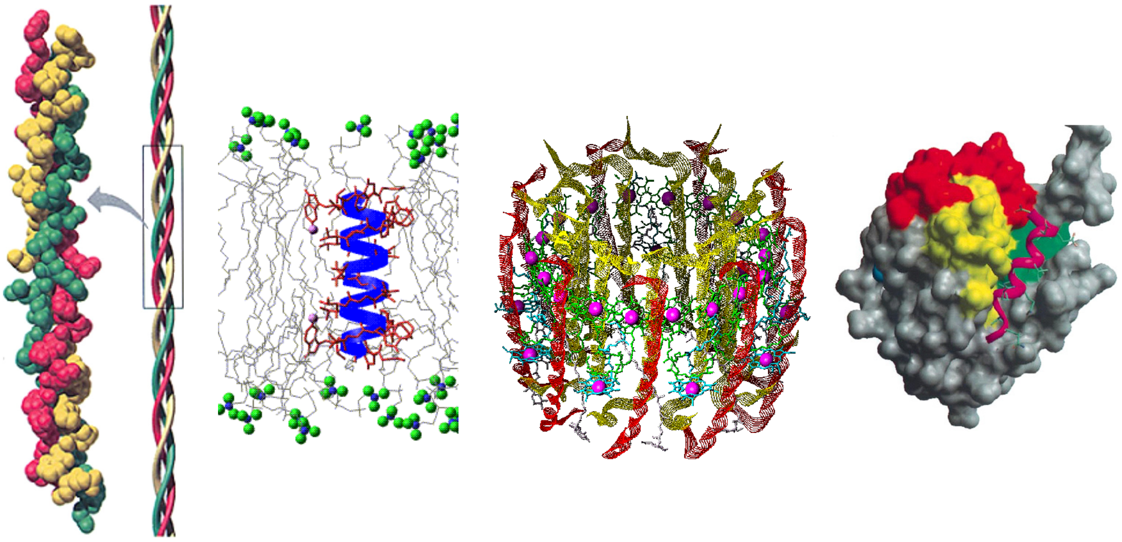
Chapter 1

Introduction

The ability of biomacromolecules to perform a variety of complicated functions such as information storage and molecular recognition is based on their ability to adopt specifically folded conformations. Synthetic macromolecules have been designed to mimic the structural and functional features of their superior biological counterparts. This chapter describes briefly the synthesis and properties of synthetic oligomers and polymers mimicking the important class of helical motifs.

Part of this chapter has been published: *Top. Curr. Chem.* **2005**, *245*, 89.

The helix is among the most abundant structural motifs in Nature due to its inherent chirality and advantageous geometric features. Oligonucleotide helices in form of double stranded DNA are responsible for storing and copying the genetic information and therefore carry out one of the most essential tasks in the organization of life. Peptide helices perform diverse biological functions including: (i) molecular recognition at the helix surface due to the well-defined arrangement of amino acid side chains, for instance mediating the Bak peptide – Bcl-x$_L$-protein interaction that regulates cell apoptosis related to the development of cancer;[1] (ii) selective chemical transport through the helix interior due to transmembrane channel forming properties, for instance illustrated by the gramicidin A channel;[2] (iii) mechanical strength due to formation of supramolecular superhelical fibers, for instance in the triple helical, bundled collagen cable;[3] (iv) scaffolding due to its inherent rigidity and well-defined binding sites, for instance used for the arrangement of the different bacteriochlorophyll pigments in the light harvesting complex II in bacteria (Figure 1).[4]



collagen fiber gramicidin A channel light-harvesting complex II Bak @ Bcl-X_L complex

Figure 1. Few examples of peptide helices performing complex biological functions in Nature.

The astonishing variety of naturally occurring helical motifs serves as inspiration for the design of artificial helices. Recent years have seen a tremendous progress in the design and synthesis of non-natural oligomers and polymers that mimic the structure and properties of natural biomolecules.

Synthetic polymers can exist in a variety of different conformations. These range from randomly coiled chains to more spatially ordered structures. Polymers with specific shape and conformation are attractive candidates for future technologies. For example molecular frameworks can be designed based on helical polymers for systematic arrangement of chromophores or functional groups in space that can be used for molecular recognition, catalysis or optical data storage.

