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Notes

Synthesis and Helix Formation of Poly(*m*-phenylene)s Bearing Optically Active Oligo(ethylene oxide) Side Chains in Protic Media

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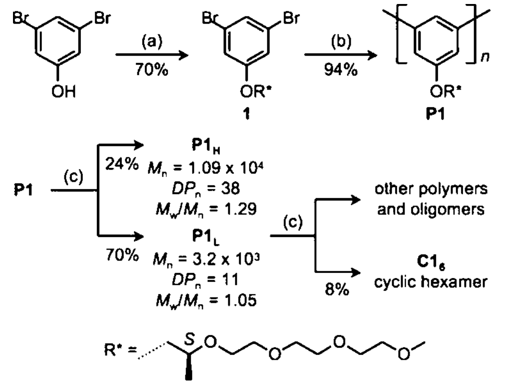
Introduction

The poly(*m*-phenylene) has attracted an intermittent but increasing attention arising from its rigid-rod backbone, high thermal stability, and electronic properties due to the broken conjugation.[1] Of particular interest to note is the 5_1-helical conformation that the poly(*m*-phenylene) adopts in the solid state,[2] which was disclosed by a single-crystal X-ray study of *m*-deciphenyl[2a,b] and subsequently by an X-ray powder diffraction study of the poly(*m*-phenylene).[2c] Upon dissolution, however, the helical conformation is readily unraveled to take a random coil conformation in solution. Hence, combined with the fact that the structurally analogous oligo(*m*-phenyleneethynylene) has emerged as a versatile foldamer motif,[3,4] the poly(*m*-phenylene) should be regarded as a potential candidate for a new structural motif for foldamers.

We have recently found that a 2-hydroxylated *m*-phenylene hexamer, **I** (R = OH, *n* = 6), forms a double-stranded helicate bridged by two spiroborates,[5] whereas the 4,6-dihydroxylated *m*-phenylene oligomers or oligoresorcinols, **II** (R = OH, *n* = 6, 9, 11), self-assemble into double-stranded helices in water, driven by aromatic interactions (Chart 1).[6] As part of our program to develop synthetic helical polymers and oligomers based on poly(*m*-phenylene), we have synthesized a new poly(*m*-phenylene) derivative with a substituent at the 5-position, **III**, for the purpose of investigating the effect of the substituent positions on the helix formation behavior. Optically active oligo(ethylene oxide) chains were selected as the substituent at the 5-position, since they are known to enhance the solubility of organic compounds not only in polar solvents, such as alcohols and water, but also in less polar solvents, such as chloroform, which is advantageous to investigate chiroptical properties of the polymers in a wide rage of solvents. In this paper, we report the synthesis and the excess one-handed single-helix formation of the poly(*m*-phenylene) bearing an optically active oligo(ethylene oxide) chain at the 5-position in protic media.

Scheme 1. Synthesis of the Poly(*m*-phenylene) with an Optically Active Oligo(ethylene oxide) Chain at the 5-Position[a]



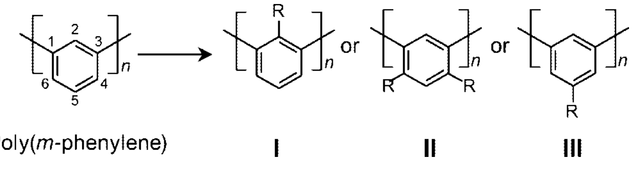
[a] Conditions: (a) R*OH (**2**), diisopropyl azodicarboxylate, PPh_3, THF, 0 °C, 1 day; (b) (i) bis(1,5-cyclooctadiene)nickel(0) (Ni(cod)$_2$), 2,2′-bipyridyl (bpy), 1,5-cyclooctadiene (cod), DMF, 80 °C, 1 day, (ii) H_3O^+; (c) HPLC fractionation.

