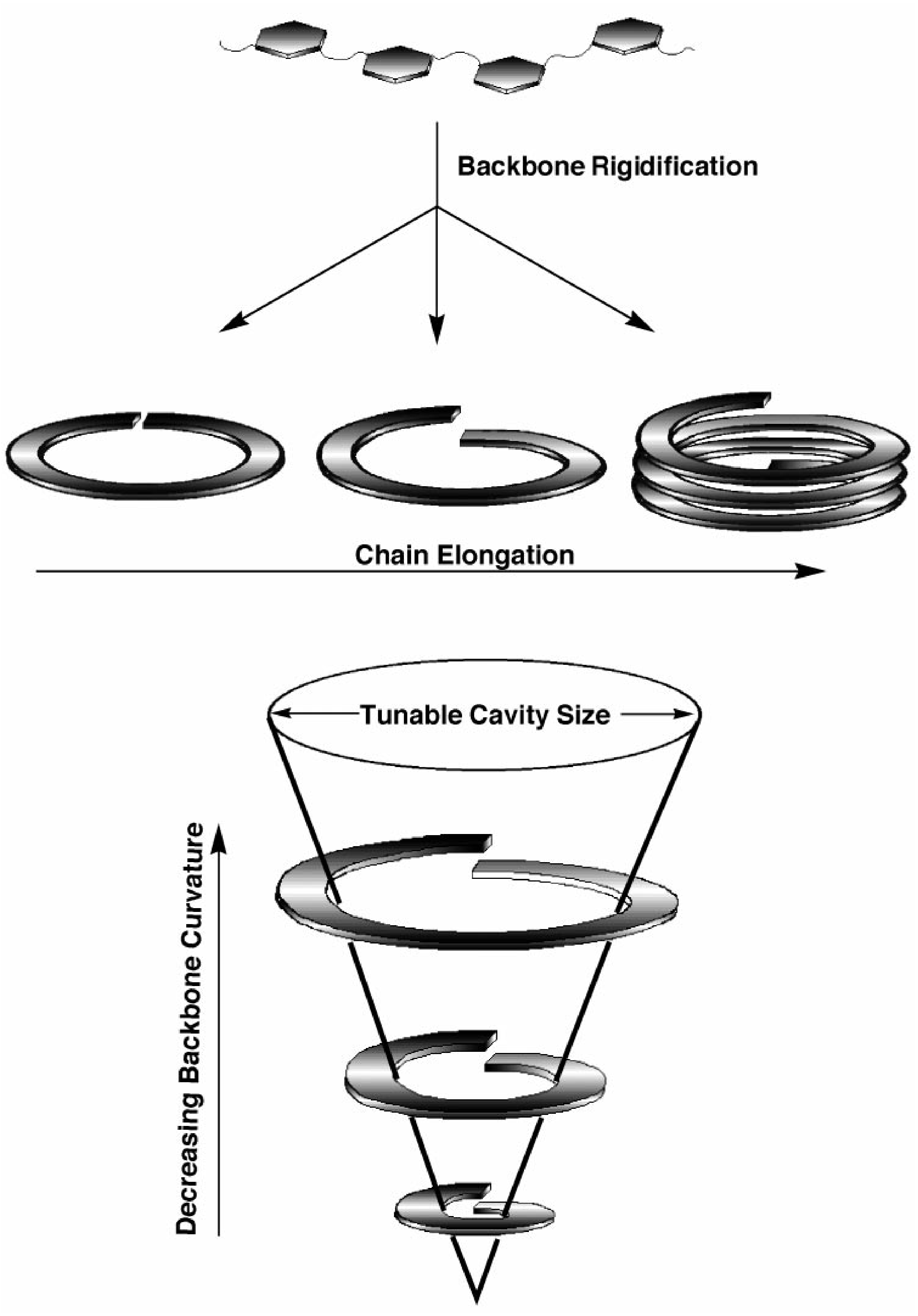

Backbone Rigidification
Chain Elongation
Tunable Cavity Size
Decreasing Backbone Curvature

