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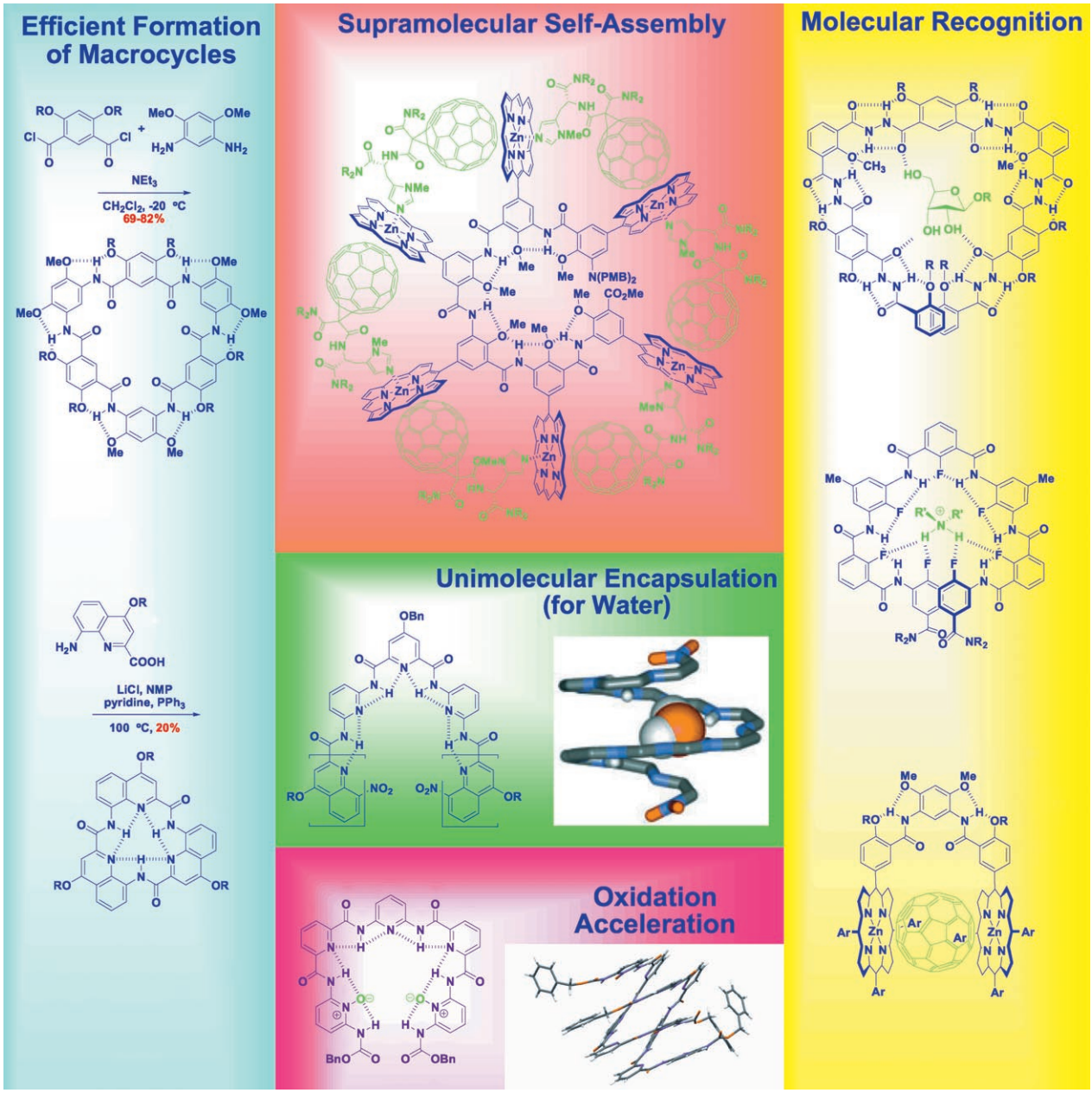
Shape-Persistent Aromatic Amide Oligomers: New Tools for Supramolecular Chemistry

Zhan-Ting Li,* Jun-Li Hou, Chuang Li, and Hui-Ping Yi[a]

Dedicated to Professor Xi-Kui Jiang on the occasion of his 80th birthday



Abstract: With an increasing number of folding and helical structures available, chemists have begun to pay greater attention to the functions of this family of structurally unique oligomers. Hydrogen-bonding-mediated aromatic oligoamide foldamers have the features of good structural predictability, synthetic facility, and structural modification, which make them very promising as scaffolds or platforms for supramolecular chemistry. Recent advances in the applications of this class of shape-persistent oligomers in the promoted synthesis of macrocycles, design of new nonring receptors, supramolecular self-assembly, molecular encapsulation, and reaction acceleration, are highlighted in this Focus Review.

Keywords: amides · foldamers · hydrogen bonds · molecular recognition · self-assembly

1. Introduction

Nature is a master in the use of noncovalent forces to control the folding and self-assembly of biological macromolecules. In peptides and proteins, the combination of noncovalent forces, such as hydrogen bonding and hydrophobic, electrostatic, and van der Waals interactions, is encoded in the primary structure, the sequence of amino acids. As a result, thermodynamically and kinetically stable secondary and/or tertiary structures can be produced, and sophisticated chemical operations or functions, such as catalysis, selective binding or recognition, controlled flow of electrons, directed crystallization of inorganic phases, and so on, can be realized.

In the last decade, chemists have been actively engaged in developing foldamers, the artificial systems that are induced by noncovalent forces to adopt specific compact conformations.[1–6] Among other noncovalent interactions such as metal–ligand coordination and donor–acceptor and solvophobic interactions, the hydrogen-bonding motif has proven to be a highly efficient tool in inducing the formation of folding or helical patterns owing to its directionality and strength.[6a] Examples of folded aliphatic β-peptides, γ-peptides, δ-peptides, and many other nonnatural backbones were reported.[2] With an increasing number of folding patterns available, the functions or applications of synthetic foldamers were investigated in recent years. For example, Cheng, Gellman, and DeGrado extensively investigated the antibacterial and antimicrobial activity of β-peptides,[7] whereas Hamilton and co-workers used aromatic oligoamide foldamers to mimic the binding surface of protein helices.[8] Since 1996, a large number of aromatic amide-based foldamers have been reported.[9–11] This Focus Review focuses on the design and functions of hydrogen-bonding-mediated aromatic oligoamide secondary structures in the direction of molecular recognition and supramolecular self-assembly. Other systems induced by non-covalent forces are also briefly discussed in the related sections.

2. Intramolecular Hydrogen-Bonding Patterns

For any stable secondary structure to be formed from aromatic oligoamides, rotation about the Ar–CONHAr and Ar–NHCOAr bonds have to be restricted. Intramolecular hydrogen bonding provides the most-simple, efficient, and reliable approach for this purpose.[5,6a] Figure 1 shows the typical intramolecular hydrogen-bonding patterns that have been used to restrict the rotation of the Ar–CONHAr bond

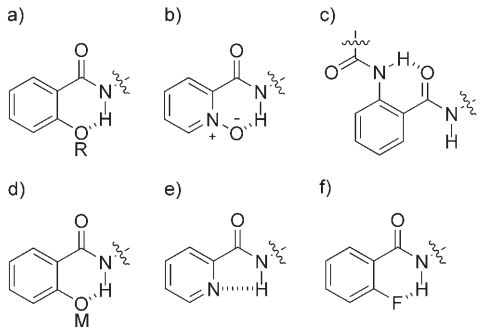


Figure 1. Typical intramolecular hydrogen-bonding patterns for restricting the rotation of the Ar–CONHAr bond.