Results and Discussion

The poly(*m*-phenylene) bearing optically active oligo(ethylene oxide) side chains was synthesized according to Scheme 1.[7] The monomer, **1**, was prepared from the Mitsunobu reaction of 3,5-dibromophenol using an optically active alcohol, **2**.[7,8] The polymerization of **1** was carried out using a nickel-mediated homocoupling reaction in *N*,*N*-dimethylformamide (DMF)[9] that produced a waxy product, **P1**, which showed a bimodal molecular weight distribution in the size exclusion chromatography (SEC) (Figure S1A).[7] **P1** was then subjected to SEC fractionation to afford two portions: the high molecular weight part, $\mathbf{P1_H}$ ($M_n = 1.09 \times 10^4$, $M_w/M_n = 1.29$), and the low molecular weight part, $\mathbf{P1_L}$ ($M_n = 3.2 \times 10^3$, $M_w/M_n = 1.05$) (Figure S1A).[7] While $\mathbf{P1_H}$ consisted of linear polymers with an average degree of polymerization (DP_n) of 38, $\mathbf{P1_L}$ mainly contained cyclic oligomers from 5-mer to 8-mer, as evidenced from the ^{1}H NMR and matrix-assisted laser desorption/ionization (MALDI) mass spectroscopies (Figures S1B and S1C).[7] In fact, a cyclic hexamer, $\mathbf{C1_6}$, was isolated from $\mathbf{P1_L}$ by further recycling HPLC purification (Figure S2).[7]

The structures of $\mathbf{P1_H}$ and $\mathbf{C1_6}$ in $CDCl_3/CD_3OD$ and CD_3OD/

Chart 1. Introduction of Substituent (R) to *m*-Phenylene Unit



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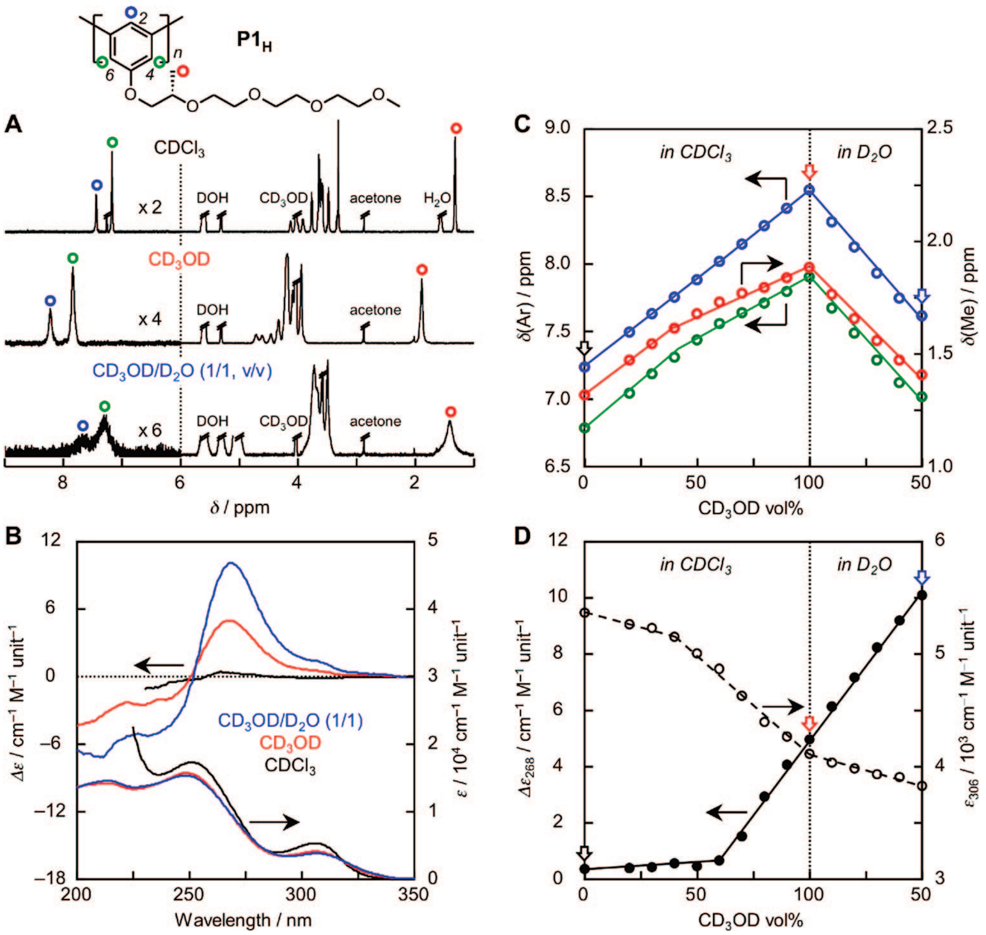

