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Covalent Reinforcement of Hydrogen-Bonded Discs into Stably Folded Helical Structures

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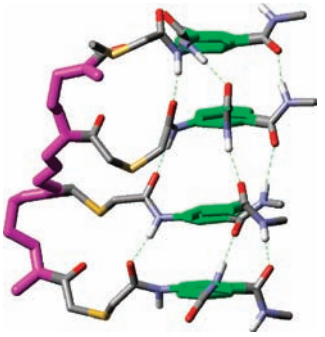
ABSTRACT



The presence of covalent tethers significantly enhanced the stability of structures consisting of helically arranged benzenetricarboxamide units that otherwise undergo very weak hydrogen-bonding interaction. The resultant molecular structures were probed by computational study, which predicted folded conformations consisting of helically arranged discs. Experimental studies confirmed the H-bonding interaction between the disk units, the monomeric nature of the corresponding molecules in solution, and the helical conformations of such molecules.

Various columnar assemblies have resulted from the stacking of disk-like and cyclic molecules.[1] Reported examples include stacks of aromatic molecules,[2] hydrogen-bonded columns formed by 1,3,5-benzenetricarboxamides,[3] and tubular assemblies formed from stacked cyclic peptides[4] and oligosaccharides.[5] Columnar assemblies have attracted wide interest because they represent unique motifs for creating nanoscaled structures. Unfortunately, the self-assembly of disk-like or cyclic molecules is difficult to control. The resultant stacks usually have ill-defined

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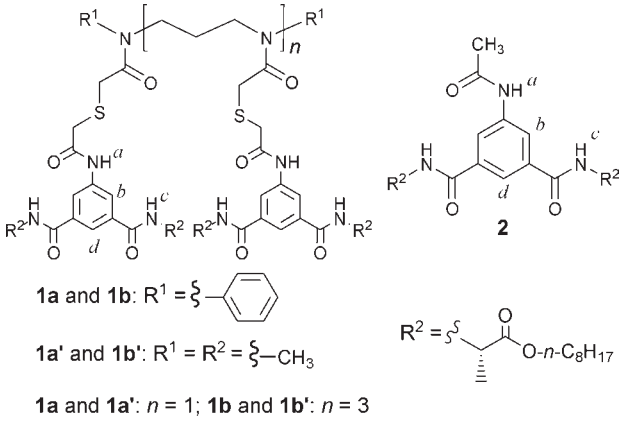
lengths, with few systems providing well-aligned columns. Strategies for controlling both the length of a stack and the alignment of the constituent discs or rings not only provide new insights into the organization of the corresponding assemblies but also enhance the ability to construct new structures and to manipulate various materials properties associated with the generated structures.[6] A particularly effective strategy for curbing the growth of a self-assembling stack is to introduce oligomeric tethers[7] that define the number of stacking units, which, in many cases, may lead to new foldamers.[8] Polymeric tethers[9] have also been adopted to enhance the alignment and stability of columnar structures consisting of stacked discs. Herein we describe the creation of folded helical structures consisting of multiply H-bonded aromatic rings that are covalently grafted to tethers derived from oligoamines.



Compounds **1a** and **1b**, consisting of 1,3,5-benzenetriamide ("disc") units attached to oligoamine tethers, were designed. Compound **2**, corresponding to a single disc of **1a** or **1b**, serves as a control. These structures are designed based on these considerations: (1) analogous 1,3,5-benzenetricarboxamides were reported to self-assemble into H-bonded columns of undefined lengths in the solid state and to undergo H-bond-mediated assembly in organic solvents (e.g., hydrocarbon) of very low polarity;[3] (2) chiral side chains based on the *n*-octyl ester of alanine allow the chirality of covalently tethered stacks to be probed; (3) the synthesis of the oligoamine tethers consisting of the $-NH(CH_2)_3-$ units and other analogous tethers is known,[10] which allows the total length, and thus the number of NH groups, of an oligoamine tether to be controlled and adjusted. In addition to defining the number of "discs", the presence of the covalent tethers serves to greatly enhance the otherwise weak intermolecular H-bonds between the discs into much more favorable intramolecular ones, leading to discrete stacks with significantly enhanced stabilities.

