**Molecular Shuttles**

# Foldamers: They're Not Just for Biomedical Applications Anymore**

*Panchami Prabhakaran, Gowri Priya, and Gangadhar J. Sanjayan*

foldamers · foldaxanes · molecular shuttles · nanotechnology

Conformationally ordered synthetic oligomers, called foldamers, are a class of compounds that have ushered into prominence, and interest in these systems continues unabated, primarily as a result of the fact that they hold considerable promise for potential applications in biomedical sciences.[1] These synthetic oligomers may provide excellent starting points for the elaboration of peptide mimics that could only be designed with difficulty on the basis of small-molecule scaffolds. By means of diverse synthetic tools, the "bottom-up" foldamer approach is also highly useful in engineering new frameworks that can be successfully molded to mimic the structure and functions of biopolymers.[1b] The scope and feasibility of this concept is reflected in the exponential growth from its foundation in the early 21st century to the present stage.[2] The recent launch of the heterofoldamer concept has further fuelled activity in this area, essentially because the conformational space that is available for foldamer design can be enormously augmented by developing oligomers that feature a variety of building blocks in the backbone.[3] Despite offering considerable promise because of the enormous structural diversity, a breakthrough in applications of the foldamers in material science,[4] in particular in molecular machines, is yet to be realized.

The technique of using foldamers as dynamic receptors for rod-like guest molecules was first described by Moore and co-workers.[5] In their interesting study, it was demonstrated that *m*-phenylene ethynylene oligomers fold into macromolecular receptors and adopt a helical architecture that binds to hydrophobic guests. In the helical conformation, these oligomers bind nonpolar ligands within the tubular hydrophobic cavity. Along this line, Huc and co-workers recently reported a fascinating finding that conveys clear indications that the time has come to scan the wide repertoire of foldamers for the purpose of developing molecular machines and nanodevices.[6] This idea is valid because foldamers of any desired shape/architecture can be engineered by using

delicate and flexible noncovalent interactions, among which the highly directional hydrogen-bonding interaction assumes prime importance.[1b] In their classic paper, Huc and co-workers demonstrated that double helical foldamers that are coiled around rod-shaped guest molecules can perform a screw-type motion, which is an unusual phenomenon that is not observed in other molecular machines (Figure 1a). The heterofoldamers described by Huc and co-workers, called
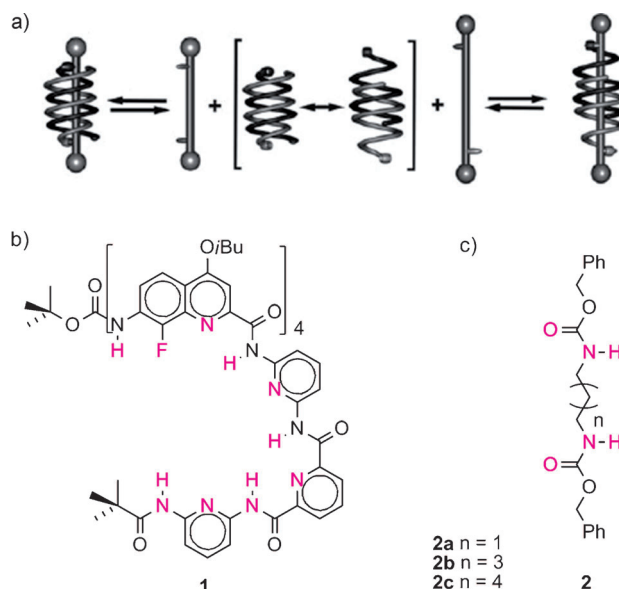


***Figure 1.*** a) Representation of screw motion in the foldaxane. b) Molecular structure of the duplex-forming foldamer **1**. c) Molecular structure of rod-shaped guests **2** of varying length. *Note*: Hydrogen-bonding sites are colored in magenta for ready identification.

foldaxanes by analogy with rotaxanes,[6a] are able to hybridize into a stable, antiparallel, double-helical architecture by means of a collection of hydrogen-bonding and π-stacking interactions (Figure 1b). The formation of the stable foldamer complexes that feature the rod-shaped guest molecules (Figure 1c) is driven by the intermolecular hydrogen-bonding interactions between the 2,6-pyridinedicarboxamide units at one end of each strand in the duplex and the hydrogen-bonding acceptor sites of the carbonyl group on the guest molecule. The crystal structures of these complexes, along with NMR titration studies, give convincing evidence about

