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Chiral Architectures from Macromolecular Building Blocks

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I. Introduction

In the course of evolution, Nature has developed a multitude of biomacromolecules tailored to deal with complicated tasks such as information storage, support of tissue, transport, and the performance of localized chemical transformations. Although large numbers of researchers in the fields of chemistry and physics have been, and still are, pursuing the same goals using synthetic systems, nucleic acids and proteins still outclass man-made materials. This has made an increasing number of scientists over the past decades turn their eye to Nature to design and synthesize increasingly precise nanoscopic and even mesoscopic structures using polymeric materials.

For the structuring of matter, Nature uses the self-assembly of both low- and high-molecular-weight compounds as a tool. Many biological architectures, the dimensions of which may range over several orders of magnitude, for their robustness rely on two structural components: the α-helix and β-sheet structures of peptides. It is the secondary structure of these two components which, in a delicate interplay among steric, hydrophobic, electrostatic, and hydrogen-bonding interactions, gives rise to the tertiary structure of Nature's main building blocks, the proteins. To achieve the high levels of organization, information must be built into the smallest building blocks, i.e., the amino acids. Indeed these building units do contain this information in the form of chirality, hydrogen-bonding capacity, steric demands, electrostatic properties, hydrophilic or hydrophobic character, or metal ion binding capability. Supramolecular chemistry since its early days has been inspired by biological assembly methods and has already delivered a large number of architectures of macromolecular size based on these secondary interactions.[1,2]

In our view, the same principles, when applied to polymer chemistry, allow the construction of large and complex, but precise, macromolecular architectures. In this review, focus will be on chiral polymers with a defined secondary structure in solution (section III) and on chiral macromolecular architectures arising from the aggregation of polymers (section IV).[3] Some examples from supramolecular chemistry relevant to the design of chiral self-organizing polymers will be given in the following section. In this section we will also discuss the different approaches for the construction of chiral oligomeric structures (foldamers).[4]

II. Chiral Architectures from Low-Molecular-Weight Compounds

1. Supramolecular Chirality. By building-in structural information, researchers have designed and synthesized self-assembling low-molecular-weight surfactants preprogrammed to form chiral superstructures such as “cigars”, twisted ribbons, helices, tubes, braids, boomerangs, and superhelices in aqueous media.[5−11] Comparable structures were generated by aggregation of other low-molecular-weight compounds in organic solvents.[12,13] The sensitivity to molecular geometry is highlighted by dramatic differences in the aggregation behavior of two regioisomeric phospholipid analogues, **1** and **2**, both having the (*R*) configuration (Figure 1). Phospholipid **1** forms platelike aggregates, whereas **2**, which has a more linear shape, is able to pack in such a way that its molecular chirality is expressed on the supramolecular level, leading to the formation of helices, all with a diameter of 22 nm and a regular pitch of 92 nm.

One other important principle to be learned from Nature is that when the structural dimensions of the architectures enter the multi-micrometer domain, different levels of organization are involved, e.g., as in collagen, which consists of polypeptide strands that are organized in triple helices (tropocollagen) that assemble to form fibrils and ultimately generate the

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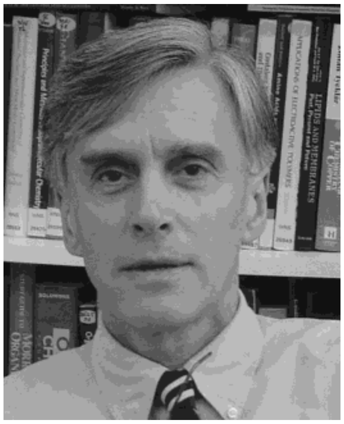
Jeroen J. L. M. Cornelissen started to study chemistry in 1992 at the University of Nijmegen, from which he graduated in 1996 after working on conducting polymers (in the group of E. W. Meijer, Eindhoven University of Technology) and substrate-selective catalysis (in the group of Roeland J. M. Nolte). In the latter group, he subsequently performed his Ph.D. research on chiral architectures from polymers and block copolymers of isocyanopeptides. Since June 2001 he has been working as a postdoctoral fellow at the IBM Almaden Research Center in San Jose, CA.

Alan E. Rowan completed his Ph.D. in physical organic chemistry in 1991 at the University of Liverpool, England. After a period of postdoctoral research at the University of Otago, New Zealand, he returned to Europe and became Assistant Professor at the University of Nijmegen in 1996. His scientific interests are in the design and construction of supramolecular assemblages possessing catalytic and electronic properties.



Roeland J. M. Nolte received his Ph.D. in physical organic chemistry from the University of Utrecht (1973), where he stayed and became Assistant Professor and then Associate Professor. In 1981, he was a visiting scientist at UCLA in the group of Donald J. Cram. In 1987, he moved to the University of Nijmegen and became Professor of Organic Chemistry, and since 1994 he has also been Professor of Supramolecular Chemistry at the Eindhoven University of Technology. His principal research interest is supramolecular chemistry, focusing on the design of catalysts and polymeric materials.

Nico A. J. M. Sommerdijk obtained his Ph.D. (Cum Laude) in 1995 at the University of Nijmegen for his study of the synthesis and aggregation behavior of chiral surfactant molecules. After this, he did postdoctoral work with John D. Wright at the University of Kent (U.K.) on sol–gel-based sensor materials and with Brigid R. Heywood at Keele University (U.K.) on the influence of self-assembling surfactants on the crystallization of inorganic materials. In 1997, he returned to Nijmegen to work on supramolecular assemblies of surfactants and polymeric materials. After this, he moved to the Eindhoven University of Technology in 1999, where he became Assistant Professor of Biomimetic Materials Chemistry. His key research interests are the fabrication of organic–inorganic composite materials and the construction of polymer–enzyme hybrid systems using the tools from supramolecular and macromolecular chemistry.

collagen fibers.[14] Several accounts of similar hierarchical order have also been reported for aggregates of synthetic low-molecular-weight compounds.[15] The possibility to organize matter by hierarchical self-assembly is exemplified by the aggregation behavior of the imidazole-modified amphiphilic gluconamide **3** in an aqueous medium in the presence of copper(II) ions (Figure 2).[13a] The molecules of **3** form 4:1 complexes with Cu^{2+} which subsequently organize into double-layered sheets. These sheets roll-up into left-handed helical tubes, which cluster to form fibrils with a thickness of 150 nm. These fibrils further organize to form the supermolecular braids as is shown in Figure 2.

Another important lesson from Nature teaches us that the way chirality is expressed depends not only on the chiral information encoded in the molecules, or on the level of organization. It may also be triggered or altered by changes in the local environment of the aggregate, such as polarity, the presence of specific ions, pH, or temperature. The supercoiling of DNA is such a process that is influenced by small changes in the local ionic strength which can cause the reversal of the helical twist in the DNA coils.[16] Similar phenomena have been reported for surfactant aggregates,[17] first exemplified by the self-assembly behavior of compound **2**, which organizes into left-handed helices that may either cluster to form ropes with the same handedness or aggregate to form right-handed superhelices with widths of 350 nm, a pitch of 250 nm, and lengths exceeding 10 μm (Figure 1).[3e]

These examples demonstrate how low-molecular-weight chemistry may be a guideline on how to use chirality as a tool in the construction of highly ordered polymeric materials since it will give a bias

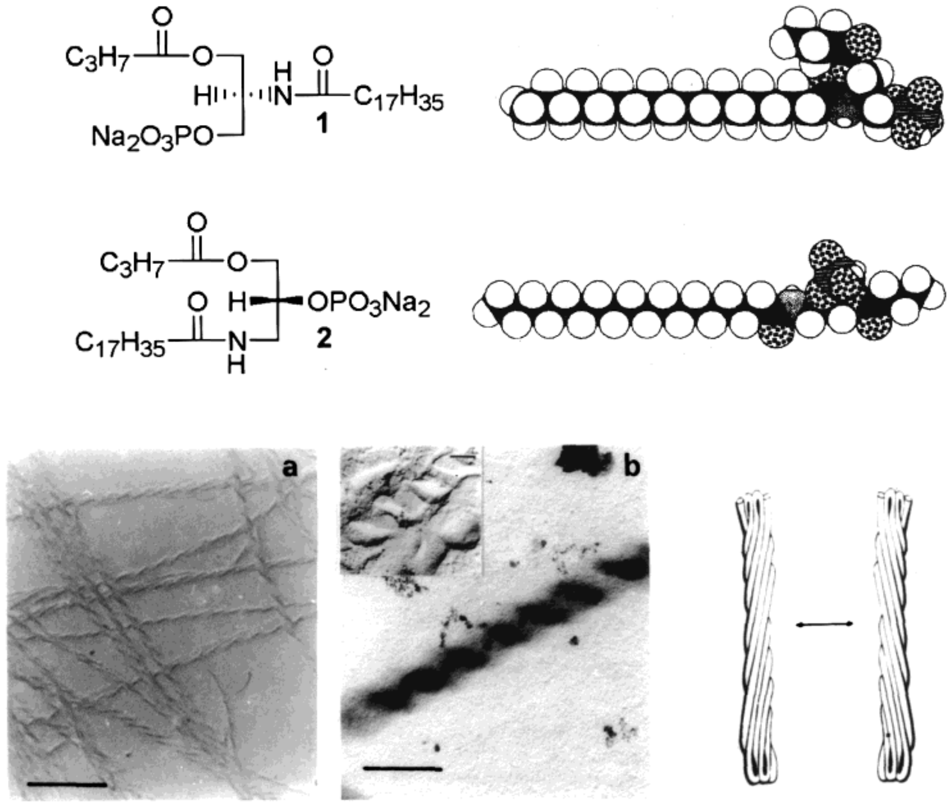


Figure 1. Top: Structures and CPK models of regioisomeric phospholipid analogues. Bottom: (a, b) TEM micrographs of aggregates of **2**. (a) Right-handed helices. (b) Superhelices formed by further assembly of the helices shown in (a). Inset: freeze-fractured replica of the superhelix. (c) Schematic representation of the superhelical winding.

as to how building blocks at the monomeric level will be built into the polymer chains. Together with other molecular information embedded in the monomers, it will dictate how polymer chains will fold and, ultimately, interact with neighboring chains to form well-defined polymeric architectures.

The aggregation of small chiral molecules can be used not only as a guideline for the construction of chiral polymer structures; the following examples show that it may also be directly applied to generate polymer architectures, e.g., by serving as a template for the organization of macromolecules into larger structures, to organize amphiphilic monomers, or even to form polymeric strands based on strong supramolecular interactions.

Lipid molecules with specific ligands or binding sites for selected protein templates have been demonstrated to direct the organization of these proteins into tubular structures with an outer shell consisting of a crystalline layer of biomacromolecules packed in a perfect helical arrangement.[18] Helical polymer architectures can also be obtained from chiral lipids and surfactants carrying polymerizable groups which can be fixed by photopolymerization as has been reviewed by O'Brian et al.[19] Already in 1985, Yager, Schoen, and co-workers reported on polymerized lipid tubes comprising helically folded bilayer sheets.[20] More recently Percec et al. demonstrated the control over the backbone conformation of different polymers through the programmed self-assembly of monomers (Figure 3a).[21] The polymerization of styrenes and methacrylates equipped with tapered gallic acid-derived monodendrons induces a helical conformation in the backbones of the resulting cylindrical polymer architectures above a critical degree of polymerization (>20 for styrene, >15 for methacrylate).[22,23]

The double helix of DNA exemplifies Nature's ability to construct complex chiral structures in an aqueous medium by making use of both hydrogen-bonding and hydrophobic interactions. Inspired by this phenomenon, Sijbesma and Meijer used dimeric building blocks equipped with 4-fold hydrogen-bonding units to obtain true polymeric structures in solution based on supramolecular interactions. By the interplay between the stacking of the aromatic hydrogen-bonding units and the incorporated enantiomerially pure solubilizing side chains, they were able to generate helical self-assembled polymeric architectures in organic solvents as well as in aqueous media (Figure 3b,c).[24]

2. Foldamers: Oligomers with a Preferred Helical Conformation. With the design of polymers with well-defined secondary and tertiary structures as the ultimate goal, researchers have taken up the task of identifying and synthesizing new structural elements that contain the information required for the programmed folding of molecular chains. This has led to the development of a class of compounds generally referred to as "foldamers" and defined by Gellman as polymers "with a strong tendency to adopt a specific compact conformation".[25] Essential in the design of foldamers is the identification of new backbones with well-defined structural preferences, and foldamers are thus further defined as oligomers of modest length that in solution display such a specific conformational preference. As the two most

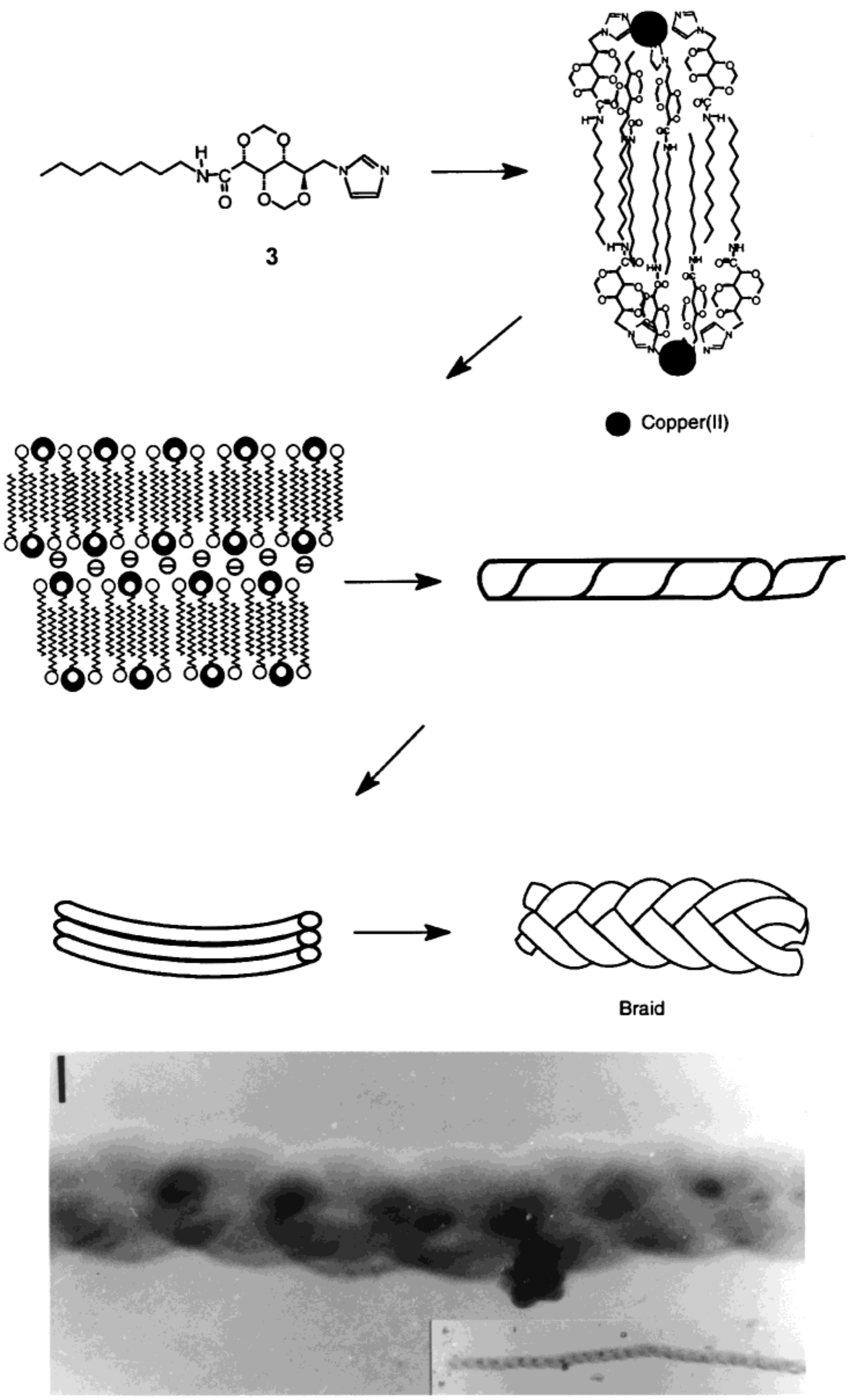


Figure 2. Hierarchical organization in the aggregation of an amphiphilic imidazole-containing gluconamide in the presence of copper(II) ions.

common structural elements found in Nature are helices and β-sheets, the realization of their synthetic equivalents has been adopted as a research target by a large number of scientists.[26] In this review, we will limit ourselves to examples in which the research has concentrated on systems with homogeneity in the backbone since a polymer approach may be applied to these materials and we will not go into the fields of polypeptide synthesis and peptidomimetics. Poly(amino acid)s probably are the most simple example of how structural information in the polymer backbone can dictate the folding of the molecules in a predefined manner. Some of these polymers, e.g., poly(benzyl glutamate), have now been sythesized in a true polymer approach by the ring-opening reaction of *N*-carboxyanhydride monomers (see also section III.A).[27] The preference of these poly(α-amino acid)s **4** (Chart 1) for the α-helix and the 3/10-helical

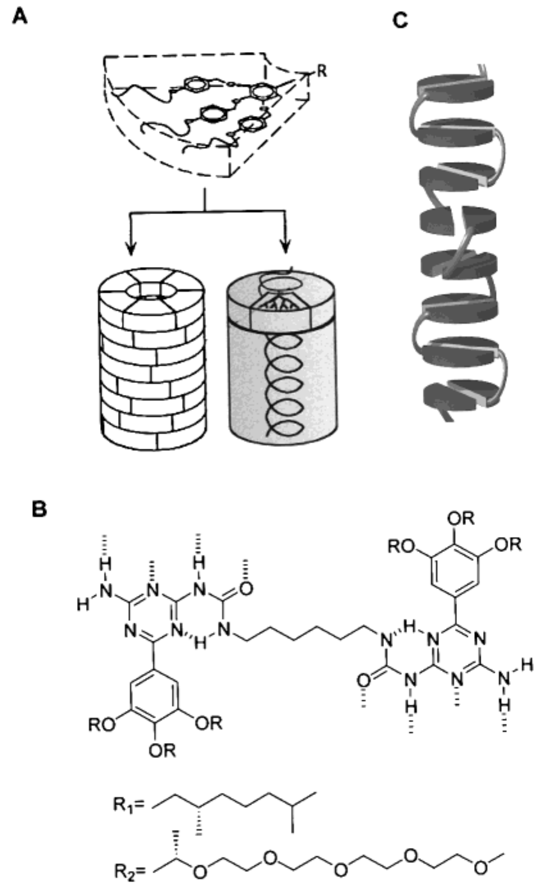


Figure 3. (a) Formation of helical macromolecular structures through the polymerization of preorganized monomers bearing tapered side groups. (b) Structure of dimeric hydrogen-bonding units able to form helical self-assembled polymers in organic (R_1) or aqueous (R_2) solution. (c) Schematic representation of a right-hand helical self-assembled polymer.

structure has been extrapolated to the design of other helical structures based on oligomers of β-peptides **5**. The groups of Gellman and Seebach have provided methodologies and guidelines for the construction of defined helical architectures from these compounds.

