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Hollow Crescents, Helices, and Macrocycles from Enforced Folding and Folding-Assisted Macrocyclization

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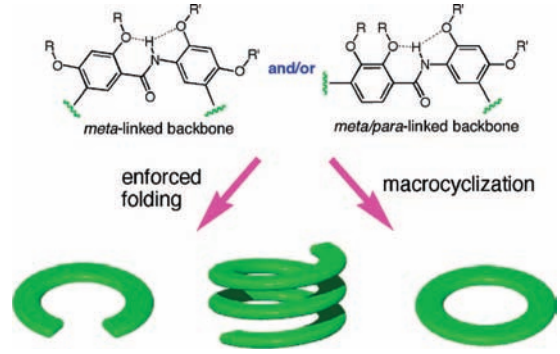
CONSPECTUS



This Account reviews the progress made by us on creating porous molecular crescents, helices, and macrocycles based on aromatic oligoamides. Inspired by natural pore- or cavity-containing secondary structures, work described in this Account stemmed from the development of foldamers consisting of benzene rings linked by secondary amide groups. Highly stable, three-center intramolecular hydrogen bonds involving the amide linkages are incorporated into these aromatic oligoamides, which, along with *meta*-linked benzene units that introduce curvatures into the corresponding backbones, leads to tape-like, curved backbones. Depending on their chain lengths, aromatic oligoamides that fold into crescent and helical conformations have been obtained. Combining results from modeling and experimentally measured data indicates that the folding of these oligomers is readily predictable, determined by the localized intramolecular three-center H-bonds and is independent of side-chain substitution. As a result, a variety of reliably folded, modifiable scaffolds can now be constructed. The well-defined crescent or helical conformations contain noncollapsible internal cavities having multiple introverted amide oxygen atoms. Changing the backbone curvature by tuning the ratio of *meta*- to *para*-linked benzene units leads to crescents or helices with cavities of tunable sizes. For example, oligoamides consisting of *meta*-linked units contain cavities of ~9 Å across, while those with alternating *meta*- and *para*-linked units have cavities of over 30 Å across. The generality of such a folding and cavity-creating strategy has also been demonstrated by the enforced folding of other types of aromatic oligomers such as oligo(phenylene ethynylene)s, aromatic oligoureas, and aromatic oligosulfonamides. More recently, the folding of aromatic oligoamides was found to assist efficient macrocyclization reactions, which has provided a convenient method for preparing a new class of large shape-persistent macrocycles in high yields. The folded and cyclic structures were extensively characterized based on multiple techniques such as one- and two-dimensional NMR, mass spectrometry, and X-ray crystallography, as well as theoretical calculations. The enforced folding and folding-assisted cyclization of oligomers have provided a predictable strategy for developing crescent, helical, and cyclic structures containing nanosized voids that are mostly associated with the tertiary and quaternary structures of proteins. The availability of these porous molecules has supplied a new class of nanosized building blocks that provide both opportunities and challenges for creating the next-generation nanostructures capable of presenting multiple introverted functional groups, forming various pores and channels, and finally, developing protein-like pockets.

Introduction

Hollow structures containing pockets and pores formed by oligopeptides and proteins are involved in numerous biological processes.[1−3] Except for a small number of hollows associated with secondary structures, most voids in Nature are associated with tertiary and quaternary structures of proteins.[3] One of the most important aspects of natural hollow structures is the exquisite complementarity between their sizes and functions and those of the corresponding guest molecules, processes, and reactions. With their complementarity, natural cavities and pores

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provide microenvironments that lead to specific binding, catalysis, transportation, and other functions. Since the discovery of crown ethers, many macrocycles have been created as hosts for various guests.[4,5] The majority of synthetic macrocycles and their acyclic analogs have flexible backbones and thus collapsible cavities. Over the past decade, substantial progress has been made in constructing molecular hosts that emulate protein pockets.[6] Examples include macrocyclic, macrobicyclic, and macrooligocyclic phanes consisting of carefully designed organic and metallic building blocks.[7] In contrast to the sophisticated pockets found at the binding, catalytic, and transporting sites of proteins, most synthetic cavities only allow little or monotonous control on their sizes and functions.

On another front, peptidomimetic oligomers that fold into secondary structures (foldamers) have attracted intense interest since the pioneering reports of Gellman[8] and Seebach[9] on β-peptides. Currently known peptidomimetic foldamers include oligomers of α-aminooxy acids,[10] γ-peptides,[11,12] δ-peptides,[13,14] and peptoid oligomers.[15] Most of these oligomers fold into secondary structures stabilized by multiple interactions that require the participation of both backbones and side chains, with the overwhelming majority being helical conformations with no cavities.

Hollow Crescents and Helices Based on Backbone-Rigidified Oligomers

While most cavities and pores are associated with the tertiary and quaternary structures, some helical oligopeptides are known to contain pores. For example, the antibiotic oligopeptide gramicidin A folds into a β-helix containing a small ($\sim$4 Å across) pore.[16] Inspired by gramicidin, we started a project in late 1998 to develop unnatural oligomers that fold into hollow helical conformations. The initial concept was simple: an oligomer having a rigid, curved backbone should adopt a crescent conformation. As its chain length extends, the two ends of such an oligomer should eventually meet. To avoid crowding, one end must lie above the other, leading to a helical conformation. In addition, the curvature of the backbone should be adjustable, resulting in crescent or helical structures containing cavities of different sizes.

