Macromolecular helicity induction and static helicity memory of poly(biphenylylacetylene)s bearing aromatic pendant groups and their use as chiral stationary phases for HPLC

Tomoyuki Ikai,* Shogo Okuda, and Eiji Yashima*

Abstract: Two novel poly(biphenylylacetylene)s (PBPAs) bearing achiral alkylphenyl groups at the 4'-position of the biphenyl pendant through ester linkers with different sequences were synthesized by the rhodium-catalyzed polymerization of the corresponding monomers. The influence of the alkylphenyl pendants and the ester sequences on the macromolecular helicity induction and subsequent static helicity memory was investigated. In addition, the chiral recognition ability as chiral stationary phases for high-performance liquid chromatography of the helicity-memorized PBPAs was also examined. Both almost perfect right- and left-handed helical conformations through noncovalent chiral interactions with enantiomeric alcohols and their induced macromolecular helicities were completely retained ("memorized") after removal of the helix inducer. A PBPA bearing a 4-*n*-butylphenoxycarbonyl pendant group with a static helicity memory showed a remarkably high chiral recognition ability toward a wide variety of chiral aromatics, including simple point chiral compounds, axially chiral biaryls, a chiral spiro compound, helicenes, and planar chiral cyclophanes, particularly under the reversed-phase conditions.

Keywords: ester sequence, helical polymers, polyacetylenes, resolution, reversed-phase chiral HPLC

1 Introduction

Direct enantioseparation by high-performance liquid chromatography (HPLC) and supercritical fluid chromatography with chiral stationary phases (CSPs)[1-10] is recognized as one of the most powerful and widely used techniques for both the trace analyses of chiral molecules and industrial-scale productions of optically-pure ingredients.[11-19] Okamoto and co-workers achieved the first asymmetric synthesis of a one-handed helical poly(triphenylmethyl methacrylate) (PTrMA)[20-25] by the helix-sense-selective polymerization of an achiral bulky vinyl monomer with a chiral catalyst in 1979 and discovered its remarkable chiral separation ability when used as a CSP for HPLC, which was then commercialized in 1982 as the first practical helical polymer-based CSP. Since then, a variety of CSPs consisting of one-handed helical polymers, including polyacetylenes[26-34] and polyisocyanides,[35-38] have been developed.[25,39,40] Among the helical polymers, the helical polysaccharide derivatives (e.g., cellulose and amylose derivatives)[25,41-44] developed by Okamoto et al. are recognized as the most used commercially available CSPs in the world.

We previously reported that poly(biphenylylacetylene) (PBPA) derivatives with the appropriate substituents at the 2,2',4'-positions of the biphenyl pendants formed a preferred-handed helical conformation accompanied by an excess one-handed axially twisted structure of the biphenyl units through noncovalent chiral interactions with optically active guests, such as (*R*)- and (*S*)-1-phenylethanol ((*R*)- and (*S*)-PEA; Figure 1), and both the induced macromolecular helicity and pendant axial chirality were efficiently retained (memorized) after removal of the chiral inducers.[45-49] Taking advantage of this "macromolecular helicity induction and subsequent static helicity memory" strategy, we have succeeded in developing helical polymer-based CSPs with a static helicity memory from inherently optically inactive PBPAs composed of fully achiral[45,50-52] or racemic[53] repeating monomer units, some of which showed a unique switchable enantioseparation,[45,52] that is, switching of the elution order of the enantiomers, based on the reversible macromolecular helicity control in the column. The effect of the polar functional groups introduced at the 4'-position of the biphenyl pendants, such as ether, ester, and carbamate groups, on the chiral recognition abilities of the PBPA-based CSPs was investigated.[52] Among them, poly(**1**-Bu) and poly(**2**-Bu) (Figure 1) bearing alkoxycarbonyl and acyloxy groups at the 4'-position, respectively, and a carbamate-functionalized PBPA with a static helicity memory were found to show better resolution abilities than the ether-functionalized counterpart.[52]

In this study, we designed and synthesized two novel PBPAs (poly(**1**-Ph) and poly(**2**-Ph)) bearing achiral aromatic ester groups at the 4'-position of the biphenyl pendants with different

Department of Molecular and Macromolecular Chemistry, Graduate School of Engineering, Nagoya University, Nagoya 464-8603, Japan

Correspondence
Tomoyuki Ikai and Eiji Yashima, Department of Molecular and Macromolecular Chemistry, Graduate School of Engineering, Nagoya University, Nagoya 464-8603, Japan
Email: ikai@chembio.nagoya-u.ac.jp;
yashima@chembio.nagoya-u.ac.jp

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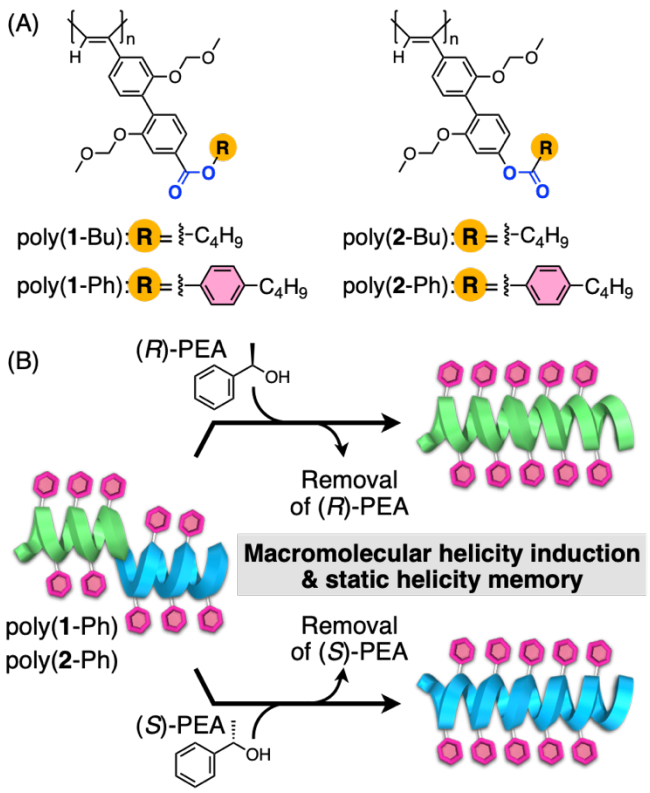


FIGURE 1 (A) Structures of poly(biphenylylacetylene) (PBPA) derivatives (poly(**1**-Bu), poly(**2**-Bu), poly(**1**-Ph), and poly(**2**-Ph)). (B) Schematic illustration of macromolecular helicity induction and subsequent static helicity memory in poly(**1**-Ph) and poly(**2**-Ph) bearing aromatic pendant groups through noncovalent chiral interactions with optically active alcohols ((*R*)- and (*S*)-PEA).

sequences (-COO- or -OCO-, respectively). Their macromolecular helicity induction and subsequent static memory behaviors along with their stabilities of the helicity memory and chiral recognition abilities as CSPs for HPLC under the normal- and reversed-phase conditions were investigated (Figure 1).

