# Double helix formation of poly(*m*-phenylene)s bearing achiral oligo(ethylene oxide) pendants and transformation into an excess of one-handed single helix through cholate binding in water†

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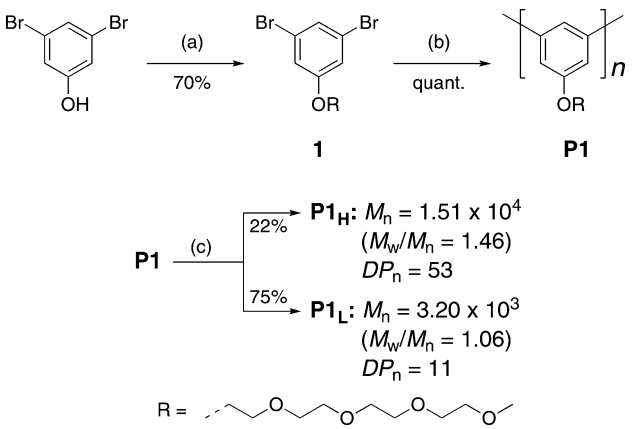
**A water-soluble poly(*m*-phenylene) bearing an achiral oligo(ethylene oxide) chain at the 5-position was synthesized by the Ni(0)-mediated homo-coupling polycondensation of a 3,5-dibromophenol monomer. The poly(*m*-phenylene) adopted a single helical conformation in protic media and self-assembled into a double helix in water through aromatic interaction, while it took a random-coil conformation in chloroform. Upon the addition of sodium cholate in water, the double helical poly(*m*-phenylene) was transformed into single strands, which bound the cholate molecules to form an excess of one-handed single helix.**

Polynucleotides and polypeptides adopt a specific structure such as a helix, and further assemble into three-dimensional higher-order structures that are indispensable for their sophisticated biological functions. Therefore, chemists have been continuously attracted by the design, synthesis, and applications of artificial helical polymers,[1] especially water-soluble helical polymers, since most important biological events occur in water. However, in contrast to a large number of helical polymers and oligomers which have been developed so far, water-soluble helices are still limited in number.[2] In addition, the synthetic, water-soluble double helices prepared so far are constructed from discrete oligomers prepared by organic synthesis,[3,4] and their polymeric counterparts are hitherto unknown.

We have discovered previously that oligo(4,6-dihydroxy-*m*-phenylene)s, or oligoresorcinols, self-assembled into double helices through aromatic interactions in water.[3a,e] They also formed pseudorotaxanes and hetero-double helices with cyclic and linear oligosaccharides, respectively, with high affinity and stereoselectivity.[3b,c] Recently, we have designed and synthesized poly(*m*-phenylene)s with chiral oligo(ethylene oxide) side chains, which are insoluble in water but form an excess of one-handed helix in protic media.[3d] In this paper, we report the synthesis and double helix formation of a new water-soluble poly(*m*-phenylene) with achiral oligo(ethylene oxide) chains in water along with transformation into an excess of one-handed single helix formation through the binding of lipids such as sodium cholate in water, thus showing an induced circular dichroism.

The poly(*m*-phenylene) bearing achiral oligo(ethylene oxide) side chains was synthesized according to Scheme 1. The monomer, **1**, was prepared by the Mitsunobu reaction[5] of 3,5-dibromophenol using an alcohol, ROH. The polymerization of **1** was carried out using a nickel-mediated homo-coupling reaction[6] in *N*,*N*-dimethylformamide (DMF) that produced a waxy product, **P1**, which exhibited a bimodal molecular weight distribution in size exclusion chromatography (SEC) (Fig. S1). **P1** was then subjected to SEC fractionation to obtain two portions, the high molecular weight part, $\mathbf{P1_H}$ ($M_n = 1.51 \times 10^4$, $M_w/M_n = 1.46$) and the low molecular weight part, $\mathbf{P1_L}$ ($M_n = 3.20 \times 10^3$, $M_w/M_n = 1.06$) (Fig. S1A). Although $\mathbf{P1_H}$ consisted of linear polymers with an average degree of polymerization ($DP_n$) of 53, $\mathbf{P1_L}$ was found to mainly contain cyclic oligomers from 5-mer to 8-mer with a $DP_n$ of 11, as evidenced from the $^1$H NMR spectroscopy and matrix assisted laser desorption/ionization (MALDI) and electron-spray ionization (ESI) mass spectrometries (Fig. S1B–D). $\mathbf{P1_H}$ was readily soluble in water, as opposed to its water-insoluble counterpart bearing chiral oligo(ethylene oxide) side chains.[3d] Thus, the methyl group on the chiral side chain greatly affects the solubility of the polymers in water.




