FOLDING ARCHITECTURES CONTAINING PHENYLENE ETHYNYLENE OLIGOMERS AND POLYMERS

INAUGURAL – DISSERTATION

zur Erlangung des akademischen Grades
Doktor der Naturwissenschaften
Dr. rer. nat.

des Fachbereichs
Biologie, Chemie und Pharmazie
der Freien Universität Berlin

vorgelegt von
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im August 2006

Die vorliegende Arbeit wurde in der Zeit von September 2002 bis Dezember 2004 am Institut für Chemie/Organische Chemie der Freien Universität Berlin und von Januar 2005 bis August 2006 am Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr unter der Anleitung von Herrn Priv.-Doz. Dr. Stefan Hecht durchgeführt.

1. Gutachter: Priv.-Doz. Dr. Stefan Hecht

2. Gutachter: Prof. Dr. Rainer Haag

Tag der Disputation: 19.10.2006

„Die Grenzen des Möglichen lassen sich nur dadurch bestimmen,
dass man sich ein wenig über sie hinaus ins Unmögliche wagt.“

Arthur C. Clarke

Danksagung

Herrn Dr. Stefan Hecht danke ich für die interessante Themenstellung, die Bereitstellung der hervorragenden Arbeitsbedingungen und vor allem die stets freundliche und engagierte Betreuung. Ohne die vielen anregenden fachlichen als auch privaten Gespräche wäre diese Zeit nur halb so lehrreich gewesen.

Meinen langjährigen Laborkollegen Sebastian Hartwig, Christian Kaiser, Anzar ul haq Khan, Robert Meudtner, Maike Peters und Ragnar Stoll möchte ich für die gute, kooperative Zusammenarbeit und die fortwährend nette Atmosphäre danken. Mit ihnen hat die Zeit im und außerhalb des Labors sehr viel Spaß gemacht.

Herrn Prof. Dr. A.-D. Schlüter und den Mitgliedern seiner Arbeitsgruppe möchte ich für das offene Entgegenkommen, den fachlichen Rat und die Unterstützung bei jedweder Art von Problemen danken.

Allen Mitarbeitern des Instituts für Organische Chemie, FU Berlin, sowie den Mitarbeitern der Serviceabteilungen am MPI für Kohlenforschung danke ich für die zuverlässig und freundlich vollbrachten Serviceleistungen.

Insbesondere unseren Festangestellten in Mülheim möchte für ihre Unterstützung, Herrn Hauschild für die verlässlichen GPC-Messungen sowie Herrn Blumenthal für spontane praktische und organisatorische Hilfestellungen, danken.

Ein großer Dank geht an die Studienstiftung des deutschen Volkes, die mich ideell und finanziell unterstützt hat.

Besonderen Dank gilt natürlich meiner Familie, insbesondere meinen Eltern, Muma und Tante Lotti, die mich immer während meines Studiums und meiner Doktorarbeit unterstützt haben, sowie meiner Freundin Maike.

Schließlich möchte ich noch all meinen Freunden inner- und außerhalb meiner Schaffensstätten danken für die schöne und abwechslungsreiche Zeit, die wir zusammen während dieser ganzen Zeit hatten.

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1 Introduction

1.1 On the Generation of Nanoobjects

The continuously accelerating miniaturization of any kind of man-made device – but especially in electronic technology – continues to have a major impact on the technological and economical development and the medicinal, ecological, cultural, and social advances. Being the key driving force in the emerging field of nanotechnology,[1] the limits of further miniaturization of established so-called top-down fabrication methodologies are nearing, and research and engineering is beginning to sketch the potential of bottom-up approaches starting at the atomic or molecular level to design nanoobjects of defined shapes and dimensions,[2] as already envisioned by Feynman in his famous talk "There is Plenty of Room at the Bottom"[3] (Figure 1). In the last half century, the field of macromolecular chemistry has matured while the understanding of supramolecular chemistry has made tremendous progress. The merging of both disciplines represents the most promising approach to design discrete shape-persistent nanoobjects via self-assembly, generate long-range patterns via intermolecular forces at interfaces, and at the same time introduce, locally fix, and control functionality via the varying chemical composition of macromolecules (e. g. heterosequence of polymer strands) and the static or dynamic organization at the intra- and supramolecular level (e. g. assembly modes, conformations, segregation).

