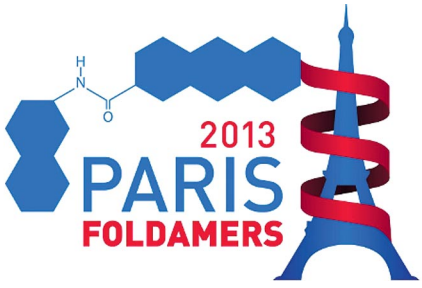
EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201300676

Foldamers

Claudia Tomasini,*[a] Ivan Huc,*[b] David J. Aitken,*[c] and Ferenc Fülöp*[d]



Foldamers are artificial folded molecular architectures inspired by the structures of biopolymers and have become the focus of a very active area of chemical research. The word "foldamers" was coined by Samuel Gellman in 1998 to describe discrete artificial polymers that adopt specific and stable conformations similar to those seen among proteins and nucleic acids.[1] Today, this neologism implicates "folded oligomers" and refers mainly to medium sized molecules (about 500–5000 amu) that fold into regular secondary structures (i.e., helices, turns and sheets), thus, being able to mimic biomacromolecules despite their smaller size. The essential requirement of a foldamer is to possess a well-defined, repetitive secondary structure, dictated by conformational preferences of the monomeric units, attractive and/or repulsive noncovalent intramolecular interactions and solvent effects. Before the term foldamer was coined, many nucleic acid analogues and peptide analogues had already been successfully designed to mimic the structures and, potentially, the biological properties of their natural counterparts.

In 2001, Jeffrey Moore proposed the following narrower definition: "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] He also divided foldamers into two large families: "biotic" foldamers whose backbones are chemically related to biopolymers (nucleotidomimetic and peptidomimetic foldamers) and "abiotic" foldamers, which emanate from a bottom-up design approach (for example aromatic foldamers); this classification was exploited and emphasized by Guichard and Huc in a recent review.[3]

Biotic foldamers are molecules whose design has been guided by analogy to biopolymers with which they share comparable folding principles. The seminal work of Gellman and Seebach on the synthesis and conformational analysis of β-peptides, demonstrated that β-peptides may adopt helical conformations that can be more stable than those of α-peptides. The research field blossomed to include investigations of the higher γ and δ peptide homologues and mixed peptide combinations, offering a myriad of possibilities for the construction of sophisticated folded architectures with possible applications in areas ranging from biomedicine to material science. Other peptide backbone variations involve the replacement of the secondary amide bonds by, for example, *N*-methyl-amides, imides, ureas, hydrazides or hydroxyamides, and the use of peptoids, in which the side chains are connected to the nitrogen atoms of the peptide backbone. A recent review from Martinek and Fülöp demonstrated that the diversity of peptidic foldamers is ramping up at all levels.[4]

Concomitantly, abiotic foldamers have been proposed and synthesized by several research groups. These types of foldamers employ mainly aromatic-rich sequences: oligo-phenylene-ethynylenes; sequences of alternating aromatic electron donors and acceptors; aryl-oligomers in particular those based on aza-heterocycles (pyridines, pyrimidines, pyridazines, etc.); aromatic tertiary amide, imide or urea oligomers; aromatic oligoamides.[5]

In addition to the "synthetic foldamers" mentioned above, which are generally produced by stepwise chemical synthesis, the use of the term foldamers was recently extended to include other families of compounds: polymeric

[a] Dipartimento di Chimica "G: Ciamician", Università di Bologna
Via Selmi 2, 40126 Bologna, Italy
Fax: +39-0512099456
E-mail: claudia.tomasini@unibo.it
Homepage: www.unibo.it/Faculty/default.htm?upn=claudia.tomasini%40unibo.it&TabControl1=TabContatti
[b] Univ. Bordeaux, CNRS UMR5248, Institut Européen de Chimie et Biologie
2, Rue Robert Escarpit, 33607 Pessac Cedex, France
Fax: +33-540002215
E-mail: i.huc@iecb.u-bordeaux.fr
Homepage: http://www.iecb.u-bordeaux.fr/teams/HUC/
[c] ICMMO - Université Paris Sud
15, rue Georges Clemenceau, 91405 Orsay Cedex, France
Fax: +33-169156278
E-mail: david.aitken@u-psud.fr
Homepage: http://www.icmmo.u-psud.fr/Labos/LSOM/cv/da_eng.php
[d] Institute of Pharmaceutical Chemistry, University of Szeged, 6720 Szeged, Eotvos u. 6, Hungary
Fax: +36-62-545-705
E-mail: fulop@pharm.u-szeged.hu
Homepage: http://www2.pharm.u-szeged.hu/gyki/English/Munkatars/fulop.htm

foldamers, metallofoldamers and biofoldamers. All these compounds share the ability to adopt well-defined, folded conformations on which their function is based. They have high potential for application in therapeutic or materials chemistry contexts. Some remarkable examples have been shown to display biological activity even without resembling naturally occurring counterparts. Others may be "decorated" with pharmacophores for applications in medicinal chemistry. It is hoped that these compounds should display novel and favourable metabolic profiles and possibly bridge the gap in molecular weight between small molecule drugs and protein-based drugs.