At that time, few folding oligomers with rigidified backbones were known. One example involved oligomers with rodlike conformations enforced by intramolecular H-bonds.[17] Another system was reported by Hamuro et al. in 1997.[18] This system was based on (1) intramolecular H-bonds between the amide-NH and -CO groups of anthranilamide residues and (2) bending of the oligoamide backbone by incorporating two

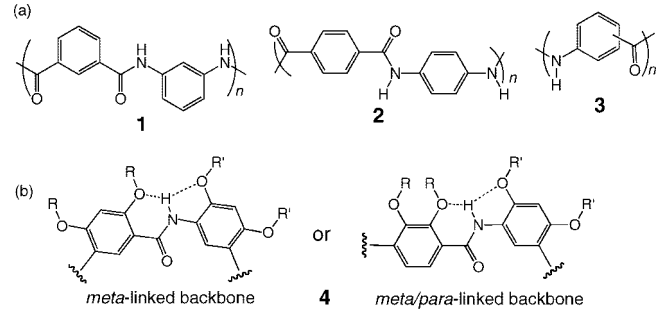


FIGURE 1. (a) Known aromatic polyamides and (b) the general structure of aromatic oligoamides that are forced to adopt defined conformation by the localized intramolecular three-center H-bond.

other residues derived from pyridine-2,6-carboxylic acid and 4,6-dimethoxy-1,3-diaminobenzene. A nonamer of this series was found to crystallize into two polymorphs, one of which had a conformation with two turns of uninterrupted helical sense and the other of which consisted of two halves of opposite handedness. The reversal of helical sense in the second polymorph was due to the interruption of an intramolecular H-bond in one of the anthranilamide residues. This work demonstrated the feasibility of enforcing folded conformations based on rigidification of backbones. However, in this system, the helical conformations contain no internal cavities. In addition, the interruption of an intramolecular H-bond cast uncertainty on the effectiveness of H-bonding in enforcing folded conformations. Another class of unnatural foldamers, based on oligo(*m*-phenylene ethynylene)s carrying polar side chains, were reported in 1997 by Nelson et al.[19] In polar solvents, the flexible hydrophobic backbones of these oligomers adopt a helical conformation containing a hydrophobic cavity of $\sim$8 Å across.

To develop helical structures containing well defined, noncollapsible cavities with tunable sizes, we based our design on aromatic oligoamides consisting of simple repeating units. The building blocks involve benzene rings carrying amino and carboxyl groups. Coupling these building blocks based on well-known amide chemistry[20] should lead to the corresponding aromatic oligoamides (Figure 1a). In fact, aromatic polyamides such as **1** (Nomex), **2** (Kevlar)), and **3** (polymers of *m*- or *p*-aminobenzoic acid) are important materials because of their superb tensile strength and good flame resistance.[21] However, these polymers are not suitable for developing folded structures because of their random conformations due to the relatively free rotation around the aryl−amide bonds. In addition, these aromatic polyamides are notoriously insoluble due to extensive intermolecular H-bonding. To address these limitations, a class of aromatic oligoamides, **4** (Figure 1b), was derived from the backbones of polymers **1**−**3**. The ether oxy-

gen atoms of **4** act as H-bond acceptors, forming a three-center H-bond with the corresponding amide H atom. The ether side chains (R and R′ groups) also help determine the solubility of the oligoamides. Obviously, the three-center H-bond shown in **4** plays a decisive role in enforcing the folded conformation and, at the same time, prevents undesired intermolecular H-bonding interactions. An oligomer containing benzene residues *meta*-linked by such amide linkages should have a rigid, bent backbone. The first paper describing our initial results was submitted in late 1999 and published in early 2000,[22] which provided the basis for the subsequent creation of many molecular crescents and helices. Later in the same year, Lehn and Huc reported an elegant system of double helical aromatic oligoamides consisting of pyridine residues and with backbones rigidified by intramolecular H-bonds.[23] Since then, oligomers with stably folded conformations enforced by intramolecular H-bonds have been extended into different systems, including those developed by us[24] and others such as the notable contributions from the groups of Huc[25] and Li.[26] Although this Account focuses mostly on our work, several other hollow helices acting as hosts have also appeared in recent years,[27–29] which demonstrate the exciting prospect of hollow foldamers.

A Robust Three-Center Hydrogen Bond

The previously unknown three-center H-bond (Figure 1b) was extensively investigated by us.[30,31] *Ab initio* calculations were carried on amide **5a** and its isomers **5b**–**d**. The results obtained revealed an obvious positive cooperativity, that is, the two two-center components of the three-center H-bond reinforce each other. For example, relative to the NH bond of **5d**, that of **5a** shows a much larger red shift in its NH stretching frequency than the NH bond of either **5b** or **5c**. The ^{1}H NMR signal of the amide proton of **5a** shows the largest downfield shift, followed by those of **5b** and **5c**, as compared with **5d**. *Ab initio* results also indicated that the NH bond of **5a** is the longest among those of the four isomers. Experimentally measured IR and NMR data closely paralleled those from the computational studies. These results are consistent with the mutual reinforcement of the two two-center components of the three-center H-bond in **5a**.

The three-center H-bond was also observed in the crystal structure of **5a** (Figure 2a), in which the NH group of **5a** is involved in a H-bonded five-membered ring and a six-membered ring, resulting in a planar arrangement typical of three-center H-bonds.[32] The intramolecular H-bond of **5b** is preserved in its solid-state structure, leading to a flat conformation. In contrast, the intramolecular H-bond of **5c**, which exists in solution as suggested by IR and NMR data, is disrupted in the solid-state structure in which the NH group is involved in intermolecular H-bonding.[31] Positive cooperativity in the three-center H-bonding in **5a** is clearly demonstrated by these results: the presence of the H-bonded six-membered ring helps the formation of the five-membered ring which would otherwise be disrupted as shown by the packing of **5c** in the solid state.[31]

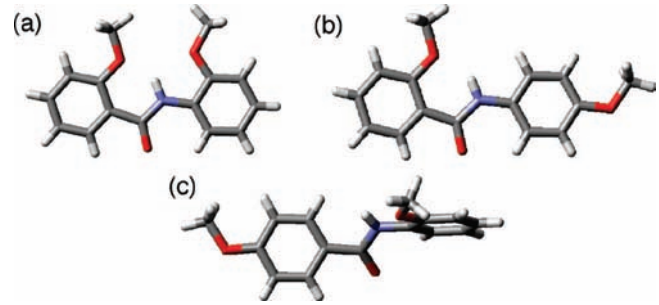
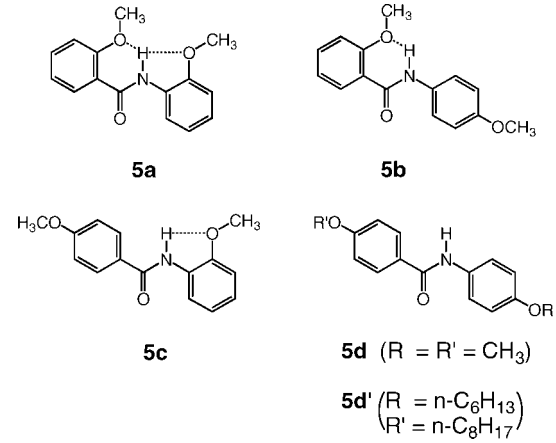


FIGURE 2. The crystal structures of (a) **5a**, (b) **5b**, and (c) **5c**.