Gellman's efforts have concentrated on conformationally rigidified monomers, aiming at the realization of helical structures with long-term stability.[28] Molecular modeling calculations predicted that oligomers of *trans*-2-aminocyclohexanecarboxylic acid (**6**) and of *trans*-2-aminocylcopentanecarboxylic acid (**7**) (Chart 1) have particular preferences for the formation of a 14-helix and a 12-helix, respectively. The crystal structure of oligomers **6** (based on the former monomer) indeed revealed a perfect 14-helix, but although strong indications for the presence of a similar structure in solution were obtained, no definitive solution data have been presented yet.[29] For a hexamer (**7a**) and an octamer (**7b**) of the cyclopentane-derived β-peptide, the solution structure was determined using NMR. This supported the existence of the 12-helix structure which was also found in the solid state.[30] More recently also X-ray data on the packing of these helices in the solid state have become available, which may help to design tertiary structures based on these foldamers.[31]

Seebach and co-workers have developed hetero-hexa-β-peptides, e.g., **8** (Chart 1), which form helical structures in water as well as in organic solvents.[32] They demonstrated that the conformational restrictions in the backbone imposed by the use of cyclic monomers were not a prerequisite for the formation of these helical structures. Gellman's group later showed, however, that the incorporation of cyclic β-amino acids in the sequence *does* have a positive effect on the stabilization of the helix.[33] Exploring the possibilities of these types of monomers, Seebach and co-workers demonstrated that also β-sheets and turns can be realized,[34] and that the 14-helix can also be attained through the use of γ-amino acids.[35]

Other foldamers that have been reported are the vinylogous amino acids **9**,[36] the β-sulfonopeptides **10**,[37] and the vinylogous sulfonopeptides **11** (Chart 1).[38] Related to this work are also the investigations carried out on peptide nucleic acids (PNAs) which have recently been reviewed by Nielsen.[39] PNAs are a new class of flexible oligomeric DNA analogues in which the base pairs are carried by a peptide backbone. When this backbone consists of cyclohexyl-derived amino acids, the molecules adopt a more rigid conformation and are able to also form a double-helical structure.[40]

Hamilton and co-workers have prepared oligomers from anthranillic acid and pyridine-2,6-dicarboxylic acid moieties which use hydrogen bonds between nearest-neighbor groups to rigidify their structure and maintain a helical conformation.[41] Lehn's group has published a similar approach using oligoisophthalamides which can fold into helical aggregates through the formation of hydrogen bonds. In this work, cyanuric acid is used as a template around which the oligomer folds into a helix, forming hydrogen bonds to the guest molecule.[42] The helices aggregate, thereby generating fibers, which in turn cluster to form bundles of lengths up to several micrometers. A templating agent is not required for the folding of oligo(pyridinecarboxamide)s **12** (Chart 2). These molecules fold by the formation of intramolecular hydrogen bonds into double helices that reversibly dissociate into single-helical strands upon heating.[43]

Rather than relying on hydrogen bonding to achieve the appropriate folding of oligomeric compounds, Lokey and Iverson used attractive aromatic electron donor−acceptor (AEDA) interactions between dialkoxynaphthalene and naphthalenetetracarboxylic diimide. Oligomers **13** (Chart 2) containing these groups were termed "aedamers" and were shown to give pleated structures in solution, yielding a distinct "plum color" due to broad charge-transfer absorption bands in the visible region.[44] By using different amino acids as the linkers between the donor and acceptor units, solubility could be tuned; Nguyen and Iverson used hydrophilic and hydrophobic residues, alternatingly, as linkers between the aromatic units, yielding amphiphilic stacks which aggregated in aqueous media.[45]

The folding of oligo(m-phenyleneethynylene)s (Figure 4) into helical stacks driven by solvophobic effects was reported by Moore and co-workers.[46] These

Chart 1

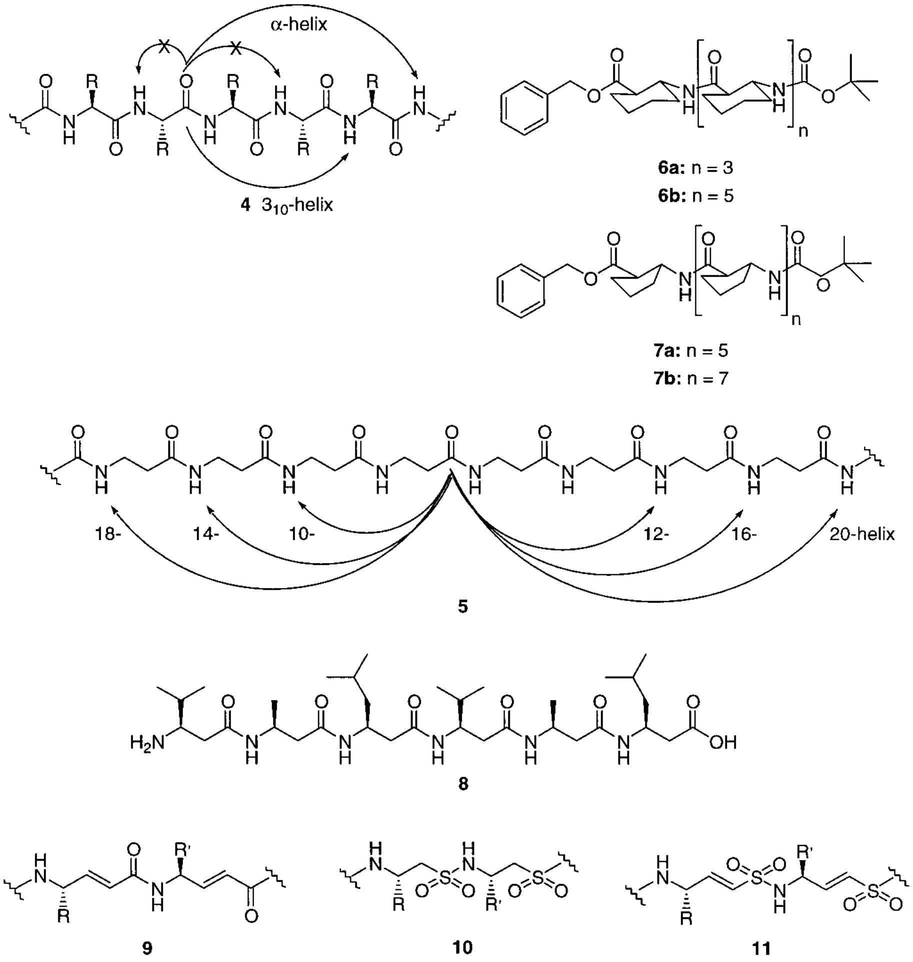
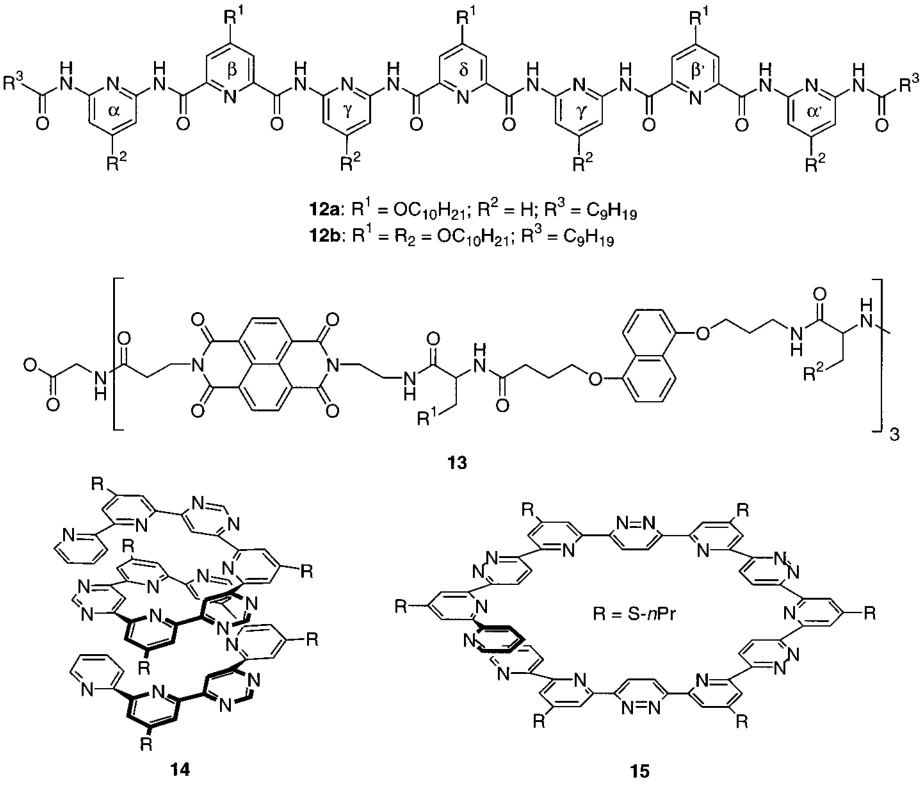


Chart 2



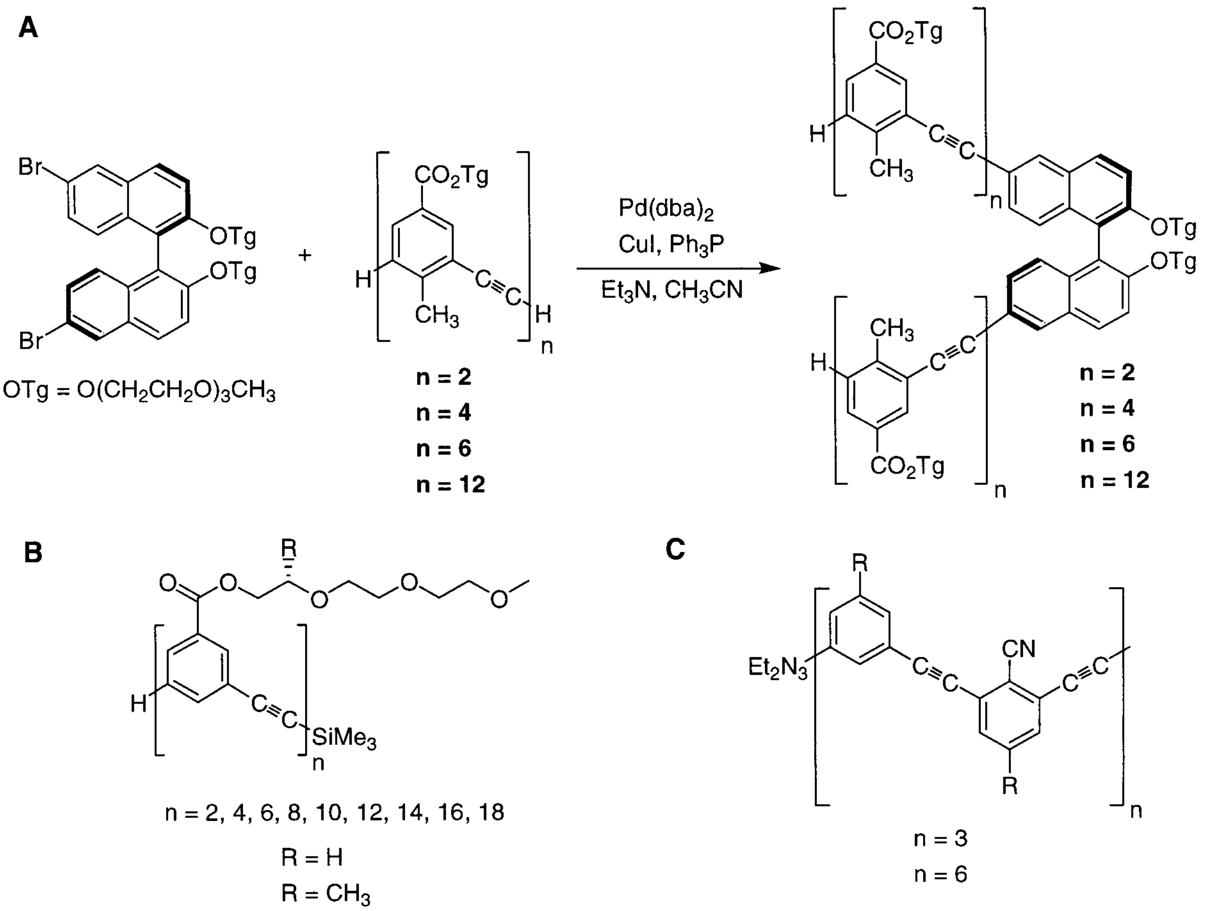


Figure 4. (a) Synthesis of oligo(*m*-phenyleneethynylene)s containing a chiral binaphthyl group. (b) Structure of oligo(*m*-phenyleneethynylene)s with optically active ethylene oxide side chains. (c) Same as (b) but with cyano groups that allow the binding of metal ions.

molecules exhibit a large degree of conformational flexibility due to the fact that rotation is possible around the ethynylene linkers, which allows switching between the transoid and cisoid states, the latter of which leads to a helical conformation. The aromatic backbone bears pendant oligo(ethylene oxide) chains to ensure solubility in a large variety of solvents, and oligomers consisting of up to 18 repeat units were prepared. To obtain a helical bias, initially binaphthyl groups were incorporated into the backbone of the oligomers;[47] later chiral side chains were used.[48] By equipping every second phenylene group with a cyano group on the free meta position, silver ions could be bound into the interior of these foldamers, which aided the stability of the helices[49] (Figure 4).

Metal ion complexation has been used to direct the helical folding of many oligomeric compounds. The resulting complexes are known as helicates and have been reviewed by Williams,[50] and by Piguet et al.[51]

The group of Lehn has demonstrated how by careful design oligomeric strands **14** (Chart 2) of alternating pyridine and pyrimidine can fold into helical structures using the geometry of the molecules, without the further need of specific directing forces or agents.[52] In their design, they used the fact that when these aromatic building blocks are linked at the appropriate positions the preference for a transoid conformation automatically leads to a helical structure. When pyridazines **15** (Chart 2) are used instead of pyrimidine groups, the helices organize themselves into a long tubular structure with an internal diameter of 8 Å. These fibers display a helical twist and stretch out over several micrometers.[53]

III. Chiral Macromolecules: Secondary Structure

A chiral organization *within* a macromolecule in most cases is present as a helical conformation of the polymeric backbone. In the 1950s, it was first recognized that the polymerization of substituted olefins could lead to the formation of macromolecules with a helical conformation.[54] Experimental evidence for the existence of such a structure *in solution* was first reported in 1960 by Pino and Lorenzi[55] and later also by others.[56,57] The properties of these helical macromolecules are highly dependent on the helix inversion barrier. The screw sense of one particular strand is stable at room temperature when this helical inversion barrier is high ($\geq\sim85$ kJ·mol^{-1}), whereas the two screw senses may be in equilibrium when the inversion barrier is lower.[58] In the case of nonchiral side chains, the left- and right-handed helices are enantiomers, having equal free energies. When the polymer contains chiral side chains, the helices are diastereomers and consequently have different free energies (Figure 5). Polymers with low helix inversion barriers have dynamic properties which can be used to build chiral architectures that respond to interactions with small molecules, light, or subtle changes in monomer composition or temperature as will be

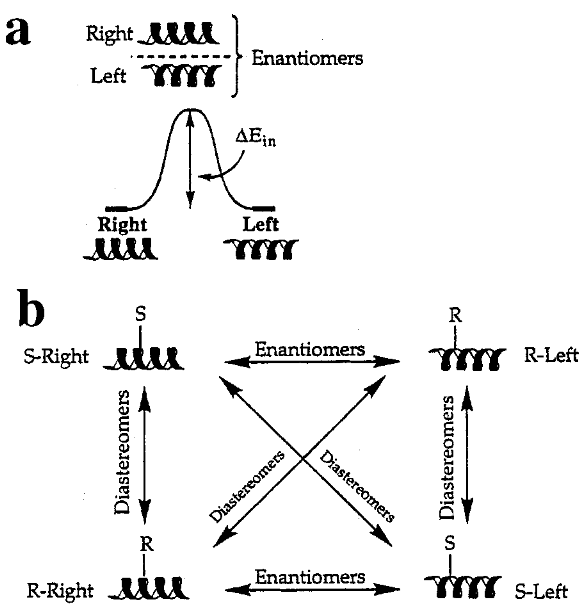


Figure 5. (a) Energy relationships between helical polymers from achiral monomers. (b) Relational diagram between helical polymers from chiral monomers. (Modified from ref 58.)

discussed in the following section. When the helix inversion barrier of the polymer is high, the helical conformation is formed under kinetic conditions. This implies that upon incorporation into the growing chain each monomer contributes to the helix, and is sterically locked into its conformation. These types of polymers will be discussed in part B of this section.

A. Helical Polymers Having Low Helix Inversion Barriers

1. Polyisocyanates. Polyisocyanates (Nylon 1) are stiff helical polymers, which have been extensively investigated in the last 20 years in particular due to the pioneering work of Goodman and Chen[59] and more recently the elegant studies of Green.[60] Their stiffness is a result of the partial double-bond character of the backbone amide bonds. The polymer backbone is helical due to steric constraints, which prevent the amide bonds from being planar whether they are in a cis or trans conformation (Figure 6).

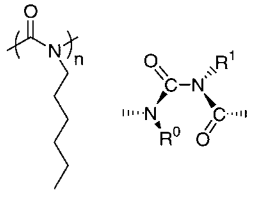


Figure 6. Structure of poly(*n*-hexyl isocyanate) and a generalized polyisocyanate structure indicating the steric restrictions in these polymers.

The helical nature of these polymers was confirmed by analysis of the X-ray crystal structure of poly(butyl isocyanate) in the late 1960s, which revealed a 3/8-helix, in which the monomeric units are translated along the helical axis by 1.94 Å per monomer and rotated by 135° per monomer.[61] This helical conformation is also adopted in solution for both poly(alkyl isocyanates) and poly(aryl isocyanates) although the latter are less well defined than the former. When an achiral monomer is polymerized, left- and right-handed helices are formed, which are distributed throughout the polymer chains and are dynamically interconverting. Empirical force field studies on poly(alkyl isocyanates) predict a barrier of 52 kJ·mol^{-1} for the cis–trans isomerization of the conjugated, partial double bonds in the polymer backbones, which agrees closely with the observed experimental data.[62]

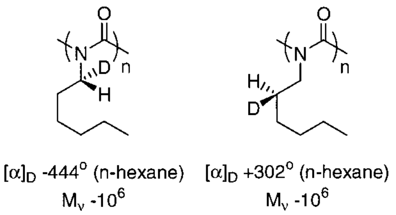


Figure 7. Introduction of optical activity in polyisocyanates by H/D substitution.