In Europe several research groups currently engaged in the study of foldamers have participated in a joint network and collaborative and training program funded by the European Union, constituted by two Actions:

(1) The COST Action CM0803 entitled "Foldamers: Building Blocks, Structure, and Function" (http://foldamer.org/);

(2) The Marie Curie Industry–Academia Partnerships and Pathways project titled "Foldamers Against Protein–Protein Interactions" (FP7-PEOPLE-IAPP-2008-230662-FOLDAPPI).

The COST action CM0803 lasted from May 2009 to May 2013 and associated 35 research groups, coming from 14 European countries. It was organized in three working groups: WG1: Foldamer building blocks (coordinator: Prof. David J. Aitken), WG2: Foldameric secondary structures and controlled self-assembly (coordinator: Prof. Rosa M. Ortũno) and WG3: Functional foldamers (coordinator: Prof. Andrew Wilson). The Chair of the management committee was Prof. Ferenc Fülöp.

In the past four years the COST Action organized eight events, to which researchers interested in any aspect of foldamer chemistry were invited from all over the world. The events were organized in Szeged (September 2009), Bordeaux (January 2010), Bologna (October 2010), Barcelona (April 2011), Leeds (September 2011), Bordeaux (January 2012), Regensburg (August 2012) and Paris (April 2013). Three events (Bordeaux 2010, Bordeaux 2012 and Paris 2013) were organized in conjunction with the FOLDAPPI project.

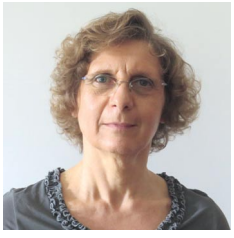
This special issue of the *European Journal of Organic Chemistry* is devoted to foldamers and is the latest of a series of special issues that have been recently published in Europe (*Amino Acids*, **2012**, *41*, issue 3; *Organic & Biomolecular Chemistry*, **2012**, web themed issue; *Tetrahedron*, **2012**, *68*, issue 23).

This issue contains eighteen full articles, covering a wide variety of aspects of foldamer research, mainly dealing with synthetic foldamers. These contributions have been submitted by eleven European research groups, four Asian research groups and three American research groups: research on both peptidic foldamers (biotic foldamers) and aromatic foldamers (abiotic foldamers) is reported.

Conformational studies and structural characterizations of peptidic foldamers are described in the papers of Balaram, Gellman, Formaggio, Martinek, Sanjayan and Sharma, while Kirshenbaum reports on the antimicrobial activity of cyclic peptoids and Nowick presents macrocyclic foldamers containing amyloidogenic pentapeptide sequences. Perczel describes a comprehensive study on calculations of foldamer stability coupled to aggregation propensity of elongated Trp-cage miniproteins. Hilvert reports that simple tripeptides are versatile ligands for iridium-catalysed transfer hydrogenations. Finally, some synthetic studies on the preparation and the preferential conformations of some new pseudopeptide monomers are described by Granja, Ortũno and Tomasini.

Conformational studies on aromatic foldamers are reported by Hjelmgaard, who describes the preparation of aromatic oligoamides with a rare *ortho*-connectivity, and by Wilson, who presents the application of aromatic oligoamide foldamers as inhibitors of protein–protein interactions. Hamilton describes an extensive series of bis-oligobenzamides and bis-oligopyridylamides, that give double-helix mimics. Finally, two applications of aromatic foldamers are reported by Brunsveld and Wu: monovalent building blocks, decorated with a single bioactive ligand, that self-assemble into columnar polymers displaying multiple ligands and a series of aromatic oligoureas that adopt a helical structure in the solid state, binding two chloride anions.

This collection of publications gives a flavour of how the foldamers research area is continuously growing and expanding and we trust that it will be informative and stimulating for the organic chemistry community. Finally, we would like to thank *EurJOC* for publishing this special issue, as well as of course, the authors for their contributions and the referees for their time and effort.



Claudia Tomasini

Ivan Huc

David J. Aitken

Ferenc Fülöp

[1] S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173–180.
[2] D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893–4011.
[3] G. Guichard, I. Huc, *Chem. Commun.* **2011**, *47*, 5933–5941.
[4] T. A. Martinek, F. Fülöp, *Chem. Soc. Rev.* **2012**, *41*, 687–702.
[5] D.-W. Zhang, X. Zhao, J.-L. Hou, Z.-T. Li, *Chem. Rev.* **2012**, *112*, 5271-5316.