Helical macromolecules can be classified in to two types, one that is inherently helical due to linkage geometry and steric requirements. This class is represented by helical polymers[5] for example polyisocyanides and polyacetylenes etc. The other class is comprised of flexible molecular chains that undergo conformational transition and adopt a helical structure dictated by non-covalent interactions between neighboring and/or non-neighboring repeat unit as well as entropic factors. This group is represented by foldamers.[6]

The first class (helical polymers) can further be divided into dynamic helical polymers and static helical polymers based on the helix inversion barrier. The helix inversion barrier can be defined as the activation energy required to convert one helical screw sense into the other. This barrier depends on several factors. The important factors are the size and steric nature of the side chains and the intrinsic stiffness of the polymer backbone. The polymers with a high inversion barrier exist as either right or left handed helices irrespective of their environment and racemize very slowly due to the high energy needed to overcome the barrier, while polymers with a low inversion barrier dynamically interconverts into right and left handed helices and leads to faster racemization.

Dynamic helical polymers

These polymers are characterized by having a low helix inversion barrier. Such polymers are inherently dynamic and can be used to construct ordered chiral objects that respond to different kinds of stimuli such as light, solvent or temperature. Examples of these kinds of polymers include polyisocyanates, polyacetylenes, polysilanes, etc.

Polyisocyanates[7]

The helical conformation of polyisocyanates is due to a combination of steric interactions and partial double bond character of the amide bond. The unfavorable steric interactions between oxygen atom of carbonyl group and substituent on nitrogen atom force the molecule to be non-planar (Scheme 1).

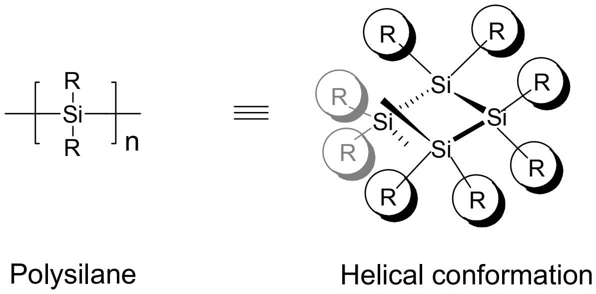
Scheme 1

These polymers have a persistent length of about 60 nm. This property makes them good materials for different kind of studies. Green and coworkers have studied polyisocyanates extensively and contributed significantly to the understanding of chiral amplification in macromolecules. They demonstrated the sensitivity of the helix sense to subtle bias in the chirality of the monomer. Substitution of a proton for a deuterium in the monomer induced a preferential helical sense in the resulting polymer (Kinetic Isotope Effect).[8] The same group discovered that the presence of even a small amount of chiral monomer induces the helical preference upon polymerization with the achiral monomer (Sergeant-Soldier Effect).[9] They also found that when a mixture of enantiomeric isocyanates with minor excess of one isomer was polymerized randomly, the monomer with slight majority dictated the helix sense in overall polymer chain (Majority rule).[10]

Polysilanes[11, 12]

Polysilanes are σ-conjugated polymers with interesting electronic properties. Polysilanes bearing small substituents exist as flexible chains but with bulky substituents the polymer adopts a 7_3 helical conformation (7 repeat units per 3 turns) (Scheme 2).[13]

Scheme 2



These are synthesized by sodium mediated reductive coupling reaction. It is demonstrated that the optoelectronic properties of these polysilanes are directly related to their conformation.[14, 15] For example the lowest Si (σ)–Si (σ∗) absorption band of polysilanes exhibits a logarithmic dependence on viscosity; (which influences the helical segment length) of the polymer. The properties of these polymers can furthermore be controlled by temperature and solvent.[16] While upon cooling, the number of helix reversals increases due to tightening of the chains, addition of poor solvent leads to aggregation. A very interesting and noteworthy feature of this polymer class is that the M-helical segments are more tightly wound (low helical pitch) than the P-helical segments and hence the optoelectronic properties of the two helices significantly differ from each other. The absorption band of M-helical segments is blue shifted compared to the P-helical segments. [17] This interesting phenomenon allowed the selective photolytic cleavage of M-helices in the presence of P-helices.