2 Materials and Methods

Biphenylylacetylene monomers (**1**-Ph and **2**-Ph) were prepared according to Scheme S1.

2.1 Synthesis of 1-Ph

To a mixture of [2,2'-bis(methoxymethoxy)-4'-carboxyl-4-biphenylyl]acetylene (0.20 g, 0.58 mmol), *N*,*N*-dimethyl-4-aminopyridine (DMAP) (86 mg, 0.70 mmol), and 4-butylphenol (0.11 g, 0.70 mmol) in anhydrous dichloromethane (6 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC-HCl) (0.13 g, 0.70 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. After removing the solvent under reduced pressure, the residue was diluted with ethyl acetate and the solution was washed with aqueous 1 N HCl, saturated aqueous $NaHCO_3$, and brine, and then dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude product was purified by silica gel chromatography using *n*-hexane/ethyl acetate (7/3, v/v) as the eluent to give the desired product as a white solid (0.25 g, 91% yield). Mp: 75.1-75.7 °C. IR (KBr, cm^{-1}): 3238 (≡CH), 2104 (C≡C), 1712 (C=O). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.99 (d, J = 1.5 Hz, 1H, Ar–H), 7.91 (dd, J = 7.8, 1.2 Hz, 1H, Ar–H), 7.38-7.36 (m, 2H, Ar–H), 7.24-7.20 (m, 4H, Ar–H), 7.12 (d, J = 8.3 Hz, 2H, Ar–H), 5.15 (s, 2H, OCH_2O), 5.09 (s, 2H, OCH_2O), 3.36 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.11 (s, 1H, C≡C-H), 2.64 (t, J = 7.7 Hz, 2H, Ar–CH_2), 1.65-1.59 (m, 2H, Ar–CH_2CH_2), 1.41-134 (m, 2H, CH_2CH_3), 0.94 (t, J = 7.4 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 165.14, 154.95, 154.65, 148.98, 140.69, 134.06, 131.63, 131.58, 131.21, 130.51, 129.48, 129.11, 125.78, 123.76, 123.07, 121.46, 118.95, 118.91, 116.76, 95.30, 95.23, 83.52, 77.66, 56.30, 56.27, 56.20, 56.17, 35.21, 33.76, 22.45, 14.08. HRMS (ESI+): *m*/*z* calcd for $C_{29}H_{30}NaO_6$ ($M+Na^+$), 497.1935; found 497.1912.

2.2 Synthesis of 2-Ph

To a mixture of [2,2'-bis(methoxymethoxy)-4'-hydroxy-4-biphenylyl]acetylene (0.20 g, 0.64 mmol), DMAP (93 mg, 0.76 mmol), and 4-butylbenzoic acid (0.14 g, 0.76 mmol) in anhydrous dichloromethane (6 ml) was added EDC-HCl (0.15 g, 0.76 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. After removing the solvent under reduced pressure, the residue was diluted with ethyl acetate and the solution was washed with aqueous 1 N HCl, saturated aqueous $NaHCO_3$, and brine, and then dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude product was purified by silica gel chromatography using *n*-hexane/ethyl acetate (9/1, v/v) as the eluent to give the desired product as a white solid (0.28 g, 94% yield). Mp: 74.9-75.8 °C. IR (KBr, cm^{-1}): 3236 (≡CH), 2106 (C≡C), 1711 (C=O). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.12 (d, J = 8.3 Hz, 2H, Ar–H), 7.36 (s, 1H, Ar–H), 7.32 (d, J = 8.3 Hz, 2H, Ar–H), 7.26 (d, J = 8.3 Hz, 1H, Ar–H), 7.21 (s, 2H, Ar–H), 7.10 (d, J = 2.2 Hz, 1H, Ar–H), 6.94 (dd, J = 8.3, 2.2 Hz, 1H, Ar–H), 5.08 (s, 4H, OCH_2O), 3.37 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.09 (s, 1H, C≡C-H), 2.71 (t, J = 7.8 Hz, 2H Ar–CH_2), 1.68-1.62 (quint, J = 7.6 Hz, 2H, Ar–CH_2CH_2), 1.42-1.35 (m, 2H, CH_2CH_3), 0.95 (t, J = 7.3 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 165.33, 155.64, 154.91, 151.51, 149.59, 131.68, 130.43, 129.65, 128.85, 128.82, 127.05, 125.83, 125.81, 122.53, 119.12, 119.08, 115.12, 109.42, 109.40, 95.34, 83.70, 77.34, 56.18, 56.14, 35.95, 33.41, 22.46, 14.05. HRMS (ESI+): *m*/*z* calcd for $C_{29}H_{30}NaO_6$ ($M+Na^+$), 497.1935; found 497.1914.

2.3 Polymerization

Rhodium-catalyzed polymerizations of **1**-Ph and **2**-Ph were carried out according to Scheme 1 in a dry Schlenk flask under dry nitrogen using [(norbornadiene)rhodium(I) chloride]$_2$ ([Rh(nbd)Cl]$_2$) in a similar way as previously reported,[45,46,50-53] and the polymerization results are summarized in Table 1 (entries 1 and 2). For comparison, poly(**1**-Bu)[50] and poly(**2**-Bu)[52] were also prepared in a similar way (entries 3 and 4); their spectroscopic data were consistent with the reported ones. The *cis–transoidal* stereoregular structures of the new homopolymers were confirmed by their ^1H NMR (Figures S12 and S13)[54-58] and Raman spectra (Figure S1)[59-62] based on the literature.

