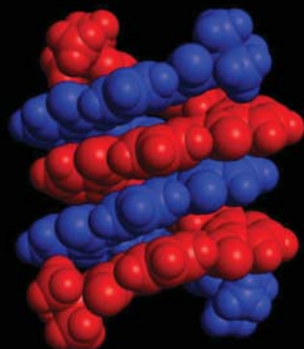


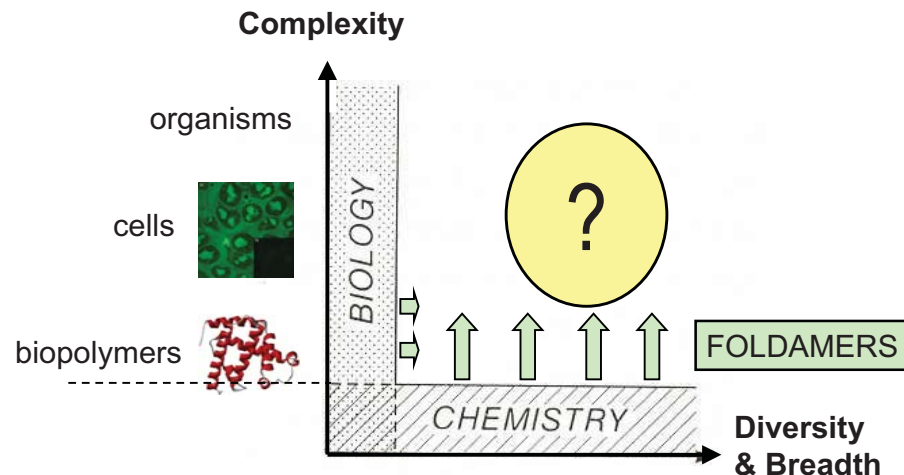
FOLDAMERS: EXPANDING THE CHEMICAL SPACE

Dr. Ivan Huc, European Institute of Chemistry and Biology – Bordeaux



Ischia Advanced School of Organic Chemistry
Ischia (Naples), September 22-26 2012

A view of the chemical space

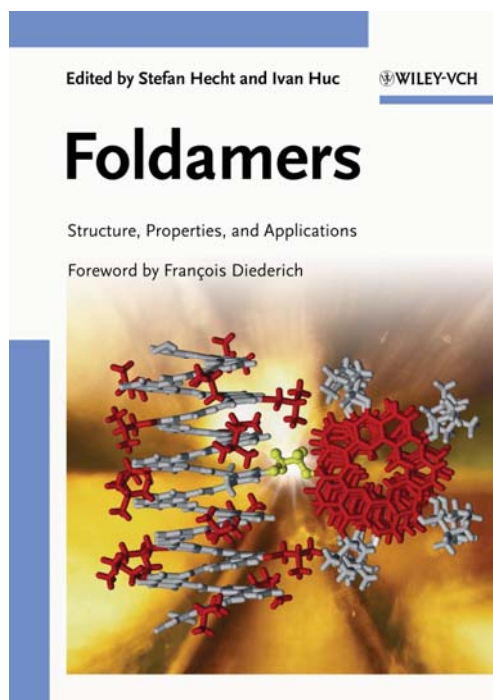


Jean-Marie Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, 1995

Foldamers:
Artificial folded molecular architectures

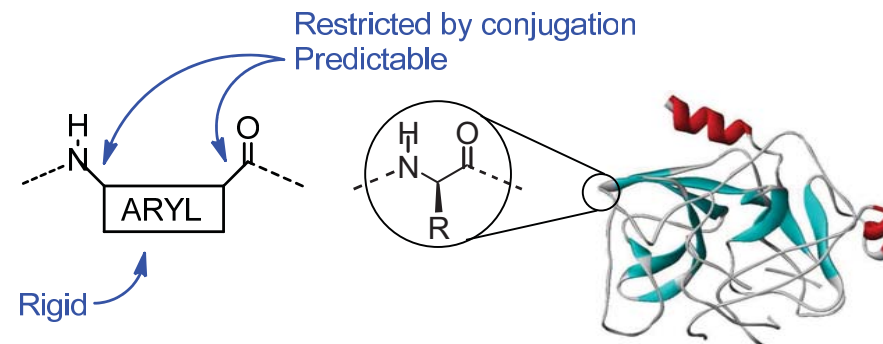
Includes:

- Synthetic oligomers
- Helical polymers
- Modified biopolymers



Folding synthetic oligomers:

- How large ?
- How complex ?
- What functions ?

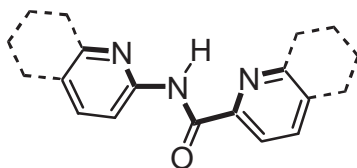


Mimicking is not copying !

