

# Symposium on Foldamers

**2015** January 26-28  
IECB, Bordeaux-Pessac, France



## Program and Abstract Book





*Image courtesy of Dr. Soumen De (Poster 4).*

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## **Welcome to the 4<sup>th</sup> Symposium on Foldamers 2015**

Dear participants,

Welcome to the 2015 Foldamer Symposium and welcome to Bordeaux !

This symposium follows earlier editions that took place in Bordeaux in 2010, 2012 and in Paris in 2013. This series of conferences dedicated to Foldamer science was initiated in the frame of a COST (European Cooperation in Science and Technology) action dedicated to the advancement of foldamers that took place between 2009 and 2013.

With almost 100 participants from more than 17 countries across America, Asia, and Europe, this edition also makes a strong case for continuing to hold an international event focusing on foldamer science.

The program of the 2015 conference once again illustrates the liveliness of the field showing that foldamer science is truly interdisciplinary, with topics ranging from synthetic oligomers to folded polymers and to protein and nucleic acid design.

We are particularly grateful to the sponsors, both private and public, that supported the symposium.

We hope that you will enjoy the program and your time in Bordeaux and wish you a very fruitful symposium.

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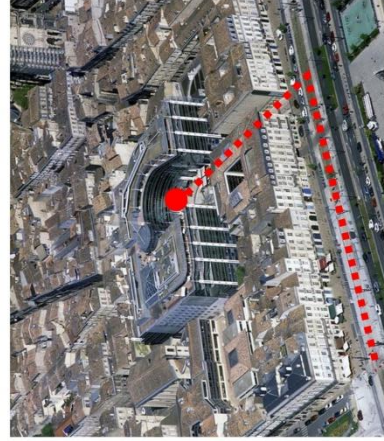
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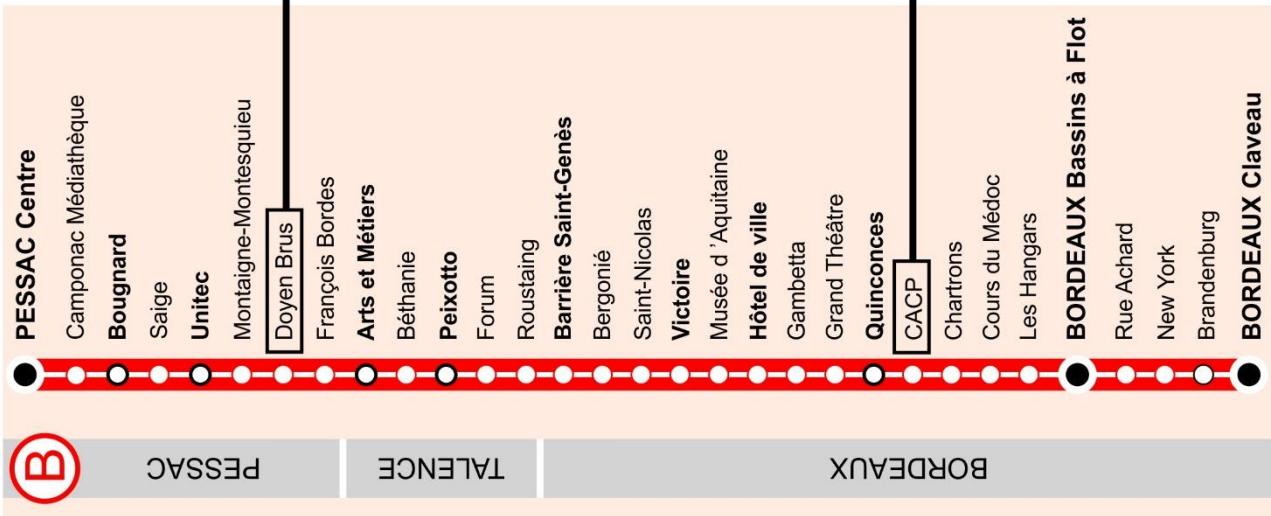
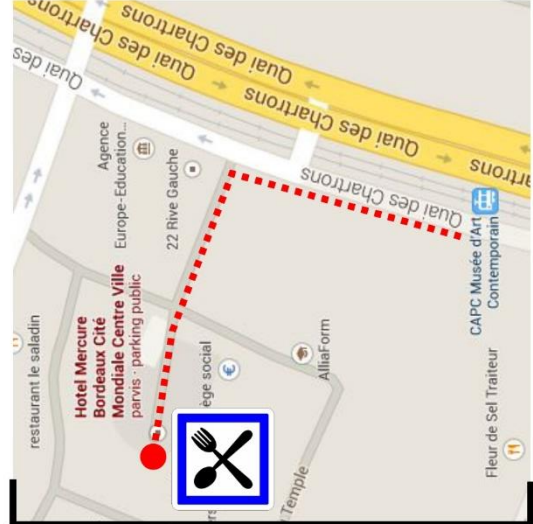
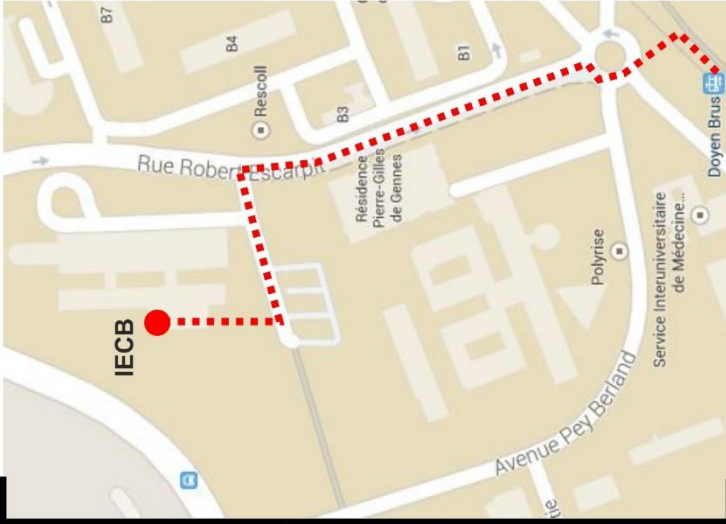
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## Conference Program Overview

	Monday	Tuesday	Wednesday
9:00			
10:00		K. Gothelf	V. Pecoraro
		B. Pentelute	K.-S. Jeong
11:00		Coffee	Coffee
		V. Pophristic	I. Mandity
12:00		S. Pellegrino	U. Lewandowska
		J. Crassous	I. Huc
13:00	Registration	Lunch Poster Session	R. Micura
14:00	Welcome		Lunch
	F. Stoddart		A. Flood
15:00	W. S. Horne	L. Brunsveld	C. Tomasini
	A. Miranker	T. Martinek	S. H. Choi
16:00	Coffee	T. Ohwada	J. Clayden
	A. Rowan	G. Maayan	Coffee
17:00	C. Baldauf	Coffee	D. Yang
	G. Collie	M. Suginome	E. W. Meijer
18:00	F. Formaggio	T. Yeates	
	Welcome Reception		Closing
19:00			
20:00			
21:00		Banquet	

# Symposium Program

Monday, January 26

12:30-14:00 *Arrival/registration / poster installation*

14:00-14:15 *Welcome address*

## Session Chair: Amar Flood

14:15-15:05 **PL1 Fraser Stoddart (Northwestern Univ., USA)**

*"Viologen-Based Foldamers"*

15:05-15:35 **KL1 W. Seth Horne (Univ. Pittsburgh, USA)**

*"Foldamer mimics of protein tertiary structures through systematic engineering of backbone connectivity in biological sequences"*

15:35-15:55 **OC1 Andrew D. Miranker (Yale Univ., USA)**

*"Islet amyloid and the shared molecular origins of membrane poration and cytotoxicity"*

15:55-16:25 *Coffee Break*

## Session Chair: Tomohiko Ohwada

16:25-16:55 **KL2 Alan Rowan (Univ. Nijmegen, The Netherlands)**

*"Self-Assembling Polymer Networks: the key to cell control"*

16:55-17:15 **OC2 Carsten Baldauf (Fritz Haber Institute, Germany)**

*"Structure and dynamics of foldamers from first principles simulations"*

17:15-17:35 **OC3 Gavin Collie (CNRS & Univ. Bordeaux, France)**

*"Programmable aqueous quaternary assembly of non peptide foldamers"*

17:35-18:05 **KL3 Fernando Formaggio (Univ. Padova, Italy)**

*"Exploring  $\alpha$ -,  $3_{10}$ -,  $2_27$ -, and  $2_05$ -helical structures with quaternary  $\alpha$ -amino acids"*

18:05-19:15 *Welcome reception*



**Session Chair: Jean-Marc Escudier**

- 9:30-10:20 **PL2 Kurt Vesterager Gothelf (Aarhus Univ., Denmark)**  
*"DNA-Programmed Assembly of Molecules and Materials"*
- 10:20-10:50 **KL4 Bradley Pentelute (Massachusetts Institute of Technology, USA)**  
*"Cysteine arylation enables production of abiotic peptides and proteins"*
- 10:50-11:20 **Coffee Break**

**Session Chair: Tamás Martinek**

- 11:20-11:40 **OC4 Vojislava Pophristic (Univ. Sciences, Philadelphia)**  
*"Conformational control of arylamide foldamers: Predicting oligomer structures in solution through molecular dynamics simulations"*
- 11:40-12:00 **OC5 Sara Pellegrino (Univ. degli Studi di Milano, Italy)**  
*" $\beta^{2,3}$  diaryl amino acids: effective tools in foldamer chemistry"*
- 12:00-12:30 **KL5 Jeanne Crassous (Univ. Rennes, France)**  
*"Molecular engineering of helixenes"*
- 12:30-14:50 **Buffet lunch at premises and Poster Session**

**Session Chair: Miriam Royo**

- 14:50-15:20 **KL6 Luc Brunsveld (Technical Univ. Eindhoven, The Netherlands)**  
*"Foldamers Targeting Nuclear Receptors - Controlling Helix Length"*
- 15:20-15:40 **OC6 Tamás Martinek (Szeged Univ., Hungary)**  
*"Dark and light sides of protein mimicry: strands, sheets, sandwiches and fibers"*
- 15:40-16:00 **OC7 Tomohiko Ohwada (Univ. Tokyo, Japan)**  
*"Robust Cis- and Trans-Amide Helical Structures of Oligomers of Bicyclic Mimics of  $\beta$ -Proline: Full Control of Amide Cis-Trans Equilibrium"*
- 16:00-16:20 **OC8 Galia Maayan (Technion- Israel Institute of Technology, Israel)**  
*"Biomimetic Utilization of Metal-Binding Peptoids for Cooperative Catalysis and Recognition"*
- 16:20-16:50 **Coffee Break**

**Session Chair: Dan Yang**

- 16:50-17:20 **KL7 Michinori Suginome (Kyoto Univ., Japan)**  
*"New Functions of Chirality-Switchable Helical Macromolecules"*
- 17:20-18:10 **PL3 Todd Yeates (UCLA, USA)**  
*"Designing Highly Symmetric Self-Assembling Protein Structures"*
- 20:00 **Gala Dinner at Hotel Mercure Bordeaux Cité Mondiale**

**Session Chair: Jonathan Clayden**

- 9:30-10:20 **PL4 Vincent L. Pecoraro (Univ. Michigan, USA)**  
*"Designing Peptides to Probe Metal Ion Geometry, Dynamics and Catalysis"*
- 10:20-10:50 **KL8 Kyu-Sung Jeong (Yonsei Univ., Republic of Korea)**  
*"Indole and Indolocarbazole Oligomers: Folding and Functions"*
- 10:50-11:20 **Coffee Break**

**Session Chair: Vojislava Pophristic**

- 11:20-11:40 **OC9 István M. Mándity (Szeged Univ., Hungary)**  
*"Development of a packed bed reactor for the synthesis of peptides and foldamers: a revolutionary reduction of the amino acid excess"*
- 11:40-12:00 **OC10 Urszula Lewandowska (ETH, Switzerland)**  
*"Hierarchical Supramolecular Assembly of Sterically Demanding  $\pi$ -Systems by Conjugation with Oligoprolines"*
- 12:00-12:20 **OC11 Ivan Huc (CNRS & Univ. Bordeaux, France)**  
*"Iterative evolution of an abiotic foldamer sequence: Structure-based design of helically folded receptors for saccharides"*
- 12:20-12:50 **KL9 Ronald Micura (Univ. Innsbruck, Austria)**  
*"Folding and ligand recognition of RNA riboswitches"*
- 12:50-14:30 **Buffet lunch at premises**

**Session Chair: Jeanne Crassous**

- 14:30-15:00 **KL10 Amar Flood (Indiana Univ., USA)**  
*"Manipulating Chloride using Triazole Foldamers and the Hydrophobic Effect"*
- 15:00-15:20 **OC12 Claudia Tomasini (Univ. Bologna, Italy)**  
*"Pseudopeptide Foldamers Promoting Photoinduced Intramolecular Electron Transfer"*
- 15:20-15:40 **OC13 Soo Hyuk Choi (Yonsei University, Republic of Korea)**  
*"Residue-Dependent Folding Propensity of the  $\alpha/\beta$ -Peptide 11/9-Helix"*
- 15:40-16:00 **OC14 Jonathan Clayden (Univ. Manchester)**  
*"Dynamic foldamers as receptor mimics: Induced global conformational change in solution and in membranes"*
- 16:00-16:30 **Coffee Break**

**Session Chair: Kyu-Sung Jeong**

- 16:30-17:00 **KL11 Dan Yang (Honk-Kong Univ., Hong Kong)**  
*"Aminoxy Acids as Building Blocks of Foldamers"*
- 17:00-18:00 **PL5 Bert Meijer (Technical Univ. Eindhoven, The Netherlands)**  
*"Folding of single-chain macromolecules; towards synthetic enzymes"*
- 18:00-18:15 **Closing address**

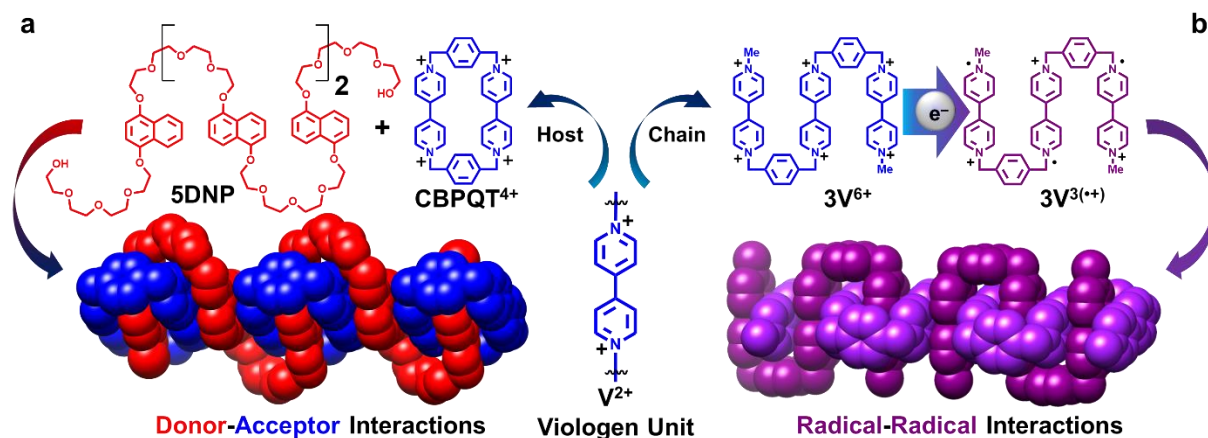
# **Oral Presentation Abstracts**

## Viologen-Based Foldamers

J. Fraser Stoddart<sup>\*,†</sup>

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The donor-acceptor charge transfer interactions between electron-deficient 4,4'-bipyridinium ( $V^{2+}$ ) units—expressed in the context of the host, cyclobis(paraquat-*p*-phenylene) ( $CBPQT^{4+}$ )—and electron-rich 1,5-dioxynaphthalene (DNP) units, have been well known now for some considerable time. By taking advantage of these interactions, a series of pseudorotaxanes and polyrotaxanes, adopting well-defined folded secondary structures in solution and in the solid state, have been obtained<sup>[1–3]</sup>. By studying their folding behaviors systematically in solution, we have been able to gain a deeper understanding of their dynamics and translational isomerism. Solid-state superstructures of the pseudorotaxanes above a certain length (between three to five repeating units) show no difference in comparison with an infinite polymer, opening the door to predicting the secondary structures (with support from <sup>1</sup>H NMR spectroscopy in solution) of related polyrotaxanes which are reluctant to crystallize, i.e., solid-state structures are not available. More recently, radical-radical interactions between the reduced state  $V^{\bullet+}$  of  $V^{2+}$  have been employed in designing foldamers based on oligoviologen chains<sup>[4]</sup> whose folded secondary structures are stabilized by radical-radical interactions. Solution studies suggest that their folding properties are controlled by their lengths and concentrations under redox stimuli, while the solid-state superstructures display an infinite stacking of  $V^{\bullet+}$  as a result of radical-radical interactions, providing a unique example of artificial foldamers with highly-ordered secondary superstructures.



**Figure 1.** Space-filling representations of solid-state superstructures of viologen-based foldamers formed as a consequence of (a) donor-acceptor and (b) radical-radical interactions

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## **Foldamer mimics of protein tertiary structures through systematic engineering of backbone connectivity in biological sequences**

W. Seth Horne

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The construction of unnatural oligomeric species with the intricate structural and functional features of peptides and proteins is an important and growing area of research. As chemists work to push the complexity of these “foldamer” scaffolds toward protein-like tertiary folding patterns, a significant challenge of design becomes apparent. This talk will cover recent work from our lab on development of strategies for protein mimicry by foldamers based on engineering the backbone of biological sequences.<sup>[1]</sup> Blending natural alpha-amino acid residues with diverse unnatural building blocks can create heterogeneous backbone oligomers that show protein-like folding when they display native side-chain sequences. Topics covered will include: (1) design principles for modifying sheet, helix, turn, and loop secondary structures in a tertiary fold context;<sup>[2]</sup> (2) the relationship between backbone connectivity and its susceptibility to proteolytic enzymes; and (3) changes to thermodynamics of folding that result from altered backbone structure.<sup>[3]</sup>

### **References**

- [1] Z. E. Reinert, W. S. Horne, *Org. Biomol. Chem.* **2014**, *12*, 8796-8802.
- [2] Z. E. Reinert, G. A. Lengyel, W. S. Horne, *J. Am. Chem. Soc.* **2013**, *135*, 12528-12531.
- [3] Z. E. Reinert, W. S. Horne, *Chem. Sci.* **2014**, *5*, 3325-3330.

## Islet amyloid and the shared molecular origins of membrane poration and cytotoxicity

Sunil Kumar<sup>a</sup>, Diana E. Schlamadinger<sup>a</sup>, Mark A. Brown<sup>b</sup>, Joanna M. Dunn<sup>a</sup>,  
Brandon Mercado<sup>b</sup>, James A. Hebda<sup>c</sup>, Ishu Saraogi<sup>d</sup>,  
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Small molecule based foldamers and mimetics were synthesized by design to target the putative membrane bound  $\alpha$ -helical oligomeric intermediates of islet amyloid polypeptide (IAPP). IAPP is a peptide cosecreted with insulin by pancreatic  $\beta$ -cells. IAPP proceeds through a series of conformational transitions from random coil to  $\beta$ -sheet via transient  $\alpha$ -helical intermediates. An unknown subset of the structures and dynamics of these events are associated with seemingly disparate gains-of-function including catalysis of  $\beta$ -sheet rich amyloid, membrane penetration, loss of membrane integrity, mitochondrial localization and cytotoxicity, the latter being a central component of diabetic pathology. We use small molecule design and synthesis to probe the relative contribution of IAPP substructures to these processes. Oligoquinoline and oligopyridine based constructs both show that lipid bilayer bound, catalyzed self-assembly of IAPP can be deliberately targeted with a high degree of structural specificity. Moreover, secondary assessments in solution and in cell culture indicate a common and specific molecular basis for this diverse set of gains-of-function.

