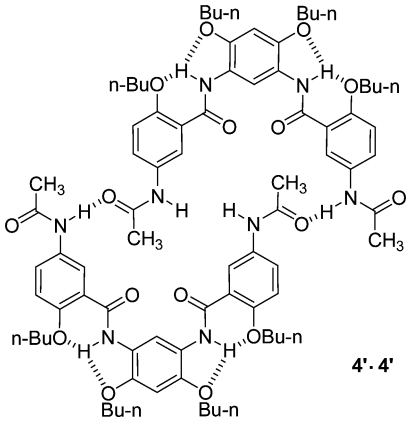
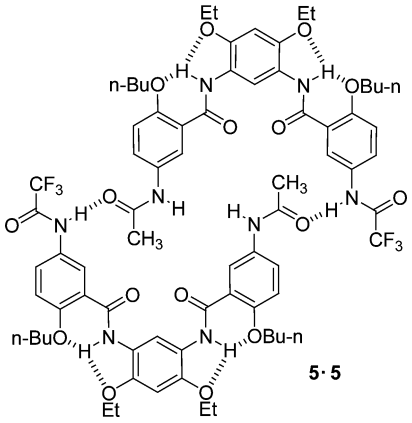


Chart 6



attributed to the increased confinement of the rotation of these amide units around the N−C(Ph) bond as a result of increased binding stability of the duplexes. However, in a $CDCl_3/CD_3CN$ (9:1, v/v) mixture of higher polarity, their ^1H NMR spectra were of high resolution, obviously due to reduced self-binding affinity; the ^1H NMR spectrum of **7** is provided in Figure 8f.

Dilution of the solution of compound **4** in $CDCl_3$ from 25 to 0.2 mM caused significant upfield shifting of the signal of the protons of the appended amides (Figure 9). Fitting the data of the change of the chemical shift against the concentration to a 1:1 self-binding mode afforded a K_{assoc} of $(2.6 \pm 0.3) \times 10^2$ M^{-1} for dimer **4·4**. With an identical method, the K_{assoc} values of dimers **9·9**[35] and **5·5** in $CDCl_3$ were determined to be ca. 10 and $(1.2 \pm 0.2) \times 10^2$ M^{-1}, respectively. For the case of **5**, the signal of the NH proton of its trifluoroacetamide was used as a

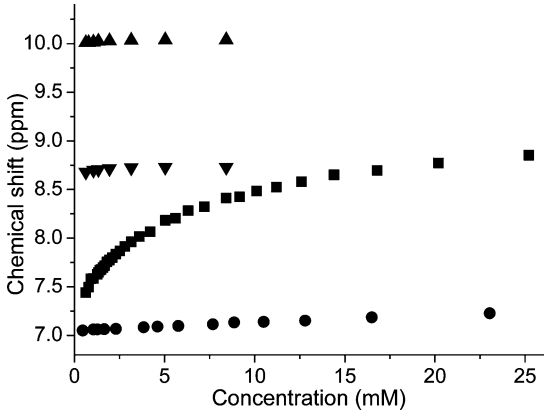


Figure 9. Plots of the chemical shifts of AcN*H* of **9** (●), AcN*H* of **4** (■), NH-b (▼) of **6**, and NH-a of **6** (▲) versus their concentration in $CDCl_3$ at 25 °C.

