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A 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

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KEYWORDS. helical polymer, helicity control, helix inversion, chiral stationary phase, high performance liquid chromatography, poly(phenylacetylene), switching, chiral recognition ability, metal cation

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ABSTRACT: An unprecedented three-state switchable chiral stationary phase (CSP) for high-performance liquid chromatography (HPLC) was developed using a helical poly(phenylacetylene) bearing a chiral (*R*)-*α*-methoxyphenylacetic acid residue as the pendant (poly-**1**). The left- and right-handed helical conformations were induced in poly-**1**-based CSP upon coordination with a catalytic amount of soluble sodium and cesium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate salts (MBArF), respectively, which are soluble in the HPLC conditions [hexane−2-propanol (95:5, v/v)]. The switch between the two different helical states of poly-**1** can be easily achieved by rinsing the poly-**1**-based CSP with MeOH and the subsequent addition of the proper MBArF salt. Using this dynamic helical CSP, we demonstrate how changes on the orientation of the secondary structure of a chiral polymer (right-handed, left-handed and racemic helices) can alter and even invert the elution order of the enantiomers. This study was done without adding chiral additives or changing the mobile phase, which could produce changes on the retention times and make it more difficult to determine the role of the secondary structure during the chiral recognition process.

INTRODUCTION

The separation of enantiomers by high-performance liquid chromatography (HPLC) using a chiral stationary phase (CSP) is one of the most popular and effective methods for both analytical and preparative purposes.[1-7] In this separation technique, the synthesis of a CSP showing a good chiral recognition ability toward a variety of racemates is essential to attain efficient separation of enantiomers for practical use. Although a significant number of CSPs with excellent resolving abilities have been synthesized, the development of novel CSPs with good chiral recognition ability remains highly desirable because there exist several racemates that cannot be resolved using existing commercially available CSPs. Among CSPs developed so far, helical polymer-based CSPs with a helix-sense bias, as represented by single-handed helical poly(triphenylmethyl methacrylate) (PTrMA)[8-10] and polysaccharide derivatives,[11-13] tend to exhibit good resolving abilities toward a wide range of racemates.[14-16]

Recently, helical polymers capable of controlling the helix-sense (right- and left-handed) by external stimuli have been attracting great attention because they can be used as switchable chiral materials.[17-18] Until now, switchable asymmetric catalysts and circularly polarized luminescent materials have been reported.[19-26] We recently reported the first example of elution-order switchable CSP composed of an optically inactive helical polyacetylene carrying 2,2′-biphenol-derived pendants.[27] Both the macromolecular helicity and axial chirality of the biphenyl pendants were induced in this polymer upon non-covalent interaction with a chiral alcohol in the solid state, as well as in solution, and were automatically memorized after complete removal of the chiral alcohol. Based on its unique feature, we have succeeded in switching the elution order of enantiomers by switching the helix-sense of the polymer when this polymer was used as a CSP for HPLC. In this case, an excess amount of the chiral guest was necessary to control the helix-sense.[27-29] Another switchable CSP composed of a foldamer showing reversible coil-to-helix transition has also been developed,[30] which showed different chiral recognition ability depending on their two different conformations (helix and random states) of the polymer. The multi-state switching function of CSPs will increase the number of resolvable racemates and its versatility for practical use.

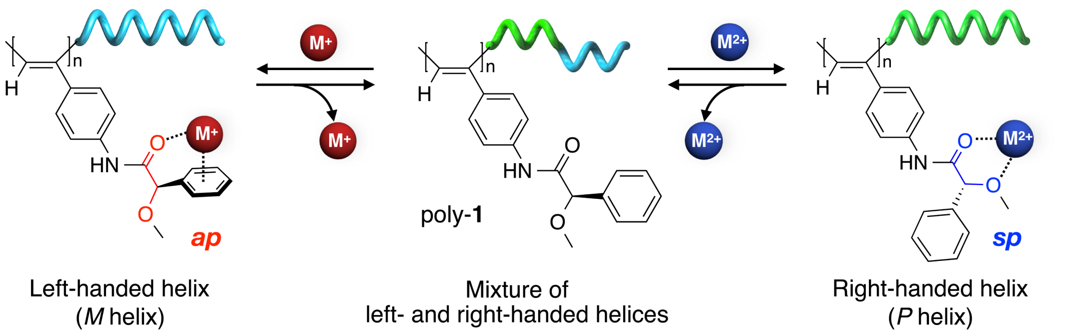


Figure 1. Schematic illustration of macromolecular helicity modulation in poly-**1** through conformational switching of the MPA pendants using metal cations in solution.