2.3.1 Spectroscopic data of poly(1-Ph)

IR (KBr, cm^{-1}): 1758 (C=O). ^1H NMR (500 MHz, $CDCl_3$, 50 °C): δ 7.91-7.80 (br, 1H, Ar–H), 7.74-7.60 (br, 1H, Ar–H), 7.20-6.86 (br, 7H, Ar–H), 6.64-6.46 (br, 1H, Ar–H), 6.14-5.98 (br, 1H, C=CH),

5.00-4.83 (br, 2H, OCH_2O), 4.83-4.60 (br, 2H, OCH_2O), 3.17-3.07 (br, 3H, OCH_3), 3.07-2.94 (br, 3H, OCH_3), 2.64-2.48 (br, 2H, Ar–CH_2), 1.62-1.52 (m, 2H, Ar–CH_2CH_2), 1.39-1.28 (m, 2H, CH_2CH_3), 0.90 (t, J = 7.2 Hz, 3H, CH_2CH_3). Calcd for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37. Found: C, 73.44; H, 6.39.

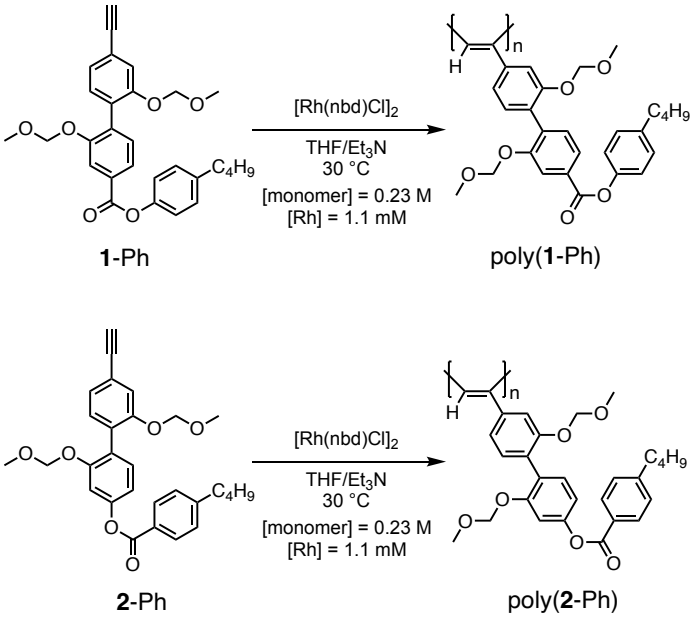
2.3.2 Spectroscopic data of poly(2-Ph)

IR (KBr, cm^{-1}): 1760 (C=O). ^1H NMR (500 MHz, $CDCl_3$, 50 °C): δ 8.06-7.92 (br, 2H, Ar–H), 7.24-7.14 (br, 2H, Ar–H), 7.06-6.82 (br, 4H, Ar–H), 6.76-6.64 (br, 1H, Ar–H), 6.60-6.44 (br, 1H, Ar–H), 6.15-5.96 (br, 1H, C=CH), 4.95-4.79 (br, 2H, OCH_2O), 4.79-4.60 (br, 2H, OCH_2O), 3.20-3.07 (br, 3H, OCH_3), 3.07-2.90 (br, 3H, OCH_3), 2.70-2.52 (br, 2H, Ar–CH_2), 1.65-1.53 (m, 2H, Ar–CH_2CH_2), 1.40-1.26 (m, 2H, CH_2CH_3), 0.90 (t, J = 7.2 Hz, 3H, CH_2CH_3). Calcd for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37. Found: C, 73.48; H, 6.30.

3 Results and Discussion

3.1 Synthesis of poly(biphenylylacetylene)s bearing aromatic pendant groups

Two novel achiral biphenylylacetylene monomers (**1**-Ph and **2**-Ph) bearing 4-*n*-butylphenoxycarbonyl and 4-*n*-butylbenzoyloxy groups as aromatic pendants at the 4'-position of the biphenyl unit were synthesized in one-step through esterification of the corresponding biphenylylacetylenes carrying carboxyl[51] and hydroxy[52] groups, respectively (Scheme S1). These monomers were then polymerized using a rhodium catalyst ($[Rh(nbd)Cl]_2$, nbd: norbornadiene) in tetrahydrofuran (THF) in the presence of triethylamine at 30 °C according to a previously reported method (Scheme 1).[45,46,50-53] The *cis-transoidal* dynamically racemic helical PBPAs (poly(**1**-Ph) and poly(**2**-Ph)) were obtained in high yields (95%) with the number-average molar mass (M_n) of more than 4.5 × 10^5, as estimated by size-exclusion chromatography (SEC), respectively (entries 1 and 2 in Table 1 and Figure S1). For a comparative study, *cis-transoidal* optically inactive PBPAs (poly(**1**-Bu)[50] and poly(**2**-Bu)[52]) bearing aliphatic *n*-butoxycarbonyl and *n*-pentanoyloxy pendant groups were also prepared in the same way (entries 3 and 4).



SCHEME 1 Synthesis of poly(**1**-Ph) and poly(**2**-Ph).

3.2 Macromolecular helicity induction and static helicity memory

Both the right (*P*)- and left (*M*)-handed helical structures were almost completely induced in the poly(**1**-Ph) backbone in toluene in the presence of (*R*)- and (*S*)-PEA as a helix inducer (≥ 10 vol%) at 25 °C within 4 h, respectively (Figures 2A(i,iv), S2A, and S3A), based on the comparison of their induced circular dichroism (ICD) patterns and intensities with those of the previously reported completely (*P*)-handed helical PBPA carrying an optically active pendant.[47,53,63] The complete macromolecular helicity induction in poly(**2**-Ph) was also achieved with (*R*)- and (*S*)-PEA (≥ 10 vol%) in toluene (Figures 2B(i,iv) and S3B), while it took a rather longer time (ca. 24 h) to complete the one-handed helix induction (Figure S2B), indicating a faster one-handed helix formation of poly(**1**-Ph).

