

Foldamers

Edited by

Stefan Hecht and Ivan Huc

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Foldamers

Structure, Properties, and Applications

Edited by
Stefan Hecht and Ivan Huc

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

Contents

Foreword	V
Preface	XV
List of Contributors	XIX
Part 1 Structure: Foldamer Design Concepts	1
1 Foldamers Based on Local Conformational Preferences	3
	<i>Ivan Huc and Louis Cuccia</i>
1.1	Introduction 3
1.2	Rigidly Locked Molecules 4
1.3	Predictable Foldamers 5
1.3.1	Local Conformational Control 6
1.3.2	Folded Conformations of π -conjugated Systems 9
1.3.2.1	Crescents and Helices 9
1.3.2.2	Linear Strands 13
1.3.2.3	Macrocycles 13
1.3.3	Partially π -conjugated Oligomers 16
1.4	Semi-rigid Backbones 17
1.4.1	Tertiary Aromatic Amides, Imides and Ureas 18
1.4.2	Tertiary Aliphatic Amides: Polyprolines and Peptoids 20
1.4.3	Hindered Polymer and Oligomer Backbones 23
1.5	Conformational Transitions 25
1.6	Conclusion and Perspectives 27
	<i>References</i> 28
2 Foldamers Based on Remote Intrastrand Interactions	35
	<i>Philippe Le Grel and Gilles Guichard</i>
2.1	Introduction 35
2.2	What can be Learned from Strategies used to Control Conformations of α -Polypeptides? 36

2.3	Helices from Homogeneous Oligomeric Backbones with Periodicity at the Monomer Level: ω -Peptides and their Analogs	37
2.3.1	Compact Helices with Large (>10 atoms) H-bonded Rings	37
2.3.1.1	The Homologation Strategy: β - and γ -Peptide Foldamers	37
2.3.1.2	Imposing Backbone Conformational Restriction/Pre-organization for Optimal Helical Folding	39
2.3.1.3	Folding in an Aqueous Environment	43
2.3.1.4	Dynamics of β - and γ -Peptide Helices: Evidence for Noncooperative Folding/Unfolding Processes	44
2.3.2	Extended Helices with Small H-bonded Rings Centered at a Single Residue	45
2.3.2.1	α -Peptides: the γ -Helix	45
2.3.2.2	ω -Peptides with Specific Conformation-stabilizing Elements	45
2.3.2.3	Stabilizing Local Backbone Conformation by Inverse-Bifurcation Involving an Additional Heteroatom	48
2.4	Oligoamide Mixed Helices	51
2.4.1	The α -Oligopeptide Precedent: from Antibiotic Gramicidin A to Poly-Gln Aggregates in Huntington's Disease	52
2.4.2	Introducing Periodicity at the Level of a Dimer Unit in β -Peptides leads to a Remarkably Stable Mixed Helical Fold	53
2.4.2.1	By Mixing β^2 - and β -Amino Acids	53
2.4.2.2	Additional Substitution Patterns Stabilizing the Mixed 10/12- (12/10-) Helix	55
2.4.3	Extending the Concept of Mixed Helices	56
2.5	Nonperiodic Structures: Open Chain β -Turn-like Motifs and Hairpins in Designed Homo-oligomers	58
2.5.1	Sheet-forming ω -peptides	58
2.5.2	Turn Segment for Hairpin Formation	59
2.6	Expanding Structural Diversity with Heterogeneous Backbones	61
2.6.1	From Discrete ω -Amino Acid Guests in α -Helices to Helical α,ω - and β,γ -Peptide Hybrids	61
2.6.2	Hairpins from α,ω -Peptide Hybrids	65
2.6.3	Sculpting New Shapes by Integrating H-Bonding, Aromatic Interactions and Multiple Levels of Pre-organization	66
2.7	Conclusion and Outlook	67
	<i>References</i>	68
3	Foldamers Based on Solvophobic Effects	75
	<i>Yan Zhao and Jeffrey S. Moore</i>	
3.1	Introduction	75
3.2	Learning from Solvophobically Driven Assemblies – Intermolecular Solvophobic Interactions	77
3.3	Learning from Synthetic and Biological Polymers	81
3.4	Recent Advances in Foldamers Based on Solvophobic Effects	84

