ACCOUNTS
of chemical research

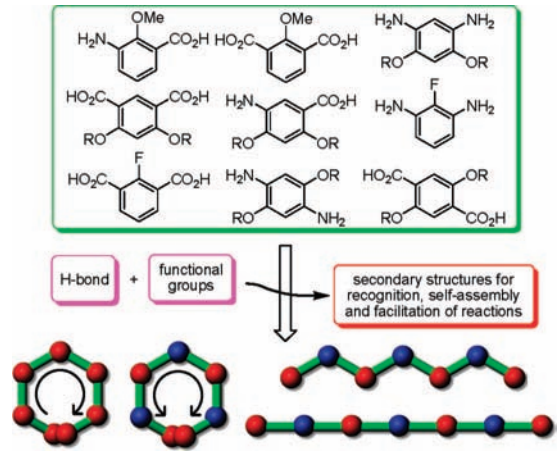
Peptide Mimics by Linear Arylamides: A Structural and Functional Diversity Test

ZHAN-TING LI,* JUN-LI HOU, AND CHUANG LI

State Key Laboratory of Bio-Organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

RECEIVED ON OCTOBER 6, 2007

CONSPECTUS



Hydrogen-bonded oligoamide foldamers represent a large family of peptide mimics. Pioneered by Gellman and Seebach (Appella, *J. Am. Chem. Soc.* 1996, *118*, 13071−13072; Seebach, *Helv. Chim. Acta* 1996, *79*, 913−941), aliphatic amino acid-based mimic structures have been extensively studied. Results of these studies have found many useful applications in areas including chemical biology and drug design. This Account describes our efforts in creating arylamide-based foldamers whose compact conformations are stabilized by hydrogen bonding. The aim of our study was to test whether this class of mimic structures is sufficiently rigid to lead to new interesting functions. It was envisioned that, if our approach was workable, it might be developed into a new family of useful soft frameworks for studies toward molecular recognition, self-assembly, and materials science. Three classes of mimic structures, that is, folded or helical, zigzag, and straight oligomers, have been constructed by simply changing the positions of the substituents at the benzene rings in the backbones. Both amide and hydrazide units have been employed to construct the frameworks. In most cases, O···H−N hydrogen bonding was chosen to stabilize the compact conformations. Notably, for the first time the F···H−N hydrogen-bonding pattern has been used to tune the size of the cavity. To test their usefulness, these frameworks have been extensively modified and functionalized. ^{1}H NMR, UV–vis, fluorescence, circular dichroism, and X-ray diffraction techniques have all been employed to establish the compact structures and their interactions with guest molecules.

The properties or functions of the mimic structures have been studied in seven aspects. (1) Acyclic molecular receptors: The amide foldamers can bind amine cations, while the hydrazide foldamers can complex saccharides. (2) Acceleration of anisole hydrolysis: Several folded oligomers are able to bind alkali metal cations and consequently promote the hydrolysis of the nitro-substituted anisole by alkali hydroxides. (3) Facilitation of macrocyclization: The straight and zigzag backbones can be readily functionalized, from which two classes of macrocycles have been prepared. (4) Homoduplex assembly: Zigzag oligomers that are appended with amide units at one side can form stable homoduplexes through the cooperative self-binding of the amide units. (5) Assembly of molecular tweezers: Discrete binding moieties are introduced at the ends of the oligomers, which can bind structurally matched guests. (6) Assembly of nano networks: F···H−N hydrogen-bonded foldamers can stack with fullerenes; thus a mixture of fullerenes with a trifoldamer generates honeycomb-styled nanoarchitectures. (7) Assembly of dynamic [2]catenanes: A preorganized porphyrin tweezer has been synthesized, from which dynamic three-component [2]catenanes have been assembled in high yields.

Our results demonstrate that hydrogen-bonding-driven arylamide oligomers are a class of structurally unique mimic structures. The folded oligomers themselves can be used as synthetic receptors for binding different guest molecules, while incorporation of different segments into one system can produce many desired shapes. In addition, all of the rigid frameworks can be readily functionalized at specific sites. We believe that our results have helped to open the door for some new chemistry in molecular recognition, self-assembly, and other related areas.

Published on the Web 03/25/2008 www.pubs.acs.org/acr
10.1021/ar700219m CCC: $40.75

Introduction

One primary goal in research on peptide mimics is to understand the rules that dominate the structure–property relationship of peptides and proteins. Because natural molecules are mainly composed of α-amino acids, most efforts in this field have been devoted to the creation of mimic structures with various aliphatic β-, γ-, or δ-amino acid segments. The progress achieved so far has been great, leading already to wide applications of the mimicking systems in biomolecular design and drug development. Oligomers consisting of arylamide units represent another family of mimic structures that have also aroused considerable interest in recent years. Since stable folding conformations are prerequisite to the formation of the three-dimensional structures and functions of peptides and proteins, mimic structures that have strong tendency to adopt similar compact states have received particularly great attention.[1–5] Pioneered by Gellman and Seebach,[6,7] studies on such oligoamides have developed into a new field of "foldamers", as coined by Gellman.[2]

One promising class of foldamers are those composed of arylamide segments and stabilized by intramolecular hydrogen bonding.[8–11] As a result of the directionality of the hydrogen bonding and the intrinsic rigidity and planarity of the arylamide units, mimic structures of this class usually display a relatively high conformational predictability. The first example of arylamide-based foldamers was reported by Hamilton et al. in 1996.[12] Since then, Lehn, Gong, Huc, and others have developed many elaborate frameworks starting from different arylamide segments that are stabilized by discrete hydrogen-bonding patterns.[13–19] As more structurally elegant frameworks are created, it becomes increasingly likely to design systems that are capable of exhibiting tailored functions. For example, several pyridine-derived foldamers have been utilized to mimic the binding surfaces of protein helices.[19] Our efforts in this field have been concentrated on the investigation of the structure–property relationship by designing new arylamide-based frameworks. We logically viewed this strategy as a new approach to mimicking the secondary structures and, more importantly, functions of natural peptides. The strategy has been proven successful and allowed us to create a variety of molecular receptors, synthetic methodologies, self-assembling patterns, and nanoscaled architectures. These results are summarized in this Account.

Design Consideration

In 2002, we became motivated to search for new forms of artificial secondary structures. In particular, we hoped to construct frameworks that are capable of exhibiting interesting functions such as recognition, self-assembly, or catalysis, that are common for peptides and proteins. Studies on the recognition behavior of linear molecules may be traced back to as early as the 1970s, when Vögtle and Weber investigated the complexing properties of oligo(ethylene glycol) derivatives toward metal ions.[20] In 2000, Lehn et al. reported a new linear oligo-isophthalamide strand that folded to bind a cyanuric acid derivative.[21] However, from the standpoint of molecular recognition, flexible receptors may not be the most ideal because their conformations become confined upon binding, producing important negative entropy. Also in 2000, Moore et al. showed that hydrophobically driven oligo(*m*-phenylene ethynylene) foldamers could bind guests of complementary size and shape.[22] The depth of the cavity produced by this family of foldamers can be regulated by changing the length of the backbones,[23] but the width of the cavity seems quite difficult to modify. We have devoted our efforts to hydrogen-bonded arylamide oligomers, which are relatively easy to synthesize and modify. Another consideration was that by simply changing the positions of functional groups in the segments, we could create oligomers of other extended conformations, as shown in an earlier report by Hamilton et al.[19]

There are two main classes of monomeric building blocks that can be used to construct arylamide oligomers. One class is various aryl amino acids, which resemble natural α-amino acids, giving rise to backbones of one-way sequence. Another class consists of a combination of aryl diamines and diacids, from which symmetric oligomers are constructed. Both classes of oligomers can be readily prepared by successive amide couplings, as for the synthesis of natural peptides. Nevertheless, compared with those of the one-way sequences, ^{1}H NMR spectra of the symmetric oligomers are significantly simplified, which is advantageous for the structural characterization of longer oligomers.

The design concept for our self-organized frameworks is presented in Figure 1. The folded backbones are structurally common, but they have been designed to generate well-defined cavities with potential binding sites, such as MeO, F, or C═O units, in the central area. The zigzag and straight backbones may be conceptually regarded as an extension of the common "folded" foldamers. Benzene-derived monomers were chosen for all the frameworks, because their intramolecular five- and six-membered hydrogen-bonding motifs are well-established.[8,9] Further modifications of both backbones and side chains can be readily performed at different positions, as indicated in Figure 1 by arrows.