**Scheme 1** Synthesis of the poly(*m*-phenylene) with an achiral oligo(ethylene oxide) chain at the 5-position. (a) ROH, diisopropyl azodicarboxylate, $PPh_3$, THF, 20 °C, 1 day; (b) (i) bis(1,5-cyclooctadiene)-nickel(0) ($Ni(cod)_2$), 2,2′-bipyridyl, cod, DMF, 80 °C, 1 day, (ii) $H_3O^+$; (c) recycling SEC chromatography.

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The structure of $\mathbf{P1_H}$ in $CDCl_3/CD_3OD$ and $CD_3OD/D_2O$ mixed solvent systems were investigated using $^1H$ NMR and absorption spectroscopies (Figs. 1 and S2). In $CDCl_3/CD_3OD$, an increase in the $CD_3OD$ content caused downfield shifts of the aromatic proton signals of $\mathbf{P1_H}$ in the $^1H$ NMR spectra, which is mainly attributed to the change in the solvent polarity. However, a transition point was observed at *ca.* 50% $CD_3OD$, over which the downfield shifts decreased. In addition, a distinct hypochromicity of the absorption spectra was observed above 40% $CD_3OD$, suggesting the presence of aromatic interactions (Figs. 1A and S2). These results suggest that $\mathbf{P1_H}$ adopted a single helical conformation through solvophobic effects in protic media, as observed in the previous poly(*m*-phenylene) bearing chiral oligo(ethylene oxide) chains.[3d,7] On the other hand, $\mathbf{P1_H}$ showed large upfield shifts of the $^1H$ NMR signals in the $CD_3OD/D_2O$ mixtures, indicating an increase in the content of the helical segments. Furthermore, a drastic transition point was found at *ca.* 60% $D_2O$, over which both $H_2$ and $H_{4,6}$ protons showed larger upfield shifts. This is attributed to the formation of a double helix with a $5_1$-helical conformation, as is observed in the case of oligoresorcinols in water.[3a] The dynamic light scattering (DLS) results strongly support the double helix formation of $\mathbf{P1_H}$ in water; the hydrodynamic diameter of $\mathbf{P1_H}$ in $H_2O$ was estimated to be 250 nm, while $\mathbf{P1_H}$ did not show light scattering in MeOH nor in $CHCl_3$ (Fig. S3). This extremely high hydrodynamic volume of $\mathbf{P1_H}$ indicates the formation of large aggregates presumably through Vernier-type complex formation, since $\mathbf{P1_H}$ has a molecular weight distribution, as in the case of the double-stranded helical polymers consisting of complementary homopolymers of amidine and carboxylic acid.[8,9] Thus, $\mathbf{P1_H}$ with a random coil conformation in $CHCl_3$ adopted a single helical conformation through the aromatic interactions in MeOH, and assembled into a double helix in $H_2O$ (Fig. 1B).

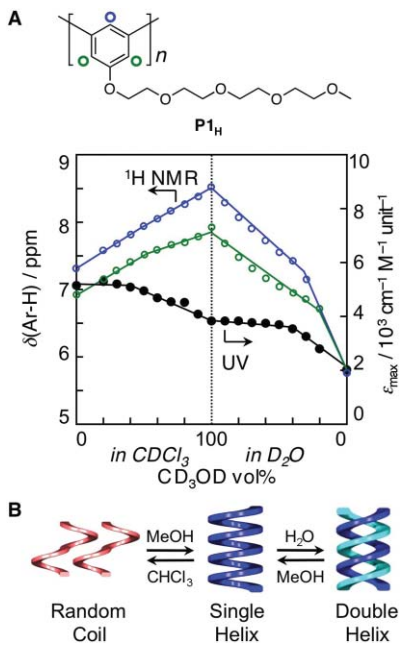


**Fig. 1** (A) Plots of the chemical shifts of the aromatic-$H_2$ (blue circles) and the aromatic-$H_{4,6}$ (green circles), and the molar absorptivity values at *ca.* 300 nm ($\varepsilon_{max}$, black filled circles) of $\mathbf{P1_H}$ in various solvent mixtures at 25 °C. [$\mathbf{P1_H}$] = 1 mM unit$^{-1}$. (B) Schematic illustration of the single- and double helix formation of $\mathbf{P1_H}$.