The extraordinary stability of the H-bonded diarylamide structure was demonstrated by the nuclear Overhauser effect (NOESY) spectrum of **6** recorded in 1:1 D_2O and DMSO-d_6. The persistence of the three-center H-bond was revealed by two strong NOEs corresponding to contacts between the amide proton and those of the methoxy groups (Figure 3). Even in the presence of 50% D_2O, the amide proton of **6** underwent very slow exchange, which allowed the NOESY spectrum to be recorded. In longer oligomers, the half-lives of amide H–D exchange ranged from days to too long to be measurable by ^{1}H NMR.[31,33]

These studies confirmed the reliability of the three-center H-bond in enforcing the corresponding conformations. Aromatic oligoamides consisting of this H-bonded motif should thus have H-bond-rigidified backbones.

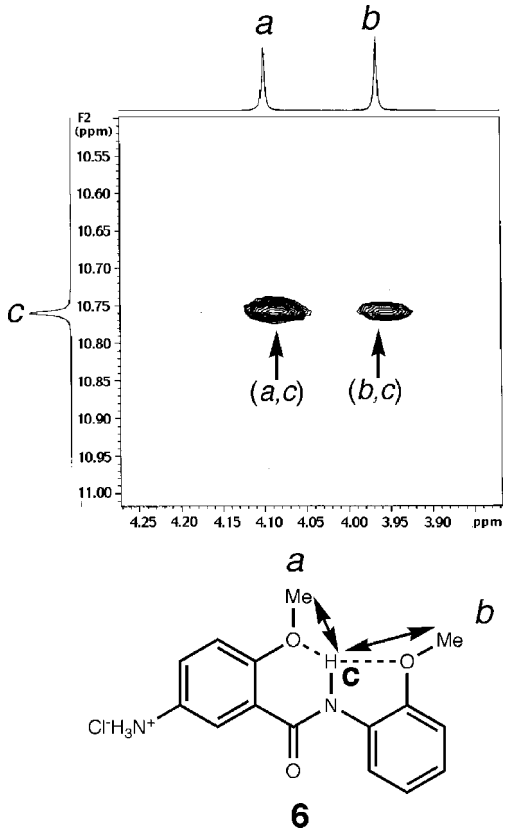
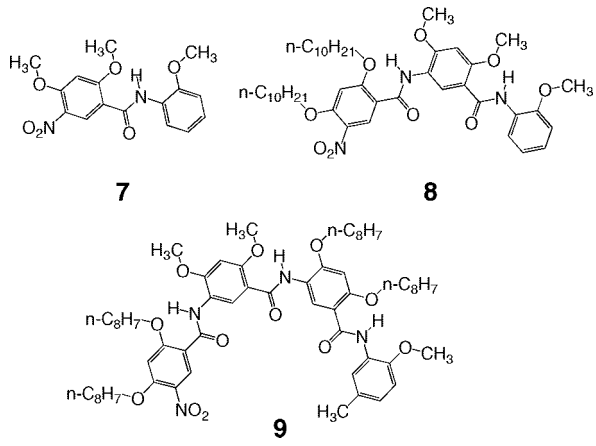


FIGURE 3. The partial NOESY spectrum of **6** (6 mM) recorded in 50% DMSO-d_6/50% H_2O (500 MHz, mixing time 0.5 s, 298 K). The NOEs are indicated by arrows.

Molecular Crescents

Stepwise coupling of monomers derived from 2,4-dialkoxy-5-nitrobenzoic acid via the corresponding acid chlorides and amines leads to dimer **7**, trimer **8**, and tetramer **9**. The terminal nitro groups of these oligomers are converted into amino groups by catalytic hydrogenation before each coupling step. These oligomers were first studied by two-dimensional ^{1}H NMR (NOESY or rotating-frame Overhauser enhancement spectroscopy, ROESY), which revealed strong NOEs between each of the amide protons and its neighboring ether side chain.[31,33,34] The amide−side chain NOEs have been consistently detected for homologous oligoamides of various lengths. For example, the NOESY spectrum of tetramer **9** recorded in $CDCl_3$ shows three cross peaks for each of the amide protons, corresponding to contacts with protons of the methyl, α-, and β-methylene groups of the adjacent side chains (Figure 4). The same amide−side chain NOEs were also detected in aqueous media and have since served as a reliable indicator of the three-center H-bond, which reflects the rigidification and the folding of the corresponding oligomers in solution.



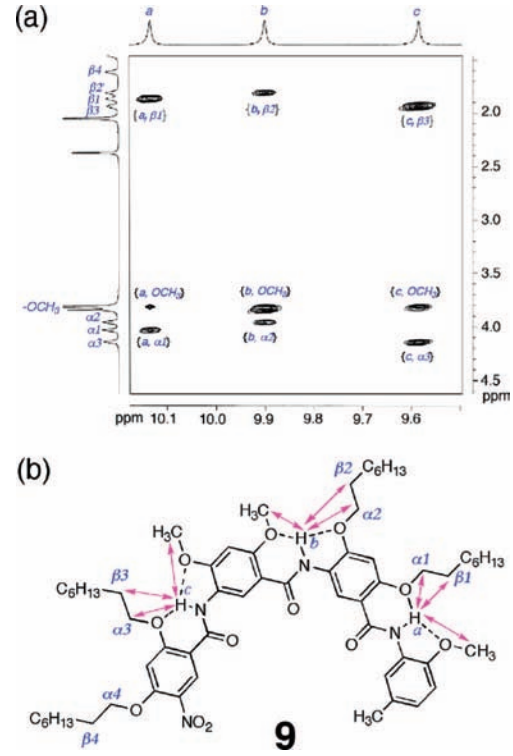


FIGURE 4. The partial NOESY spectrum of tetramer **9** recorded in $CDCl_3$ (50 mM, 800 MHz, 300 K, mixing time 0.3 s). NOEs between the amide protons and the protons of the side chains are indicated by arrows.