## Self-Assembling Polymer Networks the key to cell control

Maarten Japers, Zaskia Eksteen Akeroyd, Matthieu Koepf, Vincent A.A. Le Sage, Chris Wilson  
Eduardo Mendes, Paul H.J. Kouwer, and Alan E. Rowan

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Cell fate is a coordinated response caused by biomechanical and biochemical interactions with the extracellular matrix (ECM). Numerous synthetic gels have been developed as mimics of the extracellular matrix, in the hope of understanding how cells respond to the mechanical properties of the tissue microenvironment, with the goal being to develop a fully synthetic extracellular matrix for regenerative medicine applications. In contrast to all synthetic gels developed to date, the extracellular matrix proteins such as collagen type I, and fibrin, display nonlinear mechanical properties such as strain stiffening and negative normal stress <sup>[1]</sup>. In these materials the elastic modulus of the gel increases by several orders of magnitude as the applied strain increases such that the resistance that a cell feels is strongly depended of the strain that it applies. In this presentation I will demonstrate the unique cytomimetic properties of hydrogels based on oligo(ethylene glycol) grafted polyisocyanopeptides <sup>[2]</sup>. These extremely stiff helical polymers <sup>[3]</sup> form gels upon **warming** at concentrations as low as 0.005 %-wt polymer, with materials properties almost identical to these of intermediate filaments and extracellular matrices. The macroscopic behaviour of these gels can be described in terms of the molecular properties of the basic stiff helical polymer and a multi-step hierarchical self-assembly, which results in strain stiffening <sup>[4]</sup>. The unique ability of these materials and their application in cell growth and drug therapeutics will be discussed.

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- [2] Schwartz, E. et al., *Chem. Soc. Rev.* **2010**, 39(5), 1576-1599.
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## Structure and dynamics of foldamers from first principles simulations

Carsten Baldauf,<sup>a</sup> Adriana Supady,<sup>a</sup> Franziska Schubert,<sup>a</sup> Markus Schneider,<sup>a</sup>  
Volker Blum,<sup>a,b</sup> Matthias Scheffler<sup>a</sup>

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We study the structure formation and dynamics of peptides and peptide foldamers using first-principles methods,<sup>[1]</sup> specifically we employ density-functional theory (DFT) corrected for van der Waals interactions. Navigating the conformational space of such flexible (bio-)oligomers is a challenge in itself that we currently tackle with force field based pre-sampling (with basin hopping or replica-exchange molecular dynamics) and then complement with extensive DFT calculations. We compare our results to actual gas-phase experiments, i.e., ion mobility mass spectrometry and vibrational spectroscopy (especially to experiments by K. Pagel at FU Berlin and G. von Helden at FHI Berlin). I would like to cover three topics in my contribution:

With peptides that feature central prolyl-peptide bonds and that model  $\beta$  turns, we studied the effect of monovalent cations on the structure formation. Cations locally disrupt the hydrogen-bonding network and enforce, by favorable electrostatic interactions, otherwise not observed conformations on the peptide's backbone.<sup>[2]</sup>

Helix formation of peptides Ac-Ala<sub>n</sub>-LysH<sup>+</sup> in the gas phase has been studied for years now.<sup>[3]</sup> We added a new direction by studying the effect of increased backbone flexibility on the helix forming properties. For that the  $\beta$  peptide Ac-( $\beta^2$ hAla)<sub>6</sub>-LysH<sup>+</sup> was designed and investigated. We demonstrated for the first time that  $\beta$  peptides from acyclic monomers can form native-like helices (similar to  $3_{10}$ ,  $\alpha$ ,  $\pi$ ). At the same time, the stability order of the three helix-types seems to be inverted with respect to their natural  $\alpha$  peptide counterpart.

Last, I would like to briefly introduce our efforts towards a conformational search and sampling approach that is entirely based on DFT and avoids the use force fields. The performance of the genetic-algorithm search is assessed by comparison to data for capped amino acids (in house reference data, to be published) and two non-natural  $\alpha/\gamma$  hybrid peptides.<sup>[4]</sup>

### References

- [1] C. Baldauf, H.-J. Hofmann, *Helv. Chim. Acta* **2012**, *95*, 2348-2383.
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## Control of quaternary assembly of water-soluble non-peptide foldamers.

Gavin William Collie,<sup>a</sup> Karolina Pulka-Ziach,<sup>a</sup> Caterina Maria Lombardo,<sup>a</sup> Cameron Mackereth,<sup>b</sup> Juliette Fremaux,<sup>a</sup> Frederic Rosu,<sup>b</sup> Marion Decossas,<sup>c</sup> Laura Mauran,<sup>a</sup> Olivier Lambert<sup>c</sup>, Valerie Gabelica<sup>b</sup> and Gilles Guichard<sup>a</sup>

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A large number and variety of foldamers able to fold into stable secondary structures have been reported, however, reports of foldamers with the ability to fold into precise higher-order arrangements (i.e. tertiary or quaternary folding) are far fewer. Indeed, there is considerable interest (and difficulty) in the creation of water-soluble foldamers able to self-assemble in aqueous conditions into well-defined precise quaternary assemblies – a necessary achievement if foldamers with sophisticated functions (such as enzyme activity) are to be developed. Towards this goal, we report here the design and characterization (including high-resolution X-ray crystal structures) of a series of water-soluble amphiphilic oligourea foldamers bearing proteinogenic side-chains, able to self-assemble into precise, well-defined protein-like quaternary arrangements in aqueous conditions. In addition, we show that the final quaternary topology can be controlled at the primary sequence level, permitting the formation of discrete helical bundles or extended super-helical channels with water-filled interior pores.

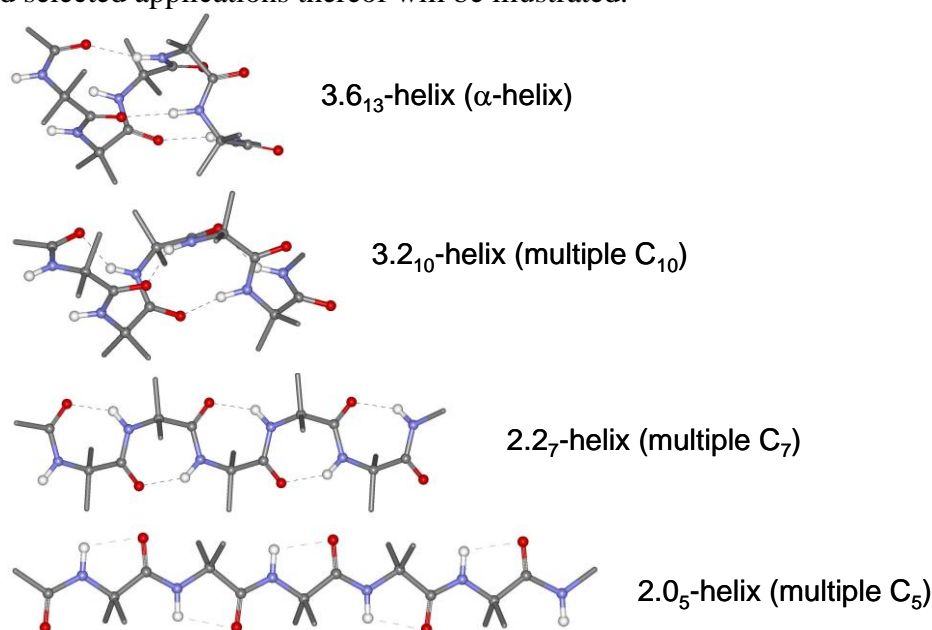
## Exploring $\alpha$ -, $3_{10}$ -, $2.2_7$ -, and $2.0_5$ -helical structures with quaternary $\alpha$ -amino acids

Alessandro Moretto, Cristina Peggion, Marta De Zotti, Marco Crisma, Claudio Toniolo, Fernando Formaggio

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Quaternary  $\alpha$ -amino acids (or  $C^\alpha$ -tetrasubstituted  $\alpha$ -amino acids) are known for their propensity to induce helical ( $\alpha$ - or  $3_{10}$ -) structures in peptides.<sup>[1]</sup> However, homo-peptides made of some  $C^\alpha$ -ethylated  $\alpha$ -amino acids, both chiral and achiral, may adopt the fully-extended conformation ( $2.0_5$ -helix, also known as multiple  $C_5$ ).<sup>[1,2]</sup> This structure, extremely rare in proteins, is the most elongated accessible to an  $\alpha$ -peptide. Interestingly, we have shown that the  $2.0_5$ -helix can be converted to the less elongated  $3_{10}$ -helix by changing solvent.<sup>[2]</sup> Applications of this molecular transition can be easily envisaged. Recently, we also started exploring the ability of some quaternary  $\alpha$ -amino acids to promote contiguous, multiple  $\gamma$ -turns, which generate incipient or fully-developed  $2.2_7$ -( $\gamma$ -)helices.<sup>[3]</sup> Thus, it appears that quaternary  $\alpha$ -amino acids can be tailored to generate different types of 3D-structures (Figure 1). This variety, in turn, can be exploited to design scaffolds and spacers for spectroscopic, supramolecular and bioorganic investigations.<sup>[4-6]</sup> Examples of the mentioned peptide structures and selected applications thereof will be illustrated.



**Figure 1.** Molecular models of a same pentapeptide arranged into an  $\alpha$ -,  $3_{10}$ -,  $2.2_7$ -, and  $2.0_5$ -helix.

### References

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- [2] C. Peggion, M. Crisma, C. Toniolo, F. Formaggio, *Tetrahedron* **2012**, 23, 4429.
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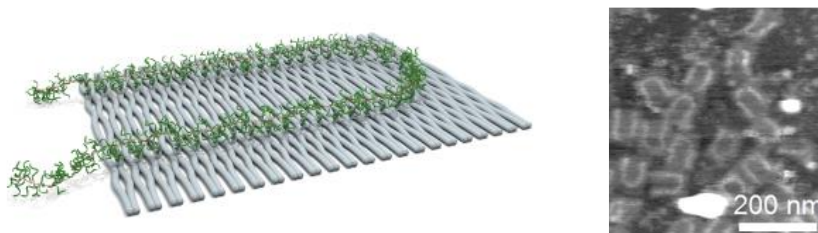
## DNA-Programmed Assembly of Molecules and Materials

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We are using DNA as a programmable tool for directing the self-assembly of molecules and materials. The unique specificity of DNA interactions and our ability to synthesize artificial functionalized DNA sequences makes it the ideal material for controlling self-assembly and chemical reactions of components attached to DNA sequences. Recently, we applied these methods to DNA templated conjugation of DNA to proteins such as antibodies.<sup>[1]</sup> In particular we are using DNA origami, large self-assembled DNA structures as a template for positioning of materials such as organic molecules, dendrimers and biomolecules.<sup>[2-4]</sup> We have also used DNA origami to image chemical reactions with single molecule resolution<sup>[4]</sup> and to make a 3D DNA origami box with a controllable lid.<sup>[5]</sup> The main focus of the presentation will be on a recently prepared DNA-phenylene vinylene polymer and its self-assembly on DNA origami for studies of electronic and optical properties (**Fig 1**).



**Figure 1.** Illustration and AFM image of poly(DNA-phenylene vinylene) on DNA origami.

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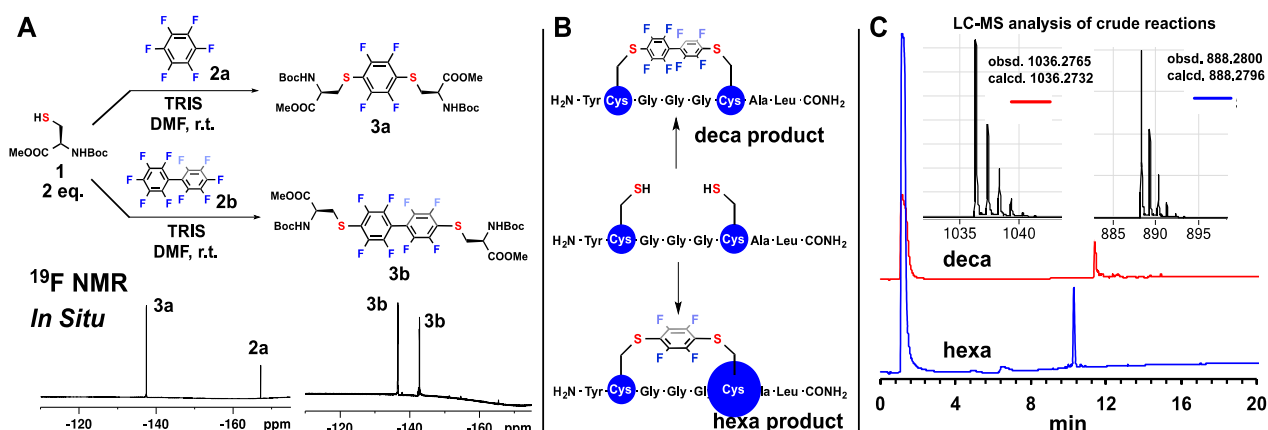
# Cysteine arylation enables production of abiotic peptides and proteins

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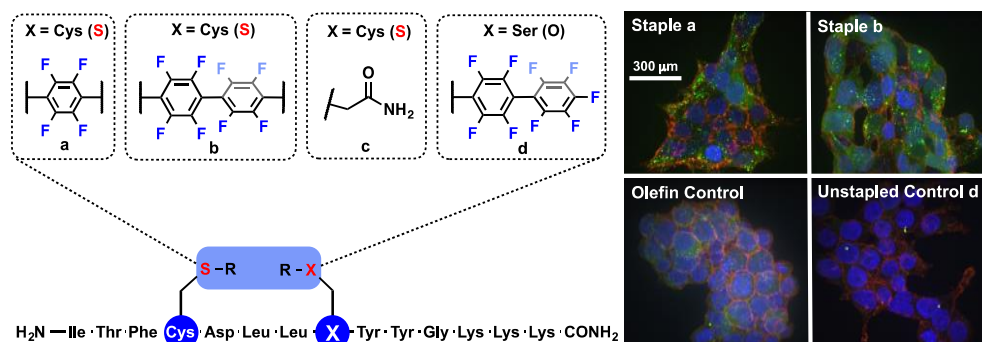
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Here we present our results that show *highly regio- and chemoselective cysteine perfluoroarylation* under mild conditions for the synthesis of abiotic biopolymers (*JACS* **135**:5946, 2013; *ACIE* **52**:14001, 2013; *OBC* **12**:566, 2014; *OL* **16**:3652, 2014) Cysteine perfluoroarylation is compatible with unprotected peptides. Reactions can be monitored with  $^{19}\text{F}$  NMR spectroscopy and LCMS *in situ*. 1,4- and 1,10- substitution patterns (*para*) were exclusively observed for reactions with hexafluorobenzene and decafluorobiphenyl respectively under the developed conditions (Fig. 1).



**Figure 1.** A) Model perfluoroarylation reactions between cysteine and commercially available hexafluorobenzene or decafluorobiphenyl. The reaction yields were >95% in 4 hours as indicated by *in situ*  $^{19}\text{F}$  NMR. B) Cysteine perfluoroarylation with model peptides and C) *in situ* LC-MS traces of the respective reactions.

Improved properties of bioactive peptides were observed when stapled in an *i, i + 4* arrangement with hexafluorobenzene or decafluorobiphenyl (Fig. 2). Model studies were undertaken with stapled peptides that target the C-terminal domain of an HIV-1 capsid assembly polyprotein. Variants penetrate cells at levels comparable to hydrocarbon-linked peptide reported by Cowburn *et al.* (Fig 2). Stapling is required for cell penetration; experiments with non-crosslinked variants that contained pentafluorobenzene or nonafluoro-biphenyl displayed no cellular uptake. Following this work, we discovered an enzyme-catalyzed version of the cysteine arylation capable of operating in water, as well as a more comprehensive study aimed at optimizing arylation chemistry for macrocyclization. Lastly, we will discuss the use of arylation chemistry for the site-specific modification of antibodies by use of a novel mini self-labeling protein.



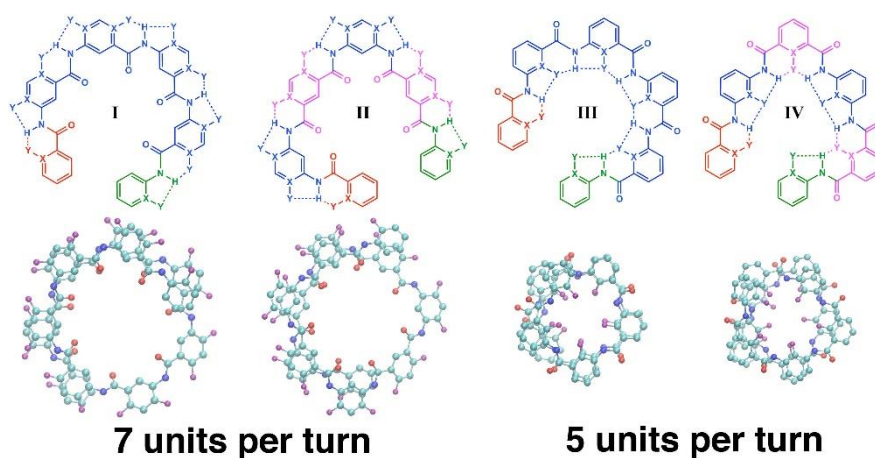
**Figure 2.** Peptide inhibitors of the C-terminal capsid assembly polyprotein (C-CA). Confocal microscopy images of HEK293T cells treated with 5  $\mu\text{M}$  of FITC modified peptides a, b, and d (Z-stack accumulated; DNA – blue; cell membrane – red; peptides – green; Cowburn *et al.* olefin control hydrocarbon crosslinked variant, NYAD).

## Conformational control of arylamide foldamers: Predicting oligomer structures in solution through molecular dynamics simulations

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We present a comprehensive molecular dynamics (MD) study on a series of helical arylamide oligomers with systematically varying building blocks and linkage types.<sup>[1]</sup> This study showcases our recently developed computational approach for the prediction of secondary structure properties of arylamide foldamers and their solution dynamics. We demonstrate that conformational characteristics of foldamers, such as number of units per turn, helical pitch, and pore diameter, can be predicted by MD simulations of small oligomers. Furthermore, the curvature angle, the key geometrical parameter in helical arylamide structures, can be accurately determined by MD simulation of tetramers, entities with often less than one helical turn. The curvature angle is found to be a local property associated with one single residue/unit, which enables intuitive and highly accurate predictive power for designing oligomers with various scaffolds and sizes. In addition, MD simulations with the improved force field parameters capture solvent effects both in terms of protic solvent competition with intramolecular H-bonds and solvophobic effects. The developed computational approach can provide useful insight into dynamical, mechanistic and functional properties of the arylamide oligomer class, which will facilitate rational design of foldamers.



**Figure 1.** Top: Schematics of the four types of helical arylamide foldamers that can be constructed from one aromatic building block type. Dotted lines denote H-bonds. Bottom: Snapshots from MD simulations showing differences in helical diameters of four helical arylamides built from fluorene derivatives.

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**$\beta^{2,3}$  diaryl amino acids: effective tools in foldamer chemistry**

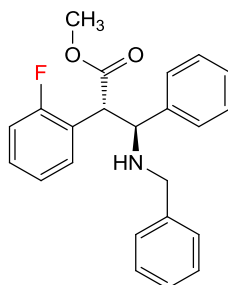
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The preparation of  $\alpha/\beta$ -peptides, *i.e.* synthetic polymers containing alternating  $\alpha$ - and  $\beta$ -aminoacids, is of great interest in a wide range of applications, from catalysis to electrochemistry, biology and nanomedicine.<sup>[1]</sup>  $\alpha/\beta$ -peptides have expanded the scope of foldamers, leading to new molecular architectures, whose type depends mainly on the substitution on C<sub>2</sub> and C<sub>3</sub> atoms of the  $\beta$ -residue.<sup>[2]</sup> Recently, we have reported on a new class of  $\beta$  amino acids, containing aryl substituents on both  $\beta^2$  and  $\beta^3$  positions. Their diastereoselective synthesis was obtained through a very efficient TiCl<sub>4</sub>/TEA-catalyzed Mannich-like reaction.<sup>[3]</sup>

Here we present the preparation and the conformational studies of different  $\alpha,\beta$ -peptide sequences, containing *L*-Ala alternated with the new  $\beta^{2,3}$ -diaryl amino acid having a fluorine substituent on the  $\beta^2$ -aryl group (Figure 1). We found that, depending on the stereochemistry of the  $\beta$  amino acid and on the length of the sequences, it was possible to switch from helix to extended conformation. Finally, self-assembly studies have been performed on these peptides.