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in folding oligomers. The six- and five-membered rings formed by O···H–N and N···H–N hydrogen bonding (Figure 1 a–e) are well-established.[9a,11a] Replacement of the OR (Figure 1 a) with an OH group lowers the stability of the conformation shown because the OH proton can also form a six-membered hydrogen bond with the neighboring carbonyl oxygen atom.[5] On the other hand, a phenoxide salt (Figure 1 d, M = K) was reported to form the expected intramolecular hydrogen bonding that is used to induce the formation of ionic foldamers.[12] It is well-established that fluoride ion is a very strong proton acceptor. However, covalently bound fluorine is considered a very weak hydrogen-bond acceptor.[13] Our recent studies demonstrated that this is not the case; intramolecular F···H–N hydrogen bonding, as shown in Figure 1 f, can be readily formed.[14,15]

Figure 2 presents representative examples of intramolecular hydrogen-bonding patterns that restrict the rotation of the Ar–NHCOAr bond in foldamers.[9a,11a,16] These hydrogen-bonding patterns combine with those shown in Figure 1 to lead to the construction of a variety of well-defined secondary structures. Notably, although intramolecular hydrogen bonding has always been proposed and evidenced to stabilize the conformations shown in Figures 1 and 2, the repulsive interactions between the proton acceptor and the amide oxygen atom should also make a contribution. A four-membered hydrogen-bonding mode was also observed in 2-aminopyridine-derived amides and related folding or helical structures (Figure 2 g).[5]

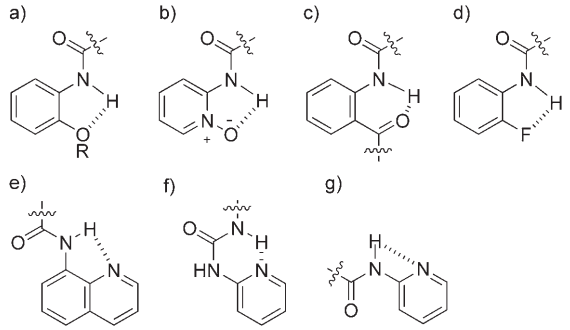


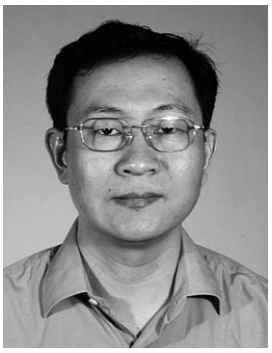
Figure 2. Typical intramolecular hydrogen-bonding patterns for restricting the rotation of the Ar–NHCOAr bond.

Abstract in Chinese:

近年来, 越来越多的非天然折叠和螺旋结构被报道出来, 对它们的功能和性质研究也逐渐引起化学家的重视. 氢键诱导的芳酰胺折叠体具有可预测的二级结构, 合成相对简单并且易于修饰, 可以作为超分子化学研究的砌块和骨架. 本文总结了近年来形状固定的芳酰胺寡聚物在促进大环化合物合成, 新的非环受体的设计, 超分子自组装、分子包结及反应加速等方面的应用进展.

3. Extended Secondary Structures

A foldamer is defined as "any oligomer that folds into a conformationally ordered state in solution, the structures of which are stabilized by a collection of noncovalent interactions between nonadjacent monomer units".[2] Although most of the synthetic secondary structures reported have a



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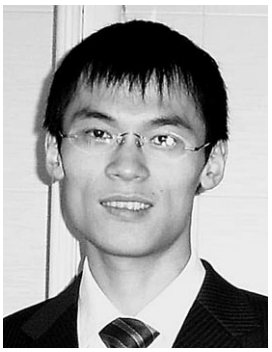

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folding or helical conformation, there are a number of "foldamers" that adopt other types of extended conformations. Such extended secondary structures not only provide structural diversity for this rapidly expanding family, more importantly, as we will demonstrate in the following sections, they also represent new unique assembled scaffolds for the construction of a new generation of functional molecular architectures. Therefore, representative examples of such extended secondary structures are summarized below.

The first class of extended secondary structures are those with a relatively straight planar conformation (Figure 3). The linear motif **1**, which consists of 3,3′-diamino-2,2′-bipyridine and 2,5-bis(2-aminophenylene)pyrazine units, was reported by Meijer and co-workers.[17] The backbone of this motif is not made from amides, which are instead utilized to stabilize the planar conformation through intramolecular hydrogen bonding and to provide solubility in organic solvents. Another series of straight secondary structures **2**, oligoamides of 6-*iso*-proxy-5-aminopicolinic acid, were developed by Hamilton and co-workers.[8] The amide protons in these molecules form intramolecular hydrogen bonding with both the oxygen and nitrogen atoms of the neighboring ether and endocyclic pyridine units. This series of oligomers have been used as α-helix mimetic scaffolds to recognize protein surfaces because the distance between the neighboring *iso*-proxy residues in the oligomers is close to that between the side-chains along one face of the polyalanine α-helix. More recently, we found that anthranilamide oligomers **3a** and **3b**

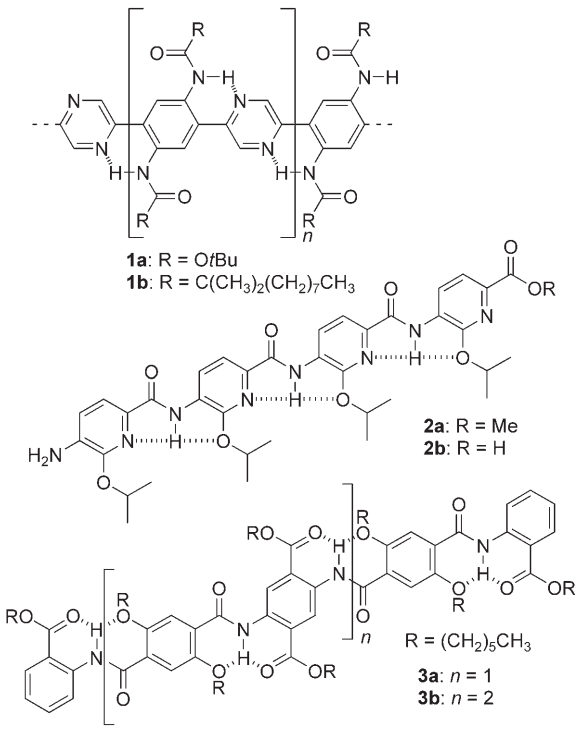

Figure 3. Rigidified, straight, and planar conformations induced by intramolecular hydrogen bonding.

can be readily prepared from dialkoxylated *p*-phenylenediamine and *p*-phthalic acid derivatives.[18] Due to strong intramolecular three-centered hydrogen bonding, these oligomers self-assemble into highly stable straight and planar molecular ribbons, which have been characterized by X-ray crystallography and ^{1}H NMR, IR, and UV/Vis spectroscopy.

The second class of extended secondary structures are those that have a rigid planar conformation but a zigzag skeleton (Figure 4). The first example of this type of structure, oligoamide **4** of anthranilic acid, was reported by Hamilton and co-workers.[9a] X-ray diffraction analysis of a dimeric analogue of **4** revealed the formation of the expected six-membered rings through hydrogen bonding in these oligomers. The rotation of the Ph–NHCOPh bond is restricted by the inherent co-planarity of the aromatic amide and the repulsion between the neighboring benzene units. Recently, this hydrogen-bonding-free conformational preference of aromatic amides were successfully used to construct two series of oligoamide foldamers.[19,20] With continual three-centered intramolecular hydrogen bonding as the driving force, we recently constructed another series of planar zigzag structures **5** (Figure 4),[21] which have found applications in the self-assembly of new macrocyclophanes and synthetic receptors for fullerene guests (see below).

