RESEARCH ARTICLE

Racemic Monomer-Based One-Handed Helical Polymer Recognizes Enantiomers through Auto-Evolution of Its Helical Handedness Excess

Tomoyuki Ikai,[a] Tomoyuki Kurake,[a] Shogo Okuda,[a] Katsuhiro Maeda,[b,c] and Eiji Yashima*[a]

[a] Dr. T. Ikai, T. Kurake, S. Okuda, Prof. E. Yashima
Department of Molecular and Macromolecular Chemistry
Graduate School of Engineering, Nagoya University
Chikusa-ku, Nagoya 464-8603 (Japan)
E-mail: yashima@chembio.nagoya-u.ac.jp

[b] Prof. K. Maeda
Graduate School of Natural Science and Technology
Kanazawa University
Kakuma-machi, Kanazawa 920-1192 (Japan)

[c] Prof. K. Maeda
Nano Life Science Institute (WPI-NanoLSI)
Kanazawa University
Kakuma-machi, Kanazawa 920-1192 (Japan)

Supporting information and the ORCID identification numbers for the authors of this article can be found under: https://doi.org/10.1002/anie.2020XXXX.

Abstract: *The homochirality of bio(macro)molecules is a vital feature in living systems definitely responsible for their sophisticated functions. Obviously, any bio- and synthetic polymers composed of racemic monomers will show no chiral functions. Herein, we report that a racemic monomer-based optically-inactive polyacetylene folds into a one-handed helix assisted by a nonracemic alcohol, which can separate various enantiomers as a chiral stationary phase in chromatography. The chiral-resolving power is virtually identical to that of the enantiopure monomer-based one-handed helical polyacetylene. Because of its unique static memory of the induced helicity, the original racemic polyacetylene expresses an "auto-evolution" of its helical handedness over time, and at the same time, chirality of the nonracemic alcohol is discriminated accompanied by successive enhancement of its optical purity enantioselectively adsorbed on the helical polyacetylene due to the "chiral filter effect" as directly monitored by NMR, which contributes to further enhancing the helix-sense-excess of the helical polyacetylene.*

Introduction

The vital functions in living systems are ingeniously regulated by biological macromolecules, such as DNA and proteins,[1] which definitely rely on the homochirality of their components, D-sugars and L-amino acids, thereby enabling them to form the one-handed helical structures, *i.e.*, the right-handed double helix[2] and the right-handed α-helix,[3] respectively. Obviously, racemic sugars and amino acids, when they are randomly polymerized, would mostly produce nonhelical polymers,[4-6] thus showing no optical activity and hence biological functions related to chirality, such as chiral recognition, asymmetric catalysis, replication, etc., will not be expected at all by most definitions. Nearly racemic monomers can produce a preferred-handed helical polymer through significant amplification of the chirality/helicity in covalent and noncovalent helical systems ("majority rule" effect),[7] but the use of nonracemic (enantioenriched) monomers is an indispensable prerequisite for biasing the helical handedness.[6b,7-9]

Contrary to such a preconceived notion, we have recently succeeded in producing either a right (*P*)- or a left (*M*)-handed helical poly(biphenylylacetylene) (PBPA) (*h*-poly(*rac*-**1**))[10] using (*R*)- and (*S*)-1-phenylethanol ((*R*)- and (*S*)-PEA) as a helix-inducer (Figure 1a) even though the repeating monomer units are totally *racemic* based on the noncovalent helicity induction and subsequent static memory of the helicity strategy[11] that we previously developed for PBPA derivatives composed of achiral monomer units, such as poly-**2a**[11,12] and poly-**2b**.[13] This finding has a great advantage in that the optically pure or nonracemic ingredients, which are expensive and require time-consuming multistep processes to obtain, are no longer necessary for producing one-handed helical polymers, which can be prepared from racemic monomers.[14,15]

We now report a *racemic* monomer-based one-handed helical polymer (*h*-poly(*rac*-**3**)) that can be readily synthesized in a helix-sense-selective manner using a catalytic amount of nonracemic 1,1'-bi-2-naphthol (BINOL) of low enantiomeric excess (ee) as well as (*R*)- and (*S*)-PEA as a helix-inducer (Figure 1b). The one-handed helical *h*-poly(*rac*-**3**) with the static helicity memory obtained after removal of the chiral PEA and BINOL can separate a variety of racemic compounds including *rac*-BINOL into enantiomers when used as a chiral stationary phase (CSP) for high-performance liquid chromatography (HPLC).[16] The chiral separation ability is virtually identical to that of a one-handed helical PBPA (poly(*S*-**3**)) composed of optically pure (*S*)-monomer units (Figure 1c). We are not aware of any precedent in *racemic* systems that function as a chiral material. During the course of this study, we found that the progress of the helix-sense excess (*hse*) enhancement of the as-prepared poly(*rac*-**3**) induced by the nonracemic BINOL can be directly followed by NMR through which a dynamically racemic helicity of poly(*rac*-**3**) expresses continuous evolution over time to form a one-handed helix, and at the same time, the chirality of the nonracemic BINOL is