Crescent Oligoamides: From Acyclic “Macrocycles” to Folding Nanotubes

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Abstract: Oligoarylamides whose backbones are rigidified by intramolecular hydrogen bonds (H-bonds) are found to adopt well-defined conformations in both solution and solid state. Depending on the length of their backbones, these folding oligoamides are crescents, broken macrocycles, or helices. A large (≈ 10 Å) interior cavity is associated with the “macrocycles” and helices. The folded conformations are independent of chain length and are found in both nonpolar and polar solvents. This strategy is being extended to the construction of folding acyclic “macrocycles” and nanotubes with larger tubular cavities.

Keywords: amides · folding · helices · hydrogen bonds · nanotubes · oligomers

Introduction

In recent years there has been intense interest in the design and analysis of synthetic oligomers and polymers that adopt compact and well-defined folding patterns.[1] One type of well-organized structure is the helical and multiple helical structures that are found throughout Nature. These structures include simple α-helical polypeptides, double-helical nucleic acids, and the more complex helical protein structures, such as the microtubules and the protein coat of the tobacco mosaic virus.[2] Indeed, most of the current effort directed at creating well-defined structures is inspired by these natural helical structures and has focused on designing synthetic oligomers and polymers that fold into helices.[3] Examples of folded, potentially functionalizable helical structures include β-peptides developed by Gellman et al.[4] and Seebach et al.,[5] γ-peptides by Hanessian et al.,[6] and peptoid oligomers described by Zuckermann, Dill, Cohen and co-workers,[7–9] and many other foldamers involving unnatural backbones.[10–18] In addition, Lehn et al. has reported polyheterocyclic strands that fold into extended helical structures.[19, 20] Moore and co-workers recently described an approach toward building nanotubes by designing oligomers that undergo solvent-driven folding.[21] Experimental data support a helical conformation with a tubular cavity for the folded structure.

Despite the progress made so far, the field of unnatural folding oligomers and polymers is still in its infancy. Few examples have shown the diversity in structure and function similar to that exhibited by biological macromolecules, which are realized from just three backbone constitutions. Nature’s approach for constructing macromolecules, that is, the build up of a polymeric backbone from a common repeating unit, is characterized by very simple and highly efficient chemistry, which offers synthetic economy while allowing enormous structural variation through side chain modification.

While the evolution of biological macromolecules has been restricted by various factors over a very long period of time, the design of unnatural folding oligomers and polymers is perhaps limited more by human imagination than by physical barriers. These folding molecules may find a wide range of applications in biological and materials sciences. For example, polymers that fold into structures with nanoscale holes down the center might function as ion channels in a manner similar to the peptide antibiotic gramicidin A, as novel conduits for transporting ions and small molecules ,and as hosts for separation and catalysis. Polymers that fold into robust secondary structures also have tremendous potential as abiotic scaffolds for constructing large, complex molecular systems reminiscent of proteins.

We have been interested in developing robust folding motifs based on simple, readily available common repeating units that can be easily functionalized. Building blocks allowing stepwise and repetitive synthesis are linked into unnatural backbones with well-defined secondary structural preferences that are independent of the side chains. Here the design of backbone-rigidified oligomers that fold into helices with tunable nanosized cavities are discussed.

Design Principle

An oligomer with a rigidified backbone can be constructed by introducing, in addition to the covalent bonds that link the subunits, at least one additional set of interactions that minimize conformational freedom. Such an oligomer can be

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viewed as a tape. If a tape is curved, that is, with a crescent conformation, a short oligomer with such a conformation can be regarded as an acyclic "macrocycle" (Figure 1 a). As the backbone reaches a certain length, the oligomer should be forced to adopt a helical conformation in which one end of the molecule must lie above the other because of crowding (Figure 1 b). The all-aromatic helicenes[22] in which the second set of backbone-rigidifying interactions are covalent bonds, and the oligomers whose backbones are rigidified by localized intramolecular H-bonds as described by Hamilton et al.[10] and Lehn et al.,[20] belong to this category. Eventually, polymers and oligomers with long enough backbones should fold into helices (Figure 1c).