Figure 1. ^1H NMR (A), CD and absorption (B) spectra of $\mathbf{P1_H}$ in $CDCl_3$, CD_3OD, and CD_3OD/D_2O (1/1, v/v) at 25 °C ($[\mathbf{P1_H}]$ = 1 mM/unit). Plots of the chemical shifts of the aromatic-H_2 (blue circles), aromatic-$H_{4,6}$ (green circles), and the methyl group on the side chain (red circles) (C) and the molar circular dichroism values at 268 nm ($\Delta\epsilon_{268}$, black filled circles) and the molar absorptivity values at 306 nm (ϵ_{306}, black open circles) (D) of $\mathbf{P1_H}$ in various solvent mixtures.

D_2O mixed solvent systems were investigated using ^1H NMR, circular dichroism (CD), and absorption spectroscopies (Figure 1 and Figure S3).[7] In $CDCl_3/CD_3OD$, an increase in the CD_3OD content produced downfield shifts of the all signals of $\mathbf{P1_H}$ in the ^1H NMR spectra as well as hypochromicity of the absorption spectra, which are mainly attributable to the change in the solvent polarity (Figure 1C,D). However, an apparent transition point was observed at ca. 40% CD_3OD, over which the downfield shifts decreased and the hypochromicity was enhanced, suggesting the presence of aromatic interactions. In addition, distinct Cotton effects appeared above 60% CD_3OD, implying that $\mathbf{P1_H}$ adopts a helical conformation with a bias in the helix sense arising from the chiral side chains (Figure 1B,D). In the CD_3OD/D_2O mixtures, $\mathbf{P1_H}$ showed large upfield shifts of the ^1H NMR signals as well as hypochromicity of the absorption spectra, indicative of the increase in the content of the helical segments. The aqueous solution became turbid above 50% D_2O, which precluded further investigation. These results suggest that $\mathbf{P1_H}$ with a random coil conformation in $CDCl_3$ adopted a helical conformation with a helix-sense bias through aromatic interactions above 40% CD_3OD, and the helical segments with an excess one-handedness increased with an increase in CD_3OD in the $CDCl_3/CD_3OD$ mixture or D_2O in the CD_3OD/D_2O mixture, viz. an increase in solvent polarity.[10,11] The drastic changes in the specific rotation ($[\alpha]_D^{25}$) of $\mathbf{P1_H}$ from −16° ($CHCl_3$) to +80° (MeOH) and +140° (MeOH/H_2O (1/1, v/v)) also support the helical structure formation in MeOH and MeOH/H_2O.[7] The CD and absorption spectra did not show any change in the range of 0.02−5 mM/unit at a solvent composition of $CDCl_3/CD_3OD$ (20/80, v/v) or CD_3OD/D_2O (80/20, v/v), where $\mathbf{P1_H}$ partly forms the helical structure (Figure S4),[7] indicating that $\mathbf{P1_H}$ adopts not a double- but a single-helical conformation that should be independent of the concentration.[12] Furthermore, dynamic light scattering (DLS) experiments performed on the $\mathbf{P1_H}$ solutions in $CHCl_3$/MeOH confirmed that $\mathbf{P1_H}$ exhibited almost no change in size regardless of the solvent compositions, supporting the single-helix formation.