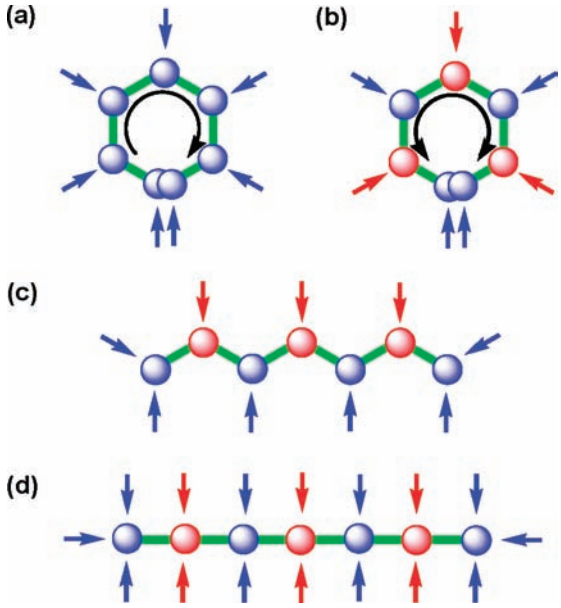


FIGURE 1. Self-organized arylamide frameworks (all with heptamer as an example) for the structural and functional diversity test: (a) one-way folded oligomers, consisting of the identical monomer segments, and symmetric (b) folded, (c) zigzag, and (d) straight oligomers, consisting of two different monomer segments. The balls represent aryl units, and the arrows show the positions where modifications may be performed.

Acyclic Molecular Receptors

In the past decades, crown ethers and cyclophanes have been widely studied as synthetic receptors. Moore et al. have shown that folded *m*-phenylene ethynylene oligomers complex some neutral organic guests through hydrophobic interactions.[23] We have developed several series of hydrogen-bonding-induced foldamers that possess cavities of defined size, as exemplified by compounds **1**–**4** (Chart 1).[24–27] The compact conformations of these oligomers have been characterized by a combination of X-ray analyses of model compounds and various (2D) ^{1}H NMR experiments. For **2**, **3b**, and **4**, intramolecular cross-ring nuclear Overhauser effect (NOE) connections were observed, as shown in **2**, which provide convincing evidence for their helical conformations.

The six methoxyl groups of **1** are located at the central region due to successive intramolecular hydrogen bonding.[24] Fluorescent experiments showed that in chloroform **1** formed a 1:1 complex with ammonium cation **5** or **6**. Their association constants (K_a's) have been estimated to be 200 and 150 M^{-1}, respectively. The binding has been attributed to intermolecular C═O···H−N hydrogen bonding and cation−π interactions. The stabilities of the complexes are moderate. Obviously, the presence of centrally orientated methyl groups is unfavorable for binding (Figure 2).

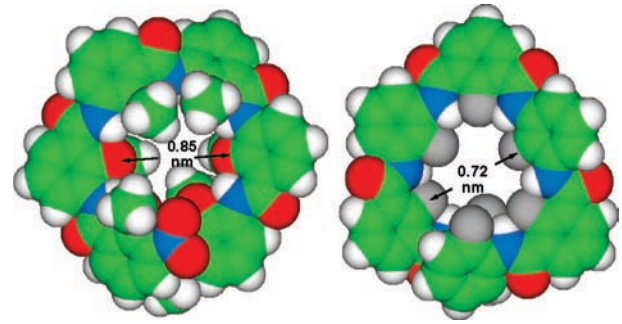
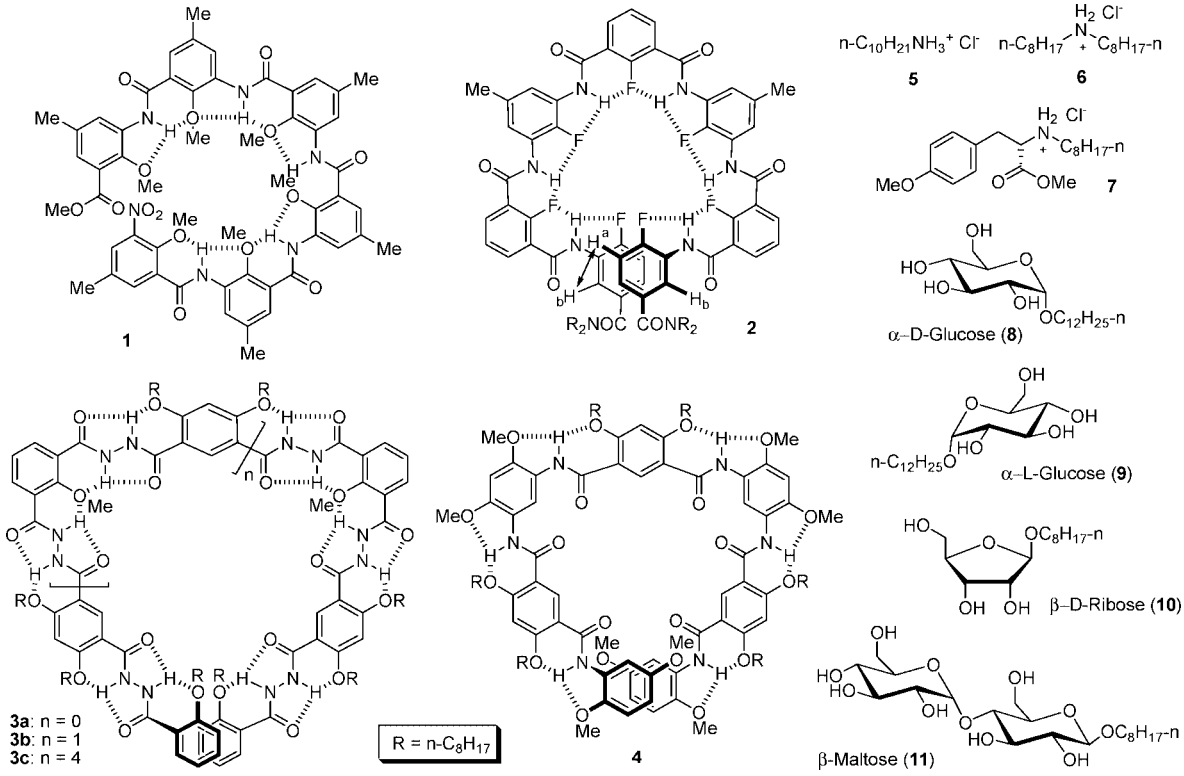


FIGURE 2. Energy-minimized conformations of hydrogen-bonded six-mer **1** (left) and seven-mer **2** (right). The appended groups are removed for simplification.

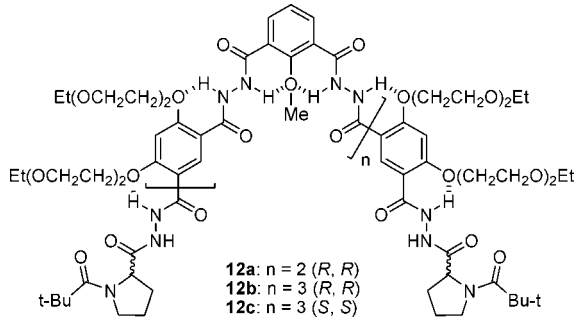
If the methoxyl groups in foldamer **1** are replaced by groups that are smaller but are still able to form intramolecular hydrogen bonds, the resulting structures may exhibit an enhanced binding ability for ammonium ions. Fluorine appeared to be the choice for this purpose. Somewhat surprisingly, early studies have suggested that fluorine in organic molecules has only a weak ability to serve as proton acceptor.[28] In order to test this hypothesis, the solid-state structures of several model molecules have been obtained,[25,29] which showed that both five- and six-membered F···H−N hydrogen bonds occur between their adjacent fluorines and amides. Encouraged by this observation, we first chose to use 5-alkylated 2-fluoro-3-amino-benzoic acids to construct one-way oligomers that are similar to **1**. Unfortunately, the corresponding amide intermediates were obtained in very low yields (usually <10%), presumably due to the low reactivity of the amino groups. Symmetric oligomers, including **2**, were therefore designed and prepared.[25] Dynamic modeling revealed that this class of folded structures did possess an enlarged cavity (Figure 2), although the fluorine-defined cycle was smaller than its oxygen-defined counterpart in **1**. Fluorescent experiments indicated that in chloroform **2** exhibited a remarkably high binding ability toward ammoniums **6** and **7**. The K_a's of their 1:1 complexes were evaluated to be 4.9×10^6 and 4.9×10^6 M^{-1}, respectively, which are considerably higher than those of the complexes formed between dibenzo[24]crown-8 and similar ammonium cations.[30] Clearly, the preorganization of the oligomers played a key role in strengthening the intermolecular F···H−N hydrogen bonding.