Figure 1. Oligomers and polymers with rigidified, crescent backbones. a) A short oligomer can be viewed as a macrocycle. b) When the backbone reaches a certain length, a helical conformation is adopted. c) A helix of multiple turns can result from a long oligomer or polymer chain. Changing the curvature of the backbone leads to the adjustment of the diameter of the interior cavities in each case.

A helix can be viewed as a tube if it contains a tubular cavity. In spite of the fact that the majority of unnatural folding oligomers and polymers reported so far involve helical structures, few systems have shown interior cavities of any meaningful sizes. Examples with adjustable interior tubular cavities have not appeared. Recently, we set about designing oligomers and polymers that are characterized by not only folded, helical conformations, but also adjustable interior cavity sizes and modifiable outside surfaces.

The first generation of our design involved oligoamides consisting of subunits derived from the readily available 5-amino-2,4-dihydroxybenzoic acid. Such an oligomer should have an overall crescent backbone: The curved backbone is forced by the *meta*-disubstituted benzene ring and the two intramolecular hydrogen bonds that rigidify each of the amide linkages in the molecule. A large (≈10 Å) cavity is created. As shown in Figure 2, when the number of subunits is equal to or greater than seven, such an oligomer should be forced to adopt a helical conformation in which one end of the molecule lies above the other. An additional stabilizing factor, that is, an aromatic stacking interaction between the benzene rings, becomes important for oligomers with more than six or seven residues. As a result, two driving forces are behind the folding of the helices: 1) two localized intramolecular hydrogen bonds that lead to the rigidification of each of the amide linkages, and 2) an aromatic stacking interaction that further stabilizes the formed helix. The two driving forces act cooperatively: The aromatic stacking interaction is possible because of the curved shape of the backbone; the stacking interaction in turn helps stabilize the hydrogen bonds by retaining the helical conformation of the molecule, which partially shields the intramolecular hydrogen bonds, making them less accessible to solvent molecules. Since these two stabilizing factors are associated with the backbone, a robust helical structural motif that is versatile as well as resilient toward structural variation of the side groups (OR groups) is expected. As the length of the backbone increases, the aromatic stacking interaction is expected to play an increasingly dominant role.

The above subunits can only result in "macrocycles" and helices with internal diameters of the same size (≈10 Å), because the amide linkages on the same benzene ring are *meta* to each other. If on some of the subunits the two amide linkages are *para* to each other, the internal diameters can be adjusted. This can be easily achieved by incorporating the corresponding building blocks into the backbones. Three examples are shown in Figure 3.

This strategy is very versatile because it allows the adjustment of internal cavities by changing the ratio of the two (*meta* and *para*) types of building blocks. The building blocks are not limited to the examples described above. Oligomers and polymers consisting of two different residues, one derived from a diacid and the other from a diamine (Figure 4) should also adopt crescent conformations.

These designs are very similar to those shown in Figure 2 and Figure 3, with adjustable internal diameters and an easily modifiable outside surface. The only difference between the designs shown in Figure 2 and Figure 3 and that in Figure 4 is the orientation of the amide linkages. These designs should facilitate polymer synthesis, which can be carried out by treating the corresponding diacid chlorides with the diamines.