[*] G. Priya, Dr. G. J. Sanjayan
Organic Chemistry Division, National Chemical Laboratory (CSIR)
Dr. Homi Bhabha Road, Pune, 411008 (India)
E-mail: gj.sanjayan@ncl.res.in

Dr. P. Prabhakaran
School of Chemistry, University of Leeds, LS2 9JT (UK)

the structural architecture of the species that is involved in the shuttling motion, the antiparallel alignment of the helices, and the proposed screw motion.

The single-crystal X-ray structures of the complexes formed from the foldamer **1** and guests of varying lengths **2** unequivocally confirmed the stoichiometry, symmetry, and the overall structural architecture of the double-helical foldaxanes embedded with the rod-shaped guests (Figure 2). Closer inspection of the crystal structures reveals that the two
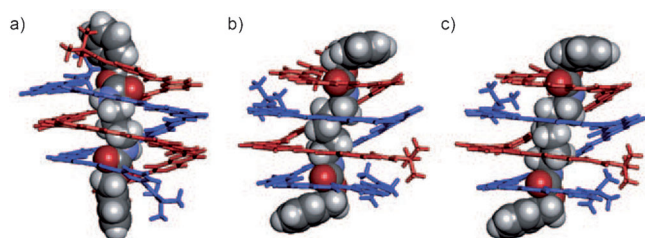


*Figure 2.* Crystal structures of the complexes with guests of different lengths. a) $(\mathbf{1})_2$–$\mathbf{2a}$; b) $(\mathbf{1})_2$–$\mathbf{2b}$; and c) $(\mathbf{1})_2$–$\mathbf{2c}$. The antiparallel strands of $(\mathbf{1})_2$ are shown in tube and the rod-shaped guests are shown in CPK representations.

helical strands, which are aligned in an antiparallel fashion, accommodate the rod through strong hydrogen-bonding interactions that involve the amide groups of the foldamer and the carbonyl groups of the guest molecule. The terminal benzyl groups of the guests are apparently too large to be threaded through the $C_2$-symmetrical helical structure, which suggests the operation of a helix unfolding/refolding mechanism in the formation of the double-helical foldaxanes, as had been previously demonstrated by Huc and co-workers for single-helical foldaxanes.[7]

Extensive NMR studies furnished clear evidence for the screw motion in the complexes in solution. It is noteworthy that the formation of the complex $(\mathbf{1})_2$–$\mathbf{2}$ is set in motion by the dissociation of the helical duplex $(\mathbf{1})_2$ first, and subsequent winding of two helical strands around the rod-shaped guest molecule. The unusual motion of this assembly is different from the generally observed molecular movements, such as rotation, translation, or spring-like extension/contraction.[8] Thus, it provides an opportunity to study and implement the screw motion at the nanometer level in the design of nanodevices with new functional properties. Another interesting finding is that these foldaxane complexes can behave as dynamic guest-adaptive hosts and, thus, this is another advantage of foldaxanes over the commonly used host molecules.

Foldaxane formation with embedded rods that have bulky terminal units cannot be realized by threading of a rod into the cylindrical cavity of the foldamers, but happens by an unfolding/refolding mechanism, which necessitates overcoming a high kinetic barrier. Thus, once the foldaxanes are formed, they attain relatively high stability. Huc and co-workers utilized this property of foldaxanes to further explore the shuttling motion. It was demonstrated that when guest molecules have two helix-binding "stations" (sites) of differ-

ent lengths, the foldamer duplex shuttles between these stations with a controlled screw/unscrew motion, and the shuttling rate is much faster than disassembly of the foldaxane (Figure 3a). Thus, similar to "biomachinery", these nanomachines perform their action at a much faster rate than their
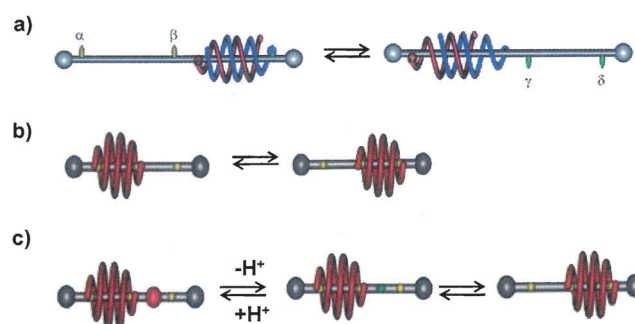