Freire and co-workers previously reported a metal cation-responsive helical poly(phenylacetylene) derivative (poly-**1**) bearing optically active pendants derived from (*R*)-*α*-methoxyphenylacetic acid (MPA), whose helix-sense bias was modulated by the addition of a small amount of metal cations in solution (Figure 1).[31-33] In the absence of metal cations, stereoregular (*cis*) poly-**1** exists as an equal mixture of right-handed (*P*) and left-handed (*M*) helical segments in chloroform as confirmed by no CD signal in the absorption region of the polymer backbone. This is because the chiral MPA pendants exist in two different conformations, that is, synperiplanar (*sp*) and antiperiplanar (*ap*) conformations depending on the orientation around the O=C–C–OCH_3 bond. However, upon the addition of a monovalent cation, such as a sodium ion, the MPA pendants take an *ap* conformation owing to a cation–π interaction, which induces a predominantly *M* helix in the main-chain. However, the MPA pendants favor an *sp* conformation when coordinated with a divalent cation, such as a calcium ion, which results in the opposite *P* helix formation in a highly co-operative fashion.[31] This unique metal cation-triggered conformational change of poly-**1** stimulated us to apply poly-**1** as a CSP for HPLC. In this system, from a single chiral pendant group, it is possible to obtain the two opposite helical senses in the polymer using achiral metal cations as external stimuli without changing the solvent conditions. We anticipated that the *M* and *P* or racemic helical poly-**1** might show largely different chiral recognition abilities toward enantiomers depending on its helix-sense if the helical sense control works in the solid state.

RESULTS AND DISCUSSION

Macromolecular Helicity Control Using Metal Cations in the Solid State. A thin film of poly-**1** was prepared first by spin-coating its chloroform solution onto a quartz disk to investigate whether the helix-sense of poly-**1** can be controlled using metal cations as an external trigger even in the solid state. The as-prepared poly-**1** film showed almost no induced circular dichroism (ICD) in the absorption region of the polymer backbone (a in Figure 2A), which suggested that the poly-**1** exists as an approximately equal mixture of *P* and *M* helical segments in the as-prepared film.

The chiral amplification studies of poly-**1** in the solid state, using the metal perchlorate salts described by Freire and co-workers in their work, failed owing to the poor solubility of the metal salts in the HPLC conditions [hexane–2-propanol eluents]. Thus, it was necessary to look for different metal salts, which are soluble in the HPLC conditions, and where the anion of the salt is inert to the polymer. It was found that sodium salts of triflate (OTf), triflimide (NTf_2), and tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF) (Figure 2B) meet these requirements and were used as monovalent cation sources.