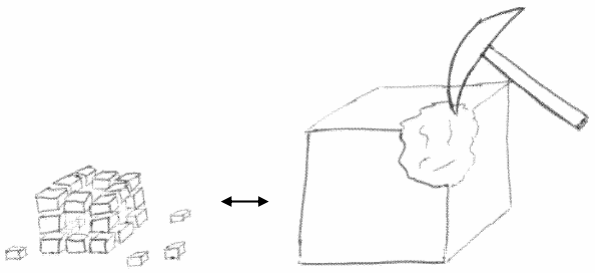

Figure 1: Cartoon illustrating the difference of bottom-up (left) and top-down (right) approaches to nanosized objects.

Every construction of complex three-dimensional nanoobjects out of macromolecules requires the complete control at all hierarchical levels (Figure 2). Not only is the correct formation of chemical bonds during the build-up of a macromolecule important, influencing parameters like degree of polymerization, length dispersity, branching, and tacticity. Also the conformation of the macromolecule driven by intramolecular forces and environmental stimuli leading to the secondary structure has to be considered, determining shape and flexibility or rigidity of the generated object. On the tertiary structure level, long-range

intramolecular forces and other subtle hardly predictable interactions further shape the molecular entity, and finally the forces of intermolecular self-assembly and self-organization lead to the quaternary structure and generate the amazingly complex constructs of materials and machinery found in Nature.

The controlled construction of complex supramolecular architectures with macromolecules resembles an exciting field of research trying to unravel Nature's secrets, to mimic its design principles, hierarchical order, and highly selective and specific functions, and in the end to freely design and construct custom-tailored novel materials.[4]

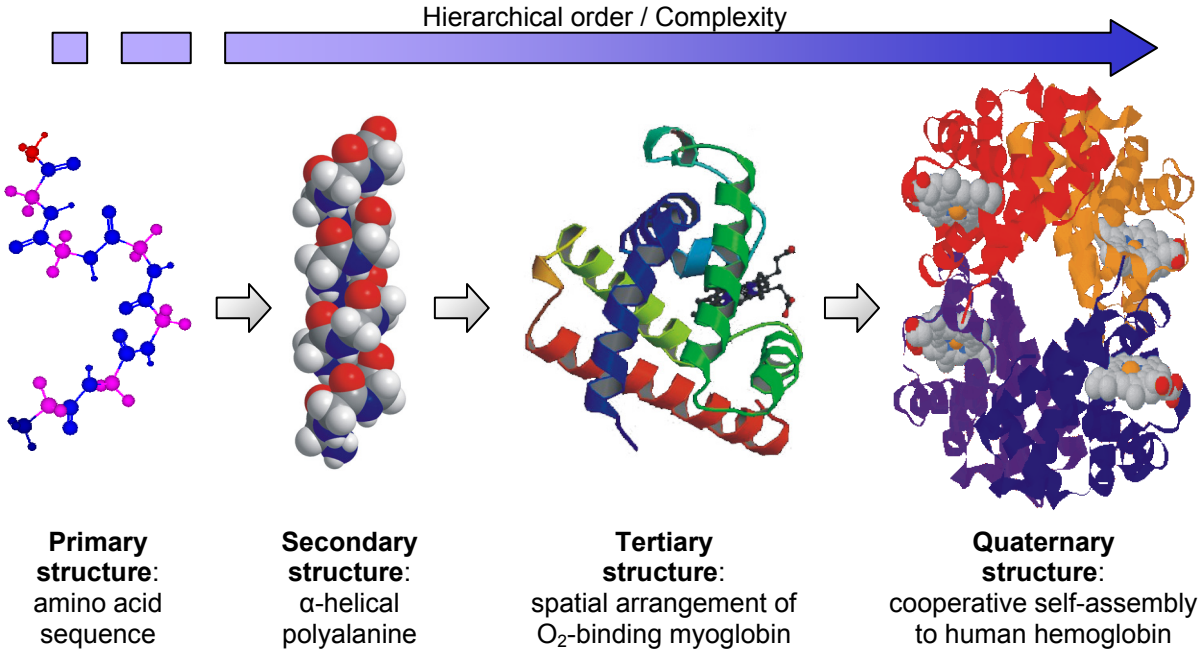

Figure 2: Hierarchical order in the construction of nanoobjects in whole's Nature.