The helical sense of the polymer can be controlled by a variety of means, such as inclusion of a chiral monomer, the use of a chiral solvent, or the use of a chiral initiator for the polymerization. The group of Green has elegantly demonstrated that the helical sense of poly(alkyl isocyanate)s is extremely sensitive to even slight chiral biases in the monomer. They showed that substitution of a proton for a deuterium (Figure 7) is sufficient to induce a preferential helical sense in the resulting polymers.[60,63] It is remarkable that this substitution induces such an effect, especially since in hexane at 25 °C this isotopic effect would favor a P-helix over the M-helix by only 3.1 J·mol^{-1}, implying that the P-helix would exist in excess of the M-helix by only 0.12%. However, for a long polymer chain ($n = 2000$), this minute excess is amplified by a cooperative mechanism to give a ratio of 67:33 (P-helix:M-helix). The same research group further highlighted the cooperative nature within the polymeric helices by investigating the helical preference of copolymers of chiral and achiral polyisocyanates. They discovered that the presence of even a minor amount of chiral monomer induced a helical preference upon polymerization of the achiral monomer. Somewhat surprisingly it was also discovered that a polyisocyanate constructed from a random copolymerization of monomers containing nearly equal numbers of mirror image units exhibits the same CD spectrum as a polyisocyanate obtained from the homopolymerization of the enantiopure monomers (Figure 8). The ability of the majority unit to impose itself upon the minority (majority rules concept) becomes more prominent as the helical reversal becomes more difficult to attain.

The observed cooperativity arises from infrequent helical reversals, which separate long blocks of opposing helical senses, forcing many units of the chain to take the same helical sense. In this way, the chiral bias of each unit of the chain is amplified. In the case of the helical preference induced by the isotope effect, the helix reversal was found to cost 6.3 kJ·mol^{-1} and to occur on average only once in every 762 units. This long persistence length, which in turn is the result of the infrequent helical reversals, accounts for the chiral amplification in these polymer systems. More

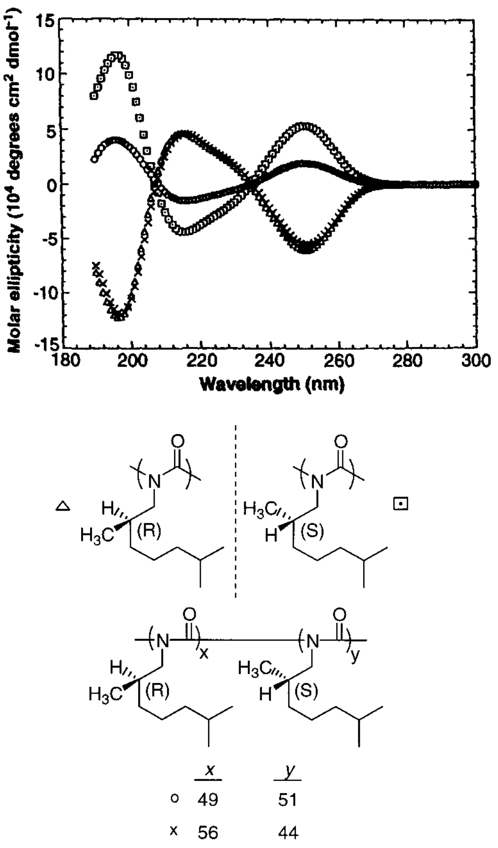
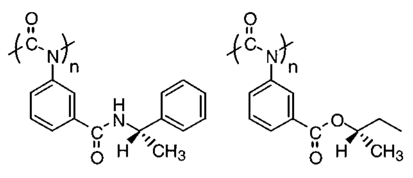


Figure 8. Majority rules effect in polyisocyanates: (left) CD spectra of homo- and copolymers; (right) structure and compostion of the polymers. (Reprinted with permission from ref 60. Copyright 1995 American Association for the Advancement of Science.)

recently the mixed copolymer experiments have been extended to include a *diluting* achiral component. The highly disproportionate relationship which arises from the majority rule effect, as was demonstrated for the mixed (*R*)- and (*S*)-copolymers,[64] was found to be unaffected by the overwhelming presence of achiral units randomly distributed along the chain.[65] Experimental results were fitted to a one-dimensional random-field Ising model, which showed that the dilution of the chiral units with achiral units increases the helical domain size in a manner that compensates for the dilution.

The sensitivity of the helical preference of polyisocyanates to small chiral influences is also observed in chiral solvents. Poly(*n*-hexyl isocyanate) was found experimentally to have a persistence length of 20−40 nm depending on the solvent in which the measurements were carried out.[66] It was hypothesized that in more polar solvents a local interaction of the solvent would give rise to larger torsional oscillations around the backbone bonds. It was indeed observed that dissolution of poly(*n*-hexyl isocyanate) in non-racemic chiral solvents, e.g., (*S*)-1-chloro-2-methylbutane, changed the persistence length and in addition also resulted in an excess of one helical sense.[67] The chiral bias favoring one helical sense by itself is miniscule, but due to the cooperativity, a chiral preference is observed. More recently it was noted that the circular dichroism of these polymers decreases upon the addition of an achiral or racemic cosolvent, which can be quantitatively interpreted as reflecting the composition of the solvent mixture in contact with the helical backbone of the polymer.[68]

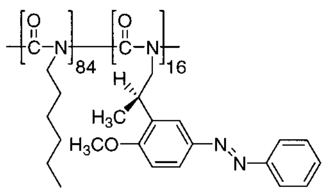
Chart 3



Poly(aryl isocyanate)s possessing a phenyl group directly connected to the polymer main chain have until recently been considered to adopt a random-coil conformation in solution due to the lack of stiffness of the polymer main chain.[69] The group of Okamoto, however, has demonstrated that when an optically active anionic initiator is used in the polymerization reaction, chiral polymers are obtained, which have a one-handed helical structure dictated by the initiator. The polymer main chains are stiff enough to maintain this helical conformation in solution.[70] The same group more recently reported that chiral aromatic isocyanates can be polymerized to give well-defined polymers with a helical preference. (*S*)-**16** (Chart 3) showed a very large negative optical rotation, $[\alpha]^{25}_{365}$ −1969°, which was found to be temperature independent, implying that (*S*)-**16** (Chart 3) adopts a perfect helical conformation in solution even at room temperature. Polymerization of achiral monomers in the presence of chiral monomers gave helices that exhibited cooperative effects similar to the ones seen for their alkyl equivalents.[71] Optically active (*S*)-**17** (Chart 3) was found to display an unusual conformational change accompanied by inversion of the helical structure when the temperature was changed. At −45 °C in THF, **17** possessed a predominantly one-handed helical conformation with a helical sense opposite to that at 25 °C.[72]

Switching the helical sense of polyisocyanates is a research topic that is receiving increasing attention. This is due to the result of the extreme sensitivity of the helices to slight chiral influences arising from the large cooperativity present in these polymers. In 1996, the group of Zentel polymerized optically active isocyanates containing azo chromophores to give polymers with a preferred helical twist and photoswitchable functions.[73] Their preliminary studies revealed that upon photoswitching the chromophore from the trans to the cis state, the percentage of right-handed (P) helical segments increases and the observed CD effect for the polymer reverses. Films consisting of a copolymer of photochromic isocyanate and *n*-hexyl isocyanate (**18**) (Chart 4) embedded in poly(methyl methacrylate) (PMMA) exhibited stable photochromic switching, whereas upon irradiation the preferential helical sense of the polymer was reversed. Upon thermal relaxation of the chromophore, the photoinduced helical preference was retained. The inclusion of the polymer within the PMMA matrix increases the barrier to helix reversal, thereby fixing the polymer.[74] In a similar approach, the group of Green demonstrated that achiral polymers containing racemic photoresolvable ketones (**19**)

Chart 4



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can be switched from one helical preference to another upon photoexcitation of the chromophore (Figure 9).[75] A small enantiomeric excess produced by irradiation, even diluted by a large proportion of achiral pendants, is capable of enforcing an excess of one helical sense in the polymer. An elegant approach to the manipulation of the helical sense of polyisocyanates is the polymers synthesized by Green, which possess two different nonracemic chiral molecules that are in competition with each other to control the polymer sense.[76] The competition leads to thermal switching of the helical sense at a compensation point that depends continuously and predictably on the composition of the polymers.

Stiff, rodlike polymers are known to aggregate to form lyotropic nematic liquid crystals[77] and to self-assemble to form gels.[78] The helical nature of the polyisocyanates is transferred into the properties of the aggregates. When the polymer contains monomers bearing chiral side groups, the liquid crystalline superstructure is no longer nematic but cholesteric. This switching of the liquid crystalline phase can also be attained by doping with small chiral molecules, mimicking the chiral solvation effect seen for the polymers in solution.[67] The number of helical reversals per polymer changes upon aggregation to a gel. Molecular modeling predicts that at the reversal point the polymer has a kink of 150°. It was observed by recording optical activity that a reduction in the number of helical reversals (and hence an increase in persistence length) in the polymer chains occurs due to close parallel packing of the polymer rods.

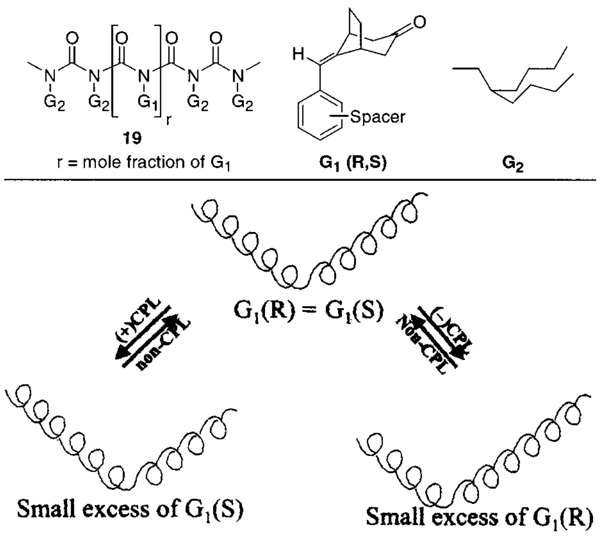


Figure 9. Switching of photosensitve polyisocyanates between two helical preferences by irradiation with circularly polarized light (CPL). (Reprinted with permission from ref 75. Copyright 2000 American Chemical Society.)

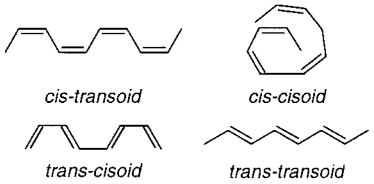
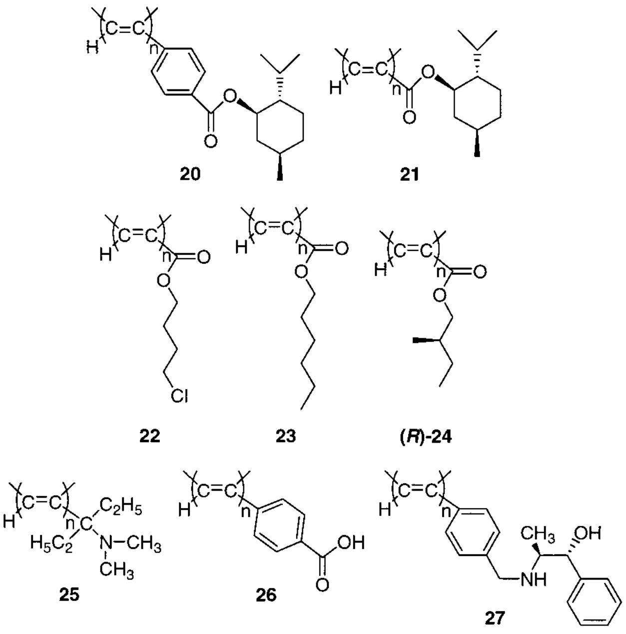


Figure 10. Possible configurations of polyacetylene.

Chart 5

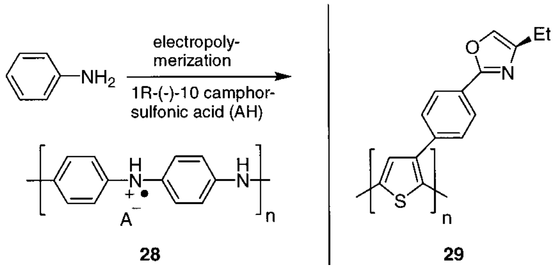


2. Chiral π-Conjugated Polymers. Polyacetylenes can exist in four different conformations: the cis-cisoid, cis-transoid, trans-cisoid, and trans-transoid conformations (Figure 10).[79] Although this type of conjugated polymer has interesting electronic properties (e.g., *trans*-polyacetylene has a low-energy $\pi-\pi^*$ electronic absorption of 1.8 eV[80]) and substituted *trans*-polyacetylenes have been investigated extensively, studies on substituted polyacetylenes with a predominantly cis configuration are limited. A helical geometry was proposed for the cis-cisoid and cis-transoid polyacetylenes on the basis of the findings of Simonescu et al., who for the first time prepared and identified all four stereoisomers of poly(phenylacetylene).[81] This structure was later confirmed for other polyacetylenes using experimental and computational methods.[79,82] Characteristic for these helices is the very short persistence length of the helical domain, exemplified by the high population of helix reversal points present along the polymeric backbone of poly(phenylacetylene).[83] Already in 1967 Ciardelli and co-workers synthesized the first chiral polyacetylene by polymerizing (*S*)-4-methyl-1-hexyne.[84] Polyacetylenes equipped with chiral appendages may be prepared by ring-opening metathesis polymerization,[85] but the most widely applied route is the addition polymerization using $[Rh(nbd)Cl]_2$ (nbd = norbadiene) complex as a catalyst, leading to highly regioregular cis-transoidal polyacetylenes.[86,87]

With the aim of preparing membranes for optical resolution, acetylene polymers **20** (Chart 5) were synthesized for which, on the basis of the high optical activity, a helical conformation was proposed.[88] The optical rotation and ellipticity of the related polymer **21** (Chart 5) prepared using the $[Rh(nbd)Cl]_2$ catalyst were much higher than those prepared by a $MoOCl_4$–Bu_4Sn catalyst, which produces a much more irregular macromolecular chain.[89] In a more extended investigation, a similar comparison was made for a variety of poly(propiolic ester)s with other chiral substituents.[90] It was concluded that the appearance of intense CD effects, originating from a helical backbone conformation, corresponded with a large band gap energy (ca. 3.2 eV). Furthermore, the introduction of bulky substituents into the polymers was found to enhance the persistence length of the single-handed helix, leading to an increase in the magnitude of the Cotton effects and optical rotations. Conformational studies in solution were undertaken to elucidate the helical structure of poly(propiolic ester)s.[91] The chiroptical properties of copolymers of **21** and **22** (Chart 5) were found to be strongly related to the enantiomeric excess of the monomer of **21**, which suggested that these polymers had a long helical persistence length. In contrast, the copolymer of **23** and **24** had random-coil character when the (*R*)-**24** (Chart 5) content was 60%.

A number of optically inactive polyacetylenes were prepared by Yashima and others to study the induction of helicity upon their complexation of an optically active compound in organic solvents, in thin films, and in water.[92] In the case of aliphatic polyacetylene derivatives, a helical conformation was only induced in **25** (Chart 5) when this polymer was complexed with mandelic acid.[93] Poly(arylacetylene)s substituted with optically active pendant groups adopt a helical backbone conformation.[94–96] Using optically inactive poly[(4-carboxyphenyl)acetylene] (**26**) (Chart 5), a CD spectrum could be induced upon complexation of chiral amines[97] and amino alcohols in DMSO solutions and in films.[98] Interestingly, the sign and shape of the induced CD effect was found to depend on the stereochemistry, bulkiness, degree of substitution (primary, secondary, or tertiary), and absolute configuration of the amines. Nonlinear correlations were found between the enantiomeric purity of the complexing agents and the observed ellipticity, and between the concentration of the chiral amines and the amount of helicity induced in the macromolecules. Poly[(4-dihydroxyborophenyl)acetylene][99] and poly(arylacetylene)s bearing an amine group[100] have been used in the chirality assignment of carbohydrates and steroids, and carboxylic acids, respectively. Polymer **27** (Chart 5) in DMSO solution exists as a right-handed helix, but it reverses handedness upon the addition of mandelic acid.[101] For **26**, the induced helicity can be "memorized" when the optically active amine is replaced by various achiral amines. Although this helicity is self-repairing, small structural changes in the achiral component strongly influence the efficiency of helix retention.[102] Furthermore, helical polyacetylenes with pendant lactose side groups have been applied for the molecular recognition of lectin,[103] and derivatives bearing (*R*)-(1-phenylethyl)carbamoyl groups have been used as a chiral stationary phase for HPLC.[104]

Scheme 1. (Left) Synthesis of Polyaniline by Electropolymerization in the Presence of an Optically Active Acid and (Right) Structure of Oxazoline-Containing Polythiophene 29



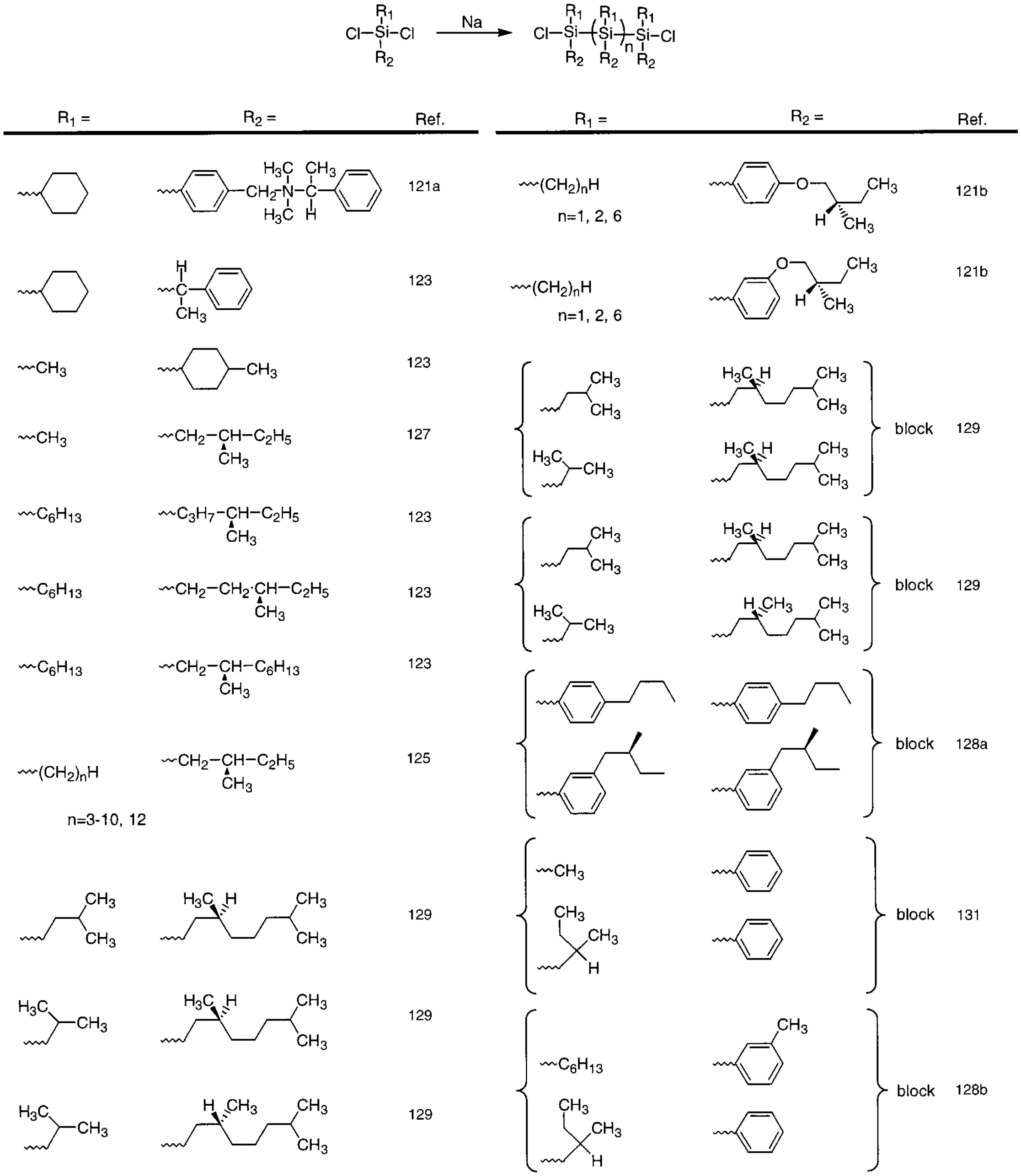
Many papers have appeared on the synthesis and characterization of other chiral-conjugated polymers for possible applications in, among others, membrane resolution of racemates,[105] enantioselective HPLC,[106] and asymmetric catalysis.[107] Remarkably, only for a relatively small number of these chiral π-conjugated polymers, which have been reviewed by Pu,[108] the strong optical activity in the $\pi-\pi^*$ transition is ascribed to the presence of a secondary structure, i.e., to a helical conformation of the polymer backbone in solution. Most of them only display helicity in an aggregated form. In fact, apart from the polyacetylenes, the aforementioned foldamers, and "binaphthyl-based polymers" (see section B), only a few examples of conjugated polymers with a helical main chain exist. Main chain helicity has been reported for one substituted poly(phenylenevinylene),[109] for an oligo(β-pyrole),[110] for a cyclophane analogue of poly(*p*-phenylene), and for polyanilines.[111,112]

A special feature of the polyanilines (**28**) is the fact that they are prepared by electrochemical polymerization in the presence of a chiral dopant (Scheme 1). Polymers prepared in the presence of enantiomeric counterions give rise to CD spectra with completely different signs. These signals are lost completely upon deprotonation of the polymer. This suggests that the helicity is maintained by hydrogen-bonding and/or electrostatic interactions with the counterions.