Polyacetylenes

Polyacetylenes have been the subject of intense theoretical and experimental studies due to their fascinating optical and conformational properties. Polyacetylenes can exist in four different conformations (Scheme 3).[18]

Scheme 3

cis-transoid *cis-cisoid*

trans-cisoid *trans-transoid*

The backbone conformation has a direct influence on the optical properties of these conjugated polymers. In case of *trans*-polyacetylene, the alternating double bonds are in one plane and hence the $\pi-\pi*$ transition occurs at low energy. However, when bulky substituted acetylene monomers are polymerized the resulting polymer adopts a helical *cis*-conformation, which shows high-energy visible absorption spectra due to the non-planarity of conjugated double bonds. The helical conformation arises due to the steric interaction between the substituents. These helices have typically short persistence length and a high number of helix reversals. These polymers can be synthesized by rhodium-catalyzed polymerization and found to be very stereoregular.[19] However, other catalyst system such as molybdenum results in an irregular stereochemistry of the molecular chain. These findings were proved by the optical activity of the resulting polymer. A variety of non chiral polyacetylenes were also prepared by Okamoto and Yashima. They demonstrated the helicity induction in achiral polyacetylene by complexation with small chiral molecules.[20] This helicity induction is transcribed to the polymers and remains even when the chiral entities are removed from the solution (Figure 2).

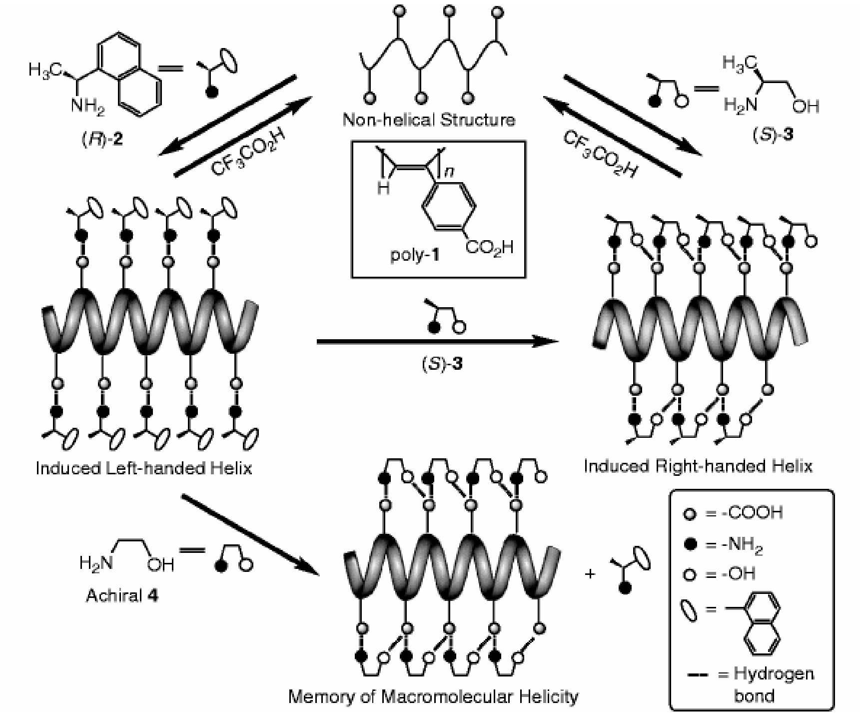


Figure 2. Schematic representation of helicity induction in polyacetylene-1. Complexation of (*R*)-2 (middle left) and (*S*)-3 (middle right) can induce single handedness which is memorized by the polymer (bottom).

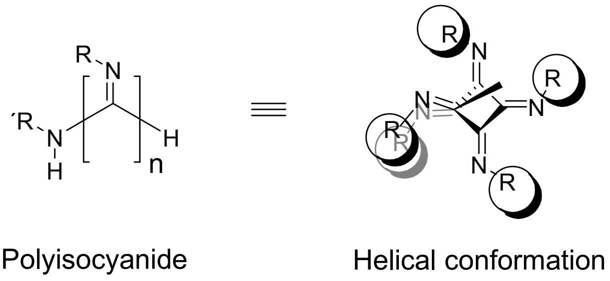
Stable helical polymers

When the helix inversion barrier of the polymer is high, the helical conformation is formed under kinetic control. This means that during polymerization the growing chain is ordered and helical and each incoming monomer adds to the helix in a defined stereochemical fashion. Examples of these kinds of polymers include poly(methacrylates), polyisocyanides, polyaldehydes, binaphthyl based polymers etc.

Polyisocyanides[21]

Each carbon atom of polyisocyanides bears a double bond to nitrogen atom. This restricts the rotation around the adjacent C-C single bonds and results in the formation of stable and rigid helices with 4_1 helical conformation (4 repeat units per turn) (Scheme 4).