*Figure 3.* a) Foldaxane shuttling on a rod-shaped guest molecule that has two nondegenerate binding stations. b) Single helical foldaxane shuttling on a rod-shaped guest molecule that has two degenerate binding stations. c) Helix shuttling in response to pH.

assembly/disassembly process. In a recent related work reported by Huc and co-workers, helix shuttling was detected between two degenerate binding stations (Figure 3b).[7] The foldamer binds with the rod-shaped guest molecule to form a single-helical complex. Furthermore, it was possible to control the shuttling behavior of the single-helical foldaxane with an external stimulus, such as pH (Figure 3c).

The idea of exploring foldamers for developing nanodevices/molecular machines assumes further significance, as another independent report has also appeared in the literature just recently, in support of this idea. Li and co-workers have demonstrated that arylamide foldamers can serve as a deformable moiety to modulate the switching kinetics and metastability in switchable pseudorotaxanes.[9] Again, noncovalent forces have been used as the key component in the design of foldamer-based pseudorotaxanes.

Thus, foldamers open up yet another promising application in the repertoire of materials science, one which is squarely different from the traditional area of biomedical science. Foldamer-derived molecular shuttles offer immense scope in nanotechnology that is aimed at controlling molecular motions. Considering the similarities with "biomachinery", it can be envisaged that foldamer-based molecular shuttles will help in understanding the functioning of biomotors and the assembly of small molecules to build higher-order structures.

[1] a) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173; b) S. Hecht, I. Huc, *Foldamers: Structure, Properties, and Applications*, Wiley-VCH, Weinheim, **2007**.

[2] a) T. A. Martinek, F. Fulop, *Chem. Soc. Rev.* **2012**, *41*, 687; b) P. G. Vasudev, S. Chatterjee, N. Shamala, P. Balaram, *Chem. Rev.* **2011**, *111*, 657.

[3] a) W. S. Horne, S. H. Gellman, *Acc. Chem. Res.* **2008**, *41*, 1399; b) A. Roy, P. Prabhakaran, P. K. Baruah, G. J. Sanjayan, *Chem. Commun.* **2011**, *47*, 11593.

[4] For stimuli-responsive foldamers, see: D. Bléger, Z. Yu, S. Hecht, *Chem. Commun.* **2011**, *47*, 12260.

[5] a) T. Nishinaga, A. Tanatani, K. Oh, J. S. Moore, *J. Am. Chem. Soc.* **2002**, *124*, 5934; b) A. Tanatani, T. S. Hughes, J. S. Moore, *Angew. Chem.* **2002**, *114*, 335; *Angew. Chem. Int. Ed.* **2002**, *41*, 325.

[6] a) Y. Ferrand, Q. Gan, B. Kauffmann, H. Jiang, I. Huc, *Angew. Chem.* **2011**, *123*, 7714; *Angew Chem. Int. Ed.* **2011**, *50*, 7572; b) C. Bao, Q. Gan, B. Kauffmann, H. Jiang, I. Huc, *Chem. Eur. J.* **2009**, *15*, 11530.

[7] Q. Gan, Y. Ferrand, C. Bao, B. Kauffmann, A. Grelard, H. Jiang, I. Huc, *Science* **2011**, *331*, 1172.

[8] a) S. Saha, J. F. Stoddart, *Chem. Soc. Rev.* **2007**, *36*, 77; b) S. Silvi, M. Venturi, A. Credi, *Chem. Commun.* **2011**, *47*, 2483; c) N. Ruangsupapichat, M. M. Pollard, S. R. Harutyunyan, B. L. Feringa, *Nat. Chem.* **2011**, *3*, 53.

[9] K. D. Zhang, X. Zhao, G. T. Wang, Y. Liu, Y. Zhang, H. J. Lu, X. K. Jiang, Z. T. Li, *Angew. Chem.* **2011**, *123*, 10040; *Angew. Chem. Int. Ed.* **2011**, *50*, 9866.