**Figure 1.****References**

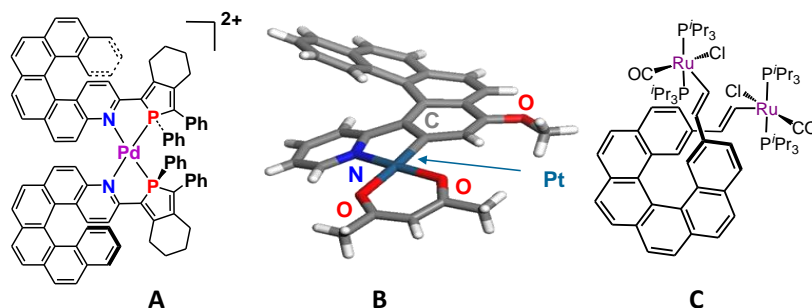
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## Molecular engineering of helicenes

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Helicenes possess a unique screw-shape and  $\pi$ -conjugated structure which provides them with peculiar properties such as huge optical rotation values.<sup>[1a]</sup> These helicene derivatives may have applications as chiroptical materials or in catalysis. One challenge set to chemists is to develop synthetic strategies that provide efficient access to a variety of helicene-based frameworks with tunable chiroptical properties. We have therefore investigated diverse routes for the molecular engineering of helicenes involving organometallic and coordination chemistry of helicene derivatives.<sup>[1b]</sup> For example, phosphole-modified azahelicenes that act as 1,4-P,N-chelates towards metal ions afforded chiral metal-bis(helicene) complexes (**A**) via stereoselective coordination.<sup>[2]</sup> The metal center has a great impact on the chiroptical properties of these novel helicene derivatives. Furthermore, the first organometallic helicenes (**B**) incorporating a transition metal into their *ortho*-annulated  $\pi$ -conjugated backbones<sup>[3a]</sup> have been prepared, by a simple *ortho*-metalation reaction and assemblies of platinahelicenes bearing an original Pt(III)-Pt(III) scaffold have revealed unprecedented enhancement of the chiroptical properties through  $\sigma$ - $\pi$  conjugation.<sup>[3b]</sup> Finally, molecular redox chiroptical switches have been obtained by grafting ruthenium centers onto vinyl-helicene cores (**C**).<sup>[4]</sup>



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## Foldamers Targeting Nuclear Receptors - Controlling Helix Length

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The most abundant protein secondary structure in nature – the  $\alpha$ -helix – is frequently found at protein interfaces, making it an important lead structure for the design of small molecule modulators of protein–protein interactions (PPIs).<sup>[1]</sup> Nature's ability to precisely control the length of  $\alpha$ -helices, especially in the context of helix-mediated PPIs, is key to ensuring the optimal interaction of protein partners. By extension, precise control over the length of  $\alpha$ -helix mimetics is necessary to ensure optimal disruption of  $\alpha$ -helix-mediated PPIs. Using the Nuclear Receptor – Cofactor Interaction as  $\alpha$ -helix-mediated PPI per excellence, we highlight the emerging importance of helix length control<sup>[2]</sup> using a set of contemporary chemical approaches. Based on chemical scaffolds such as miniproteins,<sup>[3]</sup> small folded peptides,<sup>[4]</sup> and mixed  $\alpha/\beta$ -peptides a set of novel helix mimetic inhibitors was identified with exact molecular control over  $\alpha$ -helix length. These foldamers have set the stage to ultimately identify and further develop small molecules targeting the Nuclear Receptor PPIs.<sup>[5]</sup>

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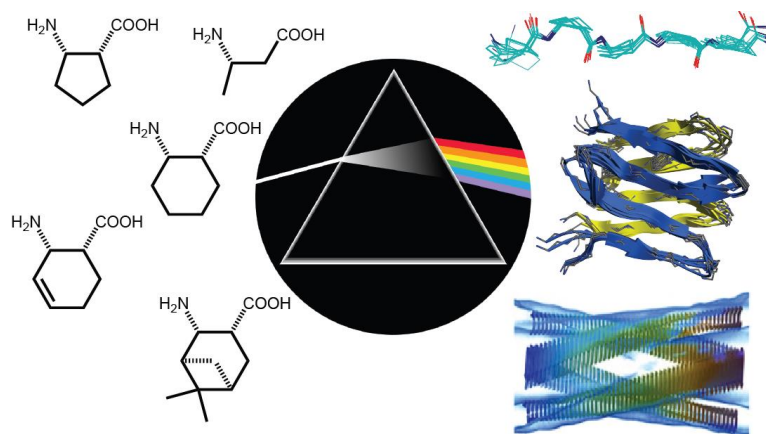


## Dark and light sides of protein mimicry: strands, sheets, sandwiches and fibers.

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There are a large number of known  $\beta$ -sheet-rich protein interfaces, which are potential biological targets,<sup>[1]</sup> but the mimicry of protein-sized  $\beta$ -sheet structures with peptidic foldamers is a great current challenge. The long-range interactions are essential to construct water-soluble  $\beta$ -sheet mimetic foldamers. The steric requirements of the tight hydrophobic packing and the H-bonding between the strand segments must be simultaneously optimized, otherwise the system remains disordered or undergoes aggregation. Here we discuss the extension of the backbone stereochemical patterning method to build foldameric strands in a bottom-up approach.<sup>[2]</sup> These standalone strands tend to form nanostructured fibers, of which morphology is sequence-dependent and internal H-bonding network is amyloid-like in terms of electronic structure and fluorescent properties.<sup>[3]</sup> Recently, we tested the possibility of the top-down design of foldameric sheet and sandwich mimetics. Systematic  $\beta^3$ -amino acid mutations were carried out on anginex, which is an antiangiogenic 33-mer peptide. We found that interaction with the target was able to induce the  $\beta$ -sheet formation even in the presence of the  $\beta^3$ -residues, which resulted in bioactive sequences.<sup>[4]</sup> The feasibility of introducing  $\beta$ -amino acids in the hydrophobic core of a  $\beta$ -sandwich was investigated by using betabellin-14 as a template structure. Screening of various open-chain and cyclic  $\beta$ -residues revealed that (1*R*,2*S*)-2-aminocyclohexanecarboxylic acid could fit into the H-bonding network and into the hydrophobic core. This foldameric  $\beta$ -sandwich model contains 25% unnatural building blocks, and displayed protein-like thermal denaturation behavior.



**Figure 1.** Strand, sheet and fiber mimetics built by using various  $\beta$ -amino acid building blocks

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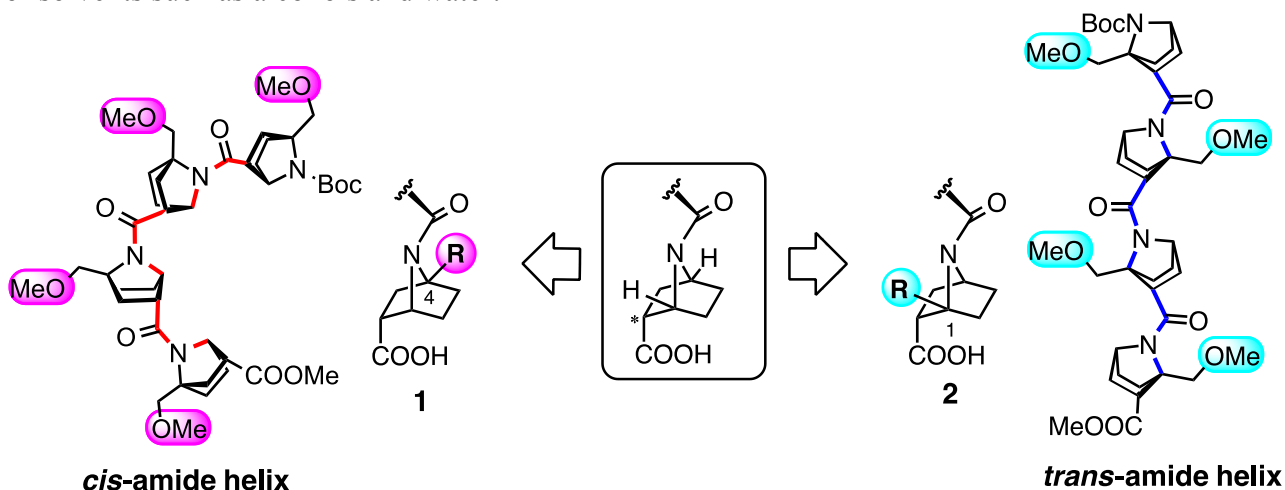
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## Robust *Cis*- and *Trans*-Amide Helical Structures of Oligomers of Bicyclic Mimics of $\beta$ -Proline: Full Control of Amide *Cis-Trans* Equilibrium

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Homooligomers of 7-azabicyclo[2.2.1]heptane-2-*endo*-carboxylic acid, a bridged  $\beta$ -proline analogue (**1**) with a substituent installed at the C4-bridgehead position completely biased the amide *cis-trans* equilibrium to the *cis*-amide structure.<sup>[1]</sup> We expected that introduction of a substituent at the C1-bridgehead position adjacent to the carboxylic acid moiety (**2**) would tip the *cis-trans* amide equilibrium towards *trans*-amide structure. Herein we show that indeed oligomers of this analog take a consistent helical structure involving all-*trans*-amide linkages, independently of the number of residues, from the dimer up to the octamer.<sup>[2]</sup> These unique helical structures show some similarity in shape to *trans*-amide based polyproline II (PPII) helix. These helices were stable in various kinds of solvents such as alcohols and water.



**Figure 1.** Generation of all-*cis*-amide helix and all-*trans*-amide helix on the basis of bicyclic  $\beta$ -proline mimic.

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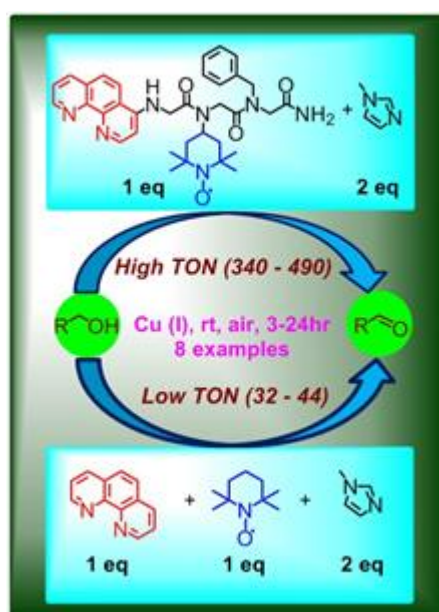
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## Biomimetic Utilization of Metal-Binding Peptoids for Cooperative Catalysis and Recognition

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N-substituted glycine oligomers, “peptoids”, are a class of peptidomimetics that are generated from primary amines rather than from amino acids. Thus, their facile and efficient synthesis on solid phase support enables the incorporation of various functional groups at specified *N*-positions along their spine. Capitalizing on this property, we design and produce peptoid sequences having metal-binding ligands displayed in a specific manner, and investigate whether their interaction with biologically relevant metal ions can induce biomimetic function. We demonstrate that: (1) catalytic Cu(I)-TEMPO peptoids can perform with much higher activity in the oxidation of alcohols than a mixture of Cu(I) and TEMPO and (2) peptoids incorporating two different ligands enable both the selective binding of two different metal ions, one at each site, as well as the selective binding of Cu(II) from a mixture of numerous metal ions in higher concentrations.



**Figure 1.** Metal-binding peptoids as highly efficient cooperative intramolecular catalysts for alcohol oxidation.

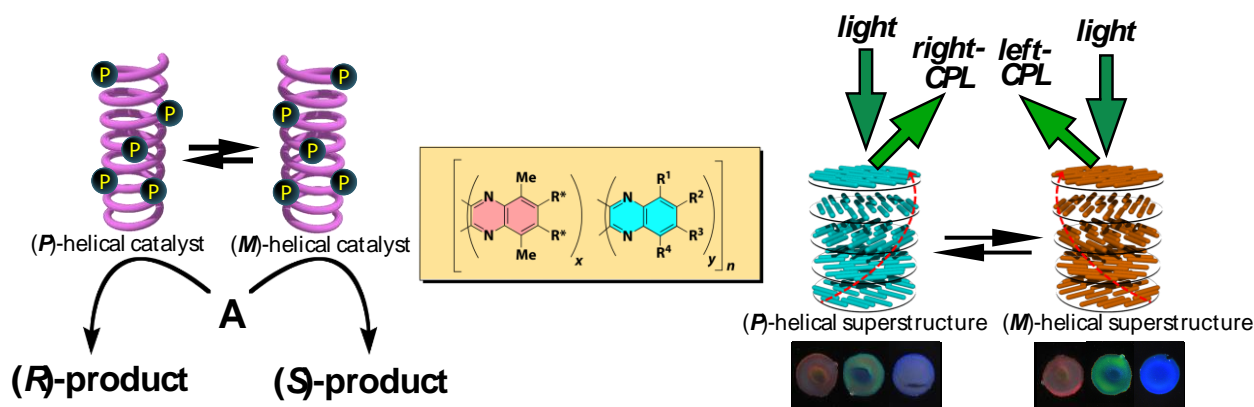
## New Functions of Chirality-Switchable Helical Macromolecules

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Much effort has been devoted to the study of non-racemic helical polymers, aiming to find new molecular and supramolecular functions on the basis of their characteristic chiral backbone structures. We have recently established poly(quinoxaline-2,3-diyl)s bearing chiral side chains as a new polymer scaffold that undergoes reversible switch of its helical conformation by external stimuli such as solvent effect.<sup>[1-4]</sup> By accommodating coordination sites, the chirality-switchable polymer serves as new chiral ligands in transition-metal catalyzed asymmetric reactions, which are able to produce either enantiomeric products with high enantioselectivities.<sup>[2-8]</sup> Furthermore, incorporation of haloalkyl side chains into the polyquinoxaline scaffolds afforded a new solid polymer film, which shows physical color on the basis of selective reflection of visible light by the formation of cholesteric supramacromolecular structure.<sup>[9]</sup> The color and the handedness of the reflected circularly polarized light (CPL) can be switched reversibly by tuning composition of the polymers as well as external stimuli.



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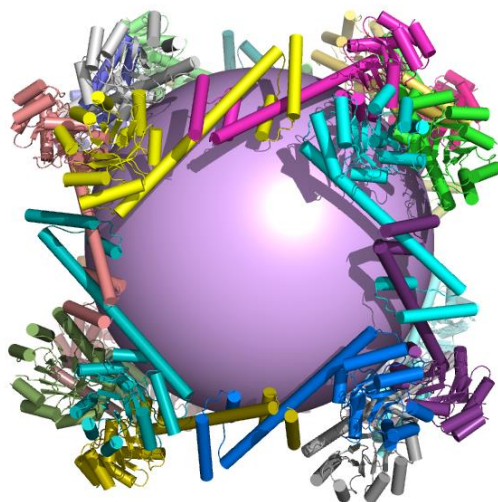
## Designing Highly Symmetric Self-Assembling Protein Structures

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Wide ranging efforts are underway to use macromolecules of various types as building blocks for designing supramolecular structures; nucleic acids, peptides and large proteins, and various synthetic analogues are all the subject of active investigation. In our work we are focusing on natural protein molecules as the starting materials for designing biomolecules that self-assemble into highly regular geometric structures, such as large cages and shells. Symmetry plays an important role in various strategies that have led to recent successes in the laboratory<sup>[1-4]</sup>. These include assemblies built from 12 and 24 subunits in the shapes of tetrahedra and cubes, with diameters exceeding 200Å in some cases. We have been able to validate our designed assemblies by X-ray crystallography (along with other techniques) in order to confirm the designs in atomic detail. The ability to design precise three-dimensional structures on this scale opens up numerous possible applications, from synthetic vaccines, to drug delivery, to active biomaterials. Recent progress will be discussed.



**Figure 1.** Structure of a designed protein that assembles from 24 copies to form a cube 220Å in diameter with a 130Å inner cavity<sup>[4]</sup>. The crystal structure is shown with an imaginary inner sphere to convey depth.

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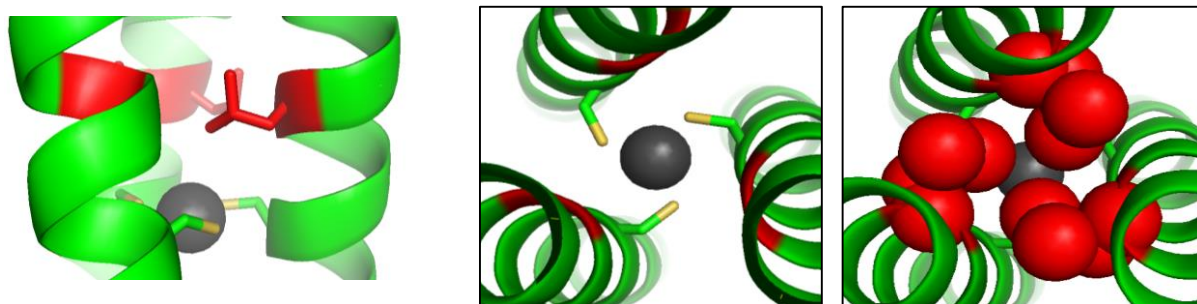
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## Designing Peptides to Probe Metal Ion Geometry, Dynamics and Catalysis

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We have previously shown that short, synthetic peptides in the TRI, GRAND and CoilSer (CS) family will associate at neutral to moderate pH as three stranded coiled coils (TRI sequence= G(LKALEEK)<sub>4</sub>G; GRAND= G(LKALEEK)<sub>5</sub>G; CS= ). When the hydrophobic interior of these peptides is modified to include a cysteine (e.g., TRI L12C) a trigonal binding site for heavy metals is formed. We will show that a variety of heavy metals including Hg(II), Cd(II) and As(III) can be accommodated into these sites resulting in peptides that serve as excellent models for the binding of heavy metals to metalloregulatory proteins such merR and CadC. We will discuss the ability to control coordination number of Cd(II) by outer sphere protein modifications such as using non-coded amino acids (e.g., penicillamine). We will also demonstrate how different peptide isomers permit control of metal structure. These peptides can then be used to assess the dynamics of metal insertion and solvent access to the encapsulated metal centers. If time permits, we will also look at metal binding to histidine rich sites that lead to catalytic reactions for carbonic anhydrase and Cu nitrite reductases and will discuss how systematic variation of interior residues results in great than 1000-fold increases in catalysis.