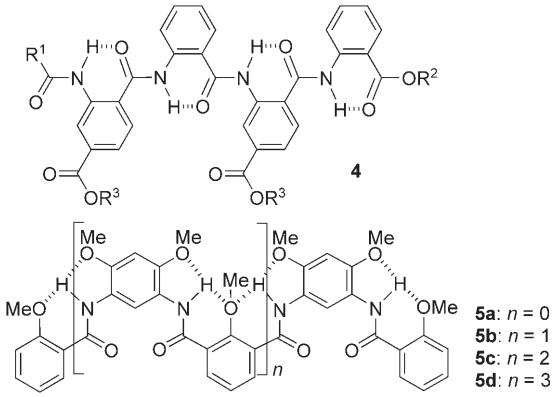

Figure 4. Examples of zigzag conformations induced by intramolecular hydrogen bonding.

Branched oligomers can also be induced by intramolecular hydrogen bonding to adopt extended flat conformations. For example, Parquette and co-workers utilized this driving force to rigidify pyridine-2,6-dicarboxy-linked anthranilamide dendron **6** (Figure 5).[22] Well-defined folded dendrimers were assembled based on this structurally unique building block. Meijer and co-workers reported that branched oligomers **7** can form a rigid flat conformation that is also stabilized by intramolecular hydrogen bonding (Figure 5).[23] Such rigidified extended structures can stack to generate hierarchical columnal aggregates, and chiral peripheral chains can transfer their chirality to the entire columnal aggregate by efficient stacking of the rigid branched structures.[24]

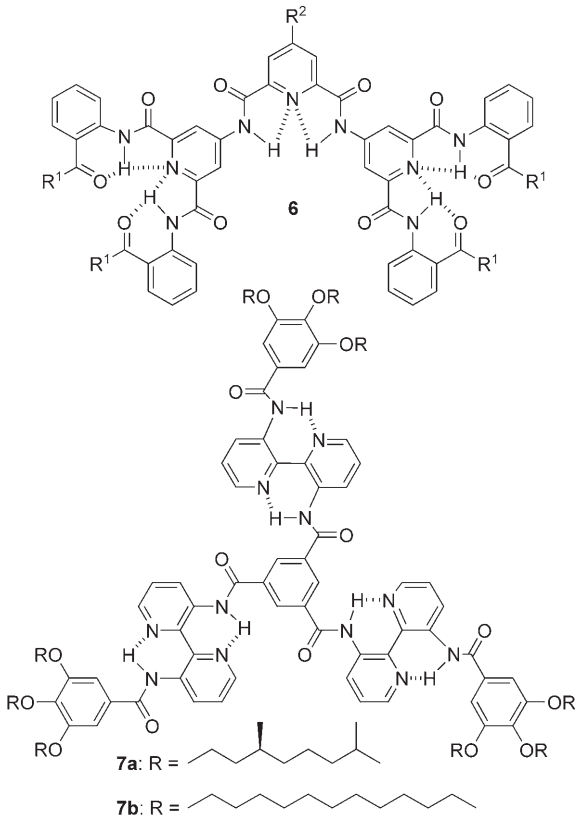

Figure 5. Examples of rigidified branched structures stabilized by intramolecular hydrogen bonding.

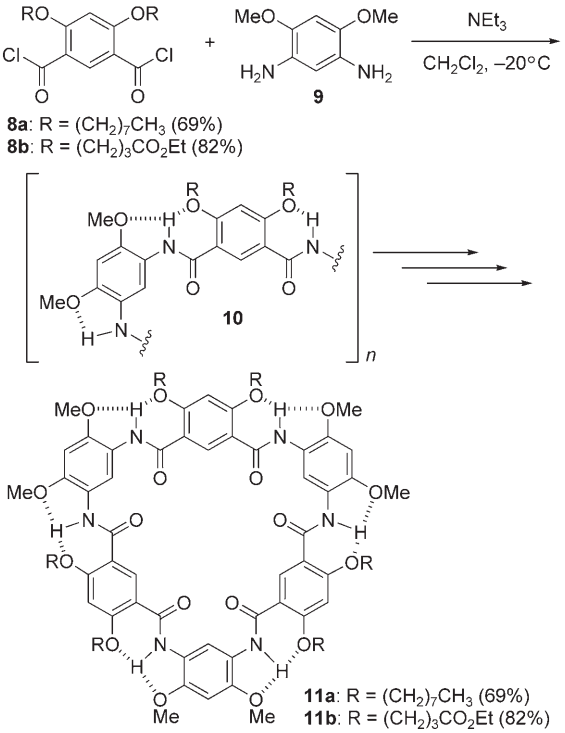

Figure 6. One-step synthesis of macrocycles **11** promoted by intramolecular hydrogen bonding.

4. Self-Assembly of Macrocyclophanes Promoted by Preorganization

In the last few decades, macrocycles have received intense interest because of their widespread occurrence in nature and their versatile properties and applications. The synthesis of macrocyclic molecules is usually of low efficiency owing to the disfavored entropic effect and frequently needs high-dilution or template techniques. Advances in foldamer research have brought a new approach to the synthesis of macrocylic architectures by preorganizing the conformation of monomeric or oligomeric precursors. For example, Gong and co-workers reported that the one-step reactions of diacid chlorides **8a** and **8b** with diamine **9** in dichloromethane at −20 °C, at the relatively high concentration of 0.98 mM, afforded the corresponding macrocyclic products **11a** and **11b** in 69% and 82% yields, respectively (Figure 6).[25] In contrast, even under conditions of high dilution and in the presence of calcium chloride as template, the reaction of isophthaloyl chloride and *m*-phenylenediamine produced the corresponding cyclic hexamer product, similar to **11**, in only 4–11% yield.[26] The folding induced by intramolecular hydrogen bonding and preorganization of the noncyclic intermediates **10** are clearly responsible for the abundant formation of macrocyles **11**.

The synthesis of metallomacrocyclophanes can also be facilitated by preorganization of the precursor ligands directed by intramolecular hydrogen bonding. For example, metallocyclophanes **15** and **16** were assembled from the reactions of **12** with hydrogen-bonding-mediated diacetylenes **13** and **14** (Figure 7).[27] The yields were moderate. However, in the absence of three-centered hydrogen bonding, no similar macrocycles were produced from the reaction of **12** with a diacetylene derivative similar to **13**. Therefore, the intramolecular hydrogen bonds in **13** and **14** are required to force the two terminal acetylene units to orientate to one side of the backbone and promote the formation of the metallocyclophanes. On the basis of similar approaches, metallocyclophanes **17**–**19** were also prepared in moderate yields from the corresponding hydrogen-bonding-mediated preorganized precursors (Figure 8).[21,28] With rigidified backbones and controllable size, these new shape-persistent cyclophanes may serve as building blocks for the construction of nanoscale supramolecular architectures or new synthetic receptors. Fluorescence studies revealed that cyclophanes **15** and **16**, with amide oxygen atoms located on the inside of the macrocyclic ring, are able to complex alkylated sugars in chloroform.[27]

Huc and co-workers found that, even in highly polar media, intramolecular hydrogen bonding can still direct the formation of macrocyclic compounds by inducing the folding conformation of intermediates.[29] Thus, heating a solution of **20** in the highly polar solvent of NMP/pyridine resulted in the formation of cyclic trimer **21** in 20% yield (Figure 9).