probe because this proton had been revealed by X-ray analysis (Figure 7) to be a hydrogen-bonding donor for the formation of dimer **5·5**. The K_{assoc} value for dimer **4·4** is substantially larger than that of **9·9**, supporting that cooperativity exists for the two acetamide units of **4** in inducing the formation of dimer **4·4**. The K_{assoc} of dimer **5·5** is notably lower than that of dimer **4·4**, which may be attributed to the increased spatial hindrance of the trifluoromethyl group relative to its fluorine-free counterpart. Dilution of the $CDCl_3$ solution of compound **6** from 8.0 to 0.2 mM did not lead to significant shifting of the NH-a (<0.03 ppm) and NH-d (<0.07 ppm) signals. Also, by assuming a conservative estimate of 90% association, we could obtain a lower limit of 2.3×10^5 M^{-1} for the K_{assoc} of homoduplex **6·6** (Chart 7).[5d,32] The signals of the NH protons of the appended acetamides of **7** in the ^1H NMR spectrum in $CDCl_3$ are of low resolution (Figure 9e). Therefore, no useful information could be obtained for duplex **7·7** (Chart 7) from the ^1H NMR dilution experiments. To explore the dependence of the stability of this series of self-assembled architectures on the length of the monomers, ^1H NMR dilution experiments were performed for **9**, **4**, **6**, and **7** in the more polar $CDCl_3/CD_3CN$ (9:1, v/v) mixture (see the Supporting Information), which gave rise to K_{assoc} values of <5, 80 ± 9, $(1.2 \pm 0.2) \times 10^3$, and $(1.4 \pm 0.2) \times 10^4$ M^{-1} for duplexes **9·9**, **4·4**, **6·6**, and **7·7**, respectively.

The association constants of the new series of amide-mediated homoduplexes and the related free energies are summarized in Table 1. Figure 10 provides the plot of the stability of the homoduplexes ($-\Delta G$) against the number of binding amides. The graph clearly shows the increase in the binding stability of the duplexes with the elongation of the oligomeric monomers. One general trend is that the series of $CONH_2$-mediated duplexes is more stable than that of the AcNH-mediated counterparts with an identical number of binding units. This may be attributed to the increased number of intermolecular hydrogen bonds in the former series. It is also noteworthy that the stability of duplex **6·6** is substantially greater than that of duplex **4·4** and is comparable to that of the compact and rigid DDD−AAA binding motif, which has been reported to be most stable for the recognition mode of three hydrogen bonds.[36] We propose

(35) The analysis for **9** is based on the assumption that monomer−dimer equilibrium is the predominant self-binding process; see ref 7 and also: Tobe, Y.; Utsumi, N.; Kawabata, K.; Nagano, A.; Adachi, K.; Araki, S.; Sonoda, M.; Hirose, K.; Narmura, K. *J. Am. Chem. Soc.* **2002**, *124*, 5350.
(36) Zimmerman, S. C.; Corbin, P. S. *Struct. & Bonding* **2000**, *96*, 63.

Chart 7

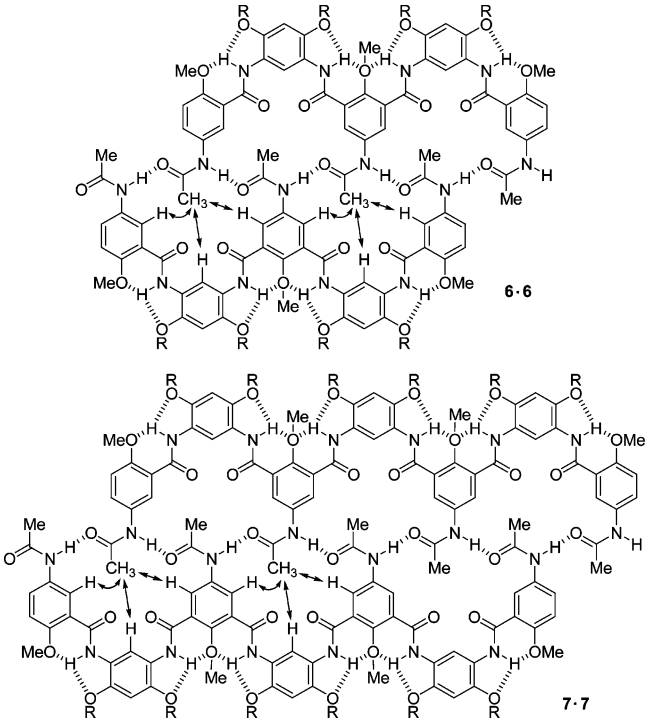


Table 1. Association Constants of the Homoduplexes in $CDCl_3$ at 25 °C, Determined by the ^1H NMR Dilution Method