Urea derivatives have been extensively used in hydrogen-bonding-mediated self-assembly,[31,32] while hydrazide units have found applications in the construction of artificial β-sheets.[33] These analogues of amides can be employed to build both symmetric and unsymmetric structures and are therefore potentially useful for the construction of folded frameworks.[17] Our early investigation has revealed that hydrogen-bonded hydrazides

CHART 1



possessed very rigid and planar structures in the solid state.[34] We therefore became interested in building new foldamers from hydrazide segments because this type of framework not only is symmetric but also should produce a larger cavity (ca. 1.0 nm). Compounds **3a**−**c** are examples of this series of foldamers.[26] Half of their carbonyl units are located inwardly and therefore can unite to bind saccharide derivatives **8**−**11** in chloroform. Molecular modeling showed that the longest tridecamer **3c** had a tubular structure of two turns. Not surprisingly, its complex with disaccharide **11** gave rise to the largest K_a (6.9×10^6 M^{-1} in chloroform). Circular dichroism (CD) experiments revealed that the strong complexation led to important supramolecular chirality. Induced CD spectra of mirror symmetry could be observed in



the presence of enantiomeric **8** or **9**. Reducing the size of the cavity has helped to weaken the binding. For example, the C═O oxygen-defined ring in **4** is smaller (ca. 0.86 nm) than that of **3b**.[27] The K_a of its complex with **11** in chloroform was evaluated to be 7.2×10^3 M^{-1}, which is lower than that of **3b** (3.0×10^4 M^{-1}).

The backbones of the hydrazide-based foldamers have also been incorporated with chiral proline units to afford **12a**−**c**.[35] It was reasoned that the resulting derivatives would lead to the formation of an energetically favorable chiral conformation,[36] which should be able to form diastereomeric complexes with enantiomeric saccharides. This was actually proven to be the case. For example, the K_a's of such complexes **12a**·**9** and **12a**·**8** in chloroform were estimated to be 2.6×10^5 and 1.8×10^3 M^{-1}, respectively, which corresponds to a 144-fold difference. As expected, enantiomers **12b** and **12c** exhibited CD spectra of mirror shape (Figure 3, left). When enantiomeric **8** or **9** was added, the shape of the spectra changed significantly due to intermolecular interaction. However, mirror symmetry was always observed for the two pairs of complexes of identical mixture concentrations (Figure 3, right), **12b**·**8** vs **12c**·**9** and **12b**·**9** vs **12c**·**8**. Consequently, it can be substantiated that enantiomeric complexes were formed.

Anisole Hydrolysis Acceleration

Due to their perfect preorganization, rigid spherand and many of its derivatives can complex alkali metal ions.[37] Foldamer **1**

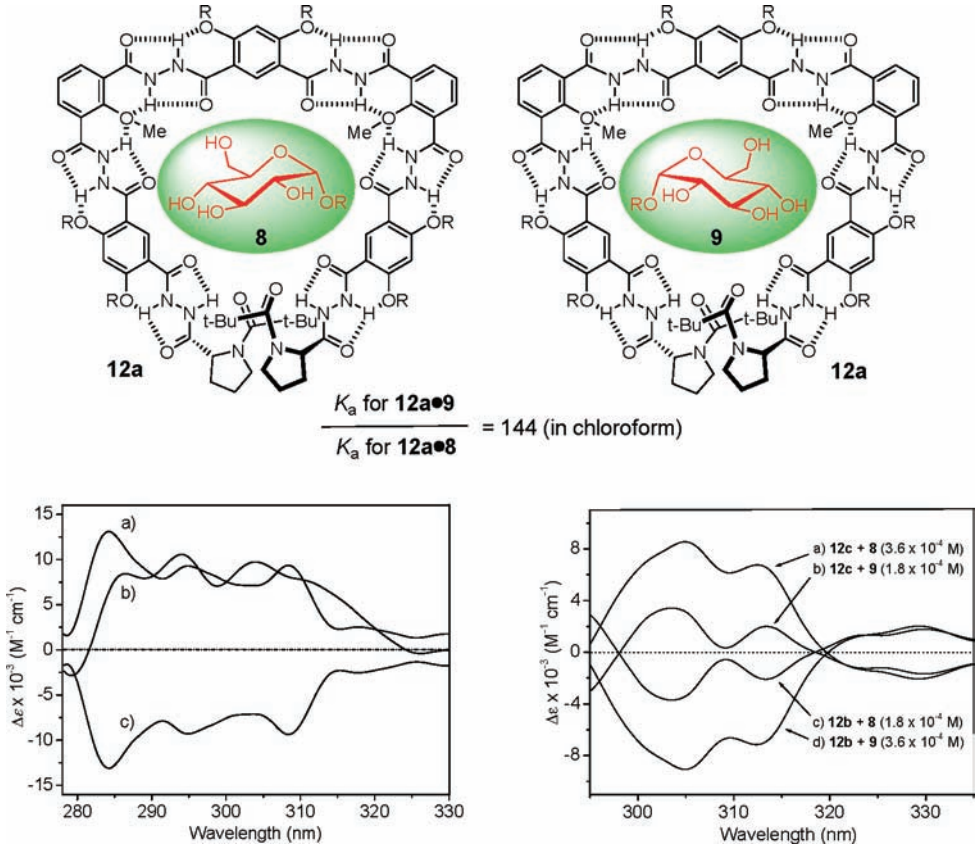
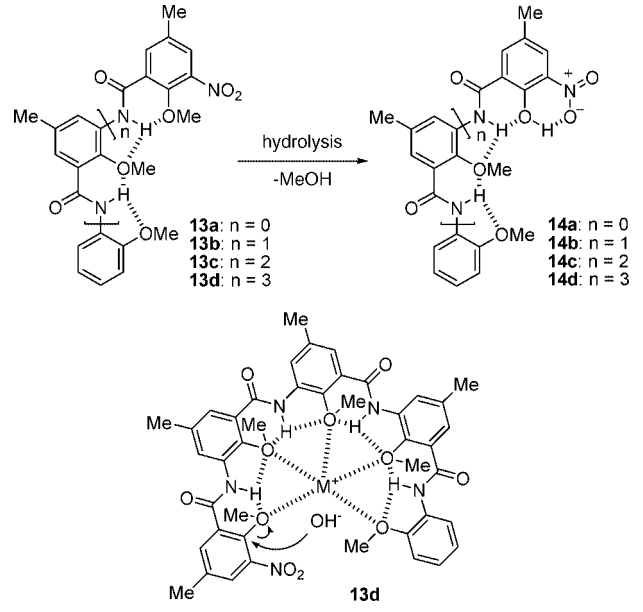


FIGURE 3. The CD spectra of (a) **12b**, (b) **12a**, and (c) **12c** (left) in chloroform (6.0×10^{-5} M) at 25 °C and of the 1:1 mixtures (right) of **12b** and **12c** (5.1×10^{-5} M) with **8** and **9** in chloroform at 25 °C.

resembles spherand in that all its hydrogen-bonded methoxyl groups are regularly orientated in its central area. We envisioned that such preorganized frameworks might have similar complexing capacity. For the mixtures of **13a**–**d** with alkali hydroxides,[38] it was expected that such a complexing interaction would increase the effective concentration of the OH^- anion around the cavity and simultaneously weaken both the MeO–C(Ph) bond of the nitro-appended anisole and the ionic bond of the alkali hydroxide. Consequently, the possible hydrolytic reaction of the nitro-appended anisole might be accelerated (Scheme 1). Kinetic study on the reactions of **13a**–**d** with alkali hydroxides in hot water–dioxane (1:4, v/v) revealed that the hydrolytic rates of longer and, naturally, larger oligomers **13b**–**d** were modestly higher (3- to 5-fold) than those of **13a**. Adding excessive potassium chloride to the reaction solutions reduced the hydrolytic rates, and the values of the longer oligomers also became smaller than those of **13a**. These results lend support to the fact that the complexation-accelerated hydrolytic mechanism did work for longer preorganized oligomers, as shown in Scheme 1 (with **13d** as an example).

