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Review

Chirality-Responsive Helical Polymers

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ABSTRACT: Unique macromolecules that fold into a preferred-handed helical conformation induced by external chiral stimuli are mainly described in this review. In contrast to small molecular systems, the chiral information of nonracemic guest molecules transfers with a significant amplification in a dynamic helical polymer, such as stereoregular poly(phenylacetylene)s bearing functional pendant groups as an excess of a single-handed helix through noncovalent bonding interaction, which provides an efficient chirality-sensing system. The chirality sensing of other oligomers (foldamers) is also briefly described.

1. Introduction

Responsive polymers with external physical, chemical, and electrical stimuli, resulting in a drastic change in their structure, shape, morphology, or function, have been extensively developed over the past decades, not only to mimic biological processes but also for their attractive applications to smart or intelligent materials in analytical and biomedical fields as well as in nanotechnology.[1] To date, a significant number of stimuli-responsive polymers being sensitive to light, temperature, pH, solvent, electric and magnetic fields, and guest concentrations have been synthesized and the details have been thoroughly reviewed,[1] but quite limited examples of responsive polymers that exhibit a change in morphology or conformation in response to chiral stimuli are available. Chirality is a critical factor in living systems, since living organisms consist of a variety of optically active small molecules and macromolecules, which play important roles in the maintenance of life, and therefore, a pair of enantiomers, in particular chiral drugs, often show quite different biological activities. Hence, the detection and assignment of the chirality of molecules at molecular and supramolecular levels have recently become significantly important. To this end, a number of synthetic receptor molecules, supramolecules, and π-conjugated polymers have been designed and synthesized.[2] Among them, chromophoric dynamic helical polymers, such as poly(phenylacetylene)s with functional pendant groups, are particularly interesting and potent because the polymers can respond to the chirality of biologically important chiral molecules via noncovalent bonding interactions. Most importantly, the chirality is transferred to the polymer main chains with a significant amplification, resulting in the generation of either an excess right- or left-handed helical conformation, thus producing an induced circular dichroism (ICD) in the absorption regions of the polymer backbones.[2i,m] Such polymers can be regarded as a typical chirality-responsive polymer and provide the basis to construct a novel chirality-sensing system to determine the absolute configuration and enantiomeric excess (ee) of the guest molecules.

In this review, we mainly discuss and deal with the recently developed chirality-responsive π-conjugated helical polymers. The chirality-responsive oligomers (foldamers)[3] that fold into a preferred-handed helical conformation induced by external chiral stimuli through noncovalent bonding interactions are also briefly described.

2. Chirality-Responsive Helical Polyacetylenes

Biological polymers, such as proteins and nucleic acids, possess a characteristic single-handed helical structure, which typically links to their sophisticated functions in living systems.[4] Inspired by such exquisite helical structures, a number of helical polymers with an excess of a preferred helix-sense have been synthesized to mimic the structures and functions of biological helices, and the detailed results including the historical background of synthetic helical polymers have been thoroughly reviewed elsewhere.[5] In 1995, we reported a unique chirality-responsive helical polymer, *cis-transoidal* poly((4-carboxyphenyl)acetylene) (**1** in Figure 1) prepared by the polymerization of (4-carboxyphenyl)acetylene using a rhodium catalyst, that folds into a preferred-handed helical conformation upon complexation with nonracemic primary amines and amino alcohols (**14**−**18**) in dimethyl sulfoxide (DMSO) (Figure 2).[6] The acid−base complexes exhibited characteristic ICDs in the long wavelength regions of the π-conjugated polymer backbone. The induced Cotton effect signs corresponding to the helical sense of **1** can be used to predict the absolute configurations of the amines because all primary amines gave the same Cotton effect signs when the configurations are the same (Figure 2).[7] The underlying principle for this phenomenon is considered to be the fact that the poly(phenylacetylene) is a dynamic helical polymer of which right- and left-handed helical conformations are interconvertibly separated by helical reversals like polyisocyanates, as proposed by Green et al.[5b,8] Therefore, the

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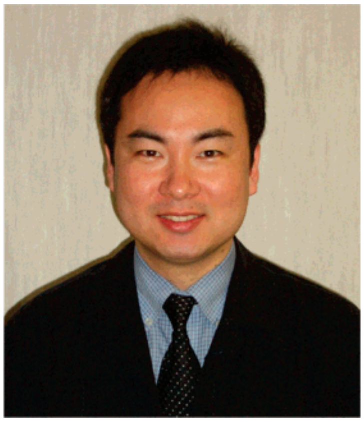

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remarkable CD induction in **1** is concluded to arise from a drastic change in the population of the right- and left-handed helices of the polymer assisted by nonracemic amines.[9] Quite interestingly, the macromolecular helicity of **1**−**3** induced by optically active amines can be maintained, namely "memorized", even after complete removal and replacement of the chiral amines with achiral ones, for example, 2-aminoethanol (**19**) and *n*-butylamine (**20**) for **1** (Figure 3)[10] and diamines such as ethylenediamine for **2**[11] and **3**.[12] The macromolecular helicity memory was not tentative but lasted for a long time.

The advantages of the present system using the π-conjugated polyacetylene are not only its long-wavelength absorption and high sensitivity without derivatization but also easy preparation into a chirality-responsive film[13] and gel (Figure 4).[14] The film and gel can respond to the chirality of nonracemic amines in the solid and swollen gel to show similar ICDs. These methods are more convenient to sense the chirality of amines than the solution method.