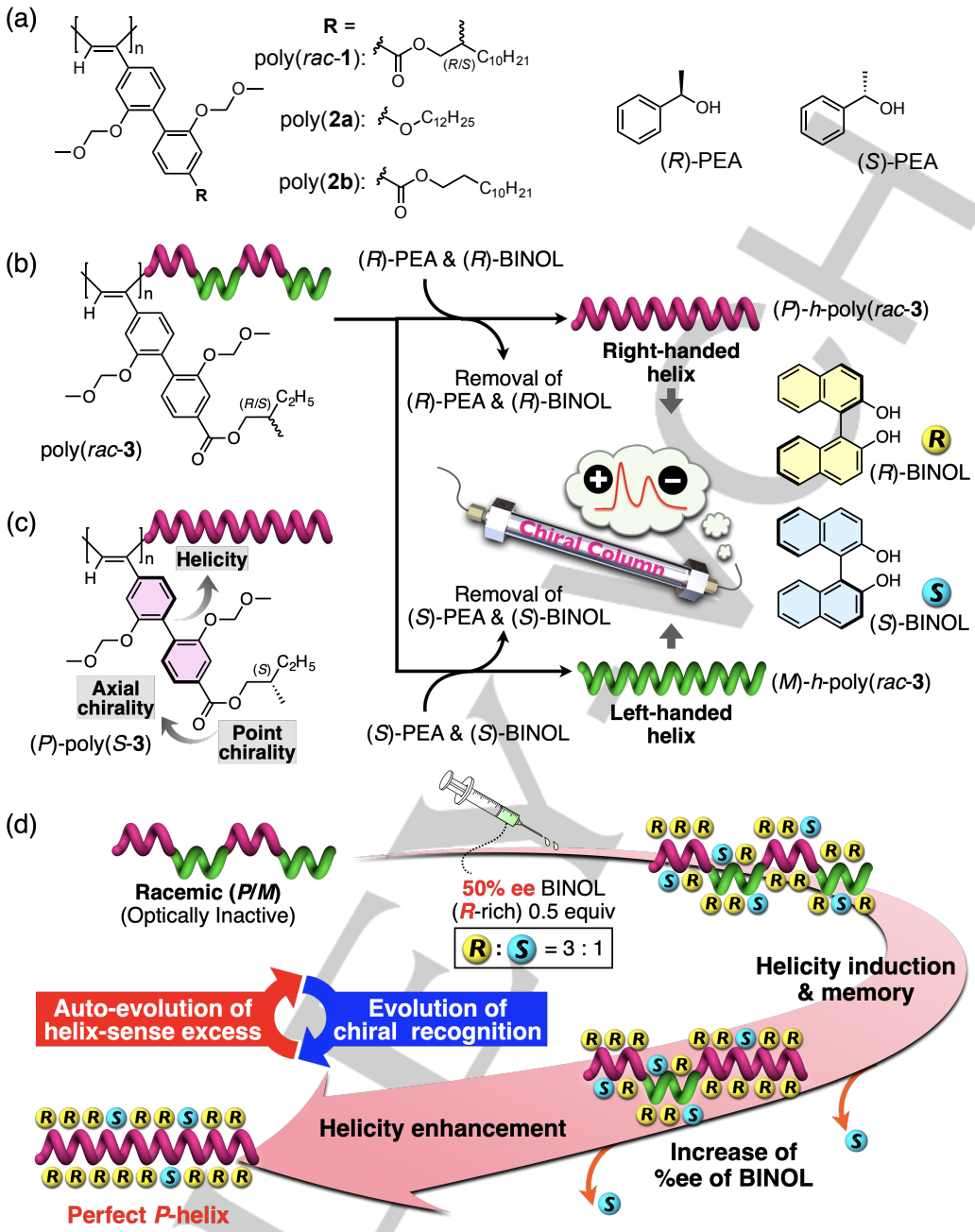

Figure 1. a) Structures of poly(biphenylylacetylene) (PBPA) derivatives (poly(*rac*-**1**) and poly(**2**)) and optically active alcohols (PEA). b) Schematic illustration of helicity induction and its subsequent memory of the macromolecular helicity in poly(*rac*-**3**) bearing racemic pendant groups through noncovalent chiral interactions with (*R*)- or (*S*)-PEA and -BINOL. c) Sequential chiral information transfer in a PBPA composed of chiral monomer units (poly(*S*-**3**)) from optically active pendants with point chirality to biphenyl units with dynamic axial chirality and further to the polyacetylene backbone with dynamic helical chirality. d) Schematic illustration of auto-evolution of helix-sense excess of a helical PBPA consisting of racemic repeating units assisted by a nonracemic BINOL followed by successive enhancement of its chiral recognition ability toward nonracemic BINOL.