1.2 Helices in Nature

Nature handles the fabrication of well-defined macromolecules possessing highly hierarchic structures with ease and elegance, while synthetic systems still struggle to imitate size and shape control, monodispersity, durability, and most important function. Even when natural systems are prone to decay, accompanying mechanisms for continuous repair or replacement are available.

Surprisingly from a chemical point of view, Nature restricts itself to a relatively small set of building blocks for biopolymers, e. g. the immense multitude of peptides and proteins for any imaginable function are generated out of a pool of 20 amino acids only, all solely present as the *L*-configured enantiomers. Most often it is the tertiary and quaternary structure that generates sophisticated (bio-)chemical functions since on the lower secondary structure level

there is not enough structural variation to allow for full freedom in arrangement of functional groups and generation of selective and specific active sites among other. As an even more drastic example, the DNA strand consists of only four nucleic acid-based building blocks to safely and redundantly encode the entire genetic code of every living entity. Its flexible hierarchical order and self-complementarity allow for replicating and securing the encoded information via single and double stranded conformations, respectively, as well as for gene regulation via supra-structural configurations like loops and supercoils.

The above examples heavily rely on a helical secondary structure and the helix represents by far the most frequently occurring secondary structural motif, used by Nature for a multitude of purposes. Examples for helices' versatile utility include the double stranded DNA (Figure 3, a) storing and securing genetic information,[5] the triple helical bundled collagen cable (Figure 3, b) providing mechanical strength and stability in bone and tissue,[6] the Bak peptide - Bcl-x_L complex (Figure 3, c) regulating cell processes via protein interactions related to cell apoptosis,[7] the light harvesting complex II (Figure 3, d) leading to scaffolding of complex arrangements of different bacteriochlorophyll pigments via the helices' inherent rigidity and well-defined binding sites,[8] as well as the gramicidin A channel (Figure 3, e) allowing for selective transport of chemicals through cell membranes.[9]

Mimicking such helices and tubular structures with artificial, man-made constructs is of great interest. To control their inherent geometric features such as aspect ratio, rigidity, inner