The change in the ^1H NMR and absorption spectra of $\mathbf{C1_6}$ exhibited downfield shifts and a hypochromicity, respectively, similarly to $\mathbf{P1_H}$ with increasing amounts of CD_3OD in $CDCl_3/CD_3OD$ mixtures (Figure S3).[7] In contrast to $\mathbf{P1_H}$, no apparent transition point was observed, indicating the absence of any aromatic interactions. In CD_3OD/D_2O, $\mathbf{C1_6}$ showed upfield shifts of the ^1H NMR signals and hypochromicity of the absorption with the increasing D_2O content and exhibited a transition point at ca. 60% D_2O, which suggests an intermolecular aromatic interaction that leads to the formation of columnar aggregates. Diffusion ordered ^1H NMR spectroscopy (DOSY)[13] measurements showed that the hydrodynamic size of $\mathbf{C1_6}$ did not change in $CDCl_3/CD_3OD$, while it exhibited a considerable increase with the increasing content of water in CD_3OD/D_2O (Figure S5),[7] supporting the formation of columnar aggregates in the aqueous solutions.

The temperature dependence of the Cotton effects and absorptivities was examined for $\mathbf{P1_H}$ in MeOH and MeOH/H_2O (1/1, v/v) (Figure 2). The CD intensities of $\mathbf{P1_H}$ in both solvents

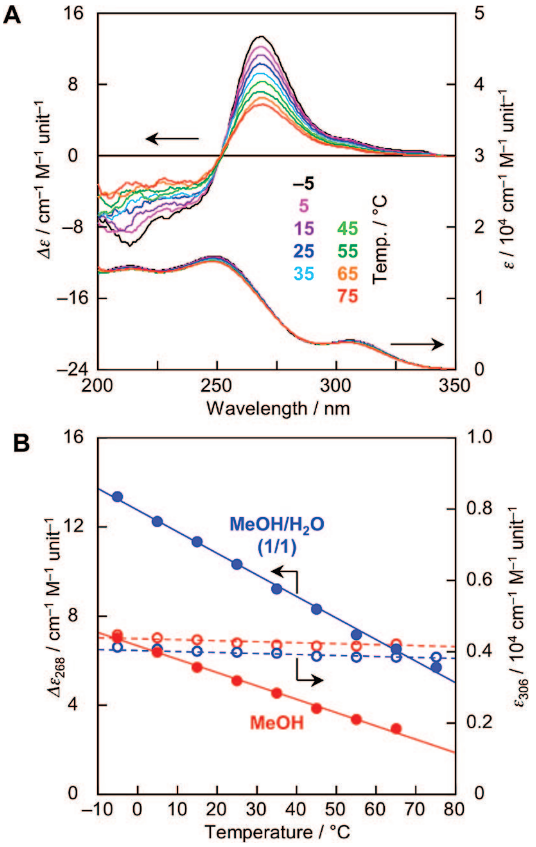

Figure 2. (A) Changes in the CD and absorption spectra of $\mathbf{P1_H}$ in MeOH/H_2O (1/1, v/v) at various temperatures (−5 to 75 °C) ([$\mathbf{P1_H}$] = 1 mM/unit). (B) Plots of the molar circular dichroism values at 268 nm ($\Delta\epsilon_{268}$, filled circles) and the molar absorptivity values at 306 nm (ϵ_{306}, open circles) of $\mathbf{P1_H}$ in MeOH (red) and MeOH/H_2O (1/1, v/v) (blue) at −5 to 75 °C.

gradually decreased with increasing temperature (−5 to 75 °C), whereas the absorptivities hardly changed even under the same conditions. This result unambiguously indicates that a helix-sense bias of $\mathbf{P1_H}$ increased with a decrease in temperature similarly to the case of the double-stranded helices of chiral oligoresorcinols bearing optically active substituents at both ends.[6a] On the other hand, a solution of $\mathbf{C1_6}$ in water showed a very weak CD (−5 to 35 °C) and became turbid at above 45 °C,[7] probably because of large aggregates at high temperatures as in the case of the thermoresponsive polyacrylamides (Figure S6).[14]