Folded structures

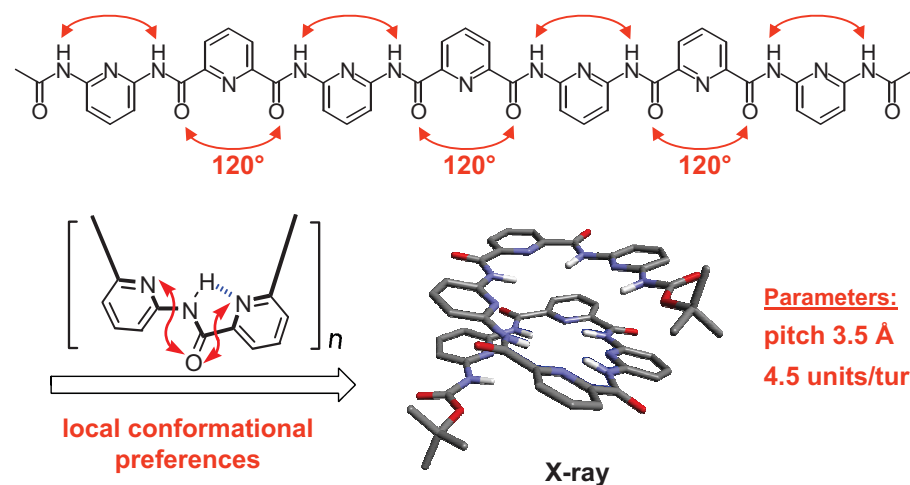
Dynamics & Assembly

Functions



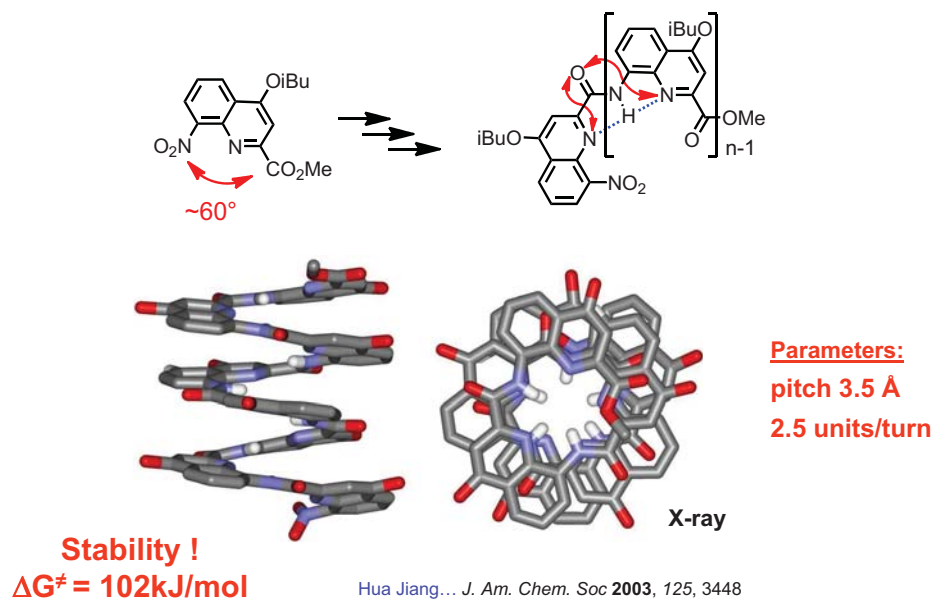
1 – Designing helical structures

Molecular helical programming



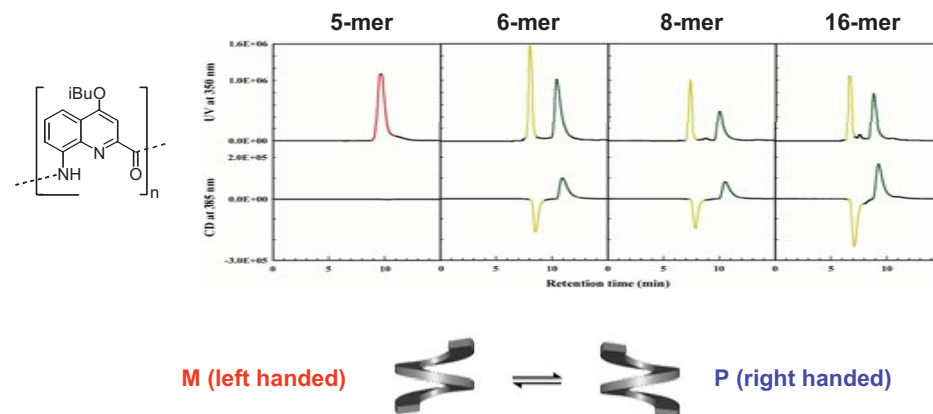
Volker Berl... Chem. Eur. J. 2001, 7, 2798

Decreasing the number of units per turn



Hua Jiang... J. Am. Chem. Soc 2003, 125, 3448
Hua Jiang... Tetrahedron 2003, 59, 8365

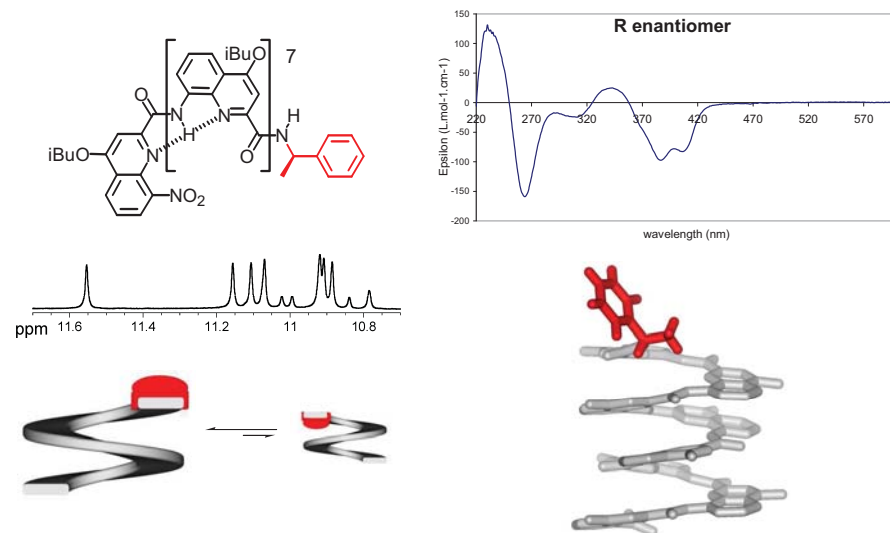
Kinetics of racemization (Collab. H. Ihara, M. Takafuji, Kumamoto Univ.)



Stability depends on the solvent
 $\text{CHCl}_3 < \text{CHCl}_3/\text{hexane} < \text{MeOH} < \text{H}_2\text{O}$

N. Delsuc, T. Kawanami... ChemPhysChem 2008, 9, 1882
T. Qi, H. Noguchi... Chem. Commun 2012, in press

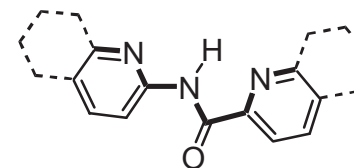
Intramolecular Induction of Handedness



X-RAY: Christel Dolain... *J. Am. Chem. Soc.* **2005**, 127, 12943
 VCD: Thierry Buffeteau... *Chem. Commun.* **2006**, 2714
 A. Kendhale... *J. Org. Chem.* **2011**, 76, 195