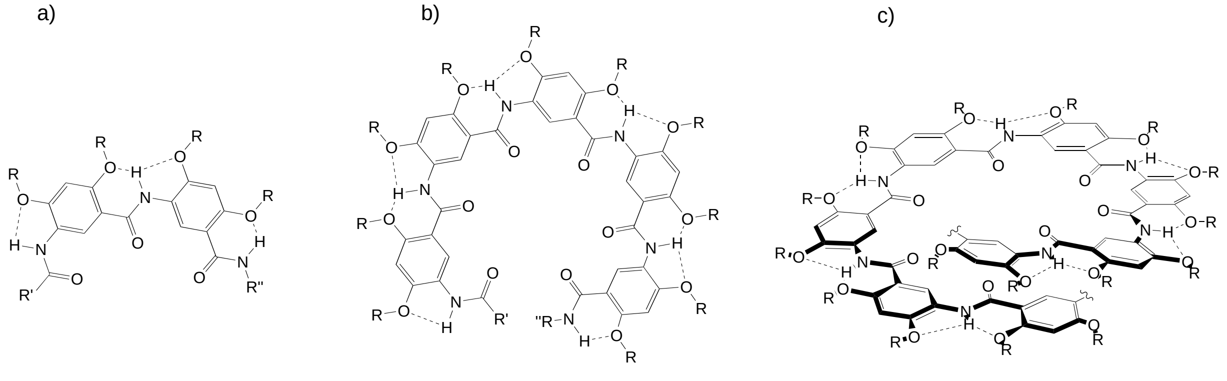
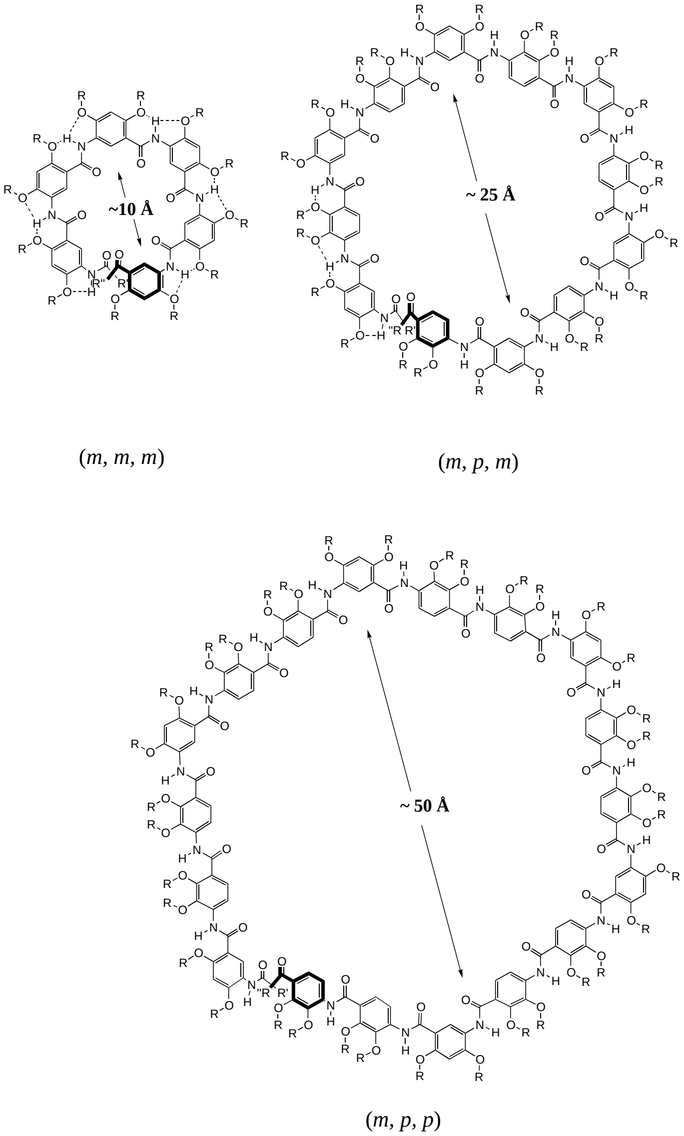


Figure 2. Oligoamides with crescent backbones (a). The intramolecular hydrogen bonds minimize the conformational freedom of the backbones. A cavity with a diameter of about 10 Å is created in a "macrocycle" (b) and in a helix (c).