discriminated in time by the resulting preferred-handed helical *h*-poly(*rac*-**3**) because of its static helicity memory (Figure 1d).[11,12] As a result, the poly(*rac*-**3**) potentially expresses a unique "*auto-evolution*" type chiral discrimination behavior,[17] which further enables it to enhance the optical purity of the nonracemic BINOL adsorbed on the *h*-poly(*rac*-**3**) resulting from the "*chiral filter effect*"[18] through which the minor enantiomer of BINOL is excluded by the helical sense of *h*-poly(*rac*-**3**) formed by the excess enantiomer of the nonracemic BINOL.

Results and Discussion

Synthesis of PBPAs composed of racemic or optically pure monomer units

Cis-transoidal poly(*rac*-**3**) and its optically active counterpart (poly(*S*-**3**)) composed of optically pure (*S*)-monomer units were prepared according to a previously reported method (Scheme S1)[10,11,19] by polymerization of the corresponding monomers with a rhodium catalyst ([Rh(nbd)Cl]$_2$, nbd: norbornadiene), yielding *cis-transoidal* polymers[20] with the number-average molar mass

(M_n) of more than 2.8 × 10^5 in high yields (Table S1). Shorter alkyl chains were introduced at the pendants of the polymers (Figure 1a,b) to improve the durability against solvents when used as a CSP (see below).

Enantioseparation on racemic monomer-based one-handed helical polymers with the static helicity memory

Both the (*P*)- and (*M*)-helices could be induced in poly(*rac*-3) using (*R*)- and (*S*)-PEA as an optically active co-solvent in toluene (20/80, v/v: [PEA]/[monomer units of poly(*rac*-3)] > 1000) at 25 °C, respectively (Figures 2(i,ii) and S2), and the induced (*P*)- and (*M*)-helices (*h*-poly(*rac*-3)) were subsequently memorized after complete removal of the (*R*)- and (*S*)-PEA (Figures 2(iii,iv) and S3) as reported for poly(*rac*-1).[10] The (*P*)- and (*M*)-*h*-poly(*rac*-3)s with static memory of the helicity showed a full induced circular dichroism (CD) like that of the (*P*)-helical homopolymer (poly(*S*-3)) (Figure 2(v)), indicating that fully one-handed helical structures are helix-sense selectively produced from the *racemic* poly(*rac*-3).

Surprisingly, the (*P*)- and (*M*)-*h*-poly(*rac*-**3**)s with the static helicity memory successfully separated a variety of racemic compounds (**4** – **12** in Figure 3a) into enantiomers when used as CSPs for HPLC as shown in the typical chromatograms for the base-line enantioseparations of BINOL and **4** with opposite elution orders from each other (Figure 3b,c; for details of the preparation of CSPs, see Section 7 in the Supporting Information (SI)).[11,13] The chiral recognition abilities of the CSPs can be

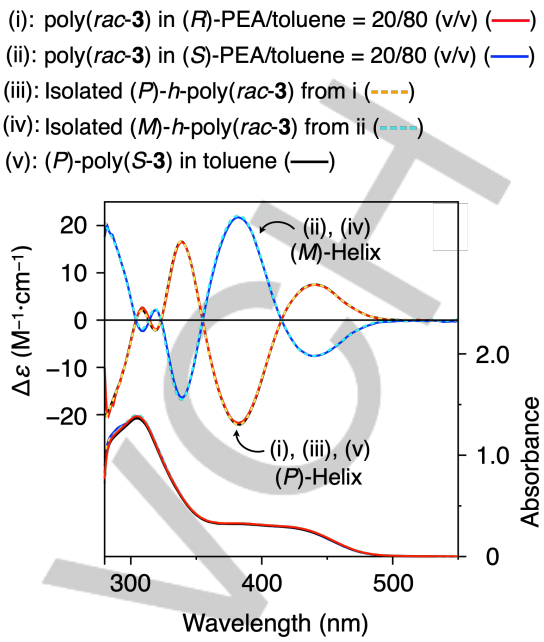

Figure 2. CD and absorption spectra of poly(*rac*-**3**) in the presence of (*R*)-PEA (i) and (*S*)-PEA (ii) in toluene (PEA/toluene = 20/80, v/v) measured at –10 °C after allowing to stand at 25 °C for 48 h, and the isolated poly(*rac*-**3**) recovered from i (iii) and ii (iv), measured at –10 °C. [Polymer] = 1.0 mM. CD and absorption spectra of poly(*S*-**3**) measured in toluene at –10 °C (v) are also shown.

