Foldamers

Structure, Properties, and Applications

Edited by
Stefan Hecht and Ivan Huc

Foreword by
François Diederich

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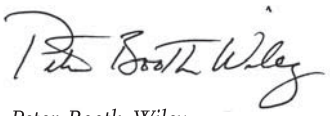

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Foreword

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*

Contents

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 *Stefan Hecht and Ivan Huc*
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Part 1
Structure: Foldamer Design Concepts

1
Foldamers Based on Local Conformational Preferences

Ivan Huc and Louis Cuccia

1.1
Introduction

Folding, as it occurs in biopolymers, refers to the prevalence of well-defined conformers in solution and, in most cases, to proximity in the folded state between chemical groups that are remote in the molecules' backbones. As illustrated in the first three chapters of this book, a multitude of non-natural folding oligomeric molecules – termed *foldamers* – have been designed, prepared and characterized [1–3]. The factors that promote folding of a linear molecular strand are manifold: specific attractive or repulsive interactions between sites remote in oligomeric sequences, solvophobic effects, local conformational restrictions or any combination thereof. This chapter deals with arguably the most important route to promote well-defined conformations within oligomers. It consists of introducing backbone rigidity through local conformational preferences that stabilize folded structures and also reduce the number, and raise the energy level, of non-folded states. Even when other strong effects are at play as, for example, hydrogen bonding (see Chapter 2) and solvophobic effects (see Chapter 3), their efficiency at promoting folding relies on the premise that the molecular backbone is sufficiently rigid so that the entropic cost of adopting a well-defined conformation is not excessive.

In this chapter, we focus on foldamers whose folding occurs mainly due to backbone rigidity, determined locally at the molecules' rotatable bonds, in the absence of other strong factors. Backbone rigidity can be imparted in many ways and occurs in quite diverse families of folding oligomers. It is not our intention to make an exhaustive presentation, but rather to select representative examples of these families. We may also add that determining which factors dominate a given folding event is often not a clear cut issue: some of the examples presented in this chapter may appear in Chapters 2 or 3 and vice versa. It remains that several general characteristics emerge from the diverse families of ''rigid'' foldamers presented here: the first is a high level of predictability of the folded conformation, be it by advanced computational means (see Chapter 6) or by a simple paper

sketch, structure prediction in rigid foldamers is, in many cases, reliable. A second general characteristic is a relatively low solvent dependence of the prevailing folded conformations in solution. A third important aspect is that, owing to the narrow distribution of conformations in solution, "rigid" foldamers tend to be much more crystalline than others: a majority of foldamer X-ray crystal structures belong to the families of molecules presented in this chapter.

1.2 Rigidly Locked Molecules

Different levels of rigidity can be imparted to a molecular backbone leading to various degrees of "foldability". Folding is a dynamic process that supposes, *a priori*, an ability to unfold. In extreme cases, the nature of intramolecular connections may result in a single-well energy landscape corresponding to a rigidly locked conformation. Although these molecules may not be considered foldamers *per se* because they show poor capacity to unfold, they do provide a firm starting point for this chapter.

[*n*]Helicenes are π-conjugated helical molecules consisting of *n* all-*ortho* annulated benzene rings (for example, [9]helicene; Fig. 1.1a) [4]. At first glance, one would expect helicenes with more than five fused aromatic rings to be rigidly locked into either a right- or left-handed helical conformation. However, a distribution of molecular deformations over a large number of bonds does allow for racemization of helicenes ranging from hexahelicene to nonahelicene [5, 6]. In geländer helices the building blocks are perpendicular compared with helicenes. In the case of a bridged *para*-terphenylophane geländer (Fig. 1.2b), the molecule

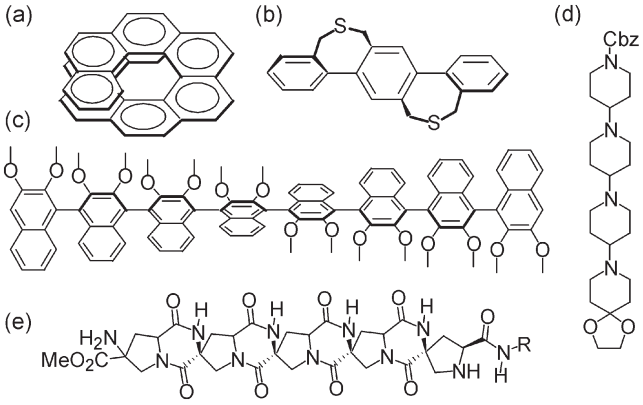

Fig. 1.1 Rigidly locked molecules: (a) helicenes; (b) geländer helices; (c) molecular ribbons; (d)–(e) molecular rods. These molecules are termed oligomeric in the sense that there is a repeating motif.