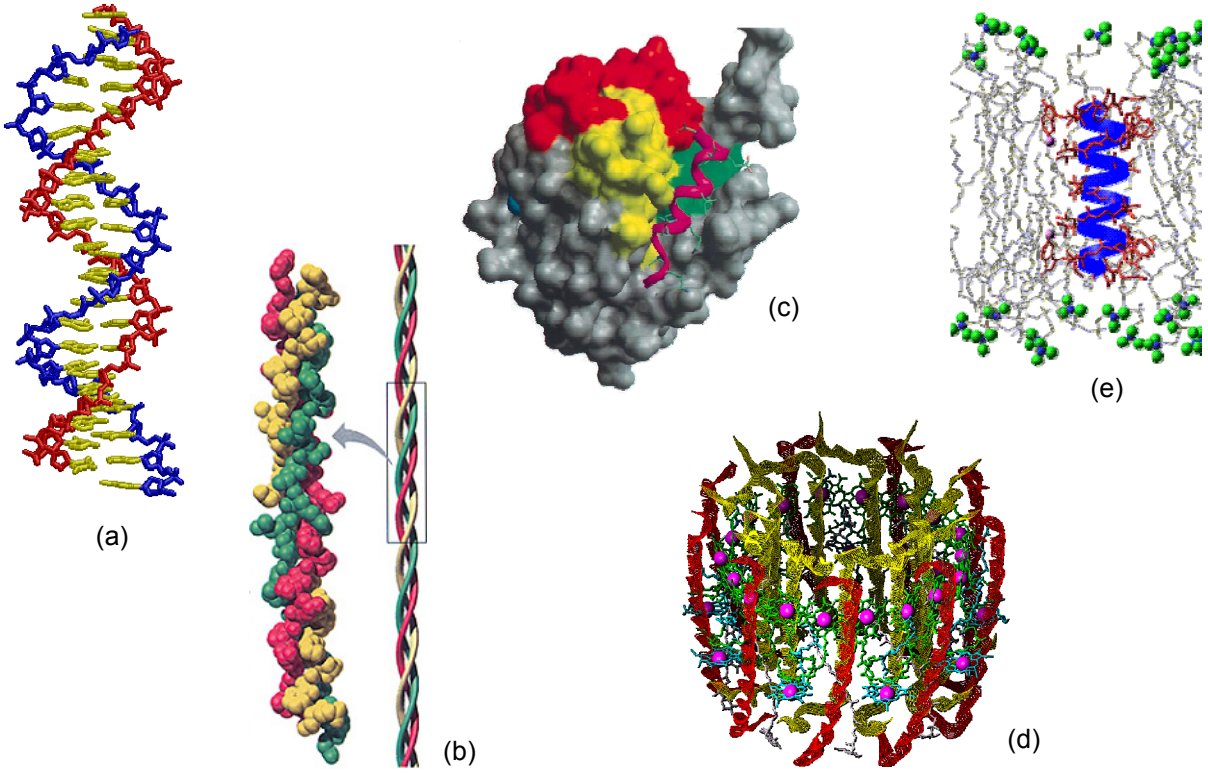

Figure 3: Helical motifs in Nature: (a) dsDNA, (b) collagen, (c) Bak@Bcl-X_L complex, (d) light harvesting complex II, and (e) gramicidin A channel.

cavity, defined inner and outer surfaces, and spatial segregation represents a major challenge for chemists, and diverse helical and tubular designs including purely covalent as well as fully self-assembly-based approaches have been reviewed.[10]

1.3 Synthetic Helical Polymers and Foldamers

Synthetic helical macromolecules can be classified in two categories: classic helical polymers on one hand and more sophisticated foldamers on the other hand. Helical polymers gain their helicity mainly from steric repulsions of side chains that force the linear backbone into a curved conformation, thereby inducing a screw sense. Depending on the inversion barrier between left- and right-handed helices, flexible and stiff helical polymers are differentiated. Polyacetylenes, polyvinylenes (i. e. polystyrene- and polyacrylate-derivatives), polyisocyanides, polyisocyanates, polyaldehydes, and polysilanes belong to this class of polymers (Figure 4).[11, 12]

Figure 4: Helical polymers: generic backbone of a polyacetylene, polyvinylene, polyisocyanide, polyisocyanate, polyaldehyde, and polysilane (from left to right).

The term "foldamer" is restricted to oligomers and polymers that adopt a helical conformation because of attractive non-covalent interactions including H-bonding, aromatic π-stacking,[13] metal coordination, or solvophobic forces. As foldamers represent the more sophisticated class of helices, a short introduction into this field of macromolecules will be given here, whereas excellent reviews by Moore[14] and Gellman[15] should be consulted for further in-depth information.

Closest to natural helices are artificial peptides based on natural and non-natural α-, β-, and higher amino acids. Here, the restricted conformational space available due to the rigidity of amide bonds and directing and stabilizing H-bonding interactions lead to the formation of α-helices[16] and β-helices.[17] A major class of foldamers is represented by aromatic oligoamides, where aromatic units are mostly connected via *meta*-linkages and forced by H-bonding interactions between neighboring repeat units into helical conformations stabilized by aromatic π-π-interactions.[18] For example, Gong and coworkers reported on helical diarylamides (Figure 5, A) with either *meta*- or alternating *meta-para*-connectivity displaying helical conformations via outer-rim H-bonding and allowing for tuning of the inner cavity.[19] Folding among diaminopyridine-pyridinedicarboxamide oligomers driven by internal H-bonding between pyridine-nitrogens and amide-hydrogens (Figure 5, B) has been studied by

the group of Huc,[20] and switching between different helical conformations via the degree of pyridine protonation has been demonstrated.[21] The repulsion of both nitrogens on 2,2'-bipyridines has also been utilized as driving force to fold *meta*-connected pyridine-pyrimidine systems (Figure 5, C).