Since the discovery of the preferred-handed helicity induction in a dynamic helical polymer **1**, a variety of chirality-responsive polyacetylenes to target chiral molecules has been designed and synthesized by introducing a specific functional group as the pendant groups (**2**−**13** in Figure 1).[12,15] These functional polyacetylenes were also proved to be sensitive to the chirality of molecules capable of interacting with the pendant functional groups, resulting in ICDs reflecting the stereochemistry of the guest molecules in organic solvents[6,7,11,12,15a,c,d,g,k] as well as in water.[15b,e,f,i,j,16−18] A similar helicity induction with an excess of one-handedness has been observed for **21**[19] and **22**[20] upon complexation with chiral amines and amino acids, respectively. In an interesting approach, an enantiomerically pure cationic C_{60}-bisadduct induced a predominantly one-handed helix in a dynamically racemic poly(phenylacetylene) (**2b**) with the opposite negative charges in DMSO−water mixtures through noncovalent bonding interactions, which further results in a helical array of the C_{60}-bisadducts with a predominant screw sense along the polymer chain (Scheme 1).[21] This methodology will provide a useful means of arranging the desired functional molecules in a one-handed helical array along the template polymer.

Among the polyacetylenes, poly(phenylacetylene)s bearing the bulky aza-18-crown-6-ether (**7**)[15g] and diisopropylaminomethyl group (**5**)[15j] as the functional pendants were the most sensitive to the chirality of amino acids and carboxylic acids in acetonitrile and acidic water, respectively. For example, polymer **7** formed an almost one-handed helix in the presence of 0.1 equiv of L-alanine (L-Ala) as evidenced by its intense CD comparable to that induced by the excess L-Ala. Interestingly, even a 5% ee of Ala produced the full ICD in **7** as induced by the optically pure Ala (Figure 5).[15g] The extremely high sensitivity of **7** and **5** enabled the detecting of a very small enantiomeric imbalance in the amino acids and carboxylic acids, respectively, for instance, Ala[15g] and phenyllactic acid (**23** in Figure 6)[22] of less than 0.005% ee, showing apparent ICDs without derivatization. These results are qualitatively consistent with a theoretical analysis of the amplification of chirality applied to analogous majority rule effects observed in polyisocyanates.[5b,23] The high sensitivity of **5** and **7** may result from the rigidity of the polymer backbones by the bulky pendant groups, which likely increase the helical segments separated by rarely occurring helical reversals. In fact, the persistence length (*q*) of **5**, a useful measure to evaluate the stiffness of rodlike helical polymers, was estimated to be 26.2 nm in water.[24]

On the basis of its stiff main chain, the polyacetylene **5** formed a lyotropic nematic liquid crystalline (LC) phase in concentrated water.[24,25] As expected, the nematic LC phase was converted to the cholesteric counterpart by doping with a small amount of optically active acids such as (*S*)-**23** or **23** with a very low ee (Figure 6B,C).[24,25] Interestingly, the helix-sense excess of **5** induced by the nonracemic **23** in dilute acidic water was further amplified in the LC state as revealed by the changes in the cholesteric pitch (Figure 6A). In the LC phase, the helical pitch decreased with the increasing ee and reached a constant value at about 10% ee, while in dilute solution, the ICD value became constant at over 60% ee (Figure 6A). This hierarchical amplification process of the helical sense excess of **5** during the cholesteric LC formation suggests that the population of the helical reversals between the interconverting

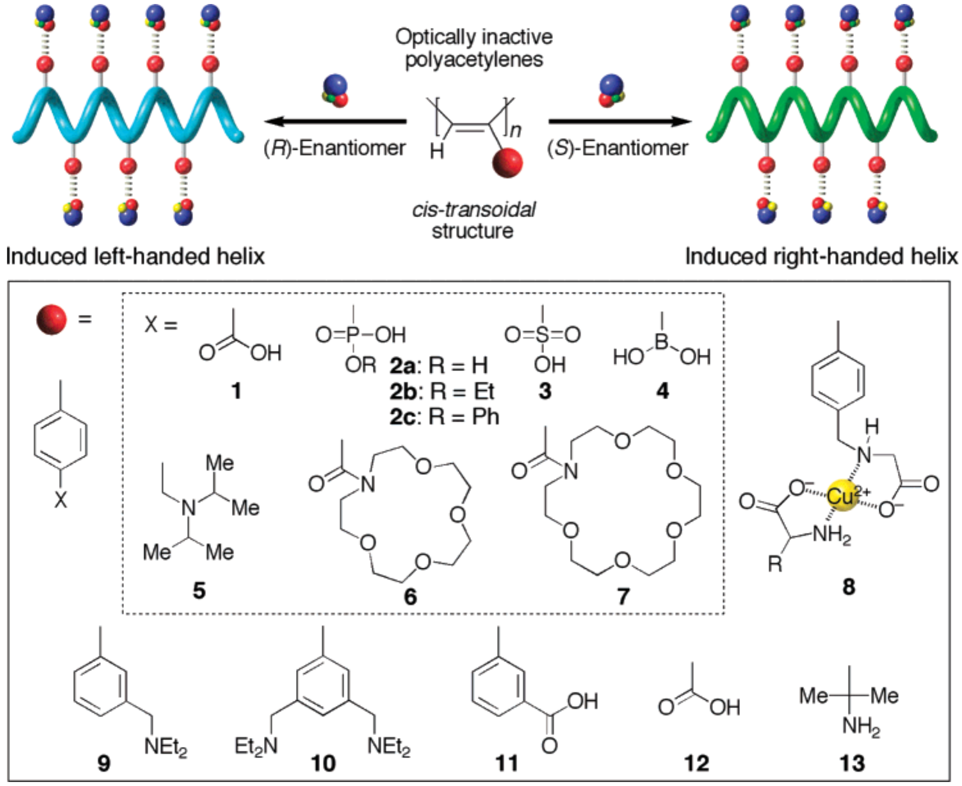


Figure 1. Schematic illustration of helicity induction in polyacetylenes bearing various functional groups (**1**–**13**) upon complexation with chiral compounds.