Another very interesting class of chiral conjugated polymers, which has been explored by Swager and co-workers,[113] comprises macromolecules in which the monomeric units are equipped with receptor groups. Binding of analyte molecules leads to changes in the folding of the polymers and consequently to changes in their electrooptical properties, allowing them to act as effective sensors for a variety of different analytes. Surprisingly, only one example has been reported in which the binding of the guest leads to a change in the helical conformation of the reporter polymer. The regioregular polythiophene **29** (see also section IV) bearing chiral oxazoline-derived side groups only gives rise to a CD effect in poor solvents such as alcohols. However, exposure to copper(II) ions in a good solvent such as chloroform gives rise to a strong Cotton effect in the CD spectrum of the polymer which was attributed to the induction of a helical conformation in the polythiophene backbone.[114]

3. Polysilanes. Polysilanes are linear polymers of silicon in which the σ-electrons in the polymer

Scheme 2. Wurtz Coupling of Enantiopure Dichlorosilanes and the Structure of the Resulting Chiral Polymers



backbone are delocalized. This σ-conjugation gives rise to electronic properties that allow for possible applications as electroluminescent, nonlinear optical, lithographic, and semiconductor materials.[115] Since polysilanes are electroactive main chain polymers, the properties of these macromolecules are strongly related to the substituents on silicon. Not only the direct electronic effects of substitution but also its indirect effect on the conformation of the polymer backbone, along which conjugation occurs, affects the optoelectronic properties of these polymers.[116]

The parent polysilane chain is extremely flexible, and for tetrasilane, the energy barriers between the gauche−gauche and gauche−anti rotation were calculated to be only 6.3 ± 0.8 and 2.9 + 0.4 kJ·mol^{-1}, respectively.[117] For permethylated silanes, still no distinct conformational preferences could be determined; however, for the more bulky *n*-hexyl substituents, a preference for a dihedral angle of 150° was found which corresponds to a 7/3-helix, a structure which is remarkably similar to the one proposed for the solid-state structure of poly(di-*n*-butylsilane) and poly(di-*n*-pentylsilane).[118−120] By the introduction of enantiopure substituents in the dialkyldichlorosilane monomers, polysilanes can be prepared displaying a preferred handedness of the helical backbone (Scheme 2).[121,123−127] This backbone chirality can also be induced by using terminal chiral substituents as was demonstrated for oligosilanes with isopropyl side groups.[122] In a detailed study by Fujiki, it was demonstrated that the optoelectronic properties of such helical polymers are directly related to their conformational properties, since the folding of the all-silicon backbone affects the effective conjugation length.[123] Fujiki synthesized a large number of chiral polysilanes using the Würtz synthesis (Scheme 2) and

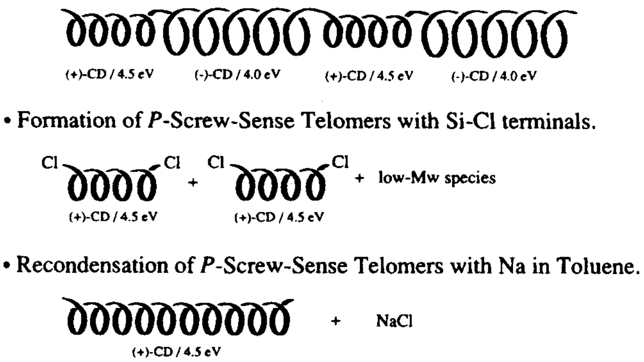


Figure 11. Screw-sense-selective photolytic cleavage of the M-helical segments in poly[methyl(2-methylbutyl)-silane] and subsequent Würtz coupling of P-helical segments. (Reprinted with permission from ref 127. Copyright 1994 American Chemical Society.)

found that the lowest excitonic Si(σ)−Si(σ^*) absorption band and the bandwidth at half-height of a large number of fractionated chiral polysilanes have a logarithmic relation with the viscosity index of these polymers, which relates to their helical segment length. Poly[alkyl(2-methylbutyl)silane]s have a helical-rod structure and can be regarded as a model for a 5 Å wide quantum wire.[124] For poly[*n*-decyl((*S*)-2-methylbutyl)silane], the rigidity was even high enough that the polymer chain could be visualized by AFM.[125] It was demonstrated by Fujiki and co-workers that the properties of such polymers can be regulated by varying the temperature and the solvent.[126] For poly-[((*S*)-2-methylbutyl)(6,9,12-trioxytetradecyl)silane], the predominantly left-handed (M) helical segments were found to tighten and increase in length upon cooling, and also an increase in the number of helix inversions was found. Upon addition of a poor solvent, the number of kinks in the polymer backbone increased as may be expected upon aggregation of the polymer strands.

Fujiki further showed that poly[methyl(2-methylbutyl)silane] chains in solution consist of diasteromeric segments with opposite handedness.[127] A special feature of this polymer was that the M-helical segments were more tightly wound than the P-helical ones. Consequently, the absorption and CD bands of the former were blue shifted with respect to those of the latter ones. This allowed the screw-sense-selective photolytic cleavage of the M-helical segments in CCl$_4$, leaving only the P-helices which became substituted with terminal chloride atoms (Figure 11). Recondensation of these segments using a Würtz-type coupling with sodium in toluene resulted in single-handed P-helical polymers.

Reversible control over the helix sense in polysilanes was achieved in the case of poly(diarylsilanes)[128] as well as in (co)polymers of ((*S*)-3,7-dimethyloctyl)(3-methylbutyl)silane,[129] which both showed helix reversal upon heating. For the latter polymer (Figure 12a), it was calculated that the potential curve has a double-well ("W") shape (Figure 12b) with a slight preference for the M-helix over the P-helix. CD spectroscopy indeed revealed that above the transition temperature the ordered (low-entropy) M-helical conformation becomes less stable than the entropically more favored P-helical state (Figure 12c,d).

The optically inactive poly(methylphenylsilane) (PMPS) was considered for many years to exist in an all-trans conformation. However, although calculations had indicated that PMPS could possibly exist as a loosely wound 15$_7$-helix,[130] it was only very recently that is was experimentally demonstrated that this polymer indeed adopts a helical backbone

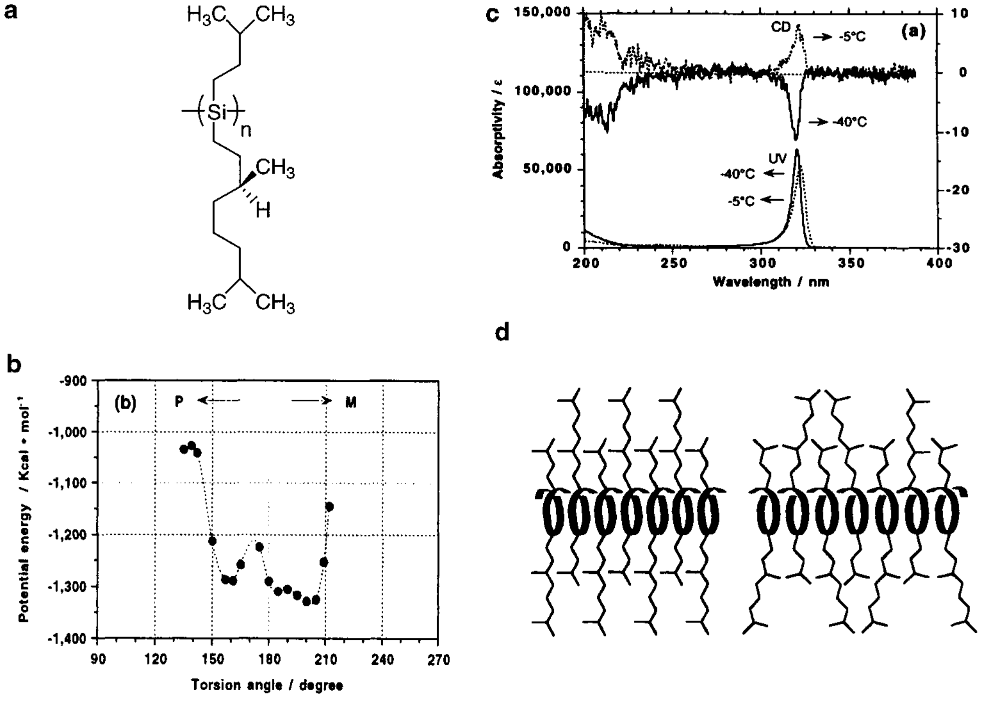


Figure 12. (a) Structure of poly[((*S*)-3,7-dimethyloctyl)(3-methylbutyl)silane]. (b) Energy diagram showing the double-well shape. (c) CD and UV spectra of both screw senses. (d) Schematic representation of the two helical forms. (Reprinted with permission from ref 129. Copyright 2000 American Chemical Society.)

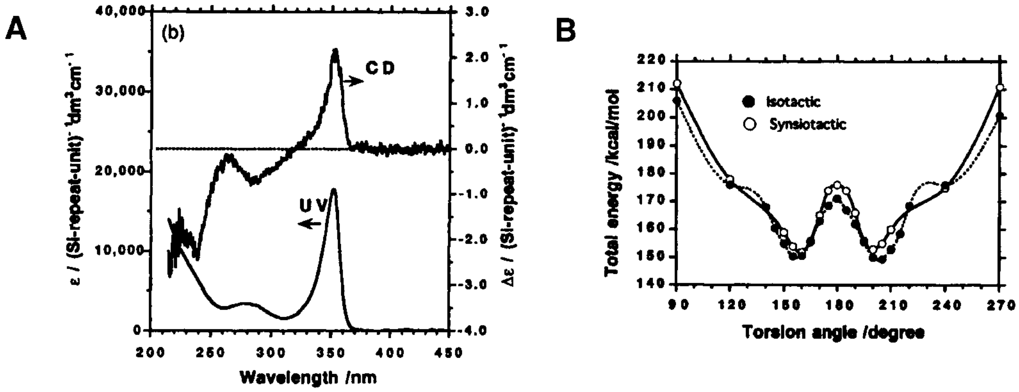


Figure 13. (a) CD and UV/vis spectra of optically active doped poly(methylphenylsilane). (b) Calculated energy diagram of this polymer. (Reprinted with permission from ref 131b. Copyright 2000 American Chemical Society.)

Scheme 3. Polymerization of Amino Acid *N*-Carboxyanhydrides Resulting in Poly(amino acid)s

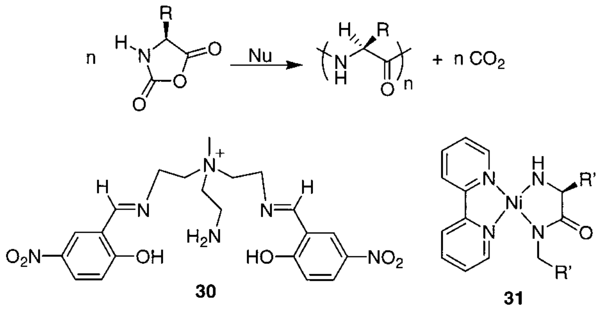
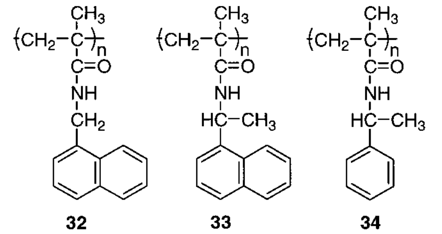


Chart 6

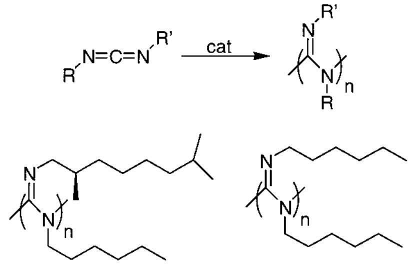


conformation (with an equal distribution of left- and right-handed helical conformations).[131] In these experiments, which showed similar results for poly(*n*-hexyl-*m*-tolylsilane), the PMPS was doped with a chiral monomer [((*S*)-2-methylbutyl)phenylsilane]. The resulting (atactic) copolymers showed a cooperative preferential helical ordering, giving rise to a distinct CD effect (Figure 13a). Molecular modeling indeed indicated the preference of both syndiotactic and isotactic polymers for a helical structure with torsion angles that deviate approximately 25° from the all-trans conformation (Figure 13b).[132] The helical order in PMPS can be expressed on a supramolecular level in helical aggregates of PMPS-*co*-poly(ethylene oxide) block copolymer as will be discussed in section IV.[133]

4. Miscellaneous. The combined set of secondary interactions, ultimately resulting in the well-defined folding of peptides, can be divided into separate contributions as was concluded from a detailed study on poly(amino acid)s. Polymers can be prepared from amino acids with an inherent propensity for adopting a given secondary structure (e.g., helices, sheets, turns), using chemical (opposite to biological) synthesis, which also allows the incorporation of D-amino acids as well as artificial amino acids.[134,135] Poly(amino acid)s have been prepared in the past from the corresponding *N*-carboxyanhydrides (NCAs) using amines or transition metals as initiators (Scheme 3). This procedure, for example, was used for growing polymers from a surface.[136,137] It results, however, in polymers with ill-defined lengths. A major advancement in controlling the degree of polymerization was achieved by Deming. Using a Ni(II) based on ligand **30** catalyst, control over the molecular weight was achieved in the polymerization of Glu–NCA.[138] Later the procedure was improved by using catalyst **31**,[139] and it was found that next to nickel also cobalt and iron initiators could be employed.[27] Using this approach, it was possible to prepare di-or triblock copolymers by subsequent polymerization of different NCAs. This allows the synthesis of polymers consisting of α-helical or random-coil blocks, as well as polymers with differently charged regions. This method clearly is suited to provide control over the parameters that are important for the organization of these macromolecules into more highly organized (tertiary) structures.[27]

Nakahari and co-workers prepared polymethacrylamides **32**–**34** (Chart 6) to study the effect of intramolecular hydrogen bonding between the amide functionalities in the side chains on the conformation of the polymers. Without stabilizing effects (e.g., without sterically demanding substituents), these types of polymers had very low helix inversion barriers and no organized secondary (helical) macromolecular structure could be observed at room temperature. From ^{1}H NMR and IR studies, it was concluded that the amount of hydrogen bonding was substantially higher for isotactic **32** and **33** than for the atactic derivatives of these polymers, although a monomolecular reference compound showed intermolecular hydrogen bonds in the same solvent even at lower concentrations.[140] More detailed studies on optically active polymers **33** and **34** led to the conclusion that more stable intramolecular hydrogen bonds are formed in the former polymer than in the latter. It was proposed that these polymers have at least a partial helical secondary structure since they maintain their structure in dioxane, a hydrogen-bond-accepting solvent. The organization in these macromolecules was disrupted by the addition of

Scheme 4. Synthesis of Polyguanidines via the Polymerization of Carbodiimines



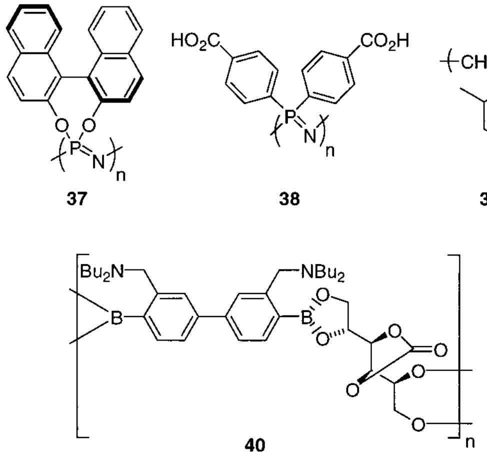
35 36

TFA.[141] Remarkably, the hydrogen bonds in **33** and **34** are weaker in thin films than in solution, although XRD measurements pointed to a hexagonal arrangement of the macromolecules, suggesting that also in this case they possess a rodlike structure.[142]

An interesting class of rigid helical polymers is obtained by the polymerization of carbodiimides (Scheme 4). These polymers, referred to as polyguanidines, can be prepared by using titanium(IV) complexes[143] and both copper(I) and copper(II) amidinate complexes[144] as catalysts. The chiroptical properties of polyguanidines have been investigated using **35** and **36** as examples, the former, in contrast to the latter, being optically active. Surprisingly, the optical rotation of **35** directly after polymerization was comparable to that of the monomer, but changed sign and increased significantly upon annealing at elevated temperatures. It was found that a kinetically controlled structure is formed during polymerization, which changes to the thermodynamically controlled helical one upon annealing (for this process $E_a = 26.8 \pm 1.3$ kJ·mol^{-1}). This process was catalyzed by acid, and addition of optically active camphorsulfonic acid to **37** (Chart 7) resulted in an excess of one helical sense from an initially racemic mixture of macromolecular helices.[145]

Studies performed by Carriedo et al. indicated that the spirocyclic phosphazene polymer **37** can adopt a helical conformation in solution.[146] Yashima et al. subsequently investigated the chiroptical response of **38** (Chart 7) upon complexation with (*R*)-α-phenylethylamine in DMSO.[147] The resulting optical rotation and its response to changes in temperature suggest that a helical conformation can also be induced in this polyphosphazene.