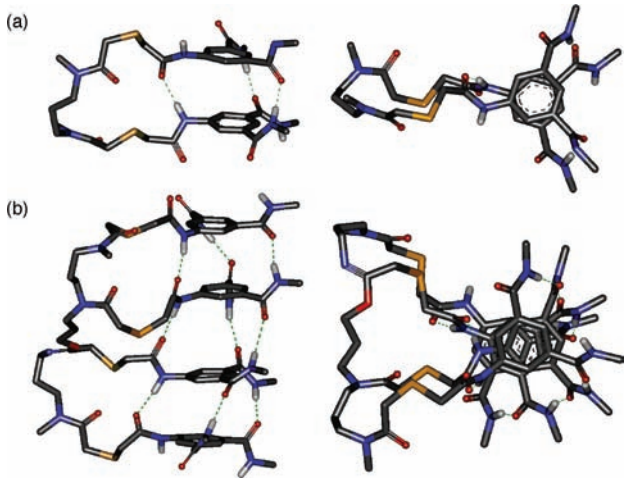


Figure 1. Side (left) and top (right) views of the structures of (a) **1a′** and (b) **1b′** optimized using the density functional theory (DFT) within generalized-gradient approximation in the form of a BLYP functional.[11] For clarity, hydrogen atoms other than those of the amide groups are not shown. Hydrogen bonds are shown as green dashed lines.

To probe the conformations of covalently tethered discs, the structures of **1a′** and **1b′**, which correspond to **1a** and **1b** with R^1 and R^2 being replaced by methyl groups, were computationally optimized. As shown in Figure 1a, the two parallel discs of **1a′** associate with each other via three

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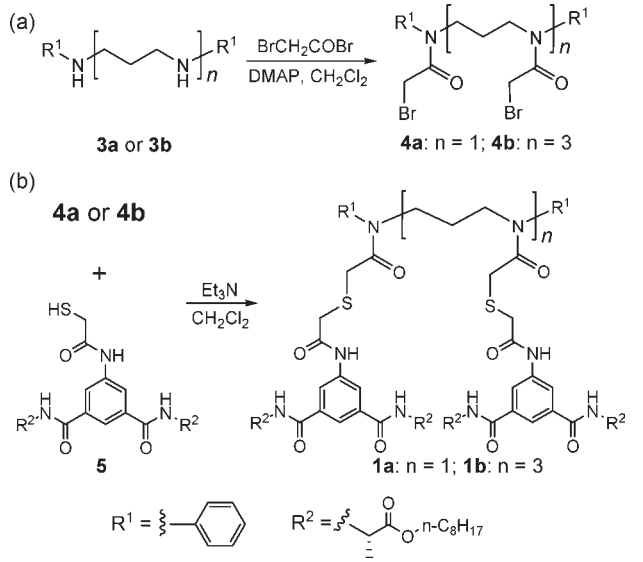
intramolecular H-bonds among their amide side chains, with an interdisc distance of ~3.6 Å. The simultaneous satisfaction of the side-chain H-bonding distance (~4.9 Å between the amide groups) and the interplanar stacking distance leads to an overall helical conformation. Similar to **1a**′, the conformation of **1b**′ is defined by a helically arranged stack, with an average distance of ~5 Å between two H-bonded side chain amide groups and interplanar distances of ~3.6 to 3.8 Å between adjacent discs (Figure 1b). The optimized conformation of a model compound reveals that the $-(CH_2)_3-$ spacer adopted for **1a** and **1b** provides a length (~5 Å between adjacent N atoms) matching the distance (~4.9 Å) between H-bonded side-chain amide groups. In contrast, the conformations of another model compound indicate that a $-(CH_2)_2-$ spacer is too short to accommodate two H-bonded amide groups.[11]