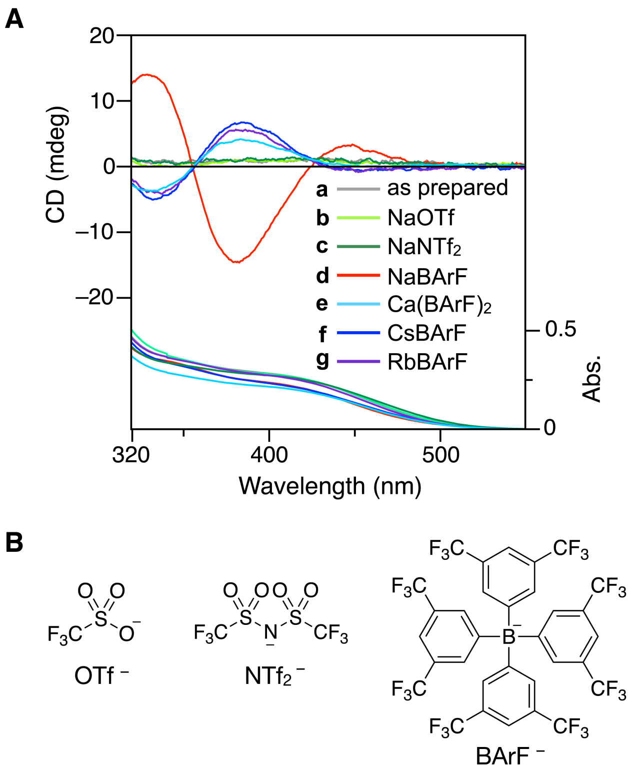


Figure 2. (A) CD and absorption spectra of the poly-**1** films before (a) and after soaking in the solutions of sodium salts (NaOTf (b), $NaNTf_2$ (c), and NaBArF (d)), $Ca(BArF)_2$ (e), CsBArF (f), and RbBArF (g) in hexane–2-propanol (95:5, v/v) followed by rinsing with hexane–2-propanol (95:5, v/v) ([sodium salts] = [CsBArF] = [RbBArF] = 2.0 mM, [$Ca(BArF)_2$] = 0.2 mM). CD spectra were normalized with respect to the absorbance at 380 nm. (B) Structures of the counter anions.

Poly-**1** films were soaked in the different sodium salt solutions {[Na^+] = 2.0 mM in hexane–2-propanol (95:5, v/v)} for 20 minutes followed by rinsing with a large amount of hexane–2-propanol (95:5, v/v), and their CD and absorption spectra were then measured. When NaOTf and $NaNTf_2$ were used, no ICD signal was observed above 320 nm (b and c in Figure 2A), which indicated that these counterions were strongly linked to the Na^+ ion impeding its coordination to the pendant group (no changes in the IR spectra of poly-**1**, see Figure S1A and B).

Interestingly, an intense negative Cotton effect was induced around at 380 nm in the poly-**1** film soaked in a solution of NaBArF (d in Figure 2A). This fact indicated that the expected coordination to the pendant group and the corresponding chiral amplification effect were taking place in the solid state (see Figure S1C). The negative Cotton effect induced around at 380 nm indicated the formation of a predominantly *M* helical conformation of the polymer backbone, in accordance with the adoption of a preferred *ap* conformation in the MPA pendants by coordination with the monovalent sodium cation (Figure 1).[31] The ICD intensity increased with time and when the concentration of NaBArF in hexane−2-propanol (95:5, v/v) increased. It was found that the ICD intensity reached a constant value after 20 min at [NaBArF]= 2.0 mM (Figure S2). During these studies, it was found that the maximum ICD intensity depended on the poly-**1** film thickness. The ICD intensity decreased when the film thickness was higher than that corresponding to $Abs_{381.5}$ = 0.6, probably owing to the insufficient permeation of a NaBArF solution (Figure S3). Hence, we found the conditions to induce an *M* helix in a poly-**1** film by using a NaBArF salt as an external stimulus. This metal salt can deliver a sodium cation in the naked form, which allowed for its coordination to poly-**1** even in the solid state.[34-36] Therefore, the use of the non-coordinating $BArF^-$ as the counter anion is a key for the induction of a preferred-handed helicity in poly-**1** in the solid state upon interaction with metal cations.

Next, the induction of the *P* helix in the poly-**1** film was investigated. $Ca(BArF)_2$ was used as a divalent metal cation source taking into account that Ca^{2+} induced a *P* helix in poly-**1** in solution.[31-33] As expected, when the film was soaked in a solution of $Ca(BArF)_2$ {$[Ca^{2+}]$ = 0.2 mM in hexane−2-propanol (95:5, v/v)}, an opposite positive Cotton effect was observed at 380 nm, which indicated that predominantly a *P* helical conformation was induced in the polymer backbone in the solid state by coordination with Ca^{2+} (e in Figure 2A). However, the CD intensity induced by $Ca(BArF)_2$ was much smaller than that induced by NaBArF (d in Figure 2A), which indicated the presence of a lower excess of a *P* helix. This result was explained owing to the poor solubility of $Ca(BArF)_2$ in hexane–2-propanol, which made it impossible to increase the concentration of $Ca(BArF)_2$ in hexane–2-propanol (95:5, v/v) higher than 0.2 mM.[37]