Chart 7



37 38 39

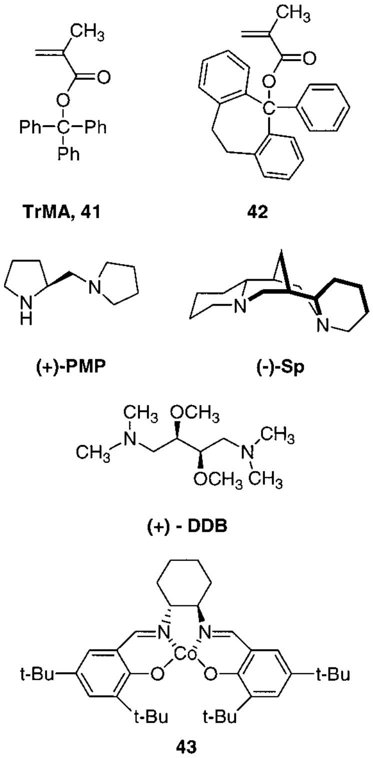
40

Isotactic vinyl polymers often possess a helical conformation in the solid state; however, without bulky substituents present (vide infra) in solution at room temperature, helix−helix reversal takes place fast and no optical activity is observed. Ortiz and Kahn reported a borderline case in which a nonbonded interaction between the monomers leads to the formation of isotactic **39** (Chart 7) by anionic polymerzation at −78 °C. Optically active polymers can be isolated, but in solution the proposed one-handed helicity is lost in less than 1 h.[148] An intriguing class of polymers formed by polycondensation of diboronic acid and chiral tetraalcohols has been studied by Mikami and Shinkai and is exemplified by polymer **40** (Chart 7). In this D-mannitol-based polymer, the noncovalent intramolecular interaction between the amines and the boron atoms imposed a sp^3-hybridization on boron, which, according to calculations, results in a helical conformation of the macromolecule.[149]

B. Helical Polymers Having High Helix Inversion Barriers

1. Sterically Restricted Poly(methacrylate ester)s. It was recognized by Okamoto and coworkers[150] that the anionic polymerization of triphenylmethyl methacrylate (TrMA, **41**) (Chart 8) at low temperature in the presence of an optically active initiator results in the formation of an isotactic, optically active polymer. The helical conformation of the backbone in these macromolecules is the result of steric interactions between the bulky trityl groups, as was shown by the loss of optical activity upon their conversion to methyl ester groups. This class of bulky

Chart 8



TrMA, 41 42

(+)-PMP (-)-Sp

(+) - DDB

43

Table 1. Asymmetric Polymerization of TrMA with (−)-Sp, (+)-DDB, and (+)-PMP−FiLi Complexes in Toluene at −78 °C[a]

			B/H[b]-insoluble part						
initiator	time (h)	yield[c] (%)	yield (%)	$[\alpha]^{25}{}_{D}$[d] (deg)	$[\theta]^{e} \times 10^{-4}$ (235 nm)	$[\theta]^{e} \times 10^{-5}$ (210 nm)	DP[f]	M_w/M_n[f]	tacticity[g] (%), mm
(i)-Sp−FiLi	24	99	82	+383	+9.42	+2.32	60	1.31	>99[h]
(+)-DDB−FiLi	24	100	93	+344	+8.45	+1.86	47	1.10	>99[h]
(+)-PMP−FiLi	3	100	94	+334	+7.78	+1.76	39	1.12	>99[h]

[a] Reprinted with permission from ref 153. Copyright 1992 American Chemical Society. Conditions: TrMA, 1.0 g; toluene, 20 mL; [TrMA]/[Li] = 20. [b] A mixture of benzene and hexane (1:2, v/v). [c] CH_3OH = insoluble part. [d] $c = 0.5$ (tetrahydrofuran). [e] The CD spectrum was measured in tetrahydrofuran at ca. 25 °C. Units: $cm^2\ dmol^{-1}$. [f] Determined by GPC of poly(MMA) derived from poly(TrMA). [g] Determined by ^1H NMR of poly(MMA) derived from poly(TrMA). [h] The signals due to the racemo sequence were found only in the termination end.

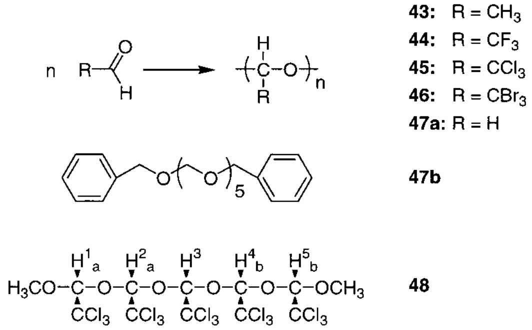
poly(methacrylate ester)s has been extensively explored and reviewed by Okamoto and his group,[151,152] and only a brief outline is given here.

Different chiral auxiliary ligands (Chart 8) can be used in the polymerization of **41** with organolithium compounds, resulting in polymers with high optical activities and an almost perfect isotactic configuration of the polymer backbone.[153] Some of the results of this asymmetric polymerization reaction are summarized in Table 1. It appears that the optical activity of the resulting macromolecules increases with the length of the polymer chain and that apart from the highly optically active polymer also a small amount of oligomers with low optical activity is formed. On the basis of these observations, it has been assumed that growing chains with a specific favorable stereoconfiguration propagate relatively fast, while others having the other, unfavorable stereochemistry do not grow beyond the oligomer stage. This kinetic control over the helicity has been confirmed by helix-induced asymmetric polymerization experiments.[154] Using the aforementioned approach, a helical TrMA prepolymer was synthesized, the living chain end of which could be used to subsequently polymerize bulky methacrylate esters in an asymmetric manner.

Screening of an impressive series of polymers derived from different bulky methacrylate esters, e.g., **42** (Chart 8), and using a variety of chiral ligands has revealed the scope of the process of forming helical poly(methacrylate ester)s and their applicability in, for example, the separation of chiral compounds.[151] These polymers were prepared not only by anionic polymerization, but also by cationic, free-radical, and Ziegler−Natta techniques. Recently, Nakano and Okamoto reported the use of a cobalt(II)−salophen complex (**43**) in the polymerization of methacrylate ester **41**.[155] The free-radical polymerization in the presence of this optically active metal complex resulted in the formation of an almost completely isotactic polymer with an excess of one helical sense.

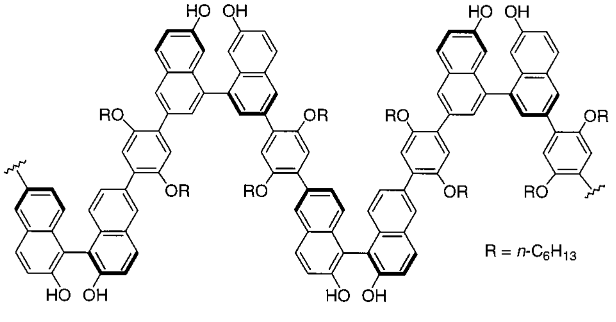
2. Phthalocyaninatopolysiloxane. Engelkamp et al. have demonstrated that dihydroxyphthalocyanatosilicon modified with eight (*S*)-citronellol side groups can be polymerized using procedures developed for the related *n*-alkyl derivatives.[156] The resulting material had an estimated degree of polymerization of 27 and was found to be strongly CD active. The CD effects were attributed to a rotational offset of the neighboring monomers, leading to a helical organization in the polymer chain. This arrangement was shown to be different in gel-assembled stacks of the corresponding metal-free crown ether phthalocyanines and is possibly imposed by the fixed intermonomer distances. These helices do not show any sign of helix reversal up to temperatures of 120 °C as was concluded from VT NMR experiments.

Scheme 5. Synthesis of Polyaldehydes



3. Polyaldehydes. Polyaldehydes are characterized by an oxymethylene repeat unit (Scheme 5), and depending on the substituents present on the carbon atoms, a helical conformation can be present. Research activities related to these compounds have recently been reviewed by Vogl.[157−159] The all-gauche and hence helical organization of oligoformaldehyde **47** in the solid state was demonstrated by a single-crystal X-ray study.[160] Polymerization of higher aldehydes generally takes place in the gel phase, a condition which appears to contribute significantly to the stereoregularity of the resulting polymers. The most intensively studied polyaldehyde is poly(trichloroacetaldehyde) (polychloral, **45**). Isotactic polychloral is prepared by anionic polymerization and is insoluble in organic solvents. By using optically active lithium alkoxides as initiators, polymers are obtained which display high optical activities in films. For polychloral, a 4/1-helical conformation with a helical pitch of 0.51 nm was found using X-ray diffraction analysis. Due to the insolublitity of these materials, no conformational studies have been performed in solution; however, molecular mechanics calculations and NMR spectroscopic and crystallographic studies indicated similar helical characteristics for well-defined oligomers. Although pentamer **48** is symmetric, nonequivalent signals were found for all protons in the solution NMR spectra at 30 °C and attributed to a helical conformation. From VT NMR

Chart 9



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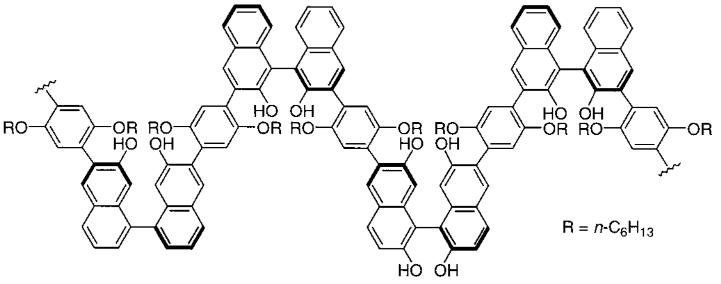

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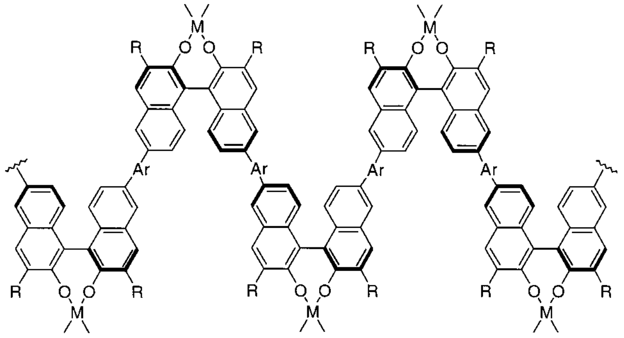


51'

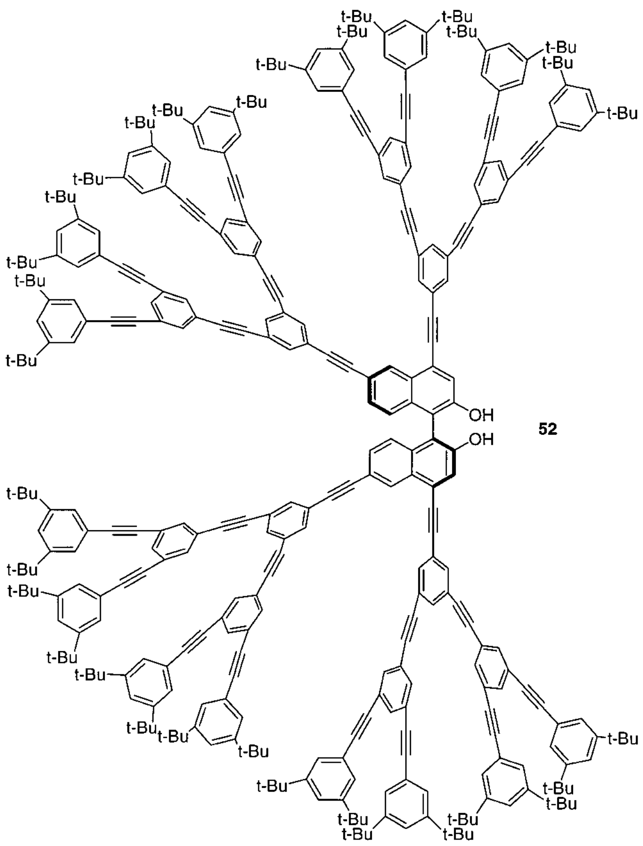
experiments, the activation energy (E_a) and the rate of transition from one helical conformation to the other one were determined to be 68.6 kJ·mol^{-1} and 3.9 s^{-1} at 20 °C, respectively.[161]

4. Binaphthyl-Based Polymers. Molecules that derive their chirality from their molecular geometry, e.g., helicenes, can be used to construct architectures in which the chirality of the individual molecules is amplified and perpetuates over long distances (see also section II).[162] Katz et al. have prepared oligomers with more than one helical turn based on bissalicylaldimine.[163] The helical conformation of these molecules has a marked effect on their optical properties; i.e., very intense absorption bands and CD effects were observed compared to those of the low-molecular-weight parent compounds. Extending this concept further, higher-molecular-weight materials have been obtained via the linking of conjugated segments with optically active 1,1′-binaphthyl groups as was reported and recently reviewed by Pu.[108] Pu et al. have used binaphthyl linkers to connect a large variety of conjugated molecules such as aryleneethynylenes, phenylenevinylenes, polythiophenes, oligophenylenes, and oligoethynylenes (e.g., **49**) (Chart 9). In the cases where the linkers contain phenyl groups, meta as well as para substitution has been used. In the former case, this leads to the introduction of an extra turn in the polymer backbone, whereas, in the latter case, the turns are exclusively due to the binaphthyl groups. The resulting materials have a rigid helical comformation and can be applied to anchor catalytic complexes based on Al(III) and Zn(II) via the hydroxy groups on their naphthyl units.[164] The twist in the backbone of the polymer molecules can be tuned by connecting the conjugated segments either via the 3,3′-positions or via the 6,6′-positions (**50**) (Chart 9). Connection at the 3,3′-positions provides better control over the conformation of the catalytic center, and also allows interaction of substituents on the conjugated segments with the metal. These modifications allow tuning of the catalytic properties and have led to the finding of good chemical yields and excellent enantioselectivities in, e.g., the asymmetric reduction of aldehydes and the epoxidation of α,*β*-unsaturated ketones. By synthesizing copolymers containing alternating BINOL and BINAP groups, a mixed Ru(III)−Zn(II) catalyst was prepared (**51**). This catalyst was able to perform an asymmetric tandem reaction involving a diethylzinc addition to acetylbenzaldehyde and the subsequent catalytic hydrogenation of the product to form the corresponding diol in chemical yields larger than 99% and with diastereoselectivities of 75−87%.

On the basis of the same principles, Pu et al. have synthesized a chiral dendritic compond (**52**) (Chart 10) which shows fluorescence quenching upon binding of amino alcohols. An enantioselective response was observed on addition of a number of amino alcohols; the most significant effect was obtained with phenylalaninol.[165]

5. Polyisocyanides. Polymers of isocyanides have the exceptional feature that every carbon atom in the main chain is provided with a substituent (Scheme 6). It was already proposed by Millich[166] that these macromolecules would have a helical conformation as the result of a restricted rotation around the single bonds constituting the polymeric backbone. Until Nolte's report on the applicability of Ni(II) as a catalyst for the polymerization of isocyanides, routes toward polyisocyanides were limited.[167] This transition-metal catalyst allowed the polymerization of the sterically demanding poly(*tert*-butyl isocyanide) (**53**), which subsequently could be resolved by chromatography into the left- and the right-handed helical forms using poly[(*S*)-*sec*-butyl isocyanide] as the stationary phase.[168] These experiments confirmed the

Chart 10



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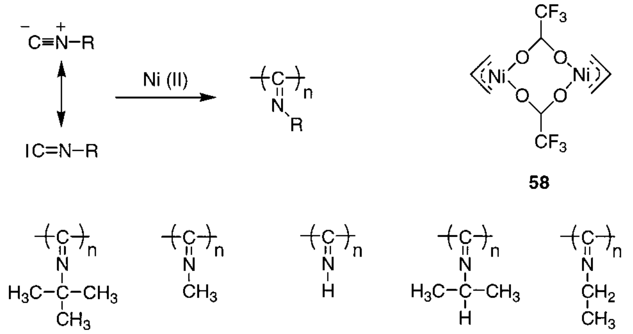
Scheme 6. Nickel(II)-Catalyzed Polymerization of Isocyanides



58

53 54 55 56 57

structural proposition of Millich and provided the first example of an optically active polymer solely based on the stable helical conformation of the backbone.[168]

The nickel(II)-catalyzed polymerization of isocyanides proceeds relatively fast, a remarkable observation given the steric crowding that is introduced upon formation of the polymer chain. The driving force for the reaction is the conversion of a formally divalent carbon in the monomer into a tetravalent carbon in the polymer, yielding a heat of polymerization of 81.4 kJ·mol^{-1}.[169] For this polymerization reaction, a *merry-go-round mechanism* has been proposed. Upon mixing of the isocyanides with the Ni(II) catalyst, a square-planar complex is formed (Scheme 7), which in some occasions can be isolated when bulky isocyanides are used. Subsequent attack by a nucleophile on one of the isocyanide ligands is the initiation step of the polymerization reaction. Via coordination to the nickel (step a), this nucleophile migrates to the isocyanide and a carbene-like intermediate is observed (step b). In the presence of a chiral bias (introduced in the monomer or in the nucleophile), there is a preference for reacting with specifically one of the two neighboring isocyanide monomers on the nickel. After this step, the free coordination position is occupied by an isocyanide from solution (step c), the reaction sequence continues in the direction of the initial step (i.e., one particular helical sense is formed), and each rotation around the nickel adds one turn to the helix (step d). In the absence of a chiral bias, there is an equal probability of attack of the carbene-like carbon atom on both neighboring ligands, leading to a racemic mixture of helical polymers. The easy formation of the tightly coiled helix is explained by the preorganizing effect of the nickel center: only a slight rearrangement of bonds is required to form the polymer molecule.