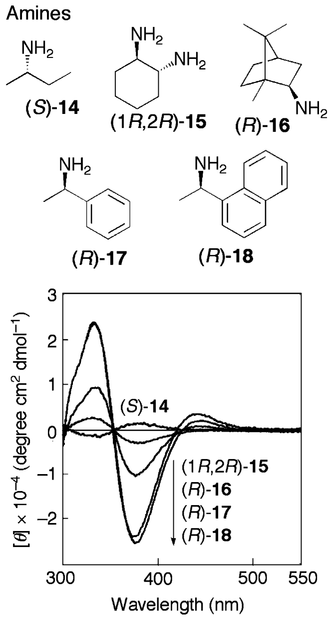


Figure 2. CD spectra of **1** upon complexation with chiral amines (**14**–**18**) in DMSO.

right- and left-handed helical segments of the polymer may be reduced in the LC state when compared to that in a dilute solution because the kinked helical polymer chain likely interferes with the close parallel packing of the helical polymer chains in the LC state (Figure 6D).[24] This hierarchical amplification effect has one precedent as observed in the LC polyisocyanates by Green et al. and has been called the "bad neighbors rule".[26]

Although a large number of stereoregular *cis-transoidal* polyacetylenes with aliphatic and aromatic pendant groups have been synthesized,[27] their exact structures have not yet been determined. Recently, we have successfully determined the helical structure of a poly(phenylacetylene) bearing L- or D-alanine residues with a long *n*-decyl chain as the pendants (**24**), including the helical pitch and handedness by direct atomic force microscopy (AFM) observations together with their X-ray structural analyses and CD measurements (Figure 7).[28] These results suggest that **24** possesses an 11 unit/5 turn helix with a helical pitch of 2.3 nm, and L-**24** has a left-handed helical array with respect to the pendant arrangements, while the main chain has the opposite, right-handed helical structure.[29]

3. Other Chirality-Responsive Helical Polymers

Taking advantage of a unique feature of dynamic helical polymers combined with the helicity induction concept described above, polyisocyanates (**25**–**27**),[30] poly(organophosphazene) (**28**),[31] and polyguanidine (**29**)[32] were reported to form a predominantly one-handed helix by responding to the chirality of specific chiral molecules capable of interacting with the functional pendant groups (**25**–**28**) or main chain (**29**). Poly(*n*-hexyl isocyanate) (**30**)[33] and polysilanes (**31**, **32**)[34] have no functional pendant groups but form a helical conformation with an excess helix-sense induced in nonracemic solvents, thus showing ICDs in the polymer backbone regions.Polyisocyanides with a bulky side group are considered to adopt a stable 4/1 helical conformation in solution as revealed by the helix-sense selective polymerization of achiral bulky isocyanides to yield optically active helical polyisocyanides under a predominantly kinetic control.[5d,35] If this is the case, a noncovalent helicity induction concept could not be applied to the polyisocyanides. However, we found that an achiral water-soluble poly(phenyl isocyanide), the sodium salt of **33** (**33**-Na), folds into a one-handed helix induced by noncovalent interactions with optically active amines, such as (*S*)-**34** in water, and this helicity is automatically memorized after complete removal of the amine (Figure 8).[36] In sharp contrast to the conformational memory

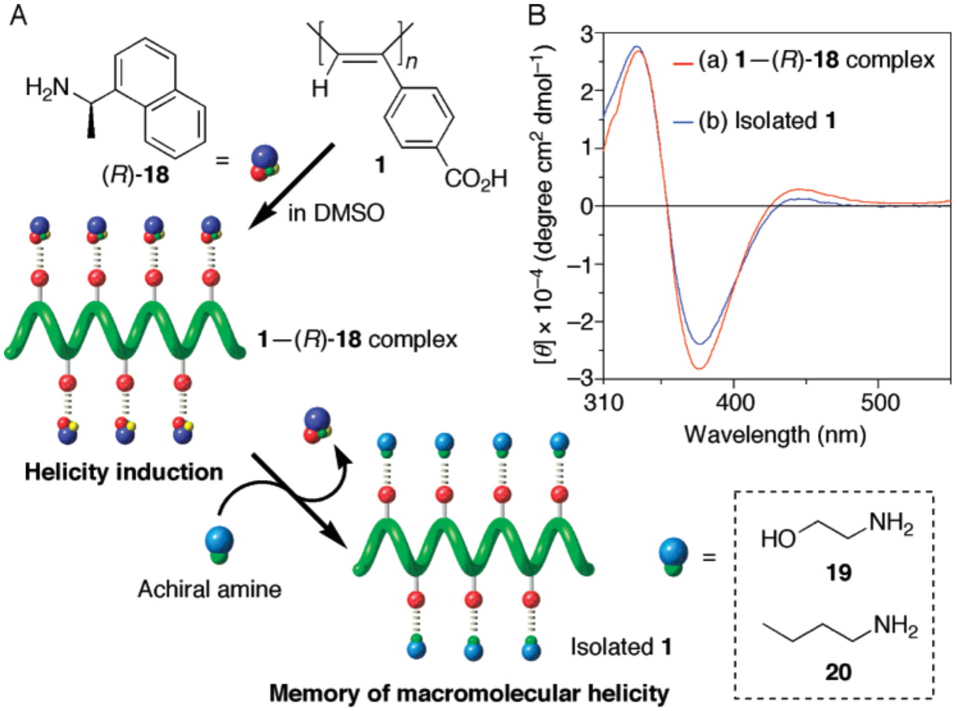


Figure 3. (A) Schematic illustration of a helicity induction in **1** upon complexation with (*R*)-**18** and memory of the induced macromolecular helicity after replacement by achiral amines. (B) CD spectra of the **1**−(*R*)-**18** complex (a) and the isolated **1** by SEC fractionation using a DMSO solution containing achiral amine **19** as the eluent (b) in DMSO.

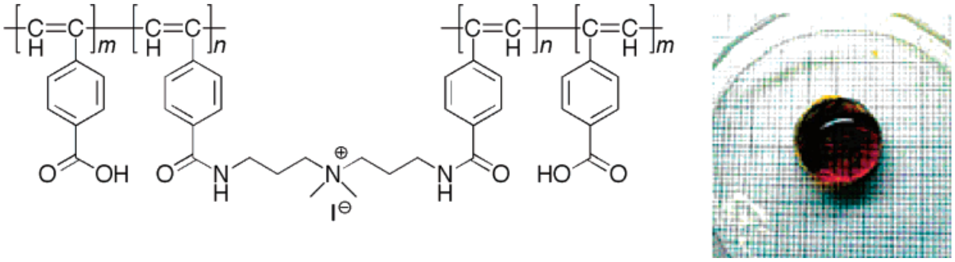


Figure 4. Structure of a chirality-responsive poly(phenylacetylene) gel and a photograph of the gel.