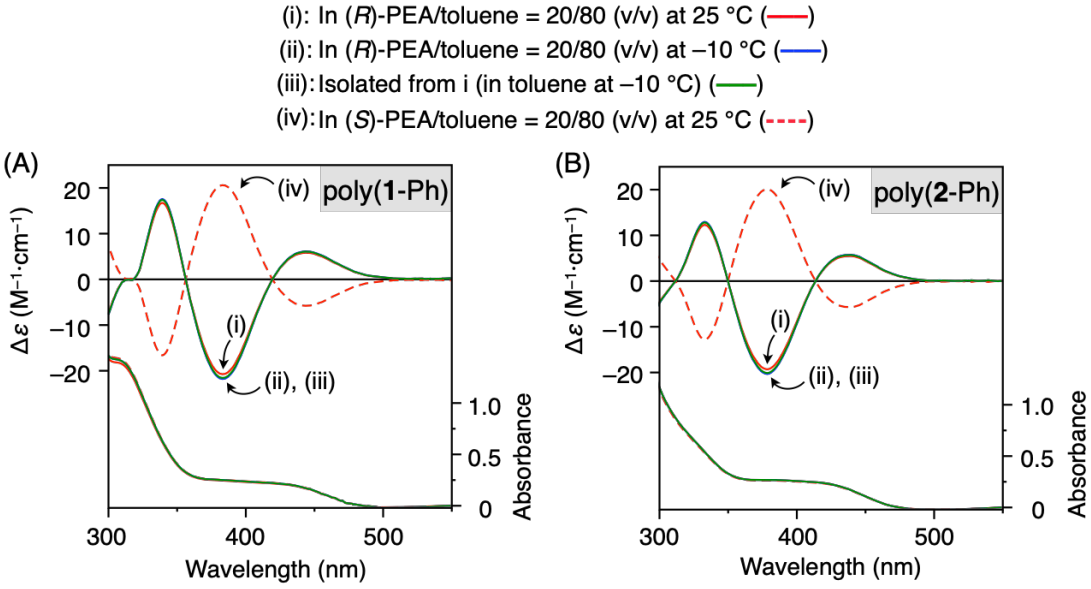


FIGURE 2 CD and absorption spectra of poly(**1**-Ph) (A) and poly(**2**-Ph) (B) in the presence of (*R*)-PEA (i,ii) and (*S*)-PEA (iv) in toluene (PEA/toluene = 20/80, v/v) measured at 25 (i,iv) and –10 (ii) °C after allowing them to stand at 25 °C for 24 h. CD and absorption spectra of the isolated polymers recovered from i, measured in toluene at –10 °C, were also shown in (iii). [Polymer] = 1.0 mM (calculated based on the monomer units).

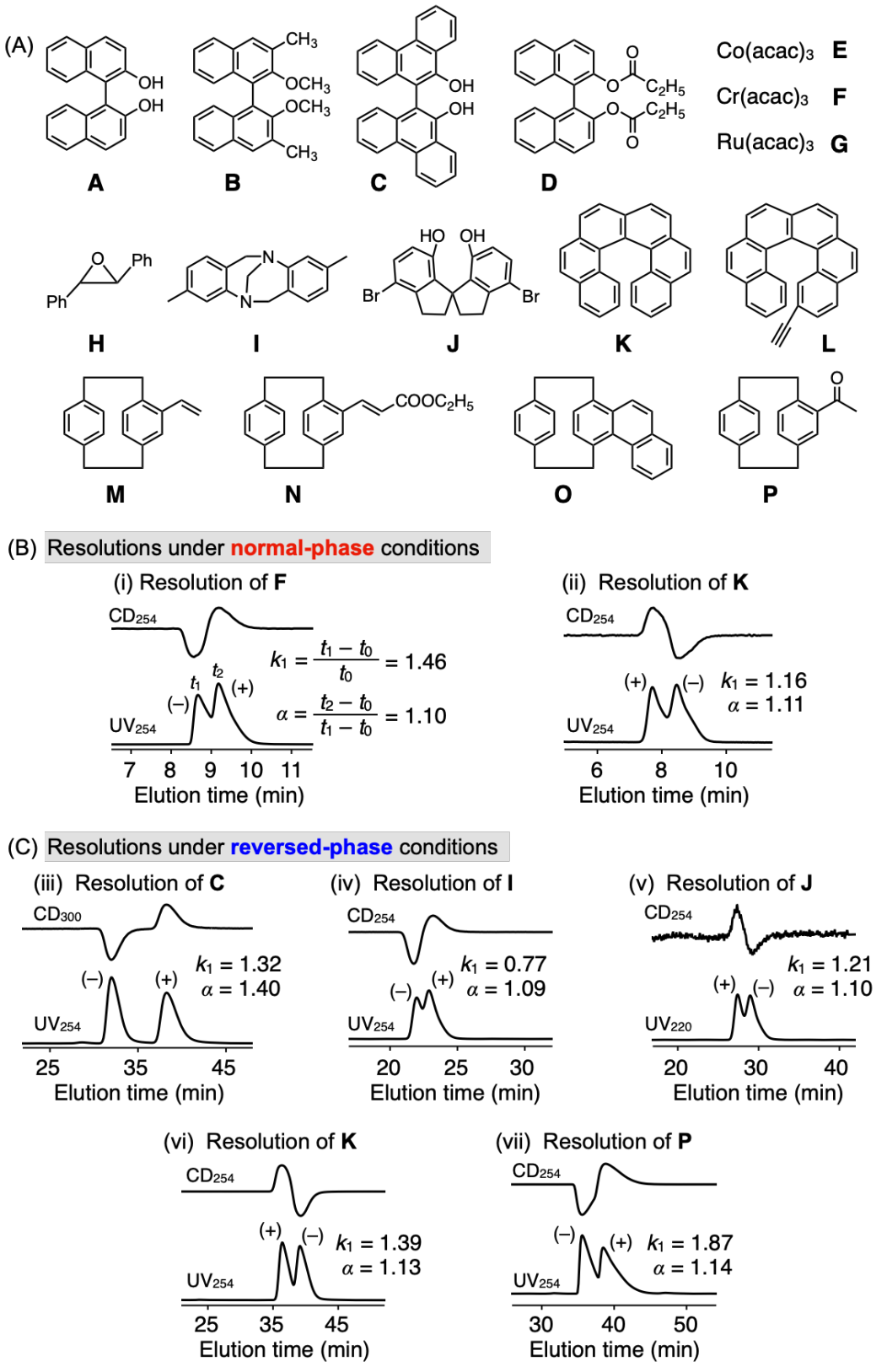


FIGURE 3 (A) Structures of racemates. (B,C) HPLC chromatograms for the resolutions of **F** (i), **K** (ii,vi), **C** (iii), **I** (iv), **J** (v), and **P** (vii) on the (*P*)-*h*-poly(**1**-Ph)-based CSP with static helicity memory under normal-phase (B; 10 °C) and reversed-phase (C; 0 °C) conditions. Eluent: *n*-hexane/2-propanol (97/3, v/v) (i,ii), methanol (iii,vii), methanol/water (90/10, v/v) (iv, v), or ethanol (vi).