The crescent shapes of oligomers **7**, **8**, and **9** were revealed by their crystal structures.[31,33,34] As shown in Figure 5, the amide groups of these oligomers are all involved in three-center H-bonding, leading to backbones that are almost completely planar due to the presence of their three-center H-bonds. In these solid-state structures, no intermolecular H-bonding interaction exists since all amide hydrogens are "saturated" by participating in three-center H-bonding interactions.

These results indicate that each of the oligoamides has a convex edge bearing its ether side chains and a concave side carrying inward-pointing amide oxygen atoms. In addition to stabilization from the three-center H-bonds, the very likely

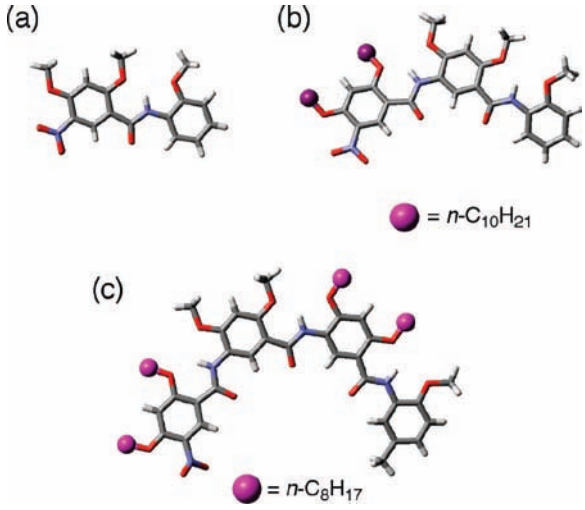


FIGURE 5. The crystal structures of (a) dimer **7**, (b) trimer **8**, and (c) tetramer **9**.

C−H···O attractive interactions[35] between the amide oxygen atoms and the inward-pointing aromatic hydrogen atoms should provide further stabilization to the crescent conformations. Thus, the reliability of the three-center H-bonds in rigidifying the oligoamide backbone is once again demonstrated by the well-defined, crescent conformations of oligomers **7**−**9**. Further extension of such backbones should lead to oligomers that fold into "broken macrocycles", that is, noncyclic oligomers with nearly enclosed cavities and helices that contain lumens with multiple inward-pointing amide oxygens.

Hollow Helices

An aromatic oligamide with a sufficiently long (≥7 units) backbone should fold into a helical conformation due to the crowding of its two ends, which requires one end to lie above the other. It was not clear whether the H-bond-rigidified backbone could tolerate the strain posed by such crowding. If not, the presumed helical conformation would be interrupted.

The folding of nonamer **10a** (Chart 1) was examined by recording its NOESY spectrum.[34] In addition to the presence of numerous amide−side chain NOEs characteristic of the three-center H-bonds, the NOESY spectrum of **10a** also revealed a strong cross peak between the protons of the end methyl (Me) groups and aromatic proton *b1*, along with a much weaker cross peak between the methyl and amide proton *b* (Figure 6). The ^{1}H NMR signal of the end methyl groups appears in a region (around 2.1 ppm) where no other signal is present and serves as a convenient spectroscopic label for assigning the 1D and 2D spectra. The symmetrical structure of **10a** means that the observed Me···*b1* or Me···*b* cross peak actually corresponds to two identical remote NOEs. Given that the NOESY spectrum of pentamer **11** (∼half of **10a**) failed to reveal any contact between the protons of its end methyl group and proton *b1* or *b*, the observed NOEs for **10a** can only be explained by its adopting a helical conformation. The same remote NOE was also detected in a mixed solvent with up to 50% DMSO-d_6 in $CDCl_3$, suggesting that **10a** was folded in this polar solvent. Subsequent studies showed that the Me···*b1* NOE was also associated with other nonamers that differed from **10a** only in their side chains, indicating that the folding of these oligomers was independent of side chains.[33]

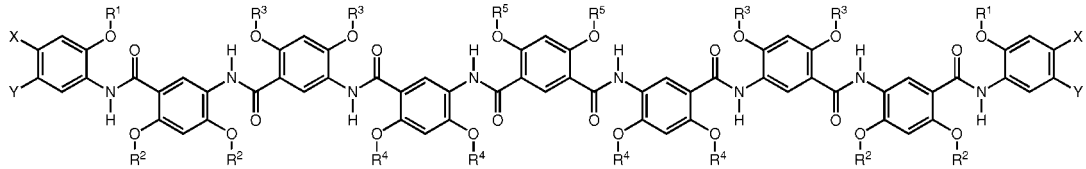
The crystal structure of nonamer **10b** reveals a helical conformation that is fully consistent with the 2D NMR results (Figure 7). The helical structure has a cavity (∼10 Å across) containing disordered water and DMF molecules, with about 6.5 residues to make a helical turn. In this crystal structure, none of the three-center H-bonds are disrupted, although some of the H-bonded five-membered rings are more distorted than the six-membered ones.[34]

Variable-temperature NOESY experiments performed on **10a** showed that the Me···*b1* NOE diminished more rapidly than the amide−side chain NOEs, suggesting that the rigidified backbone was quite resilient toward heating.[33] Most likely, this molecule contracts and extends like a spring while maintaining its overall helical conformation.

The above nine-unit, one-turn helices have very short overlapping segments of approximately two units. Due to the rigidity of the oligoamide backbone, oligomers with a length well beyond one helical turn may not fold properly due to too much strain. To address this uncertainty, undecamer **12a** was synthesized and studied using NOESY in $CDCl_3$.[33] Numerous amide−side chain NOEs were detected, consistent with a three-center H-bond-rigidified backbone. In addition, three sets of long-range NOEs (Figure 8a) were detected for **12a**. These remote NOEs were not found in the NOESY spectrum of hexamer **13** that is about half of**12a**, supporting a helical conformation adopted by **12a**. For nonamers **10** and undecamer **12**, aromatic stacking between the two ends of the corresponding molecules may provide further stablization to the folded conformations.