duplex	K_{assoc} (M^{-1})	$-\Delta G$ (kJ/mol)
2·2	$(3.0 \pm 0.2) \times 10^3$	19.8
2·2[a]	$(8.0 \pm 1.0) \times 10^2$	16.6
3·3[b]	$>2.3 \times 10^5$	30.6
3·3[a]	$(2.1 \pm 0.3) \times 10^4$	24.6
4·4	$(2.6 \pm 0.3) \times 10^2$	13.8
4·4[a]	80 ± 9	10.9
5·5	$(1.2 \pm 0.2) \times 10^2$	11.9
6·6[b]	$>2.3 \times 10^5$	30.6
6·6[a]	$(1.2 \pm 0.2) \times 10^3$	17.6
7·7[a]	$(1.4 \pm 0.2) \times 10^4$	23.6
9·9	10	5.7
9·9[a]	<5	4.0

[a] In $CDCl_3/CD_3CN$ (9:1, v.v). [b] Lower limit of value.

the consecutive hydrogen-bonding pattern to explain the increased binding affinity of the longer oligomers, in which an increase of one amide unit will increase to two the number of intermolecular hydrogen bonds.

Conclusion

Two new series of dimeric, trimeric, and/or tetrameric homoduplexes have been developed, based on the self-recognition of the amide units, the simplest motif of the hydrogen-bonding-driven self-assembly. The most important feature for the self-assembly of the new series of homoduplexes is the accurate control of the anthranilamide backbones by consecutive stable intramolecular hydrogen bonding. As a result, all the recognition residues can be preorganized at the ideal positions for the formation of efficient intermolecular hydrogen bonding, which leads to remarkable coorperativity. Therefore, although the self-binding of a single amide unit is rather weak, iterative introduction of this simple self-binding motif can give rise to a robust force to generate duplex structures of high stability.

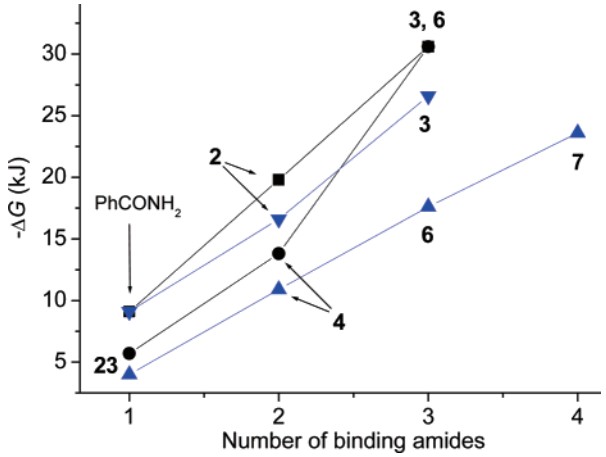


Figure 10. Free energies of binding ($-\Delta G$) of the homoduplexes in $CDCl_3$ (in black) and $CDCl_3/CD_3CN$ (9:1, v/v) (in blue) plotted against the number of the appended amides.

In the past decade, artificial secondary structures based on aromatic amide oligomers and many other linear species have received increasing attention. The present work well demonstrates that incorporation of additional functional units at rationally designed positions could produce new interesting assembling functions. It is expected that polymeric structures consisting of the same repeated segments will form supramolecular DNA-like duplex architectures, while replacement of the self-binding amide units with other binding residues such as urea units should lead to the generation of artificial duplexes of increased stability. Endeavors in these directions may ultimately lead to the creation of nanoscale functional oligomeric or polymeric supramolecular materials.

Acknowledgment. We thank the National Natural Science Foundation of China (Nos. 20321202, 20332040, 20372080, 20425208, and 20572126) and the Chinese Academy of Sciences for financial support.

Supporting Information Available: Experimental Section; method for measurement of the association constants; X-ray crystal structure of **4** (grown from dichloromethane); ^1H NMR dilution data of **9**, **4**, **6**, and **7** in $CDCl_3/CD_3CN$ (9:1, v/v); ^1H NMR dilution spectra of **6** in $CDCl_3$; 2D NOESY spectra of **2**, **3**, **4**, **6**, and **7** in $CDCl_3$; and crystallographic information (CIF files) on **2**, **4**, **5**, and **8** and three related compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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