To overcome this problem, we decided to use CsBArF and RbBArF as a metal cation source owing to their good solubility in hexane–2-propanol (95:5, v/v). These two cations—Cs^+ and Rb^+—were not used in Freire's previous studies owing to the poor solubility of $CsClO_4$ and $RbClO_4$ in chloroform. Interestingly, we found that these salts—CsBArF and RbBArF—induce a positive Cotton effect at 380 nm with a higher intensity than $Ca(BArF)_2$ in the solid state despite the fact that Cs^+ and Rb^+ are monovalent cations (f and g in Figure 2A). From previous studies we know that monovalent metal ions, such as Na^+, can stabilize the *M* helix in poly-**1** by the presence of a cation-π interaction. In some cases, depending on the monovalent metal ion and the solvents used to deliver the metal salt, this supramolecular interaction is not produced. In such a case, the metal ion chelates the pendant group through the carbonyl and methoxy groups stabilizing the *sp* conformation and inducing a *P* helix in poly-**1**.[33, 38] Therefore, when Cs^+ and Rb^+ are used as external stimuli in this solvent condition, hexane–2-propanol (95:5, v/v), the cation-π interaction is not produced. As a result, a *P* helix is induced in poly-**1** owing to the stabilization of the *sp* conformation at the pendant by coordination with these metal ions (see Figures S1D and S4).[39]

We explored the reversibility of the helical sense induction process of poly-**1** towards an *M* or a *P* helix by NaBArF or CsBArF salts, respectively, and analyzed if the starting racemic helical poly-**1** could be recovered once a preferred-handed helical sense was induced in poly-**1**. MeOH was used as a solvent to rinse the poly-**1** film treated with NaBArF or CsBArF. It was found that the CD signals above 320 nm of the polymer film became almost null after MeOH rinsing. This outcome indicated that the metal salts, NaBArF or CsBArF, were removed from the polymer film. These results were confirmed by infrared studies (Figures S1 and S5).

These chiral amplification studies in the solid state, selectively inducing the *P* or *M* helical sense in a racemic helical polymer by using different external stimuli, constitute the foundations to determine how important is the helical sense induced in a chiral polymer—poly-**1**—in the enantiomeric resolution of racemic mixtures.

Chiral Recognition Ability as a Switchable CSP for HPLC. To investigate the chiral recognition ability of poly-**1** as a CSP for HPLC, the poly-**1**-based CSP was prepared as follows: poly-**1** dissolved in chloroform was coated on macroporous silica gel and the obtained packing material was then packed into a stainless-steel column (25 × 0.20 cm (i.d.)) using a conventional high-pressure slurry packing technique.[40] The column was treated with MeOH to ensure that poly-**1** adopts a racemic helical conformation as supported by no CD signal above 320 nm in the film state. Helicity induction of poly-**1** in the column was performed by passing a solution of the metal cation salts through the column. The column was then rinsed with hexane−2-propanol (95:5, v/v) to remove the excess metal cations that did not coordinate to the MPA pendants (Figure 3A). The chiral recognition ability of the poly-**1**-based CSP was evaluated using racemic compounds **2**–**10** using hexane−2-propanol (95:5, v/v) as the eluent (Table 1).

In the first study, it was found that the racemic helical poly-**1**—mixture of *P* and *M* helices—obtained either after treatment with NaOTf and $NaNTf_2$, or even after rinsing with MeOH, could not separate racemates **2** and **3** (entries 1 and 2 in Table 1 and Table S2).

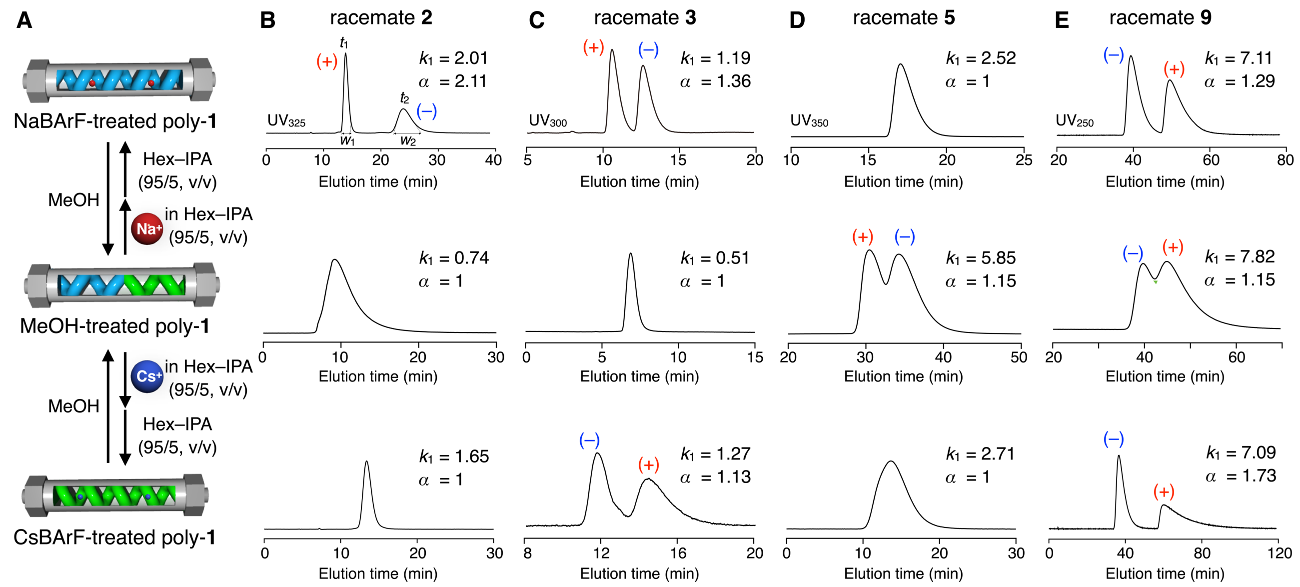
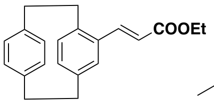