3.4.1	Foldamers Stabilized by Adjacent, Identical Aromatic Units	85
3.4.2	Foldamers Stabilized by Adjacent Donor–acceptor Aromatic Units	87
3.4.3	Foldamers Stabilized by Nonadjacent Aromatic Units	92
3.4.4	Foldamers Stabilized by Aliphatic Units	100
3.5	Conclusions and Outlook	103
	<i>References</i>	104
4	Foldamer Hybrids: Defined Supramolecular Structures from Flexible Molecules	109
	<i>Carsten Schmuck and Thomas Rehm</i>	
4.1	Introduction	109
4.2	Hybridization of Oligomers with Well-defined Structures	112
4.2.1	Coiled Coils and Helix Bundles	112
4.2.2	Intertwined Strands	116
4.2.3	Stacks of Helical Strands and Macrocycles	117
4.2.4	Tapes and Hydrogen-bonded Sheets	120
4.3	Hybridization-induced Folding of Unstructured Molecules	122
4.3.1	Hydrogen-bonded Tapes	122
4.3.2	Helices Based on Metal-ligand Interactions and Salt Bridges	127
4.3.3	Double-stranded Hybrids Based on Aryl-aryl Interactions and Hydrophobic Contacts	130
4.3.4	Hybrids Based on DNA-base-pairing Recognition	132
4.4	Formation of Large Polymeric Aggregates via Self-assembly	136
4.5	Applications of Foldamer Hybridization	139
4.6	Conclusion	143
	<i>References</i>	143
5	Control of Polypeptide Chain Folding and Assembly	147
	<i>Rajkishor Rai and Padmanabhan Balaram</i>	
5.1	Introduction	147
5.2	Helix Promotion by Backbone Substitution	150
5.2.1	α -Aminoisobutyric Acid (Aib) and Related Dialkyl Amino Acids	150
5.2.2	Diproline Segments	152
5.3	Hairpin Design using Obligatory Turn Segments	155
5.3.1	^D Pro-Xxx Turns	155
5.3.2	Aib- ^D Xxx Turns	157
5.3.3	Asn-Gly Turns	159
5.3.4	Expanded Loop Segments	161
5.3.5	Choice of Strand Residues	161
5.4	Helix–Helix Motifs	162
5.5	Multi-stranded β -Sheets	164
5.6	Mixed Helix-Sheet (α/β) Structures	165
5.7	Conclusions	167
	<i>References</i>	168

6	Simulation of Folding Equilibria	173
	<i>Wilfred F. van Gunsteren and Zrinka Gattin</i>	
6.1	Introduction	173
6.2	Dynamical Simulation of Folding Equilibria under Different Thermodynamic and Kinetic Conditions	175
6.3	Variation of the Composition of the Polypeptide Analogs and the Solvent	178
6.4	Convergence of the Simulated Folding Equilibrium	181
6.5	Sensitivity of the Folding Equilibrium to the Force Field Used	184
6.6	Comparison of Simulated with Experimentally Measured Observables	185
6.7	Characterization of the Unfolded State and the Folding Process	186
6.8	Conclusion	190
	<i>References</i>	190
Part 2	Function: From Properties to Applications	193
7	Foldamer-based Molecular Recognition	195
	<i>Jorge Becerril, Johanna M. Rodriguez, Ishu Saraogi and Andrew D. Hamilton</i>	
7.1	Introduction	195
7.2	Small Molecule Recognition Using Foldamers	196
7.2.1	Receptors for Water Molecules	196
7.2.2	Receptors for Ammonium Cations	198
7.2.3	Receptors for Hydrophobic Small Molecules	201
7.2.4	Receptors for Saccharides	204
7.2.5	Receptors of Other Organic Molecules	207
7.3	Protein Recognition	210
7.3.1	Abiotic Synthetic Foldamers	211
7.3.2	Peptidomimetic Foldamers	212
7.4	Mimicry of Biomineralization: Recognition of Crystal Surfaces Using Foldamers	217
7.4.1	Introduction to Biomineralization	217
7.4.2	Biomimetic Synthesis of Calcite Using Foldamers	220
7.4.3	Biomimetic Synthesis of CdS Using Foldamers	224
7.5	Conclusion	224
	<i>References</i>	225
8	Biological Applications of Foldamers	229
	<i>Marc Koyack and Richard Cheng</i>	
8.1	Introduction	229
8.1.1	β -Peptides	230
8.1.2	Peptoids	231
8.1.3	Peptide Nucleic Acids (PNA)	231