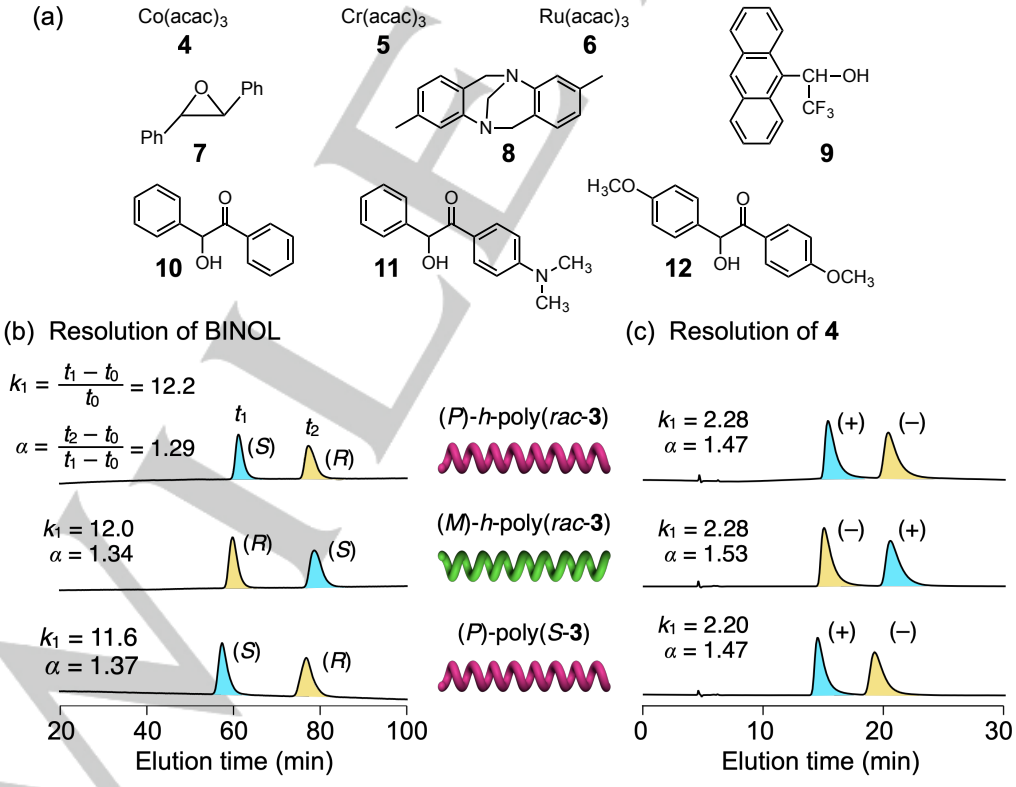

Figure 3. a) Structures of racemates (**4** – **12**). b,c) HPLC chromatograms for the resolutions of BINOL (b) and **4** (c) on CSPs consisting of (*P*)- and (*M*)-*h*-poly(*rac*-**3**)s with static helicity memory and (*P*)-poly(*S*-**3**) at –10 °C. Eluent: *n*-hexane/2-propanol (97/3, v/v). The k_1 and α values are defined as $(t_1 - t_0)/t_0$ and $(t_2 - t_0)/(t_1 - t_0)$, respectively, where t_0, t_1, and t_2 are the hold-up time and the retention times of the first- and second-eluted enantiomers, respectively.

Table 1: Resolution results of racemates (PEA, BINOL, and **4**–**12**) on CSPs consisting of (*P*)- and (*M*)-*h*-poly(*rac*-**3**)s with static helicity memory and (*P*)-poly(*S*-**3**) at –10 °C.[a]

Racemates	(*P*)-*h*-poly(*rac*-**3**)		(*M*)-*h*-poly(*rac*-**3**)		(*P*)-poly(*S*-**3**)	
	k_1	α	k_1	α	k_1	α
PEA	0.42	1.0	—	—	—	—
BINOL	12.2	1.29 (*S*)-(+)	12.0	1.34 (*R*)-(–)	11.6	1.37 (*S*)-(+)
4	2.28	1.47 (+)	2.28	1.53 (–)	2.20	1.47 (+)
5	2.18	1.49 (–)	2.18	1.54 (+)	2.19	1.42 (–)
6	3.52	1.38 (–)	3.50	1.42 (+)	3.72	1.24 (–)
7	0.42	1.12 (+)	0.38	1.13 (–)	0.37	1.15 (+)
8	1.24	1.04 (–)	1.27	1.04 (+)	1.15	1.06 (–)
9	4.35	1.06 (+)	4.39	1.06 (–)	4.25	1.04 (+)
10	2.88	1.21 (+)	2.97	1.30 (–)	2.91	1.41 (+)
11	7.84	1.16 (–)	7.81	1.20 (+)	7.36	1.19 (–)
12	9.38	1.13 (–)	9.32	1.18 (+)	9.09	1.23 (–)