Figure 3. (A) Schematic illustration of helicity induction of poly-**1**-based CSP in the column. (B–E) HPLC chromatograms for the resolution of racemates **2** (B), **3** (C), **5** (D), and **9** (E) on the NaBArF- (top), MeOH- (middle), and CsBArF-treated (bottom) poly-**1**s. Eluent: hexane–2-propanol (95:5, v/v).

Table 1. Resolution Results of Racemates on NaBArF-, MeOH-, and CsBArF-treated Poly-1[a]

		poly-**1**								
		MeOH-treated			NaBArF-treated			CsBArF-treated		
entry	racemates	k_1	α	R_s	k_1	α	R_s	k_1	α	R_s
1	**2**	0.74 (−)	*ca.* 1	—	2.01 (+)	2.11	3.48	1.65 (−)	*ca.* 1	—
2	**3**	0.51 (+)	*ca.* 1	—	1.19 (+)	1.36	1.57	1.27 (−)	1.13	0.97
3	**4**	1.00 (−)	*ca.* 1	—	0.79 (+)	2.14	2.19	0.60	1	—
4	**5**	5.85 (+)	1.15	1.04	2.51	1.00	—	2.71	1.00	—
5	**6**	1.47 (−)	*ca.* 1	—	2.24 (−)	1.13	1.12	2.58 (−)	*ca.* 1	—
6	**7**	2.74 (−)	*ca.* 1	—	4.99 (+)	1.10	0.94	6.05	1.00	—
7	**8**	13.9 (−)	1.27	1.14	6.89 (−)	1.25	1.29	10.2 (−)	1.72	1.88
8	**9**	7.82 (−)	1.15	1.01	7.11 (−)	1.29	1.49	7.09 (−)	1.73	1.70
9	**10**	28.9 (−)	1.27	1.50	5.18 (−)	2.00	3.83	7.60 (−)	1.34	1.10



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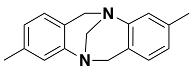

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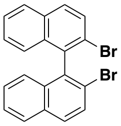

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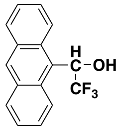

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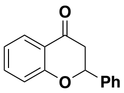

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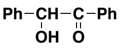
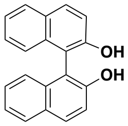


$$\mathrm{Ph{-}\underset{OH}{CH}{-}\underset{\overset{\|}{O}}{C}{-}Ph}$$

7



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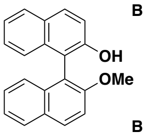

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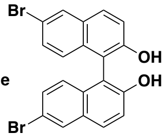

10

[a] Conditions: column, 25 × 0.20 cm (i.d.); flow rate: 0.2 mL·min^{-1}; eluent, hexane–2-propanol (95:5, v/v); temperature, 0 °C (NaBArF- and CsBArF-treated) and *ca*. 25 °C (MeOH-treated). The signs in parentheses represent the Cotton effect sign at 254 nm of the first-eluted enantiomers.