(*m*, *m*, *m*) (*m*, *p*, *m*)

(*m*, *p*, *p*)

Figure 3. Incorporation of "*para*" building blocks into the backbones of the "macrocycles" and the helices leads to interior cavities of various sizes. The composition of each backbone is indicated in parenthesis. *m*: subunit with the two amide linkages at *meta* positions; *p*: subunit with the two amide linkages at *para* positions.

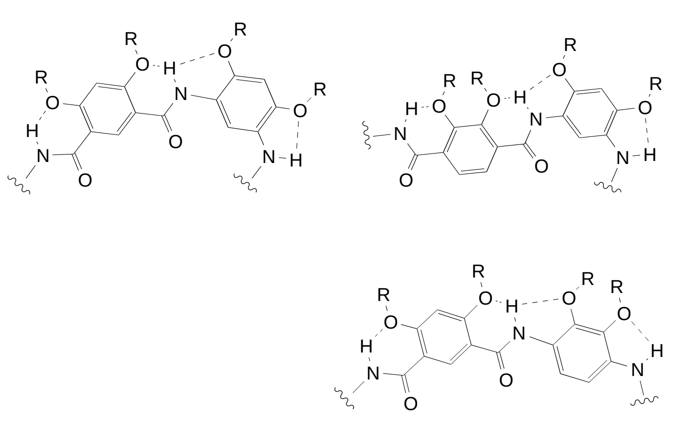
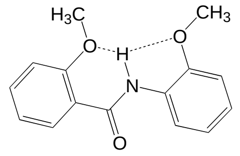


Figure 4. Alternative designs: Molecules with these backbones should also adopt crescent conformations.

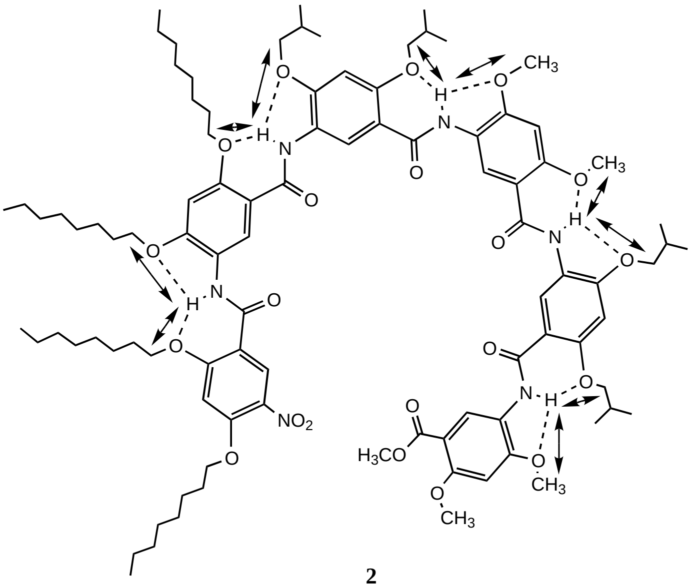
Discussion

Short oligomers with crescent backbones:[23] Ab initio calculations indicate that the lowest energy conformation of dimer **1** is planar and contains two strong intramolecular hydrogen



1

bonds that are the components of a three-center hydrogen bond. Our recent experimental and theoretical work indicates that the formation of the three-center, hydrogen bond in **1** shows positive cooperativity between the two-center components.[23] The existence of the three-center hydrogen bond in **1** and related analogues is confirmed in both the solid state and in solution. It was found that the folded conformation of **1** existed in the very polar solvent DMSO as well as in chloroform, which lays the foundation for the design of oligomers that adopt well-defined conformations in a variety of environments. Higher homologues of **1** also showed folded, crescent conformations both in solution and in the solid state. In both $CDCl_3$ and $[D_6]DMSO$ solutions, strong NOEs between the amide protons and the corresponding adjacent alkoxy protons were detected by 2D ^1H NMR (NOESY) experiments, which is consistent with folded conformations rigidified by the three-center hydrogen bonds. Based on 2D NMR results, the following oligomer **2** was assigned the crescent conformation as shown. The NOEs are indicated by arrows. The hexamer **2**, which almost forms a full circle and thus a nearly closed cavity, can be viewed as a macrocycle with the amide O atoms pointing inward. A large (ca. 10 Å based on computer modeling) hydrophilic cavity is formed. Such a cavity may accommodate a variety of metal ions and small molecules. Crescent conformations are also evident in the solid state. Figure 5 shows the crystal structure of a dimer, a trimer, and a tetramer.