Helicates[22] represent supramolecular coordination compounds, where linear oligomer strands possessing ligand sites such as bipyridines or catechols bind to metal centers and arrange them in linearly spaced fashion. Bi- and tridentate chelating ligands in combination with tetrahedrally or octahedrally coordinating metal ions possess a helical twist, thus leading to a helical conformation of the macromolecular backbone around the metal centers forming double or triple stranded helicates (Figure 5, D). Similarly, oligo(indole ethynylene)s were reported to wrap around chloride anions in a helical fashion (Figure 5, G).[23]

Another major class of foldamers is based on *meta*-connected phenylene ethynylenes pioneered by Moore (Figure 5, E),[24] where the driving force for folding arises from solvophobic effects due to the amphiphilicity present in these oligomers. A more thorough introduction to these foldamers and the principle governing their folding behavior will be given in Chapter 2. Finally, also oligoresorcinols were reported to fold into double helices in water driven by solvophobic effects (Figure 5, F).[25]

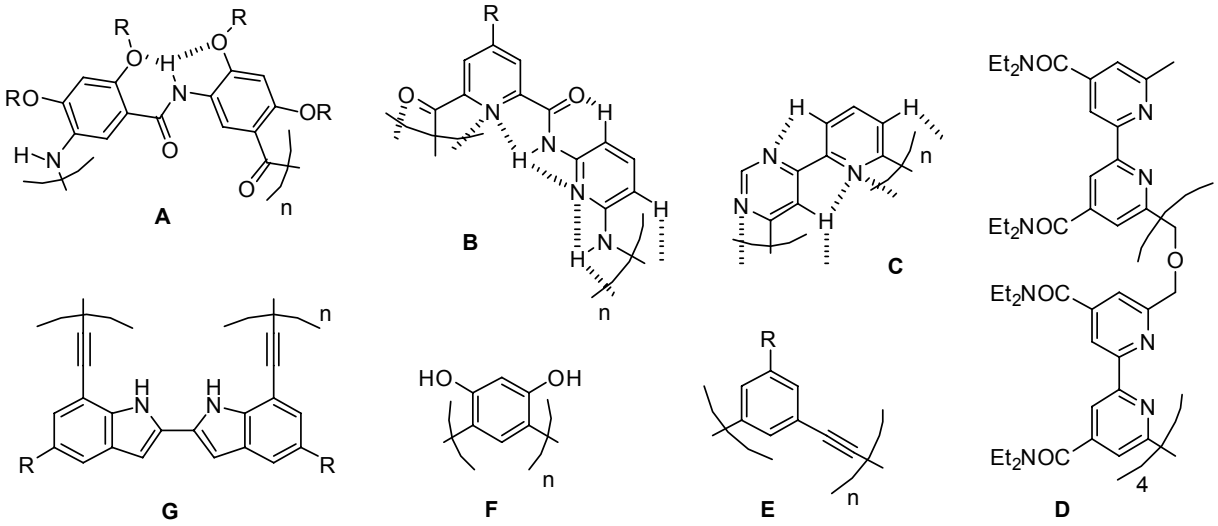

Figure 5: A potpourri of foldamers: A: oligo(diarylamide)s, B: alternating oligo(diaminopyridine-pyridinedicarboxamide)s, C: alternating oligo(pyridine-pyrimidine)s, D: oligo(bipyridine-ether)s, E: oligo(phenylene ethynylene)s, F: oligo(resorcinol)s, G: oligo(indole ethynylene)s.

1.4 Incorporating Chirality

When oligomer or polymer strands adopt a helical conformation, an arbitrary screw sense is adopted during folding and thus a racemate of so-called *M*- and *P*-helices are present in a 1:1 mixture. The introduction of optically active sites into the molecular structure discriminates

both helix types, as they represent now diastereomeric pairs, differing in energy.[11, 26] Chirality can either be incorporated into the strand, reside within the side chains, or be induced by chiral guests via supramolecular interactions. Concerning the backbone, Moore incorporated binaphthol[27] or helicene[28] units into his oligo(*meta*-phenylene ethynylenes) and could effectively bias the screw sense as monitored with the aid of circular dichroism (CD) spectroscopy. When the optically active site is present in the side chain, chirality transfer depends on the chiral center's distance to the folding backbone and the flexibility of the spacer in between,[29] the degree of intramolecular backbone order,[30] the packing mode of the side chains and naturally the amount of chiral side chain incorporation. With increasing distance of the chiral center to the backbone chiral induction – as monitored by CD spectroscopy with a series of self-assembling oligothiophenes – diminishes quickly, at the same time a so-called odd-even effect is observed as the chiral, e. g. methyl, group is moved bond-by-bond outwards manifesting itself in alternating signs of the CD signal.[31]