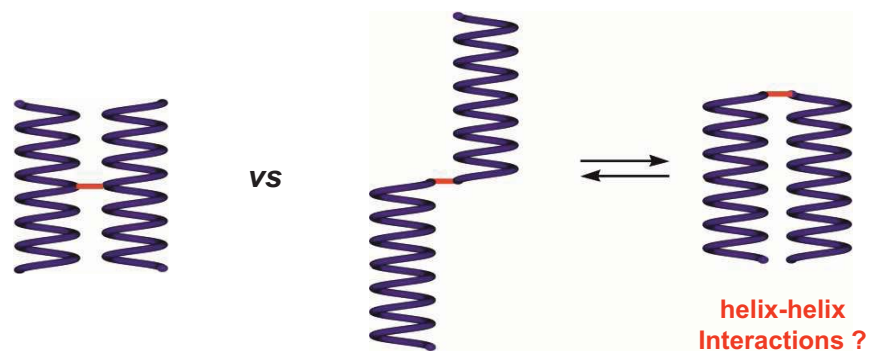
S chirality => P helix
 R chirality => M helix

Folded structures Dynamics & Assembly Functions

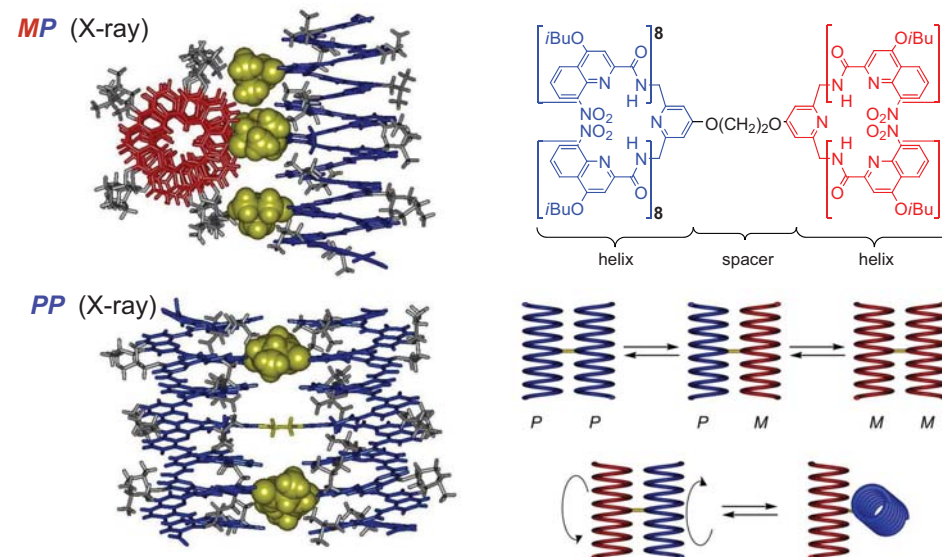


2 – Protein sized foldamers

Towards tertiary structures - helix zippers

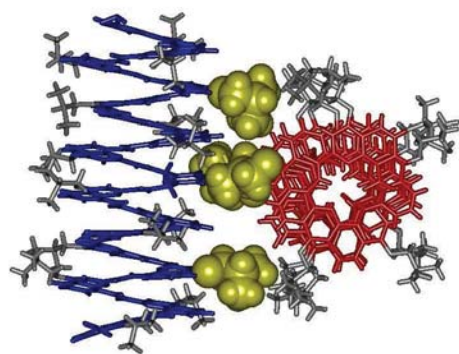


Towards tertiary structures - helix zippers



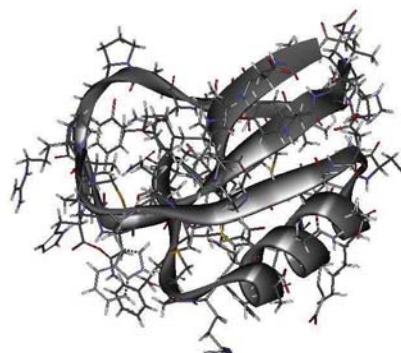
Nicolas Delsuc... *Angew. Chem. Int. Ed.* **2007**, 46, 214; *J. Am. Chem. Soc.* **2011**, 133, 3165

Towards tertiary structures - helix zippers



Synthetic zipper

$C_{464}H_{464}N_{70}O_{74}$
MW 8.2 kD

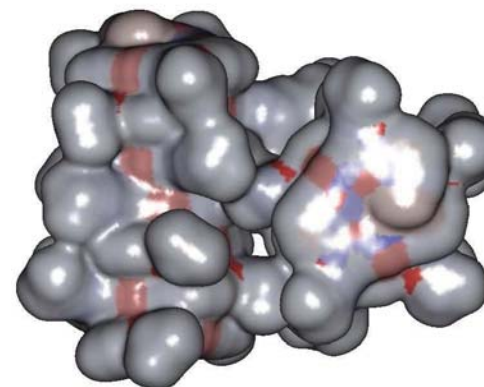


Scorpion Toxin Protein (65aa)

$C_{311}H_{423}N_{86}O_{95}S_8$
MW 7.1 kD

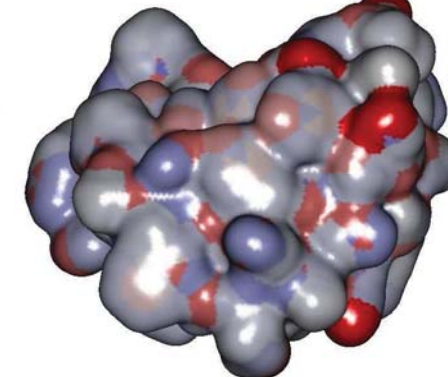
Nicolas Delsuc... *Angew. Chem. Int. Ed.* **2007**, 46, 214; *J. Am. Chem. Soc.* **2011**, 133, 3165

Towards tertiary structures - helix zippers



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Scorpion Toxin Protein (65aa)

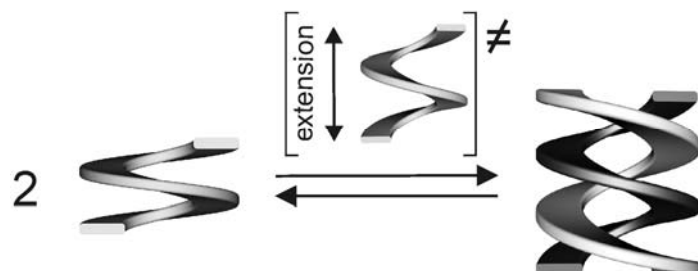
$C_{311}H_{423}N_{86}O_{95}S_8$
MW 7.1 kD

Nicolas Delsuc... *Angew. Chem. Int. Ed.* **2007**, 46, 214; *J. Am. Chem. Soc.* **2011**, 133, 3165

