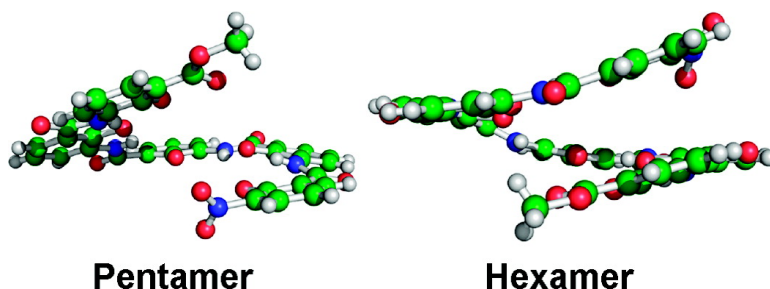


Helical Organization in Foldable Aromatic Oligoamides by a Continuous Hydrogen-Bonding Network

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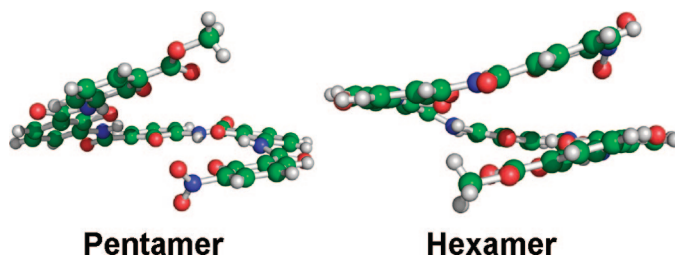
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ABSTRACT



Introduction of a continuous internal hydrogen-bonding network suppressed the conformational flexibility of a series of oligoaromatic foldamers with a lengthened backbone. The helical ordering over up to six aromatic repeating units was established in solution by a 2D NOESY study and in the solid state by an X-ray diffraction method. Computational molecular modeling further corroborates the experimentally observed helical propagation in this class of foldable molecular strands.

Largely driven by a strong desire to build biopolymer-like functions into much simpler yet completely abiotic systems, much progress has been made in elegantly designed unnatural folding helices that mimic helices in Nature.¹ In particular,

the helical organization emanating from multiple centered hydrogen bonds (H-bonds) has attracted special interest in recent years.^{1a–k} Despite the progress,² the exact helical dimensions and other structural features for a large portion of reported helices have remained unknown due to lack of three-dimensional structures.^{1j,3} Obtaining quantitative descriptions of structural properties at the molecular level is critically important as it very often leads to insightful, testable hypotheses^{2i,m–o} and novel applications such as in functional foldamer design.^{1j,m,4} It can also reveal gaps in our current understanding that need to be filled in order to move the field forward.

Early investigations^{3c,5} have established a crescent folding backbone in the solid state for internally H-bonded dimers and trimers with repeating units represented by oligomers 1–3. However, the corresponding helical conformation for longer oligomers in either solution or solid state has not been established. Moreover, a molecular modeling^{5a} on a hexamer 3 using the MM3 force field suggested that it should adopt a crescent, two-dimensional conformation that encloses an

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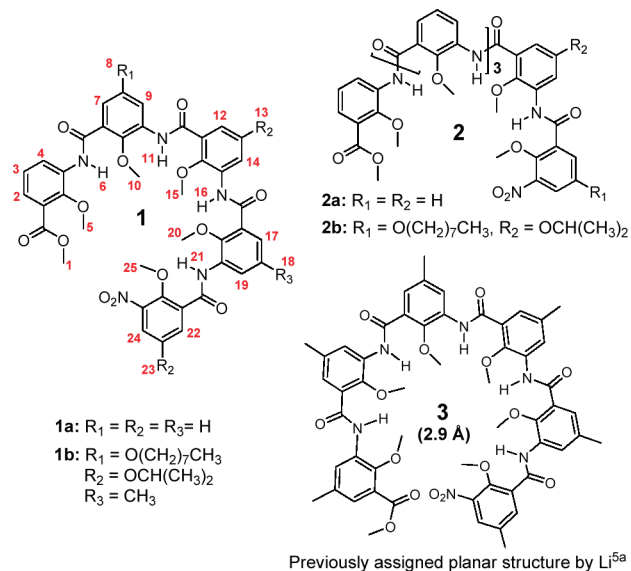
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acyclic, open-ended cavity of $\sim 4.3 \text{ \AA}$ in a radius defined by six interior methoxy oxygen atoms (or 2.9 \AA after deducting a covalent radius of 1.4 \AA for oxygen atom); on this basis, a hexameric, head-to-tail binding mode was proposed to account for the helicity induction in a porphyrin-modified hexamer by six chiral C60-incorporating histidines.^{3c} The existence of a cavity as large as 2.9 \AA may seem quite uncertain as amide linkages are known to exhibit a significant degree of plasticity in bond angles, allowing the backbone to curve due to H-bonding interactions.^{1f,2c} To test this hypothesis, we carried out computational molecular modeling at the level of B3LYP/6-31G* on **1a**, and indeed, the results⁶ (Figure 1b) showed that oligomers higher than tetramers should take up a helical backbone rather than the planar conformation as proposed previously.^{3c,5a} Consequently, a helical cavity of $\sim 1.4 \text{ \AA}$ in a radius that is much smaller than 2.9 \AA should result. This helical conformation was