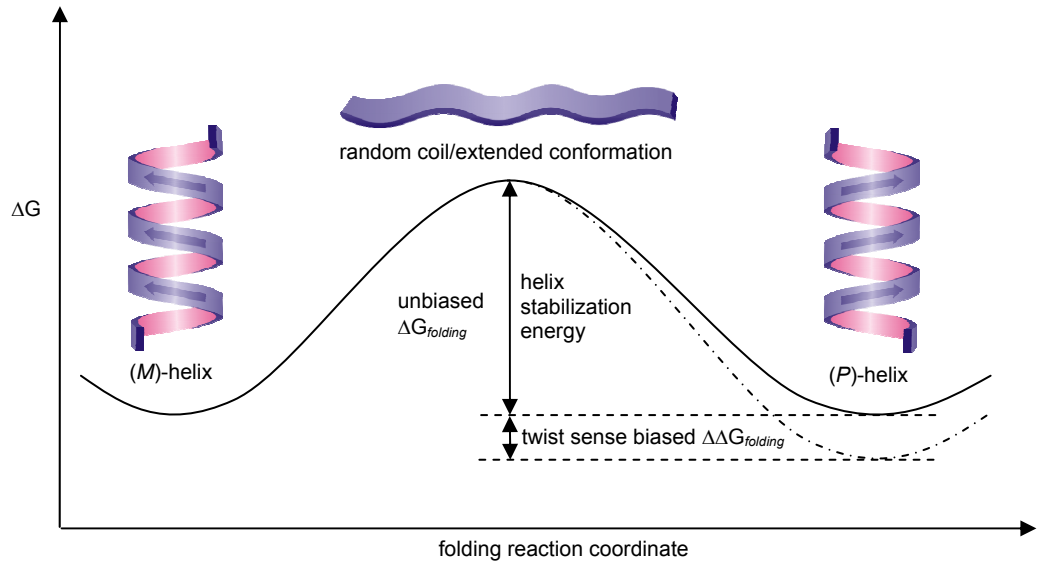

Figure 6: Folding thermodynamics: moderate helix inversion barriers lead to an equilibrium between helices of left- and right-handed twist sense. Chiral side chains (not shown) may increase the stabilization energy of one preferred helix (in the cartoon the P-helix) and dramatically shift equilibrium to this conformation.

The chirality transfer depends on sometimes very subtle effects, especially when cooperativity and chiral amplification are operating.[32] Even chirality in a monomer generated by a hydrogen-deuterium exchange is sufficient to strongly bias the helix sense among a folding backbone. When cooperativity arises, the so-called "Majority rule" and "Sergeant and Soldier principle"[32, 33] govern the screw sense behavior: This means that the incorporation of a small amount of chiral side chains is sufficient to introduce a large overall twist sense of the backbone. Analogous, among helices carrying chiral racemic side chains, a slight excess of

one enantiomer effectively overcomes the other and helices of solely one twist sense are formed.

Examples for supramolecular chirality induction are manifold and embrace host inclusion in hollow helices,[34] host-guest complexations at the side chain,[35] or salt bridges with chiral counter-ions.[36]

1.5 Self-Assembly and Hierarchical Organization of Polymers

(Macro-)molecular assemblies are accessible by designing and synthesizing building blocks with complementary regions that recognize each other, interlock, and automatically – or externally assisted – organize into larger entities held together by non-covalent interactions, and biological principles to the assembly and selection of synthetic superstructures are progressively better understood.[37] Despite today's complexity of biostructures, in biological evolution the possibilities are limited by the specific environmental situation, and further restriction arises from the fact that only advances are selected when they lead to an immediate evolutionary benefit. In contrast, modern organic and supramolecular chemistry can rely on a much wider pool of organic reactions, program lock-and-key situations, and thus potentially design entities with novel functions that Nature has never needed to evolve.