[a] Column: 25 × 0.20 (i.d.) cm; eluent: *n*-hexane/2-propanol (97/3, v/v); flow rate: 0.15 mL min^{-1}. The signs in parentheses represent the Cotton effect signs at 254 nm of the first-eluted enantiomers.

evaluated based on the separation factor (α) and the resolution results of **4** – **12** on (*P*)- and (*M*)-*h*-poly(*rac*-**3**)s along with those on (*P*)-poly(*S*-**3**) are summarized in Table 1. We note that the enantioseparation abilities of the (*P*)- and (*M*)-*h*-poly(*rac*-**3**)s composed of entirely racemic units are virtually identical to those of the (*P*)-poly(*S*-**3**) prepared from the corresponding enantiopure (*S*)-monomer (Figures 3b,c and S4 and Table 1). The observed remarkably high resolving abilities most likely result from the one-handed helicities of the polymer backbones that further induce the axially chiral biphenyl pendants into one-handed twist-senses, and therefore, independent of the pendant chiralities. We thus succeeded in developing high-performance chiral materials based on racemic components. So far, some efficient helical polymer-based CSPs have been developed, which have been prepared by the polymerization of optically pure monomers[16b,21] or by the helix-sense-selective polymerization of achiral bulky monomers,[9a,22] but *racemic*-component based CSPs have never been reported.[23]

Catalytic helicity induction with nonracemic BINOL and subsequent static memory of the helicity

We used a large amount of a chiral alcohol, (*R*)- or (*S*)-PEA ([PEA]/[poly(*rac*-**3**)] > 1000) to completely induce a one-handed helix in PBPAs including poly(*rac*-**3**) (Figure 2(i,ii)). Recently, we reported that a small amount of a hydrophobic alcohol, such as (*R*)- or (*S*)-BINOL (0.2 equiv), is sufficient to produce a one-handed helical PBPA derivative bearing amphiphilic achiral oligo(ethylene glycol) units at the pendants, which was possible only in water because the BINOL can be specifically encapsulated within the hydrophobic cavity of the polymer in water, whereas no helical sense bias was observed in toluene.[24] By careful examination of the resolution results of *rac*-PEA and *rac*-BINOL on the (*P*)-*h*-poly(*rac*-**3**)-based CSP, we noticed that (*R*)-BINOL interacts more strongly on the polymer than (*S*)-BINOL and PEA, resulting in a longer retention time (t_2) with a complete base-line separation, while the *h*-poly(*rac*-**3**)-based CSP did not resolve *rac*-PEA at all (α = 1.0) (Figure 3b and Table 1).

As shown in Figure 4(i,ii), the fully (*P*)- and (*M*)-handed helices were induced in poly(*rac*-**3**) with a small amount of (*R*)- and (*S*)-BINOL (0.1 equiv) at a high concentration of poly(*rac*-**3**) in toluene (160 mM) at 25 °C, respectively, indicative of a strong chiral amplification (Figures S5 and S6a,b); the CD intensities (the molar circular dichroism ($\Delta\varepsilon$)) of the (*P*)- and (*M*)-*h*-poly(*rac*-**3**)s that correspond to their *hse* values remained unchanged after isolation followed by dilution (1.0 mM) due to the static helicity memory effect during the helicity induction process (Figures 4(iii,iv) and S7c,d).[12] Under the condition (160 mM, 0.1 equiv), (*R*)-PEA induced a negligibly weak CD in poly(*rac*-**3**) (Figures S5a and S6c). Further amplification of the chirality during the noncovalent helicity induction in poly(*rac*-**3**) took place even with a rather small amount of nonracemic BINOL (0.5 equiv) of 50% ee, affording a completely one-handed (*P*)-*h*-poly(*rac*-**3**), thus showing a high-level of the "majority rule" effect[7a] (Figures 5a and S8a; for the mirror-image CDs obtained using nonracemic BINOL