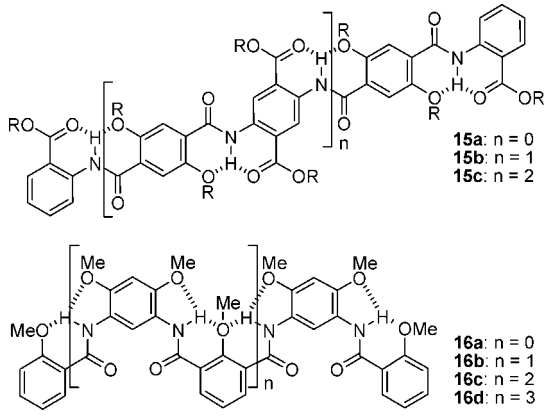
SCHEME 1



Zigzag and Straight Frameworks. Shape-Persistent Macrocycles

Most of the arylamide-derived secondary structures reported so far have a folded or helical conformation. However, by simply changing the position of the substituents on benzene rings,

we should be able to create other types of extended structures. Actually such unfolded "foldamers" have been used by Hamilton et al. to mimic α-helices.[19] Our studies demonstrate that they are also versatile frameworks for assembling new well-defined architectures. Our efforts in this direction have been concentrated on two series of oligomers, **15** and **16**.[39,40]

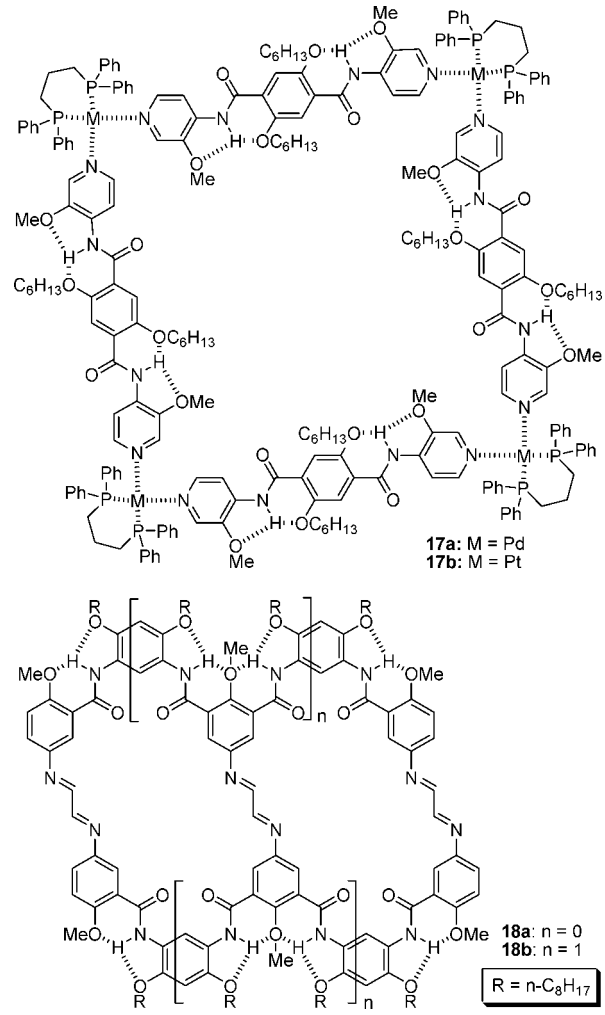


The ester units in series **15** may also be replaced by alkoxyl groups.[41] In principle, combining different building block monomers into one system may produce many backbones of desired conformations or shapes, while the side chains and the benzene rings at the ends of both series and the 5-positions of the isophthalamides of series **16** can also be easily functionalized. Through such kinds of variations or modifications, we have constructed a variety of molecular systems that exhibit interesting structures and properties.[41−53]

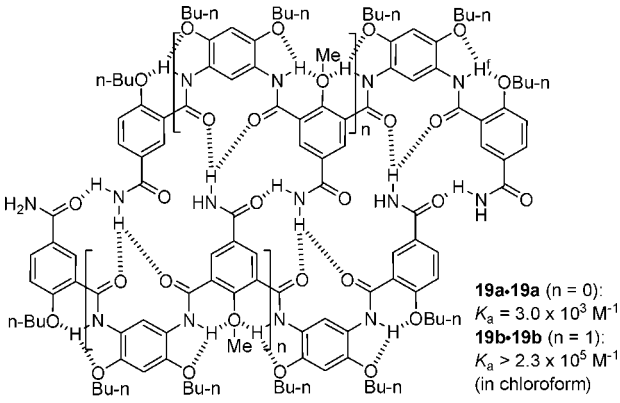
One application of the self-organized backbones is that they can be utilized to facilitate the formation of metallocyclophanes. For example, giant square macrocycles **17a** and **17b** have been assembled in 70% and 40% yields from the corresponding bispyridine and transition metal complex precursors.[41,42] By using the dynamic covalent approach,[54] we have also recently succeeded in preparing **18a** and **18b** in 88% and 95% yields from the reactions of the corresponding diamine and triamine precursors with oxalaldehyde in DMF of high polarity.[43] The fact that the dimacrocycle was obtained in higher yield than the monomacrocycle in polar medium suggests that more complicated multimacrocyclic architectures may also be produced from longer preorganized precursors.

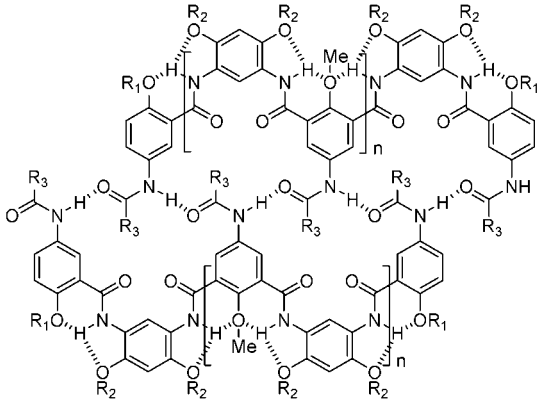
Homoduplex Self-Assembly

Development of artificial duplexes is of fundamental importance to understand the principles of biomacromolecular self-assembly and to construct functional multicomponent and polymeric architectures. Rigid arylamide oligomers provide ideal scaffolds for creating preorganized building block monomers. By iteratively introducing amide groups, the simplest self-binding units, at the 5-positions of the benzamide and isophthalamide moieties of frameworks **16**, we have prepared two series of monomers **19a**,**b** and **20a**−**e**.[44,45] The long oligomers were found to form highly stable homoduplexes in chloroform.[44]



By using compounds that bear two self-binding sites as models, we first evaluated the ability of discrete amide units, including carbamyl, formamido, acetamido, and trifluoroacetamido, in driving the formation of simple homoduplexes in $CDCl_3$ by the ^1H NMR dilution method.[45] The carbamyl group was found to be most efficient. Considering that this unit is small but has two amide protons, the result is not surprising. Actually the solid-state structure of **19a** exhibited a dimeric binding pattern that was stabilized by six intermolecular hydrogen bonds.[44] The formamido group was also found to be efficient, but the synthesis of the corresponding longer oligomers were difficult due to their instability during the coupling reactions. Therefore, we have prepared longer oligomers **19b**, **20d**, and **20e** for the assembly of new homoduplexes.[44]