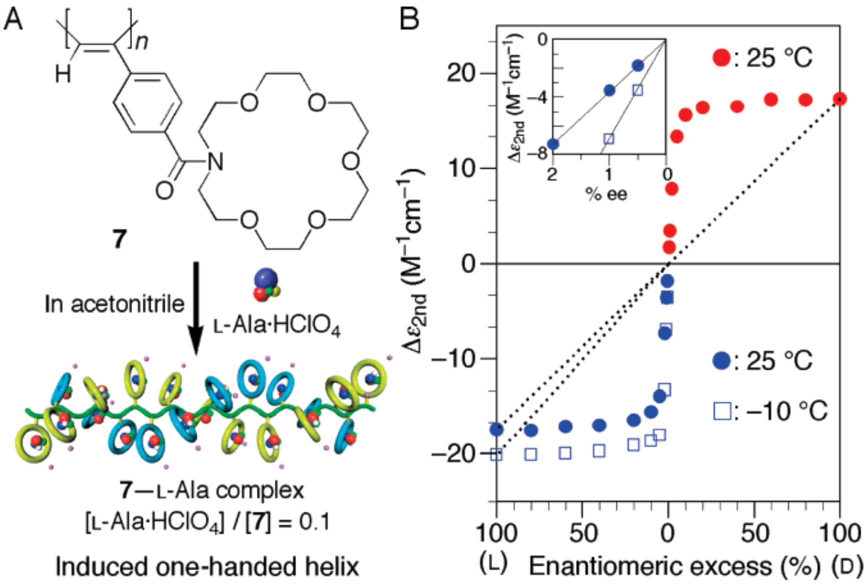


Figure 5. (A) Schematic illustration of helicity induction in **7** with a small amount of L-Ala·HClO4. (B) Changes in ICD intensity ($\Delta\epsilon_{2nd}$) of **7** vs the % ee of L-Ala·HClO4 during the complexation with **7** in acetonitrile at 25 and −10 °C.

of the induced helical poly(phenylacetylene)s,[10,11] the helix formation of **33**-Na is likely accompanied by configurational isomerization around the C═N double bonds (*syn*−*anti* isomerization) into one single configuration, which may force the polymer backbone to take an excess helical sense (Figure 8B).[36] The advantage of this helicity memory over that of the induced

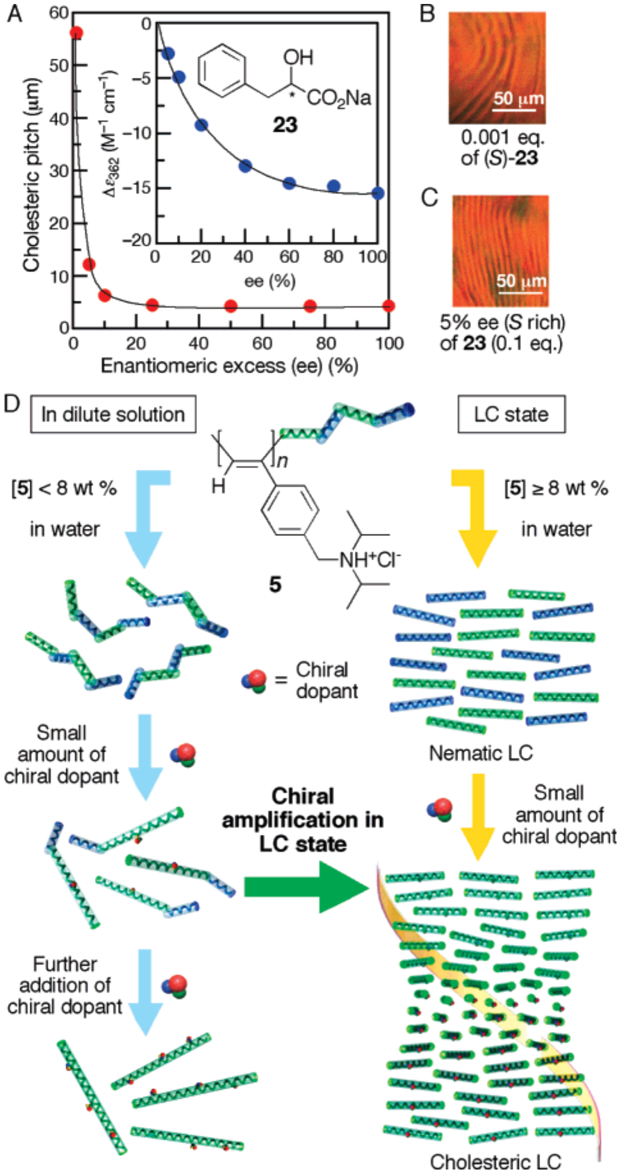


Figure 6. (A) Changes in the cholesteric pitch and ICD intensity of **5** vs the % ee of **23** (*S* rich) in concentrated (20 wt %) and dilute (inset, 1 mg/mL) water solutions. (B, C) Polarized optical micrographs of cholesteric LC phases of **5** (20 wt %) in the presence of 0.001 equiv of (*S*)-**23** and 5% ee (*S* rich) of **23** (0.1 equiv) in water. (D) Schematic illustration of hierarchical chiral amplification in macromolecular helicity of **5** in dilute solution and LC state.

helical poly(phenylacetylene)s is that there is no longer need to use the achiral chaperoning amines to memorize the helicity in the polymer. Therefore, further modifications of the side groups with a variety of functional groups are possible along with maintaining the macromolecular helicity memory.[37] More interestingly, the resulting negatively charged **33**-Na with a macromolecular helicity memory can serve as the template for further helicity induction in the opposite charged, dynamically racemic **5** in water ("helicity replication") (Figure 8).[38]