**Figure 1.** Proposed structure of a trigonal Cd(II) site in a designed peptide.

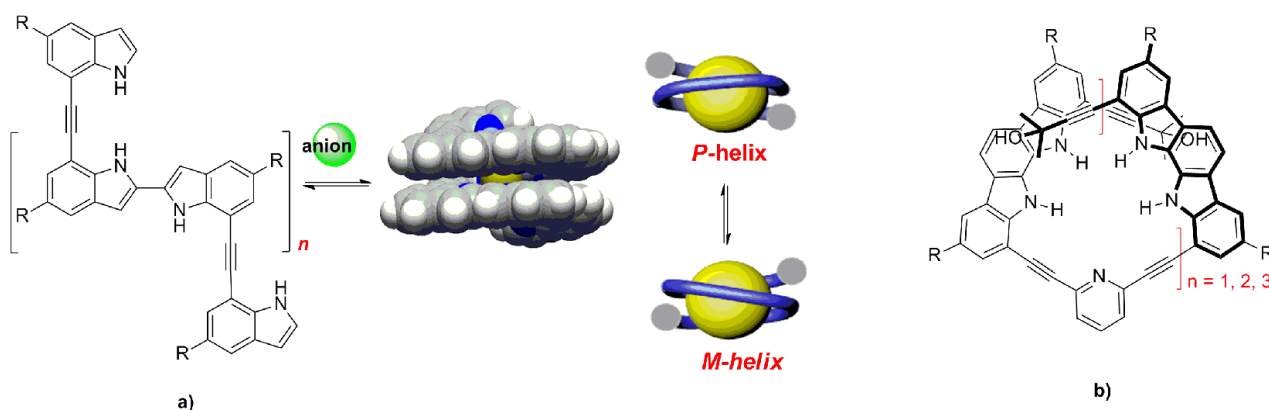
## Indole and Indolocarbazole Oligomers: Folding and Functions

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A series of oligoindoles and oligoindolocarbazoles have been prepared which can function as anion receptors or anion-responsive chiroptical molecular switches.<sup>[1]</sup> These oligomers exist in unfolded zig-zag conformations but fold to give helical structures upon anion binding by hydrogen bonds with indole NHs. The binding affinity and selectivity for a specific anion may be modulated with changing the chain length of the oligomers and/or the kind of linkers connecting repeating monomers. Moreover, the helical orientation has been controlled by the incorporation of chiral segments or binding of chiral guests, which give rise to characteristic circular dichroism (CD) signals for the implementation of chiroptical molecular switches.<sup>[2]</sup>

We have also prepared indolocarbazole/pyridine foldamers wherein two repeating indolocarbazole and pyridine are alternatively connected through ethynyl spacers. Owing to dipole interactions, the adjacent indolocarbazole NH proton and pyridyl nitrogen tend to adopt a syn-conformation which, in combination with  $\pi$ -stacking interactions, leads to the helical folding of the indolocarbazole/pyridine foldamers.<sup>[3]</sup> The folding structures with a channel-like tubular cavity have been characterized in solution (<sup>1</sup>H NMR, absorption and emission spectroscopy) and in the solid state (single crystal X-ray analysis). Details will be described in the presentation.



**Figure 1.** a) Oligoindoles: Anion-driven helical structures and helicity control, and b) indolocarbazole/pyridine foldamers with an internal channel-like cavity.

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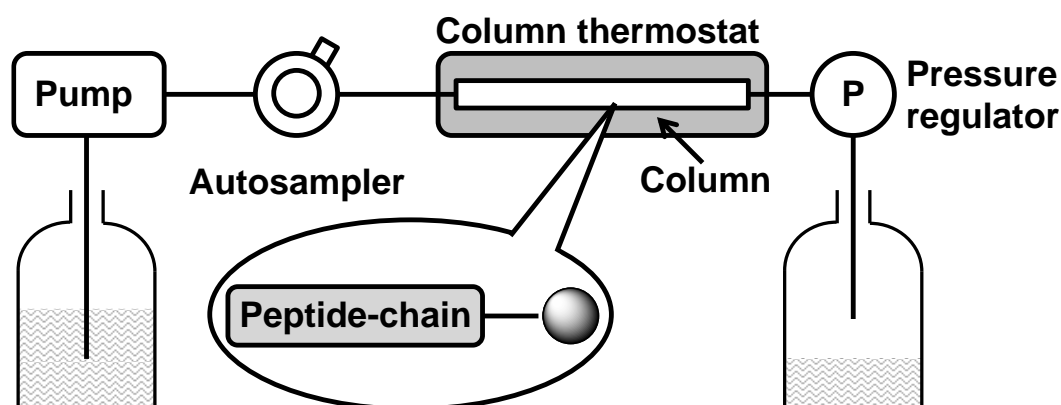
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## Development of a packed bed reactor for the synthesis of peptides and foldamers: a revolutionary reduction of the amino acid excess

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The importance of synthesis of peptides and foldamers is warranted by the need for peptide-based medicines, the roles of peptides and foldamers in drug discovery, etc. Since its introduction by Merrifield, peptide synthesis was performed almost exclusively on solid supports. It has been applied for the synthesis of foldamers as well.<sup>[1]</sup> The solid-phase peptide synthesis (SPPS) technique has subsequently been progressively developed. However, still a general property of these methodologies are the high number of amino acid equivalents required for total coupling.<sup>[2]</sup> Continuous-flow (CF) approaches have recently gained in significance among synthetic techniques.<sup>[3]</sup> We show here that the number of amino acid equivalents used for SPPS can be lowered drastically to around 1.5 equivalents through the application of a CF technique and by complete reaction parameter optimization.



**Figure 1.** Schematic representation of the constructed CF reactor

Under the optimized conditions the couplings of all 20 proteinogenic amino acids with 1.5 amino acid equivalents proceeded with excellent conversions. To demonstrate the efficiency of the CF-SPPS methodology, known difficult sequences were synthesized in automated way. The purities of the resulting crude peptides were comparable with literature result, but the CF-SPPS methodology requires much less amino acid and solvent. As further evidence of the effectiveness,  $\beta$ -peptide foldamers with alicyclic side-chains were synthesized in excellent yields. Importantly, exotic and expensive artificial amino acids were incorporated into sequences by an automated way through the use of exceptionally low numbers of amino acid equivalents at low costs.<sup>[4]</sup>

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# Hierarchical Supramolecular Assembly of Sterically Demanding $\pi$ -Systems by Conjugation with Oligoprolines

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and Helma Wennemers<sup>a</sup>

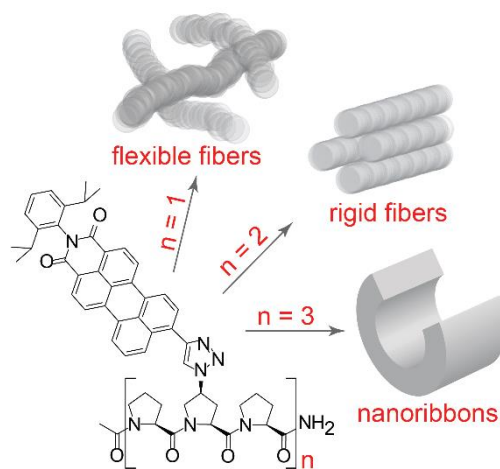
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Precise control over the incorporation of functional building blocks into larger, organized systems has enormous potential for material science. Efforts have been made to create well ordered, functional structures based on DNA scaffolds and polypeptide backbones which can be easily decorated with the desired functionality.<sup>[1-3]</sup> Until now the use of rigid, non-selfaggregating scaffolds for such purposes has been limited.

Functionalizable, azidoproline-containing oligoprolines direct the self-assembly of  $\pi$ -conjugated systems as they adopt (already at a short chain lengths of six residues) the conformationally well-defined polyproline II (PPII) helix, in which every third residue is stacked on top of each other in a distance of  $\sim 1$  nm.<sup>[4]</sup> Covalent conjugation of this rigid peptidic scaffold with  $\pi$ -systems which do not self-assemble on their own allowed for the hierarchical supramolecular aggregation of hybrid molecules in solution and on the solid support. Thus, the use of functionalizable azidoproline (Azp) rich oligoproline as scaffolds constitutes new and efficient approach to the design of the self-assembly of functional  $\pi$ -conjugated systems as precise control over the molecular design enables control over the aggregation process.<sup>[5]</sup>



**Figure 1.** Covalent functionalization of rigid peptidic scaffold which has no structural features allowing for its aggregation with sterically demanding  $\pi$ -systems allows for the hierarchical self-assembly of conjugates.

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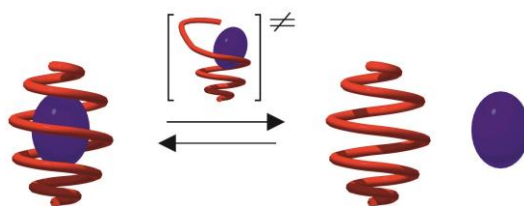
## Iterative evolution of an abiotic foldamer sequence: Structure-based design of helically folded receptors for saccharides

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We have developed synthetic foldamers – oligomers that adopt stable helical folded conformations – derived from aromatic amino acids.<sup>[1]</sup> Some of these folded objects have shown unprecedented conformational stability,<sup>[2]</sup> and constitute convenient building blocks to elaborate synthetic, very large (protein-sized) folded architectures (Fig. 1).<sup>[3]</sup> They possess a high propensity to assemble into double, triple and quadruple helices, or to fold into sheet-like structures.<sup>[4]</sup> This lecture will focus on foldamers having cavities endowed with molecular recognition properties,<sup>[5]</sup> and show how detailed structural information about host-guest complexes and modular foldamer synthesis allow to iteratively modify the foldamer sequence and elicit binding of a specific guest.<sup>[6]</sup>



**Figure 1.** Schematic representation of the encapsulation of a molecular guest in a helical capsule having a reduced diameter at both ends. Guest binding and release require a partial unfolding of the helix.

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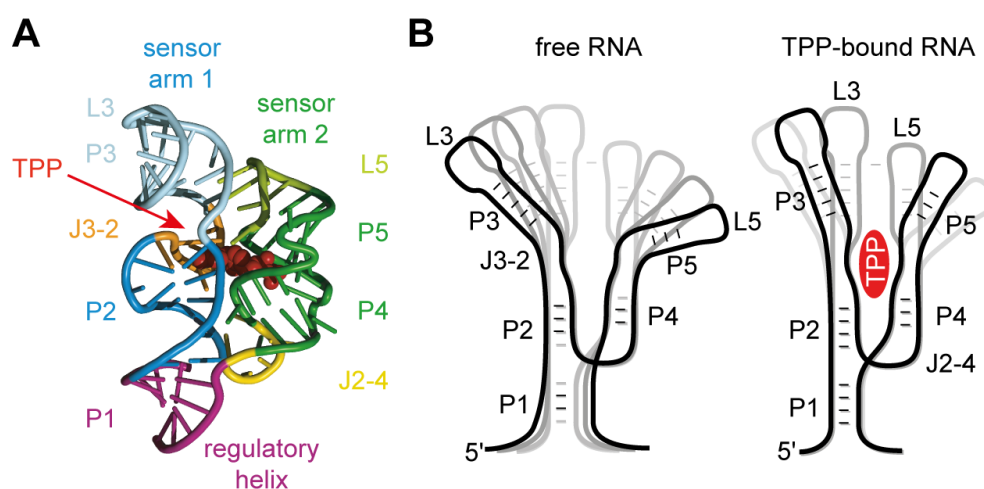
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## Folding and ligand recognition of RNA riboswitches

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Thiamine pyrophosphate (TPP)-sensitive mRNA domains are the most prevalent riboswitches known. Despite intensive investigation, the complex ligand recognition and concomitant folding processes in the TPP riboswitch that culminate in the regulation of gene expression remain elusive.<sup>[1,2]</sup> We used single-molecule fluorescence resonance energy transfer imaging to probe the folding landscape of the TPP aptamer domain in the absence and presence of magnesium and TPP.<sup>[3]</sup> To do so, distinct labeling patterns were used to sense the dynamics of the switch helix (P1) and the two sensor arms (P2/P3 and P4/P5) of the aptamer domain. The latter structural elements make interdomain tertiary contacts (L5/P3) that span a region immediately adjacent to the ligand-binding site. In each instance, conformational dynamics of the TPP riboswitch were influenced by ligand binding. The P1 switch helix, formed by the 5' and 3' ends of the aptamer domain, adopts a predominantly folded structure in the presence of Mg<sup>2+</sup> alone. However, even at saturating concentrations of Mg<sup>2+</sup> and TPP, the P1 helix, as well as distal regions surrounding the TPP-binding site, exhibit an unexpected degree of residual dynamics and disperse kinetic behaviors. Such plasticity results in a persistent exchange of the P3/P5 forearms between open and closed configurations that is likely to facilitate entry and exit of the TPP ligand. Correspondingly, we posit that such features of the TPP aptamer domain contribute directly to the mechanism of riboswitch-mediated translational regulation.



**Figure 1.** Structure and dynamics of the *E. coli thiM* TPP riboswitch aptamer. **A)** Crystal structure of the RNA-ligand complex. **B)** Cartoon representation that highlights the dynamic structural elements of the TPP riboswitch in the absence (left) *versus* presence (right) of ligand as revealed by fluorescence spectroscopic methods.

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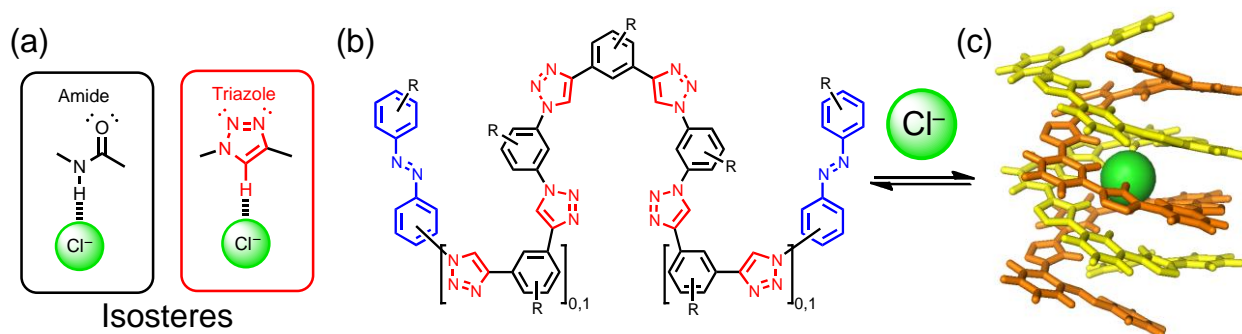
# Manipulating Chloride using Triazole Foldamers and the Hydrophobic Effect

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Chloride is an abundant ion that plays critical roles in human biology and chemical processes. For these reasons, mastering ways to manipulate its availability across many environments will have far-reaching consequences. We are using supramolecular chemistry for this task by taking advantage of triazole-based receptors (Figure 1) that are easy to make and modify.<sup>[1]</sup> Triazoles (colored red in Figure 1a) are amide isosteres that bind anions using strong, yet non-traditional, CH hydrogen bonds.

Taking inspiration from biology's halorhodopsin, a new class of light-active foldamers has been created<sup>[2]</sup> that make use of the photoisomerizable azobenzenes (colored blue in Figure 1b). The foldamers can catch and release chloride to regulate its concentration. We then move out of organic solvents, again taking biology's lead, to tackle one of the grand challenges in host-guest chemistry: Extracting highly-hydrated chloride ions from aqueous solutions. We were the first to discover that, when the foldamers intertwine into a duplex (Figure 1c), the hydrophobic effect provides the driving force needed to extract the hydrophilic chloride from semi-aqueous solutions.<sup>[3]</sup> Ultimately, we found that foldamers' helical pre-organization, as controlled by their structure and solvation properties, is key to their functionality.



**Figure 1.** (a) Triazoles are the basis for binding anions and (b) for preparing the photoactive foldamers that (c) can wrap up chloride ions.

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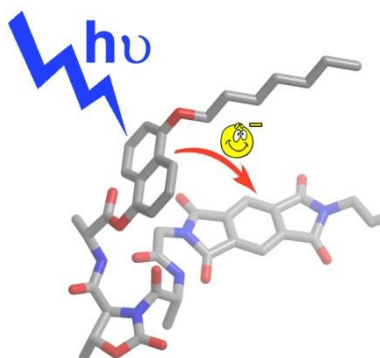
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## Pseudopeptide Foldamers Promoting Photoinduced Intramolecular Electron Transfer

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We have designed and prepared three pseudopeptide foldamers, called dyads **1**, **2** and **3**, equipped with a donor and an acceptor unit to promote intramolecular electron transfer after light excitation.<sup>[1]</sup> All the three dyads contain the same donor and acceptor, which are a derivative of 1,5-dihydroxynaphthalene and a derivative of pyromellitic diimide, respectively. The donor and acceptor units are separated by hybrid foldamers of different length in order to vary both their distance and relative orientation.<sup>[1]</sup> Specifically, one, two or three L-Ala-D-Oxd (Ala = alanine, Oxd = 4-carboxy-5-methyl-oxazolidin-2-one) units are contained in dyads **1**, **2**, and **3**, respectively. Dyad **1** folds in a bent conformation in which the donor and acceptor units lie one close to the other, while dyads **2** and **3** preferentially assume an extended conformation. In all the three dyads both the donor and acceptor emissions are efficiently quenched via intramolecular electron transfer, as suggested by photophysical and electrochemical investigations. Because of its bent conformation dyad **1** exhibits a charge-transfer (CT) band at 410 nm in CH<sub>2</sub>Cl<sub>2</sub> solution and a photoinduced electron transfer that occurs more efficiently than in dyads **2** and **3**. Upon dissolving dyad **1** in DMSO, a competitive solvent for hydrogen bonds that establish in the pseudopeptide linker, the CT band disappears and the efficiency of electron transfer slightly decreases, in agreement with an unfolded conformation in which donor and acceptor units are no longer in close contact.<sup>[3]</sup>



**Figure 1.** Preferential conformation of dyad **1** that accounts for the formation of a NH hydrogen bond and for a charge-transfer (CT) band at 410 nm in CH<sub>2</sub>Cl<sub>2</sub> solution and a photoinduced electron transfer.

### References

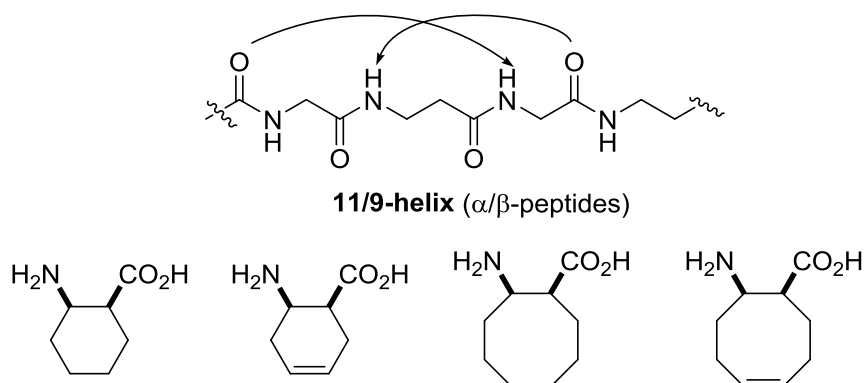
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## Residue-Dependent Folding Propensity of the $\alpha/\beta$ -Peptide 11/9-Helix

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The  $\alpha/\beta$ -peptide 11/9-helix is a unique helical structure that arises from two types of alternating hydrogen bonds along the helical axis. We have discovered that cyclic  $\beta$ -amino acids with a six- or eight membered ring constraint can promote  $\alpha/\beta$ -peptides 11/9-helices (Figure 1).<sup>[1,2]</sup> The structural parameters for the 11/9-helix were derived from a series of crystal structures of 11/9-helical  $\alpha/\beta$ -peptides containing *cis*-2-aminocyclohexanecarboxylic acid (*cis*-ACHC) in racemic mixtures.<sup>[1]</sup> Some crystal structures that were obtained from enantiomeric  $\alpha/\beta$ -peptide oligomers displayed partially disrupted 11/9-helical conformations because of the inclusion of water molecules<sup>[2]</sup> or undesired local conformations of  $\alpha$ - or  $\beta$ -residues, suggesting that the 11/9-helix may be susceptible to polar solvent conditions and need to be stabilized by residue modification. CD and X-ray crystallographic analyses revealed that *cis*-ACHC derivative with an additional methyl substituent could lock the desired local conformation of the residue, and stabilizes 11/9-helical folding of  $\alpha/\beta$ -peptides in protic solvent mixtures. In addition, the residue requirements for the 11/9-helix were derived by analyzing  $\alpha/\beta$ -peptides in which several types of  $\alpha$ - and  $\beta$ -residues were incorporated.