Scheme 4

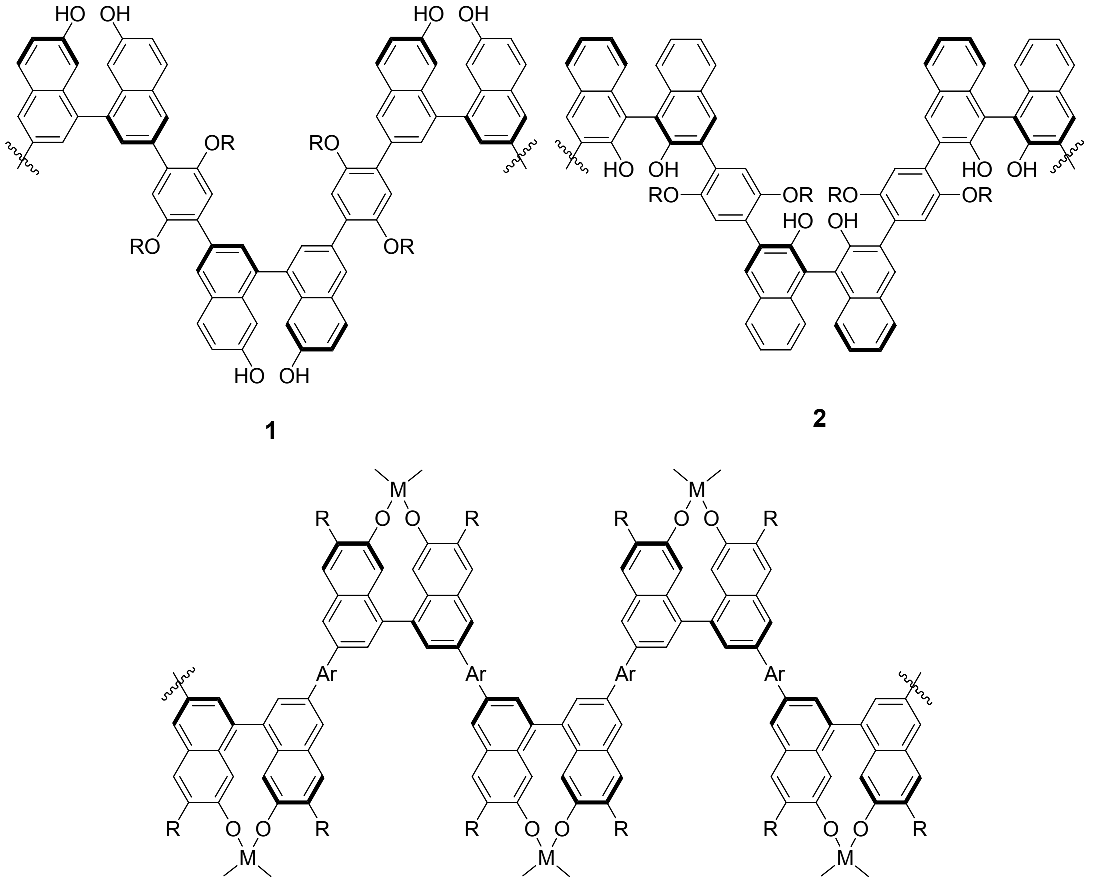


These polymers can be prepared via nickel-catalyzed polymerization.[22] The polymerization is initiated by a nucleophile (an amine or alcohol) and during the reaction the isocyanide monomers coordinates to the metal center and get incorporated into the growing chain by a series of consecutive insertion reactions. Studies have shown that polyisocyanide helix is only stable when sterically demanding side chains are present. The helix gets slowly denatured in solution if less bulky side chains are present. An interesting variant of polyisocyanides are polyisocyanopeptides.[23] These polymers are decorated with peptide side chains. The amide groups in the side chain form intramolecular hydrogen bonds to their neighboring (n+4) side chain and impart additional stability to the helix. Interestingly, these hydrogen bonds remain intact even in aqueous environment. The unfolding of polymer in water is found to be cooperative. However, this unfolding is irreversible and only local order of the side chains can be regained. Block copolymers containing polyisocyanopeptides and carbosilane dendrimers exhibit selective binding to silver ions. Polyisocyanopeptides have also been used as molecular scaffold for arrangement of chromophores such as thiophenes,[24] porphyrins,[25] and perylenes[26] in space.

Binaphthyl based polymers[27]

These polymers are relatively different from the helical polymers discussed so far. The chirality in binaphthyl-based polymers is a result of molecular geometry of the monomer. The conformation has a significant effect on the optical properties of these polymers. The UV and CD spectra of high molecular weight polymers are very intense relative to the low molecular weight parent compounds. A number of analogues were synthesized with different conjugated molecules as linkers in between the binapthyl groups (Scheme 5).