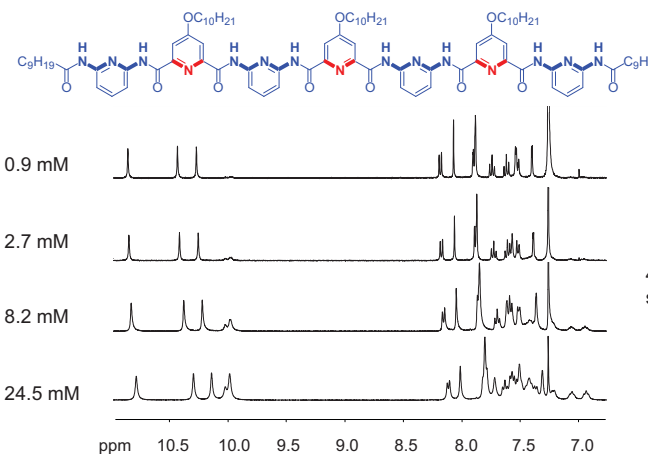
Folded Structures

Dynamics & Assembly

Functions

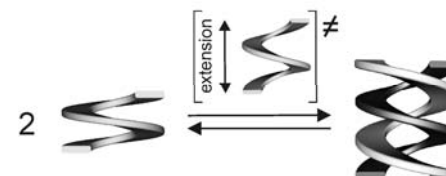


3 – Spring-like extensions

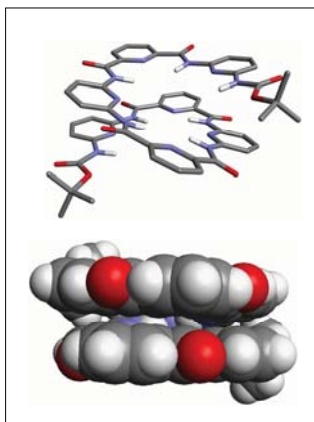
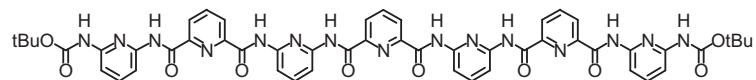


400 MHz 1H NMR
spectra in $CDCl_3$

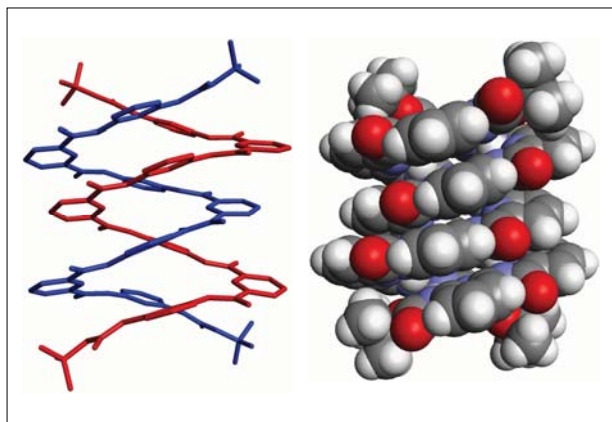
Ivan Huc, Volker Berl...
Nature **2000**, 407, 720
Chem. Eur. J. **2001**, 7, 2810
Hua Jiang...
Tetrahedron **2004**, 60, 10029



$K_{dim} = 30$ L/mol



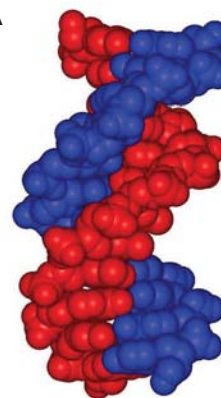
Crystals from dmsO/CH₃CN



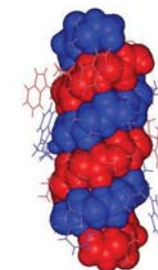
Crystals from ΦNO₂/heptane

Volker Berl, Ivan Huc...
Nature **2000**, 407, 720
Chem. Eur. J. **2001**, 2810

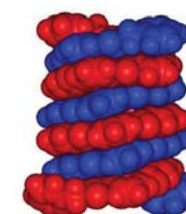
B-DNA



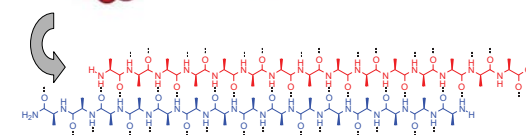
Gramicidin-D



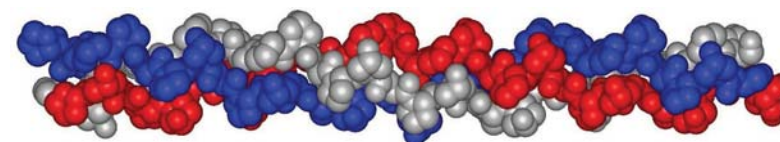
Oligoamides



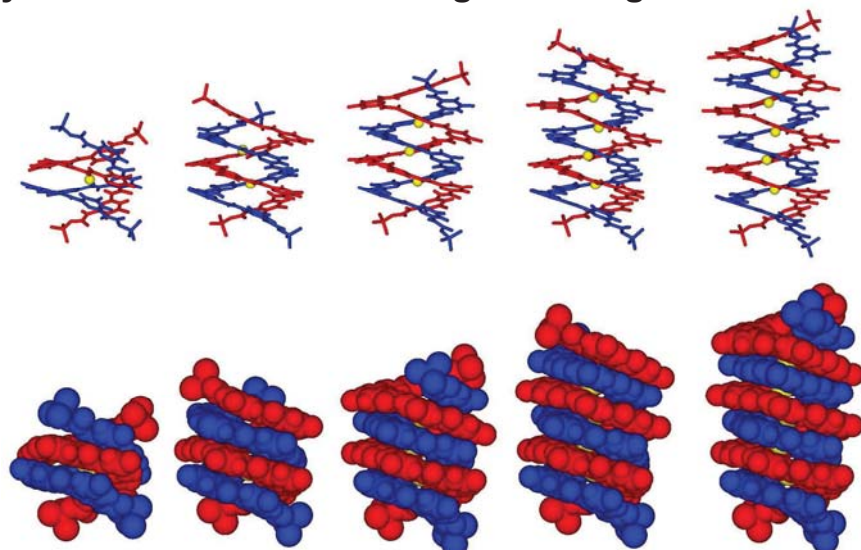
Smallest
Pitch
possible



Collagen

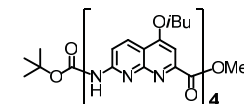
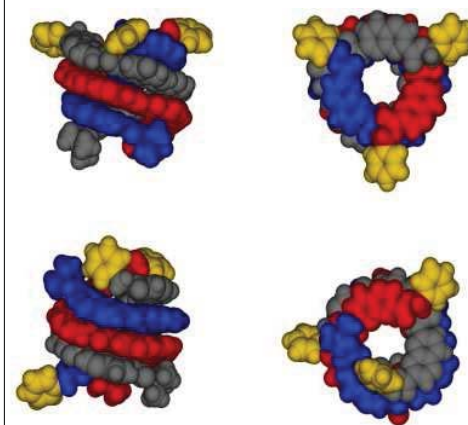