**Figure 1.** Cyclic  $\beta$ -amino acid residues that can promote the  $\alpha/\beta$ -peptide 11/9-helix.

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## Dynamic foldamers as receptor mimics: Induced global conformational change in solution and in membranes

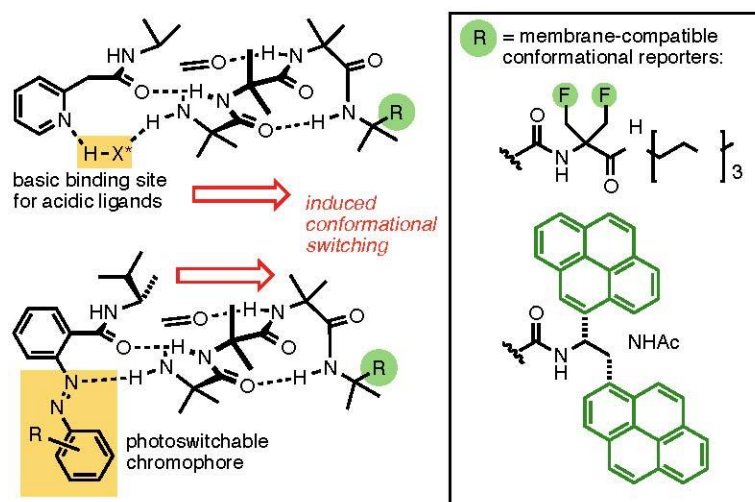
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Biology solves the problem of communicating information through cell membranes by means of conformationally switchable proteins, of which the most important are the G-protein coupled receptors (GPCRs).<sup>[1]</sup> We have explored the possibility of using synthetic foldamers as artificial mimics of GPCRs. Inspired by the structures of the peptaibols—membrane-active fungal metabolites—we have used foldamers built from 2-aminoisobutyric acid (Aib) as artificial mimics of GPCRs, and have shown that induced conformational preferences are propagated over multi-nanometre distances in solution.<sup>[2,3]</sup> Biological receptors adjust their conformation in response to non-covalent interactions with ligands, and this contribution will describe the use of competitive ion pairing and hydrogen bonding to induce the communication of information through foldamer-based receptor mimics.

The construction an artificial GPCR requires molecules that will incorporate themselves into a membrane, and also necessitates the extension of solution state analytical tools<sup>[4]</sup> to the study of conformation in the membrane phase. Methods employing the tools of solid-state <sup>19</sup>F NMR and of fluorescence spectroscopy will be described, along with their application to the development of functioning membrane-bound switchable GPCR mimics.

The proteins of vision, of which rhodopsin is a representative example, are structurally related to the GPCRs, and undergo conformational changes as a result of photochemical switching of the configuration of a covalently bound chromophore. We will describe progress towards a synthetic foldamer mimic of rhodopsin in which reversible photochemical switching of stereochemical configuration leads to detectable and quantifiable global conformational changes within the membrane phase.



**Figure 1.** Biomimetic conformational switching with dynamic foldamers.

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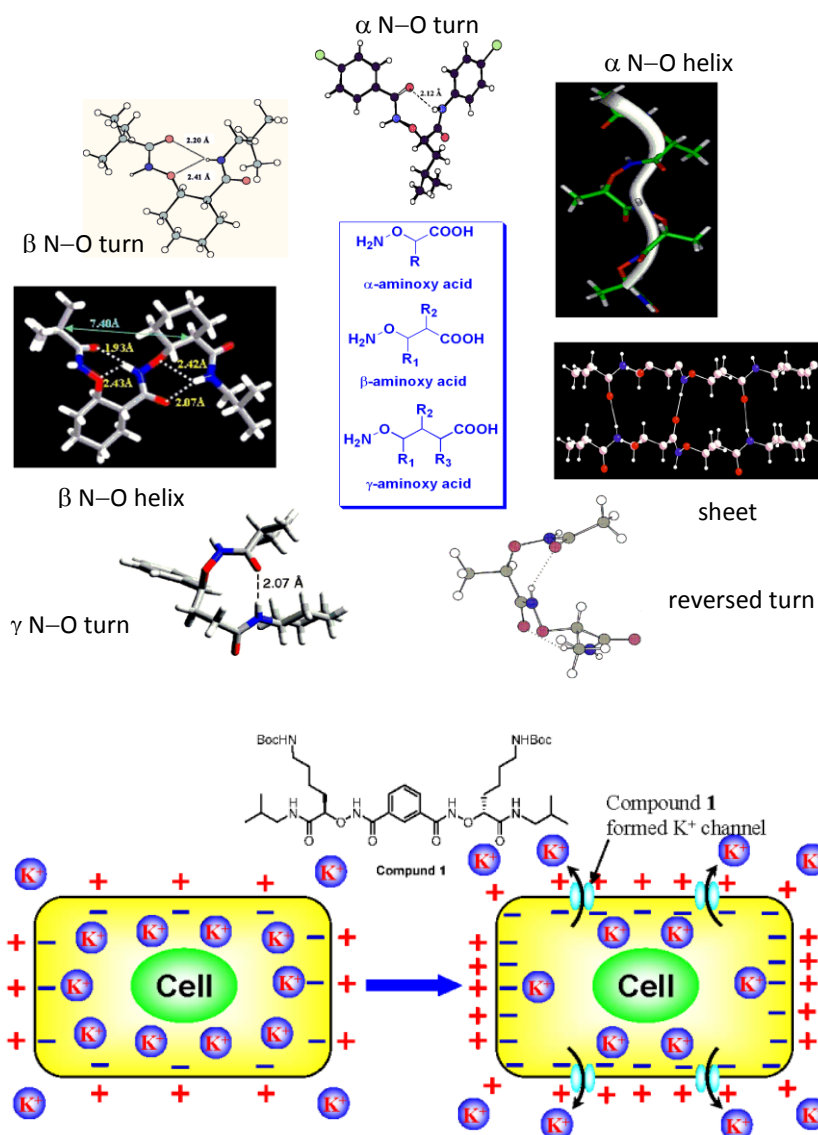
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## Aminoxy Acids as Building Blocks of Foldamers

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In this talk, I will report our foldamer research based on aminoxy acid (a class of unnatural amino acids) building blocks. Through computational and experimental studies, we showed that  $\alpha$ -,  $\beta$ - and  $\gamma$ -aminoxy acids, when incorporated into peptides, could induce novel secondary structures such as turns and helices. In addition, these turns and helices are independent of side-chains. As peptides containing aminoxy acids have excellent metabolic stability, aminoxy acids will be of tremendous potential in molecular design of peptide analogs for drug discovery. We have discovered a series of aminoxy acid-based small molecules that self-assemble into cation channels and anion channels, and explore their biomedical applications.



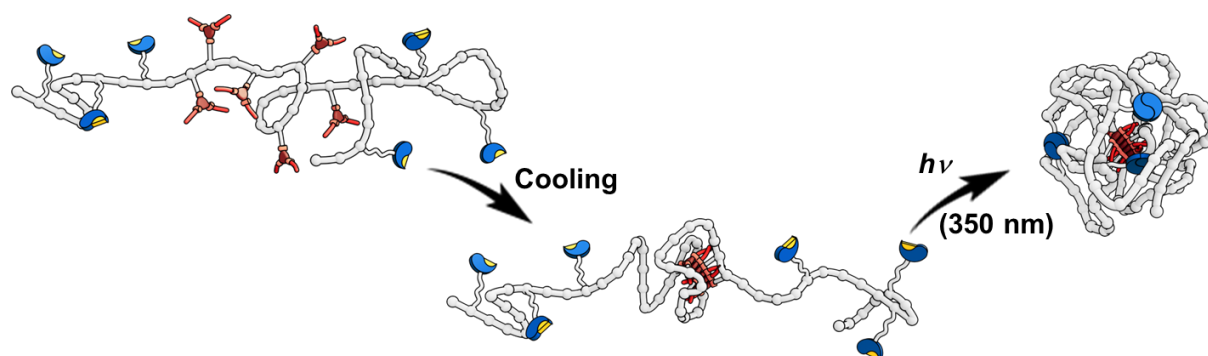


## Folding of single-chain macromolecules; towards synthetic enzymes

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The folding of proteins as well as the self-assembly of proteins into fibrillar and beta-amyloid structures is the results of specific secondary interactions within a polymer chain or between polymer chains. The diversity in protein structures and the complexity of the processes involved make studies to folding and assembly of proteins challenging research objectives. In the lecture, a number of simple artificial structures will be introduced that are studied in great detail for their self-assembly and folding processes in both organic solvents and water. Even two different self-assembly motives are used in the same polymer to arrive at step-wise folding (Figure 1). Meta-stable folded single-chain macromolecules will be used as a catalyst. An attempt will be made to elucidate the differences and similarities between these simple artificial structures and complex proteins to arrive at a few general statements on folding and assembly of (macro)molecules. Both kinetic and thermodynamic studies will be used to show some remarkable similarities in behavior of artificial structures in organic solvents and proteins in water.



**Figure 1.** Stepwise folding of a single-chain polymer nano-particle

# Poster Abstracts

## Using Adhirons to identify high affinity peptide/helix mimetics interactions

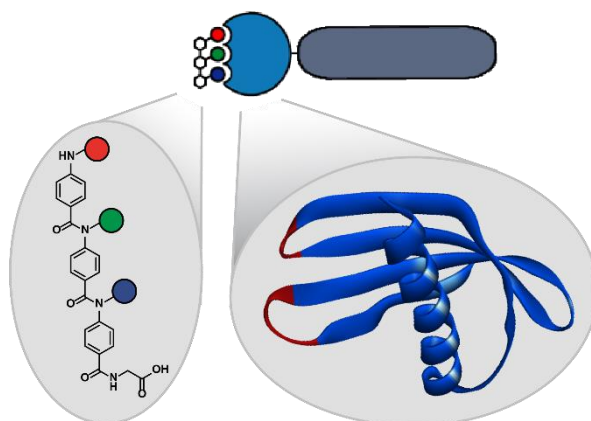
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The design of oligomeric folded molecules with 3D structural complexity approaching that of tertiary protein structure is a major challenge in supramolecular chemical biology.<sup>[1]</sup> Whilst some progress has been made with the *de novo* design of tertiary foldamers,<sup>[2]</sup> these approaches employ limited sequence diversity and result in highly symmetrical 3D structures. Alternatively, it may be possible to replace parts of bio-macromolecules sequences with non-natural building blocks.<sup>[3]</sup>

We have chosen to pursue the latter approach by studying the recognition between helix mimetics and proteins. In the current work, we focus on interactions with peptides and employ biological selection methods to accelerate the discovery of optimised amino acid sequences that bind to helix mimetics (**Figure 1**). This approach could ultimately be used 1) as a reverse screening method for discovering protein-protein interactions inhibitors by mining informatics databases for the selected sequences, 2) to build mimetic/peptide hybrids with well-defined tertiary folds.

Using orthogonal functionalisation,<sup>[4]</sup> we biotinylated *N*-alkylated aromatic oligoamides p53 mimetics and performed Adhiron display<sup>[5]</sup> to generate a randomised library of high affinity but selective binding proteins. Work is being conducted to express these proteins to further study the resulting complexes.



**Figure 1.** Cartoon representation of the helix mimetic (left)/Adhiron (right) interaction during the Adhiron display, and highlight of their structures. The red loops are randomised binding sequences.

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## Oligourea foldamers mimicking host-defense peptides Against *Bacillus anthracis* infection

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The design of unnatural oligomers with predictable folding patterns (i.e. foldamers) and function has attracted considerable attention over the last fifteen years. Potential applications in biology include the development of anti-microbial agents, cell-penetrating agents, and inhibitors of protein-protein interactions. One of the main interest for exploring biological applications of synthetic foldamers stems from their high resistance to proteolytic degradation.<sup>[1]</sup>

Our group is currently developing peptidomimetic oligomers incorporating ethylene diamine units linked by urea bonds (NH-CH(R)-CH<sub>2</sub>-NH-CO)<sub>n</sub>. These aliphatic oligomers display a strong propensity for helix formation in solution and in the solid state. It has been shown that short chain oligoureas (8-mers) designed to mimic the amphipathic character of antimicrobial peptides maintain a helical conformation in phospholipid environment, display a significant activity in vitro against both Gram negative and positive bacteria, and show some selectivity for bacterial versus eukaryotic cells.<sup>[2-3]</sup> We have now investigated the activities of such foldamers on capsulated and non capsulated pathogenic bacterium *Bacillus anthracis*. Early results on structure-activity relationship studies, pharmacokinetic properties and therapeutic activities in vivo in animal models will be reported.

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## Unprecedented Chain-Length-Dependent Conformational Conversion between 11/9- and 18/16-Helix in $\alpha/\beta$ -Hybrid Peptides

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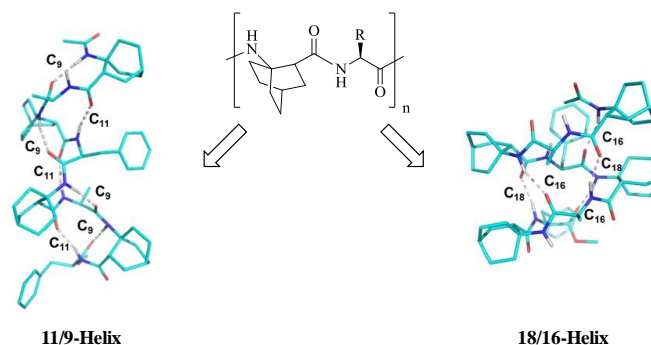
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Helices constitute the major secondary structural elements of proteins and often play a crucial role for example in mediating protein-protein and protein-nucleic acid interactions. For this reason, numerous strategies have been developed to mimic  $\alpha$ -helical structure and over the past decade peptide foldamers derived from heterogeneous backbones, referred as hybrid peptides, have been investigated.<sup>[1]</sup>

This work is part of the design of new oligomers, able to display a well-defined secondary structure, based on a rigid ring-constrained  $\beta$ -amino acid named (*S*)-ABOC, i.e. [(*S*)-aminobicyclo[2.2.2]octane-2-carboxylic acid]. This  $\beta^{2,3,3}$ -trisubstituted bicyclic amino acid has the ability to promote both a reverse turn into peptide<sup>[2]</sup> and stable helices in homo- and mixed oligomers.<sup>[3]</sup>

Herein,  $\alpha,\beta$ -hybrid oligomers of varying lengths with alternating proteogenic  $\alpha$ -amino acid and (*S*)-ABOC residues were synthesized and investigated using both X-ray crystal, NMR solution structures and DFT energy calculations. This study showed that while only an 11/9-helix was obtained in the solid state regardless of the length of the oligomers, conformational polymorphism as a chain-length-dependent phenomenon was observed in solution (Figure 1).<sup>[4]</sup>



**Figure 1:** (*S*)-ABOC/ $\alpha$ -AA pattern and 11/9- and 18-16-helix NMR solution structures for octamers.

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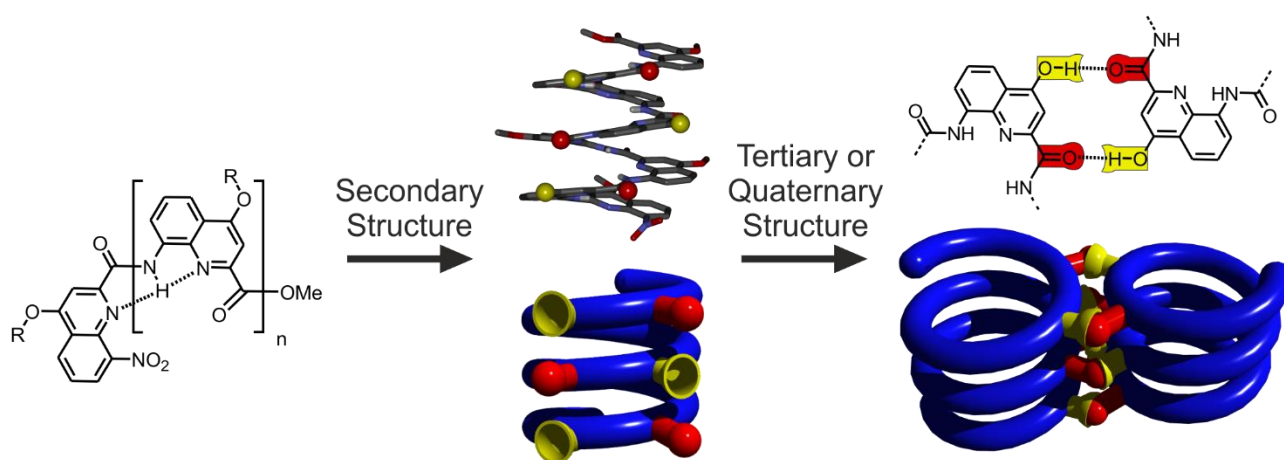
## Tertiary and Quaternary Helix Bundles of Aromatic Oligoamide Foldamers

Soumen De,<sup>a</sup> Bo Chi,<sup>a</sup> Ting Qi,<sup>a</sup> Brice Kauffman,<sup>b</sup> Thierry Granier,<sup>a</sup> Victor Maurizot,<sup>a</sup> Ivan Huc<sup>a</sup>

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Over the last decades, strong efforts have been made to develop new molecular backbones for the construction of original, predictable, and well defined folded molecular architectures: foldamers.<sup>[1]</sup> This research has mainly focused on the elaboration of architectures that mimic the secondary structures of biomolecules (helices and sheets) and has led to the development of a wide variety of building blocks and folding patterns. A current challenge in biomolecular mimicry is the construction of more complex objects such as tertiary and quaternary structures. It is within such complex structures that the advanced functions of biopolymers operate.<sup>[2]</sup> Along this line, molecular architectures (mostly helices) have been designed that have specific side chains on their outer surface to specifically interact with biomolecules or other foldamers.<sup>[3]</sup>

In this context, we have focused our attention on the design, the synthesis and the characterization of quinoline-based oligoamide foldamers that have side chains designed to interact with each other and promote the formation of tertiary dimeric helix bundles and quaternary helix bundles.



**Figure 1:** Schematic representation of helix bundle formation.

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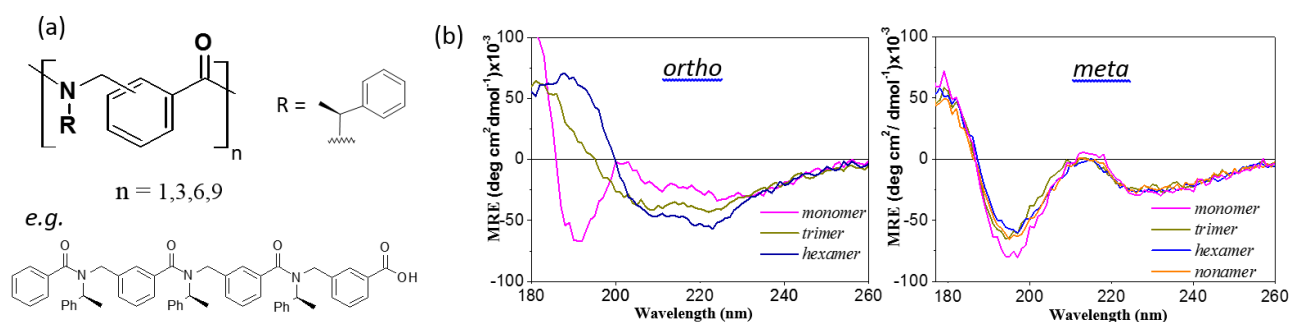
## The conformational study of arylopeptoids with *spe*-side chains

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Arylopeptoids (oligomeric *N*-substituted amino methyl benzamides)<sup>[1-3]</sup> are novel aromatic peptoid architectures which have been developed due to the importance of aromatic interactions in drug discovery. The conformational studies of *ortho*, *meta* and *para* arylopeptoids by NMR demonstrates their folding propensity as *tert*-butyl and phenyl side chains are able to direct 100% adoption of *cis* or *trans* amide conformations, respectively.<sup>[3,4]</sup> By contrast, arylopeptoids with chiral (*S*)-*N*-(1-phenylethyl) (*spe*) side chain showed broader, and partly overlapping NMR signals which indicates the presence of both *cis/trans* amide isomers.<sup>[3]</sup> Conformational information was therefore difficult to obtain from NMR data. The conformational study of arylopeptoid architectures with *ortho*, *meta*, *para* substituted backbones and the chiral *spe* side chain thus require further investigation.