Scheme 5



1 **2**

3

The helical pitch, optical and catalytic properties can be finely tuned by choice of a suitable linker. Introduction of *meta*-phenyl ring leads to an extra turn in one helical pitch. *Para*-linked conjugated molecules, such as phenylene vinylenes, polythiophenes, oligophenylenes and oligoethynylenes, result in larger degree of conjugation and lower band-gap materials. These rigid helical polymers have been used to anchor catalytic complexes via the free hydroxyl groups.[28] The role of conformation is important while acting as scaffold for the catalyst. Better catalytic properties have been found when the linkers are placed at 3-3′ position (**3**, Scheme 5) than on 6-6′position. This can be explained as follows. In former case the catalytic centers (hydroxyl groups bind to the catalyst) are well placed on the periphery of the helix, well-exposed to the reaction medium and in the later case the catalytic centers are hidden in the cavity of the helix. Good yields and excellent enantioselectivities have been observed for reaction such as asymmetric reduction of aldehydes and epoxidation of α-β unsaturated ketones when these helical polymers are used as catalytic centers. A mixed Ru(III)-Zn(II) catalyst was able to carry out an asymmetric tandem reaction involving a diethylzinc addition to acetylbenzaldehyde and the subsequent catalytic hydrogenation to the corresponding diol in 99% yield with 75-87% distereoselectivity.

Foldamers[6]

Foldamers are oligomers that fold into a conformationally well-ordered state in solution. Due to the fast growing nature of this field of research, it is difficult to cover all different kinds of foldamers reported so far. We will focus only on foldamer[29] based on oligo(phenylene ethynylene)s (OPE) due to the relevance of the work presented in this thesis.

The helical secondary structure of OPE in polar organic solvents such as acetonitrile is caused by the meta-connectivity of the backbone, π,π-stacking interactions between aromatic moieties in adjacent turns as well as segregation of the polar triglyme side chains and the non-polar phenylacetylene scaffold. In solution, an ESR study investigating line broadening as a function of the number of connecting repeat unit between two spin labels suggests that each turn is comprised of six repeat units.[30] This conformation gives rise to a tubular cavity measuring ~7 Å in diameter (Figure. 3).[31]

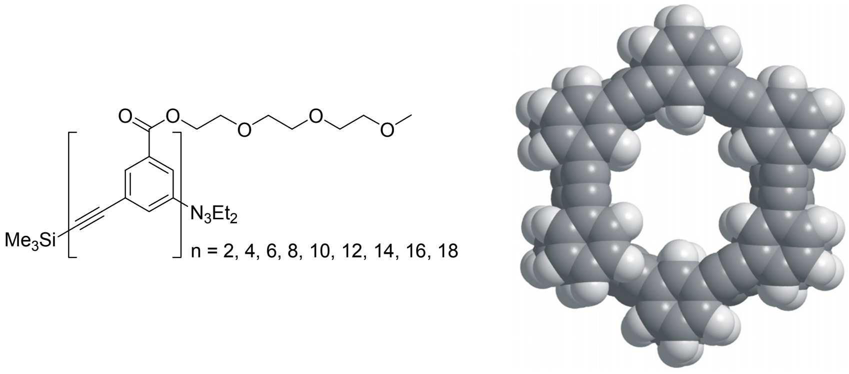


Figure 3. Moore’s amphiphilic oligo(*meta*-phenylene ethynylene)s and model of the octadecamer adopting a helical conformation (side chains are omitted for clarity).

Given the *meta*-connectivity of the backbone, several parameters have been varied and their influence on helix stability investigated. The strength of the π,π-stacking interactions can be adjusted by changing the electron density in the aromatic ring system.[32-33] Only in the case of the electron-deficient ester substituents favoring aromatic stacking, [34] helical structure formation could be observed. Additional non-covalent interactions such as H-bonding or interior metal ion binding (vide infra) can be implemented in the backbone. Also, the amphiphilicity of the system can be reversed as illustrated by incorporation of non-polar alkyl side chains that lead to folding in hydrocarbon solvents.[35] Solvents in general play a critical role and their ability to fold as well as unfold the OPE backbone has been studied in detail.[36]

Convenient optical monitoring of the conformational transition by means of UV/vis absorption as well as fluorescence spectroscopies has been established for this backbone.[29, 37] (Figure. 4). While cisoid and transoid conformations display different absorption spectra, isolated and stacked cross-conjugated monomer units show direct and excimer-like emission, respectively. The helix-coil transition is temperature dependent, however more sensitive to changes of solvent composition. Respective solvent denaturation experiments show a clear chain length dependence of the folding process (Figure. 4, bottom). Starting at the dodecamer, the helix-coil transition both sharpens and shifts to larger amounts of denaturant for higher oligomers. Quantitative analysis shows a linear relationship between chain length and helix stabilization energy as expected by the helix-coil theory.[38] An incremental stabilization energy $\Delta G \sim 0.7$ kcal/mol per repeat unit has been calculated from the data.[37] The observed high degree of cooperativity was quantified and is comparable to that of α-helix formation in protein folding.