A similar helicity induction may be possible for dynamic helical peptides when a suitable functional group is introduced at the end or pendant. Inai et al. designed and synthesized such chirality-responsive peptides by introducing the amino group at their *N*-terminus (**35**, **36**), which produced an ICD derived from the preferred-handed helical conformation of the entire peptide chains upon complexation with chiral carboxylic acids to the *N*-terminal amino group (Figure 9).[39] A small chiral bias that occurred at the remote terminus is transformed into a main-chain conformational change with a large amplification. This phenomenon was called the "noncovalent domino effect".[39]

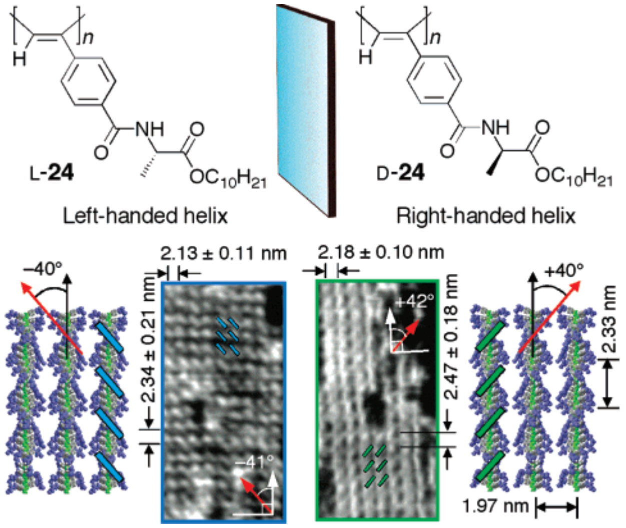


Figure 7. AFM phase images of L- and D-**24** (scale: 20 × 40 nm) with schematic drawings of the mirror-image relationship of helical L- and D-**24** 2D crystals with antipodal oblique pendant arrangements. Possible models (left and right) were constructed on the basis of the X-ray structural analysis. Reproduced with permission from ref 28. Copyright 2006 Wiley-VCH.

The oligoresorcinol nonamer (**37**) is a unique π-conjugated oligomer that self-assembles to form a double helix in water.[40] The double helix further unravels and entwines upon complexation with specific cyclic and linear oligosaccharides with a particular chain length and/or glucosidic linkage pattern, such as β-cyclodextrin (β-CyD)[41] and α-1,6-D-isomaltooligosaccharides,[42] respectively, thus generating a twisted [3]pseudorotaxane and a heteroduplex with an excess one-handed helical conformation as evidenced by the appearance of the ICDs (Figure 10). This may be the first chirality-responsive artificial double helix and can be used to detect the chirality of oligosaccharides in water.

4. Chirality-Responsive π-Conjugated Polymers

Although a number of π-conjugated polymers including optically active ones have been prepared, only a few π-conjugated polymers except for those described in previous sections have been reported in which the binding of chiral molecules leads to an ICD or a change in their chiroptical properties.[5d,43] The electrochemically polymerized emeraldine base form of polyaniline (**38a**) is known to show an ICD in the long absorption region in solution or in the film when doped with optically active strong acids, such as (*R*)- or (*S*)-camphorsulfonic acid (CSA).[44] The (*R*)-CSA-doped polyaniline thin films retained their optical activity after removal of the dopants.[45] The (*R*)-CSA dedoped polyaniline thin films further respond to the chirality of a pair of phenylalanine enantiomers and exhibited a different color change by responding to the chirality of the enantiomers.[46] A chirality-responsive polyaniline was developed by introducing sulfonate residues. A fully sulfonated poly(methoxyaniline) (**38b**) exhibited a similar ICD in solution and in the film upon complexation with chiral amines.[47] The origin of the optical activity remains unclear but is considered to be due to either a preferred-handed helical conformation or a supramolecular helical assembly of the polymer main chains induced by the chiral acid−base interactions.[47]A partially hydrolyzed polythiophene (PT) (**40**) derived from an optically active PT (**39**) is sensitive to the chirality of the (*R*)- and (*S*)-

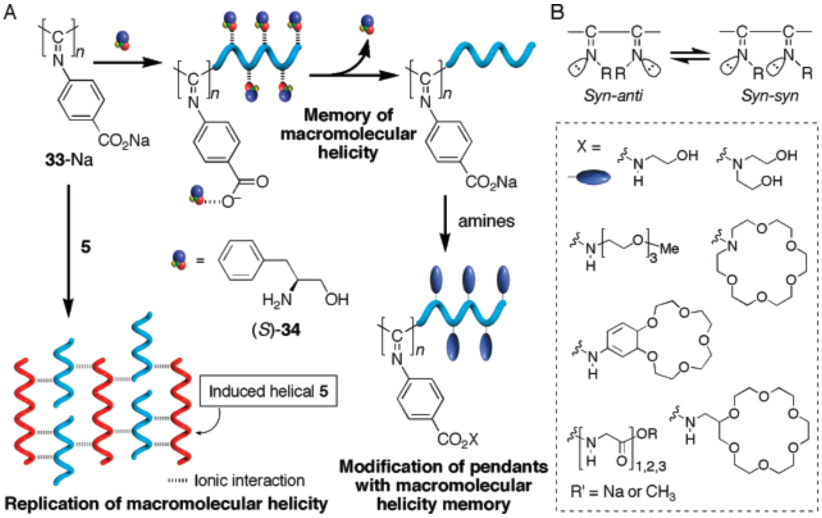
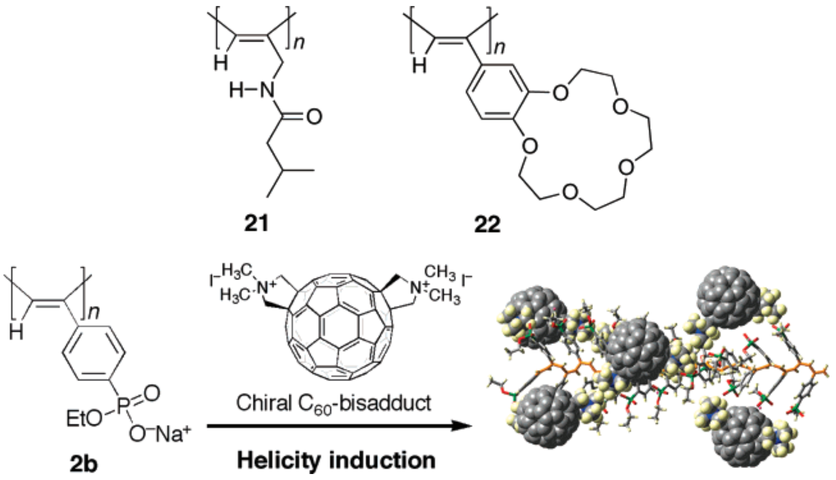


