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Aromatic Amide and Hydrazide Foldamer-Based Responsive Host–Guest Systems

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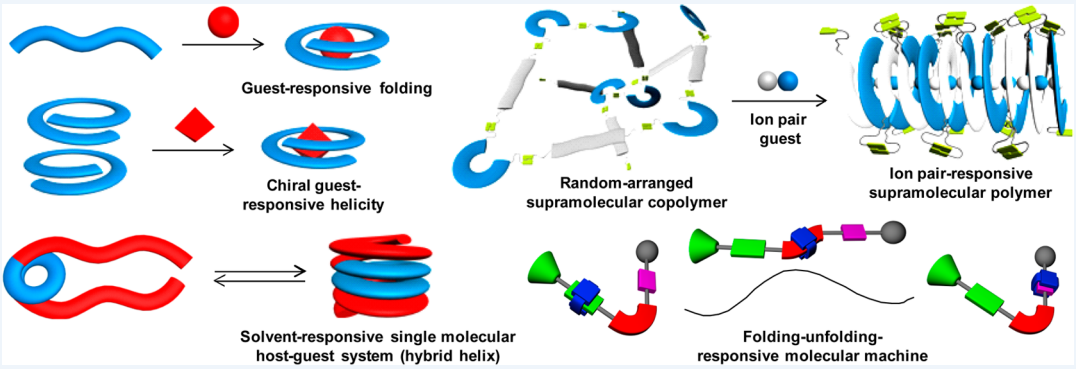


CONSPECTUS: In host–guest chemistry, a larger host molecule selectively and noncovalently binds to a smaller guest molecule or ion. Early studies of host–guest chemistry focused on the recognition of spherical metal or ammonium ions by macrocyclic hosts, such as cyclic crown ethers. In these systems, preorganization enables their binding sites to cooperatively contact and attract a guest. Although some open-chain crown ether analogues possess similar, but generally lower, binding affinities, the design of acyclic molecular recognition hosts has remained challenging. One of the most successful examples was rigid molecular tweezers, acyclic covalently bonded preorganized host molecules with open cavities that bind tightly as they stiffen.

Depending on the length of the atomic backbones, hydrogen bonding-driven aromatic amide foldamers can form open or closed cavities. Through rational design of the backbones and the introduction of added functional groups, researchers can regulate the shape and size of the cavity. The directionality of hydrogen bonding and the inherent rigidity of aromatic amide units allow researchers to predict both the shape and size of the cavity of an aromatic amide foldamer. Therefore, researchers can then design guest molecules with structure that matches the cavity shape, size, and binding sites of the foldamer host. In addition, because hydrogen bonds are dynamic, researchers can design structures that can adapt to outside stimuli to produce responsive supramolecular architectures.

In this Account, we discuss how aromatic amide and hydrazide foldamers induced by hydrogen bonding can produce responsive host–guest systems, based on research by our group and others. First we highlight the helical chirality induced as binding occurs in solution, which includes the induction of helicity by chiral guests in oligomeric and polymeric foldamers, the formation of diastereomeric complexes between chiral foldamer hosts and guests, and the induction of helical chirality by chiral guests into inherently flexible backbones. In addition, molecular or ion-pair guests can produce supramolecular helical chirality in the organogel state. Such structures exhibit remarkable time-dependence and a "Sergeants and Soldiers" effect that are not observed for other two-component organogels that have been reported. We further illustrate that the reversible folding behavior of an aromatic amide foldamer segment can modulate the switching behavior of donor–acceptor interaction-based [2]rotaxanes. Finally we show that a folded oligomer can induce folding in one or two attached intrinsically flexible oligomers, an example of a solvent-responsive intramolecular host–guest system.

INTRODUCTION

The concept of host–guest chemistry can be traced back to 1894 when Fischer postulated the *lock and key* model for explaining the specific action of an enzyme with a single substrate.[1] The first generation of artificial hosts designed by Cram were all crown ethers.[2] Systematic investigations of the recognition of these crown ethers and other macrocyclic hosts, including cryptands,[3] for discrete guests have launched the currently flourishing field of supramolecular chemistry. Given the linear arrangement of amino acid units of enzymes, the development of linear artificial hosts is also critically important. Along this line, early efforts had focused on open-chain crown ethers or podands. However, compared with the maternal crown ethers, their binding efficiency is relatively low due to increased structural flexibility.

Special Issue: Responsive Host–Guest Systems

Received: January 19, 2014
Published: March 27, 2014

dx.doi.org/10.1021/ar5000242 | *Acc. Chem. Res.* 2014, 47, 1961–1970

To overcome this drawback, the strategy of preorganization has been developed for the construction of rigid "tweezer" receptors.[4,5]

In recent years, the construction of responsive supramolecular architectures has received considerable attention due to their potential in the design of advanced materials.[6−8] In the context of host−guest chemistry, this responsivity may be roughly classified into two categories. In the first, the overall properties or functions of a host−guest system are modulated by external stimuli such as light, redox, pH, temperature, or solvent. In the second, the host−guest interaction takes place in a responsive fashion, which can stimulate the host to change its conformation, structure, or properties. In both cases, the responsive process is dynamic and reversible, making it a useful strategy in developing new smart materials.

α-Helix is the central secondary structural motif of peptides and proteins and is stabilized mainly by intramolecular hydrogen bonding and hydrophobic packing. To mimic this structural motif and also to explore new biological and material functions and applications, in the last decades, chemists have been actively engaged in the construction of artificial helices by synthesizing abiotic aliphatic amino acids or analogues.[9−11] Most of these natural and synthetic helices have no or just a small cavity and their binding toward other species heavily relies on groups appended on the side chains. In contrast, foldamers consisting of aromatic amides can generate cavities of varying size.[12−15] In most cases, the folding of the amide backbones is spontaneous, which is driven by intramolecular hydrogen bonding, electrostatic repulsion, and $\pi-\pi$ stacking. Examples of complexation-induced folding of intrinsically disordered backbones are also available,[16,17] which represent the new progress in the design of responsive host−guest systems.

In 2004, our group started to investigate the supramolecular behavior of aromatic amide and hydrazide foldamers.[18] Studies from our and other groups have illustrated that this family of aromatic foldamers are versatile acyclic receptors for constructing responsive host−guest systems.[19−23] Particularly, the binding of chiral guests can lead to dynamic responsive helical chirality for the foldamer backbones in solution, solid state, or organogels. Intrinsically disordered or less compact backbones can also be induced by a guest or even a connected foldamer to form helical or more complicated compact conformations in an adaptable manner.[24−27] In addition, the reversible folding−unfolding process of the backbones has been utilized for tuning the switching of the donor−acceptor interaction-based host−guest systems.[28] The advances in the construction of foldamer-based responsive host−guest systems are discussed in this Account.

BINDING-RESPONSIVE HELICAL CHIRALITY

Biomacromolecules such as polypeptides and nucleic acids exist as single handed helices. Synthetic polymers containing repeating chiral units can also form chiral helices. In the absence of chiral units, polymer or supramolecular polymer backbones may be induced by chiral reagents to produce helix-sense bias; these are elaborate examples of responsive supramolecular systems.[29] Typically, a large number of chiral molecules are used to bind a polymer in a cooperative manner, which maximizes the chirality transfer. As oligomers of defined length, aromatic foldamers usually form a relatively fixed cavity. Moore and coworkers reported that for oligomeric *m*-ethynylbenzene foldamers, a single chiral guest entrapped in their cavity may be strong enough to induce the backbones to produce a single handedness in the helical chirality.[30] One notable feature of hydrogen bonding-driven aromatic foldamers is that the diameter of their cavities can be tuned by choosing different repeat segments, while hydrogen bonding donors and acceptors can be oriented inward in a periodic manner.[15] Therefore, this class of aromatic foldamers has been widely used to construct responsive host−guest systems.