Hybridization at different oligomer lengths



X-rays n = 5 n = 7 n = 9 n = 11 n = 13
 Mol. Wt.: 5.4 kDa
 Debasish Haldar, Jiang Zhu, Benoit Baptiste...*Chem. Asian J.* **2010**, 6, 1364

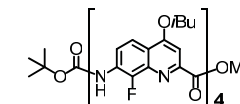
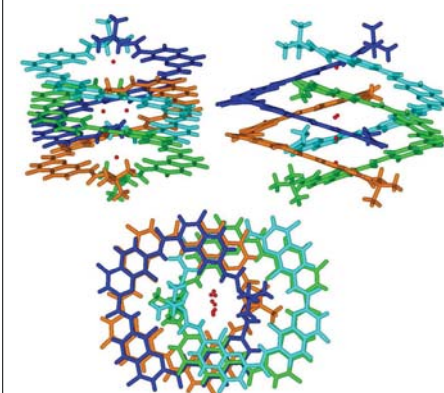
Triplexes...



X-ray

Yann Ferrand...*Angew. Chem. Int. Ed.* **2010**, 49, 1778

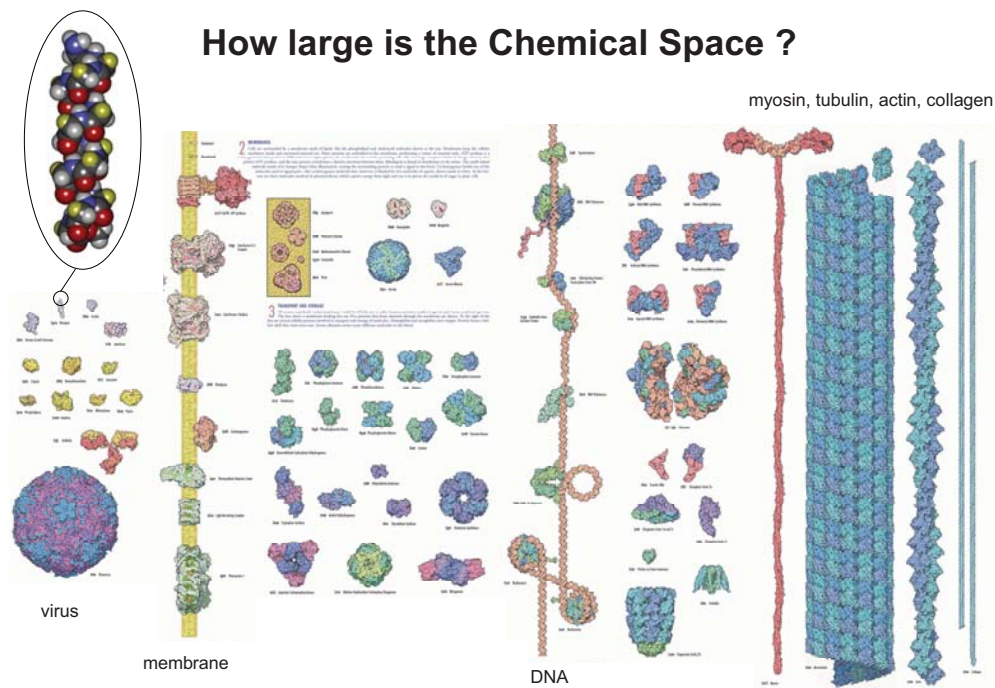
...and Quadruplexes



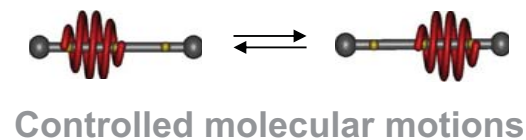
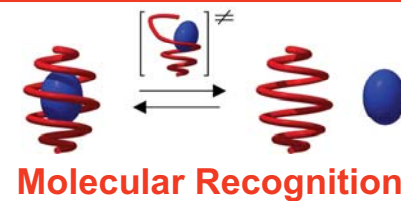
X-ray

Quan Gan... *Angew. Chem. Int. Ed.* **2008**, 47, 1715
 Coll: Prof. Jiang, CAS Beijing

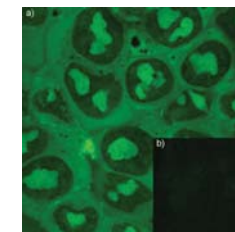
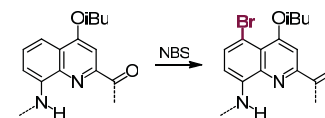
How large is the Chemical Space ?