The rigidity of aromatic rings and amide groups, along with the localized three-center H-bonds, leads to a well-defined basic structural motif (the diarylamide moiety). The folding of an oligomer can be regarded as the combination of all local conformational preferences. Based on these considerations, average structural parameters such as bond lengths, bond angles, and distances between remote atoms were retrieved from the crystal structures of short oligomers that were readily crystallized.[31,33,34] Using these parameters as structural con-

CHART 1



10a: R^1 = n-C_8H_{17}, R^2 = R^4 = CH_3; R^3 = R^5 = $(CH_2CH_2O)_3CH_3$; X = H, Y = CH_3

10b: R^1 = R^3 = -CH_3; R^2 = R^4 = -$CH_2CH(CH_3)_2$; R^5 = n-C_8H_{17}; X = -OCH_3; Y = $COOCH_3$

straints, a computer modeling method was developed to predict the folded conformations of homologous oligomers.[33] Figure 8b shows one such energy-minimized structure of undecamer **12b** that shares the same backbone with **12a**. The modeled structure of **12b** was then examined against the multiple long-range NOEs found in the NOESY spectrum of **12a**. It was found that the modeled structure not only was consistent with the measured NOEs but also explained the relative intensities of these NOEs. Similarly, a model of a nonamer also fully matched the remote NOEs observed for **10a**.

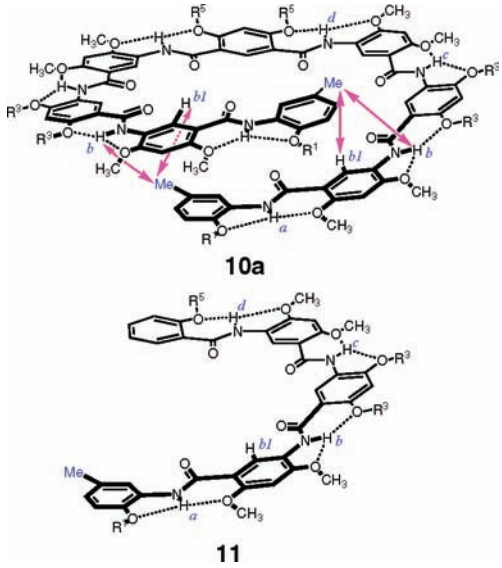


FIGURE 6. Remote NOEs (arrows) revealed by the NOESY spectra of nonamer **10a** (recorded in $CDCl_3$ or $CDCl_3$/DMSO-d_6 (1/1, v/v)) are consistent with the helical conformation shown. The NOEs were not found in the NOESY spectra of pentamer **11**, which can be regarded as half of **10a**.

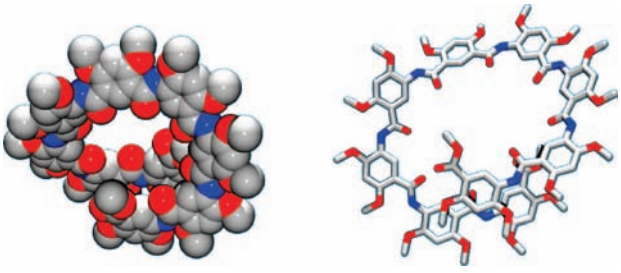


FIGURE 7. The crystal structure of nonamer **10b** (left, space-filling model; right, stick model). The side chains are replaced with methyl groups for clarity.

These results confirmed the reliability of the modeling method, which should be generally applicable to the prediction of the folded conformations of longer aromatic oligoamides. This method should be particularly valuable for oligomers to which characterization methods such NMR and X-ray crystallography fail to apply.

By keeping the same three-center H-bonds while incorporating building blocks that place the amide linkages in a *para* relationship on a benzene ring, the curvature of the backbone of an oligomer should be decreased. For example, compared with *meta*-linked oligomers, those consisting of alternating

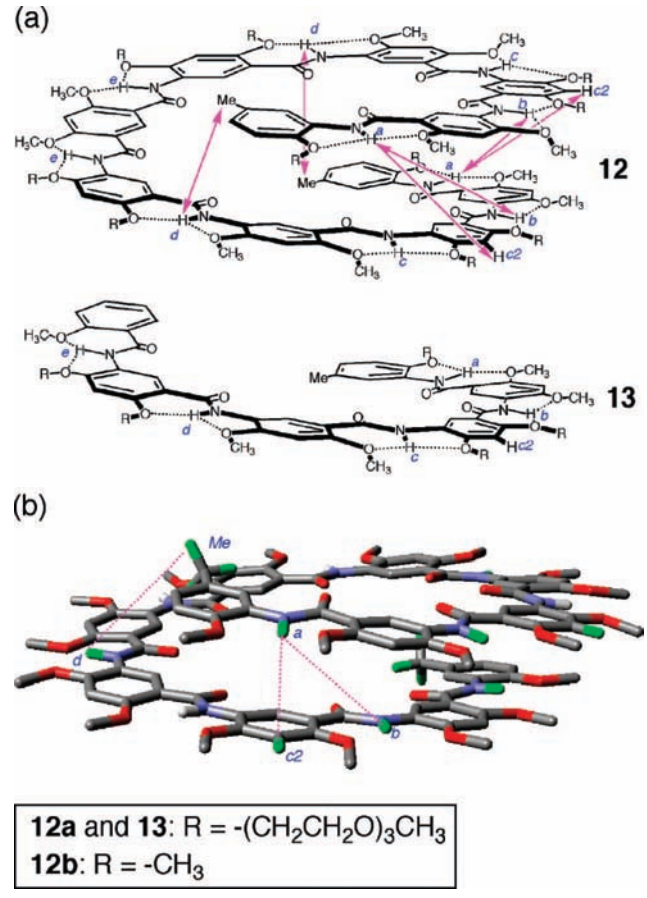


FIGURE 8. (a) Remote NOEs (purple arrows) revealed by the NOESY spectrum of undecamer **12**. These NOEs are not found in the NOESY spectrum of heptamer **13**. (b) Computer-modeled structure of **12b** based on structural parameters retrieved from the crystal structures of shorter oligomers.

