

Foldamers

Edited by

Stefan Hecht and Ivan Huc

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Foldamers

Structure, Properties, and Applications

Edited by
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Foreword by
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WILEY-VCH Verlag GmbH & Co. KGaA

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Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek

Die Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at <http://dnb.d-nb.de>.

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Printed in the Federal Republic of Germany
Printed on acid-free paper

Typesetting Asco Typesetter, North Point, Hong Kong

Printing betz-druck GmbH, Darmstadt

Binding Litges & Dopf GmbH, Heppenheim

Cover Design Grafik-Design Schulz, Fußgönheim

ISBN: 978-3-527-31563-5

Foreword

Biopolymers adopt distinct conformations in order to express functions that are key to life. Examples are the sheet, helix, and turn motifs of proteins, the double and triple helix, quadruplex, or hairpin motifs of nucleic acids, or the helical structures of carbohydrates such as starch. Without these preferred structures, expression and translation, recognition, catalysis, and transport in living systems could not be achieved. While chemists have learned since the middle of last century how to analyze conformational preferences of small molecules and to apply this knowledge to regio- and stereoselective chemical transformations, the control of the three-dimensional structure – and thereby the function – of synthetic oligomers and polymers has only recently become a hot research topic.

Foldamers, i.e. synthetic oligomers with distinct conformational preferences, are at the interface of covalent (molecular) and noncovalent (supramolecular) chemistry. Their investigation will enable chemists to develop geometrically defined oligomers that promise to rival biopolymers in their function and application. Increasingly, foldamers with covalent or supramolecular backbones are switchable under external stimuli between two defined stable states, can be prepared by dynamic combinatorial synthesis, or can assemble to functional foldamer complexes. They will find use as novel biomimetic receptors and catalysts, light and energy capturing and storage devices, delivery and transport systems for synthetic drugs and membrane-impermeable biomolecules, and materials that interface with biological tissues.

The construction of foldamers starts from small, intelligently programmed monomeric modules, which contain the information to generate oligomers with distinct three-dimensional structures. The geometries are controlled by a variety of parameters, including backbone conformational preferences, backbone interchromophoric interactions (such as aromatic–aromatic interactions), side chain interactions, solvophobic interactions, metal ion coordination, and H-bonding molecular recognition. These parameters are logically analyzed in the monograph, resulting in useful design protocols. Functions of synthetic foldamers and their relationships to biopolymers are described for systems spanning from biomimetic oligomers to π -conjugated oligomers. I strongly recommend this monograph to all academic and industrial researchers interested in fascinating

perspectives for future chemical research; it will also take its place in modern graduate student education.

Zurich, September 15, 2006

François Diederich

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Preface

Research in molecular chemistry is essentially devoted to understanding the relationships between chemical structures and their properties and functions. One key parameter of a molecule's structure is its overall shape: its three-dimensional conformation. It is thus no surprise that conformational analysis and strategies to control conformation lie at the heart of many disciplines. Not unexpectedly, Nature has evolved the ultimate realization of function based on controlling and altering conformation of its molecular machinery. Prominent examples include information storage, duplication and translation using DNA and ribosomes and cooperative oxygen transport by hemoglobin. These achievements are based on large and complex yet remarkably defined structures, which are obtained through the folding of long polymeric chains and a subtle balance of noncovalent forces. On the contrary, many synthetic systems with defined conformations rely on covalent restriction of the molecules' flexibility. Pre-organization has long been a cornerstone of molecular design, as exemplified by the fact that most drugs are cyclic or macrocyclic. However, during the past decade, chemists have been inspired by self-organized natural systems and have gained increasing knowledge of how to design molecular strands, so-called foldamers, that are capable of adopting well-defined folded conformations.

Foldamers have been loosely defined by Gellman as "polymers with a strong tendency to adopt a specific compact conformation" or more restrictively by Moore as "oligomers that fold into a conformationally ordered state in solution, the structures of which are stabilized by a collection of noncovalent interactions between nonadjacent monomer units". Usage of the term foldamer has mostly been targeted to synthetic oligomers (see Chapters 1–4). Artificial folded structures, which in fact are covered by the same definition, were studied extensively long before the term foldamer was coined and include synthetic (non-natural) α -peptide sequences (Chapter 5), artificial proteins (Chapter 9), nucleic acids (Chapter 10), and helical polymers (Chapters 11 and 12), among others.