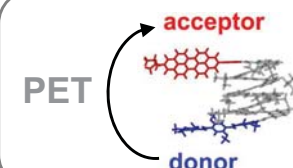
4 - Foldamer functions



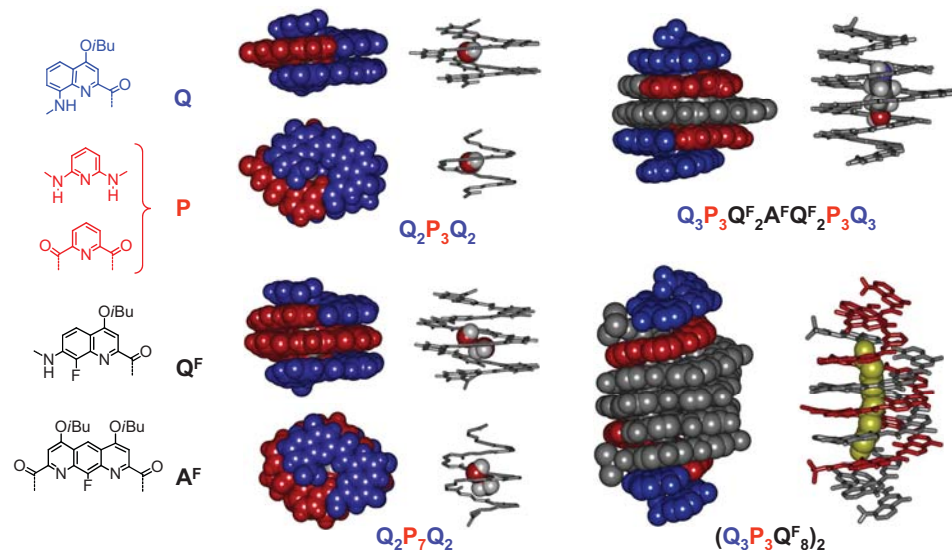
Enhanced reactions



Biological properties

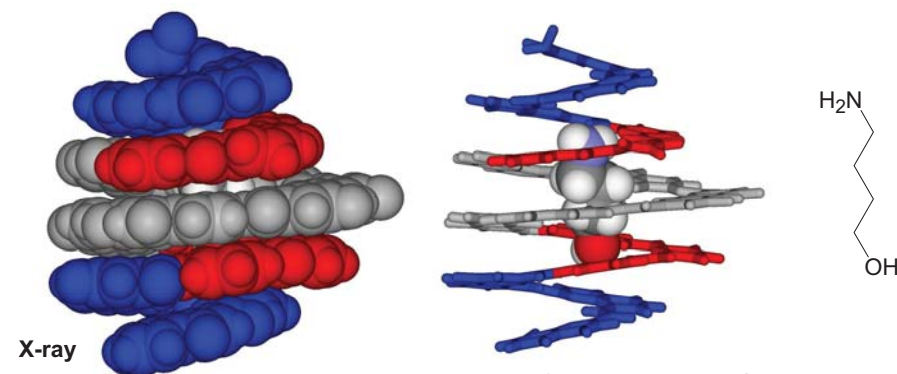
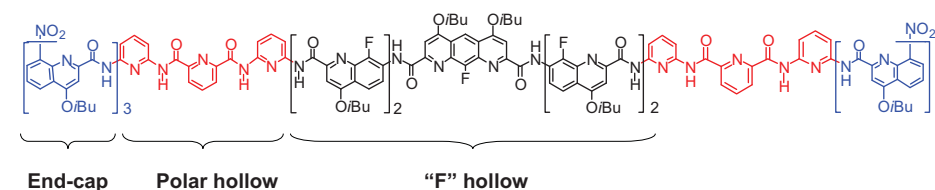


Helical Capsules

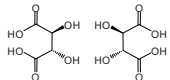
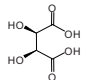
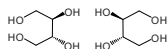
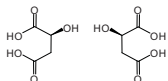


J. Garric... *Angew. Chem. Int. Ed.* **2005**, 44, 1954; *Chem. Eur. J.* **2007**, 13, 8454
C. Bao... *Angew. Chem. Int. Ed.* **2008**, 47, 4153; *Chem. Eur. J.* **2009**, 15, 11530

Helical Capsules Second Generation

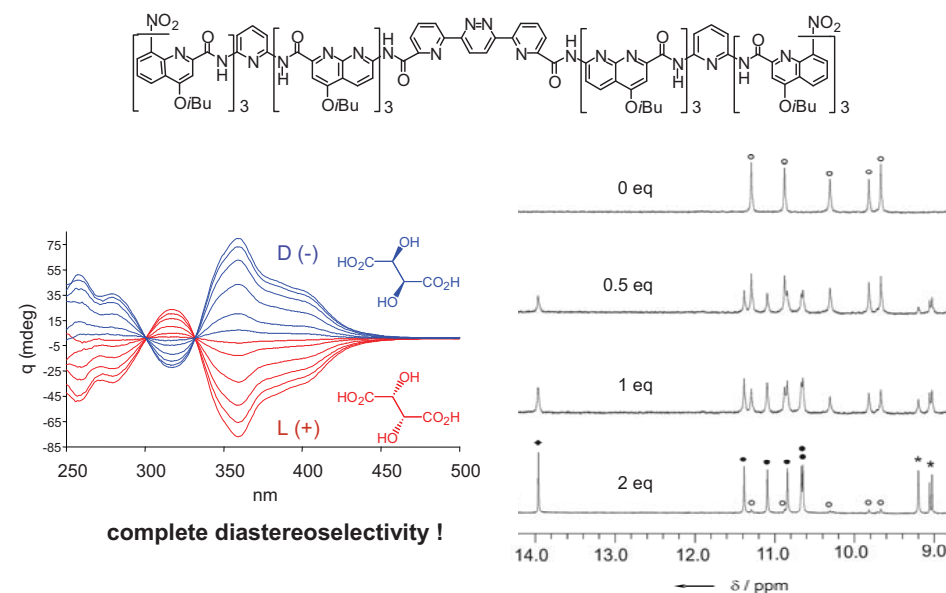


Chunyan Bao... *Angew. Chem. Int. Ed.* **2008**, 47, 4153

Guests	K_a (M^{-1}) in $CDCl_3$ /DMSO (90:10 vol/vol)
	5500 (de = 100 %)
	350
	750 (de = 71 %)
	70 (de = 100 %)
	< 1
	22
	< 1

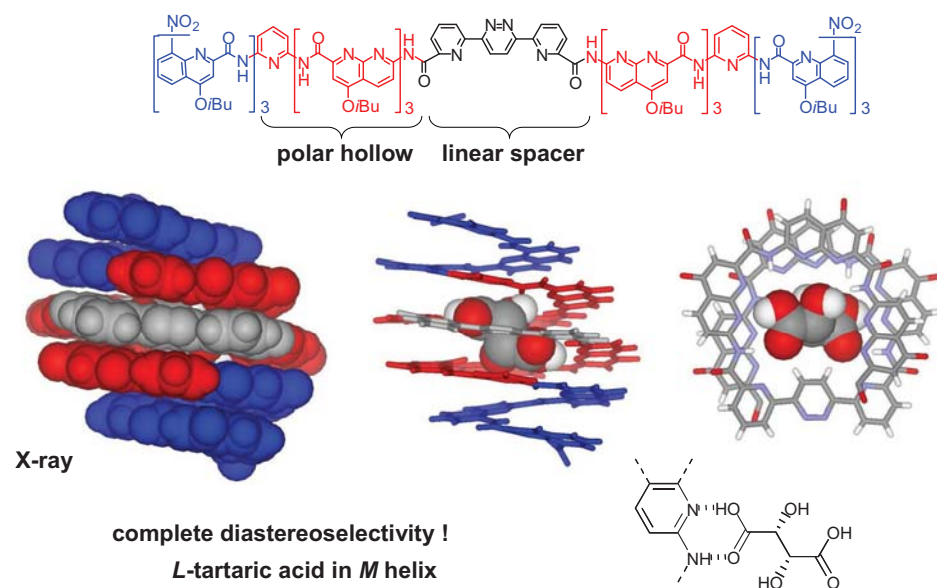
Y. Ferrand... J. Am. Chem. Soc. **2010**, 132, 7858