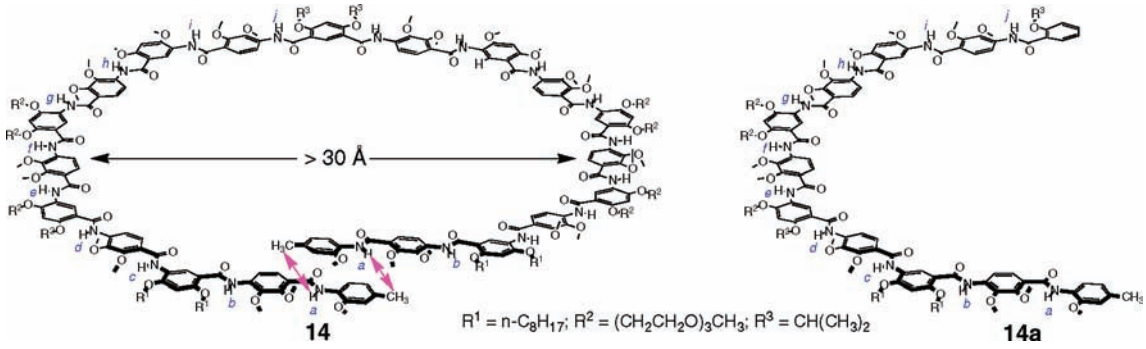


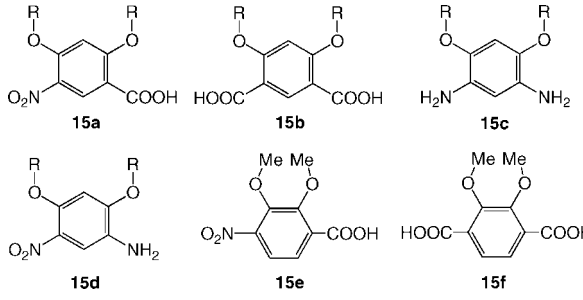
FIGURE 9. (a) Remote NOEs revealed by the NOESY spectrum of **14** (recorded at 20 °C, 1.3 mM in 53% DMSO-d_6 in $CDCl_3$). The helical conformation of **14** is consistent with the NOEs (arrows). (b) The NOESY spectrum of undecamer **14a** does not contain this NOE.

meta- and *para*-linked amide residues should be less curved, which leads to an increase of the diameters of the corresponding crescent or helical amides. Thus, the helical conformation of 21-mer **14** in solution was probed by its NOESY (Figure 9), which revealed a remote NOE corresponding to two identical contacts between the end methyl and the first amide protons *a*. This NOE was not observed in the NOESY spectrum of decamer **14a** which was half of **14**. Computer modeling showed that this helix had an interior cavity of >30 Å across.

By changing the ratio of the *meta*- and *para*-linked residues, it is straightforward to systematically tune the cavities of the corresponding crescent and helical oligomers. Such a strategy is seen in few natural or unnatural systems and has profound significance since it provides a convenient method for creating large cavities of different sizes.

Coupling Chemistry

Highly efficient preparation of different building blocks **15a**–**f** have been established in our laboratory or by modifying previously reported procedures.[36]



Based on these building blocks, efficient coupling methods for forming the backbone-rigidified oligoamides in solution have been developed.[36] The oligoamides were synthesized by stepwise coupling of the monomer building blocks based on acid chloride chemistry. The resulting nitro-terminated intermediates were hydrogenated into the corresponding amino-terminated oligomers that were subjected to the next coupling cycle. To reduce the number of coupling steps, a convergent route was also adopted. Among the coupling methods, the one involving acid chlorides and amino-terminated monomers or oligomers has consistently resulted in the best yields.

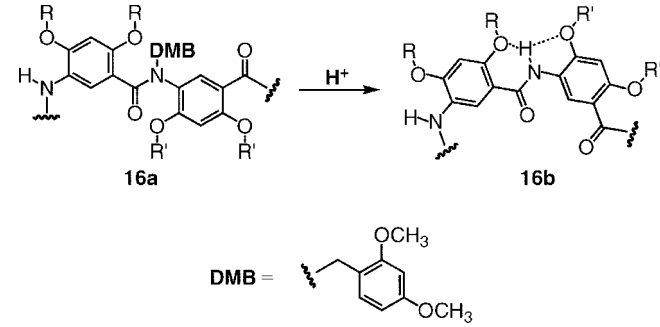
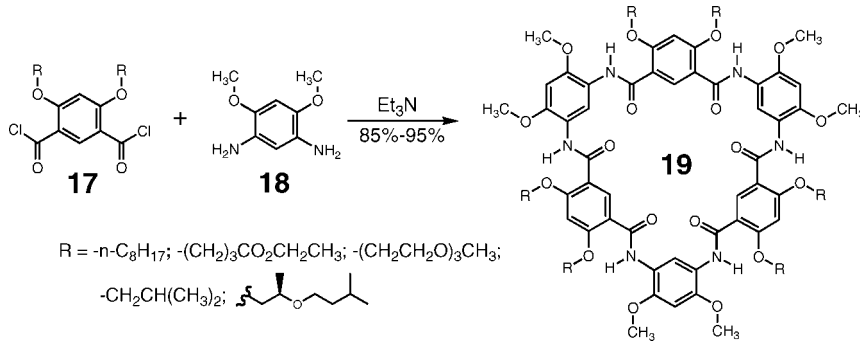


FIGURE 10. Temporary interruption of backbone-rigidifying H-bond by the DMB group leads to oligomer shown as **16a**. The folded conformation is restored for **16b** by removing the DMB group using an acid.