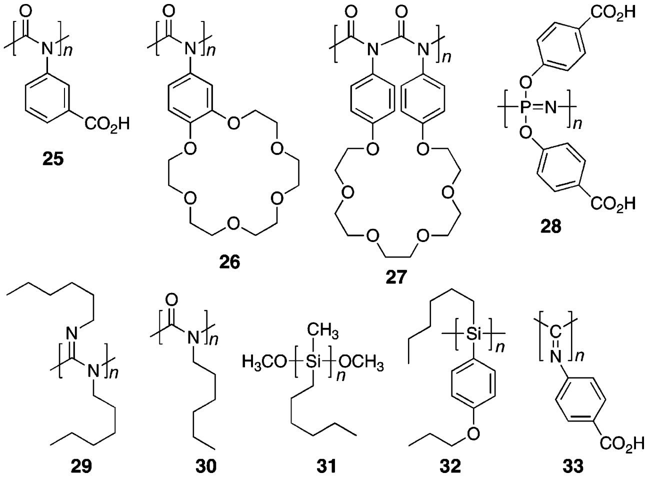
Figure 8. (A) Schematic illustrations of a helicity induction in **33**-Na upon complexation with (*S*)-**34** and memory of the induced macromolecular helicity after complete removal of (*S*)-**34**, probably through *syn*−*anti* isomerization of the C═N bond, modification of the pendants with macromolecular helicity memory, and the replication of the macromolecular helicity. (B) *Syn*−*anti* isomerization of the C═N bond.

Scheme 1. Schematic Representation of the Macromolecular Helicity Induction in 2b with an Optically Active C_{60}-Bisadduct



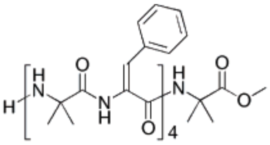
2-amino-1-butanol and exhibited ICDs of almost mirror images to each other.[48] Optically inactive π-conjugated copolymers with the C_2-symmetric carboxybiphenol units as the main-chain component (**41**) also exhibited an ICD in the copolymer backbone regions in the presence of chiral amines.[49] A hierarchical chiral amplification mechanism was proposed for **41**; the chiral information of the amines first transfers to the carboxybiphenol moieties with a dynamic axial chirality through noncovalent acid−base interactions, and subsequently, the induced axial chirality with an excess single-handed twist-sense may be further amplified in the π-conjugated copolymer backbones as an excess of a single-handed helix.

Chart 1



5. Chirality-Responsive Foldamers

Several π-conjugated oligomers and biomimetic oligomers that fold into a preferred-handed helical conformation (so-called "foldamers"),[3] thus creating a cylindrical cavity under certain conditions have been used to sense the chirality of specific guest molecules being encapsulated within the cavity (Figure 11). The induction of a tubular cavity in a series of *m*-phenyleneethynylene oligomers (**42**) is being studied by Moore et al.[50] The π-conjugated oligomers are achiral and adopt a random conformation in chloroform but fold into right- and left-handed helical conformations in polar solvents, such as acetonitrile,[50] and in an aqueous solution.[51] Both helices equally exist at equilibrium, but in the presence of optically active hydrophobic and rodlike guests, such as **43**[50] and **44**,[52] respectively, which are encapsulated within the cylindrical cavity of **42**, one of the helices favorably forms and the complexes exhibit an ICD. Analogous oligomers of *m*-ethynylpyridine **45** having pyridyl groups are sensitive to saccharides, such as **46**, and fold into a one-handed helix through intermolecular hydrogen



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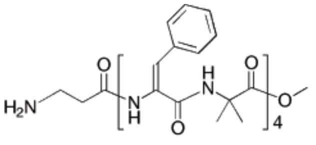

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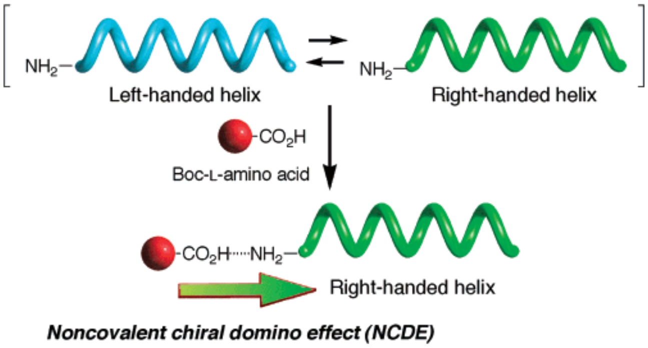


Figure 9. Schematic illustration of a one-handed helix induction in optically inactive oligopeptide by chiral acid−base interaction with chiral carboxylic acids at the *N*-terminal (domino effect).