8.1.4	DNA-Binding Oligoamides	232
8.1.5	Aryl Amides and Aryl Ureas	234
8.1.6	<i>meta</i> -Phenylene Ethynylenes (mPE)	235
8.1.7	Terphenyls	235
8.2	Design Strategies	236
8.2.1	Direct Sequence Conversion	237
8.2.1.1	RNA-binding Peptoids	237
8.2.1.2	RNA-binding Oligourea and Carbamate	238
8.2.1.3	RNA-binding β -Peptides	239
8.2.1.4	Receptor-binding β -Peptides	239
8.2.2	Distribution of Physicochemical Properties	240
8.2.2.1	Antimicrobial Peptoids	240
8.2.2.2	Antimicrobial β -Peptides	241
8.2.2.3	Antimicrobial Aryl Amides and Aryl Ureas	243
8.2.2.4	Antimicrobial <i>meta</i> -Phenylene Ethynylenes	244
8.2.2.5	DNA-binding Peptoids	244
8.2.2.6	DNA-binding β -Peptides	245
8.2.2.7	Cholesterol Uptake-inhibiting β -Peptides	245
8.2.2.8	Heparin-inhibiting Aryl Amides	247
8.2.2.9	Calmodulin-inhibiting Aryl Amides	248
8.2.3	Modular Assembly	248
8.2.3.1	DNA-binding Oligoamides	248
8.2.3.2	Nucleotide-binding Peptide Nucleic Acids	251
8.2.4	Grafting Bioactive Functionalities onto Scaffolds	253
8.2.4.1	Protein–protein Interaction-inhibiting β -Peptides	253
8.2.4.2	Protein–protein Interaction-inhibiting Peptoids	255
8.2.4.3	Terphenyl Helix Mimetics	256
8.3	Outlook and Future Directions	257
	<i>References</i>	257
9	Protein Design	267
	<i>Jean-Luc Jestin and Frédéric Pecorari</i>	
9.1	Introduction	267
9.2	Design of Proteins from Natural Scaffolds	269
9.2.1	Design of Enzymes	270
9.2.1.1	Grafting Catalytic Sites in Proteins	270
9.2.1.2	Endowing Enzymes with Two Catalytic Activities in a Single Domain	270
9.2.1.3	Grafting Allosteric Sites to Regulate Enzyme Activity	271
9.2.2	Design of Binding Proteins	272
9.3	Design of Proteins from Building Blocks	275
9.3.1	Design of Proteins from Structural Domains	275
9.3.1.1	Methods for the Identification of Stable Structural Domains	275
9.3.1.2	Identifying New Folds and New Topologies	276

- 9.3.1.3 Combining Domains 277
- 9.3.2 Design of Proteins from Secondary Structures 277
- 9.4 Design of Proteins using Altered Alphabets 280
 - 9.4.1 Design of Proteins using Reduced Alphabets 280
 - 9.4.2 Design of Proteins using Extended Alphabets 281
 - 9.4.2.1 By Codon Reassignment Strategies 282
 - 9.4.2.2 By Suppression Strategies 282
- 9.5 Design of Proteins *de novo* 284
 - 9.5.1 Computational Design of New Folds and Experimental Proofs 284
 - 9.5.2 Combinatorial and Experimental Design 284
- 9.6 Conclusion 286
- References* 287

10 Nucleic Acid Foldamers: Design, Engineering and Selection of Programmable Biomaterials with Recognition, Catalytic and Self-assembly Properties 291