It was found that the coupling of oligomeric building blocks became increasingly slow and inefficient as the length of an intermediate increased, most likely due to the steric hindrance imposed by helical conformations. For example, coupling an amino-terminated hexamer with a monomeric 4,6-dialkoxyisophthaloyl chloride led to the corresponding tridecamer in a very poor (3.7%) yield.[37] To alleviate the steric hindrance, the amide H atom was replaced with the acid-labile 2,4-dimethoxybenzyl (DMB) group, which blocked the three-center H-bond (**16a** in Figure 10). Removing the DMB group with an acid should restore the H-bond, leading to the H-bonded conformation (**16b** in Figure 10). It was found that the incorporation of the DMB groups led to a significant improvement of coupling yields. For example, by coupling an amino-terminated hexamer containing the DMB groups to a monomeric isophthaloyl chloride, a symmetrical tridecamer was isolated in 33% overall yield after removing the DMB groups.[37] Using this method, *meta*-linked oligomers with up to 15 residues (~2.5 turns) were successfully prepared in solution.

SCHEME 1



Folding-Assisted Macrocyclization

Based on results from oligomers, aromatic polyamides with backbones rigidified by the three-center H-bonds should also be forced to adopt helical conformations, leading to long hollow helices. To prepare helical polymers, diacid chlorides **17** was treated with diamine **18** in the presence of triethylamine (Scheme 1). Instead of forming long polymer chains, MALDI-TOF indicated that the six-unit macrocycles **19** were obtained in high yields from this one-pot reaction.[38] The efficient formation of the macrocycles was confirmed by purifying and characterizing the products. Macrocycles with a variety of different side chains have been obtained in excellent yields. This discovery has provided an efficient method for preparing a new class of shape-persistent macrocycles.

Macrocycles **19**, with their well-defined cavity containing six amide oxygen atoms, were found to specifically recognize the guanidinium ion.[39] In the presence of the guanidinium and numerous other cations, only the guanidinium ion was complexed by **19**. Molecular modeling shows that the guanidinium ion fits snuggly inside the cavity by forming six H-bonds with the introverted amide oxygen atoms. The observed host−guest interaction demonstrates the promising prospect of designing highly specific receptors based on functionalized, noncollapsible cavities.

The simplicity and high efficiency of our method are in contrast to many other strategies for preparing large macrocycles, which usually lead to low yields due to the entropically disfavored nature of the macrocyclization process. To improve the efficiency of macrocyclization reactions, many strategies such as noncovalent or covalent templation, intramolecular ring closure, and dynamic covalent bond formation, have been proposed and probed with various successes and limitations.[40,41]

The one-step reaction shown in Scheme 1 raises interesting mechanistic questions. The efficient formation of **19** was rationalized by the preorganization of uncyclized precursors that fold into a crescent conformation. When a length with six units is reached, the precursor, with its two reactive ends being brought into close proximity by the curved backbone, cyclizes into the corresponding macrocycle. However, such a folding-assisted picture does not account for the observed high yields of the macrocyclization reaction given the irreversible nature of amide bond formation. It is still unclear why few acyclic oligomers longer than the precursors of the six-unit macrocycles were observed. The nearly exclusive formation of **19** demands that the immediate precursors of the macrocycles are not skipped in the chain growth process. Such a process, however, contradicts a polycondensation mechanism in which all species (monomers or oligomers) have equal reactivity. Efforts are being made to elucidate the corresponding mechanism.

It was found recently that treating a *meta*-diamine with a *para*-diacid chloride led to nanosized macrocycles with 14, 16, and 18 residues in high (>85%) overall yield.[42] Compared with the formation of macrocycles **19**, the formation of these larger macrocyles is entropically much more costly, which would lead to very low yields without the preorganization of the corresponding oligomer precursors. The high efficiency of these one-pot cyclization processes has demonstrated the generality of folding-assisted macrocyclization for forming very large macrocycles. This concept is currently being applied to the preparation of other macrocycles.

Enforced Folding of Other Unnatural Oligomers

Oligomers with non-amide backbones have also been forced to fold or cyclize into hollow structures. For example, oligo(*m*-phenylene ethynylene)s (oligo(*m*-PE)s, **20**, Figure 11a) were forced to adopt crescent or helical conformations by intramolecular H-bonds.[43,44] The presence of an intramolecular H-bond limits the otherwise nearly free internal rotation (0.6 kcal mol^{-1}) of the diphenylacetylene unit, leading to a rigidified backbone. *Ab initio* calculation indicates that **20a** adopts a planar conformation that is rigidified by its intramolecular

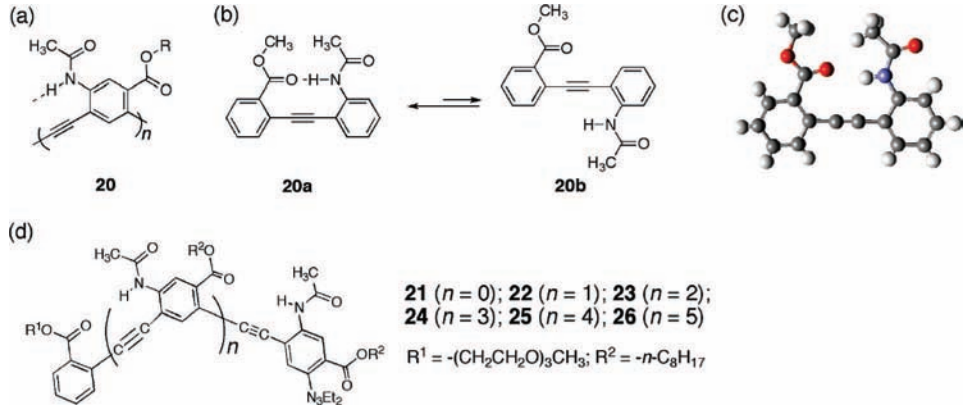


FIGURE 11. (a) Backbone-rigidified *m*-PE foldamers, (b) energies of **20a** and **20b** based on *ab initio* calculation, (c) the crystal structure of **20a**, and (d) oligo(*m*-PE)s **21**−**26** prepared and characterized.

H-bond. Deviation from the planar conformation of **20a** by interrupting the intramolecular H-bond leads to a rapid increase in energy. The H-bonded **20a** is 5.8 kcal/mol more stable than **20b** (Figure 11b). A rotational barrier of 7.19 kcal/mol exists between conformers **20a** and **20b**. The conformation of **20a** was confirmed by its crystal structure (Figure 11c), in which the intramolecular H-bond leads to a planar conformation.