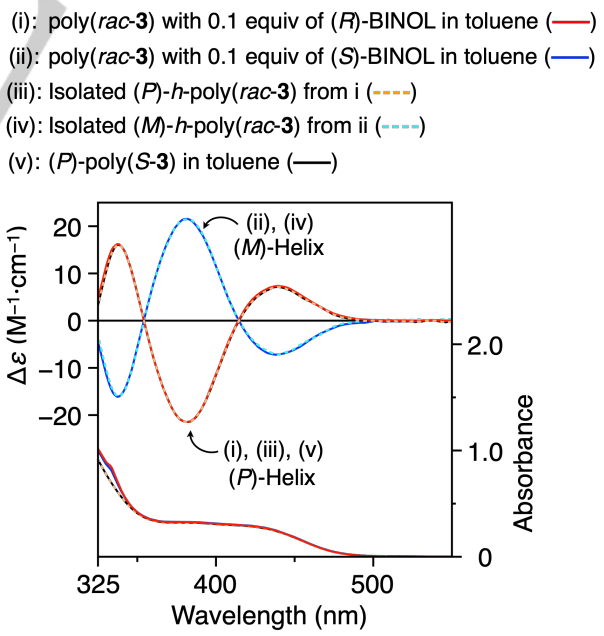

Figure 4. CD and absorption spectra of poly(*rac*-**3**) in the presence of a catalytic amount of (*R*)-BINOL (i) and (*S*)-BINOL (ii) in toluene ([BINOL]/[poly(*rac*-**3**)] = 0.1) measured at –10 °C after allowing to stand at 25 °C for 48 h ([poly(*rac*-**3**)] = 160 mM), and the isolated poly(*rac*-**3**) recovered from i (iii) and ii (iv), measured at –10 °C. All the CD measurements were performed after diluted with toluene ([poly(*rac*-**3**)] = 1.0 mM). CD and absorption spectra of poly(*S*-**3**) measured in toluene at –10 °C (v) are also shown.

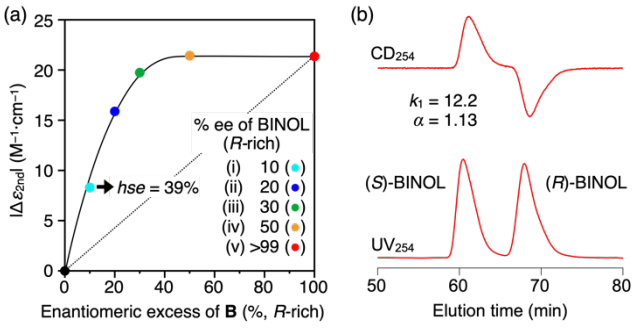

Figure 5. a) Plots of ICD intensity ($\Delta\varepsilon_{2nd}$ at 380 nm) of poly(*rac*-**3**) with nonracemic BINOL ([BINOL]/[poly(*rac*-**3**)] = 0.5) in toluene measured at –10 °C versus the % ee of BINOL (*R*-rich) after standing at 40 °C (i) and 25 °C (ii–v) for 48 h ([poly(*rac*-**3**)] = 60 mM). All the CD measurements were performed after diluted with toluene ([poly(*rac*-**3**)] = 1.0 mM). For the corresponding CD spectra, see Figure S8a. b) HPLC chromatograms for the resolution of *rac*-BINOL on (*P*)-*h*-poly(*rac*-**3**)-based CSP with 39% *hse* at –10 °C. Eluent: *n*-hexane/2-propanol (97/3, v/v).

(*S*-rich) as a helix inducer, see Figure S8b,c). Of particular interest is that *h*-poly(*rac*-**3**), rich in the (*P*)-helix with 39% *hse*, induced by 10% ee of BINOL (*R*-rich, 0.5 equiv) completely separated *rac*-BINOL when used as a CSP (Figure 5b).

Auto-evolution of helical handedness excess accompanied by emergence and successive enhancement of its chiral recognition ability

The notable chiral recognition ability of *h*-poly(*rac*-3) to *rac*-BINOL resulting from its exclusive feature of the static memory of the helicity induced by a catalytic amount of the nonracemic BINOL enables one to observe "*auto-evolution*" of its helical handedness of the as-prepared *racemic* helicity of poly(*rac*-3) assisted by a nonracemic BINOL, thereby evolving the chiral recognition toward the nonracemic BINOL itself through successive enhancement of the helical handedness of poly(*rac*-3) over time to form a one-handed helix with the static helicity memory (Figure 1d).