further supported by replica exchange molecular dynamics.⁶ To confirm this computational result, we provide here the solid-state evidence of helical organizations in **1a** and **2a** by a continuous H-bonding network as well as the convincing 2D NOESY studies that support the crescent and helically folded conformations adopted by **1b** and **2b** in solution. These distinct helically folded conformations may better explain the helicity induction observed previously.^{3c}



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Oligomers **1** and **2** were synthesized from commercially available salicylic acid and 2,5-dihydroxybenzoic acid in 12–18 steps.⁶ Crystals of **1a** and **2a** suitable for X-ray structure determination were obtained by slow evaporation of **1a** and **2a** in mixed solvents containing hexane and chloroform (1:1 v/v) for **1a** and hexane and dichloromethane (1:1 v/v) for **2a** at room temperature.⁶ Their crystal structures viewed along or perpendicular to the helical axis are presented in Figure 1a and c. The common structural features shared between **1a** and **2a** are the following: (1) Both unit cells contain two enantiomeric helices of opposite helical senses (e.g., right/left-handed) that tightly stack on each

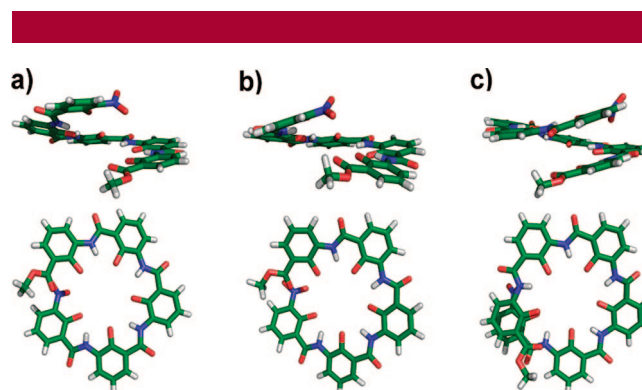


Figure 1. Side and top views of (a) crystal structure of pentamer **1a**, (b) ab initio calculated structure of **1a**, and (c) crystal structure of hexamer **2a**. Interior methoxy methyl groups are omitted for clarity.

other with no inclusion of solvent molecules. (2) Both structures possess a helical periodicity of ~ 5 repeating units per turn. (3) The interior methoxy groups, pointing up and down alternatively, fill the helix hollow cavity of ~ 1.4 Å in radius⁷ and completely prevent them from encapsulating guest molecules. (4) As expected, all the inward-pointing amide protons and methoxy oxygen atoms participate in the formation of a continuous internally located H-bonding network that comprises up to 10 intramolecular H-bonds ($\text{NH}\cdots\text{OMe} = 1.933\text{--}2.306$ Å). One difference between **1a** and **2a** involves the helical pitch. While hexamer **2a** has a pitch of ~ 3.4 Å typically observed in aromatic foldamers,^{2a–f} an appreciably larger helical pitch of ~ 5 Å is observed in **1a**. Such a large pitch may stem, in part, from the steric crowdedness involving the two end methoxy groups in the absence of favorable π – π stacking interactions, which was also found in an aliphatic peptoid foldamer in the solid state.^{2g} The solid-state structures of **1a** and **2a** (1) provide the most conclusive evidence for the adoption of a helical conformation by the foldable molecular strands **1a** and **2a**, (2) validate our conceptual reasoning and others' observations,^{1f,2c} detailing a significant effect the H-bonding forces may have on the backbone curvature of aromatic foldamers, and (3) corroborate the power of ab initio molecular modeling at the B3LYP/6-31G* level in the satisfactory prediction of 3D topologies of aromatic foldamers.^{2f,8}