As expected from the previously reported poly(**1**-Bu) and poly(**2**-Bu),[50,52] the (*P*)-handed helical poly(**1**-Ph) and poly(**2**-Ph) induced by (*R*)-PEA were almost perfectly memorized after complete removal of the helix inducer by precipitation into methanol (Figures 2A,B(iii) and S4B,E; for more details, see section 3 in the Supporting Information). The static helicity memories of (*P*)-*h*-poly(**1**-Ph) and (*P*)-*h*-poly(**2**-Ph) were relatively stable in toluene at –10 °C, and remained more than 90% of their initial state after 12 h (Figure S5A). On the other hand, at 25 °C, the ICD intensities gradually decreased with time and the half-life

time period ($t_{1/2}$) roughly estimated from the ICD intensity changes were 3.5 and 6 h, respectively (Figure S5B(i,ii)), whereas those of poly(**1**-Bu) and poly(**2**-Bu) estimated under the same conditions were 3 and 1 h, respectively (Figure S5B(iii,iv)).[52] Hence, the replacement of the alkyl groups with the 4-alkylphenyl ones at the 4'-position of the biphenyl pendants appeared to stabilize the static helicity memory, which, however, depends on the ester sequences (-COO- and -OCO-), probably due to the intramolecular π–π interactions and/or steric effect between the neighboring phenyl groups arranged along the one-handed helical polymer backbones.

3.3 Chiral recognition abilities of PBPA-based CSPs for HPLC

The novel PBPA-based CSPs consisting of (*P*)-*h*-poly(**1**-Ph) and (*P*)-*h*-poly(**2**-Ph) with a static helicity memory were then prepared by coating each polymer solution in (*R*)-PEA/toluene (10/90, v/v) showing a full ICD signal on macroporous silica gel, followed by thoroughly washing with *n*-hexane to completely remove (*R*)-PEA after evaporating the solvent (for details of the preparation of the CSPs for HPLC, see section 4 in the Supporting Information).[50-53] The (*P*)-*h*-poly(**1**-Bu)- and (*P*)-*h*-poly(**2**-Bu)-based coated-type CSPs were also prepared in the same way.[52]

The ICD intensities of poly(**1**-Ph) and poly(**2**-Ph) recovered from the CSPs using an excess of toluene slightly decreased along with a red-shift of the absorption spectra compared to those before coating onto the silica surface (Figure S6). The reason for such a change in the absorption spectral pattern during the recovery of the polymer process, while maintaining the *cis-transoidal* polymer backbone structures as supported by the ^{1}H NMR spectra (Figure S4C,F), was not clear, but the macromolecular helicity memories of (*P*)-*h*-poly(**1**-Ph) and (*P*)-*h*-poly(**2**-Ph) coated on silica gel were substantially maintained.

The enantioseparation abilities of 16 racemates, **A**–**P** (Figure 3A), on the (*P*)-*h*-poly(**1**-Ph) - and (*P*)-*h*-poly(**2**-Ph)-based CSPs were first evaluated under normal-phase conditions using *n*-hexane–2-propanol (97/3, v/v) as the eluent at 10 °C, and their resolution results along with those on the (*P*)-*h*-poly(**1**-Bu)-[50] and (*P*)-*h*-poly(**2**-Bu)-based CSPs[52] are summarized in Table 2. Figure 3B shows typical chromatograms for the resolution of the racemic **F** and **K** on the (*P*)-*h*-poly(**1**-Ph)-based CSP obtained with dual UV and CD detectors. As shown in Figure 3B(i), a pair of enantiomers of **F** showing negative (–)- and positive (+)-CD signals were eluted at the retention times of t_1 and t_2, respectively. The retention factors, k_1 [= (t_1 − t_0)/t_0] and k_2 [= (t_2 − t_0)/t_0], were determined to be 1.46 and 1.61, respectively, based on the hold-up time (t_0) of 3.52 min, leading to a separation factor α (= k_2/k_1) of 1.10.

As summarized in Table 2, the (*P*)-*h*-poly(**1**-Ph)-based CSP showed a better chiral recognition ability than the (*P*)-*h*-poly(**2**-Ph)-based CSP as observed in the (*P*)-*h*-poly(**1**-Bu)- and (*P*)-*h*-poly(**2**-Bu)-based CSPs.[52] Among the racemic **A**–**P**, the (*P*)-*h*-poly(**1**-Ph)- and (*P*)-*h*-poly(**2**-Ph)-based CSPs partially resolved six and two racemates, respectively, but their α values were mostly lower than those of the corresponding alkoxycarbonyl ((*P*)-*h*-poly(**1**-Bu))[50] and acyloxy ((*P*)-*h*-poly(**2**-Bu))[52] PBPA derivatives, respectively (Table 2), although some racemates **K**, **L**, and **P** were partially resolved on (*P*)-*h*-poly(**1**-Ph), but not separated at all on (*P*)-*h*-poly(**1**-Bu), while vice versa for racemates **A** and **C**. These results suggest that the replacement of the alkyl groups of (*P*)-*h*-poly(**1**-Bu) and (*P*)-*h*-poly(**2**-Bu) with the 4-alkylphenyl ones at the 4'-position of the biphenyl pendants hardly contributes to improving the enantioseparation abilities under normal-phase conditions, although nearly identical one-handed helical conformations were most likely induced and subsequently memorized in these four polymers as evidenced by the quite similar ICD patterns and intensities to each other (Figure 2).[50,52]

In accordance with the fact that a one-handed helical PTrMA bearing triphenylmethyl pendants with a chiral propeller conformation exhibited an exceptionally high chiral recognition when used as a CSP for HPLC, particularly in the reversed-phase mode as reported by Okamoto et al.,[20,22-25] we next investigated the resolution abilities of the (*P*)-*h*-poly(**1**-Ph)- and (*P*)-*h*-poly(**2**-Ph)-based CSPs under reversed-phase conditions using alcohols and a methanol/water mixture as the eluent at 0 °C (Figure 3C and Table 3). Unlike the normal-phase chiral HPLC separation results, the (*P*)-*h*-poly(**1**-Ph)-based CSP showed a much better chiral recognition in the reversed-phase mode than in the normal-phase mode and successfully resolved various types of chiral hydrophobic aromatics (Figure 3A), including not only simple compounds with a point chirality (**H** and **I**; Figure 3C(iv)), but also axially chiral biaryls (**B**–**D**; Figure 3C(iii)), a chiral spiro compound (**J**; Figure 3C(v)), helicenes with a helical chirality (**K** and **L**; Figure 3C(vi)), and planar chiral cyclophanes (**M**–**P**; Figure 3C(vii)) (Table 3). On the other hand, the (*P*)-*h*-poly(**1**-Bu) with aliphatic pendants on the biphenyl units showed a lower resolution ability and could resolve only three racemates, **C**, **H**, and **I** (Table 3). These results indicated the key role of the aromatic ester residues at the pendants of the (*P*)-*h*-poly(**1**-Ph), which serve as attractive chiral recognition sites under the reversed-phase conditions probably through π–π and/or hydrophobic interactions with the aromatic racemates, resulting in a significant improvement of the chiral recognition ability compared to that of the (*P*)-*h*-poly(**1**-Bu).