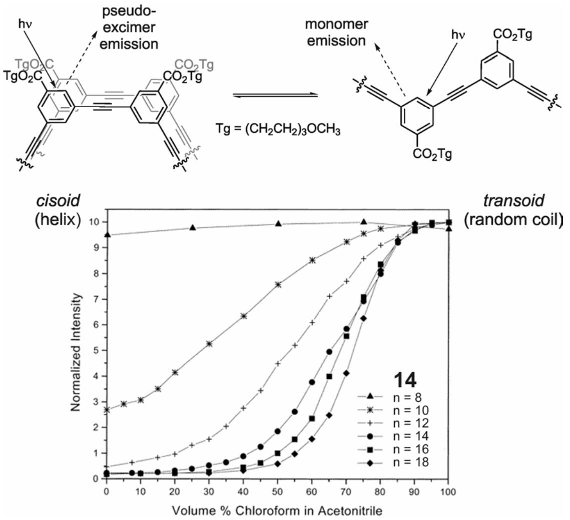


Figure 4. *Ciscoid* and *transoid* conformations reflecting the helix-coil transition (top). Solvent denaturation experiments demonstrate a chain length dependent, cooperative folding of oligo(*meta*-phenylene ethynylene)s.

The bias of the twist sense of the helical conformation has been achieved by introducing chiral units either in the main or side chains. One of the two resulting diastereomeric helices is energetically favored and causes excess helicity conveniently monitored by CD spectroscopy. While enantiopure binaphthol segments[39] as well as tartrate-based linkers[40] have been incorporated in the main chain, chiral polar[41] and non-polar side chains[35] have been attached to the backbone as well. Remarkably, a single extra methyl group in the chiral side chains is able to transfer its chirality to the backbone in a highly cooperative fashion. In 'sergeants and soldiers' experiments it was found that the intensity of the CD signal is not linearly depending on the amount of chiral side chains.[42] Although only a small amount of chiral side chains is needed to induce significant Cotton effects, the values displayed by the corresponding homochiral oligomers could not be achieved.

Host-guest interactions involving guests of complementary size and shape that fit into the inner cavity of the helically folded host have been extensively explored. For example, the foldamer receptor has been decorated with nitrile functionalities that bind two silver ions at the interior to provide an additional driving force for helix formation.[43] In another example, induction of chirality has been achieved in polar solvents by binding either $+\alpha$-pinene or $-\alpha$-pinene in a 1:1 ratio to the internal hydrophobic surface of OPE dodecamer.[44] The resulting enantiomeric complexes cause characteristic and opposite CD spectra. Also, the binding of rod-like guest molecules such as cis-(2S,5S)-2,5-dimethyl-N,N'-diphenylpiperazine within the tubular cavity was found to be chain length dependent indicating that maximizing the area of contact determines affinity.[45]

Combining the length specific binding with dynamic covalent synthesis[46] by taking advantage of reversible imine metathesis, template-controlled, size-selective oligomer synthesis of foldamer receptors has been demonstrated.[47] Utilizing further elongated templates, this supramolecular approach should in principle allow for the synthesis of well-defined oligomers of tremendous length. Under equilibrium conditions and in the absence of a template, monomer addition can solely be driven by the free energy gain due to helix formation[48] as could be demonstrated for the case of folding-driven synthesis of oligomers[49, 50] and polymers by imine metathesis.[51, 52]

Aim and Organization of this Thesis

The aim of the work presented in this thesis is to develop more efficient methods for the synthesis of oligomers and polymers that can adopt stable secondary conformations in solution, to gain a more profound understanding of their folding behavior, and to utilize the reversible helix-coil transition for tubular scaffolding and the design of stimuli-responsive materials.

Chapter 2

The folding of oligo(phenylene ethynylene)s has already been discussed in the general introduction. We aimed to extend this concept to the polymer level. The problems associated with the synthesis of high molecular weight *meta*-PPEs and relatively few examples in literature motivated us to develop a new synthetic method. Chapter 2 describes this method to access high molecular weight *m*-PPEs.