As shown in Scheme 1, treating oligoamines **3a** and **3b**[11] with bromoacetyl bromide led to **4a** and **4b**. The modified disc **5**[11] was then coupled with **4a** or **4b** via thioether linkages. The reaction between bromoacetyl and thiol groups,[12] which is well-known for its high efficiency, was chosen to ensure the attachment of the discs to all the reactive sites of the covalent tether. Indeed, compounds **1a** and **1b** were obtained in satisfactory yields (52% for **1a**, 56% for **1b**) after extensive purification using column chromatography followed by preparative TLC.[11] Compound **2** was prepared based on simple acylation.[11]

Scheme 1. Synthesis of Compounds **1a** and **1b**



The H-bonding interactions between the discs of **1a** and **1b** were probed by using ^{1}H NMR.[11] At comparable concentrations in $CDCl_3$, the amide protons of **1a** (2 mM, 9.83 ppm for protons *a*, 7.70 ppm for protons *c*) and **1b** (1 mM, 9.61−10.18 ppm for protons *a*, 7.67−8.03 ppm for protons *c*) showed significant downfield shifts in comparison to those of **2** (4 mM, 7.90 ppm for proton *a*, 7.16 ppm for protons *c*), suggesting that the amide groups of **1a** and **1b** were mostly involved in a highly favorable intramolecular H-bonding interaction. The intramolecularly H-bonded conformations of **1a** and **1b** were further supported by comparing the concentration-dependent ^{1}H NMR spectra of **1a** and **1b** with those of **2** recorded in $CDCl_3$ at room temperature.[11] The spectra of **2** showed that, from 0.1 to 32 mM, the signal of amide proton *a* underwent a significant shift from 7.33 to 8.63 ppm, while proton *c* moved from 6.85 to 7.52 ppm. The observed large shifts of the amide signals of **2** with concentration are consistent with the weak H-bonding between the molecules of **2**. In contrast, the amide ^{1}H signals of **1a** showed no detectable shift from 0.1 to 32 mM, being at 9.83 ppm (protons *a*) and 7.69 ppm (protons *c*). Similarly, the amide ^{1}H signals of **1b** did not exhibit any detectable shift from 0.1 to 32 mM, with the chemical shifts of protons *a* remaining in the range of 9.61 to 10.20 ppm and those of proton *c* appearing between 7.61 and 8.07 ppm. These results confirmed the intramolecular nature of the H-bonding interactions associated with **1a** and **1b**, which in turn is consistent with the optimized conformations shown in Figure 1.

While data from ^{1}H NMR studies demonstrate that **2** engages in intermolecular H-bonding, and point to the presence of intramolecular H-bonding among the amide side chains of **1a** or **1b**, the possibility that **1a** and **1b** may associate via intermolecular H-bonding could not be ruled out. The molecules of **1a** or **1b** could, albeit unlikely, associate via intermolecular H-bonding into dimers or higher oligomers with such high stabilities that lead to the downfield shifts and concentration-independence observed for their amide proton signals. To further examine the presence or absence of intermolecular aggregates, vapor pressure osmometry (VPO) studies were performed on **1a** and **1b** in $CHCl_3$ at room temperature.[11] Using polystyrene as molecular weight standards, VPO measurements on solutions of **1a** from 5 to 40 mM consistently gave aggregation numbers that were close to one. VPO analysis on **1b** (5 mM to 40 mM) in $CHCl_3$ revealed similar aggregation numbers around one. The VPO results confirmed that, on average, the molecules of **1a** or **1b** existed mostly as monomers in solution. Thus, the significant downfield chemical shifts observed for the amide protons of **1a** or **1b** in comparison to those of **2** must be mainly contributed by intramolecular H-bonding that results in folded conformations.