In fact, the aromatic proton resonances (Ha, Hb, and Hc) of the nonracemic BINOL (50% ee, *R*-rich) gradually split into two sets of signals corresponding to the nonracemic BINOL enantiomers (*R* : *S* = 3 : 1) in the presence of the as-prepared *racemic* poly(*rac*-**3**) (Figure 6a,b) and the difference in the chemical shifts between the (*S*)- and (*R*)-BINOL ($\Delta\delta$) increased with time (Figure 6c; see also Figure S9 for the results using (*S*)-rich BINOL (50% ee) as a helix inducer), through which a preferred-handed helix is continuously induced and subsequently memorized in poly(*rac*-3) as supported by an increase in the CD intensity with time (Figures 6c and S10a,b). Consequently, unlike previously reported covalent and noncovalent chiral recognition systems, the *racemic* polymer expresses an auto-evolution of its helical handedness in response to the chirality of the nonracemic BINOL,[25] thus creating a chiral recognition function, which definitely relies on the static memory effect of the helicity induced and enhanced by the nonracemic BINOL over time accompanied by amplification of the chirality. As expected from the chiral HPLC separation results (Table 1), the chiral recognition ability of (*P*)-*h*-poly(*rac*-3) (*hse* = 100%) toward the nonracemic BINOL by NMR (Figure 6b,c) was identical to that of the (*P*)-poly(*S*-3), which remained unchanged with time (Figures S10c and S12).

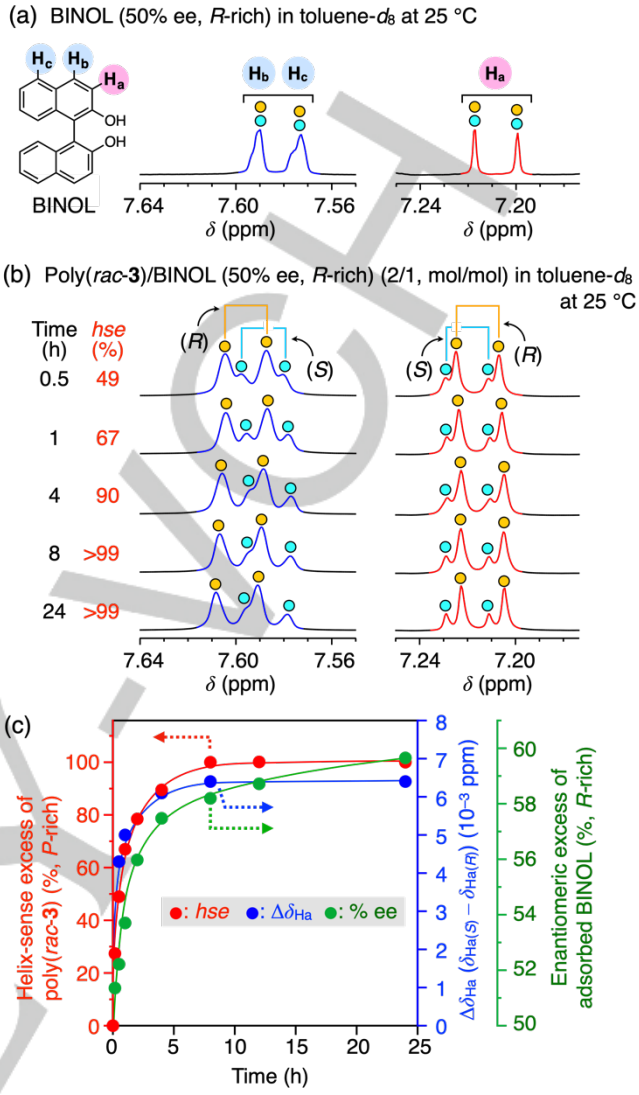

Figure 6. a) ^{1}H NMR spectrum of selected region of BINOL (50% ee (*R*-rich)) in toluene-d_8 at 25 °C. [BINOL] = 3 mM. b) Time-dependent ^{1}H NMR spectral changes of the aromatic proton resonances (Ha, Hb, and Hc) of the nonracemic BINOL (50% ee (*R*-rich), 0.5 equiv) in the presence of the optically inactive poly(*rac*-**3**) (helix-sense excess (*hse*) = 0% at initial stage) monitoring the evolution of chiral recognition toward the nonracemic BINOL through successive enhancement of the *hse* values of poly(*rac*-**3**) induced and automatically memorized by the nonracemic BINOL over time to form a one-handed helical (*P*)-*h*-poly(*rac*-**3**) (*hse* = 100%) after 24 h in toluene-d_8 at 25°C. [poly(*rac*-**3**)] = 60 mM. The peak assignments of BINOL were performed based on 2D NMR experiments (Figure S11). c) Plots of the difference in the chemical shifts (Ha) between the (*S*)- and (*R*)-BINOL ($\Delta\delta_{Ha}$) (●; inner *y*-axis) and the *hse* (●) of poly(*rac*-**3**) against time. The changes of the % ee (●; outer *y*-axis) of BINOL adsorbed on the helical poly(*rac*-**3**) with time are also plotted. For experimental conditions, see caption (b). The *hse* values of poly(*rac*-**3**) were estimated based on the CD intensities ($\Delta\varepsilon_{2nd}$ at 380 nm) of the poly(*rac*-**3**)/BINOL solution (see Figure S10a). The ee values of BINOL adsorbed on the helical poly(*rac*-**3**) were determined by chiral HPLC after precipitation of the poly(*rac*-**3**)/BINOL upon mixing with *n*-hexane (see Section 9 and Figure S13 in the SI).