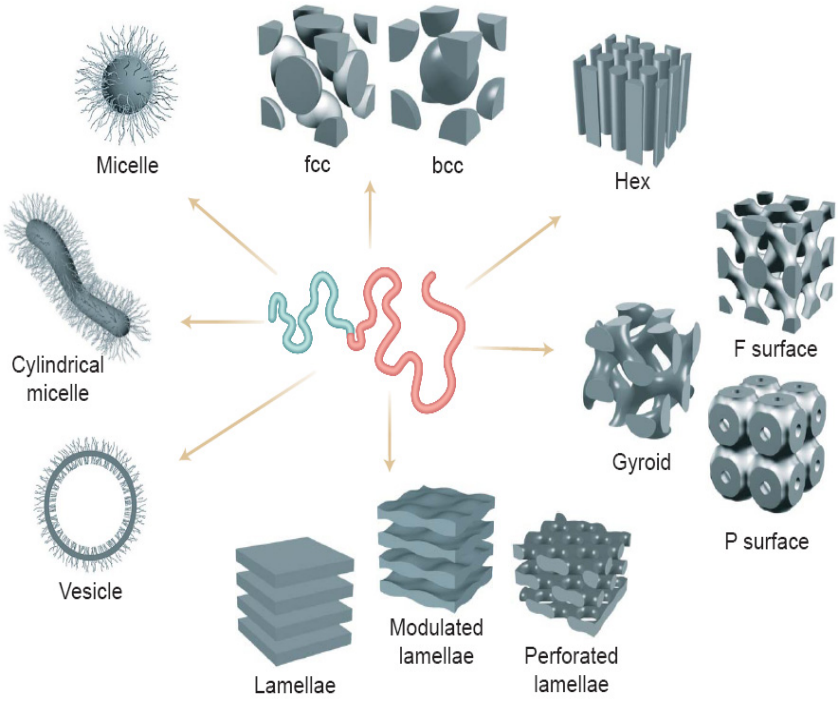

Figure 7: Self-organization of block copolymers into diverse arrangements including discrete micelles, and lamellar or porous bulk materials.

In the last decades, polymer chemistry has made tremendous progress in controlling the primary structure of homo- and heteropolymers as well as the recurring order in the bulk by

phase separation. Block copolymers resemble ideal candidates for building blocks in the construction of larger nanoobjects due to their rapid synthetic accessibility, already large dimensions, and tunable aspect ratios, while heteropolymers with irregular but defined backbone sequences represent key building blocks to more sophisticated arrangements and discrete, i. e. spatially limited, objects.

Self-assembly of macromolecules into useful objects has been realized with macrocyclic peptides[38] stacking into nanotubes and functioning as transmembrane channels. A similar application was accomplished with barrels out of rigid-rod *para*-phenylene oligomers acting as staves.[39] With block copolymers, sophisticated shapes with spherical and cylindrical geometries are already accessible,[40] although with little dimensional control and predictability, while most of the wide range of patterns that were realized with block copolymers constitute infinite periodic arrangements in the bulk (Figure 7).[41] The controlled aggregation of relatively simple homopolymers and block copolymers constitute the first step in generating nanoobjects of defined size and confined dimensions as exemplified by Stupp's "nanomushrooms".[42]

1.6 Aim of this Work

After decades of scientific progress in the field of modern organic chemistry, nearly every kind of chemical bond formation is realizable with several complementary chemical transformations to chose from. The vast number of chemical reactions a scientist has at his dispose enables (in theory) the synthesis of any arbitrary chemical structure. In particular in the area of macromolecular chemistry and more general materials science, focus moves beyond the discovery of truly novel reactions and mere bond formation towards designing function and in particular towards creating responsive, so-called "smart" materials.