The (*P*)-*h*-poly(**2**-Ph)-based CSP, which is only different from the (*P*)-*h*-poly(**1**-Ph) with respect to the ester sequence (-OCO- or -COO-, respectively), also exhibited a poor chiral recognition under reversed-phase conditions toward all the tested racemates except for the helicenes, **K** and **L** (Table 3), despite having the one-handed helical conformations with a static helicity memory in (*P*)-*h*-poly(**1**-Ph) and (*P*)-*h*-poly(**2**-Ph) as already described (Figures 2 and S6). In contrast, several racemates (**C** and **H**–**L**) were separated into enantiomers on the (*P*)-*h*-poly(**2**-Bu) under reversed-phase conditions, but some of them were not resolved on the (*P*)-*h*-poly(**2**-Ph) (Table 3). Although the origin of the crucial difference in the chiral recognition abilities between the (*P*)-*h*-poly(**1**-Ph) and (*P*)-*h*-poly(**2**-Ph) still remains unclear, but is probably attributed to the difference in the chiral/helical arrangements of the achiral phenyl pendants along the one-handed helical polymer backbones. The remarkably high chiral recognition observed for the (*P*)-*h*-poly(**1**-Ph)-based CSP toward racemic hydrophobic aromatics, in particular, under reversed-phase conditions, is most likely derived from the achiral aromatic pendants linked through the -COO- linkage that can be favorably arranged/oriented in a one-handed helical fashion along the helical polyacetylene backbone with a static helicity memory. However, the achiral aromatic pendants linked through the -OCO- linkage of (*P*)-*h*-poly(**2**-Ph) may not be arranged in such a way, resulting in a poor chiral recognition ability both in the normal- and reversed-phase modes. Thus, the proper and rational design of achiral functional aromatic pendant groups introduced at the 4'-position of the biphenyl groups of the helical PBPAs with a static helicity memory is of key importance in achieving an efficient enantioseparation capability.

We also confirmed that the resolution power of the (*P*)-*h*-poly(**1**-Ph)-based CSP remained virtually unchanged after allowing the column filled with methanol to stand at ca. 0 °C for 2 weeks, thereby demonstrating its sufficiently high stability of the static helicity memory and durability when used as a CSP for reversed-phase HPLC (Figure S7).

Conclusion

In summary, we have synthesized two novel PBPA derivatives containing achiral *n*-butylphenyl pendants at the 4'-position of the biphenyl units through ester linkers with different sequences. Almost completely one-handed helices with a static helicity memory were successfully produced from the corresponding inherently optically inactive PBPAs based on the one-handed helicity induction and static helicity memory strategy. The resulting static helicity memories of the helical PBPAs were more stable than those of the analogous PBPAs bearing aliphatic pendant groups, probably due to cooperative intramolecular π–π interactions and/or steric effect arising from the neighboring aromatic pendants arranged along the one-handed helical polymer backbones. The chiral recognition abilities of the helicity-

memorized PBPAs with aromatic pendants as CSPs for HPLC were significantly influenced by the ester sequences of the pendant groups and chromatographic conditions (normal- and reversed-phase modes). The PBPA carrying phenoxycarbonyl pendants showed a much higher resolution ability toward various kinds of racemic aromatic compounds with point, axial, and planar chirality and helicity under the reversed-phase conditions, when compared to those of the helicity-memorized PBPAs with benzoyloxy or aliphatic pendant groups. We believe that more powerful PBPA-based CSPs with a static helicity memory capable of switching the enantioselectivity will be developed by a rational design and modification of the functional pendant groups combining the "reversible switching of the static macromolecular helicity in the column" concept[45,52] as well as a technique for immobilizing PBPAs onto silica gel through chemical bonding.[52] Work towards these goals is now underway in our laboratory.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website.