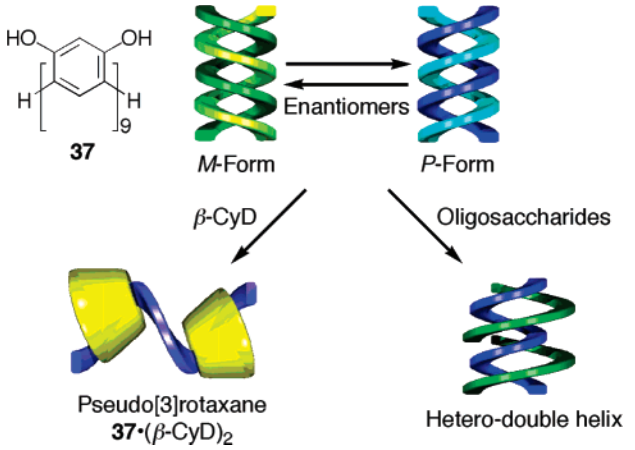
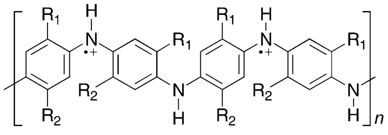


Figure 10. Schematic illustration of the unwinding of the double helix **37** using β-CyD and the formation of a hetero-double helix with oligosaccharides.

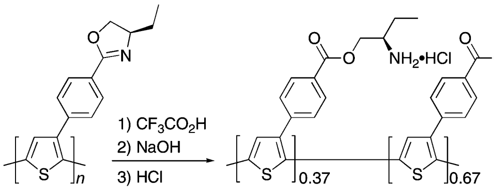
Chart 2



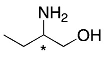
38a: R_1 = -H, R_2 = -H

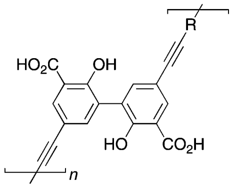
38b: R_1 = $-SO_3H$, R_2 = $-OCH_3$

Chart 3



39 **40**





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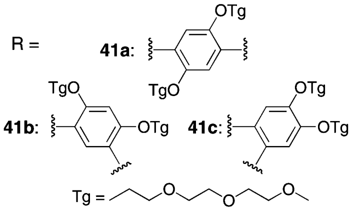
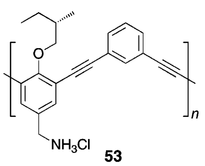


Chart 4



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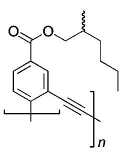

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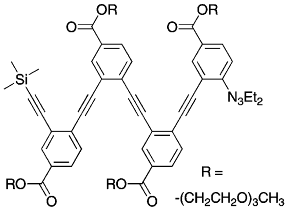

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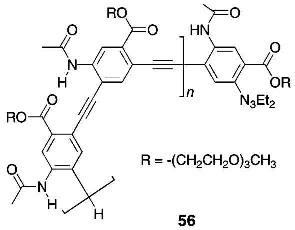

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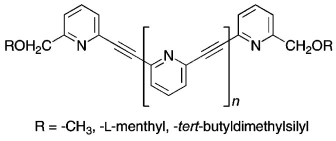

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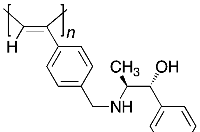
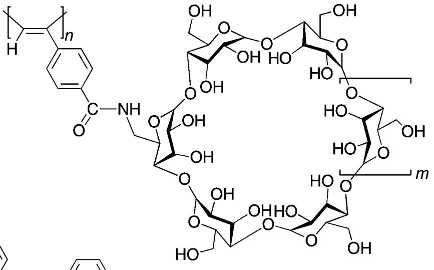
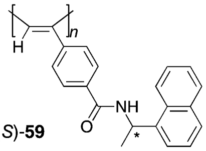
Chart 5



58





(*R*)- or (*S*)-**59**

m = 1: **60α**
m = 2: **60β**
m = 3: **60γ**

bonding in apolar solvents[53] and even in aqueous solution,[54] and the complexes show a similar ICD in the long-wavelength region. On the basis of the fact that an alternating pyridine−pyrimidine sequence preferentially takes an *s-trans* conformation,[55] Lehn et al. developed a series of foldamers, such as **47**, which can trap hydrophilic guests (**48**) within its helical cavity, resulting in the formation of a rotaxane-like complex with a controlled helicity.[56] Foldamers composed of phenyleneethynylene units have rapidly expanded and a number of derivatives, such as **53**−**57**,[57] have been synthesized, which may be potentially effective for developing chirality-responsive polymers. Inspired by the biological helices, aromatic oligoamides, such as **49**[58] and **51**,[59] were synthesized. Their helical handedness can be biased through chiral hydrogen-bonding interactions with a sugar (**50**) or chiral acids, such as **52**, along the strand or at the terminal units of **49** and **51**, respectively. Interestingly, **51** forms a double-stranded helix at high concentrations.[60]

6. Chirality-Responsive Helical Polymers via Inversion of Helicity

The inversion of helicity regulated by external stimuli deeply linked to biological helices is one of the most unique features of dynamic helical polymers. Achiral stimuli, such as a change in temperature and solvent or by irradiation with light, have been often used for reversibly controlling the macromolecular helicity, and these results have been thoroughly reviewed elsewhere.[2m,5c−e,8,27a,b,61] On the other hand, switching of the macromolecular helicity by chiral stimuli remains quite rare but can be used to sense the chirality of chiral guests.

