

# FOLDED HETEROAROMATIC BACKBONES BASED ON TRIAZOLES: COMBINING SYNTHETIC ACCESSIBILITY WITH DEFINED CONFORMATIONAL PREFERENCES

Robert M. Meudtner, Denise Zornik, and Stefan Hecht\*

Department of Chemistry, Humboldt-Universität zu Berlin  
Brook-Taylor-Str. 2, 12489 Berlin, Germany  
sh@chemie.hu-berlin.de

## Introduction

In recent years there has been a considerable effort of synthetic chemists to synthesize artificial scaffolds capable of adopting defined secondary and higher ordered structures.<sup>1</sup> Several approaches to design such foldamers have been pursued involving various bio-inspired peptidomimetic backbones as well as diverse (hetero)aromatic scaffolds. Common to most designs is the use of motifs and connections that display a strong conformational preference in solution. One of the first and particularly successful motifs relies on the preferred *anti*-conformation of 2,2'-bipyridine moieties. This so called "helicity codon" was introduced by Lehn and coworkers and forms the basis of several foldamer backbones.<sup>2</sup> However, the preparation of most truly artificial foldamers suffers from tedious and low yielding syntheses.

Here, we present our most recent work on utilizing click chemistry<sup>3</sup> to generate conformationally defined building blocks that are connected to yield extended foldamer strands.<sup>4,5</sup> We will present our general concept to access this new class of foldamers, termed "clickamers", discuss synthetic details, and present first investigations with regard to their conformational behavior in solution.

## Results and Discussion

Our approach is based on the highly efficient and regioselective Cu(I)-catalyzed<sup>6</sup> 1,3-dipolar cycloaddition reaction<sup>7</sup> of aromatic azides and alkynes yielding extended heteroaromatic building blocks. For example, 2,6-diethynylpyridines and phenyl azides yield 2,6-bis(1-phenyl-1,2,3-triazol-4-yl)pyridines (BTPs), which serve as monomer units (Figure 1).<sup>4</sup>

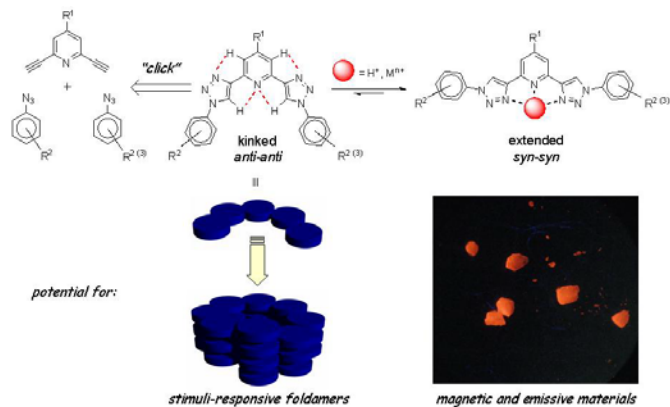


Figure 1. Click chemistry to generate new foldamer and ligand scaffolds.<sup>4</sup>

Furthermore, the BTPs represent an interesting new class of tridentate ligands, which form various metal complexes. For example, the iron complexes  $\text{Fe}(\text{BTP})_2^{2+}$  show interesting spin behavior, while the europium complexes  $\text{Eu}(\text{BTP})_3^{3+}$  display intense luminescence properties.<sup>4</sup>

In order to synthesize discrete foldamer oligomers, we have developed a repetitive synthetic route based on a monosilylated bisalkyne monomeric building block. Bidirectional growth utilizing a bisazide core gives rise to well-defined series of new foldamers. The conformational preferences of the new foldamer families can readily be adjusted by utilizing either conformationally directing pyridine or conformationally non-directing phenyl moieties (Figure 2). By comparing the resulting the isostructural foldamer series, fundamental insight into folding relating in particular to cooperativity can be gathered.

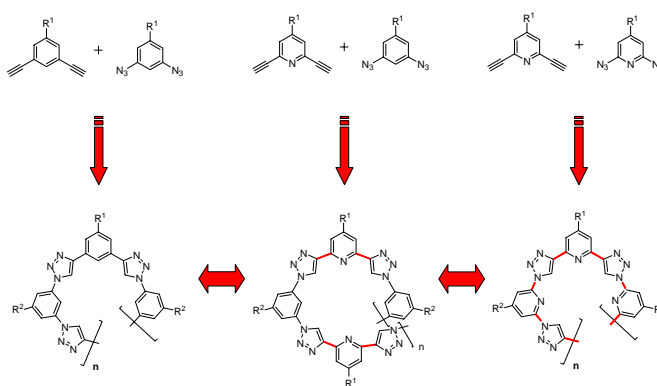


Figure 2. Series of isostructural foldamer families with increasing degree of conformational preorganization (bonds shown in red show strong conformational preference).

The synthesis of these and related heteroaromatic foldamers will be discussed and spectroscopic investigations relating to their conformational behavior in solution will be presented. In particular, the conformational response of the foldamers to various chemical stimuli, e.g. changes in pH or ion concentration, will be highlighted and their potential for sensing will be highlighted.

## Conclusions

Click chemistry has been utilized to develop a practical and efficient route to synthesize new foldamer families based on triazole-bridged heteroaromatics. While the study of their secondary structure provides valuable insights into folding behavior in general, the responsiveness of the backbone conformation to external stimuli enables the design of new sensory materials.

**Acknowledgment.** Generous support by ERA Chemistry (Project "SurConFold") is gratefully acknowledged.

## References

- (1) For a recent and comprehensive treatise on foldamers, see: *Foldamers: Structure, Properties, and Applications* (Eds.: S. Hecht, I. Huc), Wiley-VCH, Weinheim, **2007**.
- (2) For a review, see: Huc, I.; Cuccia, L. In *Foldamers: Structure, Properties, and Applications* (Eds.: S. Hecht, I. Huc), Wiley-VCH, Weinheim, **2007**, pp. 1-33.
- (3) The concept of "click chemistry" is described in: (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021. For reviews about the application of "click chemistry" in polymer and materials science, see: (b) Lutz, J.-F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1018-1025. (c) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun.* **2007**, *28*, 15-54. (d) Fournier, D.; Hoogenboom, R.; Schubert, U. S. *Chem. Soc. Rev.* **2007**, *36*, 1369-1380.
- (4) For our initial studies on the BTP platform, see: Meudtner, R. M.; Ostermeier, M.; Goddard, R.; Limberg, C.; Hecht, S.; *Chem., Eur. J.* **2007**, *in press*.
- (5) Meudtner, R. M.; Hecht, S.; *unpublished results*.
- (6) Original work: (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599. (b) Törnøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057-3064.
- (7) Please note that the non-catalyzed, thermal [4+2] cycloaddition reactions of various 1,3-dipoles have been pioneered by Huisgen, see: Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley, New York, **1984**, pp. 1-176.