REFERENCES AND NOTES

1. Davankov VA. Enantioselective ligand exchange in modern separation techniques. *J Chromatogr A*. 2003;1000(1-2):891-915.
2. Okamoto Y, Ikai T. Chiral HPLC for efficient resolution of enantiomers. *Chem Soc Rev*. 2008;37(12):2593-2608.
3. Hyun MH. Liquid chromatographic enantioseparations on crown ether-based chiral stationary phases. *J Chromatogr A*. 2016;1467:19-32.
4. Fernandes C, Phyo YZ, Silva AS, Tiritan ME, Kijjoa A, Pinto MMM. Chiral stationary phases based on small molecules: An update of the last 17 Years. *Sep Purif Rev*. 2018;47(2):89-123.
5. Ilisz I, Bajtai A, Lindner W, Péter A. Liquid chromatographic enantiomer separations applying chiral ion-exchangers based on *Cinchona* alkaloids. *J Pharm Biomed Anal*. 2018;159:127-152.
6. Ianni F, Pucciarini L, Carotti A, Natalini S, Raskildina GZ, Sardella R, Natalini B. Last ten years (2008-2018) of chiral ligand-exchange chromatography in HPLC: An updated review. *J Sep Sci*. 2019;42(1):21-37.
7. Chankvetadze B. Recent trends in preparation, investigation and application of polysaccharide-based chiral stationary phases for separation of enantiomers in high-performance liquid chromatography. *TrAC-Trends Anal Chem*. 2020;122.
8. Welch CJ. William H. Pirkle: Stereochemistry pioneer. *Chirality*. 2020;32(7):961-974.
9. Berkecz R, Tanács D, Péter A, Ilisz I. Enantioselective liquid chromatographic separations using macrocyclic glycopeptide-based chiral selectors. *Molecules*. 2021;26(11).
10. Zhang Y, Jin XN, Ma XF, Wang Y. Chiral porous organic frameworks and their application in enantioseparation. *Anal Methods*. 2021;13(1):8-33.
11. Ward TJ, Ward KD. Chiral separations: A review of current topics and trends. *Anal Chem*. 2012;84(2):626-635.
12. Desfontaine V, Guillarme D, Francotte E, Nováková L. Supercritical fluid chromatography in pharmaceutical analysis. *J Pharm Biomed Anal*. 2015;113:56-71.
13. Patel DC, Wahab MF, Armstrong DW, Breitbach ZS. Advances in high-throughput and high-efficiency chiral liquid chromatographic separations. *J Chromatogr A*. 2016;1467:2-18.
14. Basheer A. Chemical chiral pollution: Impact on the society and science and need of the regulations in the 21st century. *Chirality*. 2018;30(4):402-406.
15. Felletti S, Ismail OH, De Luca C, Costa V, Gasparrini F, Pasti L, Marchetti N, Cavazzini A, Catani M. Recent achievements and future challenges in supercritical fluid chromatography for the enantioselective separation of chiral pharmaceuticals. *Chromatographia*. 2019;82(1):65-75.
16. Ishii C, Furusho A, Hsieh CL, Hamase K. Multi-dimensional high-performance liquid chromatographic determination of chiral amino acids and related compounds in real world samples. *Chromatography*. 2020;41(1):1-17.
17. Ali I, Suhail M, Aboul-Enein HY, Kon'kova T. Recent trends in chiral separations by 2D-HPLC. *Chromatographia*. 2021;84(6):535-548.
18. D'Orazio G, Fanali C, Dal Bosco C, Gentili A, Fanali S. Chiral separation and analysis of antifungal drugs by chromatographic and electromigration techniques: Results achieved in 2010-2020. *Rev Anal Chem*. 2021;40(1):220-252.
19. Grybinik S, Bosakova Z. An overview of chiral separations of pharmaceutically active substances by HPLC (2018–2020). *Mon Chem*. 2021;152(9):1033-1043.
20. Okamoto Y, Suzuki K, Ohta K, Hatada K, Yuki H. Optically active poly(triphenylmethyl methacrylate) with one-handed helical conformation. *J Am Chem Soc*. 1979;101(16):4763-4765.
21. Yuki H, Okamoto Y, Okamoto I. Resolution of racemic compounds by optically active poly(triphenylmethyl methacrylate). *J Am Chem Soc*. 1980;102(20):6356-6358.
22. Okamoto Y, Honda S, Okamoto I, Yuki H, Murata S, Noyori R, Takaya H. Novel packing material for optical resolution: (+)-Poly(triphenylmethyl methacrylate) coated on macroporous silica gel. *J Am Chem Soc*. 1981;103(23):6971-6973.
23. Okamoto Y, Nakano T. Asymmetric polymerization. *Chem Rev*. 1994;94(2):349-372.
24. Okamoto Y. Precision synthesis, structure and function of helical polymers. *Proc Jpn Acad Ser B*. 2015;91(6):246-261.
25. Shen J, Okamoto Y. Efficient separation of enantiomers using stereoregular chiral polymers. *Chem Rev*. 2016;116(3):1094-1138.
26. Yashima E, Huang S, Okamoto Y. An optically active stereoregular polyphenylacetylene derivative as a novel chiral stationary phase for HPLC. *J Chem Soc Chem Commun.* 1994(15):1811-1812.
27. Zhang C, Liu F, Li Y, Shen X, Xu X, Sakai R, Satoh T, Kakuchi T, Okamoto Y. Influence of stereoregularity and linkage groups on chiral recognition of poly(phenylacetylene) derivatives bearing L-Leucine ethyl ester pendants as chiral stationary phases for HPLC. *J Polym Sci Part A: Polym Chem.* 2013;51(10):2271-2278.
28. Maeda K, Maruta M, Shimomura K, Ikai T, Kanoh S. Chiral recognition ability of an optically active poly(diphenylacetylene) as a chiral stationary phase for HPLC. *Chem Lett*. 2016;45(9):1063-1065.
29. Maeda K, Yashima E. Helical polyacetylenes induced via noncovalent chiral interactions and their applications as chiral materials. *Top Curr Chem*. 2017;375(4).
30. Hirose D, Isobe A, Quiñoá E, Freire F, Maeda K. Three-state switchable chiral stationary phase based on helicity control of an optically active poly(phenylacetylene) derivative by using metal cations in the solid state. *J Am Chem Soc*. 2019;141(21):8592-8598.
31. Nozaki M, Hirose D, Maeda K. Synthesis of a poly(diphenylacetylene) bearing optically active anilide pendants and its application to a chiral stationary phase for high-performance liquid chromatography. *J Chromatogr A*. 2020;1622.
32. Zhang C, Liu L, Okamoto Y. Enantioseparation using helical polyacetylene derivatives. *TrAC-Trends Anal Chem*. 2020;123:115762.
33. Zhou YL, Zhu RQ, Zhang CH, Liu XD, Wang ZP, Zhou ZJ, Liu LJ, Dong HX, Satoh T, Okamoto Y. Synthesis of