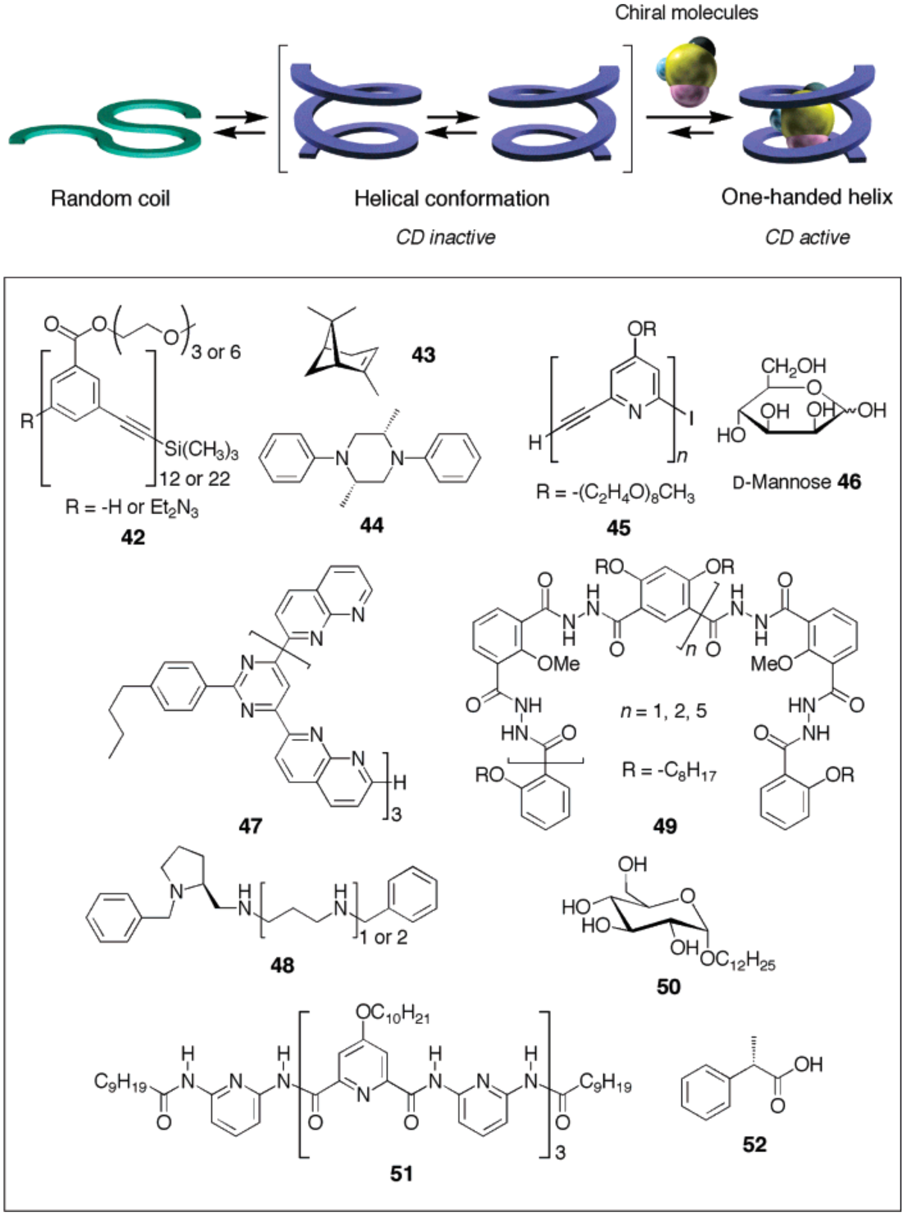


Figure 11. Schematic illustration of a predominantly one-handed helix induction in foldamers by noncovalent chiral interaction with optically active compounds.

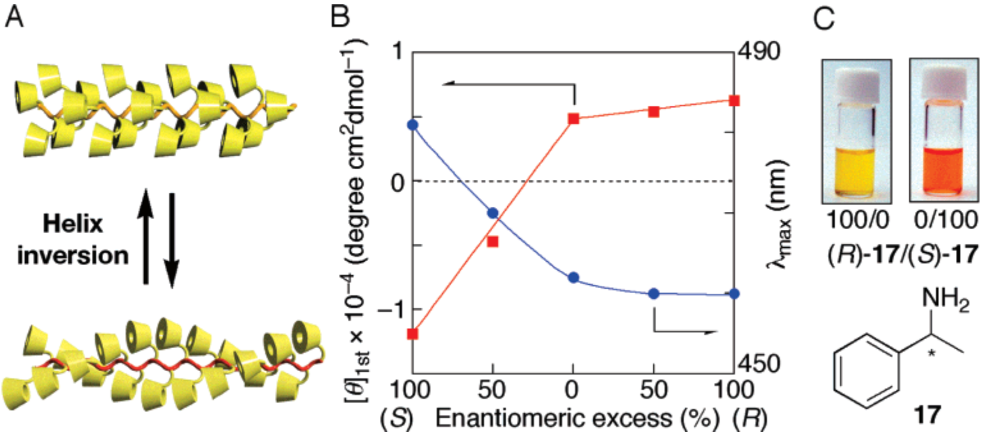


Figure 12. (A) Schematic illustration of a helix inversion in **60**β. (B) Changes in CD intensity ($[\theta]_{first}$) (red squares) and λ_{max} (blue circles) of **60**β vs the % ee of **17** in DMSO−water (8/2, v/v). (C) Visible color change of **60**β with (*R*)-**17** (left) and (*S*)-**17** (right) in DMSO−water (8/2, v/v).

A chiral stimuli-responsive, macromolecular helicity inversion was reported for dynamic helical poly(phenylacetylene)s bearing chiral pendant groups (**58**−**60**).[62,63] Among them, **60**β with β-cyclodextrin residues as the pendants is particularly interesting because it exhibits a helicity inversion accompanied by a visible color change induced by diastereomeric interactions with enantiomeric amines such as **17** (Figure 12). The color change is ascribed to a change in the twist angle of the conjugated double bonds of the main chain of **60**β. As a result, the helical pitch may be tunable. This system is conceptually new and can be applicable to a novel chirality-sensing method using a helical polymer as a color indicator.[64]

7. Summary and Outlook

In this review, the recent progress in chirality-responsive polymers, in particular, dynamic helical polymers, is mainly described. Chiral amplification that requires cooperativity during the transfer of chiral information from nonracemic guest molecules to the helical system is essential for developing a highly efficient chirality-responsive polymer. On the basis of this concept, the rational design of chirality-responsive polymers and oligomers (foldamers) can be possible using chromophoric helical backbones with a dynamic characteristic, combined with functional groups or a suitable cylindrical cavity for the target chiral guest molecules. With implications for biological helices and functions, further applications of chirality-responsive polymers to novel chiral materials as enantioselective catalysts and adsorbents will be an interesting and important challenge.[5a,65,66]

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