Oligomers **1a−c** represent the first examples of hydrazide foldamers that are stabilized by intramolecular RO···H−N hydrogen bonding.[18] Molecular dynamics calculations showed that, while **1a** formed a crescent conformation, **1b** and **1c** produced a helix of one or two turns, and the diameter of the cavity of the helices was approximately 1.1 nm. As expected, the helices exhibited no helical bias due to lack of any chiral center. Because half of the carbonyl oxygen atoms are located inward, their binding toward chiral mono- and disaccharides **2a−d** through intermolecular C═O···H−N hydrogen bonding was investigated in chloroform. ^{1}H NMR and fluorescent experiments supported a 1:1 stoichiometry and complex **1c·2d** possessed the highest stability (K_a = 6.9 × 10^6 M^{-1}). The binding induced the folded hosts to produce helical bias as evidenced by the formation of strong induced circular dichroism (ICD) signals (Figure 1). The ICD signals could be weakened by

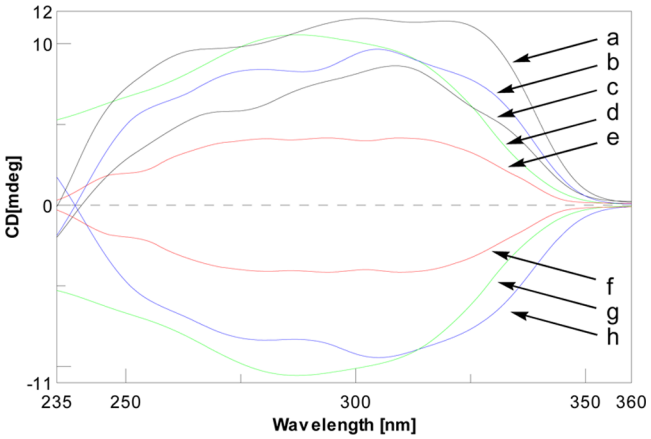
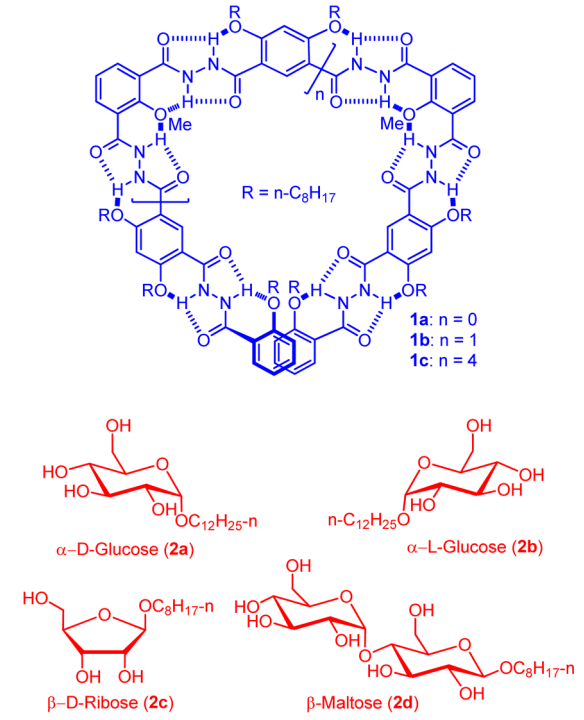


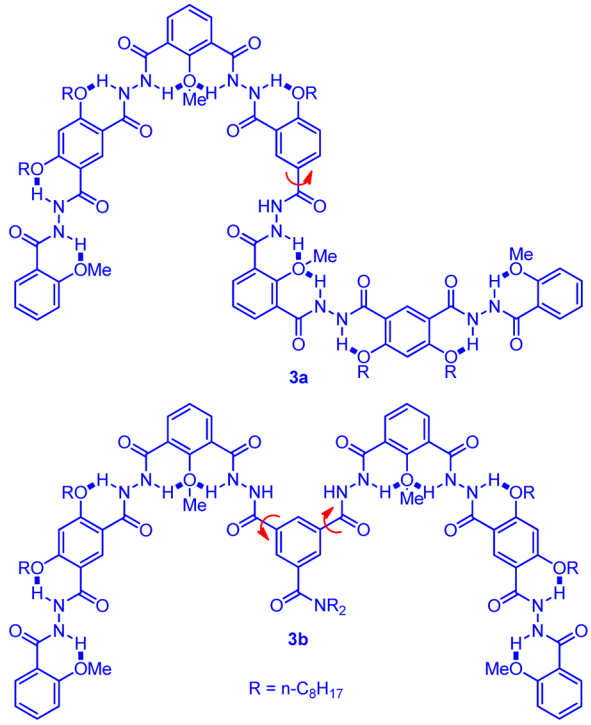
Figure 1. Induced CD spectra of complexes **1b·2d** (a), **1b·2a** (b), **1b·2c** (c), **1c·2a** (d), **1a·2a** (e), **1a·2b** (f), **1c·2b** (g), and **1b·2b** (h) in chloroform at 25 °C ([**1a**] = [**1b**] = [**1c**] = 2.0 × 10^{-4} M, [**2a**] = [**2b**] = [**2c**] = [**2d**] = 4.0 × 10^{-3} M).

polar methanol, indicating that the driving force for the binding came from intermolecular hydrogen bonding. For highly stable complex **1c·2d**, with the concentrations shown in Figure 1, >99% of **1c** would form the complex. The helical host might exist in P or M helicity. Molecular mechanics calculation for complex **1b·2c** suggested that **1b** adopted the P helicity upon binding.

For oligomers **1a−c**, the aromatic backbones were driven by successive intramolecular hydrogen bonding to fold into a crescent or helical conformation. The preorganized folded conformations were expected to enhance their ability to complex size- and binding site-matched guests due to the decreased negative entropy effect. However, if the lowest-energy folded conformation does not match with the size or shape of the guests, the host needs to adapt its conformation to maximize the binding, which would weaken the promoting effect of the conformational preorganization. To explore the overall effect of the intramolecular hydrogen bonding on binding, we also prepared heptamers **3a** and **3b**, from which one or two intramolecular hydrogen bonds were removed from the central aromatic ring.[31] Fluorescent titration experiments revealed that



the K_a values of their complexes with **2a** in chloroform were ca. 1.3×10^3 and 1.5×10^3 M^{-1}, respectively, which were substantially lower than that of **1b** (1.3×10^4 M^{-1}).[18] These results clearly show that conformational preorganization of the hosts helps to promote the intermolecular interaction. Although the stability of the complexes was decreased, CD spectra of the two mixtures gave rise to weak ICD signals, suggesting that the chiral guest still could induce the linear host to produce helical bias.



Binding-responsive chiral bias was also observed for other aromatic amide-based foldamers.[32,33] For example, F···H–N hydrogen bonding-induced foldamers **4a** and **4b** could complex chiral guest **5** in chloroform through intermolecular F···H–N hydrogen bonding.[32] The complexation caused both hosts to exhibit a negative Cotton effect around 277 nm (Figure 2),

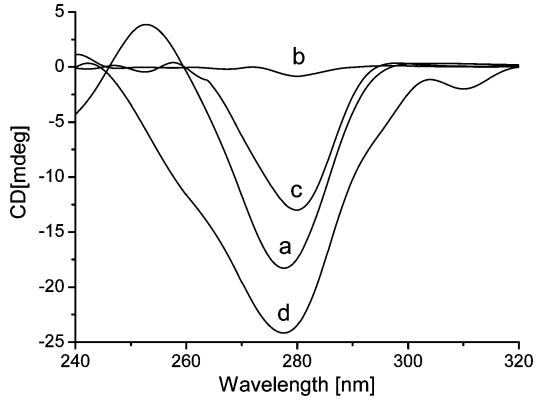
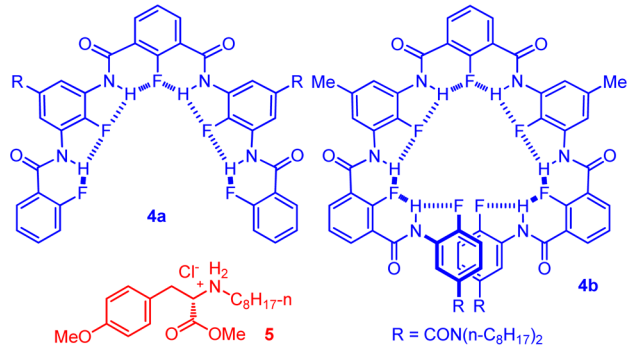


Figure 2. Induced CD spectra of complexes of **5** (1.0 mm) with (a) **4a** (1.0 mM), (b) **4b** (0.01 mM), (c) **4b** (0.05 mM), and (d) **4b** (0.2 mM) in chloroform at 25 °C.