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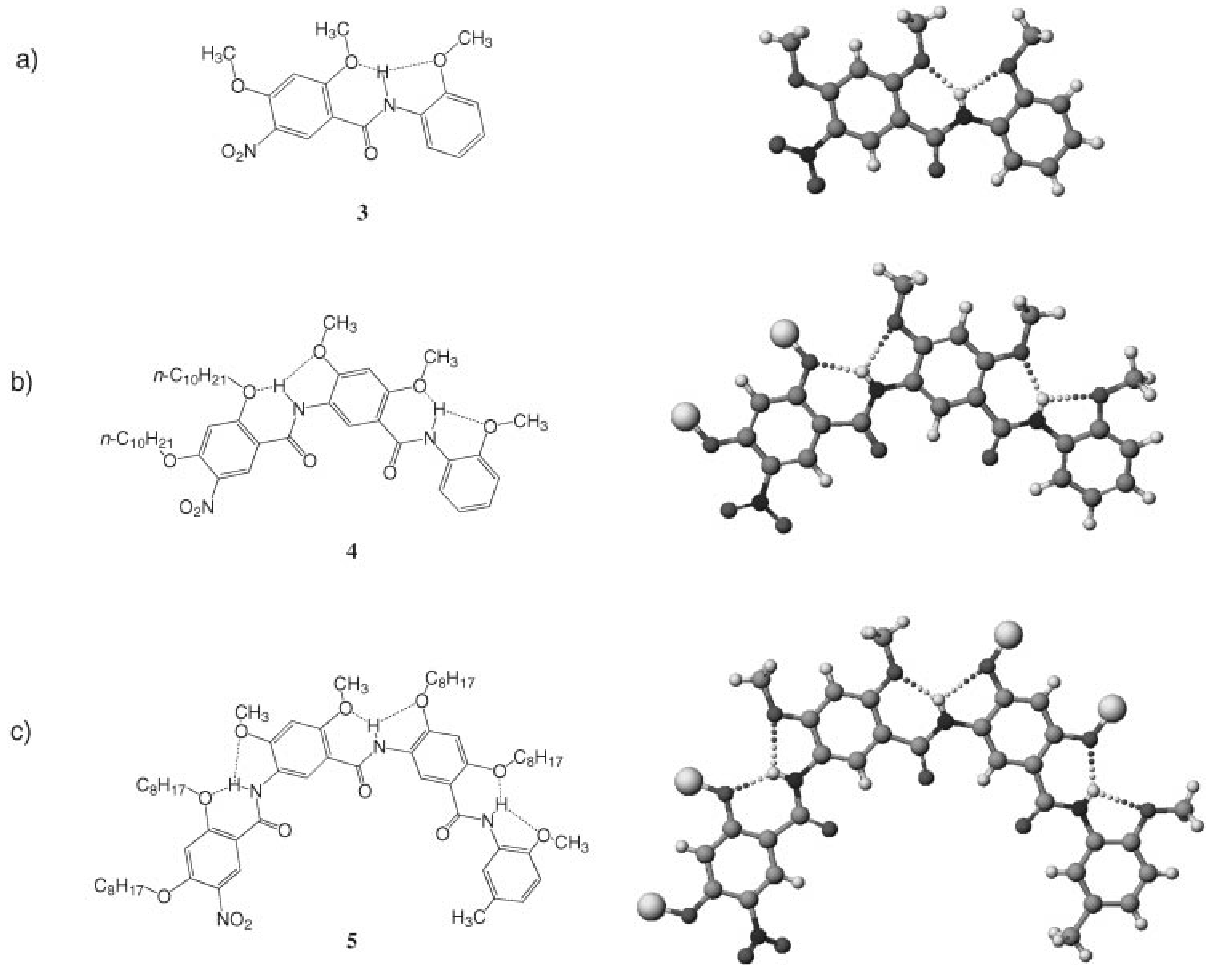