**Figure 1.** (a) General structure of arylopeptoids with the *meta* trimer as an example structure and (b) the mean residue ellipticity CD spectra of the *ortho* and *meta* family in TFE.

Using circular dichroism (CD), 17 *spe*-compounds (monomer to nonamer length) of *ortho*, *meta* and *para* architectures were studied (Figure). This allowed the conformational effect of *ortho*, *meta* and *para* substitution on the backbone to be established (Figure b). Environmental factors were employed to perturb the conformational preference *e.g.* protic/aprotic solvents, dielectric constants and temperature. These results confirmed a chain length dependence for the *ortho* family which did not occur for *meta* and *para* families. Further to this, in MeCN and MeOH, decreased solubility was evident for hexamers and nonamers of the three architectures indicating the formation of aggregates. Current investigations are focusing on the characterization of aggregates using CD, dynamic light scattering and MALDI.

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## Amphipathic urea-based foldamers for nucleic acid delivery

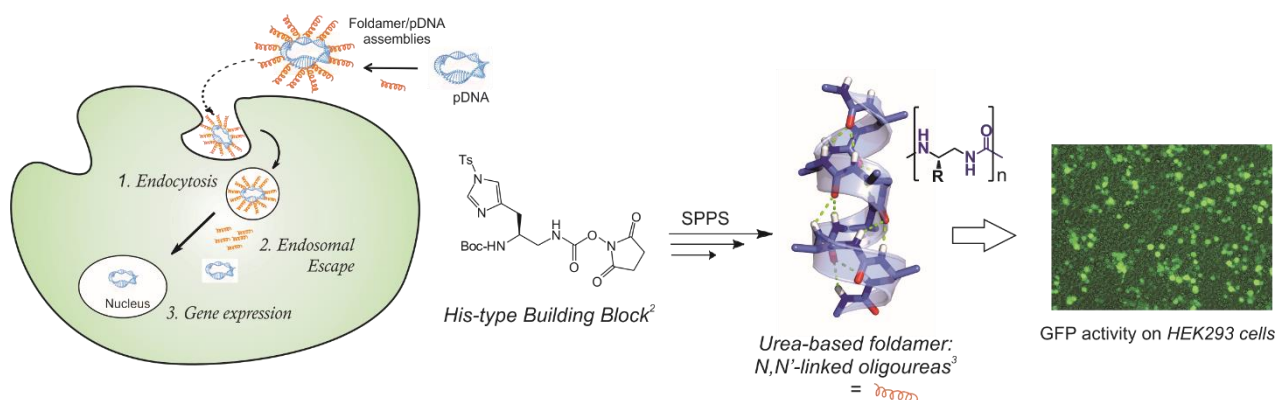
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The possibility to modulate gene expression offers the potential to use nucleic acids for modern therapeutics. However, current developments of gene therapy are facing multiple challenges. Nucleic acids are polyanionic macromolecules that cannot spontaneously translocate across cell membranes into cells. Moreover, these molecules are highly sensitive to the action of serum nucleases. Consequently, one primary requirement for developing effective nucleic acid (NA) therapy systems to treat human diseases is the efficient delivery of this macromolecule to the target cells. Among the different non viral systems reported so far, synthetic and natural cell-penetrating peptides (CPPs) have recently emerged and present the advantage to be of low molecular weight, of well-defined composition and to be less cytotoxic than purely cationic polymers (*i.e.* PEI). Furthermore to tackle the problem of endosomal entrapment, PH-responsive CPPs have been developed. LAH4 is a His-rich amphipathic helical peptide that has been shown to efficiently transport plasmid DNA (pDNA) and small interfering RNA (siRNA) within the cells.<sup>1</sup>



Mimicking this peptide with synthetic folded oligomers (*i.e.* foldamers) allow key structural features to be maintained and may constitute an original approach towards the design of novel NA transfer reagents with improved transfection efficiency and enzymatic stability.

Herein we report the synthesis of cell-penetrating foldamers (CPFs) composed of oligourease sequences (see figure above) and the effect of their dimerization on NA delivery.

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## All *cis* $\alpha$ - and $\beta$ -Peptoid Foldamers

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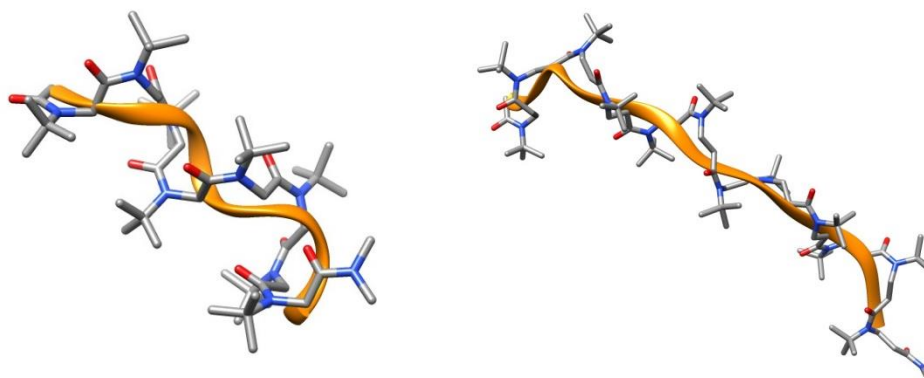
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Peptoids are *N*-substituted glycine oligomers which are similar to peptides with the side chains located on the amide nitrogen rather than the  $\alpha$ -carbon.<sup>[1]</sup> Peptoids are an interesting case of peptidomimetic foldamers. Since their backbones lack free NH amides, the capacity to form well-ordered structures is strictly related to the nature of the side chains.<sup>[2]</sup> Peptoid residues are structurally related to proline as the coupling of residues gives tertiary amide bonds which can populate *cis* and *trans* conformations. While amide bonds in peptides and proteins are mainly in the *trans* form, the polyproline type I (PPI) peptide helix featuring only *cis* amides is a typical peptoid secondary structure.<sup>[3]</sup> Recently, great efforts have been devoted to controlling peptoid amide bond geometry in order to minimize backbone conformational heterogeneity. Herein we show a series of  $\alpha$  and  $\beta$ -peptoids characterized by an *N*-*t*Bu side chain which locks the amide sites in the *cis* conformation in any solvent.<sup>[4]</sup> Synthesis of longer oligomers was optimized through a combination of the classical submonomer approach and coupling reaction of sterically hindered secondary amines. Conformational studies in solution were performed by bi-dimensional NOESY experiments and molecular modeling.



**Figure 1.** *In Silico* Simulation of  $\alpha$ - (left) and  $\beta$ - *N*-*t*Bu containing peptoid oligomers

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## Foldamer Scaffolds for Electron Transport

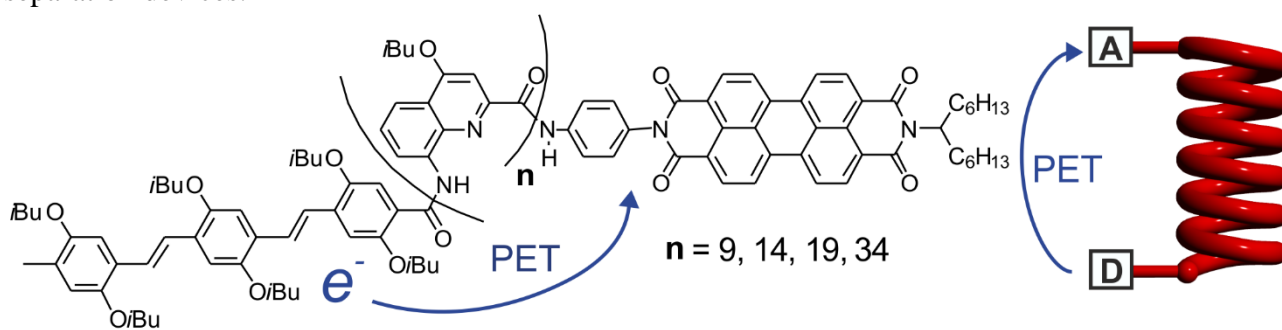
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Foldamers are inspired by biopolymers but may possess backbones chemically remote from peptides or nucleotides, which can offer functions beyond those of biopolymers albeit based on the same principles. Foldamer research has principally focused on their biological properties. On the other hand, investigations of potential use of foldamers as organic materials are rare and mainly concern self-assembly into nanofibers and nano- and micro-sized objects.<sup>[1,2]</sup> Inspired by works that consider electron transport properties of “linear” molecular organic materials such as conducting polymers, carbon nanotubes and specifically DNA, we have explored such properties on rigid helical quinoline-based foldamers developed in our group. These molecules demonstrated the ability to promote, following photoexcitation, long-distance electron transfer between an electron donor-acceptor pair tethered to opposite ends of foldamers of varying lengths (foldamers consisting of up to 9 quinoline units) with a high rate and low attenuation factor.<sup>[3]</sup>

In order to explore potential length effects on rates and mechanism of electron transfer (ET), in this study, we synthesized foldamers comprising a bridging unit of 9, 14 and 19 quinoline units, an oligo(p-phenylene vinylene) (OPV) electron donor at one terminus, and a perylene bisimide (PB) electron acceptor at the other (see figure). Electron transfer studies were performed using transient absorption spectroscopy and time-resolved fluorescence measurements, showing efficient (> 99%;  $\tau = 55$  ps) reductive PB quenching, concomitant with quinoline bridge oxidation. Subsequent OPV-to-bridge electron transfer confirms a stepwise mechanism for OPV<sup>•+</sup>-bridge-PB<sup>•-</sup> generation, with an increasing global time constant as a function of length. Interestingly, following fast ET, extremely long charge-separated states (> 80  $\mu$ s) were observed, prerequisite for implementation in charge separation devices.



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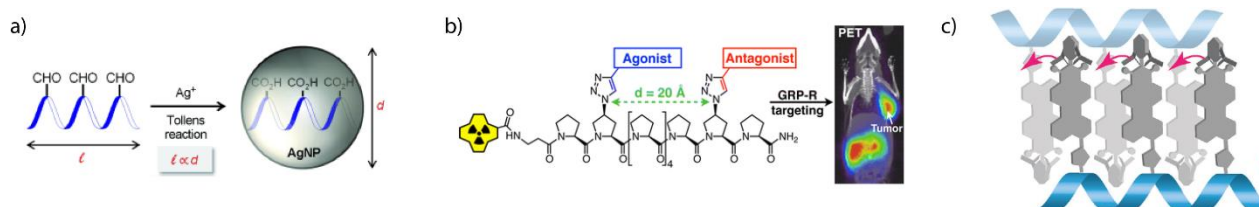
## Oligoprolines as Scaffolds for Supramolecular Systems

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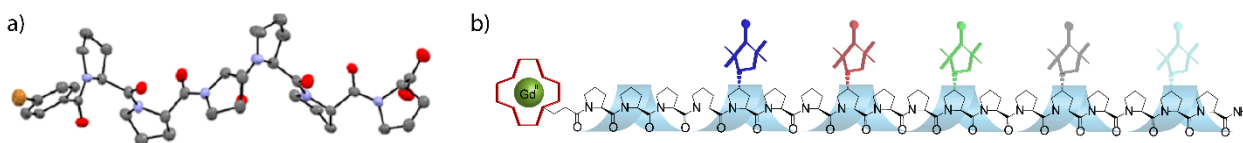
Oligoprolines are a class of conformationally well-defined peptides that adopt, even at chain lengths as short as six residues, the highly symmetric polyproline II (PPII) helix secondary structure in which every third residue is stacked on top of each other in a distance of around 0.94 nm.<sup>[1]</sup> Additionally the length and functionalization pattern of these peptides can be easily fine-tuned by chemical synthesis.<sup>[2]</sup> For these reasons oligoprolines are ideal candidates to serve as scaffolds for supramolecular systems.

We already demonstrated their efficacy by preparing functionalized oligoproline derivatives that were applied in the controlled growth of silver nanoparticles,<sup>[3]</sup> as ligands for targeting prostate cancer<sup>[4]</sup> and in hierarchical self-assembly of  $\pi$ -systems (Figure 1).<sup>[5]</sup>



**Figure 1.** Application of functionalized oligoprolines for: a) controlled formation of AgNPs; b) tumor targeting; c) hierarchical self-assembly of  $\pi$ -systems.

Recently we performed detailed structural studies to determine the parameters that define the oligoproline PPII helix both in solid-state and solution. X-ray crystallographic analysis allowed us to precisely determine the helical pitch and study the correlation between proline ring puckers, dihedral angles of the oligoproline backbone and the degree of interactions between adjacent amide bonds (Fig.2a).<sup>[6]</sup> EPR spectroscopic analysis of spin-labelled oligoproline derivatives (Fig.2b) confirmed the highly defined character and rigidity of these peptidic scaffolds in solution (all-*trans* amide bond conformation and high persistence length).<sup>[7]</sup>



**Figure 2.** a) Crystal structure of N-*p*-bromobenzoyl-hexaproline; b) double spin-labelled proline octadecamers studied with EPR spectroscopy.

Our results thus allow for a rational design of polyfunctional derivatives with defined spatial arrangement of substituents which is essential for many potential applications, such as cell targeting, molecular electronics or supramolecular catalysis.

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## Towards composite proteins: oligoureas meet zinc fingers

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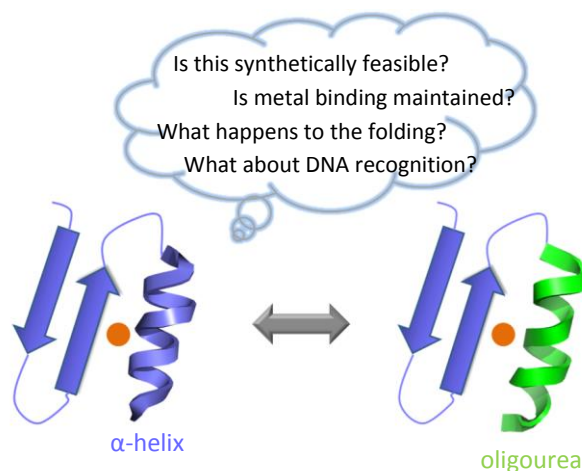
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Alpha-helices are recurrent structures in proteins, whose folding properties, stability and function have been widely investigated. They often play the key role of recognition elements between proteins, or proteins and nucleic acids. These interactions are generally regulated by the strategic presentation of a few key residues on their surface<sup>[1]</sup>.

The efforts of many groups have been devoted to the synthesis of artificial molecules (foldamers), to mimic the structural complexity of natural helices, with the aim to reach functions beyond the ones accomplished by nature. A number of foldamer backbones has been synthesised to date, and their predictability and tunability constitute a great potential for their future applications. However, attaining more complex tertiary/quaternary structures through foldamers still constitutes a challenge in the field<sup>[2,3]</sup>.

In this work we move a step forward towards this goal, by creating new composite proteins, swapping alpha-helices with oligourea helices. Our first targets have been Zn Finger domains, because of their peculiar folding, extensive structural characterisation and biological relevance. They are in fact commonly found in DNA transcription factors and they are responsible for specific nucleotide recognition<sup>[4]</sup>.

We intend to investigate the synthetic feasibility of these chimeric molecules, study their folding, assess their ability to bind Zn and other metals, and ultimately see if the DNA binding properties are preserved and eventually tunable. Our progress along these lines will be presented.



**Figure 1.** The general idea of swapping an  $\alpha$ -helix with an oligourea in an  $\alpha\beta$  zinc finger motif.

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## Modulation of Integrase Activity by means of Constrained Nucleic Acids (D-CNA)

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D-CNAs were developed to mimic biologically important non-helical secondary structures of DNA.

[1] The introduction of the 1,3,2-dioxaphosphorinane ring at key positions along the sugar-phosphate backbone locks the torsional angles  $\alpha$ - $\zeta$  of thymidine dinucleotides in canonical or non-canonical values either to access B-type mimics or to stabilize unpaired region of hairpin structures. [2] DNA preorganized structures are particularly useful for protein interaction studies as the introduction of "pre-structured" dinucleotides reduces the entropic cost of the association process.

The Holliday junction (HJ) is a key constrained DNA structure with 4 double stranded arms connected at a geometric center. This structure is produced by integron/integrase<sup>[3]</sup> and resolved by the enzyme to insert resistance cassettes leading to antibiotic resistance acquisition. We plan to monitor the impact of the geometric constraints introduced by D-CNA dinucleotide TT (D-CNA-TT) at the central cross-over region on the recombinase activity by biochemical and X-ray crystallographic approaches.

Herein we report the preparation of modified oligonucleotides by selective introduction of D-CNA-TT and the first binding assays with Int4 integrase. Firstly, the 3'-protected thymidine was either treated under Cannizzaro conditions to give 4'-hydroxymethylthymidine or after IBX oxidation, underwent a diastereoselective Mukaiyama addition on the resulting 5'-aldehyde. Reduction of the ester function afforded 5'-hydroxyethylthymidine (Figure 1).<sup>[3]</sup> The key step for the synthesis of  $\alpha,\beta$ -D-CNA and  $\alpha,\beta,\gamma$ -D-CNA-TT is the phosphoramidite coupling of 5'-O-DMTr protected thymidine 3'-phosphorodiamidite with the corresponding diols. Contrary to the previous methodology based on an intramolecular cyclisation of a 5'-tosyloxy dinucleotide phosphate precursor, thio- or seleno dioxaphosphirane analogues could now be obtained by controlling the oxidation conditions of the resulting phosphite dinucleotide. As an example, use of elemental sulfur led to  $\alpha,\beta,\gamma$ -thio-D-CNA dinucleotides further converted into their corresponding phosphoramidites and introduced into the required sequence where thio-D-CNA TT step showed improved stability during the final deprotection step. As selenium derivatization of D-CNA-TT could help solve the phase problem in X-ray crystallography for nucleic acid-proteins complexes, KSeCN was used as a selenizing agent to give  $\alpha,\beta$ -seleno-D-CNA TT, converted into suitable phosphoramidites and incorporated using automated synthesis. Successful pairing assays of Int4 integrase and HJ<sub>wt</sub> were conducted and crystallography trials of the nucleic acid-protein complex have started. HJ formation with a D-CNA modified single strand is actually under investigation. A new strategy allowed the synthesis of thio- and seleno-D-CNA-TT featuring either canonical or non-canonical constraints. They were introduced into reference sequences to get new insight into the conformational parameters governing DNA-integrase interactions and their subsequent biological effects.

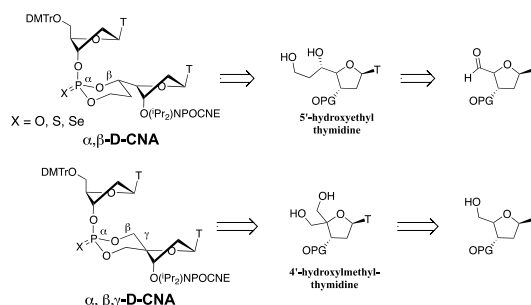


Figure 1. Retrosynthesis of CNA phosphoramidites.