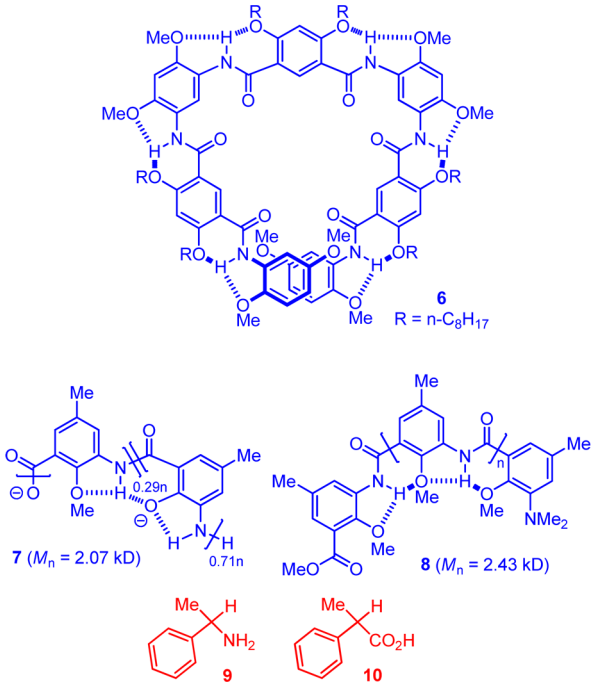
suggesting an identical chiral bias for both foldamers. The two hosts contain five and seven fluorine atoms in the cavity. All the fluorine atoms are donors for forming intermolecular hydrogen bonding with ammonium protons of **5**. For **4a**, the ammonium protons of **5** can approach the fluorine atoms within the cleft. For **4b**, which forms a closed helix of one turn, guest **5** might bind it from one side or through threading its cavity to produce a pseudo[2]rotaxane. Molecular dynamics calculations supported the second binding mode. The carbonyl oxygen atoms of foldamer **6** are all oriented inward.[33,34] In chloroform, this helix complexed saccharide guests **2a–d**.[33] Although the stability of the complexes was moderate, ICD signals were observed for all the complexes. Molecular modeling revealed that, without deforming, the cavity of this helix was not large enough to host the saccharide guests. Thus, the guests might approach the host from one side to form nonthreading complexes and induce the helix to produce chiral bias through multiple C═O···H–O hydrogen bonds.



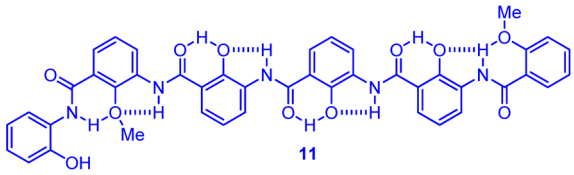
Guan and Li and co-workers prepared helical polyamides **7** and **8** via polycondensation reactions.[35] The strong intramolecular N–H···O hydrogen bonding induced the backbones to form stable helical conformations. In the highly polar solvent DMSO, the complexes formed between polymer **7** and chiral amine **9** (*R*- and *S*-) and between polymer **8** and chiral acid **10** (*R*- and *S*-) gave rise to strong ICD signals of mirror symmetry, indicating that the backbones of **7** and **8** produced significant helicity bias. Since the cavity of the helical polymers was not large

dx.doi.org/10.1021/ar5000242 | Acc. Chem. Res. 2014, 47, 1961–1970

enough to encapsulate the chiral guests, the helicity bias of the polymers has been attributed to the binding taking place at the end of the polymers via the noncovalent domino effect.

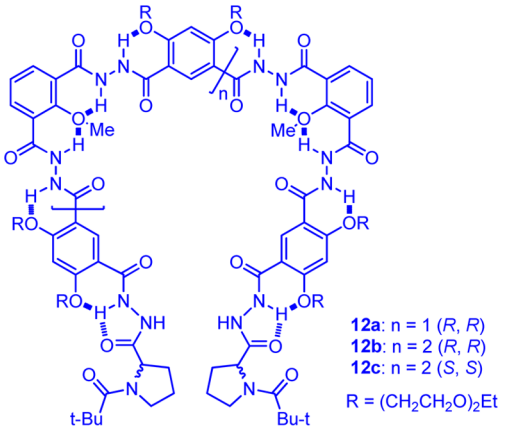


Zeng and co-workers also reported that phenol-inserted oligomers, like **11**, favored extended conformations due to the formation of the intramolecular six-membered O−H···O═C hydrogen bonding,[36] which is more stable than the common intramolecular six-membered O═C−N−H···OH hydrogen bonding. However, in the presence of an amine, more curved or helically folded states could be formed because the phenols were partially converted to phenoxides, which could form stable three-centered hydrogen bonding as observed for polymer **7**.



Huc and co-workers demonstrated that hollow aromatic amide foldamers can form single molecular capsules when the helix diameter at each end of the sequences was decreased to close the cavity.[37] Such helical capsules are able to encapsulate a matching guest and insulate it from the surrounding medium. Remarkably, when the guest is a chiral species, like D- or L-tartaric acid, the achiral helical host could be induced to adopt a unique handedness in both solution and solid state.[38]

For helical aromatic foldamers of one turn or longer, introducing a chiral group to one end or the middle could induce the folded backbones to produce helical bias.[39−41] We prepared oligomers **12a−c** by attaching two *R*- or *S*-proline units to the ends of folded hydrazide backbones.[42] Molecular dynamics simulations for **12a** and **12b** suggested that they mainly existed as the left-handed (*R*,*R*-M) helical conformer, which was energetically lower by 12−15 kcal/mol than the right-handed (*R*,*R*-P) helical conformer. As expected, CD spectra of **12b** and **12c** in chloroform were related to one another as mirror images. Similar to **1a−c**, **12a−c** also complexed **2a** and **2b**, and for the pairs of enantiomeric complexes **12b·2a** vs **12c·2b** and **12b·2b** vs **12c·2a**, mirror symmetry was observed for their CD spectra, illustrating their "enantiomeric" feature. The K_a values of the complexes were also determined by fluorescent titration experiments. It was found that complex **12a·2b** possessed the largest value, which was about 144 times higher than that of its "diastereomer" **12a·2a**. This large difference in K_a reflects that the appended chiral proline units could contribute remarkably to the chiral environment formed by the backbone for hosting a guest.



BINDING-RESPONSIVE CHIRALITY TRANSFER AND AMPLIFICATION IN ORGANOGELS

Hydrogen bonding-induced aromatic amide and hydrazide foldamers adopt crescent or helical conformations and thus resemble large discotic molecules to stack into vesicles or organogels, which are solvent-responsive.[43−46] Hydrazide foldamers could generate responsive host−guest organogels that exhibited unique time-dependent chirality transfer and amplification that are not observed for single-component organogels.[46] Compounds **13a−f**, which bear two arene units of varying size at the ends, strongly gelated organic solvents of varying polarity. Molecular mechanics calculations showed that these compounds formed a helical conformation of more than one turn. UV−vis, fluorescent, and X-ray diffraction experiments supported that the helical structures stacked in a "head-to-head" pattern to produce columnar aggregates. Adding glucoses **14a** or **14b** considerably improved the ability of the foldamers to gelate less polar solvents, although the glucoses themselves did not gelate any solvent. For example, in the presence of **14a** (1.0 equiv), the minimum gelation concentration of **13a** for toluene could be decreased from 2.60% to 0.30%. Since in the gel phases of hydrocarbons of low polarity the foldamers strongly complexed the glucoses and the glucoses should also aggregate through intermolecular hydrogen bonding, we proposed that this gelation enhancement was attributed to the capacity of the glucoses to promote the stacking of the foldamers by forming hydrogen-bonded glucose chains in the holes of the columns of the stacked foldamers.