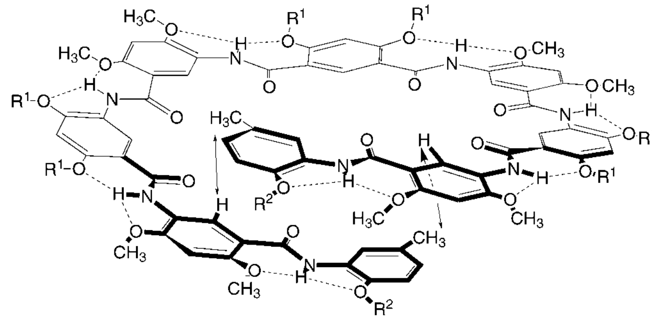
Figure 5. The crystal structures of crescent oligoamides: a) a dimer; b) a trimer; c) a tetramer. The long alkyl chains are replaced with dummy atoms for clarity.

Hollow helices with nanosized cavities:[24] As mentioned above, oligomers with long enough backbones should fold into helical conformations due to crowding at the two ends. However, the crowding may pose a potential problem to the folding process because it may disrupt the helical conformation by forcing the backbones to twist to such an extent that the two ends of the molecule turn away from each other. Indeed, this scenario was observed in a system described by Hamilton et al.[10] Another problem may be that, the accretion of subunits may become increasingly difficult due to steric hinderance caused by the folded helical conformation.

By adopting a convergent strategy, the symmetrical 9-mer **6** was synthesized by coupling two equivalents of the corresponding tetramer amine with one equivalent of the diacid using the coupling reagent *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) in DMF/$CHCl_3$ at elevated temperature. Similar reaction conditions have recently been successfully applied to the preparation of 11-mers and higher homologues, indicating that coupling involving long backbones is not impeded by the folded conformations. It is possible that, at elevated temperature and in the presence of polar solvents, the folded helical conformation may "denature" briefly, freeing the reactive ends of the molecules for further bond formation.

2D ^1H NMR (NOESY, in $CDCl_3$) spectroscopy was used to examine 9-mer **6**. Strong NOEs were observed between each of the amide protons and those of its two adjacent side groups, which supports the existence of localized, three-center hydrogen bonds that rigidify the backbone. As indicated in Figure 6, additional diagnostic NOE contacts that are consistent with a helical conformation, which brings the two ends of the molecule into close proximity, were identified between the methyl H atoms and the two of the amide protons. No NOE between the corresponding methyl H atoms and the aromatic H atom was found in the reference compound **7** which is roughly equivalent to half of 9-mer **6**. The 2D NMR data have thus provided strong evidence that is consistent with a folded, helical conformation.

The most conclusive evidence supporting a folded, helical conformation comes from the crystal structure of the diester **8**, a symmetrical 9-mer in which all the R groups are alkyl chains. Oligomer **8** was prepared by using procedures similar to those employed for **6**. As shown in Figure 7, the molecule folds into a helical conformation, with the amide O atoms pointing toward the center of a cavity of approximately 10 Å in diameter. All of the amide protons and the alkoxy O atoms are involved in forming the three-center, hydrogen bonds already observed in the shorter oligomers (Figure 5). The side chains (R groups) point radially away from the center of molecule and are not involved in the folding.