During the course of the *hse* enhancement of the helical poly(*rac*-**3**) assisted by 50% ee of BINOL over time, we found a continuous enhancement of the BINOL ee adsorbed on the helical poly(*rac*-**3**), which gradually increased with an increase in the *hse* values of the helical poly(*rac*-**3**) with time (Figure 6c and Table S2). After 24 h, the ee of the nonracemic BINOL adsorbed on the complete (*P*)-helical *h*-poly(*rac*-**3**) (*hse* = ca. 100%) recovered in ca. 30% yield reached ca. 60% (*R*-rich) (Figures 6c and S13; see

also Figures S9b and S14 and Table S3 for the results using (*S*)-rich BINOL (50% ee) as a helix inducer). These results indicated that the helical poly(*rac*-**3**) acts as a *chiral filter*, thus exhibiting enantioselective adsorption of one of the BINOL enantiomers, which further contributes to improve the *hse* of the poly(*rac*-**3**) with an imperfect helical sense, leading to further enhancement of the optical purity of BINOL adsorbed on the poly(*rac*-**3**), finally resulting in the formation of a complete one-handed helix with the static helicity memory after 24 h (Figure 6c; see also Figures S9b and S12b). Of particular interest was the fact that a typical dynamic helical polymer, poly(4-carboxyphenylacetylene) showing the dynamic memory effect,[26] did not show such a chiral filter effect at all, and hence no chiral recognition toward nonracemic molecules.[27]

Conclusion

In summary, we have succeeded in developing an unprecedented helicity-memorized polymer-based chiral material composed of *racemic* components based on a catalytic helicity induction and subsequent static memory of the helicity. The chiral material when used as a CSP resolved a wide range of racemates and its chiral recognition ability was virtually identical to that of the one-handed helical polymer consisting of the corresponding optically pure components, demonstrating that optically active components are no longer necessary for creating chiral functions. Because of the unique static memory of the helicity in response to noncovalent chiral interactions with nonracemic BINOL, the original *racemic* polymer expresses an auto-evolution of its helical handedness and at the same time, chirality of the BINOL could be discriminated accompanied by successive enhancement of the BINOL ee adsorbed on the static helical polymer. The present results will not only provide a novel solution for the synthesis of both helical polymers with specific chiral functionalities from racemic monomers but also contribute to realizing the amplification of ee of chiral molecules from nearly racemic to enantiopure in an *auto-amplification* manner[28] in the presence of a dynamically *racemic* helical polymer through spontaneous helix-induction and its static memory process assisted by a more efficient *chiral filter* process, which may shed light on a central puzzle of the homochirality of single-handed helical biopolymers.[4b,29] Furthermore, practically useful switchable helical polymers showing an asymmetric catalytic activity[15,30] and an asymmetric autocatalytic activity[31] will be produced from dynamically *racemic* helical polymers consisting of catalytically-active dynamically racemic repeating units based on our developed helicity induction and its static memory strategy. Work toward these goals is now underway in our laboratory and will be reported in due course.

Acknowledgements

We thank Dr. Nozomu Suzuki (Nagoya University) for his assistance in the NMR and HPLC measurements. This work was supported by JSPS KAKENHI (Grant-in-Aid for Specially Promoted Research, No. 18H05209 (E.Y., K.M., and T.I.).

Conflict of interest

The authors declare no conflict of interest.

Keywords: chirality • helical structures • memory • chiral separation • chiral amplification

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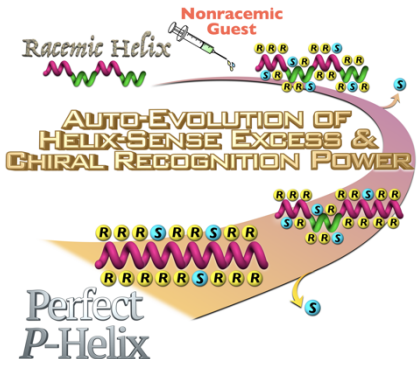

A *racemic* monomer-based polyacetylene folds into a one-handed helix assisted by a nonracemic alcohol through *"auto-evolution"* of its helical handedness over time, accompanied by successive enhancement of its optical purity adsorbed on the helical polyacetylene. The one-handed helical polyacetylene with the static helicity memory separates various enantiomers in liquid chromatography.