CD studies also showed that the binding-responsive helical chirality of the folded molecules could be maintained in the gel state, as evidenced by the formation of strong induced CD signals. Remarkably, the ICD intensities of the toluene or *p*-xylene gels of the six complexes were all time-dependent. For the samples of **13d** and **13f**, the time for the ICD intensity to reach the maximum was very quick (less than 1 min), while for **13a** and **13c**, this time was as long as 2.5 and 10 h, respectively (Figures 3a,b). These observations indicated that the stacking of the chiral

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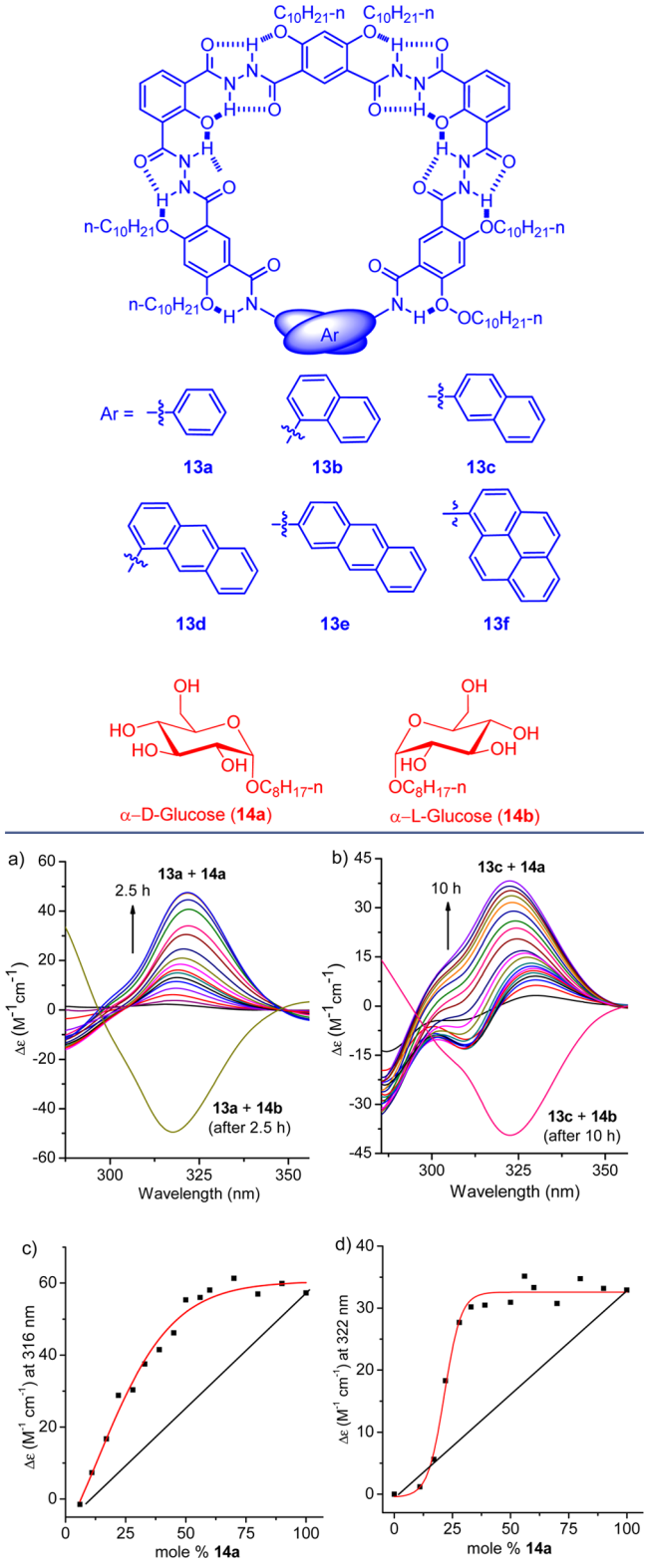
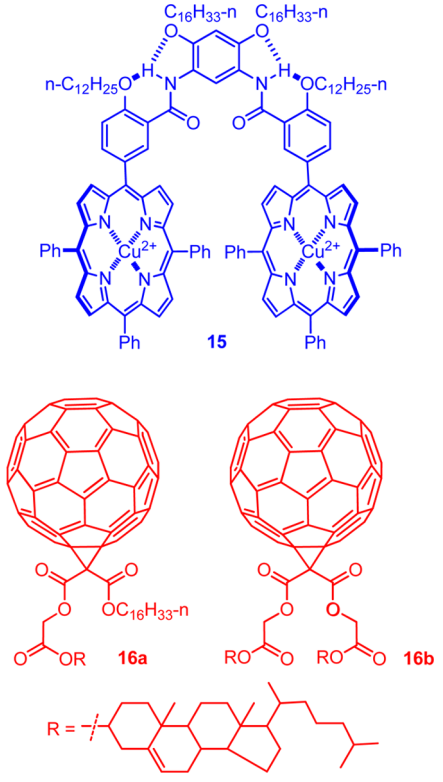


Figure 3. Time-dependent CD spectra of (a) **13a** and (b) **13c** in *p*-xylene in the presence of **14a** (1 equiv). "Sergeants-and-Soldiers" effect of the CD intensity of the *p*-xylene gels of (c) **13a** and (d) **13c** in the presence of **14a**. The concentration was 4 mM for **13a** and **13c**.

complexes in forming the fibrous networks was dynamic and self-adjustable. This binding-responsive supramolecular chirality transfer could be repeated with acceptable precision. Treating the ICD data with the Avrami equation revealed that gelation of these two-component systems underwent a two-phase nucleation–elongation mechanism.[47] The first phase was the slow nucleation, which involved stacking of single complex species into column aggregates reflected by the small and slow change of the ICD intensity, while the second elongation phase involved further aggregation of helical complexes onto the ends of the cylindrical assemblies, which led to quick enhancement of the helicity. In addition to this, the supramolecular chirality in the gels also exhibited a unique "Sergeants and Soldiers" effect.[48] That is, the ICD intensity against the mole percent of the guest showed a positive nonlinearity or sigmoidal curve: the ICD intensity changed from negative to positive nonlinearity with the addition of the guest (Figures 3c,d).

We had illustrated that preorganized bisporphyrin tweezers with a backbone similar to that of **15** strongly complexed C_{60} and its derivatives or pyridine derivatives in chloroform.[49,50] We found that the complexes of **15** with **16a** or **16b** gelated hydrocarbons, such as decalin, *n*-decane, cyclohexane, and *n*-hexane.[51] CD investigations showed that the chiral cholesterol unit could also transfer its chirality to the whole complex in the gel, as evidenced by the formation of a positive Cotton effect around 418 nm, which corresponded to the Soret band of the Cu(II) porphyrin unit. However, no time-dependence was observed for this host–guest system.



BINDING-RESPONSIVE FOLDING OF AROMATIC AMIDE OLIGOMERS

Most reported aromatic amide oligomers were introduced with successive intramolecular hydrogen bonds to induce the backbones to form folded conformations. To address the possibility of folding in the absence of intramolecular hydrogen bonding, we prepared a series of aromatic amide oligomers, including **17**, with alternating benzene and naphthalene segments.[24,52] In solvents of varying polarity, these oligomers did not fold into a compact conformation. Instead, they self-

dx.doi.org/10.1021/ar5000242 | Acc. Chem. Res. 2014, 47, 1961–1970

assembled into vesicular structures in methanol. However, in the presence of benzene-1,3,5-tricarboxylate (as tetrabutylammonium salt), the backbone could be induced to produce a folded conformation in DMSO by multiple intermolecular N−H···O hydrogen bonds, which was confirmed by ^{1}H NMR experiments.[24] This binding-responsive folding also caused the pyrene unit of oligomer **17** to generate a strong excimer emission centered at 490 nm (Figure 4). The K_a of the 1:1 complex

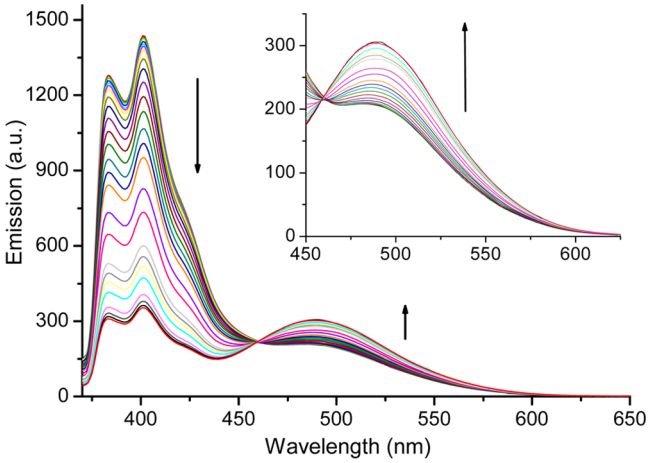
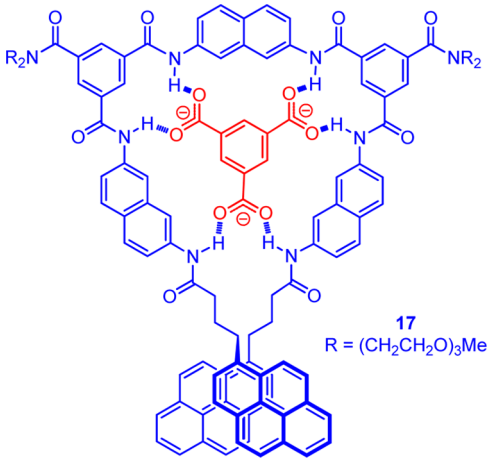
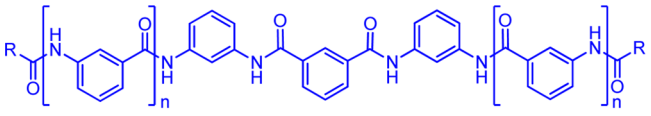


Figure 4. Fluorescence spectra of oligomer **17** (0.5 μM) with the addition of tetrabutylammonium benzene-1,3,5-tribarboxylate (0−28 μM) in DMSO at 25 °C (λ_{ex} = 349 nm). Inset, the fluorescence emission in the 450−625 nm region.

between **17** and benzene-1,3,5-tricarboxylate in DMSO was determined to be 8.6 × 10^5 M^{-1}. Given the high polarity of DMSO, this high value indicates that the intermolecular hydrogen bonds of the complex were highly cooperative.