However, the NaBArF-treated poly-**1** showed a good chiral recognition ability toward racemates **2** and **3** (entries 1 and 2 in Table 1). Figure 3B and 3C (top) show the HPLC chromatograms for the resolution of **2** and **3** after treatment of the column with NaBArF. In the case of racemate **2**, the (+)- and (–)-enantiomers were eluted at different retention times (t_1 and t_2), which showed complete baseline separation. The retention factor k_1 [= $(t_1-t_0)/t_0$], the separation factor α [= $(t_2-t_0)/(t_1-t_0)$], and the resolution factor R_S [= $2(t_2-t_1)/(w_1 + w_2)$] were 2.01, 2.11, and 3.48, respectively, where the dead time (t_0) was estimated to be 4.21 min (Figure 3B (top) and entry 1 in Table 1).

Comparison between the results obtained for the two racemic helical poly-**1**s (NaOTf- and NaNTf$_2$-treated poly-**1**s) with those obtained for the NaBArF-treated poly-**1**, clearly demonstrated that the recognition ability was greatly influenced by the macromolecular helicity induced in the main chain.

To confirm the importance of the macromolecular helicity on the chiral recognition for racemate **2**, the *cis* stereoregular poly-**1** was converted into the stereoirregular polymer (*g*-poly-**1**) by grinding poly-**1**, as reported in previous works.[41-42] The *g*-poly-**1** film prepared on a quartz disk showed no ICD in the polymer backbone even after treatment with a solution of

NaBArF, which indicated no helical sense induction in *g*-poly-**1** upon coordination with a sodium cation in the solid state (Figure S6). Moreover, the *g*-poly-**1**-based CSP showed almost no change in the chiral recognition ability before and after treatment with NaBArF, being almost the same as that observed for poly-**1** after treatment with MeOH where the racemic helical polymer was generated (Table S3). Hence, these results clearly demonstrate that the change in the helical conformation of poly-**1**, from a racemic helical polymer towards an *M* helix, plays a key role in the significant change of the chiral recognition ability of the NaBArF-treated poly-**1**.

The *α* value on the NaBArF-treated poly-**1** reached an almost constant value after flowing a 2.0 mM NaBArF solution in hexane−2-propanol (95:5, v/v) for 4 h at a flow rate of 0.2 mL·min^{-1} (Table S4). The total amount of NaBArF used for the helix induction of poly-**1** coated on silica gel was estimated to be in a [NaBArF]/poly-**1** (m.r.u.) ratio = 2.0/5.0 (mol/mol) of the amount of the poly-**1**, which was determined by TG analysis. This result indicated that the poly-**1**-based CSP needs only catalytic amounts of NaBArF to induce a single handed helix into the polymer and therefore to complete the switching of the chiral recognition ability. Additional NMR studies on the determination of the amounts of the metal cations coordinated to poly-**1**-based CSP after treatment with NaBArF were possible by extracting the metal salts from the CSP with MeOH. The ratio of the coordinating amount of NaBArF to poly-**1** {[Na$^+$]/[poly-**1**] (m.r.u.)} was estimated to be in a 1/10 (mol/mol) ratio. These results clearly confirmed that the helical sense switch of poly-**1** is produced in the solid state by using a catalytic amount of metal cations.

Next, similar studies were done for the CsBArF-treated poly-**1**. In this case, a *P* helix was induced in the poly-**1**-based CSP and it was observed that the chiral recognition ability for racemate **2** decreased (entry 1 in Table 1, Figure 3B (bottom)). An interesting phenomenon occurred during the study of the chiral recognition of racemate **3**. Now, the baseline separation was achieved by using both NaBArF and CsBArF-treated poly-**1**-based CSPs, although an opposite elution order of the enantiomers was found (entry 2 in Table 1, Figure 3C (top and bottom)).[27] Therefore, elution order switching was achieved by interchanging the main-chain helicity of a chiral polymer in the solid state by resorting to achiral metal cations. These results clearly confirmed that the enantioseparation of racemate **3** is directly related to the macromolecular helicity adopted by poly-**1**.

TGA and NMR studies for the CsBArF-treated poly-**1**-based CSP, analogous to those described above for NaBArF-treated poly-**1**-based CSP, indicated again that poly-**1**-based CSP needs only catalytic amounts of CsBArF to induce a single handed helix into the polymer and therefore to complete the switching of the chiral recognition ability.