The folded conformations of both **1a** and **1b** were then probed by using CD spectroscopy in $CHCl_3$. Consistent with the helical conformations predicted by *ab initio* computation (see Figure 1), strong CD signals with maxima at 304 nm and minima at 327 nm were observed in the CD spectra of **1a** (Figure 2a). As shown in Figure 2b, the CD spectra of **1b** and those of **1a** are very similar, with maxima at 308 nm and minima at 328 nm. The observed CD signals for both **1a** and **1b** suggested that these two

(11) Please see Supporting Information for details.
(12) Englebretsen, D. R.; Garnham, B.; Alewood, P. F. *J. Org. Chem.* **2002**, *67*, 5883.

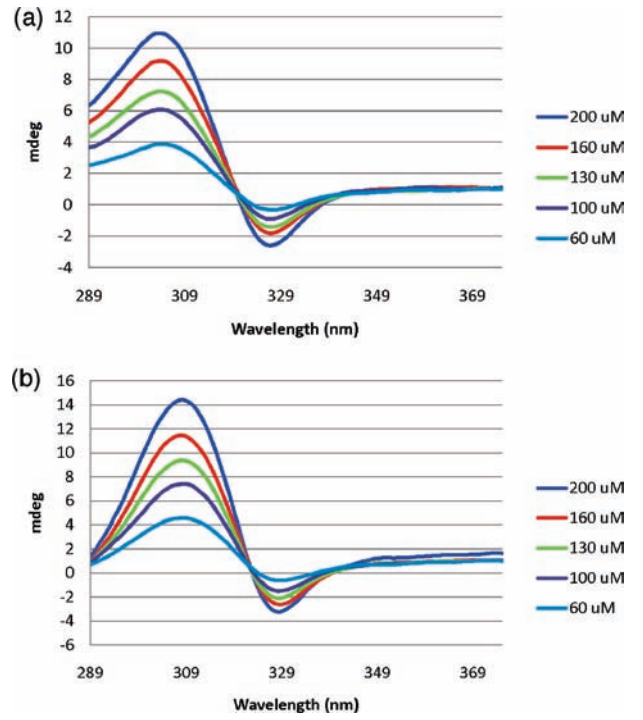


Figure 2. Concentration-dependent CD spectra of (a) **1a** and (b) **1b** recorded in $CHCl_3$ at room temperature.

compounds adopt similar chiral conformations with a handedness that is biased owing to the transfer of chirality from the UV-silent side chains to the stacked aromatic rings. From 20 to 200 μM, the CD spectra recorded for both **1a** and **1b** share the same shape (Figure 2), with the increase in the intensities of CD signals being linear across this concentration range.[11] Besides, from -10 to 50 °C, the CD spectra of **1a** and **1b** revealed little change in shape and a linear change of signal intensity with temperature. CD spectra of **1b** recorded in a solvent of enhanced polarity ($CHCl_3/CH_3OH$ = 60/40, v/v) also revealed strong CD signals with linear concentration and temperature-dependence. In contrast, no meaningful CD signals could be recorded for **2** from 20 to 200 μM in $CHCl_3$, suggesting that, within this concentration range, compound **2** could not undergo any meaningful aggregation or assembly. These observations corroborate the above conclusion made based on ^{1}H NMR and VPO studies; i.e., the chiral structures of **1a** and **1b** are of a molecular, instead of supramolecular, nature, which also demonstrates the critical role played by covalent tethers in reinforcing the association between the discs and in maintaining the chiral conformations of these two compounds.

In summary, attaching disk-like benzenetricarboxamide units to covalent tethers has led to molecular structures adopting well-defined helical conformations that are further stabilized by favorable intramolecular H-bonding. The conformations of **1a** and **1b** predicted by *ab initio* computation were supported by results from ^{1}H NMR, which revealed the dramatically enhanced H-bonding interactions between the dics; VPO, which confirmed the overall monomeric nature of the molecules in solution; and CD, which pointed to chiral confomrations that can be best rationalized with those predicted by *ab initio* calculation. This study serves to demonstrate the effectiveness of covalent tethers in guiding and stabilizing otherwise weakly associating structural units into folded molecular structures of defined conformations.

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Supporting Information Available. ^{1}H NMR spectra, CD, and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.