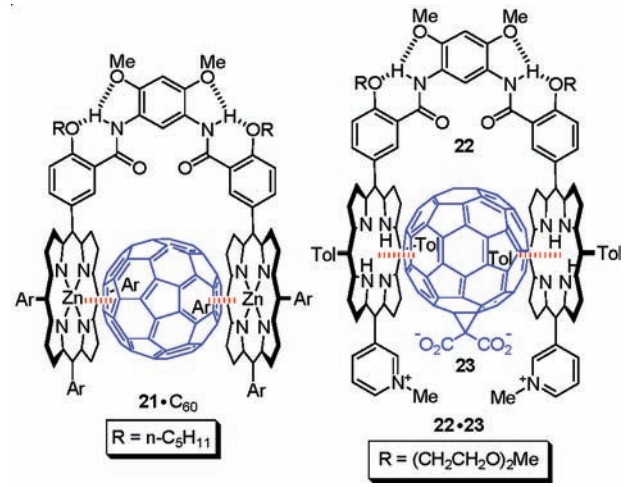


20a•20a (n = 0): R_1 = R_2 = n-Bu, R_3 = H), K_a = 2.6 x 10^3 M^{-1}
20b•20b (n = 0): R_1 = R_2 = n-Bu, R_3 = Me), K_a = 2.6 x 10^2 M^{-1}
20c•20c (n = 0): R_1 = R_2 = n-Bu, R_3 = CF_3), K_a = 80 M^{-1}
20d•20d (n = 1): R_1 = n-$C_{12}H_{25}$, R_2 = R_3 = Me), K_a > 2.3 x 10^5 M^{-1}
20e•20e (n = 2): R_1 = n-$C_{12}H_{25}$, R_2 = R_3 = Me), K_a > 2.3 x 10^5 M^{-1}
(in chloroform)

Diluting their saturated solutions in $CDCl_3$ to 0.2 mM did not cause significant shifting for the signals the amides (<0.07 ppm) in the ^{1}H NMR spectra. A conservative estimate of 90% dimerization has led to a lower K_a limit of 2.3 $\times$ 10^5 M^{-1} for their homoduplexes. The K_a's of these homoduplexes could be evaluated with the ^{1}H NMR dilution method in more polar $CDCl_3/CD_3CN$ (9:1, v/v). For example, the values of **20b**·**20b**, **20d**·**20d**, and **20e**·**20e** were approximately 80, 1.2 $\times$ 10^3, and 1.4 $\times$ 10^4 M^{-1}, respectively. The stability of the duplexes is increased substantially with the elongation of the monomers, indicating a high efficiency of the hydrogen-bonding-driven preorganization of the monomers in directing the self-assembly.

Hydrogen-Bonded Molecular Tweezers

Molecular tweezers are a class of acyclic artificial receptors that consist of two binding units and a rigid linker.[55] Traditionally the linkers have been constructed from rigid polycyclic skeletons and the binding units strictly positioned with a fixed separation. In this way, an efficient binding of structurally matched guests can be realized. However, their syntheses are usually quite challenging. With hydrogen-bonded arylamide frameworks as linkers, we have developed a general approach to construct a new generation of assembled molecular tweezers.[46–51]

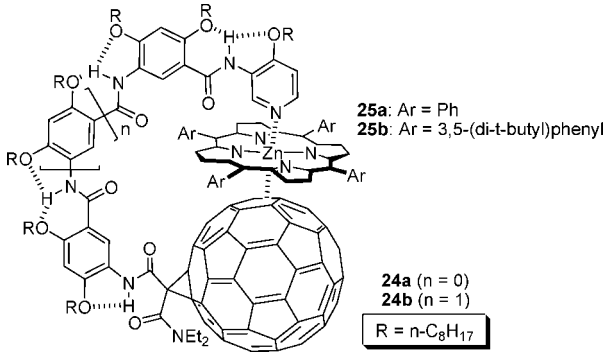


Compound **21** is our first assembled molecular tweezer, in which two appended zinc porphyrin moieties are roughly parallel to each other due to the preorganization of the arylamide backbone.[46] Molecular modeling showed that the two porphyrins had an approximately 1.2 nm of spatial separation, which is very suitable for sandwiching a C_{60} or C_{70} molecule. On the basis of UV–vis titrations, we have determined the K_a's of their 1:1 complexes (1.0 $\times$ 10^5 and 1.1 $\times$ 10^6 M^{-1}, respectively) in toluene. The values are comparable to those of a cyclic diporphyrin receptor reported by Aida et al.[56] If a chiral group was attached to the C_{60} unit, the complexation can lead to important supramolecular chirality, as evidenced by CD spectroscopy.

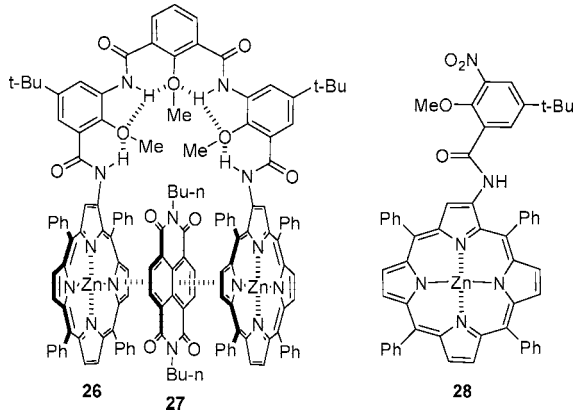
The fact that the arylamide backbones accelerated the hydrolysis of oligomers **13b**–**d** in hot aqueous medium implied that intramolecular RO···H–N hydrogen bonding did exist in highly polar solvents.[38] X-ray analyses of two model molecules also showed that crystals grown from less polar organic and aqueous media exhibited an identical stacking pattern with very similar structural parameters.[47] Based on these observations, we have further designed a series of ionic bisporphyrin derivatives such as **22** (with PF_6^- as the counterion).[47] Being different from their neutral counterparts, these compounds are soluble in highly polar solvents such as water and DMSO. UV–vis and fluorescent experiments indicated that **22** was able to bind ionic C_{60} **23** (with Na^+ as the counterion) in polar solvents. The K_a of **22**·**23** in water is as high as 1.1 $\times$ 10^5 M^{-1}. In contrast, for neutral C_{60} derivatives, a similar interaction was not observed. Therefore, an electrostati-

cally driven binding pattern has been proposed, which enabled the porphyrins to further stack with the C_{60} moiety of the guest.

Other types of binding units have also been attached to the arylamide backbones.[48–50] For example, by introducing a C_{60} unit and a nitrogen ligand, such as a pyridine or an imidazole, to the one-way arylamide backbones,[57] we have created several unsymmetric molecular tweezers, as exemplified by **24a** and **24b**.[48] Both compounds could complex zinc porphyrin guests **25a** and **25b** through Zn−N coordination and porphyrin−C_{60} stacking interactions. Quantitative UV–vis investigations in chloroform revealed that the binding stabilities of these "two-point"-bound complexes were notably higher (7–9 times) than those of the corresponding complexes of the C_{60}-free pyridine references. However, the cooperative effect of the additional porphyrin−C_{60} stacking interaction was not very high, possibly because the binding also led to intermolecular spatial repulsion.



The interacting sites of the above hydrogen-bonded molecular tweezers have well-defined spatial separations. With a more convergent arylamide backbone as linker, we have also constructed an elastic receptor **26**.[51] Dynamic modeling showed that due to the continuous intramolecular hydrogen bonding and the inherent planarity of the arylamide unit, its two electron-rich porphyrin units were forced to approach and therefore stack with each other. In the presence of a planar electron-deficient guest, such as dialkylated naphthalene, benzene diimide, or paraquat, intermolecular donor–acceptor interaction drove the guest molecule to insert between the stacking porphyrin units, leading to the formation of sandwich-styled complexes. Although the insertion of the guest weakened the intramolecular hydrogen bonding of **26** by causing the latter to partially defold, the stability of the 1:1 complexes was still higher than that of the corresponding complexes of reference molecule **28**. For example, the K_a of **26**·**27** in chloroform was estimated to be 850 M^{-1}, which was modestly higher than that of **27**·**28** (ca. 90 M^{-1}). These results suggest that hydrogen-bonding-driven rigid arylamide frameworks were able to elastically adjust their conformations to address an external stimulus, as exhibited by life systems.