The highly repetitive nature of **1a** (Figure 2a) and **2a**⁶ led to extensive ¹H NMR signal overlaps among aromatic

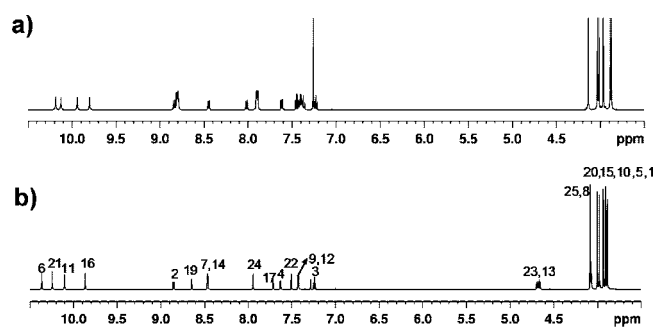


Figure 2. ¹H NMR spectra of (a) pentamer **1a** (500 MHz, 5 mM, 298 K, CDCl₃) and (b) pentamer **1b** (800 MHz, 25 mM, 298 K, CDCl₃).

protons, hampering the elucidation of their folded structures in solution. To overcome this difficulty, linear and branched alkoxy side chains as well as a methyl group *para* to the interior methoxy groups are deliberately introduced into **1b**. At 25 mM,⁹ the ¹H NMR spectrum of **1b** recorded in CDCl₃ displays highly dispersed proton resonances for most of its

(7) This helically wrapped interior cavity of radius as small as 1.4 Å is remarkably identical to the circular cavity radius found in a pentagon-shaped circular aromatic pentamer recently reported by us: Qin, B.; Chen, X. Y.; Fang, X.; Shu, Y. Y.; Yip, Y. K.; Yan, Y.; Pan, S. Y.; Ong, W. Q.; Ren, C. L.; Su, H. B.; Zeng, H. Q. *Org. Lett.* **2008**, *10*, 5127.

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protons (Figure 2b). The amide protons resonating at low fields (9.87–10.36 ppm) are in line with the existence of strong intramolecular H-bonds in **1b**.^{2c,d} Since the interatomic distances between amide and methoxy protons measured from the crystal structure of **1a** range from 2.279 to 3.690 Å, two NOE contacts between every amide proton and its adjacent methoxy methyl groups should be seen in the 2D NOESY spectrum if a folded conformation does prevail for **1b** in solution. The well-resolved amide protons and internal methoxy groups of **1b** indeed permit us to observe the expected eight NOE cross peaks, two for each amide protons (Figure 3a). Except for the NOE contact between protons 5