Encouraged by the above result, we further prepared oligomers **18a−c** and found that the longest oligomer, heptamer **18c**, exhibited the strongest ability to complex mono-, di-, and tricarboxylate anion, all as tetrabutylammonium salt, with K_a being 80−470 M^{-1} in DMSO.[53] Compound **18c** was insoluble in chloroform due to the formation of strong intermolecular hydrogen bonding,[54] but its 1:1 mixture with glutamic acid dianion was soluble in chloroform-*d* and displayed signals of clear resolution, indicating the formation of a well-defined complex. For *R*- and *S*-glutamic acid dianions, the complexes gave an ICD signal of mirror symmetry around 300 nm, supporting that the chiral dianions could induce the heptamer to form helicity bias.



ION-PAIR BINDING-RESPONSIVE ALTERNATE ARRANGEMENT OF A CHIRAL SUPRAMOLECULAR BLOCK COPOLYMER

One type of supramolecular polymer involves monomer units held together by noncovalent bonds. One system that has been widely investigated is constructed by dimerization of the ureidopyrimidone (UPy) unit through forming strong quadruple hydrogen bonds.[55] We prepared ditopic monomers **19** and **20**, which bear two UPy units connected by a foldamer segment and a flexible aromatic amide segment, respectively.[25] Compound **20** was not soluble in chloroform. However, its mixture with **19** was soluble in chloroform, suggesting the formation of a supramolecular random block copolymer. In highly polar DMSO, their copolymerization could not occur due to competitive H-bonding of the solvent molecules that suppressed the dimerization of the UPy units. Adding chiral **21a** or **21b** to the 1:1 mixture in DMSO caused the mixture to produce a strong ICD signal of mirror symmetry. In contrast, a similar signal was not observed for the solution of the two pure compounds in the presence of the guest of the same concentration. Because the foldamer segment of **19** was reported to bind ammonium ions,[56] we proposed that the two ditopic compounds were induced by the chiral salt through ion-pair binding to stack alternately into a supramolecular block copolymer, which was further stabilized by the dimerization of the UPy units (Figure 5). The supramolecular block copolymer

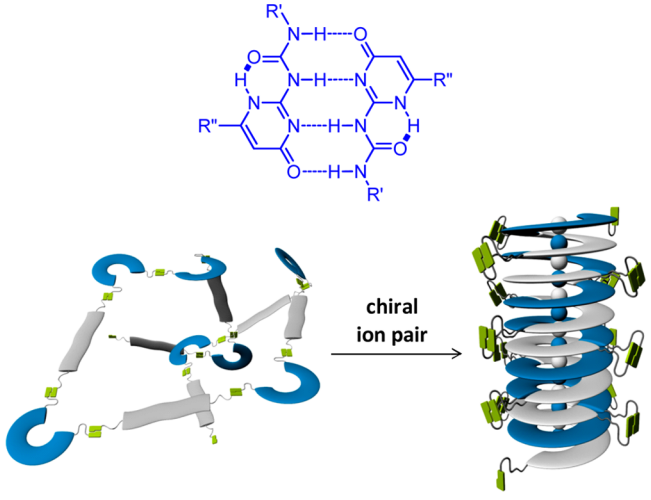
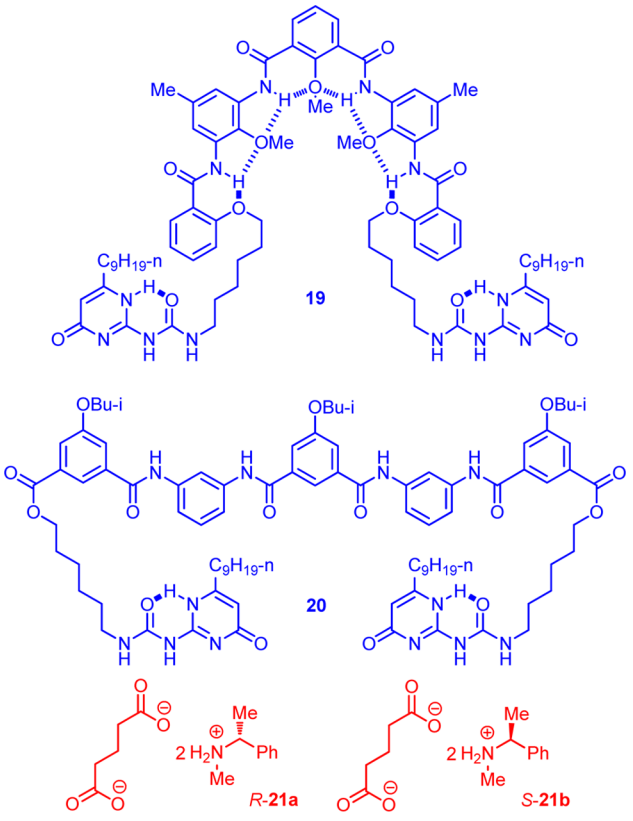


Figure 5. Quadruply hydrogen bonded UPy dimer and proposed model for the formation of chiral supramolecular block copolymers for **19** and **20** induced by their cooperative binding toward the anion and cation of a chiral ion pair guest.

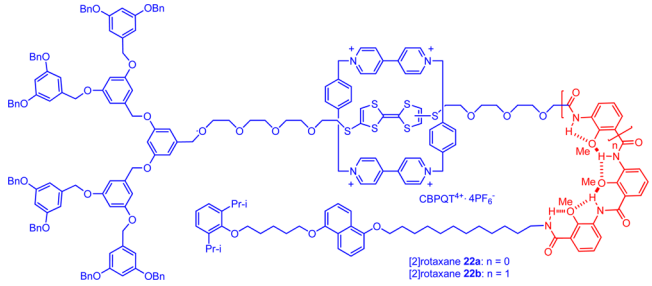
also exhibited a time-dependent ICD signal, which was very weak initially, became intensified gradually, and reached maximum strength after about 5 days. This observation suggests that the backbone of the supramolecular block copolymer, bearing two host sites, was induced by the chiral ion pair guest to produce helicity bias.

dx.doi.org/10.1021/ar5000242 | *Acc. Chem. Res.* 2014, 47, 1961−1970



TUNING THE DYNAMICS OF RESPONSIVE DONOR–ACCEPTOR (HOST–GUEST) INTERACTION

Compared with the extended state, hydrogen-bonded folded oligomers have a larger apparent size, and the reversible conversion between the folded and unfolded or extended states would break and recover the intramolecular hydrogen bonding, which has been used to tune the bulk mechanical property of methacrylate copolymers.[57] To develop a new approach for modulating molecular switches, we prepared [2]rotaxanes **22a** and **22b** by incorporating a foldamer segment into the thread component to separate the electron-rich tetrathiafulvalene (TTF) and naphthalene (NP) units, which formed a donor–acceptor interaction with the viologen units of the cyclobis(paraquat-*p*-phenylene) ($CBPQT^{4+}$) ring.[28,58] Such $CBPQT^{4+}$–TTF–NP-based [2]rotaxanes represent an important family of redox-responsive host–guest systems.[59] When the TTF unit existed in the neutral state, the $CBPQT^{4+}$ ring encircled it exclusively (Figure 6, **A**) because TTF is substantially more electron-rich than NP and the introduction of the foldamer segment does not affect the stability of this donor–acceptor system. After the TTF unit was oxidized to $TTF^{+\bullet}$ or TTF^{2+}, the $CBPQT^{4+}$ ring was repelled to slip over the foldamer segment to encircle the NP unit (Figure 6, **B** → **C**). Reduction of $TTF^{+\bullet}$ or TTF^{2+} of the preoxidized [2]rotaxanes to TTF led to the formation of a metastable state, which degenerated due to the shifting-back of the $CBPQT^{4+}$ ring to encircle the TTF unit through slipping over the foldamer segment (Figure 6, **D** → **A**). By recording the time-dependent charge-transfer absorption of the TTF–viologen interaction at 805 nm, we determined the half-lives of this shuttling of **22a** and **22b** to be 1.1 and 15.5 min in acetonitrile. In less polar chloroform, the half-life was 19.5 h for **22a**, which was 1064 times longer than that in acetonitrile, while **22b** did not exhibit similar charge-transfer absorption even after 3 days, indicating that its foldamer segment efficiently blocked this shuttling process. Clearly, the longer foldamer segment in a less polar medium would impose a larger steric barrier to deter or inhibit the shuttling of the ring component between the two electron-rich aromatic sites, and the whole process could be performed in a controllable manner.