The importance of controlling not only the primary structure of macromolecules, but also secondary and higher order structures has become eminent for addressing the given requirements presented in the preceding sections of this chapter, and some of these aspects will be addressed in this doctoral thesis. Due to the importance of the helix motif as a key building block in any nanoconstruction kit, the work presented in this doctoral thesis aims at synthesizing novel oligomeric and polymeric foldamers and revealing, and in the end controlling their helical folding and unfolding (Figure 8).

With regard to nanoelectronics, one of the obvious goals is the generation of addressable, isolated nanowires. In Chapter 2, novel π-conjugated foldamer backbones based on amphiphilic phenylene ethynylenes (PE) will be presented. First, the access to suitable *ortho*-

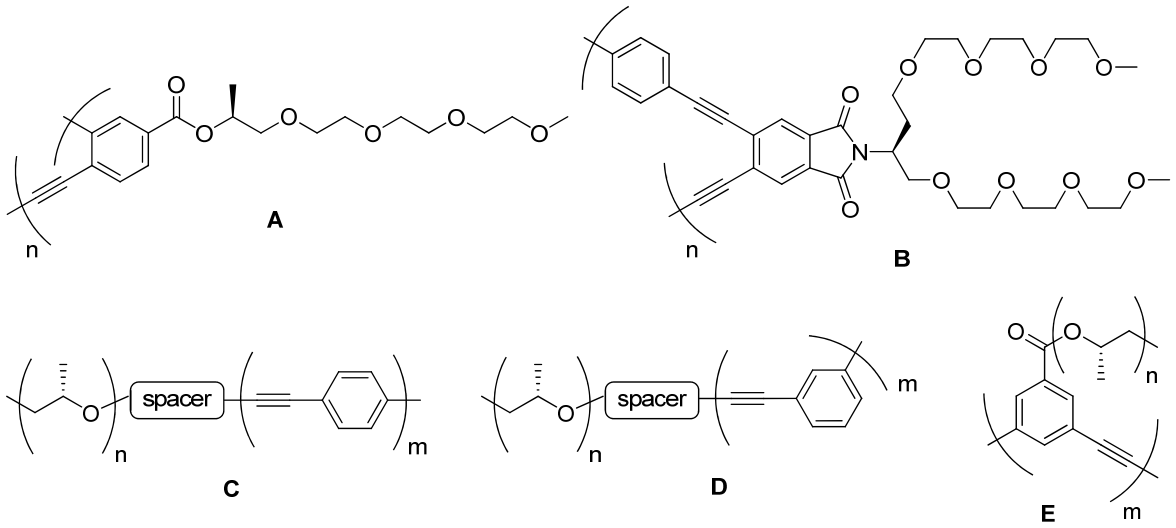

Figure 8: Targeted structures in this thesis: ortho-phenylene ethynylenes (A), ortho-alternating-para-phenylene ethynylenes (B), poly(propylene oxide)-block-poly(para-phenylene ethynylene)s (C), poly(propylene oxide)-block-poly(meta-phenylene ethynylene)s (D) and poly(propylene oxide)-graft-poly(meta-phenylene ethynylene)s (E).

connected PE oligomers via several synthetic approaches is explored and subsequently the obtained oligomers are thoroughly analyzed to elucidate their conformation in solution und to prove their helical structure induced by solvophobic effects. Second, a polymer with a novel backbone of *ortho*-alternating-*para*-connected PEs possessing a longer effective conjugation length than purely *ortho*-PEs is presented. The synthesis of the corresponding complex monomer is discussed in detail as well as its polymerization and the spectroscopic characterization to elucidate potential helical folding.

In order to simplify design and synthetic accessibility of custom-tailored nanoobjects, novel amphiphilic block copolymers and graft copolymers – also based on PEs – will be presented in Chapter 3. Poly(propylene oxide) (PPO) is chosen as the flexible and soluble segment for these copolymers. Highly isotactic, enantiopure, and non-racemic PPO is synthesized and the polymerization optimized to comply with the high demands of chirality transfer within intramolecular and supramolecular architectures. The incorporation of foldable segments into block copolymers not only extends the usage of PE foldamers known up to now, but also allows for significantly altering the aspect ratio of a given block copolymer. These conformational changes of a *meta*-PE segment in block copolymers as well as a *meta*-PE backbone in graft copolymers is studied by optical spectroscopy.

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