Chapter 3

The reversible helix-coil transition in foldamers allows to populate the global minimum structure and therefore provides a means to repair local defects. However, from a materials standpoint this reversibility might also constitute a disadvantage with regard to structural integrity and hence device stability/lifetime under a variety of environmental conditions. Chapter 3 describes the synthesis and post-functionalization of a *m*-PPE foldamer to furnish covalently stabilized helical structures.

Chapter 4

Identification of new folding backbones and their synthesis present a challenging task. Chapter 4 describes the synthesis of *ortho*- linked PPEs. The synthesis takes advantage of our method (chapter 2) to synthesize defect free PPEs.

Chapter 5

The helix-coil equilibrium in synthetic foldamers have been governed so far by quality of solvent, temperature, hydrogen bonding and metal complexation. We have demonstrated the possibility of using light as an external stimulus to control the secondary conformation of azobenzene-containing foldamers. Chapter 5 describes the synthesis and photoresponsive properties of these oligomers.

Chapter 6

The electroluminescent and photoluminescent properties of conjugated polymers have made them attractive candidates for organic electronics. However, the presence of defects in a polymer incorporated during synthesis can be harmful to the lifetime and performance of a device. With a good method in hand, Chapter 6 describes our synthesis of site-isolated, defect-free, and water soluble *para*-linked PPE, which shows remarkable fluorescence efficiency in water.

References

1 M. Sattler, H. Liang, D. Nettesheim, R. P. Meadows, J. E. Harlan, M. Eberstadt, H. S. Yoon, S. B. Shuker , B. S. Chang, A. J. Minn, C. B. Thompson, S. W. Fesik, *Science*. **1997**, *275*, 983.

2 R. R. Ketchem, W. Hu, T. A. Cross, *Science*. **1993,** *261*,1457.

3 D. S. Jackson, M. E. Grant, *Nature*. **1974**, *249*, 406.

4 G. McDermott, S. M. Prince, A. A. Freer, A. M. Hawthornthwaite-Lawless, M. Z. Papiz, R. J. Cogdell, N. W. Isaacs, *Nature*. **1995,** *374*, 517.

5 T. Nakano, N. Okamoto, *Chem. Rev*. **2001,** *101*, 4013.

6 D. G. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev*. **2001,** *101*, 3893.

7 (a) M. Goodman, S. Chen, *Macromolecules*. **1970**, *3*, 398. (b) M. Goodman, S. Chen, *Macromolecules*. **1971,** *4*, 625.

8 M. M. Green, N. C. Peterson, T. Sato, A. Teramoto, R. Cook, S. Lifson, *Science*. **1995**, *268*, 1861.

9 M. M. Green, M. P. reidy, G. Johnson, D. J. O'Leary, G. J. Wilson, *J. Am. Chem. Soc.* **1988**, *111*, 6452.

10 M. M. Green, B. A. Garetz, B. Meunoz, H. Chang, S. Hoke, R. G. Cooks, *J. Am. Chem. Soc.* **1995**, *117*, 4181.

11 R. D. Miller, J. Michl, *Chem. Rev*. **1989,** *89*, 1359.

12 A. Sen, *Acc. Chem. Res.* **1993**, *26*, 306.

13 P. Pino, F. Ciardelli, G. P. Lorentzi, G. J. Natta, *J. Am. Chem. Soc.* **1962**, *84*, 1487.

14 H. Teramae, K. Takeda, *J. Am. Chem. Soc.* **1989**, *111*, 1281.

15 M. Fujiki, *J. Am. Chem. Soc.* **1996**, *118*, 11345.

16 M. Fujiki, S. Toyoda, C. H. Yuan, H. Takigawa, *Chirality*. **1998**, *10*, 667.

17 M. Fujiki, *J. Am. Chem. Soc*, **1994**, *116*, 6017.

18 C. I. Simionescu, V. Percec, *Prog. Polym. Sci*. **1982**, *8*, 133.

19 M. Tabata, Y. Inaba, K. Yokota, Y. Nozaki, *J. Macromol. Sci.,Pure Appl. Chem.* **1994**, *A31*, 465.

20 E. Yashima, Y. Maeda, Y. Okamoto, *Nature*. **1999**, *399*, 499.

21 R. J. M. Nolte, A. J. M. van Beijen, W. Drenth, *J. Am. Chem. Soc.* **1972**, *96*, 5932.

22 R. J. M. Nolte, W. Drenth, In New Methods for Polymer Synthesis; Plenum Press, New York, **1992**, Chapter 9, p 273.

23 J. J. L. M. Cornelissen, J. J. J. M. Donners, R. de Gelder, W. S. Graswinckel, A. E. Rowan, N. A. J. M. Sommerdijk, R. J. M. Nolte, *Science*. **2001**, *293*, 676.