The merry-go-round mechanism of isocyanide polymerization can be used to explain and predict a number of the properties of polyisocyanides.[169] However, work by Deming and Novak indicated that some aspects of the mechanism are more complex and involve the reduction of Ni(II) to Ni(I) during the polymerization reaction. Using ESR, cyclic voltammetry, and magnetic susceptibility measurements, it was shown that when an excess (10 equiv) of *tert*-butyl isocyanide is added to $NiCl_2$, the isocyanide acts as a reductant and an inactive nickel(I) catalyst is formed. Under atmospheric conditions, this reduced catalyst is reoxidized by oxygen to the more active nickel(II) species. The optimum oxygen concentration appears to be at 1 atm of air. At high oxygen contents, no polymerization occurs; instead, the nickel catalyzes the oxidation of the isocyanide to the isocyanate.[170] Taking into account these observations, Deming and Novak investigated the electron-deficient η^3-allylnickel trifluoroacetate (**58**) as a polymerization catalyst. They found it to be a highly active system (Table 2) which, in a noncoordinating solvent, displayed living chain growth behavior.[171]

Detailed kinetic and mechanistic investigations have been carried out by Deming and Novak employing this type of Ni catalyst. In toluene, a linear relation was found between the monomer conversion and the degree of polymerization as well as between the catalyst-to-monomer ratio and the molecular weight, for a system consisting of **58** and α-methylbenzyl isocyanide (for racemic as well as for pure enantiomers).[171] It also appeared possible to copolymerize a second isocyanide monomer (e.g., **53**) after complete consumption of the first one. Different kinetic behavior was observed under a N_2 atmosphere compared to an O_2-rich environment. Under N_2, the polymerizaton was found to be first order in monomer, obeying the rate expression $v_p = k_{obsd}$[catalyst][monomer], with $k_{obsd}(298\ K) = 3.7(1) \times 10^{-2}\ L{\cdot}mol^{-1}{\cdot}s^{-1}$. Under O_2, the rate was found to be zero order in monomer ($v_p = k_{obsd}$[catalyst], with $k_{obs}(298\ K) = 5.1(1) \times 10^{-2}\ s^{-1}$).[172] Although these rate constants are comparable, in such cases, a zero-order

Scheme 7. Merry-go-Round Mechanism in Ni(II)-Catalyzed Isocyanide Polymerization

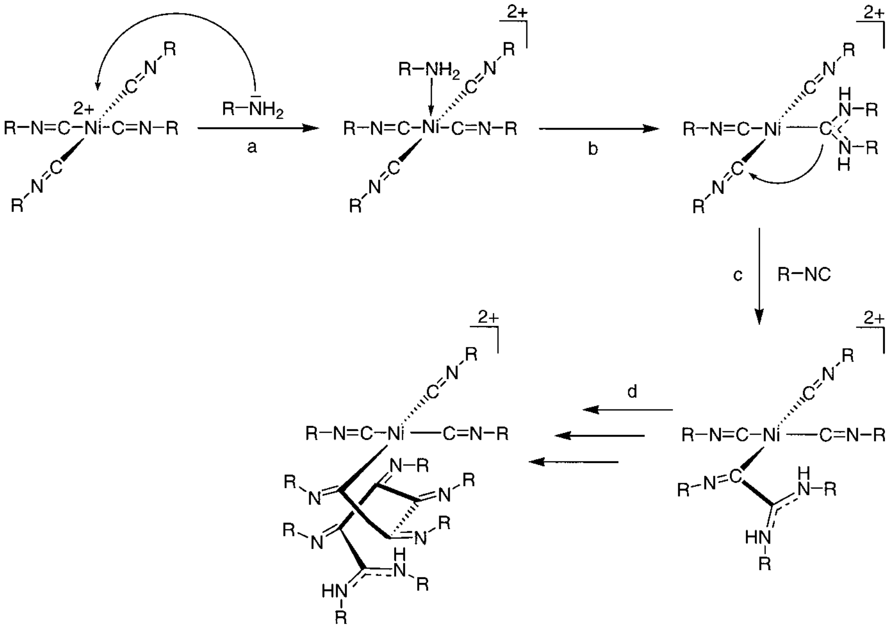


Table 2. Molecular Weight Characteristics of Selected Polymers[a]

monomer	catalyst	conditions	yield (%)	M_n	M_w/M_n
tert-C_4H_9NC	**58**	N_2, neat	100	2200	1.03
$C_6H_5CH(CH_3)NC$	$NiCl_2$	N_2, H_2O	75	13220	1.45
$C_6H_5CH(CH_3)NC$	$NiCl_2$	air, H_2O	100	7420	1.64
$C_6H_5CH(CH_3)NC$	**58**	N_2, toluene	100	24000	1.15

[a] Reprinted with permission from ref 171. Copyright 1992 American Chemical Society.

reaction will appear faster than a first-order reaction, due to the lack of rate dependence on monomer concentration. The differences in transition state were examined by determination of thermodynamic activation parameters by performing an Eyring analysis of the rate constants.[173] More kinetic data have been reported by Deming and Novak investigating substituent effects on the monomer[174] and by Hong and Fox using functional isocyanides.[175] An in-depth discussion of the mechanistic parameters based on these results is beyond the scope of this review, and for this we refer to the work cited.[176]

The conformation of polyisocyanides has been the subject of several computational studies. Using the extended Hückel theory, Kollmar and Hoffmann showed that repulsion between the lone pairs of the imino groups in a polyisocyanide chain favors a departure from a planar structure.[177] Similar repulsive effects are known to be operative in polyketones as was reported by Cui and Kertesz, who found a new type of helical Peierls-like distortion for polyketone and polyisocyanide. They suggested that as a result of the existence of partially filled crossing bands a helical structure is formed.[178] Calculations by Kollmar and Hoffman on the series of polymers **53**−**55** indicated that steric effects are more important than electronic effects in determining the polymer structure. For the hypothetical polymer **55**, a broad range of helical conformations was predicted, in contrast to **53** for which the authors proposed a rigid 4/1-helix. According to this theoretical analysis, polymer **54**, which only is moderately sterically restricted, may adopt two helical structures with different dihedral angles.

Huige and Hezemans[179,180] have performed extensive molecular mechanics calculations using the consistent force-field method on various oligo- and polyisocyanides. The hexadecamer of *tert*-butyl isocyanide was calculated to have a helical middle section and disordered ends. The dihedral angle N=C−C=N in the middle section was found to be 78.6°, and the number of repeat units per helical turn was 3.75. The latter number is in agreement with circular dichroism calculations using Tinoco's exciton theory (3.6−4.6) and De Voe's polarizability theory (3.81). The molecular mechanics calculations further predicted that the less bulky polymers **56** and **57** form helical polymers as well, whereas a disordered structure was calculated for poly(methyl isocyanide) (**55**).

Clericuzio et al. recently published ab initio and molecular mechanics studies on octameric oligoisocyanides. These calculations, in contrast to the aforementioned ones, showed the so-called syndio conformation to be the minimum-energy geometry although the 4/1 conformation was recognized as a local minimum (Figure 14).[181] The obtained set of data was used to tentatively explain some of the features in the UV/vis, CD, and ^{13}C NMR spectra of compounds prepared by Salvadori's[182] and Green's groups.[183] Regarding properties such as optical absorptions at long wavelengths, low intensity of the CD bands, and the chemical shift dispersion of backbone carbon atom resonances, the calculations were found to fit the experimental results. Nevertheless, the outcome of the calculations is the thermodynamic minimum conformation of the polymer backbone, whereas the polymerization is kinetically controlled, possibly leading to a different conformation. However, if the helix inversion barrier is not too high, the 4/1-helix imposed during the polymer-

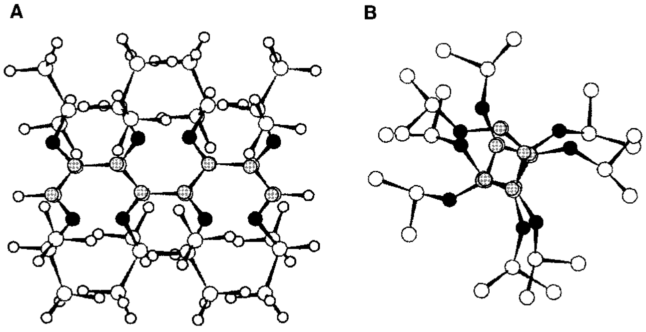


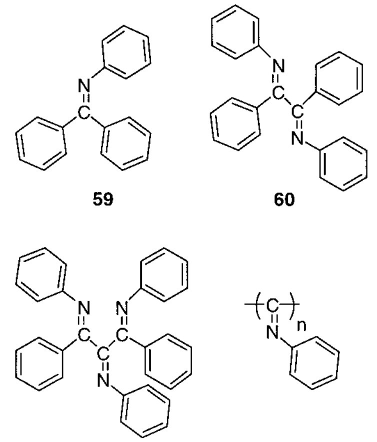
Figure 14. Models of the (a) syndio conformation and (b) 4/1-helical conformation of poly(isopropyl isocyanide) (**56**). (Reprinted with permission from ref 181. Copyright 1997 American Chemical Society.)

ization reaction may unfold to give the proposed syndio conformation.

In-depth studies of the absolute conformations of polyisocyanides are limited. Green and co-workers found,[183] using ^{13}C NMR and light scattering experiments, a limited persistence length (~3 nm) for polyisocyanides without bulky substituents. By means of NMR techniques, Spencer et al.[184,185] studied oligoimine compounds **59**−**61** as model compounds for polymer **62** (Chart 11). In particular for the triimine **61**, the conformational analysis is in line with the model of Clericuzio et al.[181] (vide infra). In the case of polymer **62**, a combination of GPC, light scattering, and X-ray diffraction showed that the native polyisocyanide has rigid-rod character, but slowly precipitates from solution as a random coil. Using UV/vis spectroscopy, the Arrhenius activation energies for this rod-to-coil transition were determined in different solvents; $E_a(CCl_4) = 44$ kJ·mol^{-1}, $E_a(THF) = 51$ kJ·mol^{-1}, and $E_a(CH_2Cl_2) = 70$ kJ·mol^{-1}.[186] These data indeed suggest that the helix inversion barrier for **62** is not sufficiently high to have a stable helical conformation at room temperature, but that as a result of the merry-go-round mechanism initially the 4/1-helix is formed as the kinetic product. Helical poly(*tert*-butyl isocyanide) (**53**), obtained by chiral resolution,[168] retains its optical activity even at elevated temperatures.[187] This enabled the use of this polyisocyanide as a chiral absorbent in liquid column chromatography although a different procedure was used for preparing it in the optically active form.[188]

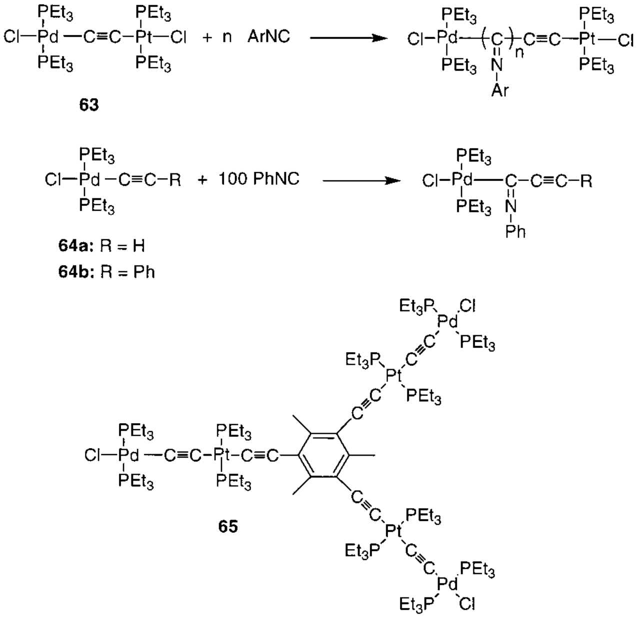
Several procedures have been established in the past for the helix-sense-selective polymerization of isocyanides.[169] For the introduction of a chiral bias, required for the discrimination of the otherwise enantiomeric helical senses, three distinct approaches can be applied. One is the use of a chiral monomer, which makes the left- and right-handed helices diastereotopic, and as a result one of the two will be energetically favorable (Figure 5). A second approach involves the use of a chiral catalyst or a chiral initiator, in which case during the initiation of the polymerization there will be a preference for the formation of one particular helical sense that will be retained upon propagation due to the helix inversion barrier. The former approach has been employed in numerous cases (vide infra); the accounts of the use of optically active Ni catalysts are limited.[189−192] The third approach is the selective restraining of the growth of one particular helix by addition of a sterically encumbered optically active comonomer to an achiral one. Polymerization of a fast propagating isocyanide of the latter type (e.g., phenyl isocyanide, 4-methoxyphenyl isocyanide) in the presence of the slowly polymerizing (*S*)-isocyanoisovaleric acid leads to the formation of P-helical high-molecular-weight homopolymers of the former isocyanide and M-helical copolymers with a substantially lower degree of polymerization. Upon copolymerization, the bulky chiral monomer prefers to be included into M-type helices and slows their propagation, while the P-helices continue to grow fast and consequently consume the majority of the achiral monomer.[193]

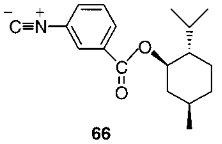
Chart 11



An alternative to the nickel-catalyzed synthesis of polyisocyanides has been developed by Takahashi and co-workers.[194] They found that the dinuclear palladium−platinum *μ*-ethynediyl complex **63**[195] is active in the polymerization of aryl isocyanides (Scheme 8),[196] but not with alkyl isocyanides. The isocyanides exclusively insert into the Pd−C bond, but not into the Pt−C bond.[197] The importance of the Pt−C bond, however, is highlighted by the fact that only one isocyanide monomer is inserted into complex **64** although a 100-fold excess was used. The living nature of the catalyst was shown by the formation of block copolymers, which was possible since the active Pd end groups remained connected to the polymer when all monomers were consumed. Using this feature, it proved to be possible to polymerize an achiral isocyanide with an oligomer prepared from an optically active isocyanide.[198] This procedure, however, was only applicable for initiating complexes in which the oligomer exceeds a critical degree of polymerization, and the optical activity is only retained in the case of sterically demanding achiral isocyanides. Initiators may carry multiple palladium−platinum *μ*-ethynediyl units as was demonstrated by preparation of polyisocyanides from **65**.[199] A detailed study on the helix-sense-selective polymerization using chiral oligomer complexes derived from isocyanides **66** and **67** gave some interesting results.[200] First, the optical activity of the polymers, expressed in their optical rotation and CD effects, drastically increased in going from the meta-substituted aryl isocyanides **66** to the para-substituted ones **67**.

Scheme 8. Polymerization of Isocyanides by a Dinuclear Palladium−Platinum μ-Ethynediyl Complex




66

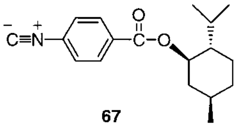

67

Chart 12

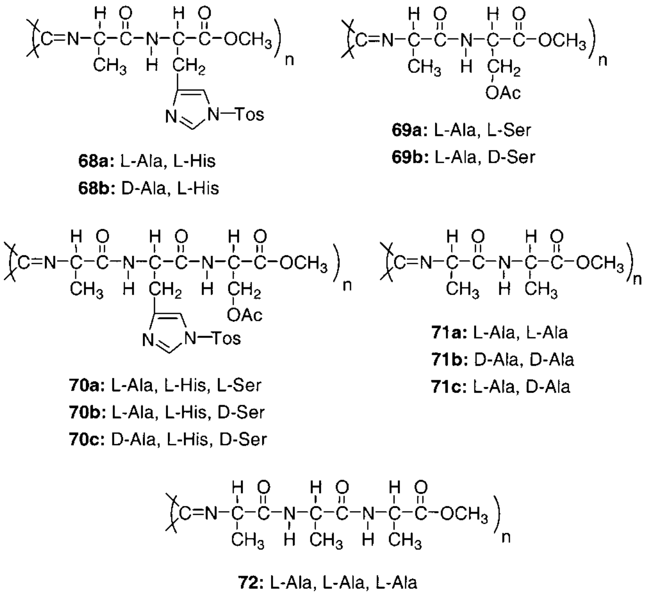

68a: L-Ala, L-His
68b: D-Ala, L-His
69a: L-Ala, L-Ser
69b: L-Ala, D-Ser
70a: L-Ala, L-His, L-Ser
70b: L-Ala, L-His, D-Ser
70c: D-Ala, L-His, D-Ser
71a: L-Ala, L-Ala
71b: D-Ala, D-Ala
71c: L-Ala, D-Ala
72: L-Ala, L-Ala, L-Ala

Table 3. Selected Infrared and ^{1}H NMR Data of Isocyanopeptides and their Polymers[207]

	isocyanopeptide			peptide polymer		
	ν_{NH}[a] (KBr)	ν_{NH}[a] **(CDCl$_3$)**	δ_{NH}[b] (CDCl$_3$)	ν_{NH}[a] (KBr)	ν_{NH}[a] (CDCl$_3$)	δ_{NH}[b] (CDCl$_3$)
71a	3279	3430[c]	6.91	3276	3265	9.18[c]
71c	3304	3416	6.97	3280	3252	9.42
72	3315	3420[d]	7.04	3300	3290	9.50
	3285		6.38	3267	3260	7.81

[a] In cm^{-1}. [b] In ppm. [c] Split signals; average values are given. [d] In a non-hydrogen-bonded state, only one signal is observed for both N−H vibrations. All measurements were performed at room temperature.

Second, the rate constants for propagation were virtually identical no matter whether the monomer that was incorporated had the same or the opposite chirality as the one constituting the initiating oligomer. This suggests thermodynamic rather than kinetic control over the helical sense, which contradicts the high helix inversion barrier previously proposed for helical polyisocyanides. However, the observation of a nonlinear relation between the optical purity of the isocyanide and the induced helical sense in the polymer[201] (majority rules concept) confirms this suggestion. These observations indicate that factors other than steric interactions may be operative during the synthesis of these particular polyisocyanides.

Nonsteric helix-stabilizing effects have recently been reported for peptide-derived polyisocyanides. Polymers built from di- and tripeptide-based isocyanides containing different functional groups have been synthesized as protease mimics (Chart 12; **68**−**70**).[202−204] More recently compounds **71** and **72** (Chart 12) were synthesized to investigate the effect of this hydrogen bonding between side chains on the conformational properties of the polymer backbone.[205−207] IR and ^{1}H NMR studies in which the amide NH characteristic bands and signals of the monomer were compared with those of the polymer showed the involvement of the side-chain amide groups in well-defined arrays of hydrogen bonds along the polymeric backbone. In these studies the single-crystal X-ray structure of the monomer of **71a** served as a reference point (Table 3).