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## Foldamers to recognize protein surfaces: Carbonic anhydrase as a model system

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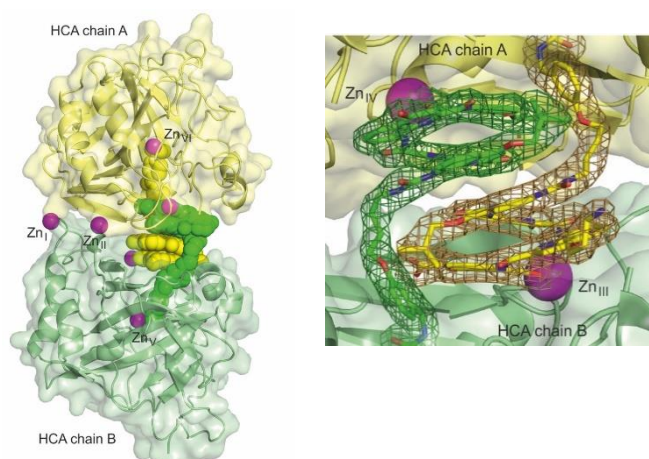
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Protein-protein interactions (PPIs) play crucial roles in many biological processes and diseases, and represent potential targets to develop new therapeutic approaches.<sup>[1]</sup> However, PPI inhibition often requires ligands that can cover large areas of protein surfaces, such as other proteins (*eg* antibodies). Current research hint at the possibility that foldamers may also meet this requirement and interfere with PPIs and/or help to elucidate their mechanism. Recently, our laboratory has developed methodologies for the synthesis of aromatic amide foldamers resulting in medium sized (1-5 KDa), highly functionalized, predictable, stable and well defined helical structures.<sup>[2]</sup>

The target protein we chose is human carbonic anhydrase II (HCAII) which is widely used as a model for structural studies of enzymes thanks to its high propensity to crystallize.<sup>[3]</sup>

We anchored an arylsulfonamide inhibitor with nanomolar affinity for HCAII<sup>[4]</sup> to different functionalized foldamers. Thanks to the inhibitor, the foldamers are held close to the protein surface and even weak interactions can be investigated. The challenge is to develop foldamers able to interact with the surface of HCAII in a specific manner, even in the absence of the inhibitor moiety.

We recently obtained a crystal structure of such a foldamer complexed with the protein HCAII confirming interactions between the two.<sup>[5]</sup> The X-ray structure also revealed a dimerization of the foldamer/protein complex. Studies are ongoing to assess the presence of such a dimer in solution and to design improved interactions at the foldamer-protein interface.



**Figure 1.** X-ray structure of a foldamer/HCAII complex

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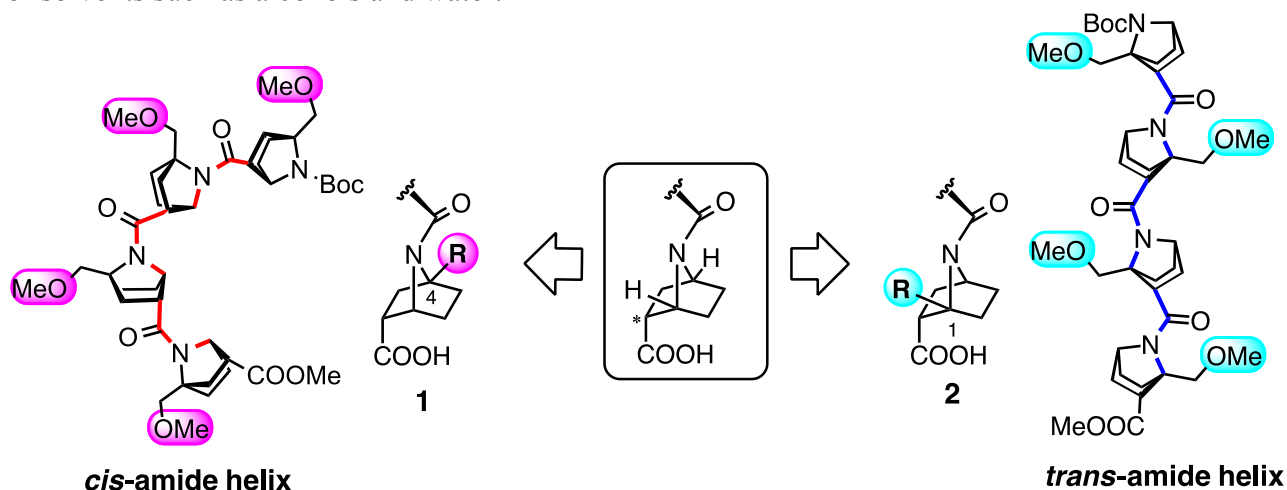
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## Robust *Cis*- and *Trans*-Amide Helical Structures of Oligomers of Bicyclic Mimics of $\beta$ -Proline: Full Control of Amide *Cis-Trans* Equilibrium

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Homooligomers of 7-azabicyclo[2.2.1]heptane-2-*endo*-carboxylic acid, a bridged  $\beta$ -proline analogue (**1**) with a substituent installed at the C4-bridgehead position completely biased the amide *cis-trans* equilibrium to the *cis*-amide structure.<sup>[1]</sup> We expected that introduction of a substituent at the C1-bridgehead position adjacent to the carboxylic acid moiety (**2**) would tip the *cis-trans* amide equilibrium towards *trans*-amide structure. Herein we show that indeed oligomers of this analog take a consistent helical structure involving all-*trans*-amide linkages, independently of the number of residues, from the dimer up to the octamer.<sup>[2]</sup> These unique helical structures show some similarity in shape to *trans*-amide based polyproline II (PPII) helix. These helices were stable in various kinds of solvents such as alcohols and water.



**Figure 1.** Generation of all-*cis*-amide helix and all-*trans*-amide helix on the basis of bicyclic  $\beta$ -proline mimic.

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## Stabilization of an $\alpha$ -helix by short adjacent accessory foldamers

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$\alpha$ -Helices often play the key role of recognition elements between proteins. In recent years, much attention has been paid to the potential of foldamers as  $\alpha$ -helix mimetics to target protein-protein interactions (PPI). However, one difficulty to the use of foldamers for mimicking protein surfaces resides in reproducing the spatial arrangement of the side chains found in the cognate  $\alpha$ -helix. One solution could be to fuse foldamer and peptide backbones in one molecule to preserve a portion of the original  $\alpha$ -helical segment and fully optimize contacts with the protein recognition surface. In addition, the possibility for the foldamer backbone to exert a dual effect by also nucleating an  $\alpha$ -helical structure (short synthetic peptides are barely helical) in the contiguous  $\alpha$ -peptide segment is appealing. Despite the potential interest, there are relatively few examples of such  $\alpha$ -peptide/foldamer chimeras in the literature <sup>[1]</sup>.

In this work, the ability of helical oligourea foldamers to nucleate  $\alpha$ -helices when fused to short  $\alpha$ -peptide segments has been explored. A variety of chimeric oligomers obtained by joining aliphatic oligoureas either to the C- or N-terminus of peptides of different chain-lengths have been designed and their conformation investigated. NMR spectroscopy and X-ray diffraction studies indicate that short oligourea/peptide chimeras can adopt well-defined helical structures with a continuous intramolecular H-bond network spanning the entire sequence and connecting two geometrically distinct helices, (i.e. an  $\alpha$ - (or  $3_{10}$ ) helix in the peptide segment and a canonical 2.5-helix in the oligourea segment <sup>[2, 3]</sup>). Our results also point to the remarkable capacity of short tri-urea segments to nucleate the formation of an  $\alpha$ -helical conformation in the fused peptide segment.

These results suggest a general approach to stabilize and mimic peptide and protein helices and pave the way for exploration and future development of oligourea/peptide chimeras as modulators of protein-protein interactions

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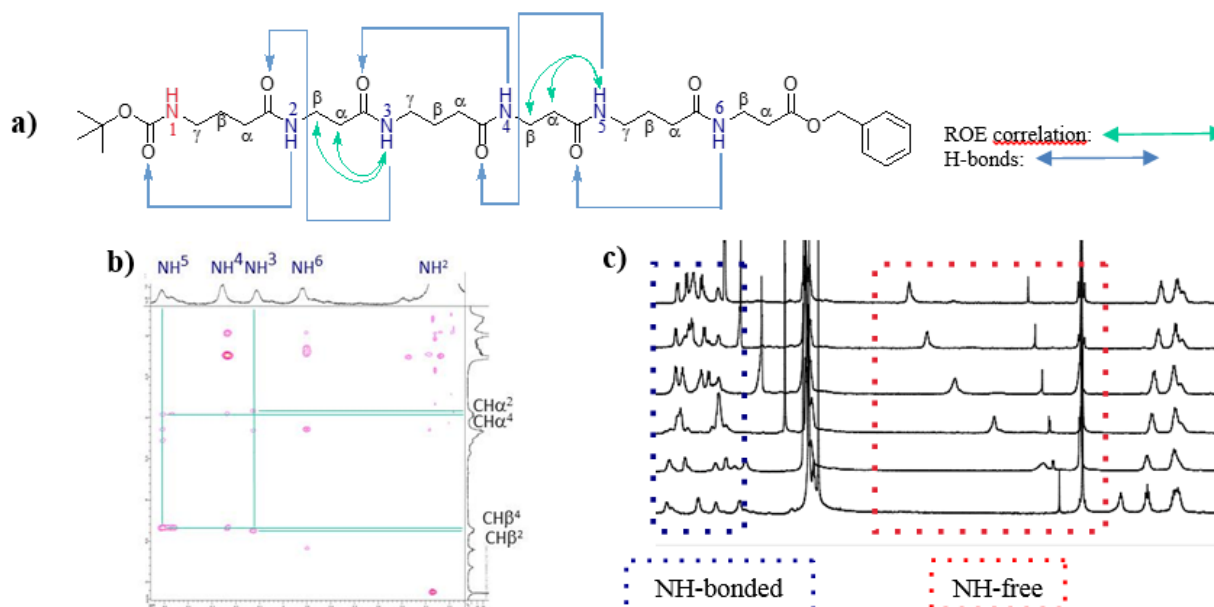
## Design of New $\beta/\gamma$ -Peptide Manifolds: the 9/8-Helix

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Oligopeptides containing  $\beta$ - or  $\gamma$ -amino acids are well known to adopt regular secondary structures whilst being resistant to proteolytic degradation, making them of considerable interest as peptidomimetic foldamers. Mixed  $\beta/\gamma$ -peptides are rather less studied but two types of helical structures have been demonstrated for such derivatives, a mixed 11/13-helix<sup>[1]</sup> and a 13-helix<sup>[2]</sup>, both of which were predicted to be stable secondary structures by computational studies.<sup>[3]</sup> The backbones of the  $\beta$ - and  $\gamma$ -amino acids used in those examples were densely substituted to impose severe constraints in order to impose the adoption of the designated folding feature.

We describe here our investigations of the folding behaviour of new mixed  $\beta/\gamma$ -peptides, designed to show folding propensity with only a minimum of sterically-imposed conformational constraints. The governing principle is to target selected residues for bearing minimal-bulk folding constraints, and allow this to induce cooperative participation of the remaining residues, which are otherwise highly flexible. Using this approach, we have been able to target the previously unknown (and unpredicted) 9/8-helix, which is stabilized by  $i, i+2$  hydrogen-bonding contacts. We will present the synthetic approaches for obtaining the appropriate  $\beta/\gamma$ -peptides, as well as the theoretical and experimental studies (notably 1D and 2D NMR, as illustrated below) which confirm and characterize the 9/8-helix structure.



**Figure 1.** a) The basis of the 9/8-helix secondary structure; only the backbone atoms are shown. b) ROESY NMR plot. c) DMSO titration in NMR (10 mM in  $\text{CDCl}_3$ ).

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## Developing aqueous soluble $\beta$ -sheet structures

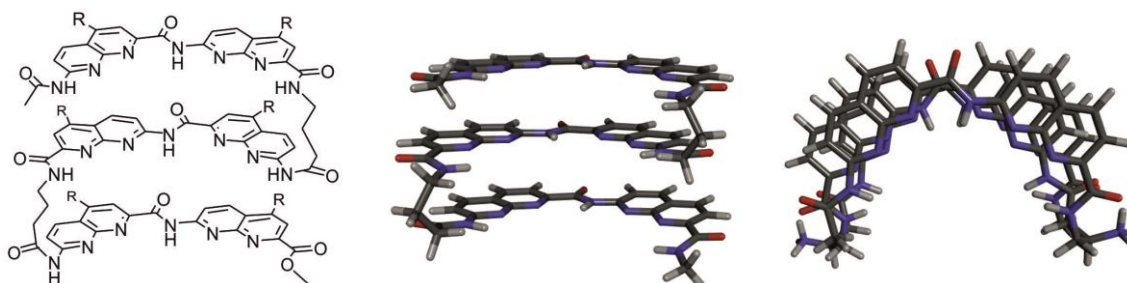
Daniel Carbajo<sup>a</sup>, Laure Sebaoun<sup>a</sup>, Marta Wylot<sup>a</sup>, Victor Maurizot<sup>a</sup> and Ivan Huc<sup>a</sup>

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The most common secondary structure for foldamers has been the helix, with its distinct ability to form discrete objects stabilized by intra-molecular non-covalent interactions. Meanwhile, foldamer based  $\beta$ -sheet-like structures are still rare. Recently, our group has been able to design and synthesize a series of foldamers composed by aromatic monomers that adopt  $\beta$ -sheet folding patterns in organic solvents<sup>[1]</sup>. These molecules combined linear flat aromatic segments and rigid hairpin turns that set the linear segments at a distance and orientation promoting intramolecular aromatic  $\pi$ - $\pi$  stacking.

In nature, protein containing  $\beta$ -sheet structures perform important duties in a living organism. Nevertheless, the low aqueous solubility of the aromatic  $\beta$ -sheets previously prepared by our group limits their future biological applications. Thus, we endeavored to apply the design principles previously developed to create  $\beta$ -sheet aromatic foldamers that would be soluble in aqueous media. Herein we report our design and preliminary results on the synthesis of these aqueous soluble  $\beta$ -sheet foldamers. In the design of these new molecules it has been assumed that the aromatic  $\pi$ - $\pi$  stacking that favor the formation of the layered aromatic structure will be stronger in water than in organic solvents and a more flexible aliphatic hairpin turn has been chosen compared to the rigid aromatic turn previously used.



**Figure 1.** Calculated structure of a  $\beta$ -sheet foldamer based on naphthyridine aromatic monomers.

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## Helically Folded Capsules Based On Aromatic Oligoamide Foldamers For The Recognition Of Chiral Guests

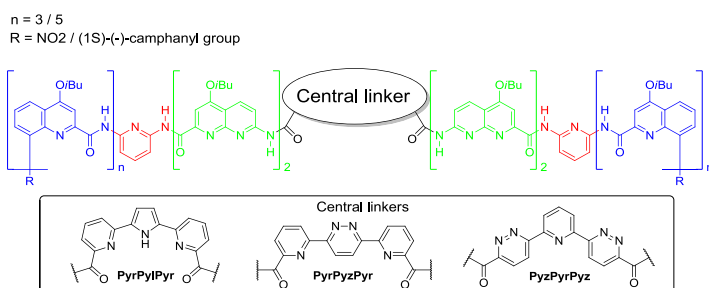
Guillaume Lautrette<sup>a</sup>, Chandramouli Nagula<sup>a</sup>, Christophe Aube<sup>b</sup>, Maxime Horeau<sup>b</sup>, Brice Kauffmann<sup>a</sup>, Virginie Blot<sup>b</sup>, Muriel Pipelier<sup>b</sup>, Yann Ferrand<sup>a</sup>, Didier Dubreuil<sup>b</sup> and Ivan Huc<sup>a</sup>

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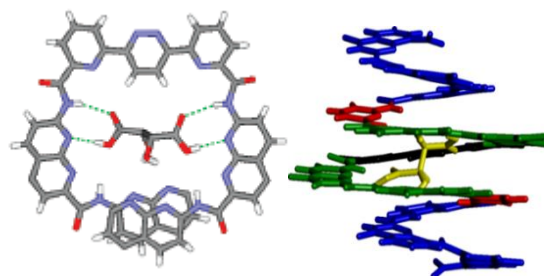
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Over the last ten years, foldamers (synthetic oligomers or polymers possessing well-defined, bio-inspired, folded conformations in solution) have fundamentally shifted our knowledge of biopolymer folding. They have shown that molecular backbones chemically remote from those that nature uses are also able to adopt folded secondary motifs such as helices, turns and linear strands. In nature, cavities for molecular recognition emerge at the tertiary and quaternary folds level, whereas in the case of foldamers we can observe them directly at secondary folds level. Thus, it proves easier to fine tune shape and functions of the recognition site. In this context, our collaborative work with Dr. I. Huc in the field of synthesis and characterization of supramolecular structures led us to elaborate oligoamidic-type foldamers including azaheteroaromatic ligands as central linkers (Figure ). We have demonstrated their ability to encapsulate small molecules such as tartaric acid (Figure ).<sup>[1,2,3]</sup> Lately, we showed that those structures were able to recognize carbohydrates with excellent specificity when tuned correctly.<sup>[4]</sup> We attempt to investigate whether or not we would be able to improve the binding or the release of a guest using a switch regulating the conformation of a helical receptor. These results thus help improve the design principles of synthetic helically molecular capsules for the conception of biological receptor mimics. Synthesis and results of such receptors will be presented in the poster.



**Figure 1.** Representation of an oligoamidic foldamer with three different central linkers



**Figure 2.** X-Ray structures of full PyrPyzPyr capsule with recognition by hydrogen bonds.

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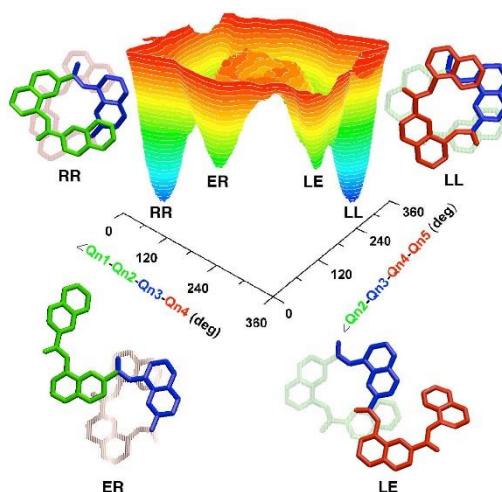
## Computational Investigations of Functional Arylamide Foldamers: Mechanism of Ligand Encapsulations and Free Energy Profile of Handedness Inversion in Helical Arylamides

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In recent years, we have developed a computational approach that allows for accurate prediction of arylamide foldamer structures and functions. In this presentation, we focus on two applications of the approach. (1) All-atom molecular dynamics (MD) simulations with the optimized aryl-amide torsional parameters identify two low energy barrier binding/release mechanisms for ligand encapsulation by a helical arylamide<sup>[1]</sup>. Both mechanisms show that the capsule helical structure is either minimally disturbed or restored quickly (within 100 ps). Furthermore, we determine the effects of ligand sizes, their chemical nature (hydrogen bonding capabilities), and solvents on binding modes and stabilities. Our findings not only support experimental observations but also provide underlying principles that allow for rational design of foldamer capsules. (2) A metadynamics study provides the first atomistic level description of the folding-unfolding mechanism for helical arylamide foldamers<sup>[2]</sup>. We determined that the handedness inversion of an arylamide helix starts from a helix terminus and propagates along the strand through simultaneous unfolding and folding of two adjacent aryl-aryl linkages, in agreement with the previously hypothesized hopping mechanism. A series of intermediates along the inversion pathway were found to have common features -one unfolded aryl-aryl linkage connecting two helical segments with opposite handedness. This all-atom classical metadynamics simulation study also provides quantitative free energy information for each step of the unfolding-folding pathway, and is in agreement with experimentally obtained kinetic data.



**Figure 1.** Free energy profile of a step-wise folding-unfolding pathway for handedness inversion of a quinoline based helical pentamer. The conformations (snapshots from MD simulations) of helices with opposite handedness (RR and LL), and two intermediates (ER and LE) are also shown.