24 D. M. Vriezema, J. Hoogboom, K. Velonia, K. Takazawa, P. C. M. Cristianen, J. C. Mann, A. E. Rowan, R. J. M. Nolte, *Angew. Chem. Int. Ed.* **2003**, *42*, 772.

25 P. A. J. de Witte, M. Castriciano, J. J. L. M. Cornelissen, L. M. Scolaro, R. J. M. Nolte, A. E. Rowan, *Chem. Eur. J.* **2003**, *9*, 1775.

26 J. Hernando, P. A. J. de Witte, E. M. H. P. van Dijk, J. Korterik, R. J. M. Nolte, A. E. Rowan, M. F. Garcia-Parajo, N. F. van Hulst, *Angew. Chem. Int. Ed.* **2004**, *43*, 4045.

27 L. Pu, *Chem. Rev.* **1998,** *98*, 2405.

28 H. B. Yu, S. Q. Hu, L. Pu, *J. Am. Chem. Soc*. **2000**, *122*, 6500.

29 J. C. Nelson, J. G. Saven, J. S. Moore, P. G. Wolynes, *Science*. **1997**, *277*, 1793.

30 K. Matsuda, T. M. Stone, J. S. Moore, *J. Am. Chem. Soc*. **2002**, *124*,11836.

31 The inner diameter has been calculated from X-ray crystallographic or modeling data by measuring the distance between opposing atoms at the inner rim, correcting for the helical pitch, and subtracting the corresponding van der Waals radii.

32 C. A. Hunter, K. R. Lawson, J. Perkins, C. J. Urch, *J. Chem. Soc. Perkin. Trans*. **2001**, *2*. 651.

33 E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem. Int. Ed. Engl*. **2003**, *42*, 1210.

34 S. Lahiri, J. L. Thompson, J. S. Moore, *J. Am. Chem. Soc*. **2000,** *122*, 11315.

35 L. Brunsveld, R.B. Prince, E. W. Meijer, J. S. Moore, *Org. Lett.* **2000,** *2*, 1525.

36 D. J. Hill, J. S. Moore, *Proc. Natl. Acad. Sci*. **2002**, *99*, 5053.

37 R. B. Prince, J. G. Saven, P. G. Wolynes, J. S. Moore, *J. Am. Chem. Soc*. **1999**, *121,* 3114.

38 B. H. Zimm, J. K. Bragg, *J. Chem. Phys.* **1959**, *31*, 526.

39 M. S. Gin, T. Yokozawa, R. B. Prince, J. S. Moore, *J. Am. Chem. Soc.* **1999**, *121*, 2643.

40 M. S. Gin, J. S. Moore, *Org. Lett*. **2000,** *2*, 135.

41 R. B. Prince, L. Brunsveld, E. W. Meijer, J. S. Moore, *Angew. Chem. Int. Ed. Engl.* **2000,** *39*, 228.

42 R. B. Prince, J. S. Moore, L. Brunsveld, E. W. Meijer, *Chem. Eur. J.* **2001,** *7*, 4150.

43 R. B. Prince, Okada T, J. S. Moore, *Angew. Chem. Int. Ed. Engl.* **1999,** *38*, 233.

44 R. B. Prince, Barnes SA, J. S. Moore, *J. Am. Chem. Soc.* **2000,** *122*, 2758.

45 A. Tanatani, M. J. Mio, J. S. Moore, *J. Am. Chem. Soc.* **2001,** *123*, 1792.

46 S. J. Rowan, S. J. Cantrill, G. R. L Cousins, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem. In.t Ed. Engl.* **2002,** *41*, 899.

47 T. Nishinaga, A. Tanatani, K. Oh, J. S. Moore, *J. Am. Chem. Soc.* **2002,** *124*, 5934.

48 D. Zhao, J. S. Moore, *Org. Biomol. Chem.* **2003,** *1*, 3471.

49 K. Oh, K-S. Jeong, J. S. Moore, *Nature.* **2001,** *414*, 889.

50 K. Oh, Jeong K-S, J. S. Moore, *J. Org. Chem.* **2003,** *68*, 8397.

51 D. Zhao, J. S. Moore, *Macromolecules.* **2003,** *36*, 2712.

52 D. Zhao, J. S. Moore, *J. Am. Chem. Soc*. **2003,** *125*, 16294.