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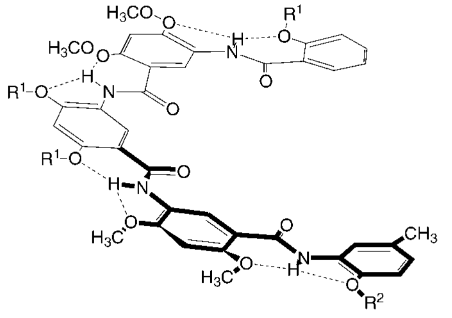
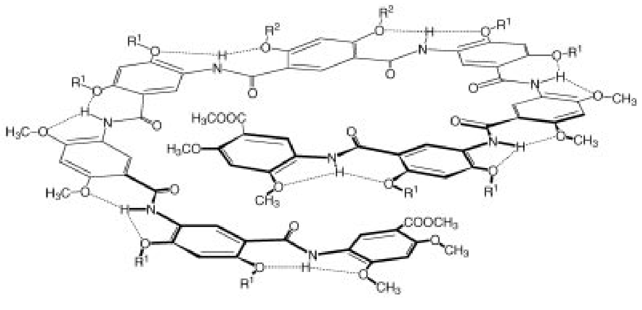


(R^1 = -$(CH_2CH_2O)_3CH_3$; R^2 = *n*-octyl)

7

Figure 6. Hydrogen bonds in **6** and **7**. NOESY spectroscopy revealed contacts between each of the amide protons and those of its adjacent R groups, and between the indicated methyl hydrogen atoms and the aromatic hydrogen atoms in the 9-mer **6**. No NOE was observed between the corresponding methyl hydrogen atoms and the aromatic hydrogen atom. These data strongly support a helical conformation for **6**.



R^1 = -$CH_2CH(CH_3)_2$; R^2 = -*n*-C_8H_{17}

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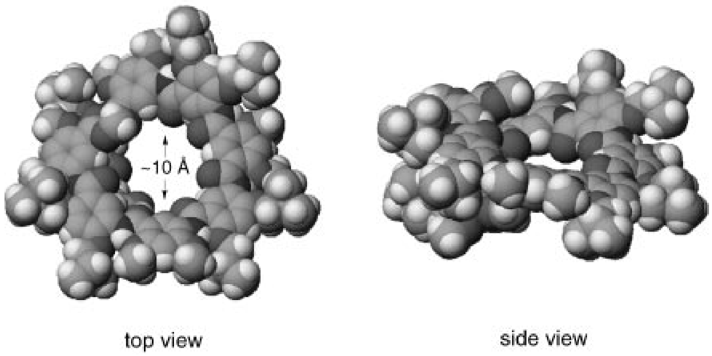

Figure 7. The crystal structure of 9-mer **8**. Both enantiomers exist in the solid state. The octyl groups are replaced with methyl groups for clarity.

Conclusion

Introduction of localized three-center hydrogen bonds into the backbones of oligoarylmides leads to a curved conformation. Consistent with our original design, experimental studies demonstrate that short oligomers such as the hexamers adopt a crescent shape, which can be viewed as a "macrocycle" with a 10 Å cavity lined with amide O atoms. These "macrocycles" may be used as a new class of hosts that may bind a variety of metal ions and small molecules. For oligomers with long enough backbones, a helical conformation was confirmed by both NMR spectroscopy and X-ray crystallography. A large cavity (≈10 Å) exists at the center of the helix. These results have thus established the feasibility of the design principles. The folded conformations are reinforced by the interplay of multiple factors: 1) the rigidification of backbones by intramolecular three-center, hydrogen bonds; 2) the rigidity of the benzene rings and the amide groups; 3) the *trans* preference of the amide bond; 4) the bond angles associated with the benzene rings and the amide groups, which introduce curvatures into the backbones, leading to the crescent and helical conformations; 5) in longer helices, possible stacking interactions between the benzene rings of adjacent helical turns. These design principles have opened a new avenue to a class of nanoporous oligomeric and polymeric materials. Nanotubes should thus result from the folding of these oligomers and polymers. Helices with larger cavities are currently being prepared. In summary, principles and strategies for constructing a class of folding oligomers and polymers with nanosized cavities have now been established. Given the current intense interest in synthetic host nanotubes, these folding "macrocycles" and nanotubes, combined with other unnatural folding oligomers we have developed,[25–27] should find numerous applications.

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