The hydrogen bonds are formed between the amide carbonyl groups in side chains *n* and the amide NH groups in side chains *n* + 4 (Figure 15). In the case of the tripeptide-derived polyisocyanide **72**, a similar β-sheet-like hydrogen-bonding arrangement was found. This chiral architecture, based on secondary interactions, represents a mimic of the naturally occurring β-helices, which are recently discovered structural motifs in proteins.[208] The additional interactions between the side chains stabilize the helical conformation of these polymers, leading to an enhanced rigidity. This rigidity was reflected, for

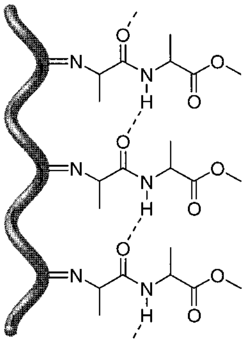
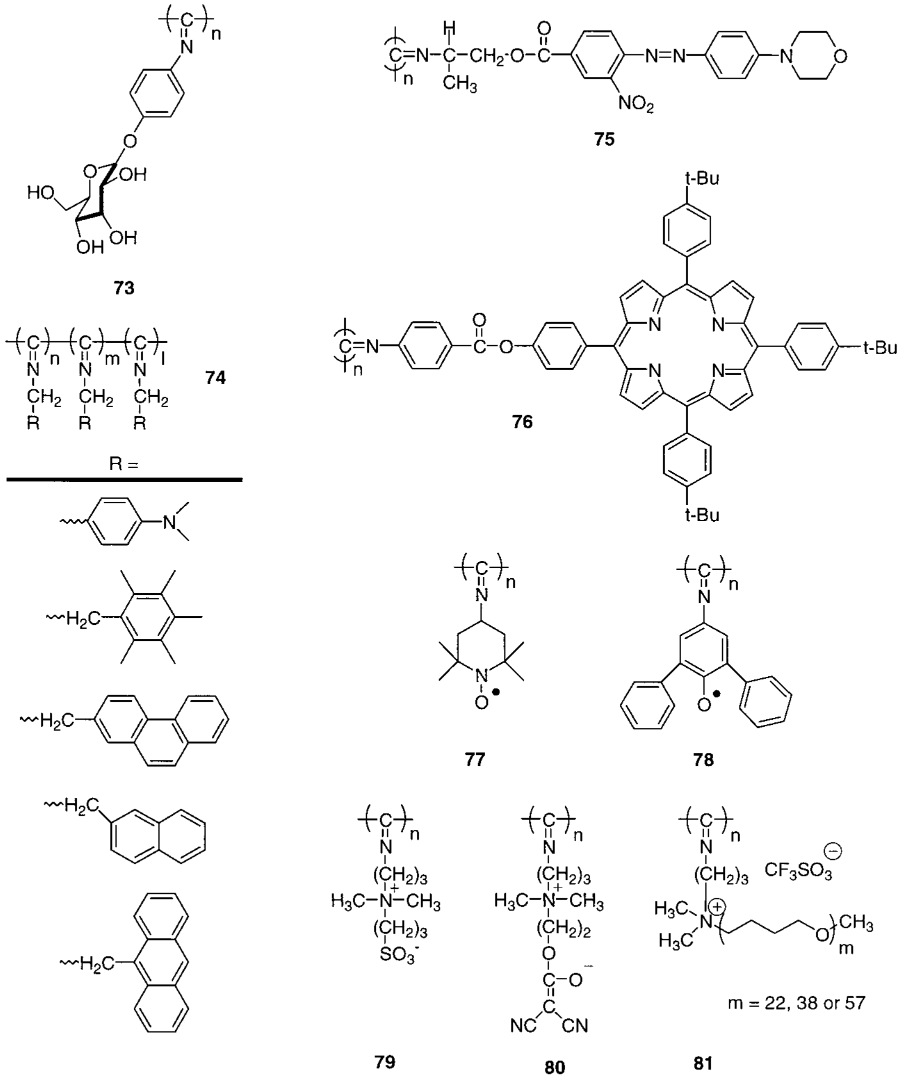


Figure 15. Schematic representation of the hydrogen-bonding array in peptide-derived polyisocyanide **71b**.

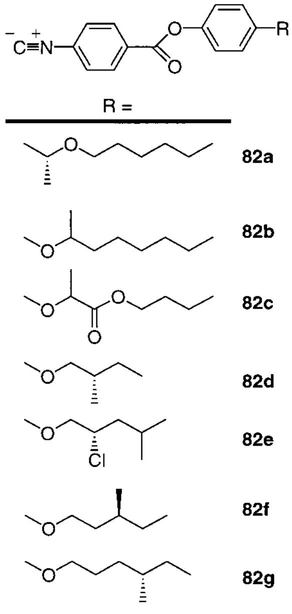
Chart 13



example, in the well-defined hexagonal organization of the molecules in the solid state as well as in the formation of a lyotropic liquid crystalline phase in concentrated $CHCl_3$ solution. Similar to the unfolding of proteins, the disruption of the hydrogen bonds in the polymers proceeds in a cooperative fashion as could be monitored by CD spectroscopy.[202] Although not recognized at that time, some of the intriguing physical properties of polyisocyanides **68**−**70** synthesized in the early 1980s, e.g., pK_a values which strongly deviate from those of amino acids and very intense Cotton effects, can now be explained by the presence of an intramolecular chain of hydrogen bonds between the peptide side groups.

Hasegawa et al. reported on glycosylated poly(phenyl isocyanide)s primarily to study the recognition of lectins by these polymers,[209] as well as the adsorption and self-organizing properties of these polymers (in particular **73**) (Chart 13) on a hydrophilic surface.[210] Molecular dynamics calculations indicated that also in this case additional stabilization of the helical backbone by hydrogen bonding between side-chain residues takes place. Due to the high saccharide density along the rigid polyisocyanide backbone, the binding affinity of lectins was approximately 100 times lower than for flexible glycoproteins. Hong and Fox[175] synthesized block copolymer **74** (Chart 13) with a rigid backbone to spatially organize chromophores and quencher groups to study directional electron transfer and energy migration.[211] Excimer formation, which is a complication observed in flexible polymeric systems, is depressed, and long-living charge-separated states are observed. Both features are in line with the rigid character of the polymer, despite the absence of limiting steric interactions close to the backbone imine groups. Extensive nonlinear optical studies have been performed by Persoons and co-workers[212,213] on **75** (Chart 13) and related compounds.[214−216] Second-harmonic light was generated by Langmuir−Blodgett films of these polyisocyanides but not by spin-coated or -cast films. This NLO activity probably results from a side-chain orientation realized at the air−water interface. In solution the orientational correlation between the side-chain chromophores led to unexpectedly high first hyperpolarizabilities (exceeding 5000 × 10^{-30} eu). The breaking of centrosymmetry, which is required for a second-order nonlinear response, could be attributed to the consistent angle of ~60° these chromophores make with the axis of the helical backbone, rather than to the helical organization itself.

Chart 14



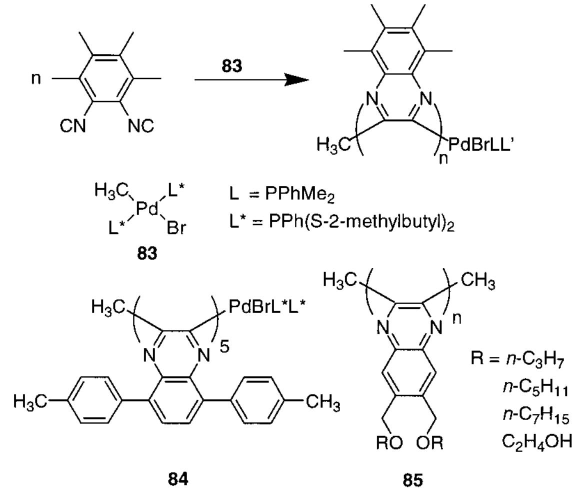
Recently, isocyanides containing a porphyrin group have been polymerized using the palladium−platinum μ-ethynediyl catalyst discussed above (e.g., **76**) (Chart 13).[217] Longer polymers (DP > 30) show a distinct splitting of the Soret band, indicating stacking of the porphyrins connected to the helical backbone. Other investigations toward polyisocyanides with potential applications as functional devices or specialty materials comprise the polymers **77** and **78** (Chart 13), designed as macromolecular ferromagnets; however, no paramagnetic bulk behavior was found.[218−220]

Galin and co-workers have synthesized the zwitterionic polymers **79** and **80** (Chart 13) as potential lyotropic liquid crystals and as complexing agents for alkali-metal salts.[221] Although only local ordering phenomena were found, the persistence length of the polyisocyanides was increased by a factor of 2, compared to poly(dizwitterionic methacrylate)s. The same group also prepared the "superhairy" polymer **81** (Chart 13), which behaved as a cationic polyamphiphile.[222] Further applications for these polymers, e.g., as lyotropic or thermotropic polymeric materials, may be foreseen.

Polyisocyanides with cholesterol-containing pendant groups have been reported to display thermotropic liquid crystalline properties.[223]

It was demonstrated that a stereocenter positioned far away from the reactive isocyanide group as in monomer **82b** (Chart 14) can still induce chirality in the main chain of polyisocyanides, resulting in the formation of an excess of one particular helix.[224−226] Kinetic control over the helix sense in the polymerization of **82b** was confirmed by the noncooperative transfer of chirality from the monomer to the macromolecule; e.g., a linear relation was found between the ee present in the isocyanide and the optical activity in the polymers formed.[227] The kinetic inhibition of the growth of one particular handedness using (S)-2-isocyanovaleric acid[184] (vide supra) is used to force **82b** and **82c** into a macromolecular helicity with a screw sense opposite that of the one preferred by homopolymers of these isocyanides. Using this procedure, it is possible to create diastereomeric helices that include monomeric building blocks of identical absolute configuration but have opposite helical secondary structures.

Scheme 9. Palladium(II)-Catalyzed Polymerization of 1,2-Diisocyanoarenes to Polyquinoxalines



The palladium-catalyzed polymerization of 1,2-diisocyanoarenes has been reported to result in the formation of a different type of helical polyisocyanide (Scheme 9), referred to as a poly(2,3-quinoxaline).[228] Using Pd complexes **83** with chiral phosphine ligands (e.g., bis((S)-2-methylbutyl)phenylphosphine) as catalysts in the polymerization of 1,2-diisocyano-3,6-di-p-tolylbenzene did not lead to polymers with a large excess of one handedness, but it was possible to separate the optically pure pentamers **84**. Because these oligomers still contained the Pd(II) center, it was possible to subsequently use these compounds as initiators for the helix-sense-selective polymerization of other 1,2-diisocyanoarenes.[229] The chiral selectivity is caused by the helical oligomer and not by the phosphine substituent as was demonstrated by ligand exchange experiments.[230] When a chiral Pd catalyst was derived from an optically active binaphthyl compound, the X-ray structure of a stable and rigid helical structure of the growing oligo(quinoxalinyl)palladium(II) complex could be solved.[231] The helical conformation of poly(2,3-quinoxaline)s was confirmed through empirical calculations. Two minimal energy conformations were determined, from which the theoretical CD spectra based on the exicton theory were calculated. It was found that the experimental CD spectrum for (+)-poly(2,3-quinoxaline) was in agreement with the spectrum calculated for a right-handed helix with a dihedral angle between the planes of adjacent quinoxalines of 135°.[232]

Homopolymers and block copolymers of poly(2,3-quinoxaline)s containing functional side chains (**85**) have been prepared employing the Pd(II)-catalyzed helix-sense-selective polymerization.[233−235] Recently is was reported that side chains can be modified without the quenching of the living site of the polymer.[236,237] The helical induction by the 1,1′-binaphth-2-ylpalladium(II) complexes has been investigated in detail, mainly using NMR techniques.

It was found that the choice of substituents on the binaphthyl groups strongly affected the diastereomeric formation of oligomeric intermediates, the screw sense of which was maintained in the further helix-sense-selective propagation steps.[238]

IV. Chiral Macromolecular Architectures: Tertiary Structure

The interaction between chiral molecules may lead to superb properties and well-defined function as is exemplified in Nature by the high tensile strength in the α-helical coiled-coil superstructure in myosin and the storage of genetic information in the double helix of DNA. The design and synthesis of chiral superstructures in synthetic macromolecular systems is currently being studied by various groups. In the generation of such tertiary structures, i.e., structures with order beyond the constituting elements, two distinct categories may be distinguished, which will be discussed in the following sections: (1) the self-assembly of chiral polymers that do not have a secondary structure in solution, leading to the formation of aggregates with induced chirality, and (2) the self-assembly of helical macromolecules in solution, leading to chiral hierarchical structures. The discussion will be limited to macromolecular assemblages in solution; thin films and bulk materials formed by these polymers will only be mentioned as examples to illustrate interesting phenomena.

1. Chiral Architectures from Nonhelical Polymers. Association of stereoregular polymers belongs to this category since for a number of these so-called stereo complexes a helical superstructure is found.[239] The formation of such macromolecular complexes can be achieved using different secondary interactions of varying strength,[245] although van der Waals forces are the most frequently observed. In particular, the complexation between isotactic (*it*-PMMA) and syndiotactic (*st*-PMMA) PMMA has been investigated in great detail.[240] Despite the intense efforts of several research groups in this area,[241,242] the exact mechanism of stereo complex formation is still under debate.[243] The same type of stereo complex is formed independent of the method of preparation and the initial *it*/*st* ratio.[244] This complex comprises a double-stranded 9/1-helix with an asymmetric unit consisting of one *it*-PMMA unit and two *st*-PMMA units (Figure 16).[245,246]

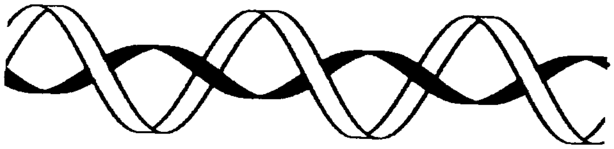


Figure 16. Schematic representation of the stereo complex of *it*-PMMA (black ribbon) surrounded by *st*-PMMA.

Another type of stereo complex, i.e., a tightly wound 3/1-helix, is formed when polymers of L-lactic acid (PLLA) and D-lactic acid (PDLA) are mixed in the blend.[247,248] Also in solution aggregation of block copolymers containing PLA segments has been found;[249,250] however, no studies toward the morphology of the aggregates have been conducted.

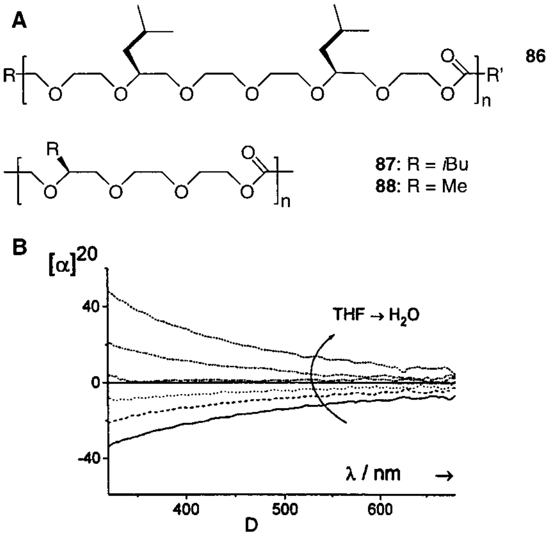
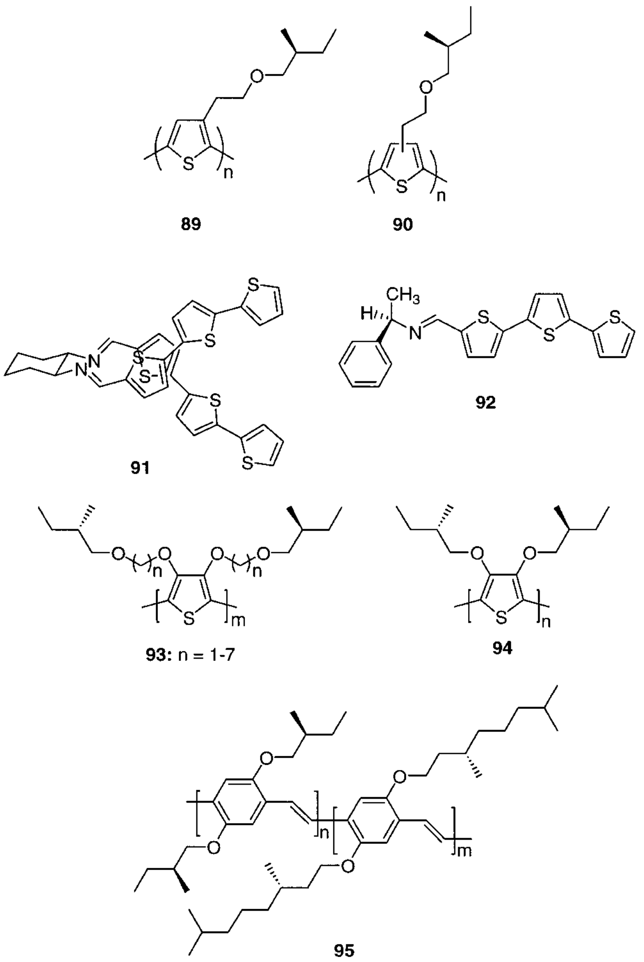


Figure 17. (a) Structures of optically active poly(ethylene oxide) derivatives. (b) ORD spectra of **88** in THF upon increasing the water content. (Reprinted with permission from ref 253. Copyright 1997 American Chemical Society.)

Meijer and co-workers[251] have reported the aggregation of ribbon-type amphiphilic polymers, based on chiral, substituted poly(ethylene oxide)s (PEOs), as synthetic analogues of coiled-coil-forming peptides (Figure 17). Polymers **86**–**88** were prepared by ring-opening polymerization of 2-oxo(crown ether) monomers or by polycondensation of the corresponding ω-hydroxycarboxylic acids.[252] The amphiphilic nature of these poly(ethylene oxide)s modified with hydrophobic side chains was confirmed by fluorescence studies, giving critical aggregation constants (cac's) covering a wide range (from 0.002 mg·mL^{-1} for **86** to 0.15 mg·mL^{-1} for **88**), depending on the size and repetition frequency of the hydrophobic segments in the polymer chain. The conformation of these macromolecules in solutions comprising different water: THF ratios was studied using ORD spectroscopy.[253] Increasing the water content led to a less negative optical rotation, and in the case of **88**, an inversion of the optical rotation was observed (Figure 17b). On the basis of reference studies in which KSCN was complexed with similar ethylene oxide derivatives, the authors concluded that helical superstructures were formed from **86**–**88** upon increasing the water content.[251] TEM studies revealed the formation of large well-defined aggregates; however, details of the hierarchical order in the aggregates could not be unveiled.

In section III.A, it was already discussed that there is a considerable interest in polymers having a π-conjugated backbone, and a number of applications have been recognized for these materials.[254] Interesting, especially with respect to interchain interactions, are the reports on chiral conjugated polymers which display only optical activity in the π–π* transition of the conjugated backbone when they are aggregated, i.e., in poor solvents and in thin films. The interaction between different polymer chains in the aggregates (microcrystallites) leads to the splitting of the excited state, i.e., exciton coupling. Introducing

Chart 15



89 **90** **91** **92** **93:** n = 1-7 **94** **95**

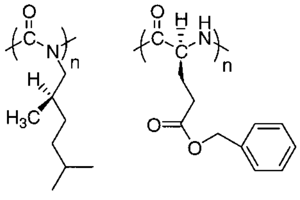
dissymmetry into this interchain organization, by optically active auxiliaries, allows the study of these interactions by chiroptical techniques. These aggregation-induced chiroptical effects have been most extensively studied for polythiophenes bearing enantiomerically pure chiral pendant groups as will be discussed below. Aggregation-induced CD effects have also been reported for chiral polydiacetylenes,[255] poly(*p*-phenylenevinylene),[256] poly(*p*-phenylene)s,[257] polypyrroles,[258] poly(*p*-phenyleneethynylene)s,[259] poly(3,3′-dialkylterthiophene),[260] poly[(dialkylthiothienylene)vinylene],[261] poly[(2′,3′-dialkylthioterthienylene)vinylene],[261] and poly(thienylenevinylene).[262] For all these polymers, the chiroptical properties are associated with exciton coupling between different conjugated chromophores and are attributed to the result of a helical packing of the polymer chains in aggregated phases. In this review, we will discuss only the organization and chiroptical properties of these polymers in aggregates since these may be considered as the tertiary structure of these materials as imposed by chirality, steric interactions, and solvophobic effects.