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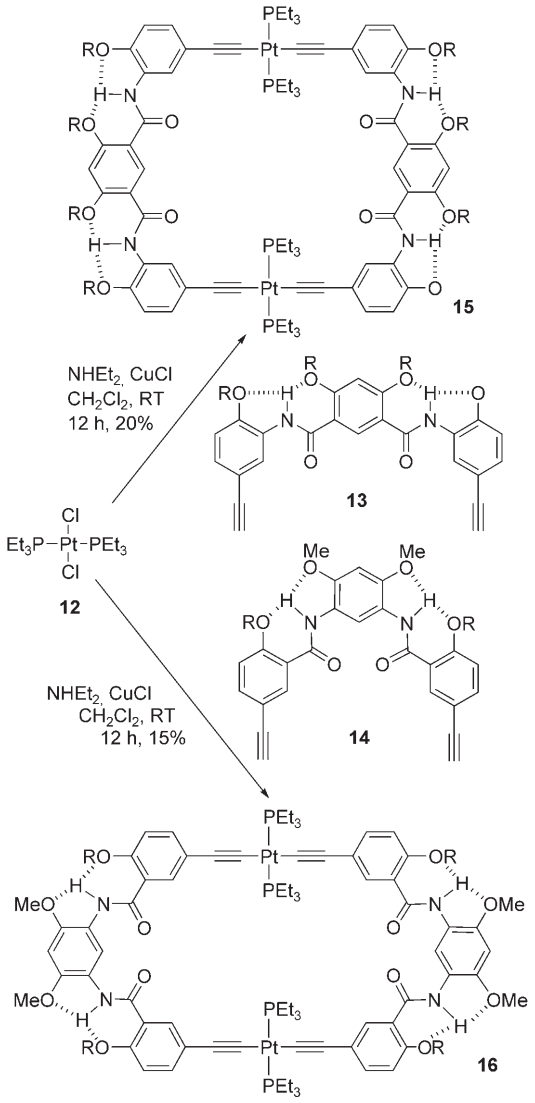

Figure 7. Synthesis of metallomacrocycles **15** and **16** promoted by intramolecular hydrogen bonding.

Given the tough reaction conditions and the very high solvent polarity, this yield is quite impressive. X-ray diffraction analysis showed that the curvature of **21** is close to that of a noncyclic trimer analogue. Thus, it is proposed that the intermediates of the cyclization reaction also adopt a folding conformation driven by intramolecular hydrogen bonding.

Recently, Gong and co-workers also found that treatment of **22** with triphosgene in hot toluene affords macrocycles **24** in very high yields (Figure 10).[30] In this system, the rigidified folding conformation of intermediate **23** was achieved by the combination of the six-membered rings from hydrogen bonding and the preference of the urea units to adopt a *cis* conformation. This conformational feature of aromatic ureas was also used to assemble a series of urea foldamers with larger cavities.[31]

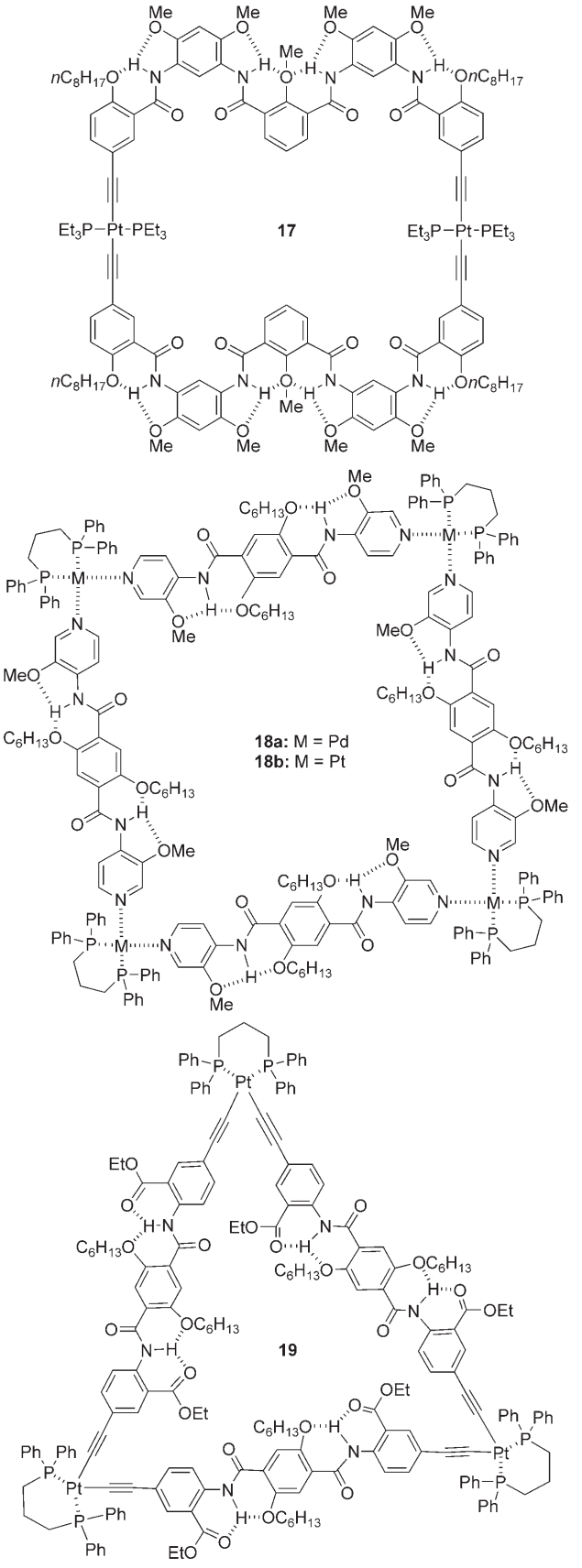

Figure 8. Structures of metallomacrocyclophanes **17**, **18**, and **19**, which were assembled from preorganized rodlike precursors.

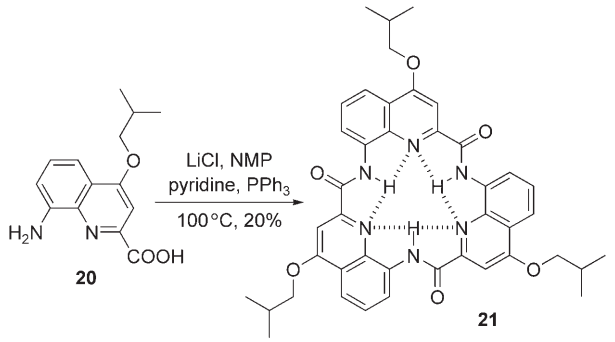

Figure 9. Synthesis of macrocycle **21** in highly polar solvent directed by intramolecular hydrogen bonding. NMP = *N*-methyl-2-pyrrolidone.

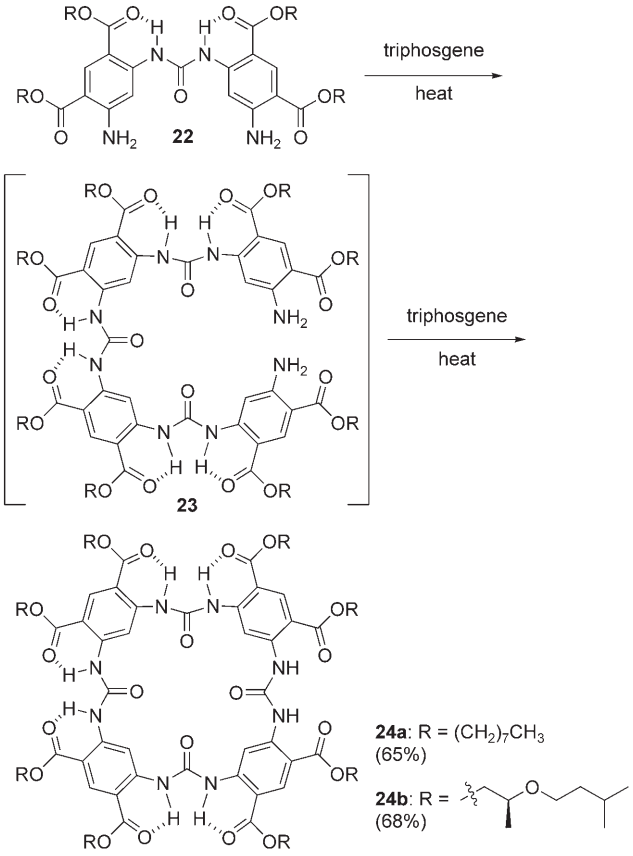

Figure 10. Formation of urea macrocycles **24** assisted by intramolecular hydrogen bonding.