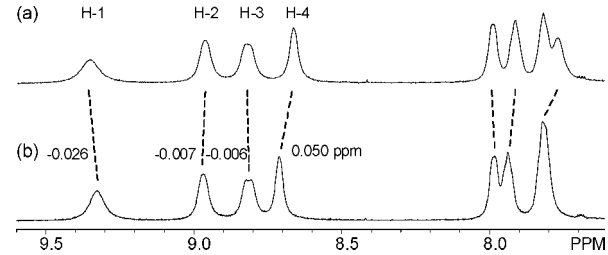
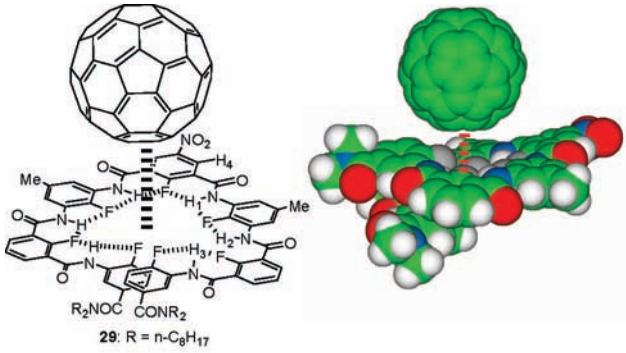
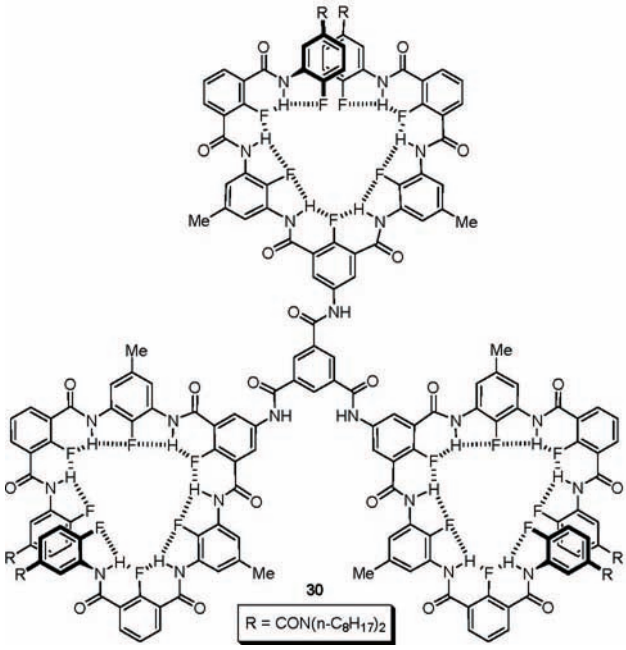


FIGURE 4. Partial ^{1}H NMR spectra of (a) **29** (8.0 mM) and (b) **29** + C_{60} (1:1, 8.0 mM) in $CDCl_3$−CS_2 (4:1 v/v) at 25 °C.

Foldamer−Fullerene Stacking Interaction and Nanonetworks

Large conjugated systems such as porphyrins and phthalocyanins have a great tendency for self-stacking or stacking with other aromatic structures. Because of the small size of fluorine, F···H−N hydrogen-bonding-induced foldamers have an extended planarity and may also interact with other conjugated systems. To test this hypothesis, we have prepared foldamer **29** and trifoldamer **30**.[52] UV–vis and fluorescent experiments revealed that strong stacking occurred between these folded structures and C_{60} or C_{70}. Adding C_{60} to the solution of **29** in $CDCl_3$ caused notable shifting of several signals of the latter in the ^{1}H NMR spectrum (Figure 4), indicating that the interaction was within intimate distance. Job's plot suggested a 1:1 stoichiometry for the complexes formed between **29** and the folded moieties of **30** and the fullerenes. The (apparent) K_a's of complexes between **29** and **30** and C_{60} in $CHCl_3$−CS_2 (19:1, v/v) were evaluated to be 1.8×10^4 and 2.3×10^4 M^{-1}, respectively. The values are close, suggesting that no cooperative interaction existed for the three folded moieties of **30** in its stacking with fullerenes. Similar stacking interaction was also observed between **1** and C_{60} (K_a = 2.8×10^3 M^{-1}) but was not as strong as that between **29** and

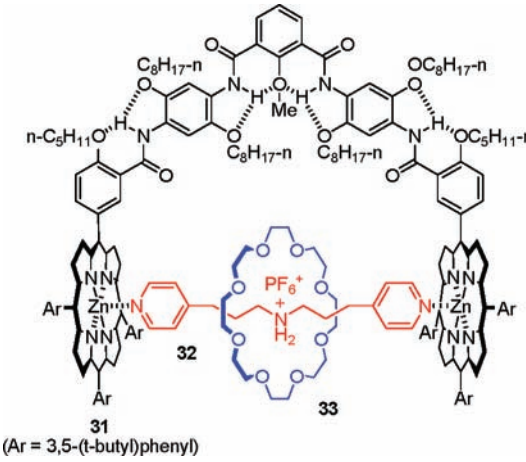




C_{60}, presumably due to the large size of its centrally positioned methyl groups. AFM studies revealed that, on the surface, the mixture of **30** and C_{60} formed a honeycomb-style nanonetwork. A column-shaped cooperative stacking pattern has been proposed to explain the formation of such a nanostructure.

Dynamic [2]Catenanes

Currently, quite a number of monomeric building blocks have been created based on discrete hydrogen-bonded arylamide segments. In principle, suitable arrangement of these monomeric segments may produce many frameworks of desired shapes. Actually we have recently constructed another bisporphyrin receptor, that is, **31**, by utilizing a V-shaped arylamide pentamer as linker.[53] This extended molecular tweezer has been found to strongly complex bispyridine−ammonium adduct **32** in $CDCl_3$−CD_3CN (4:1, v/v, $K_a = 5.7 \times 10^6$ M^{-1}). Since the linear ammonium can be driven by intermolecular N−H···O interactions to thread through the cavity of 24-crown-8 **33**, three-component dynamic [2]catenane



31·**32**·**33** has been created via a combination of three different noncovalent forces.

The conformational preorganization of **31** played a key role in the formation of the dynamic [2]catenane. It increased the stability of complex **31**·**32** and also the capacity of **32** to thread through **33**, because **32** coordinated to **31** was expected to adopt a linear conformation, facilitating the threading process. The rigidity of the linker should also reduce the possible spatial repulsion between itself and the threaded crown ether. ^{1}H NMR experiments revealed that in the 1:1:1 mixture solution (3.0 mM), the [2]catenane was generated in 55% yield at room temperature. When another equivalent of **33** was added and the temperature reduced to −13 °C, the [2]catenane could be formed quantitatively.

Conclusions and Prospects

The studies described above have established that our approach for creating hydrogen-bonding-driven arylamide-based peptide mimics is workable. Discrete folded and extended secondary structures can be constructed, and the rigid frameworks can be readily modified and functionalized. The new molecular architectures have exhibited quite a range of interesting functions, which to some extent are parallel to those exhibited by natural peptides and proteins.

Despite the progress made so far, the research field is still at its early stage, but also being expanded quickly. We herein suggest several issues that we think are worthy to receive more attention or to be addressed in the future: (1) aryl−aliphatic hybrid sequences, (2) tertiary structures, (3) methodologies for creating chiral monomers and mimic structures, (4) catalytic and transport systems, (5) long polymeric backbones with one-dimensional or tubular structures, and (6) (water-soluble) structural motifs for targeting biomolecules. We hope that this Account will stimulate further researches on this family of structurally interesting mimic protocols. We have

demonstrated that our straight and zigzag structures are well suited for iterative functionalization. Therefore, one of our present endeavors is to concentrate on the creation of one-dimensional oligo- or polyions for protein or DNA binding. The efficient formation of macrocyclic structures by the dynamic covalent approach also bodes well for the construction of porous structures from extended frameworks, which is also being investigated in our laboratory.

The research described herein was supported by the National Natural Science Foundation of China and the National Basic Research Program of China. Z.-T. L. sincerely thanks his students and collaborators, whose names are cited in the references, for their contributions. The authors are also grateful to Professors Henry N. C. Wong and Xi-Kui Jiang for helpful suggestions.