Since oligoresorcinols have been found to have a large affinity with stereoselectivity toward oligo- and polysaccharides,[3b,c] the water-soluble oligo- and poly(*m*-phenylene)s are likely to bind other biologically important molecules. As our preliminary study on developing lipid receptors, we investigated the inclusion behavior of $\mathbf{P1_H}$ toward steroids, which are ubiquitously found in living systems and display a variety of important biological functions.[10] The $^1H$ NMR titration of sodium cholate, **2**, with $\mathbf{P1_H}$ was then carried out, as shown in Fig. 2. The addition of $\mathbf{P1_H}$ caused upfield shifts of most signals of **2**, especially the two angular methyl groups (C18 and C19), which suggest that **2** was bound inside the aromatic grooves formed by $\mathbf{P1_H}$. The stoichiometry for the binding was determined to be five *m*-phenylene units of $\mathbf{P1_H}$ : **2** = 1:1 by the Job's plot, *i.e.*, five *m*-phenylene units bind one molecule of **2**.[11] From the $^1H$ NMR titration data of **2** with $\mathbf{P1_H}$, the association constant ($K_a$) was estimated to be 143 ± 3 M$^{-1}$ at 25 °C based on the five *m*-phenylene units.

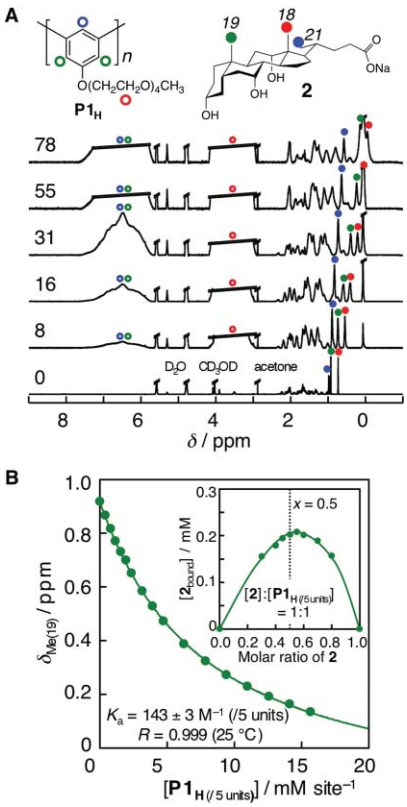


**Fig. 2** (A) $^1H$ NMR spectra of **2** with $\mathbf{P1_H}$ in $D_2O$ (pH = 7.6–8.0) at 25 °C. [**2**] = 1 mM and [$\mathbf{P1_H}$] = 0–78 mM (/5 units). (B) Plot of the chemical shift of the angular methyl (C19) protons of **2** *versus* [$\mathbf{P1_H}$]. The solid line represents the least-squares curve fitting result according to the Benesi-Hildebrand equation. (Inset) The Job plot of **2** with $\mathbf{P1_H}$ (/5 units) in $D_2O$ at 25 °C. [$\mathbf{P1_H}$ (/5 units)] + [**2**] = 2 mM. $[\mathbf{2}_{bound}] = [\mathbf{2}]_0 \times (\delta - \delta_0)/(\delta_{max} - \delta_0)$.

The circular dichroism (CD) and absorption titration experiments of **2** using $\mathbf{P1_H}$ in $H_2O$ (Fig. 3) revealed that an increase in the amount of **2** to $\mathbf{P1_H}$ in $H_2O$ caused a significant hyperchromicity of the absorption spectra above 240 nm, which is attributable to the dissociation of the double helix and the subsequent inclusion of **2**,

 

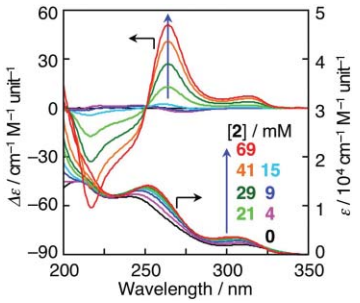


**Fig. 3** CD and absorption spectral changes of $\mathbf{P1_H}$ with **2** in $H_2O$ (pH = 7.6–8.0) at 25 °C. $[\mathbf{P1_H}] = 1$ mM unit$^{-1}$ and $[\mathbf{2}] = 0$–69 mM.

as observed for the hetero-double helix formation of oligoresorcinols with linear oligosaccharides in $H_2O$.[3c] The binding constant value was estimated to be 75 ± 8 $M^{-1}$ by the least-squares curve fitting based on five *m*-phenylene units, which is in relatively good agreement with that estimated by the $^1$H NMR titrations at 25 °C (Fig. S4). The hyperchromicity was accompanied by an intense induced CD, which indicates that the resulting inclusion complex adopts an excess one-handed, single helical conformation. The induced Cotton effects reversibly decreased at high temperatures and increased at low temperatures with negligible absorption changes (Fig. S5), suggesting the dynamic nature of the inclusion complex.