Capsules for Chiral Guests (Collab. D. Dubreuil, Univ. Nantes)



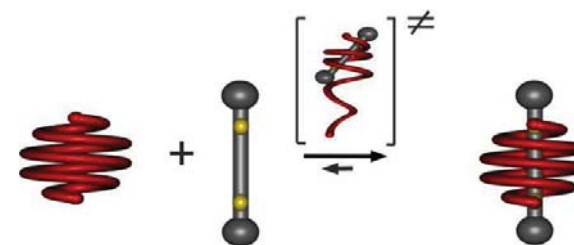
Y. Ferrand... J. Am. Chem. Soc. **2010**, 132, 7858, J. Am. Chem. Soc. **2012**, 134, 11282,

Helical Capsules Second Generation (Collab. D. Dubreuil, Univ. Nantes)



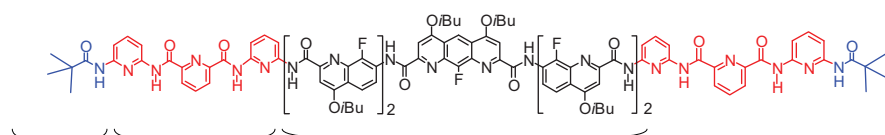
Y. Ferrand... J. Am. Chem. Soc. **2010**, 132, 7858, J. Am. Chem. Soc. **2012**, 134, 11282,

Folded Structures Dynamics & Assembly Functions

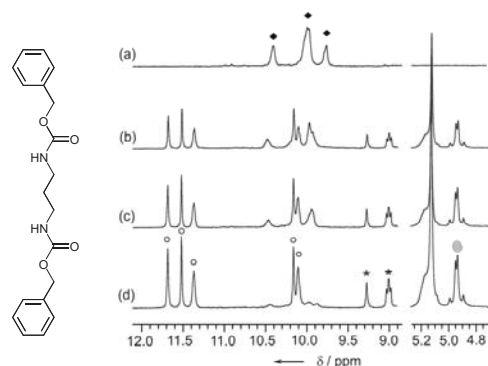
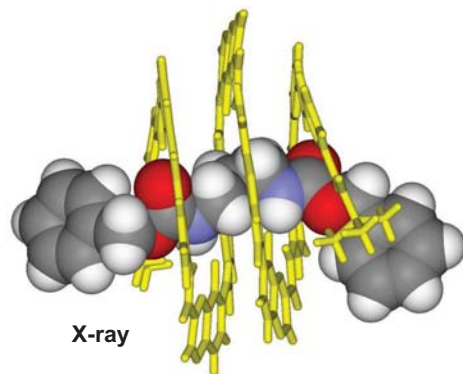


5 – Molecular Motions

FOLDAXANES, Collab. H. Jang, Institute of Chemistry, CAS

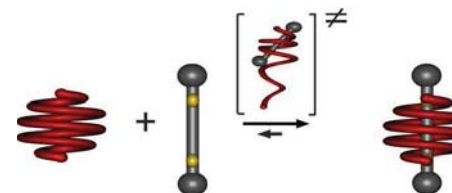
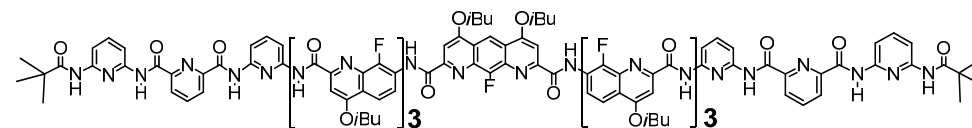


End-cap Polar hollow "F" hollow

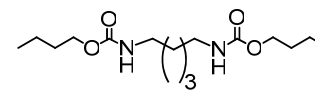


Q. Gan, Y. Ferrand... *Science* **2011**, 331, 1172

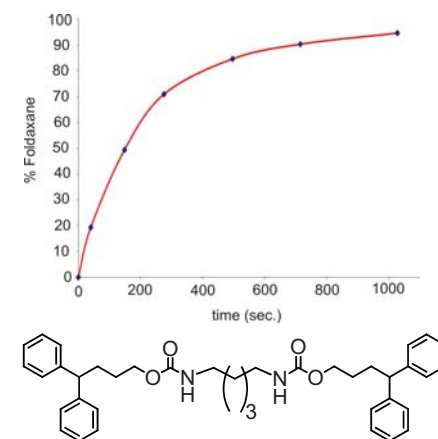
FOLDAXANES, Collab. H. Jang, Institute of Chemistry, CAS



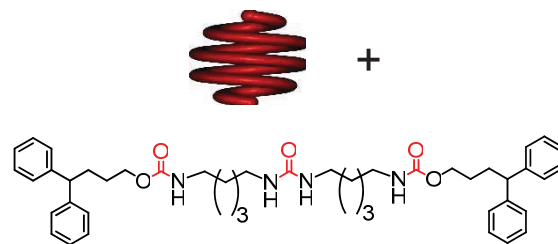
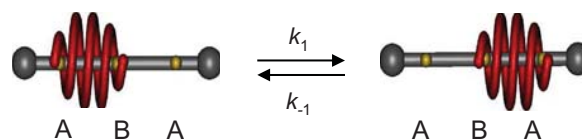
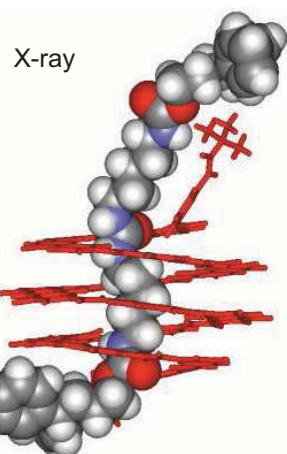
Too fast to monitor by NMR