5. Foldamers as Synthetic Receptors for Molecular Recognition

For a long time, cyclophane-based molecular recognition has been one of the central topics in supramolecular chemistry. Foldamers that are long enough may produce a well-established cavity with defined shape and size. Such rigidified nonring cyclic architectures are new ideal receptors for specific guests. Moore and co-workers and Inouye et al. investigated the binding properties of *m*-phenylene and *m*-pyridylene ethynylene foldamers.[32,33] Other series of helical structures for binding ionic guests were also reported.[34,35] Owing to their high structural diversity and adaptability, hydrogen-bonding-mediated rigidified systems are particularly useful as synthetic receptors or as scaffolds for constructing more-advanced assembled architectures for molecular recognition.

Oligomers **25a–c** represent the first class of hydrazide-based foldamers, the folding or helical conformations of which are stabilized by consecutive intramolecular hydrogen bonding (Figure 11).[36] Molecular-mechanics calculations revealed that this series of foldamers have rigid cavities of about 1 nm in diameter, and half of the hydrazide carbonyl groups are orientated inwards. ^{1}H NMR, fluorescence, and CD spectroscopic studies revealed that in chloroform these foldamers are good receptors for alkylated saccharides **26–29**. The stoichiometry of the complexes was established to be 1:1, and an association constant (K_a) of $6.9\times10^6\,\mathrm{M}^{-1}$, the largest obtained, was determined for complex **25c·29** in chloroform. Intermolecular NOE interactions were also observed, based on which a binding mode for complex **25b·28** was proposed (Figure 12). The strong binding affinity clearly originated from the well-ordered arrangement of the inward-facing carbonyl groups, which combine to bind saccharides strongly through intermolecular hydrogen bonding.

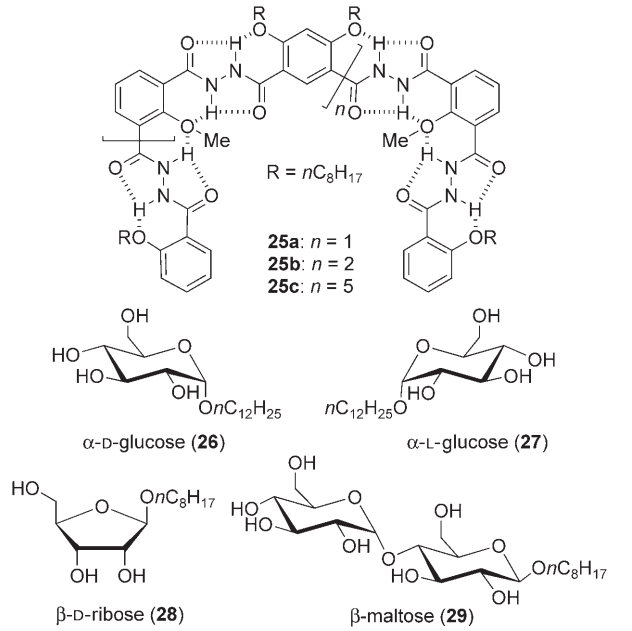

Figure 11. Structures of aromatic-hydrazide-based foldamers **25a–c** and saccharide guests **26–29**.

Another series of foldamers **30** is closely related to macrocycles **11** in that both structures contain identical repeating units.[37] The cavities of this family of foldamers are very much smaller than those of **25** (Figure 13). ^{1}H NMR and fluorescence spectroscopic studies showed that **30** also complex the above saccharides and **31**, but the stability of the resulting complexes is remarkably decreased. A largest K_a

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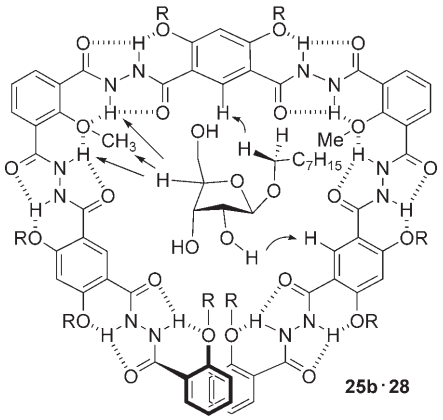


Figure 12. Observed intermolecular NOE interactions within complex **25b·28** in [D]chloroform.

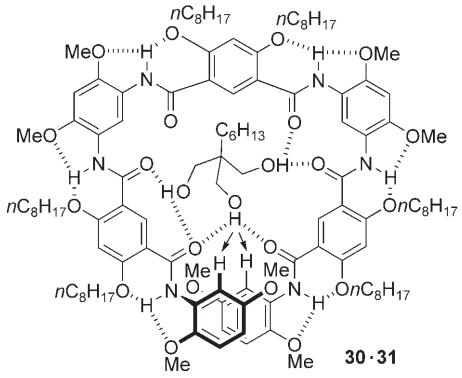


Figure 13. Intermolecular NOE interactions observed in the complex of heptamer **30** with triol **31** in [D]chloroform.

value of $7.2\times10^{3}\,\mathrm{M}^{-1}$ was estimated for the complex of **30** and **29** in chloroform. The decrease in binding stability suggests that the saccharide guest cannot enter the smaller cavity of **30** completely without denaturation of the folding conformation of the latter and, consequently, can only approach **30** from one side of the folding oligomer. However, intermolecular NOE interactions were still observed for these complexes (Figure 13).

Foldamers **32** were assembled from one repeated aromatic amino acid unit (Figure 14).[38] Unlike foldamers **25** and **30**, oligomers **32** have a one-way sequence, which is typical for the backbone of peptides. Fluorescence experiments revealed that this series of foldamers display no binding affinity to saccharide derivatives but can bind alkylated ammonium compounds **33** and **34** in a 1:1 stoichiometry. Complex **32b·34** exhibited the highest binding stability with a K_a value of $3.6\times10^{2}\,\mathrm{M}^{-1}$ in chloroform. Because all the ether oxygen atoms are involved in intramolecular hydrogen bonding, it was proposed that the complexation is driven by a combination of intermolecular hydrogen bonding and cation–π interactions.

The centrally orientated methyl groups in foldamers **32** not only decrease the effective size of the cavity of the skeletons, but also impose great spatial repulsion, which is detrimental to the formation of complexes with any other molecular or ionic guest. It was expected that, if the intramolecular hydrogen bonds remain and the spatial repulsion of the methyl groups is eliminated, more-compact and efficient binding might be achieved. This was actually proved with the fluorine-containing foldamers.[14b] Pentamer **35** and heptamer **36** represent the first family of foldamers, whose compact conformations are stabilized by F···H–N hydrogen bonding (Figure 15). The pattern of five- and six-membered rings due to F···H–N hydrogen bonding was established with

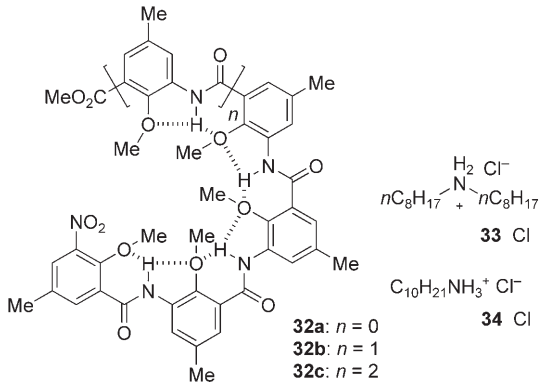


Figure 14. Structures of foldamers **32** and guest ammonium compounds **33** and **34**.