The aim of this book is to cover the breadth of the rapidly developing field of foldamer research and to unite the different aspects and schools by illustrating the generality of underlying concepts. The central theme is the synthetic construction and functional exploitation of chain molecules with a conformational preference. While the first part of the book is devoted to foldamer design

concepts, the second part covers the use of conformational control to create chemical entities with beneficial functions in biology and materials science.

Synthetic oligomers can be divided into four major families (Chapters 1–4) according to the factors that dominate folding, i.e. local rotational restrictions, interactions between sites remote in the sequence, solvophobic effects, and assembly/hybridization. This division, however, is not exclusive. Folding is often the result of a combination of these factors and, in all cases, requires intrinsic backbone rigidity. Other factors, such as electrostatic and steric repulsions, may play a less visible but no less important role in reducing the accessible (unfolded) conformational space. Experimental studies of synthetic oligomers provide insight into thermodynamics and sometimes kinetics of folding events. In parallel, molecular modeling has advanced to become a useful tool that can aid conformational analysis and “observe” missing links, as well as predict preferred folded conformations (Chapter 6). The design of new folding backbones and subsequently, but not necessarily, new functions, may be termed a “bottom-up approach” to foldamers (Chapters 1–5). In contrast, “top-down approaches” (Chapters 9, 10) start from the well-known folding behavior of proteins and polynucleotides and, through directed evolution techniques or through rational design, target functions while simplifying structures. The dynamic nature and flexibility of foldamers arise from the deliberate utilization of various noncovalent interactions for structure formation. It gives rise to adaptability and responsiveness as key requirements for efficient recognition (“induced fit”) and hence functions (e.g. in sensing). This flexible yet defined shape of foldamer-based chemical systems leads to a large variety of applications ranging from biological, such as inhibitor design and antimicrobial activity (Chapters 7–9), to the materials and nano sciences, such as biomineralization/composite materials, RNA/DNA architectonics, sensors, and functional interfaces (Chapters 7, 10–13).

It is quite surprising to note that only 15 years ago, molecular folding was thought to be associated solely with biopolymers, as if natural building blocks had characteristics unique to themselves. The huge body of recent work on foldamers has clearly demonstrated that multiple ‘abiotic’ backbone families are able to adopt folded secondary motifs as well. Nowadays, biopolymers can be viewed as one – arguably very important – class of folding molecules among many others. The secondary folding motifs discovered thus far in synthetic backbones do not differ much from those of biopolymers. Turns, helices, linear strands, and multi-stranded systems, such as double helices and sheets, seem to be the most common – perhaps universal – folding motifs. Alternate folding modes, for example knots, are possible but much less common. Furthermore, synthetic systems will undoubtedly benefit from utilizing Nature’s hierarchical organization involving control over local conformation, i.e. rotation about bonds, and orientation in larger structures thereby controlling global conformation, i.e. primary → secondary → tertiary → quaternary structure evolution.

Much has been achieved; yet foldamer chemistry is still a young field and a great deal is to be expected. For instance, tertiary abiotic folds with functions remain to be seen and constitute one of the main challenges ahead. The long-term

prospect of building fully synthetic analogs of proteins is not illusionary, though it will require even more powerful design and synthetic strategies than those currently at hand. In this respect, combining bottom-up and top-down approaches, strategies that have thus far evolved independently, may be a promising way to follow. While foldamer-based biomimicry certainly provides deeper insight into Nature's mysteries, it also allows function to be explored in a non-natural context using the increased structural diversity and chemical robustness of foldamers. The potential benefits of this endeavor are enormous. Native folded biopolymers efficiently perform a multitude of functions using sequences based on relatively small alphabets – four nucleobases and roughly 20 amino acids. As shown in artificial proteins and nucleic acids, the same alphabets can be used to achieve numerous non-natural functions. The prospect of extending such alphabets to abiotic folding motifs, either already described in synthetic oligomers or yet to be discovered, thus opens the opportunity for countless applications.

We hope that this book will serve as both inspiration to the non-expert as well as a valuable resource for the specialist and bring together scientists from different disciplines to communicate with each other, engage in a joint effort to unravel one of Nature's mysteries, and create exciting new opportunities for future discoveries.

Last but not least, we want to express our sincere thanks to the authors of the individual chapters for their unique contributions of exceptionally high quality. Furthermore, we are indebted to our students, coworkers, and colleagues, with whom we had the privilege to interact and share the interest and enthusiasm for this exciting field of interdisciplinary research. We also want to thank the Wiley–VCH team, in particular Elke Maase for establishing this fruitful endeavor as well as Manfred Köhl and Steffen Pauly for their professional assistance during the editing and publishing process.

April 2007
Mülheim an der Ruhr and Bordeaux

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