The resolution results of racemates **4**–**10** on poly-**1** in three different states as the CSP (NaBArF-, CsBArF-, and MeOH-treated poly-**1**) were compared (see Table 1). In the case of racemates **4**, **6**, and **7**, the *M* helix induced by the NaBArF-treated poly-**1**-based CSP was the only one that showed a chiral recognition ability. This fact also corroborates the importance of the macromolecular helicity adopted by a chiral polymer for its chiral recognition ability. On the other hand, racemates **5** and **8**–**10** were resolved even on the MeOH-treated poly-**1** adopting a racemic helical conformation, indicating that the chiral MPA pendant play a role for the separation of these racemates. Racemates **8**–**10** were resolved on the three different states of the chiral poly-**1**—*M*, *P*, and racemic macromolecular helicity—but it was the *P* helix (for **8** and **9**) or the *M* helix (for **10**) that provided the best results (Figure 3E). It is also noteworthy that the MeOH-treated poly-**1** resolved racemate **5**, which was not resolved by the other states (Figure 3D). Therefore, just by treating the CSP with a catalytic amount of achiral metal cations or MeOH, we can tune the state of the CSP to show the best chiral recognition ability toward the target enantiomers.

These chiral recognition abilities in the induced states were maintained over 4 days under the flow condition in continuous use (Figure S7). Furthermore, the NaBArF-treated poly-**1** CSP showed no significant change in the α value of racemate **2** after standing at −20 °C for 13 days (Table S5).

Finally, cycles of activation/deactivation of macromolecular helicity in the poly-**1**-based CSP carried out by combinations of metal salts and MeOH rinse—CsBArF/MeOH/NaBArF/MeOH/NaBArF/MeOH—were performed to determine the stability of the CSP. These studies showed that the chiral recognition ability of poly-**1**-based CSP was stable through the different repeating switches of the macromolecular helicity (Figure 4).

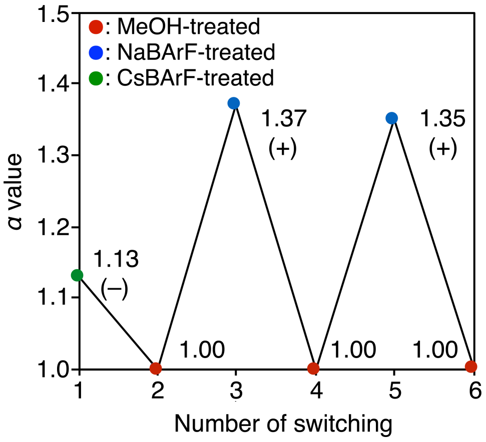

Figure 4. Plots of the α values for racemate **3** on poly-**1** at each state. Eluent: hexane–2-propanol (95:5, v/v). The signs in parentheses represent the Cotton effect sign at 254 nm of the first-eluted enantiomer.

CONCLUSION

In summary, we have demonstrated the key role of the macromolecular helicity (*P* or *M* helix) in the chiral recognition ability of a chiral stationary phase. To perform these studies, it was necessary to prepare a chiral stationary phase coated with a chiral helical polymer that could selectively adopt the two possible helical senses without changing the environmental conditions, such as solvent polarity. This study was made possible by using poly-**1** as the stationary phase. This polymer behaves as axially racemic in hexane−2-propanol (95:5, v/v), although a specific *M* or *P* helical sense can be induced in this poly-**1**-based CSP by the addition of a catalytic amount of NaBArF or CsBArF, respectively. This macromolecular helicity induction is reversible, and a single chiral stationary phase with racemic helical structure can be transformed into two chiral stationary phases with either a *P* or *M* helical structure, by rinsing it with MeOH and adding the appropriate

BArF salt of metal cations. Through this study we found that it is possible to invert the elution order of the two enantiomers of racemate **3** by switching the macromolecular helicity of a single chiral polymer through the use of an appropriate achiral external stimulus. To the best of our knowledge, this is the first example of a CSP for HPLC capable of switching reversibly its chiral recognition ability among three different states using external achiral stimuli. It was also demonstrated how the helical structure adopted can invert the retention time of the two enantiomers of a chiral molecule, or can separate a racemic mixture either in the *P* or *M* form but not in the opposite. Further research to develop a more efficient switchable CSP with higher chiral recognition ability toward many racemates is currently in progress in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXXXXXXXX.
Materials and methods and supporting data (PDF).

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