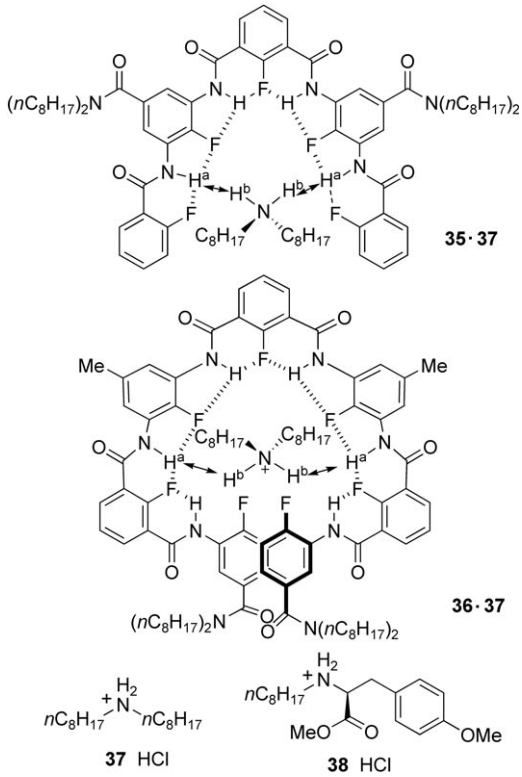


Figure 15. Structures of F···H–N hydrogen-bonding-induced foldamers **35** and **36** and ammonium guests **37** and **38**, and the intermolecular NOE interactions observed in complexes **35·37** and **36·37**.

XRD analysis and ^{1}H NMR spectroscopic studies. In this family of foldamers, all the fluorine atoms are converged towards the center of the backbones to create a polar internal cavity of about 0.7 nm in diameter. ESI MS and ^{1}H NMR and fluorescence spectroscopic investigations revealed that in chloroform both foldamers strongly bind dialkylated ammonium compounds **37** and **38**. Induced circular dichroism was also displayed for the complexes of chiral guest **38**. On the basis of the fluorescence titration experiments (Figure 16), the K_a values of complexes **35**·**37**, **35**·**38**, **36**·**37**, and **36**·**38** in chloroform were estimated to be 4.9×10^6, 2.4×10^5, 8.1×10^6, and $7.3\times10^5\,\text{M}^{-1}$, respectively. These values are significantly larger than those of the complexes between dibenzo[24]crown-8 and dialkylammonium ions ($\approx2.7\times10^4\,\text{M}^{-1}$) in the same solvent.[39] These results suggest that highly efficient intermolecular electrostatic interactions or F···H–N hydrogen bonding are formed as a result of the hydrogen-bonding-mediated rigidified conformation of the oligomers.

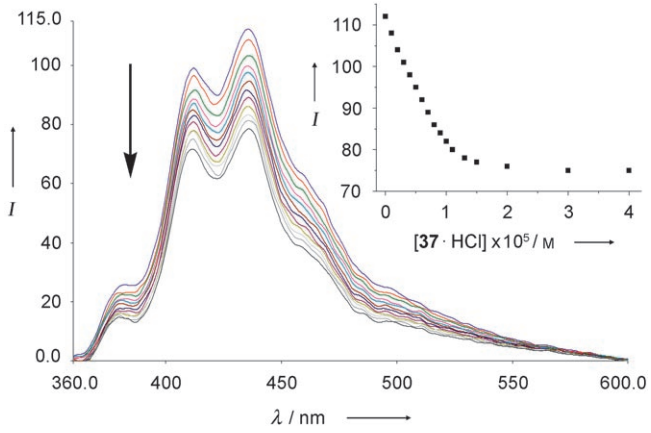


Figure 16. Fluorescence spectra of **36** (1.5×10^{-5} M, $\lambda_{ex}=330$ nm) in chloroform at 25 °C, the concentration of which was decreased gradually with the incremental addition of **37**·HCl ($0\rightarrow4.0\times10^{-5}$ M).[14b] Inset: Plot of emission intensity of **36** at 438 nm versus [**37**·HCl].

6. Preorganized Scaffolds for Supramolecular Self-Assembly

In Section 4, we demonstrated the great utility of shape-persistent aromatic amide oligomers as building blocks for the construction of new macrocylic structures. Based on rational molecular design, well-defined functionalized supramolecular architectures can also be assembled from different types of rigidified backbones.

Covalently bonded molecular tweezers are efficient receptors for the complexation of discrete guests.[40] However, their syntheses are usually time-consuming and/or of low efficiency. Folding aromatic amide oligomers provide new building blocks for the construction of new assembled supramolecular tweezers. Thus, incorporation of two zinc porphyrin units into the terminal benzene rings of shape-persistent amide trimers gives rise to assembled zinc porphyrin dimer **39** and trimer **40** (Figure 17).[41] Owing to the presence of intramolecular hydrogen bonding, the porphyrin units in **39** are arranged roughly parallel to each other and therefore produce noncovalently bonded molecular tweezers. Trimer **40** may be regarded as a combination of two molecules of **39**, and its three porphyrins produce two tweezer units. ^{1}H NMR, ^{13}C NMR, UV/Vis, and fluorescence spectroscopy revealed that these assembled tweezers are good receptors for C_{60}, C_{70}, and C_{60} derivatives. The K_a value of complexes **39**·C_{60} in toluene was determined to be $1.0\times10^5\,\text{M}^{-1}$ by UV/Vis titration. This value is much larger than those of complexes of C_{60} with palladium-linked bisporphyrin "jaws".[42] This increased binding affinity is ascribed to the preorganized conformation of the foldamer tweezers. As expected, trimer **40** can encapsulate two C_{60} molecules with an apparent K_a value of $1.5\times10^4\,\text{M}^{-1}$ in toluene.[43] Quantitative studies also revealed that C_{70} forms even more stable complexes with the foldamer tweezers owing to its increased stacking

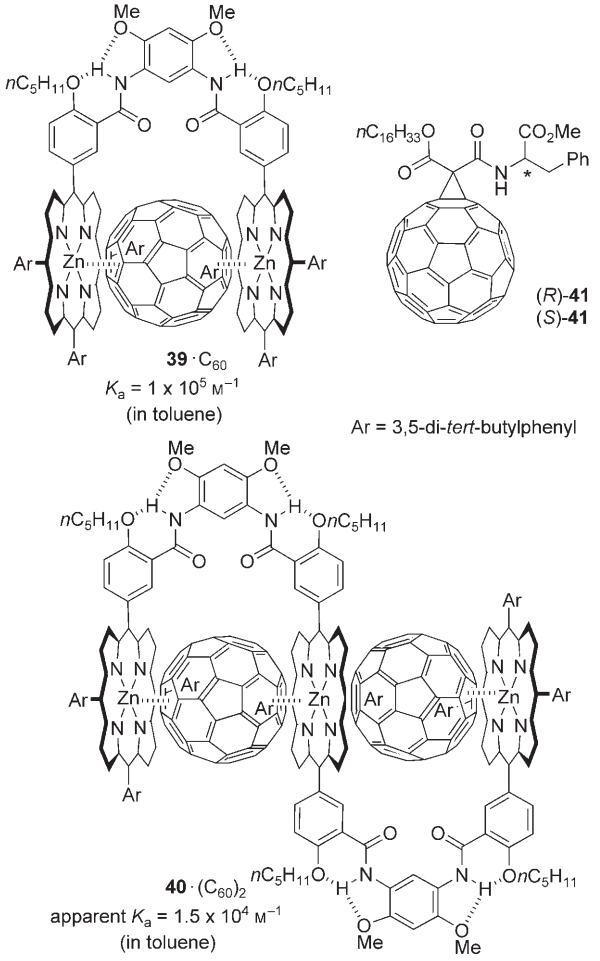


Figure 17. Binding patterns between hydrogen-bonded zinc porphyrin tweezers **39** and **40** and C_{60} and structure of chiral C_{60} derivative **41**.

region.[42a] Supramolecular chiral induction was also observed through the complexation of **39** with chiral C_{60} derivative **41** (Figure 18),[44] although the binding stability of the resulting complexes is markedly decreased.