Pure pseudo[2]rotaxanes **23a,b** were also assembled.[60] Their foldamer segment prevented the $CBPQT^{4+}$ ring from quickly slipping from the linear component. Both pseudo[2]rotaxanes formed reverse monolayer vesicles in the mixture of dichloro-

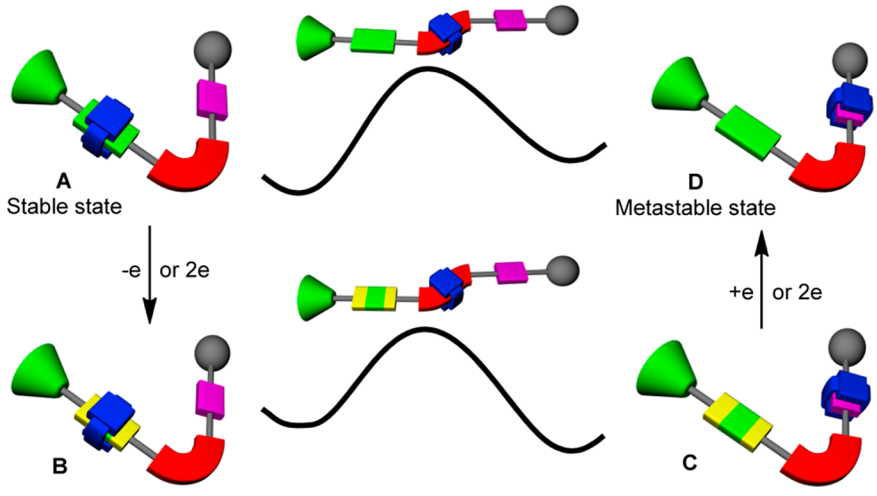
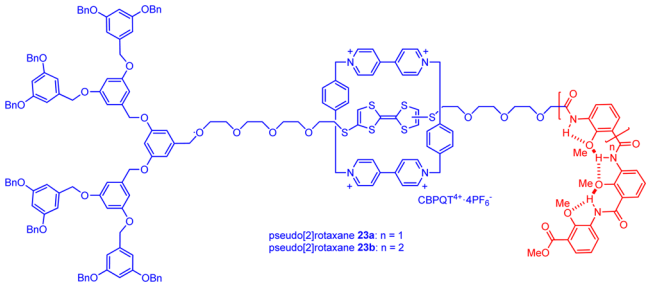


Figure 6. Schematic representation for the foldamer-tuned switching of the $CBPQT^{4+}$ ring between the TTF and NP sites in host–guest [2]rotaxanes **22a** and **22b**, with the TTF unit being neutral or oxidized to $TTF^{+\bullet}$ or TTF^{2+}.

dx.doi.org/10.1021/ar5000242 | *Acc. Chem. Res.* 2014, 47, 1961–1970

methane and cyclohexane (1:1) due to amphiphilicity. Oxidizing TTF to $TTF^{+\bullet}$ with $Fe(ClO_4)_3$ destroyed the vesicles. Upon addition of zinc powder, which reduced $TTF^{+\bullet}$ to TTF, the vesicular structures were regenerated quickly, indicating that the $CBPQT^{4+}$ ring just escaped from $TTF^{+\bullet}$ and slid onto the adjacent PEG units, but most of them did not slip off the linear component due to the existence of the foldamer segment.



FOLDING INDUCES FOLDING: A SOLVENT-RESPONSIVE INTRAMOLECULAR HOST–GUEST SYSTEM

Nature has evolved molecular chaperones, a family of proteins that assist the noncovalent folding and unfolding of other intrinsically disordered biomacromolecules, including proteins and nucleic acids. Huc and co-workers reported that folded 8-amino-2-quinolinecarboxylic acid oligomers induced the folding of attached amide oligomers to generate hybrid helices.[61] We found that a folded aromatic amide segment could induce one (**24a**, **24b**, *R*-**26**, and *S*-**26**) or two (**25**) attached triazole oligomers to fold through intramolecular stacking, which highly depended on the medium (Figure 7).[27] In highly polar DMSO,

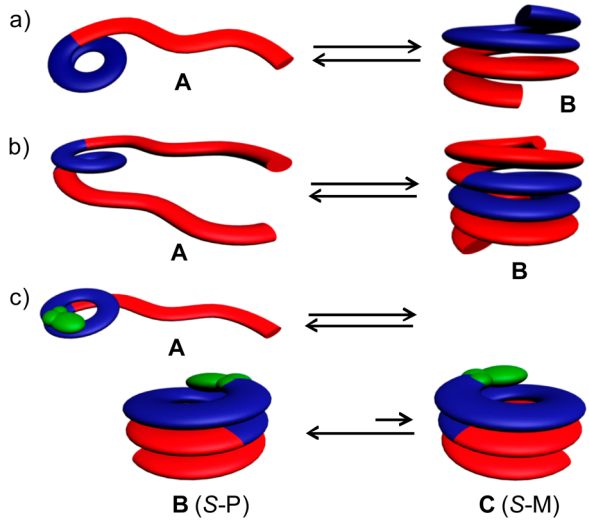
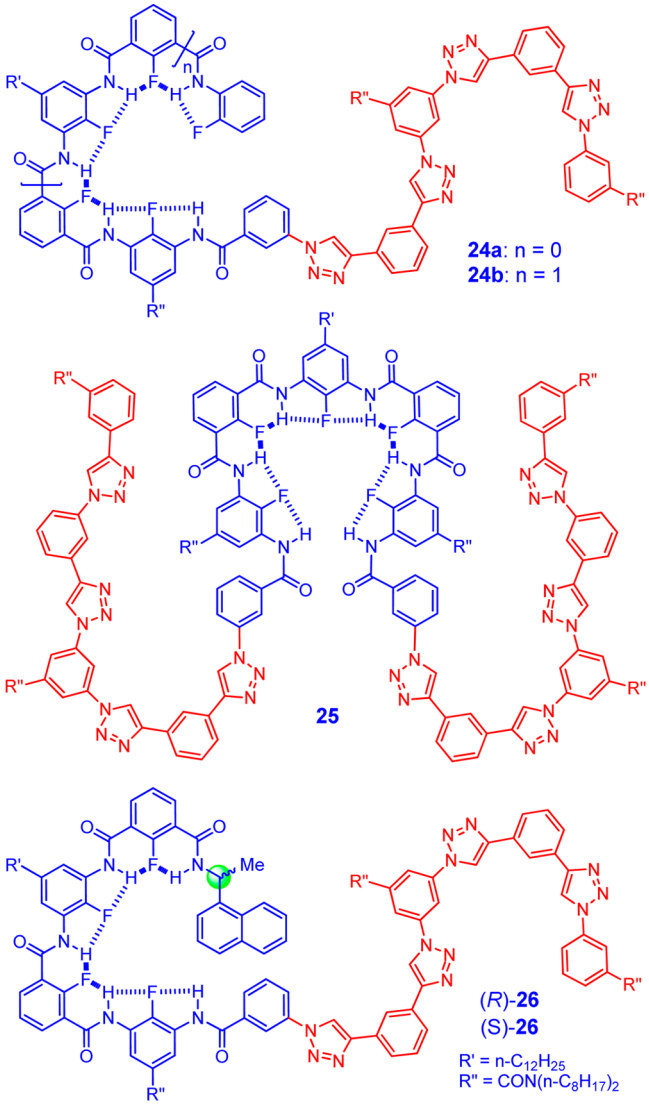