poly(phenylacetylene)s containing chiral phenylethyl carbamate residues as coated-type CSPs with high solvent tolerability. *Chirality*. 2020;32(5):547-555.
34. Shi G, Dai X, Xu Q, Shen J, Wan XH. Enantioseparation by high-performance liquid chromatography on proline-derived helical polyacetylenes. *Polym Chem*. 2021;12(2):242-253.
35. Tsuchida A, Hasegawa T, Kobayashi K, Yamamoto C, Okamoto Y. Resolution of enantiomers using sugar-carrying polyisocyanides as chiral stationary phases for HPLC. *Bull Chem Soc Jpn.* 2002;75(12):2681-2685.
36. Tamura K, Miyabe T, Iida H, Yashima E. Separation of enantiomers on diastereomeric right- and left-handed helical poly(phenyl isocyanide)s bearing L-alanine pendants immobilized on silica gel by HPLC. *Polym Chem*. 2011;2(1):91-98.
37. Miyabe T, Iida H, Ohnishi A, Yashima E. Enantioseparation on poly(phenyl isocyanide)s with macromolecular helicity memory as chiral stationary phases for HPLC. *Chem Sci*. 2012;3(3):863-867.
38. Wada Y, Shinohara K, Asakawa H, Matsui S, Taima T, Ikai T. One-step synthesis of one-dimensional supramolecular assemblies composed of helical macromolecular building blocks. *J Am Chem Soc*. 2019;141(35):13995-14002.
39. Nakano T. Optically active synthetic polymers as chiral stationary phases in HPLC. *J Chromatogr A*. 2001;906(1-2):205-225.
40. Yashima E, Ousaka N, Taura D, Shimomura K, Ikai T, Maeda K. Supramolecular helical systems: Helical assemblies of small molecules, foldamers, and polymers with chiral amplification and their functions. *Chem Rev*. 2016;116(22):13752-13990.
41. Okamoto Y, Kaida Y. Resolution by high-performance liquid-chromatography using polysaccharide carbamates and benzoates as chiral stationary phases. *J Chromatogr A*. 1994;666(1-2):403-419.
42. Okamoto Y, Yashima E. Polysaccharide derivatives for chromatographic separation of enantiomers. *Angew Chem Int Ed*. 1998;37(8):1020-1043.
43. Yamamoto C, Okamoto Y. Optically active polymers for chiral separation. *Bull Chem Soc Jpn.* 2004;77(2):227-257.
44. Ikai T, Okamoto Y. Structure control of polysaccharide derivatives for efficient separation of enantiomers by chromatography. *Chem Rev*. 2009;109(11):6077-6101.
45. Shimomura K, Ikai T, Kanoh S, Yashima E, Maeda K. Switchable enantioseparation based on macromolecular memory of a helical polyacetylene in the solid state. *Nat Chem*. 2014;6(5):429-434.
46. Maeda K, Hirose D, Okoshi N, Shimomura K, Wada Y, Ikai T, Kanoh S, Yashima E. Direct detection of hardly detectable hidden chirality of hydrocarbons and deuterated isotopomers by a helical polyacetylene through chiral amplification and memory. *J Am Chem Soc*. 2018;140(9):3270-3276.
47. Ikai T, Mizumoto K, Ishidate R, Kitzmann WR, Ikeda R, Yokota C, Maeda K, Yashima E. Catalytic One-Handed Helix-Induction and Memory of Amphiphilic Poly(biphenylylacetylene)s in Water. *Giant*. 2020;2:100016.
48. Ikai T, Ando M, Ito M, Ishidate R, Suzuki N, Maeda K, Yashima E. Emergence of highly enantioselective catalytic activity in a helical polymer mediated by deracemization of racemic pendants. *J Am Chem Soc*. 2021;143(32):12725-12735.
49. Yashima E, Maeda K. Helical polymers with dynamic and static macromolecular helicity memory: The power of helicity memory for helical polymer synthesis and applications. *Bull Chem Soc Jpn*. **2021**, DOI:10.1246/bcsj.20210282. 2021.
50. Ishidate R, Shimomura K, Ikai T, Kanoh S, Maeda K. Macromolecular helicity induction and memory in a poly(biphenylylacetylene) bearing an ester group and its application to a chiral stationary phase for high-performance liquid chromatography. *Chem Lett*. 2015;44(7):946-948.
51. Ishidate R, Ikai T, Kanoh S, Yashima E, Maeda K. Chromatographic enantioseparation by poly(biphenylylacetylene) derivatives with memory of both axial chirality and macromolecular helicity. *Chirality*. 2017;29(3-4):120-129.
52. Ishidate R, Sato T, Ikai T, Kanoh S, Yashima E, Maeda K. Helicity induction and memory effect in poly(biphenylylacetylene)s bearing various functional groups and their use as switchable chiral stationary phases for HPLC. *Polym Chem*. 2019;10(46):6260-6268.
53. Ikai T, Kurake T, Okuda S, Maeda K, Yashima E. Racemic monomer-based one-handed helical polymer recognizes enantiomers through auto-evolution of its helical handedness excess. *Angew Chem Int Ed*. 2021;60(9):4625-4632.
54. Simionescu CI, Percec V, Dumitrescu S. Polymerization of acetylenic derivatives. XXX. Isomers of polyphenylacetylene. *J Polym Sci Polym Chem Ed*. 1977;15(10):2497-2509.
55. Furlani A, Napoletano C, Russo MV, Feast WJ. Stereoregular polyphenylacetylene. *Polym Bull*. 1986;16(4):311-317.
56. Kishimoto Y, Eckerle P, Miyatake T, Kainosho M, Ono A, Ikariya T, Noyori R. Well-controlled polymerization of phenylacetylenes with organorhodium(I) complexes: Mechanism and structure of the polyenes. *J Am Chem Soc*. 1999;121(51):12035-12044.
57. Percec V, Rudick JG, Peterca M, Wagner M, Obata M, Mitchell CM, Cho W-D, Balagurusamy VSK, Heiney PA. Thermoreversible cis−cisoidal to cis−transoidal isomerization of helical dendronized polyphenylacetylenes. *J Am Chem Soc*. 2005;127(43):15257-15264.
58. Okoshi K, Sakajiri K, Kumaki J, Yashima E. Well-defined lyotropic liquid crystalline properties of rigid-rod helical polyacetylenes. *Macromolecules*. 2005;38(10):4061-4064.
59. Shirakawa H, Ito T, Ikeda S. Raman scattering and electronic spectra of poly(acetylene). *Polym J*. 1973;4(4):460-462.
60. Tabata M, Tanaka Y, Sadahiro Y, Sone T, Yokota K, Miura I. Pressure-induced cis to trans isomerization of aromatic polyacetylenes. 2. Poly((*o*-ethoxyphenyl)acetylene) stereoregularly polymerized using a Rh complex catalyst. *Macromolecules*. 1997;30(18):5200-5204.
61. Ohsawa S, Sakurai S-i, Nagai K, Banno M, Maeda K, Kumaki J, Yashima E. Hierarchical amplification of macromolecular helicity of dynamic helical poly(phenylacetylene)s composed of chiral and achiral phenylacetylenes in dilute solution, liquid crystal, and two-dimensional crystal. *J Am Chem Soc*. 2011;133(1):108-114.
62. Tang Z, Iida H, Hu H-Y, Yashima E. Remarkable enhancement of the enantioselectivity of an organocatalyzed asymmetric henry reaction assisted by helical poly(phenylacetylene)s bearing cinchona alkaloid pendants via an amide linkage. *ACS Macro Lett*. 2012;1(2):261-265.
63. Ishidate R, Markvoort AJ, Maeda K, Yashima E. Unexpectedly strong chiral amplification of chiral/achiral and chiral/chiral copolymers of biphenylylacetylenes and further enhancement/inversion and memory of the macromolecular helicity. *J Am Chem Soc*. 2019;141(18):7605-7614.