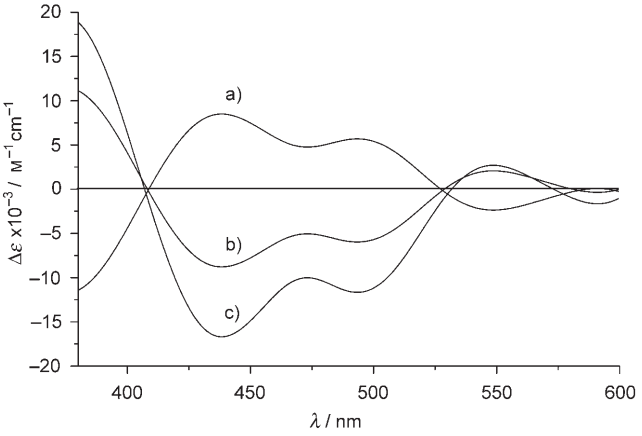


Figure 18. Induced CD spectra of a solution of foldamer tweezer **39** (3.3×10^{-4} M) in the presence of a) (*S*)-**41** (3.3×10^{-3} M), b) (*R*)-**41** (3.3×10^{-3} M), and c) (*R*)-**41** (6.6×10^{-3} M) in chloroform.[41]

Another series of zinc porphyrin appended tweezers **42** were developed by incorporating zinc porphyrin units into the skeletons of foldamers **32** (Figure 19).[45] The ^{1}H NMR spectra of **42** in [D]chloroform show that all the signals of

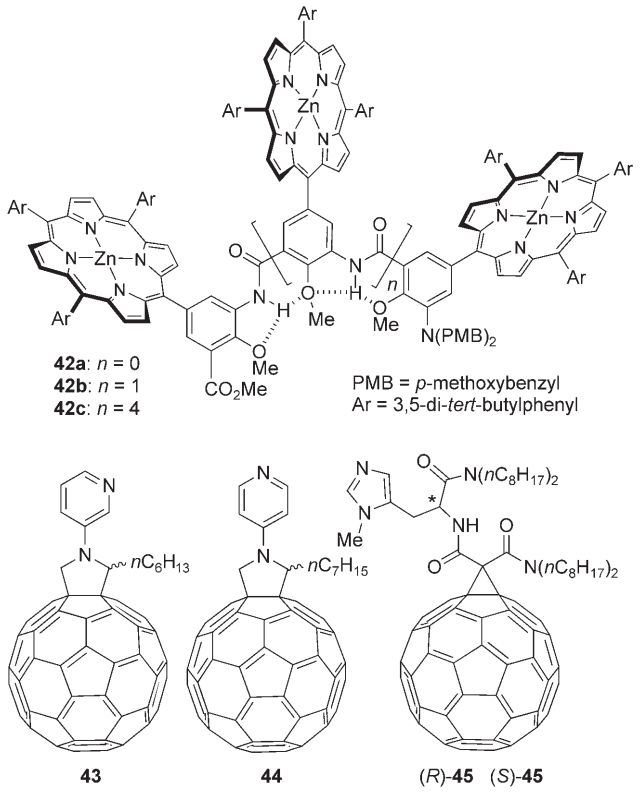


Figure 19. Structures of zinc porphyrin appended foldamers **42** and C_{60}-incorporated nitrogen ligands **43**–**45**.

the amide protons appear in the downfield region, which supports the existence of intramolecular hydrogen bonding and the folding conformation of the oligoamide skeleton. ^{1}H NMR and UV/Vis spectroscopic studies also revealed that **42a**–**c** form 1:2, 1:3, and 1:6 complexes with C_{60}-incorporated nitrogen ligands **43**, **44**, and **45**, respectively. These observations imply that each zinc porphyrin unit of the foldamers coordinates one nitrogen ligand. However, the apparent K_a value of complexes of the same C_{60}-incorporated ligand with the foldamers is increased markedly with the elongation of the foldamers. Furthermore, CD experiments showed that solutions of the longer foldamers and chiral ligand **45**, at identical concentrations of the zinc porphyrin unit and **45**, exhibit increased induced CD signals of identical shape (Figure 20). On the basis of the spectral investiga-

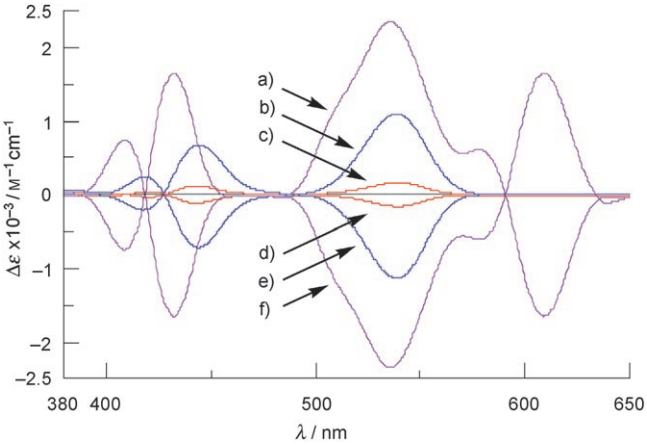


Figure 20. CD spectra of **42c** (3.3×10^{-6} M) in the presence of a) (*R*)-**45** and f) (*S*)-**45**, **42b** (6.7×10^{-6} M) in the presence of b) (*R*)-**45** and e) (*S*)-**45**, and **42a** (1.0×10^{-5} M) in the presence of c) (*R*)-**42** and d) (*S*)-**45** in chloroform at 25 °C ($[(R)\text{-}\mathbf{45}]=[(S)\text{-}\mathbf{45}]=5.0\times10^{-3}$ M).[45]

tions, a clockwise or anticlockwise one-direction binding mode is proposed (Figure 21).

7. Unimolecular Encapsulation

Oligoamide foldamers **46** (Figure 22) contain a small polar hollow.[46] XRD analysis revealed that this small hollow can include polar water molecules. This observation led to the development of the concept of "molecular apple peel" **47** (Figure 22),[47] which represents the first example of capsules generated from a single linear molecule. Owing to intramolecular hydrogen bonding, this foldamer has a large diameter at the center and reduced diameter at the ends. XRD analysis (Figure 23) and ^{1}H NMR spectroscopic studies in [D]chloroform indicate that this hollowed foldamer can encapsulate a water molecule. Variable temperature ^{1}H NMR spectroscopic experiments revealed that at low temperatures, the trapped and free water molecules outside are in slow exchange on the NMR spectroscopic timescale. Al-