BIOGRAPHICAL INFORMATION

Zhan-Ting Li was born in 1966 and received his A.B. degree in 1985 from Zhengzhou University. He earned his Ph.D. degree in fluorine chemistry in 1992 with Professor Qing-Yun Chen at Shanghai Institute of Organic Chemistry (SIOC). He did postdoctoral research with Professor Jan Becher at the University of South Denmark and with Professor Steven C. Zimmerman at the University of Illinois at Urbana–Champaign. He is currently a professor at SIOC. His research is concerned with unnatural secondary structures and molecular recognition.

Jun-Li Hou was born in 1978 and studied chemistry at Hubei University (1997–2001). He received his Ph.D. degree at SIOC (2006) under the direction of Z.-T. Li. He is currently a Research Associate with Professor Julius Rebek, Jr., at The Scripps Research Institute.

Chuang Li was born in 1979 and received his first degree from Northeast Normal University in 2002. In 2007, he completed his Ph.D. degree with Z.-T. Li at SIOC and then joined Professor Steven C. Zimmerman's group at the University of Illinois at Urbana–Champaign as a postdoctoral fellow.

FOOTNOTES

* To whom correspondence should be addressed. E-mail: ztli@mail.sioc.ac.cn.

REFERENCES

1 Seebach, D.; Matthews, J. L. β-Peptides: A Surprise at Every Turn. *Chem. Commun.* **1997**, 2015–2022.

2 Gellman, S. H. Foldamers: A Manifesto. *Acc. Chem. Res.* **1998**, *31*, 173–180.

3 Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. β-Peptides: From Structure to Function. *Chem. Rev.* **2001**, *101*, 3219–3232.

4 Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. A Field Guide to Foldamers. *Chem. Rev.* **2001**, *101*, 3893–4011.

5 Goodman, C. M.; Choi, S.; Shandler, S.; DeGrado, W. F. Foldamers as Versatile Frameworks for the Design and Evolution of Function. *Nat. Chem. Biol.* **2007**, *3*, 252–262.

6 Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. β-Peptide Foldamers: Robust Helix Formation in a New Family of β-Amino Acid Oligomers. *J. Am. Chem. Soc.* **1996**, *118*, 13071–13072.

7 Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. β-Peptides. Synthesis by Arndt-Eistert Homologation with Concomitant Peptide Coupling. Structure Determination by NMR and CD Spectroscopy and by X-Ray Crystallography. Helical Secondary Structure of a β-Hexapeptide in Solution and Its Stability towards Pepsin. *Helv. Chim. Acta* **1996**, *79*, 913–941.

8 Gong, B. Crescent Oligoamides: From Acyclic "Macrocycles" to Folding Nanotubes. *Chem.—Eur. J.* **2001**, *7*, 4337–4342.

9 Huc, I. Aromatic Oligoamide Foldamers. *Eur. J. Org. Chem.* **2004**, 17–29.

10 Sanford, A.; Yamato, K.; Yang, X. W.; Yuan, L. H.; Han, Y. H.; Gong, B. Well-Defined Secondary Structures: Information-Storing Molecular Duplexes and Helical Foldamers Based on Unnatural Peptide Backbones. *Eur. J. Biochem.* **2004**, *271*, 1416–1425.

11 Li, Z.-T.; Hou, J.-L.; Li, C.; Yi, H.-P. Shape-Persistent Aromatic Amide Oligomers: New Tools for Supramolecular Chemistry. *Chem.—Asian J.* **2006**, *1*, 766–778.

12 Hamuro, Y.; Geib, S. J.; Hamilton, A. D. Oligoanthranilamides. Non-Peptide Subunits That Show Formation of Specific Secondary Structure. *J. Am. Chem. Soc.* **1996**, *118*, 7529–7541.

13 Berl, V.; Huc, I.; Khoury, R. G.; Krische, M. J.; Lehn, J.-M. Interconversion of Single and Double Helices Formed from Synthetic Molecular Strands. *Nature* **2000**, *407*, 720–723.

14 Zhu, J.; Parra, R. D.; Zeng, H.; Skrzypczak-Jankun, E.; Zeng, X. C.; Gong, B. A New Class of Folding Oligomers: Crescent Oligoamides. *J. Am. Chem. Soc.* **2000**, *122*, 4219–4220.

15 Jiang, H.; Léger, J.-M.; Huc, I. Aromatic δ-Peptides. *J. Am. Chem. Soc.* **2003**, *125*, 3448–3449.

16 Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. Complexation-Induced Unfolding of Heterocyclic Ureas. Simple Foldamers Equilibrate with Multiply Hydrogen-Bonded Sheetlike Structures. *J. Am. Chem. Soc.* **2001**, *123*, 10475–10488.

17 Sinkeldam, R. W.; van Houtem, M. H. C. J.; Pieterse, K.; Vekemans, J. A. J. M.; Meijer, E. W. Chiral Poly(ureidophthalimide) Foldamers in Water. *Chem.—Eur. J.* **2006**, *12*, 6129–6137.

18 Baruah, P. K.; Gonnade, R.; Rajamohanan, P. R.; Hofmann, H.-J.; Sanjayan, G. J. BINOL-Based Foldamers-Access to Oligomers with Diverse Structural Architectures. *J. Org. Chem.* **2007**, *72*, 5077–5084.

19 Ernst, J. T.; Becerril, J.; Park, H. S.; Yin, H.; Hamilton, A. D. Design and Application of an α-Helix-Mimetic Scaffold Based on an Oligoamide-Foldamer Strategy: Antagonism of the Bak BH3/Bcl-xL Complex. *Angew. Chem., Int. Ed.* **2003**, *42*, 535–539.

20 Vögtle, F.; Weber, E. Multidentate Acyclic Neutral Ligands and Their Complexation. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 753–776.

21 Berl, V.; Krische, M. J.; Huc, I.; Lehn, J.-M.; Schmutz, M. Template-Induced and Molecular Recognition Directed Hierarchical Generation of Supramolecular Assemblies from Molecular Strands. *Chem.—Eur. J.* **2000**, *6*, 1938–1946.

22 Prince, R. B.; Barnes, S. A.; Moore, J. S. Foldamer-Based Molecular Recognition. *J. Am. Chem. Soc.* **2000**, *122*, 2758–2762.

23 Stone, M. T.; Heemstra, J. M.; Moore, J. S. The Chain-Length Dependence Test. *Acc. Chem. Res.* **2006**, *39*, 11–20.

24 Yi, H.-P.; Li, C.; Hou, J.-L.; Jiang, X.-K.; Li, Z.-T. Hydrogen-Bonding-Induced Oligoanthranilamide Foldamers. Synthesis, Characterization, and Complexation for Alkyl Ammonium Ions. *Tetrahedron* **2005**, *61*, 7974–7980.

25 Li, C.; Ren, S.-F.; Hou, J.-L.; Yi, H.-P.; Zhu, S.-Z.; Jiang, X.-K.; Li, Z.-T. F···H—N Hydrogen Bonding Driven Foldamers: Efficient Receptors for Dialkylammonium Ions. *Angew. Chem., Int. Ed.* **2005**, *44*, 5725–5729.

26 Hou, J.-L.; Shao, X.-B.; Chen, G.-J.; Zhou, Y.-X.; Jiang, X.-K.; Li, Z.-T. Hydrogen Bonded Oligohydrazide Foldamers and Their Recognition for Saccharides. *J. Am. Chem. Soc.* **2004**, *126*, 12386–12394.

27 Yi, H.-P.; Shao, X.-B.; Hou, J.-L.; Li, C.; Jiang, X.-K.; Li, Z.-T. Hydrogen-Bonding-Mediated Oligoanthranilamide Foldamer Receptors That Efficiently Bind a Triol and Saccharides in Chloroform. *New J. Chem.* **2005**, *29*, 1213–1218.

28 Dunitz, J. D. Organic Fluorine: Odd Man Out. *ChemBioChem* **2004**, *5*, 614–621.

29 Zhu, Y.-Y.; Wu, J.; Li, C.; Zhu, J.; Hou, J.-L.; Li, C.-Z.; Jiang, X.-K.; Li, Z.-T. F···H—N and MeO···H—N Hydrogen-Bonding in the Solid States of Aromatic Amides and Hydrazides. A Comparison Study. *Cryst. Growth Des.* **2007**, *7*, 1490–1486.