Arkadiusz Chworos and Luc Jaeger

- 10.1 Introduction 291
- 10.2 Principles of Nucleic Acid Foldamers 292
 - 10.2.1 Structural Principles: Hierarchical Organization and Modularity 292
 - 10.2.1.1 Chemical Modularity and Stability 292
 - 10.2.1.2 Secondary Structure Principles 294
 - 10.2.1.3 Tertiary Structure Principles 295
 - 10.2.1.4 Quaternary Structure Principles 298
 - 10.2.2 Functional Principles: Recognition, Switches and Catalysis 299
 - 10.2.2.1 Aptamers and Nucleic Acid Switches 301
 - 10.2.2.2 Ribozymes and DNAzymes 302
 - 10.2.2.3 Multifunctional Nucleic Acid Foldamers 302
- 10.3 Synthesis of Nucleic Acid Foldamers and Analogs 303
- 10.4 Combinatorial Approaches for Isolating Functional Nucleic Acid Foldamers 306
- 10.5 DNA Architectonics 307
 - 10.5.1 Rational Design of DNA Tiles 308
 - 10.5.2 Principle of Tensegrity and Mode of Assembly 309
- 10.6 RNA Architectonics 310
 - 10.6.1 General Approach 310
 - 10.6.2 Examples of RNA Nano-architectures 313
- 10.7 Self-assembly Strategies for Building Complex Nucleic Acid Nanostructures 315
 - 10.7.1 Programmable Self-assembly 315
 - 10.7.1.1 General Principles: “One pot” versus “Step-wise” Assembly 315
 - 10.7.1.2 Addressable Self-assembly 317
 - 10.7.1.3 Algorithmic Self-assembly 317
 - 10.7.1.4 Templated Self-assembly and Scaffolded DNA Origami 317

10.7.2	Additional Principles of Nucleic Acid Architectonics	318
10.7.2.1	Principle of Orientational Compensation	318
10.7.2.2	Applications of Principles of Symmetry	318
10.7.2.3	Fractal Nano-architectures	318
10.8	Ornamentation and Functionalization of Nucleic Acid Architectures	319
10.8.1	General Principles	319
10.8.2	Nucleic Acid Foldamers for Sensors, Medicine and Nano-electronics	319
10.9	Conclusions	321
	<i>References</i>	323
11	Helically Folding Polymers	331
	<i>Eiji Yashima and Katsuhiko Maeda</i>	
11.1	Introduction	331
11.2	Helical Polymers with High Helix Inversion Barriers (Static Helical Polymers)	332
11.2.1	Poly(triarylmethyl methacrylate)s	333
11.2.2	Polychloral	334
11.2.3	Polyisocyanides	336
11.2.4	Polyguanidines	337
11.3	Helical Polymers with Low Helix Inversion Barriers (Dynamic Helical Polymers)	338
11.3.1	Dynamic Helical Polymers Assisted by Covalent Bonding	339
11.3.1.1	Polyisocyanates	339
11.3.1.2	Polysilanes	341
11.3.1.3	Polyacetylenes	342
11.3.2	Dynamic Helical Polymers Assisted by Noncovalent Bonding	344
11.3.2.1	Induced Helical Poly(phenylacetylene)s	345
11.3.2.2	Hierarchical Amplification of Helical-Sense Excess in Liquid Crystals	347
11.3.2.3	Other Induced Helical Polymers	349
11.3.3	Memory of Induced Helical Chirality	351
11.4	Inversion of Macromolecular Helicity	355
11.5	Applications of Helical Polymers	359
11.6	Conclusion	362
	<i>References</i>	363
12	Polyisocyanides: Stiffened Foldamers	367
	<i>Matthijs B.J. Otten, Gerald A. Metselaar, Jeroen J.L.M. Cornelissen, Alan E. Rowan and Roeland J.M. Nolte</i>	
12.1	Introduction	367
12.2	Preparation	368
12.3	Conformation	370

12.4 Stiffening the Helix 377
12.5 Functionalized Polyisocyanides 387
12.6 Conclusions 398
References 398

13 Foldamers at Interfaces 403

Jan van Esch, Hennie Valkenier, Sebastian Hartwig, and Stefan Hecht

13.1 Introduction 403
13.2 Folding in Solution and at Interfaces 405
13.2.1 Types of Interactions 406
13.2.2 Thermodynamics 406
13.2.3 Design Considerations 408
13.2.4 Scope 409
13.3 Helical Structures 410
13.3.1 Adsorption of Helical Structures at Interfaces 410
13.3.2 Loss of Helicity upon Adsorption 412
13.3.3 Helical Structures Formed upon Adsorption 414
13.4 Sheet Structures 415
13.4.1 Adsorbed Sheet Structures at Interfaces 415
13.4.2 Enhanced Sheet Formation upon Adsorption 417
13.4.3 Change in Sheet Structure upon Adsorption 420
13.5 Turn Elements and Hairpins 421
13.6 Outlook 423
References 424

Index 427

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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