Figure 7. Schematic representation of the solvent-responsive folding-inducing-folding of compounds (a) **24a** and **24b**, (b) **25**, and (c) *S*-**26**.

their oligotriazole segments are all conformationally flexible (Figure 7, **A**), although the oligoamide segment may maintain its folded state, to some extent. In solvents of low polarity, such as chloroform, the oligotriazole segments can be induced by the oligoamide foldamer segment to fold to produce a hybrid helix through intramolecular stacking. A comparison of the ^1H NMR and UV spectra of **24a** and **24b** revealed that the longer amide segment in **24b** exhibited a larger inducing capacity than the shorter one of **24a** due to increase of the area stacking with the oligotriazole segment. Adding benzene or *n*-hexane of lower polarity further enhanced this inducing process. Enantiomers *R*-**26** and *S*-**26** bear a chiral center. A comparison of their CD spectra in chloroform with those of controls bearing no oligotriazole segment revealed that the two compounds produced an induced Cotton effect of mirror symmetry. The CD signal was further strengthened with the addition of *n*-hexane or the decrease of the temperature, reflecting enhanced helicity bias for the hybrid helix. Therefore, we may propose that the whole backbones of these compounds represent a new class of solvent-responsive intramolecular host–guest system where the amide segment behaves as a host and the triazole segment(s) act as guest(s).



CONCLUSION

This Account describes responsive host–guest systems that are constructed from aromatic amide and hydrazide foldamers or their derivatives. Since the concept of "Host–Guest Chemistry" was established, macrocyclic compounds have played a central role in the design of host molecules because they are able to bind guests with high stability and selectivity. Aromatic foldamers provide a robust alternative strategy for creating new acyclic hosts that not only can exhibit high stability and selectivity but

dx.doi.org/10.1021/ar5000242 | Acc. Chem. Res. 2014, 47, 1961–1970

also can implement binding in a responsive manner through conformational change and adaptability. For aromatic amide foldamers, this latter characteristic is particularly appealing due to their structural diversity and tunable cavity.

Although this Account mainly summarizes responsive helical chirality of aromatic amide foldamers, in the broader area of supramolecular chemistry, their dynamic and tunable conformational feature should find more applications. In this context, helical tabular aromatic amide polymers may provide an extremely fertile ground for new discoveries. For example, a tabular polymer may encapsulate a linear polymer to form a polymeric host−guest system. Attaching a guest to a foldamer host can lead to a single molecular system, which may be used to construct a new responsive supramolecular polymer. Extended backbones may also hold promise, particularly in the development of macromolecular systems bearing multiple host units. For these purposes, new highly efficient synthetic methods have to be developed, particularly for helical polymers of high molecular weight.

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Funding

This work was supported by MOST (Grant 2013CB834501), MOE (Grant IRT1117), STCSM (Grant 13NM1400200), and NSFC (Grants 91227108, 21172042, and 21272042).

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Fischer, E. Influence of configuration on the action of enzyme. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2985−2993.
(2) Cram, D. J.; Cram, J. M. Host-guest chemistry. *Science* **1974**, *183*, 803−809.
(3) Lehn, J.-M. Cryptates: Macropolycyclic inclusion complexes. *Pure Appl. Chem.* **1977**, *49*, 857−870.
(4) Zimmerman, S. C. Rigid molecular tweezers as hosts for the complexation of neutral guests. *Top. Curr. Chem.* **1993**, *165*, 71−102.
(5) Rebek, J., Jr.; Askew, B.; Islam, N.; Killoran, M.; Nemeth, D.; Wolak, R. Synthetic receptors: Size and shape recognition within a molecular cleft. *J. Am. Chem. Soc.* **1985**, *107*, 6736−6738.
(6) Saha, S.; Stoddart, J. F. Photodriven molecular devices. *Chem. Soc. Rev.* **2007**, *36*, 77−92.
(7) Yan, X.; Wang, F.; Zheng, B.; Huang, F. Stimuli-responsive supramolecular polymeric materials. *Chem. Soc. Rev.* **2012**, *41*, 6042−6065.
(8) Liu, K.; Kang, Y.; Wang, Z.; Zhang, X. Reversible and adaptive functional supramolecular materials: "Noncovalent interaction" matters. *Adv. Mater.* **2013**, *25*, 5530−5548.
(9) Seebach, D.; Matthews, J. L. β-Peptides: A surprise at every turn. *Chem. Commun.* **1997**, 2015−2022.
(10) Gellman, S. H. Foldamers: A manifesto. *Acc. Chem. Res.* **1998**, *31*, 173−180.
(11) Li, X.; Wu, Y.-D.; Yang, D. α-Aminoxy acids: New possibilities from foldamers to anion receptors and channels. *Acc. Chem. Res.* **2008**, *41*, 1428−1438.
(12) Huc, I. Aromatic oligoamide foldamers. *Eur. J. Org. Chem.* **2004**, 17−29.
(13) Gong, B. Hollow crescents, helices, and macrocycles from enforced folding and folding-assisted macrocyclization. *Acc. Chem. Res.* **2008**, *41*, 1376−1386.
(14) Saraogi, I.; Hamilton, A. D. Recent advances in the development of aryl-based foldamers. *Chem. Soc. Rev.* **2009**, *38*, 1726−1743.
(15) Zhang, D.-W.; Zhao, X.; Hou, J.-L.; Li, Z.-T. Aromatic amide foldamers: Structures, properties, and functions. *Chem. Rev.* **2012**, *112*, 5271−5316.
(16) Juwarker, H.; Jeong, K.-S. Anion-controlled foldamers. *Chem. Soc. Rev.* **2010**, *39*, 3664−3674.
(17) Hua, Y.; H. Flood, A. H. Click chemistry generates privileged CH hydrogen-bonding triazoles: The latest addition to anion supramolecular chemistry. *Chem. Soc. Rev.* **2010**, *39*, 1262−1271.
(18) 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.
(19) Li, Z.-T.; Hou, J.-L.; Li, C. Peptide mimics by linear arylamides: A structural and functional diversity test. *Acc. Chem. Res.* **2008**, *41*, 1343−1353.
(20) Yamato, K.; Kline, M.; Gong, B. Cavity-containing, backbone-rigidified foldamers and macrocycles. *Chem. Commun.* **2012**, *48*, 12142−12158.
(21) Ong, W. Q.; Zhao, H.; Fang, X.; Woen, S.; Zhou, F.; Yap, W.; Su, H.; Li, S. F. Y.; Zeng, H. Encapsulation of conventional and unconventional water dimers by water-binding foldamers. *Org. Lett.* **2011**, *13*, 3194−3197.
(22) Garric, J.; Léger, J.-M.; Huc, I. Encapsulation of small polar guests in molecular apple peels. *Chem.—Eur. J.* **2007**, *13*, 8454−8462.
(23) Gan, Q.; Ferrand, Y.; Bao, C.; Kauffmann, B.; Grelard, A.; Jiang, H.; Huc, I. Helix-rod host-guest complexes with shuttling rates much faster than disassembly. *Science* **2011**, *331*, 1172−1175.
(24) Xu, Y.-X.; Zhao, X.; Jiang, X.-K.; Li, Z.-T. Helical folding of aromatic amide-based oligomers induced by 1,3,5-benzenetricarboxylate anion in DMSO. *J. Org. Chem.* **2009**, *74*, 7267−7273.
(25) Shi, Z.-M.; Wu, C.-F.; Zhou, T.-Y.; Zhang, D.-W.; Zhao, X.; Li, Z.-T. Foldamer-based chiral supramolecular alternate block copolymers tuned by ion-pair binding. *Chem. Commun.* **2013**, *49*, 2673−2675.
(26) Sun, C.; Ren, C.; Wei, Y.; Qin, B.; Zeng, H. Patterned recognition of amines and ammonium ions by a stimuli-responsive foldamer-based hexameric oligophenol host. *Chem. Commun.* **2013**, *49*, 5307−5309.
(27) Wu, C.-F.; Li, Z.-M.; Xu, X.-N.; Zhao, Z.-X.; Zhao, X.; Wang, R.-X.; Li, Z.-T. Folding induces folding. The assembly of aromatic amide and 1,2,3-triazole hybrid helices. *Chem.—Eur. J.* **2014**, *20*, 1418−1426.
(28) Zhang, K.-D.; Zhao, X.; Wang, G.-T.; Liu, Y.; Zhang, Y.; Lu, H.-J.; Jiang, X.-K.; Li, Z.-T. Foldamer-tuned switching kinetics and metastability of [2]rotaxanes. *Angew. Chem., Int. Ed.* **2011**, *50*, 9866−9870.