Further evidence for the formation of the inclusion complex was obtained from the diffusion-ordered $^1$H NMR spectroscopy (DOSY) measurements (Table S1).[12] The diffusion coefficients (*D*) of $\mathbf{P1_H}$ and **2** in $D_2O$ were $0.56 \times 10^{-10}$ and $4.29 \times 10^{-10}$ $m^2$ $s^{-1}$, respectively. Upon mixing a large excess of $\mathbf{P1_H}$ with **2**, the *D* value of **2** drastically decreased to $1.68 \times 10^{-10}$ $m^2$ $s^{-1}$, while $\mathbf{P1_H}$ showed almost no change in the diffusion constant.

In order to propose a reasonable structure for the inclusion complex of $\mathbf{P1_H}$ with **2**, the 2D NOESY spectrum was recorded (Figs. 4A and S6). Several nuclear Overhauser effect (NOE) cross-peaks were observed between the aromatic protons of $\mathbf{P1_H}$ and the aliphatic protons of **2** in $D_2O$. The aromatic protons on the main chain of $\mathbf{P1_H}$ showed intense NOE cross-peaks with the two angular methyl groups, C18 and C19 protons on the hydrophobic face of **2**, but exhibited no cross-peaks with C21 protons on the hydrophilic chain of **2**. These results were consistent with the larger upfield shifts of the protons on the hydrophobic steroid backbone of **2** in the NMR titration experiments (Fig. 2).

On the basis of the above results, a reasonable model for the inclusion complex was constructed with molecular-mechanics (MM) calculations performed on a 5-methoxy-*m*-phenylene 30-mer ($\mathbf{PMP_{30}}$) and **2** (Fig. 4B). The MM calculations for $\mathbf{PMP_{30}}$ suggest a $5_1$-helical conformation as an energy-minimized structure for the single-stranded $\mathbf{PMP_{30}}$,[13] which is consistent with the absence of intra-strand aromatic-aromatic interactions as evidenced by the hyperchromicity observed in the absorption spectra of $\mathbf{P1_H}$ in the presence of **2** (Fig. 3). Six molecules of **2** were then manually placed into the interaction sites of $\mathbf{P1_H}$, the helical grooves of the $5_1$-helical **2** with the hydrophobic face of **2** locating inside and the hydrophilic face outward. The resulting complex was further energy minimized to relieve unfavorable van der Waals contacts. The energy-minimized inclusion complex model satisfies all of the NMR data including intermolecular NOEs between the

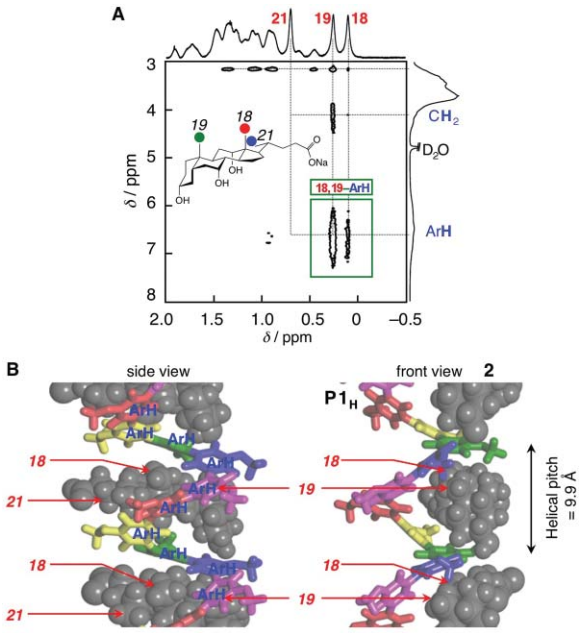


**Fig. 4** (A) Partial NOESY spectrum of $\mathbf{P1_H}$ with **2** in $D_2O$ at 25 °C. $[\mathbf{P1_H}] = 60$ mM unit$^{-1}$, $[\mathbf{2}] = 1$ mM, and mixing time = 0.3 s. (B) The energy-minimized inclusion complex model of $\mathbf{PMP_{30}}$ with **2**.

aromatic protons of $\mathbf{P1_H}$ and the aliphatic protons of the angular methyl groups of **2**.

In summary, the poly(*m*-phenylene) bearing an achiral oligo(ethylene oxide) chain at the 5-position ($\mathbf{P1_H}$) synthesized by the Ni(0)-mediated homo-coupling polymerization of the 3,5-dibromophenol monomer **1** was found to adopt a single helical conformation in protic media and a double helix in water through aromatic interactions, while it takes a random-coil conformation in chloroform. These results suggest that the poly(*m*-phenylene) is a useful structural motif for both single and double helical foldamers. Furthermore, upon the addition of cholate, the double helical $\mathbf{P1_H}$ was disassembled and bound cholate to form an excess of one-handed single helix. We believe that designer water-soluble poly(*m*-phenylene)s with positive or negative pendant groups may be capable of binding other physiologically important biomolecules, such as nucleic acids and peptides, the investigation of which is under progress.

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