Oligo(*m*-PE)s **21**−**26** were synthesized by stepwise, Pd-catalyzed (Sonogashira) coupling. These oligomers were then characterized using 1D and 2D ^{1}H NMR and UV spectroscopy. It was found that pentamer **24**, hexamer **25**, and heptamer **26** adopted well-defined helical conformations in chloroform, a solvent in which *m*-PE oligomers bearing polar side chains but lacking backbone-rigidifying H-bonds were found to denature.[19] These backbone-rigidified oligo(*m*-PEs) have provided another system of oligomers with predictable folding and conformations containing noncollapsible cavities.

Aromatic oligoureas were also forced to fold by intramolecular H-bonds.[45] NMR study revealed a crescent conformation for tetramer **27**. Macrocycle **28** was prepared in high yield from the corresponding linear precursor or from the dimerization of two dimers. Obviously, the cyclization leading to **28** was assisted by the preorganization of backbone. Macrocycle **28**, with its small, oxygen-rich cavity, showed high specificity toward the potassium ion.

In an attempt to direct the folding of aromatic oligosulfonamides, a series of tetrasulfonamide macrocycles adopting a cone-shaped conformation was discovered instead.[46,47] Tetrasulfonamides consisting of benzene and naphthalene residues maintain the same conformation but contain cavities of different sizes, as shown by the crystal structures of cyclic tetrasulfonamides **29a** and **30a** (Figure 12). These molecules are reminiscent of calix[4]arenes. NOESY spectra of **29b** and **30b** indicate that the cone-shaped conformations also persist in

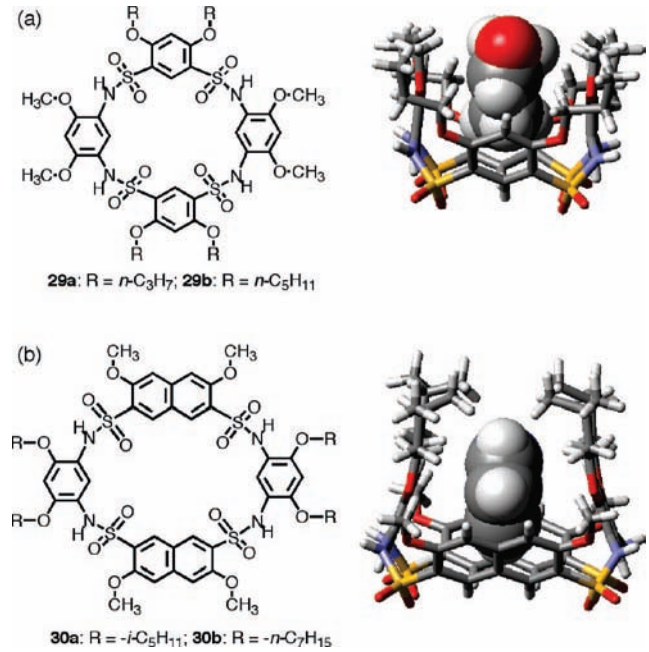
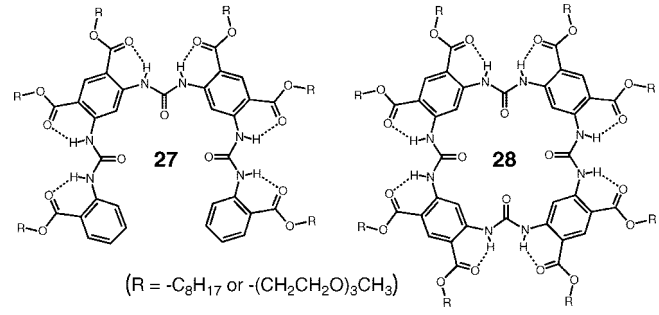


FIGURE 12. Tetrasulfonamide macrocycles (a) **29a**,**b**, along with the crystal structure of **29a**, and (b) **30a**,**b**, along with the crystal structure of **30a**. The DMF molecule in the cavity of **29a** and the pyridine molecule in the cavity of **30a** are shown in space-filling model.



solution. A DMF molecule is found in the cavity of **29a** (Figure 12a), while a pyridine molecule sits in the cavity of **30a** (Figure 12b). These readily modifiable, cavity-containing molecules provide the basis for designing new hosts and present

an example of unexpected yet interesting discovery often associated with scientific endeavors.

Conclusions and Remaining Challenges

The creation of hollow structures based on the enforced folding of aromatic oligomers has now been established as a reliable, general strategy that is applicable to a wide variety of unnatural oligomers. In these systems, intramolecular H-bonds play the critical role in enforcing the folded conformations. The three-center H-bonds associated with aromatic oligomamides and analogous oligomers have turned out to be particularly robust and effective in enforcing well-defined conformations. The ability to tune the curvature of a rigidified backbone has provided a systematic approach for the creation of crescents, helices, and macrocycles with different cavity sizes. The recently discovered folding-assisted macrocyclization has provided a powerful method for preparing new shape-persistent nanosized macrocycles. These hollow molecular structures, with their persistent shape, should provide a class of nanoscale building blocks based on which nanoporous structures capable of eventually mimicking the functions of protein pores and cavities will be created. Despite our progress, additional challenges remain. For example, efficient methods for preparing long oligomers still need to be developed. Strategies for aligning the hollow structures into well-defined supramolecular assemblies are lacking. Another challenge is the functionalization of the cavities and pores. Addressing these challenges requires a multidisciplinary effort, which eventually will lead to protein-like, functional voids.

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BIOGRAPHICAL INFORMATION

Bing Gong received his bachelor's degree in chemistry from Sichuan University in China in 1984. He attended the University of Chicago for his graduate education under the supervision of Professor David Lynn and received his Ph.D. in 1990. He was then trained in the laboratory of Professor Peter Schultz as a Damon Runyon-Walter Winchell Fund Postdoctoral Fellow at the University of California, Berkeley. In 1994, he began his independent academic career. Currently he is Professor of Chemistry at the State University of New York at Buffalo. He is interested in controlled folding and directed self-assembly of biomimetic structures.

FOOTNOTES

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