The single-helical conformation of $\mathbf{P1_H}$ was investigated by a molecular mechanics calculation study performed on a 5-methoxy-*m*-phenylene 30-mers, $\mathbf{PMP_{30}}$ (Figure 3, Figure S7, and Table S1).[7] First, the 5_1- and 5_2-helices, in which the benzene rings were tilted in one direction, were chosen for the initial structures, since they were reported to be energetically stable structures for the poly(*m*-phenylene).[15] Although both the energy-minimized structures of the 5_1- and 5_2-helices of $\mathbf{PMP_{30}}$ were calculated to be stable, they do not allow any intramolecular aromatic interactions, being inconsistent with the experimental data. Next, a 6_1-helix, in which the consecutive benzene rings are alternately tilted in both directions, was constructed on the basis of the X-ray single-crystal structure of the cyclic hexa(*m*-phenylene)[16] and subjected to MM calculation (Figure 3). The energy-minimized structure was more stable than those of the 5_1- and 5_2-helices because of a face-to-face aromatic interaction between the benzene rings, which are in good agreement with the spectroscopic data for $\mathbf{P1_H}$ in protic media.

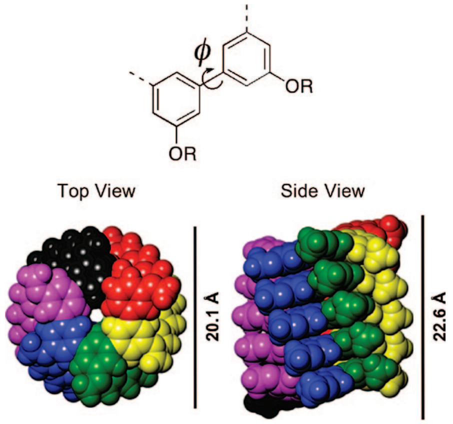

Figure 3. MM-calculated structure of 5-methoxy-*m*-phenylene 30-mer ($\mathbf{PMP_{30}}$) as the model for the poly(*m*-phenylene), $\mathbf{P1_H}$. The energy-minimized structures of 6_1-helix of $\mathbf{PMP_{30}}$ are shown. For the energy-minimized structures of the 5_1- and 5_2-helices of $\mathbf{PMP_{30}}$, see Figure S7.[7]

Conclusion

In conclusion, the poly(*m*-phenylene) bearing an optically active oligo(ethylene oxide) chain at the 5-position, $\mathbf{P1_H}$, was synthesized by the nickel-mediated homocoupling polymerization of the 3,5-dibromophenol monomer **1**. We have confirmed that $\mathbf{P1_H}$ adopts a single-helical conformation with the aid of aromatic interactions in protic media, demonstrating that the poly(*m*-phenylene) is a useful structural motif for helical foldamers, and more importantly, the positions of substituents determine whether the polymers take a single- or double-helical conformation. Since $\mathbf{P1_H}$ is soluble and forms a single helix in protic media containing water, it is expected to bind certain water-soluble biomolecules with some recognition, investigations of which are currently in progress.

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Supporting Information Available: Experimental procedures for the synthesis, separation, and characterization of **1**, $\mathbf{P1_H}$, and $\mathbf{C1_6}$, the solvent and concentration effects of $\mathbf{P1_H}$ and $\mathbf{C1_6}$, and the measurements of the hydrodynamic diameters of $\mathbf{C1_6}$ in solution. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) This behavior is similar to that of the oligo(*m*-phenyleneethynylene)s reported by Moore et al. that fold into a single-handed helical conformation driven by solvophobicity.[4a−c,f]

(11) Moore et al. suggested a possibility that the oligo(*m*-phenyleneethynylene)s formed some intermolecular aggregates in water-containing acetonitrile solutions.[4g] The poly(*m*-phenylene) may form such aggregates in aqueous methanol solutions, resulting in the white precipitates as observed in the mixed solvents containing more than 50% H_2O.

(12) These results do not exclude the possibility of double-helix formation of $\mathbf{P1_H}$ in aqueous media, where the water content is much higher (50−100%).

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