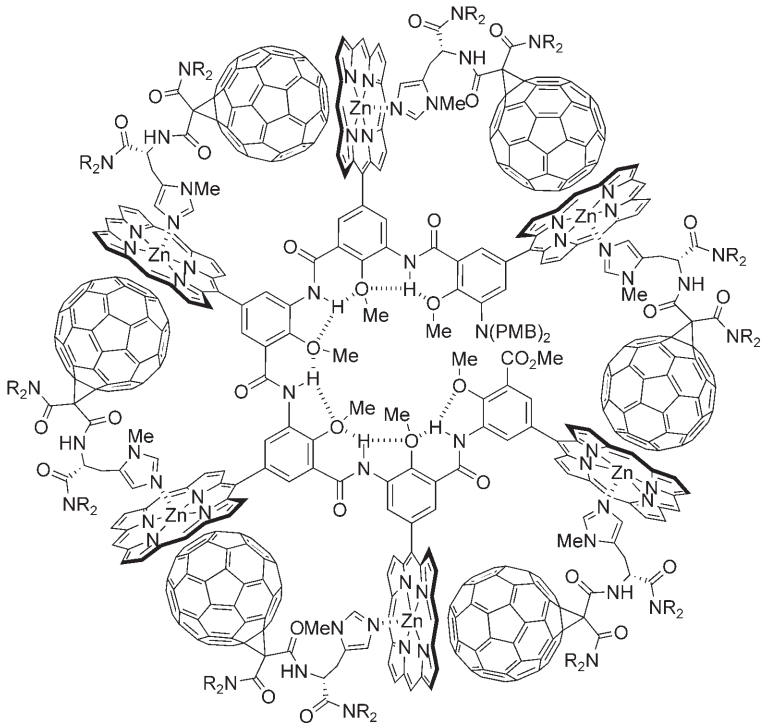
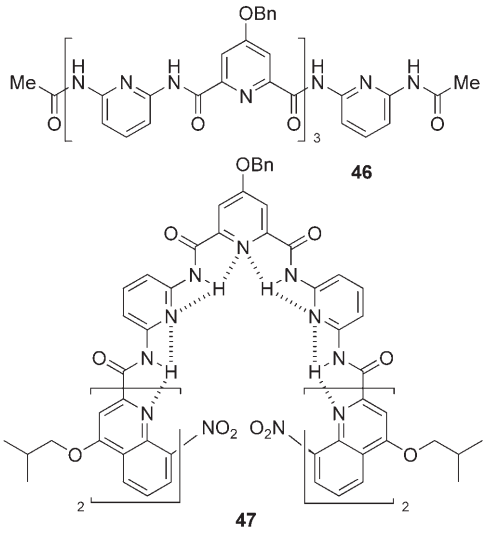


Figure 21. Proposed propeller-style binding mode for the 1:6 complex between foldamer **42c** and chiral (*R*)-**45**.[45]



46

47

Figure 22. Structures of helical oligomers **46** and **47**. Bn = benzyl.

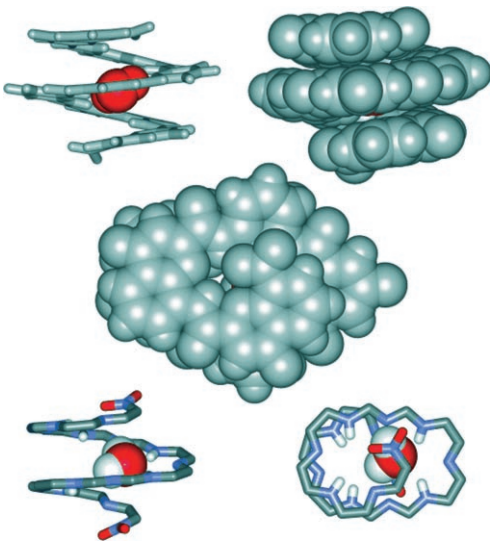


Figure 23. Views of the structure of encapsulated complex **47**⊃H_2O in the crystal. The Corey–Pauling–Koltun (CPK) views show that the water molecule is completely isolated from the surrounding medium.[47]

though what is trapped in the cavity of this foldamer is simply a water molecule, the principle provided by entrapment may present a general approach in the field of molecular encapsulation.[48]

8. Oxidation Promotion

Folding or helical backbones of enzymes provide specific active sites for selective catalysis of various reactions. Synthetic foldamers may produce special spaces with comparable catalytic function.[32] Huc and co-workers reported that the oxidation of the terminal pyridine units of **48** by *m*-chloroperbenzoic acid (*m*-CPBA) can be promoted by its folding conformation (Figure 24).[49] Although no kinetic studies have been carried out, comparing the oxidation of fragment analogues **50** and **51** to **52** and **53**, respectively, with the oxidation of **48** to **49** shows that the oxidation of **48** is remarkably faster (Figure 25). The fact that the terminal pyridines instead of the central one of **48** are selectively oxidized can be ascribed to the large steric hindrance at the central position, but the exact mechanism of acceleration of the oxidation reaction is yet unclear. It is assumed that dipolar interaction within the helical conformation plays a role, and the preassociation of the oxidative reagent in the polar cavity is also envisaged. The development of biomimetic catalysts is one of the important topics in supramolecular chemistry.[50] Owing to their structural similarity to biomacromolecules, especially enzymes, hydrogen-bonded folding structures appear to be particularly promising for this purpose.

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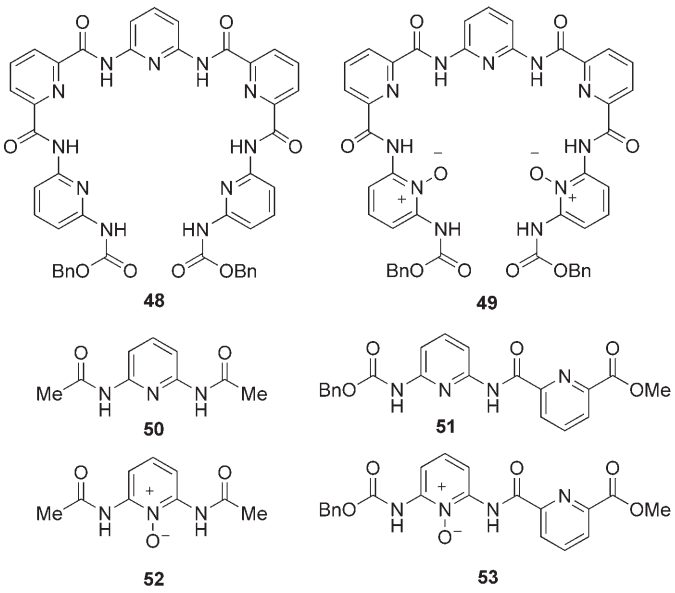

Figure 24. Structures of pyridine oligomers **48**, **50**, and **51** and their oxidative products **49**, **52**, and **53**.

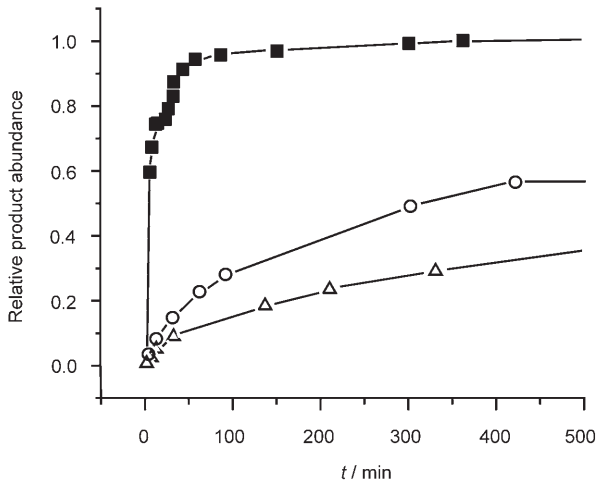

Figure 25. Oxidation of foldamer **48** (2.5 mM; ■, sum of the product and monoxidized intermediate), **50** (5 mL; ○), and **51** (5 mL; Δ) by *m*-CPBA in [D]chloroform, monitored by ^{1}H NMR spectroscopy.[49]

9. Future Prospects

In the last decade, the amazing structural and functional diversity of biological macromolecules has inspired chemists to design a large number of synthetic foldamers with well-defined structures. In a review in 2004, it was pointed out that "[a]nother essential development is the endowment of these structures with functions".[5] Two years later, we have seen that important progress has been made in different directions.[51] The directionality and strength of hydrogen bonding, the intrinsic planarity and rigidity of aromatic amides, their synthetic facility and structural adaptability all make shape-persistent aromatic amide oligomers one of the most-promising assembled scaffolds for the design of new functionalized architectures and materials.

It is expected that future developments in the research of aromatic amide foldamers and related structures will be in multiple directions. New design principles, new families of backbones, and structures of larger size and complexity will certainly be reported. Their applications in supramolecular catalysis and enzyme mimetics, self-assembly of organic nanotubes and related structures, design of synthetic receptors for molecular recognition and encapsulation, single molecular devices with advanced and tunable functions, template synthesis, molecular and ion transport, and modifications of polymer structures and properties should receive increasing attention.

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