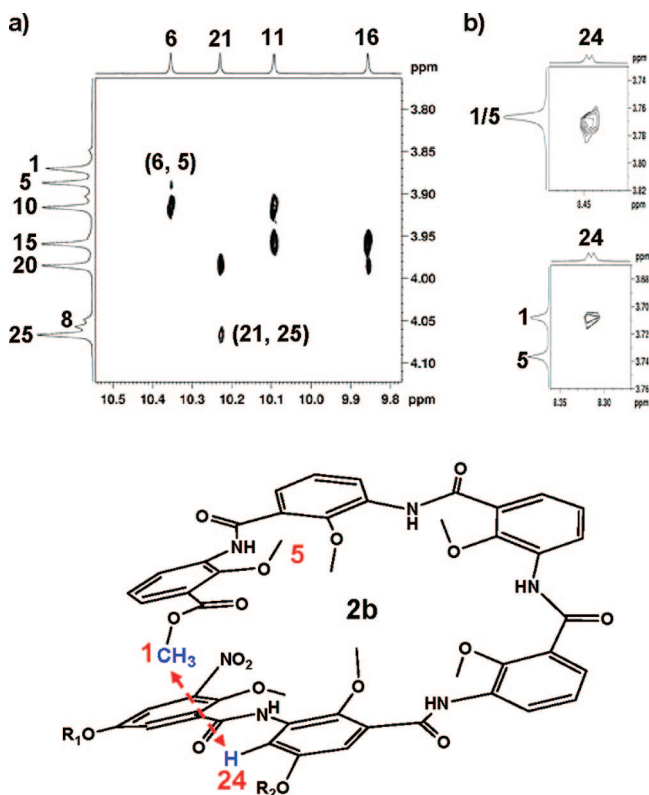


Figure 3. (a) NOE contacts (NOESY, 800 MHz, 25 mM, 298 K, 500 ms, CDCl₃) seen between amide protons and their adjacent interior methoxy protons of **1b**. (b) End-to-end NOE (top, 500 MHz, 20 mM, 283 K, 500 ms, CDCl₃) and ROE (bottom, ROESY, 500 MHz, 15 mM, 298 K, 200 ms, CDCl₃/25%DMSO-*d*₆) contacts seen between the end units of **2b**.

and 6, the NOE intensities of all the other seven NOE cross-peaks between interior methoxy protons and amide protons in Figure 3a were much stronger than those weak NOE contacts between amide protons and the neighboring aromatic protons ortho to the amide bonds (protons 4, 7, 9, etc; Figure S2a, Supporting Information),⁶ suggesting that the methoxy protons stay much closer to the amide protons than to the aromatic protons, a consequence resulting from the enforced folding of the backbone by those internal hydrogen bonds. The NOEs between the end residues that are indicative of the helical conformation of **1b** were not detected, presumably due to its unusually large helical pitch (~ 5 Å)

Similarly, the incorporation of two different side chains into **2b** at only one end differentiates the aromatic proton signals of the modified end units from all other remaining units in the same molecule in CDCl₃.⁶ Addition of 25% DMSO-*d*₆ into CDCl₃ further separates ester methyl protons 1 from the interior methoxy methyl protons 5. As such, the ROE cross peak between the end units (methoxy protons 1 and aromatic proton 24, Figure 3b) is clearly identifiable. This end-to-end ROE, along with the observation of numerous ROE contacts among amide protons and their adjacent interior methoxy protons,⁶ strongly supports the presence of the H-bond enforced helical ordering in **2b** in solution that leads to the stacking of one end over the other. Observation of these end-to-end NOE or ROE contacts in **2b** (Figure 3b) accords with the shortest interatomic distance (2.748 Å) found between protons 1 and 24 in the crystal structure of **2a**.

(9) Given the approximate dimensionality of 8 Å × 25 Å × 20 Å (estimated based on the crystal structure of pentamer **1a**) for side-chain-modified pentamer **1b**, a simple calculation shows that the separation distance between any two molecules of **1b** is more than 20 Å at 25 mM. Estimation based on **2a** suggests a similar dimensionality of 8 Å × 25 Å × 20 Å for pentamer **2b** and subsequent calculation leads to a separation distance of >30 Å at 15 mM between any two molecules of **2b**. These large separation distances suggest that the NOE/ROEs observed in Figure 3 are due to the intramolecular rather than intermolecular proton–proton interactions that occur through the space.

To summarize, the helical propagation over several internally rigidified, lengthened oligoaromatic backbones as in **1** and **2** in solution and the solid state has been established experimentally and substantiated theoretically by the computational molecular modeling at the B3LYP/6-31G* level. The detailed elucidation of such structural information contained within the helically folded framework should guide the design of supramolecular (bio)nanoarchitectures of increasing complexity via peripheral functionalizations, which may find important applications in a number of fields including materials,^{3c} medicinal^{1m,4} and biological sciences, and engineering.^{1m,4a–e}

Acknowledgment. Financial support of this work by Faculty of Science and Office of Life Sciences at National University of Singapore is gratefully acknowledged.

Supporting Information Available: Synthetic procedures for oligomers **1** and **2** along with a full set of characterization data including CIF files (**1a** and **2a**), ¹H NMR, ¹³C NMR, HRMS, NOESY, and TOCSY, as well as molecular modeling results. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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