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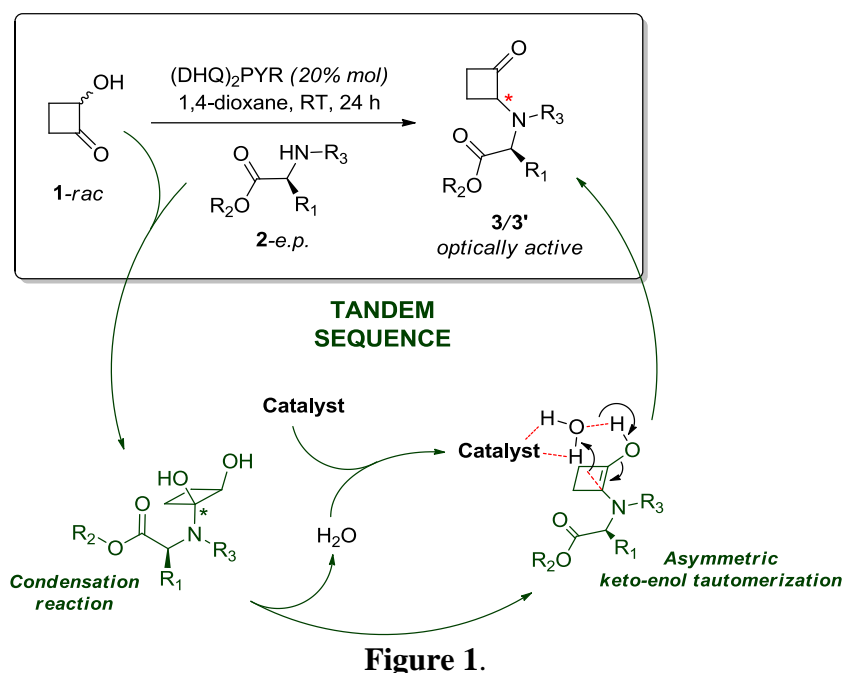
## Towards the Synthesis of New Cyclobutane-Containing Optically Active Unnatural Foldamer Building Blocks

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As part of our ongoing research program into the asymmetric functionalization of  $\alpha$ -hydroxy ketones [1, 2], we recently developed a practical method for the synthesis of optically active  $\alpha$ -amino cyclobutanone via an organocatalytic asymmetric condensation reaction between racemic 2-hydroxycyclobutanone and chiral *N*-alkyl- $\alpha$ -amino acid ester derivatives [3]. Since 2-aminocyclobutanes have a great potential value in organic synthesis [4-6], further studies on the transformation of this class of compounds into new constrained foldamer building blocks [7] are currently in progress in our laboratory.



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## Synthesis of water-soluble hybrid $\alpha$ -amino acid/quinoline oligoamide foldamers via a solid-phase strategy

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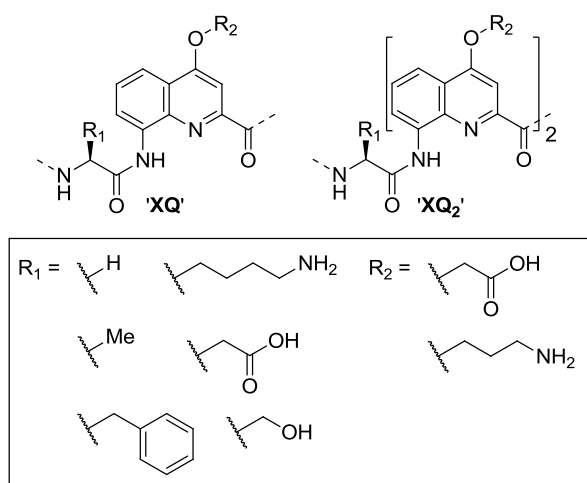
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Unknown sectors of structural and functional space may be reached in the foldamer world by creating heterogeneous backbones that combine more than one type of constituent unit. Combining 'biotic' and 'abiotic' building blocks, which follow completely different folding principles, can allow the preparation of hybrid foldamers, distinct both from synthetic homo-oligomers and from biopolymers.<sup>[1]</sup>

We have previously demonstrated that in organic solvents, hybrid  $\alpha$ -amino acid/quinoline oligoamide foldamers consisting of a trimeric **LQ<sub>2</sub>** repeat unit (L = Leu, Q = 8-amino-4-isobutoxy-2-quinolinecarboxylic acid) adopt stable helical conformations, with leucine side-chains presented in a predictable linear array on one face of the helix.<sup>[2]</sup> In contrast, foldamers based on the dimeric **LQ** repeat unit were found to adopt a partially folded zig-zag tape conformation with local conformational variability precluding long range order.<sup>[3]</sup>



**Figure 1:** XQ and XQ<sub>2</sub> foldamers.

We decided to further probe the helix-forming capabilities of these motifs in water, since aromatic oligoamide folding is dramatically enhanced in these conditions,<sup>[4]</sup> We report here a microwave-assisted methodology for the solid-phase synthesis of water-soluble **XQ** and **XQ<sub>2</sub>**-type foldamers (Figure 1) via either assembly of preformed **XQ** dimer blocks, or by coupling  $\alpha$ -amino acids during SPS as *in-situ* formed acid chlorides. This latter approach was used to synthesize a 12mer **XQ<sub>2</sub>**-type foldamer incorporating four different amino acid residues (Lys, Ala, Asp and Ser). Structural elucidation by NMR confirmed this sequence adopts a stable right-handed helical conformation in water.

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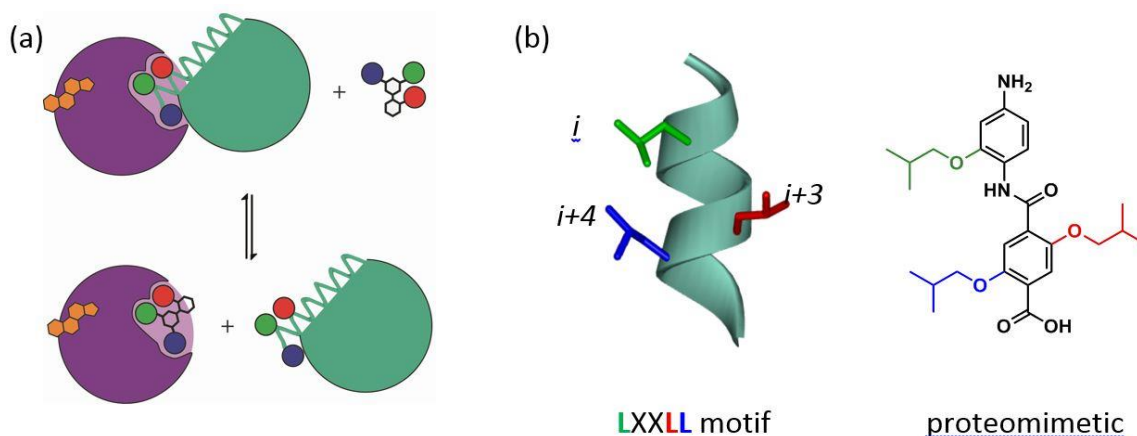
## Novel bifacial scaffolds as $\alpha$ -helix proteomimetic inhibitors of the AR and ER/Co-activator interaction

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The Androgen receptor (AR) and Estrogen receptor (ER) belong to the nuclear hormone receptor superfamily and play an important role in the progression of prostate and breast cancer, respectively.<sup>[1]</sup> Their transcriptional activity is mediated through protein-protein interactions with co-activator proteins.<sup>[2]</sup> Consequently, the AR and ER/Co-activator PPIs are attractive targets for the development of inhibitors (**Figure 1a**).<sup>[3-5]</sup>

We present the design and synthesis<sup>[6]</sup> of two bifacial scaffolds as proteomimetics of the LXXLL co-activator recognition motif. Bis-benzamide and N-(4-aminophenyl)terephthalamidic acid are the backbones and isobutyl groups reproduce the key side chains at  $i$ ,  $i+3$ ,  $i+4$  positions of the co-activator  $\alpha$ -helix (**Figure 1b**). Conformational studies in combination with molecular modeling and docking analysis provide evidence that the new dimers mimic to a high degree the residues at  $i$ ,  $i+3$  and  $i+4$  positions of the native co-activator helix. Additionally, the inhibitors show the ability to adopt the same side chain array in solution as the native peptide in its bio-active conformation, when bound into the hydrophobic pocket on the receptor surface.



**Figure 1.** (a) Bifacial helix mimetics as inhibitors of PPIs (steroid ligand in orange, ER or AR in purple,  $\alpha$ -helix containing co-activator in turquoise and key side chain residues represented as coloured circles). (b) LXXLL co-activator recognition motif (PDB ID: 3ERD) showing the key side chains at  $i$ ,  $i+3$ ,  $i+4$  positions and example of the novel bifacial scaffold structure.

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## ***Cis*-aminocyclopentanecarboxylic acid-containing helical peptides**

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Peptidic foldamers exhibit a wide range of interesting biological activities including antimicrobial, protein-protein interaction inhibition, agonism/antagonism of GPCR receptors.<sup>[1]</sup> The majority of these functions is related to helical structure of ligands. In particular, foldamers constructed from both  $\alpha$ - and  $\beta$ -amino acid residues are of high interest, due to the structural diversity of  $\alpha$ -residues and possibility of reasonable control of the three-dimensional structure by incorporation of  $\beta$ -residues.<sup>[2]</sup> A number of sequence patterns of  $\alpha,\beta$ -peptides containing *trans*-aminocyclopentanecarboxylic acid residues was studied by Gellman and co-workers.<sup>[3,4]</sup> In the case of *cis*-aminocyclopentanecarboxylic acid residue-containing peptides, we have already shown the high conformational stability of  $\alpha\alpha\beta\beta$  and  $\alpha\beta\alpha\beta$  sequence patterns.<sup>[5]</sup> Here we extend these studies and present comparison of peptides build on the basis of sequence patterns with increasing content of  $\alpha$ -residues, namely:  $\alpha\alpha\beta\beta$  and  $\alpha\beta\alpha\beta$  versus  $\alpha\alpha\beta$  and  $\alpha\alpha\alpha\beta$ . Conformational preferences and stability were analyzed using NMR and CD techniques.

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## Foldaxane Based Molecular Shuttles: Generating a Biased Brownian Motion

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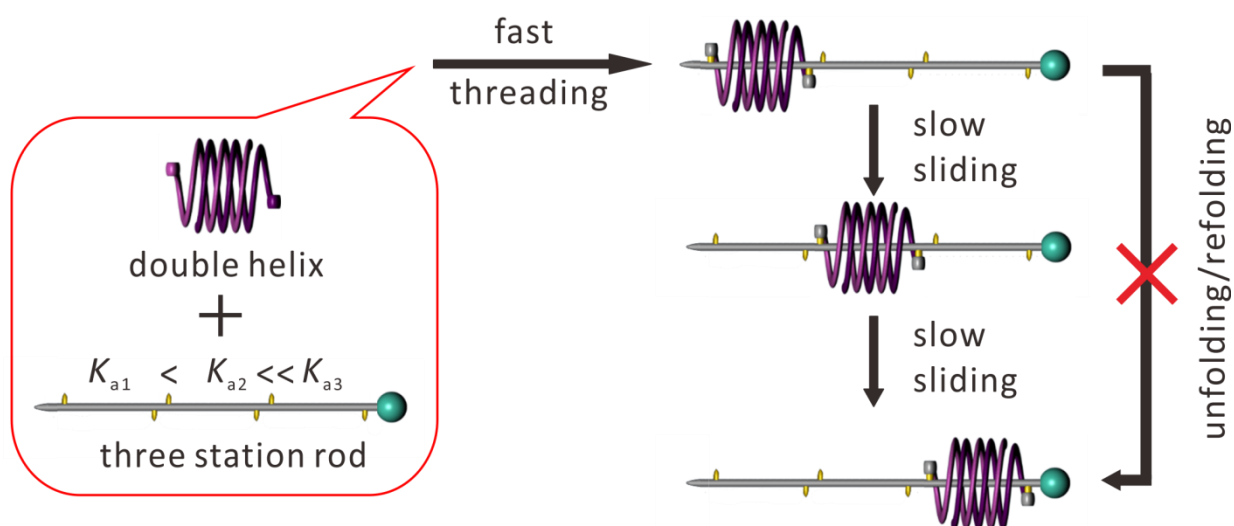
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Mechanically interlocked systems, such as rotaxanes and catenanes, are appealing systems for artificial molecular machines. In such systems, irreversible mechanical bonds define the pathways for motion and prevent dissociation.<sup>[1,2]</sup> Foldaxanes represent a class of pseudorotaxanes in which a helical structure (a foldamer) can wind or unwind around rod-like or dumbbell guests. However the folding and unfolding of the foldamer around rod remain slow, allowing shuttling motion of the helix on the rod to occur without dissociation.<sup>[3,4]</sup>

In this study, the affinities of a double helical foldamer towards single station rods of different lengths were measured using <sup>1</sup>H NMR. A ranking of the affinity of the helix for the rods could be established as a function of length. Disymmetrical rods consisting of several binding stations and bearing a single stopper at one end were prepared. When three stations with increasing affinities for the foldamer are arranged on a rod, an affinity gradient is created (Figure 1). Kinetic studies showed that the double helical foldamer can slide unidirectionally along the rod through a biased Brownian motion without unfolding/refolding.

To understand the sliding mechanism, foldaxane architectures with different single station rods were characterized by NMR and X-ray crystallography. Molecular simulations indicated that the intermolecular hydrogen bonds played a dominant role in the binding of helix toward the rod. In addition, the interplay between the hydrogen bonding and  $\pi$ - $\pi$  stacking controlled the screwing of the double helix upon binding to the rod. Further simulations on biased Brownian motion are in progress in our laboratory.



**Figure 1.** Schematic representation of a biased Brownian motion.

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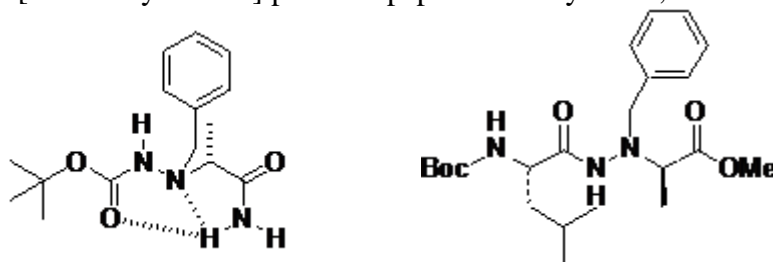
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## Spontaneous self-assembly of full protected 1:1 [ $\alpha/\alpha$ - $N^\alpha$ -hydrazino] pseudodipeptides into twisted parallel $\beta$ -sheet in solid state.

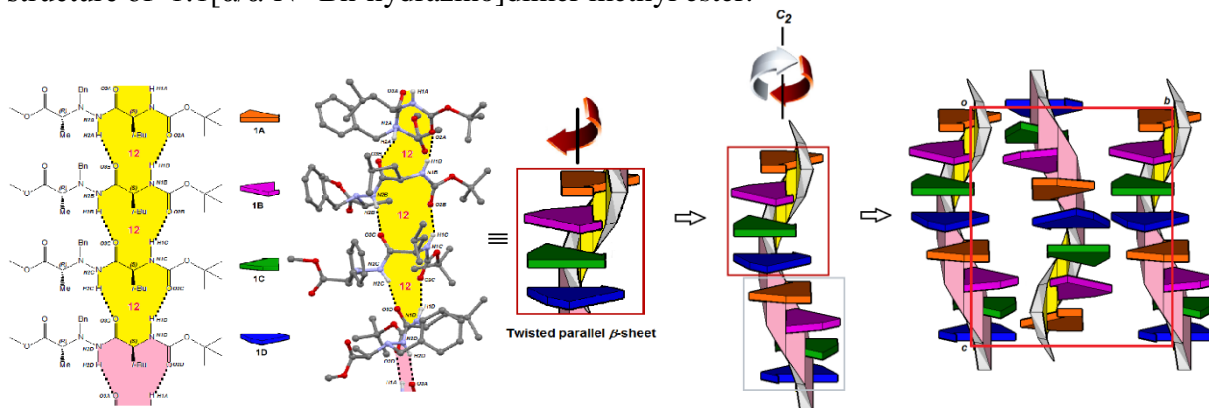
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The organization in hydrazinoturn structuration was observed for three decades on hydrazinopeptides. In fact, 1:1[ $\alpha/\alpha$ - $N^\alpha$ -hydrazino] pseudodipeptides were previously studied and linear oligomers are self-organized via a succession of  $\gamma$ -turn and hydrazinoturn in solution, including the amidic dimer.<sup>[1]</sup> Due to the absence of the amidic function, we try to understand the organization adopted by the corresponding ester dimer, in solution and solid state, thanks to the obtention of crystals. The observation of original and uncommon twisted  $\beta$ -sheet, type of supramolecular helix, with a helix hand controlled by the chirality of the amino acid unit, allows to consider using of these pseudodipeptides in biological applications.<sup>[2]</sup> Only one pseudopeptidic dimer, a depsipeptide, is described in literature and presents this structuration in solid state.<sup>[3]</sup> On the basis of NMR and IR experiments, supported by X-Ray and circular dichroism analyses, we have lifted the veil on the organization of 1:1 [ $\alpha/\alpha$ - $N^\alpha$ -hydrazino] pseudodipeptides methyl ester, in solution and solid state.



**Figure 1:** a) structure of 1:1[ $\alpha/\alpha$ - $N^\alpha$ -Bn-hydrazino]dimer amid structured in hydrazinoturn, b) structure of 1:1[ $\alpha/\alpha$ - $N^\alpha$ -Bn-hydrazino]dimer methyl ester.



**Figure 2:** Cartoon representation illustrating the formation of twisted parallel  $\beta$ -sheet and left-handed supramolecular helix in the crystals of **1**.

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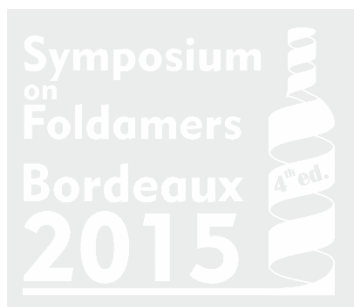
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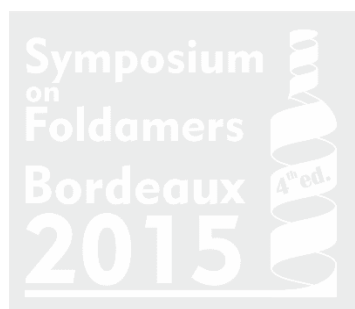




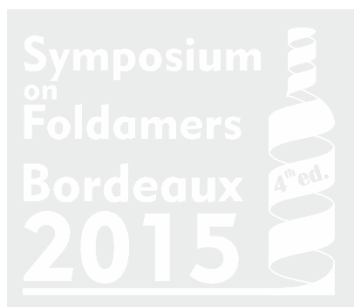
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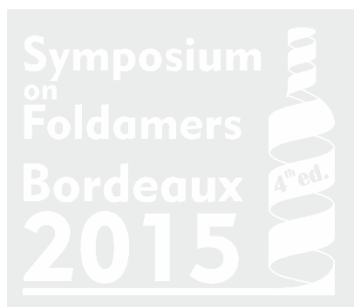
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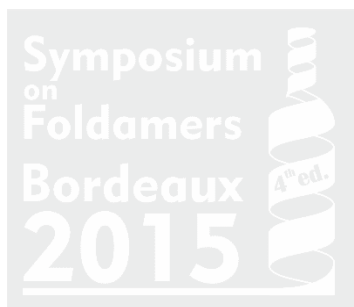
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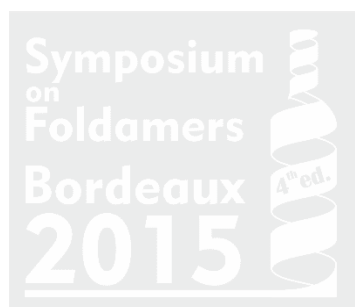
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	Monday	Tuesday	Wednesday
9:00			
10:00		K. Gothelf	V. Pecoraro
11:00		B. Pentelute	K.-S. Jeong
12:00		Coffee	Coffee
		V. Pophristic	I. Mandity
		S. Pellegrino	U. Lewandowska
		J. Crassous	I. Huc
			R. Micura
13:00	Registration	Lunch Poster Session	Lunch
14:00	Welcome		
15:00	F. Stoddart	L. Brunsveld	A. Flood
	W. S. Horne	T. Martinek	C. Tomasini
	A. Miranker	T. Ohwada	S. H. Choi
16:00	Coffee	T. Ohwada	J. Clayden
	A. Rowan	G. Maayan	Coffee
17:00	C. Baldauf	Coffee	D. Yang
	G. Collie	M. Suginome	E. W. Meijer
	F. Formaggio	T. Yeates	
18:00	Welcome Reception		Closing
19:00			
20:00			
21:00		Banquet	