Q. Gan, Y. Ferrand... *Science* **2011**, 331, 1172



A Helical Molecular Shuttle



Q. Gan, Y. Ferrand... *Science* **2011**, 331, 1172

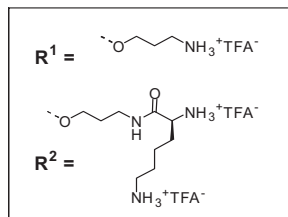
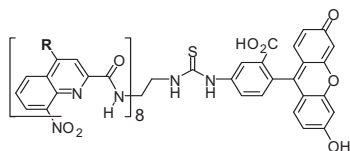
Folded Structures Dynamics & Assembly **Functions**



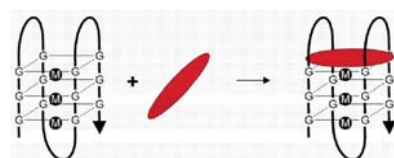
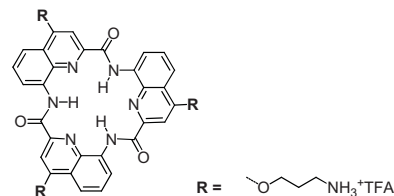
6 – Biopolymer recognition

Biological studies – nucleic acid recognition

Collab. C. Staedel (Univ. Bordeaux), S. Balasubramanian (Univ. Cambridge)



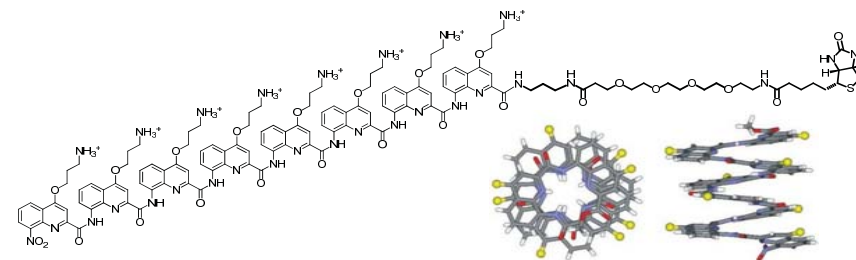
- 1) No degradation by proteases
- 2) Low toxicity to HeLa cells
- 3) Spontaneous cell internalization
- 4) Binding to G-Quadruplex DNA:
 - high selectivity vs. duplex DNA
 - record high affinity (ΔT)



E. Gillies... *Angew. Chem. Int. Ed.* **2007**, 46, 4081
 P. Shirude... *J. Am. Chem. Soc.* **2007**, 129, 11890
 P. Jena... *J. Am. Chem. Soc.* **2009**, 131, 12522
 J. Irlondo... *ChemBioChem* **2010**, 11, 1679

Deciphering foldamer-DNA interactions by SELEX

Collab. J.-J. Toulmé, Univ. Bordeaux



Selex:

- 30 nucleotide random window
- 10 selection rounds
- 60 sequences cloned
- **15 G-rich sequences found**
- parallel G-quadruplex conformations
- sub μ M binding to foldamer in 1 M KAc
- diastereoselectivity
- DNA vs RNA selectivity
- G-quadruplex sequence selectivity

```
>7' *1  TGGGGGGGTTGGTGGGTGTCCTTTCITAC
>7' *27  TGGCTGCTTGGTGGGGGTTGGGTATGTTG
>7' *34  CTAAGTCGGGGTTGGTCCGGGTGGGCACCT
>7' *36  TGTGCGGGGGGTTGGTGGGGGGGTGTTGT
>7' *43  TGGCTGTCCCGGGTGGTGGGTATGGTA
>7' *49  GACTGACITGGGGTGGTGGGGGGTCTCTCC
>7' *59  TTGTTTTTGGGTGGGTGGTGGGTAATGTG
>10' *6  GGAAGGTGGATTCTTGTTCGGTGGTGGTGG
>10' *14  GAACAGAGGGGGTGGGTGGTGGTGGTGGTA
>10' *26  GGCTTGATATTGGTGGTGGGTGGGTGGTGG
>10' *30  CGTTCGTCATAATTGGGCTGGGTGGAGGG
>10' *33  GGGTTGTCATCAGGGGGTGGGTGGAGGTT
>10' *34  TACAGTGGTGGTGGTGGCGTATTCACCTGG
>10' *42  CGTTTTTGGGTGGAGGGTGGGTGGTGGTGG
>10' *45  CAAGAAGGGGGTGGGCGGTGGTTCCTTTTC
```

L. Delaurière, Z. Dong... *Angew. Chem. Int. Ed.* **2012**, 51, 473

Take-home lessons

Aromatic oligoamides fold into very stable yet dynamic structures

Large sizes are well within reach of stepwise synthesis
 (up to ca 20 kDa so far)

Artificial backbones give access to patterns beyond the reach of natural polymers

Rational codes link primary sequence, 3D structure, and function

Selective recognition may occur between artificial backbones and biopolymers

Some chemical reactions are enhanced by folding

Collaborators

X-ray

Dr. B. Kauffmann
 Prof. J.-M. Léger
 Dr. S. Massip

Chirality

Prof. M. Takafuji ●
 Prof. H. Ihara ●

DCC

Dr. J. Nitschke ●

Mol. Capsules

Prof. H. Jiang ●
 Prof. D. Dubreuil

Biology

Dr. C. Staedel
 Dr. J.-J. Toulmé
 Prof. Balasubramanian ●

Current Lab. Members

Lecturer

Frédéric Godde

Research Associates

Yann Ferrand
 Victor Maurizot

Post-Docs

Krzysztof Ziach ●
 Michael Singleton ●

Chi Bo ●

Chandramouli Nagula ●

Simon Dawson ●

Tiny Deschrijver ●

PhDs

Christos Tsiamantas ●

Laure Sebaoun

Guillaume Lautrette

Quan Gan ●

Misae Kanai (visiting) ●

Funding

EU FP7 (People Program)

ANR

ARC

La Ligue

CNRS

Univ. of Bordeaux

Ministry of Research

Aquitaine Regional Council

Industry (Servier, UCB,
 Sanofi)