Polythiophenes are an important class of chemically and thermally stable conducting polymers. Unsubstituted polythiophene is an intractable material; however, many processable, both mono- and disubstituted, polythiophenes have become available.[263] Monosubstitution leads to asymmetry in the monomer, and consequently may lead to the formation of regioirregular materials featuring head–tail, tail–tail, or head–head linkages. Since 1992, however, procedures have been known for the preparation of poly(3-substituted thiophenes) containing head–tail couplings, exclusively.[264] With these better defined polymers, the construction of chiral architectures became feasible, and in the initial publications on regioirregular polythiophenes substituted with enantiomerically pure chiral pendant groups, strong bisignate CD effects[265] and high specific optical rotations[265,266] were reported.[267] Bouman and others showed by studying the solvatochromic and thermochromic behavior of regioregular **89** and regiorandom **90** (Chart 15) that these polymers only displayed optical activity in the $\pi-\pi^*$ transition when aggregated as microcrystallites in solution or thin films.[268] The formation of ordered crystalline domains in the aggregated phases results in an intermolecular chiral orientation of the rigid polymer chains. The enhanced crystallinity of regioregular polythiophene derivative **89** results in significantly larger chiroptical effects, when compared to those of regiorandom polymer **90**; e.g., $[\alpha]_{513} = 140000°$ for **89**, and $[\alpha]_{513} = 5000°$ for **90**. These observations are in agreement with the assumption that the induced optical activity in the $\pi-\pi^*$ transition has an intermolecular origin.

A cholesteric organization of the rigid oligothiophene chains in the aggregates has been proposed for **91** and **92** (Chart 15) on the basis of theoretical and experimental work, which is in line with the observed bisignate CD spectra.[269,270] In aggregated phases, the sign of the induced optical activity in the $\pi-\pi^*$ transition alternates with the parity of the number of atoms in the spacer of polymers **93** (Chart 15), as was reported by Ramos et al.[271] Stereomutation of the aggregated phase of chiral substituted polythiophenes, i.e., inversion of the chirality as judged from the sign of the CD effect, has been observed upon altering the solvent conditions.[272,273] Another investigation showing the sensitivity and complexity of the ordering and conformational phenomena in π-conjugated polymer chains has been conducted by Langeveld-Vos et al.[274] They reported that the "majority rules" principle applies for a copolymer of thiophenes equipped with (*R*) and (*S*) chiral side chains, and the "sergeants and soldiers" rule for aggregates consisting of chiral and achiral substituted polythiophene chains. The latter example can be regarded as an interchain effect; intrachain cooperativity has been reported for a chiral poly(*p*-phenylene).[275] Only a small percentage of the substituents in the polymer were chiral, but significant optical activity was observed in the aggregated state of the macromolecule.

For all these polymers, the chiroptical properties are associated with exciton coupling phenomena between different conjugated chromophores and are thought to result from a helical packing of the polymer chains in aggregated phases. Effects similar to those resulting from the intermolecular packing of polymeric chains have been found in connection with the intramolecular chain folding of oligo(phenylacetylene)s (see section III).[46]

Chart 16



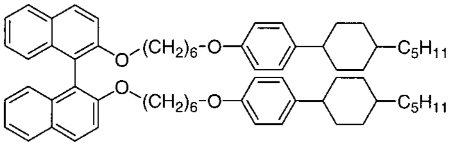
96 **97**

In a paper on the chiroptical properties of optically active poly[3,4-bis((*S*)-2-methylbutoxy)thiophene] (**94**) (Chart 15), it was demonstrated for the first time that the photoluminescence of chiral polythiophene is circularly polarized when the polymer chains are aggregated in solution.[276] The degree of crystallinity was high inside the aggregates as was evidenced by the occurrence of vibronic bands in both the UV/vis and CD spectra.[277] The observed circular polarization of the luminescence when the polymers are aggregated proves that the chiral packing of the chains is not destroyed upon photoexcitation and only a small structural reorganization takes place in the excited state, consistent with the observed small Stokes shift. By applying this phenomenon to light-emitting diode technology, circularly polarized electroluminescence was obtained from a film prepared by spin coating of **95** (Chart 15).[278]

2. Hierarchical Structures from Helical Polymers. The formation of a nematic liquid crystalline phase, characterized by orientational but not positional molecular order, is often observed for stiff helical macromolecules in solution.[279] Parameters important in describing these structures are the pitch, the radius, and the handedness of the helices. In a liquid crystalline state, the aggregation of the helices is in some cases accompanied by the formation of a cholesteric phase. The rodlike molecules in this case are no longer oriented parallel, but are twisted with respect to their nearest neigbors. Among others, poly[(*R*)-2,6-dimethylheptyl isocyanate] (**96**),[280,60] poly(γ-benzyl α,L-glutamate) (PBLG, **97**),[281,282] and schizophilan[283] (a triple-helical polysacharide rod) were found to display cholesteric liquid crystalline mesophases in concentrated solutions (Chart 16). The major models discribing the transfer of the helical chirality to the cholesteric phase are the *straight-rod*[280] and the *threaded EFJC*[77a] models. Both models approach the macromolecular helix as a screw-threaded cylinder, which implies that the aggregation of two such helices is mainly dependent on the ratio pitch/diameter. The models predict that at a critical value inversion of the helicity of the resulting superhelix will take place.

The straight-rod model predicts a right-handed cholesteric helix for **96** and a left-handed one for PBLG and schizophylan, which is in agreement with experimental results.[280] In the threaded EFJC model, the flexibility of the macromolecular helix can be freely chosen. The handedness of the cholesteric phase is based on entropic "hard core" repulsion phenomena between the helices and an enthalpic chiral dispersion force. Right-handed mesophases were predicted for solutions of **96**, **97**, and schizophylan. However, only for **96** this was in agreement with the experimentally determined handedness; a direct explanation for this discrepancy was not given.

Chart 17



(R)-(+)-98
(S)-(-)-98

An astonishing helical architecture was prepared recently by Akagi et al.[284] They polymerized acetylene in a chiral nematic reaction field. To this end, the Ziegler–Natta catalyst Ti(O-*n*-Bu)$_4$–Et$_3$Al was dissolved in the stable chiral nematic mesophase obtained by mixing 5–14 wt % (*R*)- or (*S*)-**98** (Chart 17) with a known nematic liquid crystal, and this medium was subsequently used for the preparation of polyacetylene films. It was found that polymers prepared in the (*R*) chiral nematic liquid crystals had counterclockwise (M) helical fibrillar morphologies and those prepared in the (*S*) phase clockwise (P) morphologies (Figure 18). CD spectra of these films showed a postive Cotton effect for the M-helical fibrils and a negative Cotton effect for the P-type ones, in the $\pi-\pi^*$ transition region of the polyacetylene chain. Since the helical pitch of a chiral nematic phase can be controlled by the optical purity or the type of chiral dopant, and the liquid crystalline phase templates the helicity, it was also possible to produce fibrils with a different helical pitch. An interesting hierarchical transfer of chirality was observed in this case, i.e., going from the chiral twist in **98** to the helical polymer and ultimately to the spiral morphology in the microscopic regime.

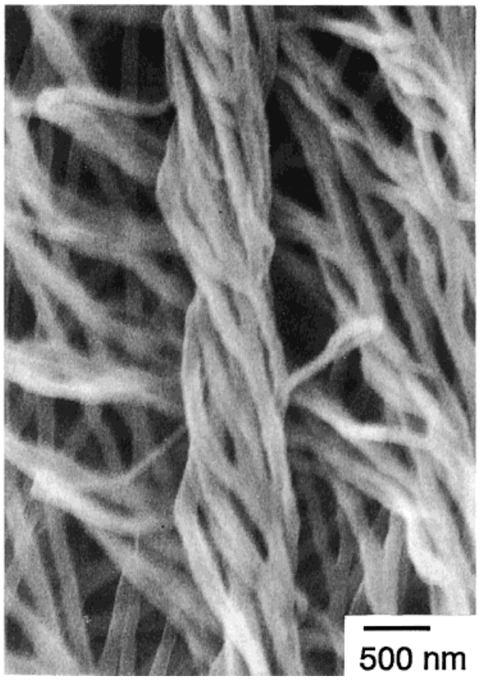


Figure 18. Scanning electron micrograph of a left-handed helical morphology formed by polyacetylene polymerized in a chiral nematic reaction field. (Reprinted with permission from ref 284. Copyright 1998 American Association for the Advancement of Science.)

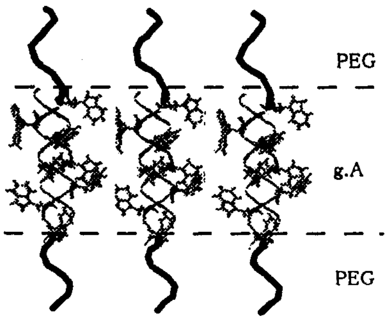
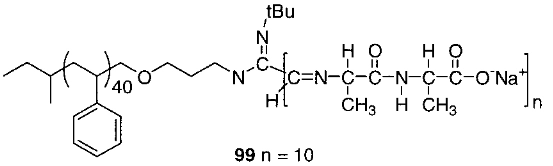
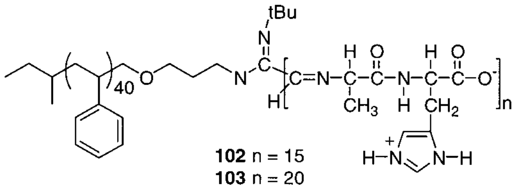


Figure 19. Proposed organization in bilayers formed by a gramicidin A−poly(ethylene oxide) hybrid. (Reprinted with permission from ref 285. Copyright 1999 American Chemical Society.)

Chart 18



99 n = 10
100 n = 20
101 n = 30



102 n = 15
103 n = 20
104 n = 30

Hybridization of gramicidin A, a hydrophobic 15-mer peptide, with a hydrophilic PEO chain resulted in the formation of an amphiphilic compound as was reported by Kimura et al.[285] Upon dispersion in water, these hybrid polymers, in which the degree of polymerization of the PEO segment was 13, gave vesicles with an average diameter of 85 nm. An illustration of the proposed organization of the molecules in the vesicle bilayer is given in Figure 19. Inclusion experiments confirmed the vesicular nature of the aggregates, while CD measurements supported the presence of the proposed antiparallel double-stranded helix conformation.

The formation of dissymmetric, helical superstructures from polymeric building blocks was first reported by Cornelissen et al.[286] An amine-end-capped polystyrene was used as the initiator for the polymerization of dipeptide-derived isocyanides (see also section III.B) which resulted in a series of amphiphilic block copolymers (**99**−**104**) (Chart 18), consisting of a hydrophobic polystyrene segment and a rigid hydrophilic helical polyisocyanide block. CD data revealed that the helical screw pitch was right-handed in the case of **99**−**101**, and left-handed in the case of **102**−**104**. The effect of a changing ratio between the hydrophilic and hydrophobic blocks on the aggregate morphology in an aqueous environment with optimized pH (pH 5.6) was investigated by TEM. For **101** and **104**, no distinct morphologies were obtained, whereas for both **100** and **103** the generation of micellar fibers was observed. Interestingly, the flexibility of the fibers formed by **103** could be tuned by varying the anion: the flexibility was found to increase on going from a mono- to a di- and then to a tricarboxylate (i.e., from acetate to tartrate to citrate) counterion. Further reduction of the helical polyisocyanide part (**99** and **102**) resulted in the formation of bilayer-type structures. In addition to collapsed vesicles and bilayer fragments, helical superstructures were observed: for **99**, a left-handed helix was found, whereas **102** gave a right-handed one (Figure 20). Remarkably, in both cases, the handedness of the superhelices had been reversed with respect to that of the polyisocyanide helices in the constituting block copolymers.

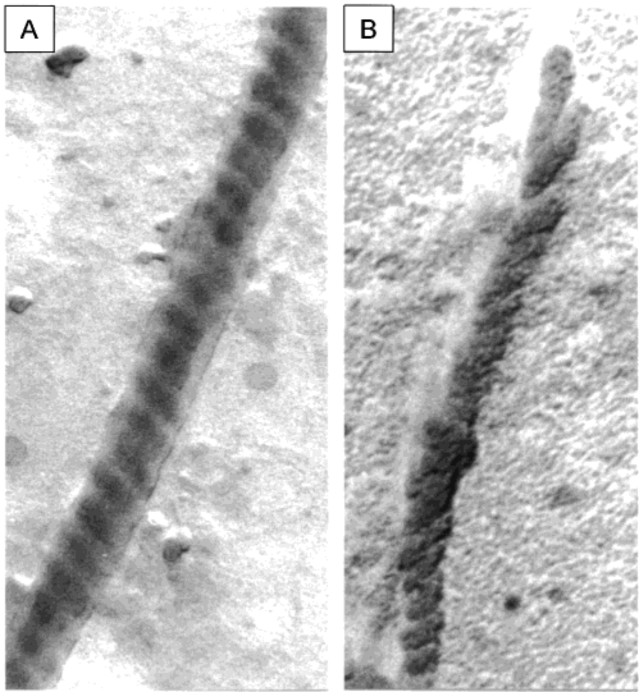
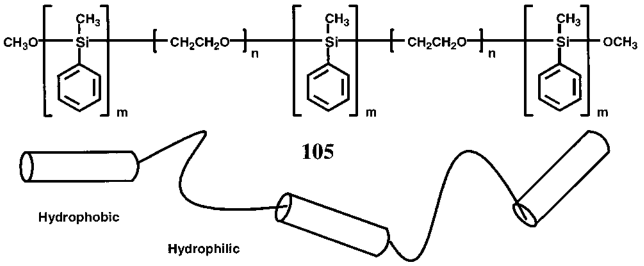


Figure 20. Transmission electron micrographs of the (a) right-handed and (b) left-handed helical superstructures obtained from assembled polystyrene−polyisocyanopeptide block copolymers **99** and **102**, respectively.

Chart 19



Although the precise mechanism of formation of these superstructures is still unclear, a hierarchical organization is evident, since transfer of chirality takes place from the amino acid in the monomer to the secondary helical structure of the polyisocyanide blocks and, ultimately upon assembly, to the helical superstructure.

The chiral structures discussed above are formed by relatively well-defined macromolecules. Interestingly, superhelical structures can also be obtained from rather polydisperse multiblock copolymers, viz., of PEO and PMPS (**105**; PDI = 1.6) (Chart 19). In a

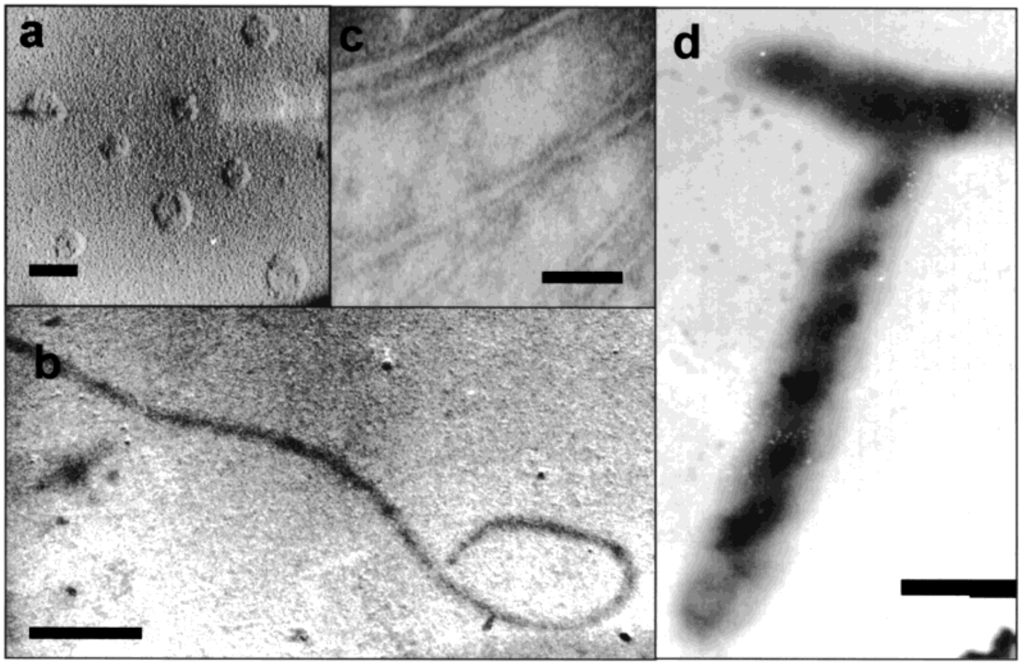


Figure 21. Transmission electron micrographs showing the formation of (a) vesicles, (b, c), micellar fibers, and (d) superhelices from a PEO−PMPS block copolymer (**105**).

preliminary communication, the formation of vesicles was reported in pure water (Figure 21a).[287] In a later paper,[133] it was described that the aggregation behavior of this amphiphilic polymer can be tuned by dispersing it in water−THF mixtures of varying composition. Below water concentrations of 40% (v/v) no aggregates were found. Electron microscopy demonstrated the presence of micellar rods in mixtures containing 40−80% (v/v) water (Figure 21b,c). In solvent mixtures containing more than 80% water, helices (Figure 21d)[133] with both left- and right-handed screw pitch were observed. Given the multiblock nature of the polymer and the polydispersity of the PMPS blocks, it is unlikely that the helical superstructures arise from preferential aggregation of PMPS segments with identical screw senses. A cooperative process was assumed to occur in which the handedness of the initial PMPS segment(s) determine(s) the handedness of the subsequent PMPS segments assembling in the same aggregate, such that a chiral architecture is formed by hierarchical assembly of these dynamic helical macromolecules.

V. Conclusions and Outlook

On the way from molecular to macromolecular and supramolecular chemistry, researchers have realized increasingly complex functional materials; however, these still lag behind compared to highly sophisticated macroscopic architectures with precise and predefined structure that are encountered in biological systems. In this review, we have summarized the first steps chemists have taken toward the construction of macromolecular architectures with defined three-dimensional structures. In the past decade, polymers with defined secondary structure mimicking one or more aspects from biological systems have been prepared. Issues important for the programmed organization of synthetic macromolecules that have been addressed include the conformational dynamics of the helicity and their effect on the (photo)physical properties of the polymers, the induction of helicity in the polymer chain, the influence of kinetics on the macromolecular secondary structure, and the use of multiple interactions in the hierarchical organization of macromolecules to well-defined supramolecular assemblies.

It is evident that mastering the organization of macromolecules is essential for the generation of materials with sophisticated properties. Since polymers with a permanent and precisely defined helical structure allow the generation of well-defined chiral superstructures, it is our contention that this class of macromolecules provides the route toward a better understanding of the principles underlying the generation of functional polymeric materials with tertiary structure from synthetic building blocks with a known secondary structure. In the future, these principles may be extrapolated to understand and ultimately predict also the assembly processes taking place between macromolecules with a more dynamic backbone conformation, ultimately allowing their application for the construction of advanced polymeric materials and devices.

VI. Acknowledgments

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(3) As chiral dendrimers do not possess a secondary or tertiary structure, they will not be included in this review. For an

excellent overview on these intriguing macromolecular architectures see: Peerlings, H. W. I.; Meijer, E. W. *Chem.—Eur. J.* **1997**, *3*, 1563.

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