can be locked into either a right- or left-handed ''spiral staircase'' conformation [7]. An intriguing variation on oligoparaphenylene helices are molecular ribbons reported by Fuji et al. (Fig. 1.2c). The locking mechanism in these configurationally defined oligonaphthalene derivatives relies on restricted rotation about single bonds due to unfavorable steric barriers (that is, atropisomerism) [8]. Molecular rods are rigid ''unfoldable'' oligomers with well-defined molecular dimensions. For example, Semetey et al. have reported the synthesis of a series of water-soluble oligopiperidine molecular rods with as many as ten piperidine rings (Fig. 1.2d). There is NMR evidence for a chair conformation of each piperidine ring with each piperidine unit in an equatorial position with combined nitrogen inversion and chair–chair inversion throughout the well-defined backbone. According to the authors, there is rotation about the C–N bonds, but this results in only small deviations of the linear geometry of the molecule [9]. A more rigid spiro-linked molecular rod was reported by Levins et al. This molecular scaffold was elegantly prepared by rigidifying a flexible oligomer *via* the formation of two diketopiperazine rings (Fig. 1.2e) [10]. With regards to molecular rods, some molecules can have unrestricted rotations along the backbone but do not fold for geometric reasons – that is, if the backbone is linear (180° connectivity) no amount of rotation will cause molecular folding (however molecular ''twisting'' can occur). This is the case for oligo(*para*-phenylene ethylene) molecular wires reported by Schumm et al. [11].

1.3
Predictable Foldamers

Fully predictable foldamers may be defined as oligomeric structures that possess numerous rotatable bonds – in contrast with the oligomers shown in Fig. 1.1 – and that may, in principle, envelop a vast array of conformations, but whose conformational space is narrowed down to a single conformer because a well-defined preference exists at each rotatable bond. There is no need to explore the conformational space accessible to the entire molecule to determine its most stable conformation since it primarily results from local conformational preferences. Taking as an illustration the Ramachandran plots used to map the torsion angles corresponding to stable folded conformations in peptides (see Chapters 2 and 5), the experimentally encountered values for the torsion angles in fully predictable foldamers are reduced to very small areas. A simple example is the secondary amide bond: rotation about this bond is possible but the equilibrium between the possible rotamers is completely shifted in favor of the *transoid* conformation. *Cis*-secondary amides are rarely observed and generally not considered in peptide structures: including a third dimension in Ramachadran plots to describe amide bond rotation is of no use.

Literature pertaining to fully predictable foldamers is already abundant and is steadily growing. Because of their features, they are archetypical structures among the molecules described in this chapter: their structure is very well-

defined, predictable, and these compounds are highly crystalline (thus easily characterized).

1.3.1 Local Conformational Control

Though the definition given above of fully predictable foldamers seems quite general, the families of molecules that fall in this category are, in fact, rather homogeneous and almost all consist of π-conjugated systems – for example, aryls, amides, esters or ureas – connected by single bonds. Evidently, π-conjugation is a very efficient means of restricting rotation about a single bond as it stabilizes conformers where two π-systems are close to being coplanar, allowing the π-orbitals of sp^2-hybridized atoms to overlap. This effect is stronger in true π-conjugated systems where *para*- or *ortho*-connectivity between aryl rings gives rise to resonance, but it remains substantial even for *meta*-connected – cross-conjugated – systems. Upon effecting a 180° rotation about the single bond between two π-systems, two degenerate conformers may be possible, but degeneracy is easily lifted. Fig. 1.2 shows a number of conformational equilibria for which a single stable conformation exists at a single bond connecting two π-conjugated systems. These examples are representative of the families of foldamers described in Sections 1.3.2 and 1.3.3, but it is clear that many alternate schemes could be devised along the same lines.

Thus, aryl–CONH single bonds adopt *syn* conformations when the aryl ring possesses a hydrogen bond donor *ortho* to the amide group (Fig. 1.2a). The hydrogen bond donor may be an exocyclic OH [12] or NH [13–17], or an endocyclic N^+H [18]: all three moieties hydrogen bond to the amide carbonyl and repel the amide proton. Conversely, the *anti* conformation of aryl–CONH linkages is stabilized by hydrogen bond acceptors on the aromatic ring (Fig. 1.2b) which attract the amide proton and repel the amide oxygen. The most common groups used as hydrogen bond acceptors are endocyclic nitrogen atoms [13, 15–42] or exocyclic ether oxygen atoms [39, 43–55], but other functional groups have also been shown to be effective, for example, exocyclic fluorine [56], imino nitrogen [57], *N*-oxide oxygen [14] and phenolate oxygen [12].

Conformations about aryl–NHCO linkages are controlled in a very similar way by hydrogen bond donors or acceptors *ortho* to the amide function on the aromatic ring. For instance, a *syn* conformation is favored by a proton [18, 37, 38, 58–60] or a metal ion [40, 61, 62] that can coordinate to an amide carbonyl (Fig. 1.2c). An *anti* conformation is favored when a hydrogen bond acceptor is introduced which binds to the amide proton and/or repels the amide oxygen (Fig. 1.2d). Effective acceptors include exocyclic ether oxygen [12, 27, 28, 40, 44, 45, 47, 49–55] or sulfur [43, 63–65] atoms; exocyclic fluorine [56]; endocyclic nitrogen [18–21, 29, 33, 37, 38, 41]; exocyclic *N*-oxides [66] or phenolates [12]; exocyclic carbonyl oxygen [16, 17, 32, 39, 48, 67–70]; as well as sp^2 nitrogen atoms belonging to connected [71] or fused [24–26, 29, 30, 34–36] aromatic rings.