(29) Yashima, E.; Maeda, K.; Iida, H.; Furusho, Y.; Nagai, K. Helical polymers: Synthesis, structures, and functions. *Chem. Rev.* **2009**, *109*, 6102−6211.
(30) Prince, R. B.; Barnes, S. A.; Moore, J. S. Foldamer-based molecular recognition. *J. Am. Chem. Soc.* **2000**, *122*, 2758−2762.
(31) Du, P.; Xu, Y.-X.; Jiang, X.-K.; Li, Z.-T. Complexation of two non-fully hydrogen bonded aromatic hydrazide heptamers toward n-octyl-α-L-glucopyranoside in chloroform. *Sci. China B* **2009**, *52*, 489−496.
(32) 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.
(33) 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.
(34) Yuan, L.; Sanford, A. R.; Feng, W.; Zhang, A.; Zhu, J.; Zeng, H.; Yamato, K.; Li, M.; Ferguson, J. S.; Gong, B. Synthesis of crescent aromatic oligoamides. *J. Org. Chem.* **2005**, *70*, 10660−10669.
(35) Lu, Y.-X.; Shi, Z.-M.; Li, Z.-T.; Guan, Z. Helical polymers based on intramolecularly hydrogen-bonded aromatic polyamides. *Chem. Commun.* **2010**, *46*, 9019−9021.
(36) Sun, C.; Ren, C.; Wei, Y.; Qin, B.; Zeng, H. Patterned recognition of amines and ammonium ions by a stimuli-responsive foldamer-based hexameric oligophenol host. *Chem. Commun.* **2013**, *49*, 5307−5309.
(37) Garric, J.; Léger, J.-M.; Huc, I. Molecular apple peels. *Angew. Chem., Int. Ed.* **2005**, *44*, 1954−1958.
(38) Ferrand, Y.; Kendhale, A. M.; Kauffmann, B.; Grélard, A.; Marie, C.; Blot, V.; Pipelier, M.; Dubreuil, D.; Huc, I. Diastereoselective encapsulation of tartaric acid by a helical aromatic oligoamide. *J. Am. Chem. Soc.* **2010**, *132*, 7858−7859.
(39) Gin, M. S.; Yokozawa, T.; Prince, R. B.; Moore, J. S. Helical bias in solvophobically folded oligo(phenylene ethynylene)s. *J. Am. Chem. Soc.* **1999**, *121*, 2643−2644.
(40) Jiang, H.; Dolain, C.; Léger, J.-M.; Gornitzka, H.; Huc, I. Switching of chiral induction in helical aromatic oligoamides using solid state-solution state equilibrium. *J. Am. Chem. Soc.* **2004**, *126*, 1034−1035.
(41) Naidu, V. R.; Suk, J.-m.; Lee, G. L.; Jeong, K.-S. Chiral oligoindole foldamers showing anion-induced helical bias. *Bull. Korean Chem. Soc.* **2009**, *30*, 482−485.
(42) 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.
(43) Cai, W.; Wang, G.-T.; Xu, Y.-X.; Jiang, X.-K.; Li, Z.-T. Vesicles and organogels from foldamers: A solvent-modulated self-assembling process. *J. Am. Chem. Soc.* **2008**, *130*, 6936−6937.
(44) Wang, L.; Xiao, Z.-Y.; Hou, J.-L.; Wang, G.-T.; Jiang, X.-K.; Li, Z.-T. Self-assembly of vesicles from the stacking of a dipodal hydrogen bonded arylamide foldamer. *Tetrahedron* **2009**, *65*, 10544−10551.
(45) Zhou, C.; Cai, W.; Wang, G.-T.; Zhao, X.; Li, Z.-T. Hydrogen bonded shape-persistent aryl hydrazide polymers: Design, synthesis and side-chain-tuned formation of vesicles and organogels. *Macromol. Chem. Phys.* **2010**, *211*, 2090−2101.
(46) Cai, W.; Wang, G.-T.; Du, P.; Wang, R.-X.; Jiang, X.-K.; Li, Z.-T. Foldamer organogels: A circular dichroism study of glucose-mediated dynamic helicity induction and amplification. *J. Am. Chem. Soc.* **2008**, *130*, 13450−13459.
(47) De Greef, T. F. A.; Meijer, E. W. Supramolecular polymers. *Nature* **2008**, *453*, 171−173.
(48) Green, M. M.; Cheon, K.-S.; Yang, S.-Y.; Park, J.-W.; Swansburg, S.; Liu, W. Chiral studies across the spectrum of polymer science. *Acc. Chem. Res.* **2001**, *34*, 672−680.
(49) 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 C_{60}, C_{70} and C_{60} derivatives. *J. Am. Chem. Soc.* **2005**, *127*, 17460−17468.
(50) Li, C.-Z.; Zhao, X.; Gao, X.; Wang, Q.-R.; Li, Z.-T. Foldamer-derived preorganized bi- and tri-zinc porphyrin tweezers for a pentafluorobenzene-bearing pyridine guest: The binding pattern study. *Chin. J. Chem.* **2013**, *31*, 582−588.
(51) Xiao, Z.-Y.; Hou, J.-L.; Jiang, X.-K.; Li, Z.-T.; Ma, Z. Complexes between hydrogen bonded bisporphyrin tweezers and cholesterol-appended fullerenes as organogelators and liquid crystals. *Tetrahedron* **2009**, *65*, 10182−10191.
(52) Xu, Y.-X.; Wang, G.-T.; Zhao, X.; Jiang, X.-K.; Li, Z.-T. Self-assembly of vesicles from amphiphilic aromatic amide-based oligomers. *Langmuir* **2009**, *25*, 2684−2688.
(53) Shi, Z.-M.; Chen, S.-G.; Zhao, X.; Jiang, X.-K.; Li, Z.-T. Meta-substituted benzamide oligomers that complex mono-, di- and tricarboxylates: Folding-induced selectivity and chirality. *Org. Biomol. Chem.* **2011**, *9*, 8122−8129.
(54) Xu, Y.-X.; Zhan, T.-G.; Zhao, X.; Li, Z.-T. Hydrogen bonding-driven highly stable homoduplexes formed by benzene/naphthalene amide oligomers. *Org. Chem. Front.* **2014**, *1*, 73−78.
(55) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. Supramolecular polymers. *Chem. Rev.* **2001**, *101*, 4071−4097.
(56) 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.
(57) Shi, Z.-M.; Huang, J.; Ma, Z.; Zhao, X.; Guan, Z.; Li, Z.-T. Foldamers as cross-links for tuning the dynamic mechanical property of methacrylate copolymers. *Macromolecules* **2010**, *43*, 6185−6192.
(58) Zhang, K.-D.; Zhao, X.; Wang, G.-T.; Liu, Y.; Zhang, Y.; Lu, H.-J.; Jiang, X.-K.; Li, Z.-T. Foldamers in pseudo[2]rotaxanes and [2]-rotaxanes: Tuning the switching kinetics and metastability linear aromatic amide foldamer-derived supramolecular architectures and materials. *Tetrahedron* **2012**, *68*, 4517−4527.
(59) Nygaard, S.; Leung, K. C.-F.; Aprahamian, I.; Ikeda, T.; Saha, S.; Laursen, B. W.; Kim, S.-Y.; Hansen, S. W.; Stein, P. C.; Flood, A. H.; Stoddart, J. F.; Jeppesen, J. O. Functionally rigid bistable [2]rotaxanes. *J. Am. Chem. Soc.* **2007**, *129*, 960−970.
(60) Zhang, K.-D.; Zhou, T.-Y.; Zhao, X.; Jiang, X.-K.; Li, Z.-T. Redox-responsive reverse vesicles self-assembled by pseudo[2]rotaxanes for tunable dye release. *Langmuir* **2012**, *28*, 14839−14844.
(61) Sánchez-García, D.; Kauffmann, B.; Kawanami, T.; Ihara, H.; Takafuji, M.; Delville, M.-H.; Huc, I. Nanosized hybrid oligoamide foldamers: Aromatic templates for the folding of multiple aliphatic units. *J. Am. Chem. Soc.* **2009**, *131*, 8642−8648.