30 Ashton, P. R.; Campbell, P. J.; Chrystal, E. J. T.; Glink, P. T.; Menzer, S.; Philp, D.; Spencer, N.; Stoddart, J. F.; Tasker, P. A.; Williams, D. J. Dialkylammonium Ion/Crown Ether Complexes: The Forerunners of a New Family of Interlocked Molecules. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1865–1869.

31 Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. Molecular Encapsulation. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488–1508.

32 Brunsveld, L.; Folmer, B. J.; Meijer, E. W.; Sijbesma, R. P. Supramolecular Polymers. *Chem. Rev.* **2001**, *101*, 4071–4098.

33 Nowick, J. S. Chemical Models of Protein β-Sheets. *Acc. Chem. Res.* **1999**, *32*, 287–296.

34 Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. Novel Hydrazide-Based Quadruply Hydrogen Bonded Heterodimers. Structure, Assembling Selectivity and Supramolecular Substitution. *J. Am. Chem. Soc.* **2003**, *125*, 15128–15139.

35 Li, C.; Wang, G.-T.; Yi, H.-P.; Jiang, X.-K.; Li, Z.-T.; Wang, R.-X. Diastereomeric Recognition of Chiral Foldamer Receptors for Chiral Glucoses. *Org. Lett.* **2007**, *9*, 1797–1800.

36 Maurizot, C.; Dolain, C.; Leydet, Y.; Léger, J.-M.; Guionneau, P.; Huc, I. Design of an Inversion Center between Two Helical Segments. *J. Am. Chem. Soc.* **2004**, *126*, 10049–10052.

37 Cram, D. J. The Design of Molecular Hosts, Guests, and Their Complexes. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009–1020.

38 Yi, H.-P.; Wu, J.; Ding, K.-L.; Jiang, X.-K.; Li, Z.-T. Hydrogen Bonding-Induced Aromatic Oligoamide Foldamers as Spherand Analogues to Accelerate the Hydrolysis of Nitro-Substituted Anisole in Aqueous Media. *J. Org. Chem.* **2007**, *72*, 870–877.

39 Wu, Z.-Q.; Jiang, X.-K.; Zhu, S.-Z.; Li, Z.-T. Hydrogen Bond-Induced Rigid Oligoanthranilamide Ribbons That Are Planar and Straight. *Org. Lett.* **2004**, *6*, 229–232.

40 Zhu, J.; Wang, X.-Z.; Chen, Y.-Q.; Jiang, X.-K.; Chen, X.-Z.; Li, Z.-T. Hydrogen Bonding-Induced Planar, Rigid, and Zigzag Oligoanthranilamides. Synthesis, Characterization, and Self-Assembly of a Metallocyclophane. *J. Org. Chem.* **2004**, *69*, 6221–6227.

41 Wu, Z.-Q.; Jiang, X.-K.; Li, Z.-T. Hydrogen Bonding-Mediated Self-Assembly of Square and Triangular Metallocyclophanes. *Tetrahedron Lett.* **2005**, *46*, 8067–8070.

42 Chen, Y.-Q.; Wang, X.-Z.; Shao, X.-B.; Hou, J.-L.; Chen, X.-Z.; Jiang, X.-K.; Li, Z.-T. Hydrogen Bonding-Mediated Self-Assembly of Rigid and Planar Metallocyclophanes and Their Recognition for Mono- and Disaccharides. *Tetrahedron* **2004**, *60*, 10253–10260.

43 Lin, J.-B.; Xu, X.-N.; Li, Z.-T. Unpublished results.

44 Zhu, J.; Lin, J.-B.; Xu, Y.-X.; Shao, X.-B.; Jiang, X.-K.; Li, Z.-T. Hydrogen-Bonding-Mediated Anthranilamide Homoduplexes. Increasing Stability through Preorganization and Iterative Arrangement of Simple Amide Binding Sites. *J. Am. Chem. Soc.* **2006**, *128*, 12307–12313.

45 Zhu, J.; Lin, J.-B.; Xu, Y.-X.; Jiang, X.-K.; Li, Z.-T. Hydrogen Bonding-Mediated Self-Assembly of Anthranilamide-Based Homodimers through Preorganization of the Amido and Ureido Binding Sites. *Tetrahedron* **2006**, *62*, 11933–11941.

46 Wu, Z.-Q.; Shao, X.-B.; Li, C.; Hou, J.-L.; Wang, K.; Jiang, X.-K.; Li, Z. T. Hydrogen Bonding-Driven Preorganized Zinc Porphyrin Receptors for Efficient Complexation of C60, C70 and C60 Derivatives. *J. Am. Chem. Soc.* **2005**, *127*, 17460–17468.

47 Liu, H.; Wu, J.; Jiang, X.-K.; Li, Z.-T. Complexation of Hydrogen Bonding-Driven Preorganized Di- and Hexacationic Porphyrin Receptors for $C_{60}C(CO_2^-)_2$ in Aqueous and Polar Organic Media. *Tetrahedron Lett.* **2007**, *48*, 7327–7331.

48 Wu, Z.-Q.; Li, C.-Z.; Feng, D.-J.; Jiang, X.-K.; Li, Z.-T. Foldamer-Based Pyridine-Fullerene Tweezer Receptors for Increased Binding of Zinc Porphyrin. *Tetrahedron* **2006**, *62*, 11054–11062.

49 Hou, J.-L.; Yi, H.-P.; Shao, X.-B.; Li, C.; Wu, Z.-Q.; Jiang, X.-K.; Wu, L.-Z.; Tung, C.-H.; Li, Z.-T. Helicity Induction in Hydrogen Bonding-Driven Zinc Porphyrin Foldamers by Chiral C60-Incorporated Histidines. *Angew. Chem., Int. Ed.* **2006**, *45*, 796–800.

50 Li, C.-Z.; Zhu, J.; Wu, Z.-Q.; Hou, J.-L.; Li, C.; Shao, X.-B.; Jiang, Li, Z.-T.; Gao, X.; Wang, Q.-R. "Two-Point"-Bound Supramolecular Complexes from Semi-Rigidified Dipyridine Receptors and Zinc Porphyrins. *Tetrahedron* **2006**, *62*, 6973–6980.

51 Feng, D.-J.; Wang, G.-T.; Wu, J.; Wang, R.-X.; Li, Z.-T. Hydrogen Bonding-Driven Elastic Bis(zinc)porphyrin Receptors for Neutral and Cationic Electron-Deficient Guests with a Sandwich-Styled Complexing Pattern. *Tetrahedron Lett.* **2007**, *48*, 6181–6185.

52 Li, C.; Zhu, Y.-Y.; Yi, H.-P.; Li, C.-Z.; Jiang, X.-K.; Li, Z.-T. Strong Stacking between Hydrogen Bonded Foldamers and Fullerenes: Formation of Supramolecular Nano Networks. *Chem.—Eur. J.* **2007**, *13*, 9990–9998.

53 Wu, J.; Hou, J.-L.; Li, C.; Wu, Z.-Q.; Jiang, X.-K.; Li, Z.-T.; Yu, Y.-H. Dynamic [2]Catenanes Based on Hydrogen Bonding-Mediated Bis-Zinc Porphyrin Foldamer Tweezer: a Case Study. *J. Org. Chem.* **2007**, *72*, 2897–2905.

54 Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. Dynamic Combinatorial Chemistry. *Chem. Rev.* **2006**, *106*, 3652–3711.

55 Zimmerman, S. C. Rigid Molecular Tweezers as Hosts for the Complexation of Neutral Guests. *Top. Curr. Chem.* **1993**, *165*, 71–102.

56 Tashiro, K.; Aida, T.; Zheng, J.-Y.; Kinbara, K.; Saigo, K.; Sakamoto, S.; Yamaguchi, K. A Cyclic Dimer of Metalloporphyrin Forms a Highly Stable Inclusion Complex with C_{60}. *J. Am. Chem. Soc.* **1999**, *121*, 9477–9478.

57 Yuan, L.; Zeng, H.; Yamato, K.; Sanford, A. S.; Feng, W.; Atreya, H. S.; Sukumaran, D. K.; Szyperski, T.; Gong, B. Helical Aromatic Oligoamides: Reliable, Readily Predictable Folding from the Combination of Rigidified Structural Motifs. *J. Am. Chem. Soc.* **2004**, *126*, 16528–16537.