JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b10981 • Publication Date (Web): 11 Jan 2018

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Direct Detection of Hardly Detectable Hidden Chirality of Hydrocarbons and Deuterated Isotopomers by a Helical Polyacetylene through Chiral Amplification and Memory

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ABSTRACT: We report the first direct chirality sensing of a series of chiral hydrocarbons and isotopically-chiral compounds (deuterated isotopomers), which are almost impossible to detect by conventional optical spectroscopic methods, by a stereoregular polyacetylene bearing 2,2’-biphenol-derived pendants. The polyacetylene showed a circular dichroism due to a preferred-handed helix formation in response to the hardly detectable hidden chirality of saturated tertiary or chiroptical quaternary hydrocarbons, and deuterated isotopomers. In sharp contrast to the previously reported sensory systems, the chirality detection by the polyacetylene relies on an excess one-handed helix formation induced by the chiral hydrocarbons and deuterated isotopomers via significant amplification of the chirality followed by its static memory, through which chiral information of the minute and hidden chirality can be stored as an excess of a single-handed helix memory for a long time.

INTRODUCTION

Chirality is critical for vital functions in living systems at the molecular, macromolecular, and supramolecular levels because of the homochirality of biological polymers and components. Therefore, a pair of enantiomers often shows quite different biological activities in living systems. Hence, the development of facile and sensitive methods for the detection and assignment of the chirality of a variety of chiral molecules has become one of the emerging research areas in chemistry, pharmacy, and biology as well as in physics.

A variety of achiral or dynamically racemic, but chromophoric receptors and helical polymers have been developed for this purpose using circular dichroism (CD) spectroscopy, one of the most powerful tools for detecting the chirality and/or optical activity of nonracemic (optically-active) molecules.[1] Upon complexation with nonracemic guests, a characteristic, exciton-type coupled Cotton effect is induced in the absorption regions of the chromophoric receptors and polymers resulting from generation of one of the enantiomeric or diastereomeric chiral conformers, which enables the prediction of the absolute configurations of the chiral guests and to determine their enantiomeric excess (ee) based on the sign and intensity of the Cotton effects, respectively.[2] Designer receptors bearing specific binding sites have been successfully used for the chiroptical sensing of various kinds of functional chiral guests, such as amino acids, sugars, amines, alcohols, carboxy acids, etc., and the resulting bimolecular host-guest complexes exhibit a characteristic induced CD (ICD) in the absorption regions of the receptors.

As anticipated, the chirality-sensing of chiral saturated tertiary (**3b**–**7b**) and quaternary (**9**) hydrocarbons composed of three and four alkyl substituents on the stereogenic carbon atom, respectively (Figure 1), and isotopically-chiral compounds derived from H/D substitution (chiral deuterated isotopomers) (**10**), by chromophoric chiral/achiral receptors and helical polymers using CD appear to be extremely difficult. Therefore, the chiroptical sensing of these chiral molecules has not been achieved at all by CD due to a lack of functionality for bimolecular interactions with receptors/polymers and chemical inertness for derivatization.[3-5]

Among the chiral saturated hydrocarbons, the chirality of saturated quaternary hydrocarbons bearing four different, but similar alkyl substituents at the stereogenic center, such as 5-ethyl-5-propylundecane (**9**) (Figure 1), is *hidden* because of no detectable optical rotation ($[\alpha]_{\lambda}^{20} < 0.001$ (200 nm < λ < 580 nm))[6] or CD[7] and such chiral molecules have been called “cryptochiral”.[8] Therefore, its direct separation into enantiomers by chiral chromatography and chirality-sensing by chiral/achiral receptors using CD still remain a challenge. To the best of our knowledge, however, there is only one precedent discriminating the hardly detectable chirality of the cryptochiral **9** that was achieved by the asymmetric autocatalytic reaction triggered by (*S*)- or (*R*)-**9** as reported by Soai et al., which was accompanied by a significant enhancement of the product ee up to 97% after repeating the reaction several times, thereby enabling the determination of the absolute configuration of **9** as well as those of chiral saturated tertiary alkanes.[11]

We now report the first direct chiroptical sensing of such a hidden chirality of cryptochiral **9** as well as a series of chiral saturated and unsaturated tertiary hydrocarbons (**3**–**8**) and chiral deuterated isotopomers (**10**), which are also very difficult to sense their chirality, by CD spectroscopy using a helical polyacetylene bearing 4-biphenyl pendants with methoxymethoxy (MOM) groups at the 2,2’-positions (poly-**1**). Poly-**1** is optically-inactive, but forms an excess one-handed helix in the presence of chiral molecules (**3**–**10**) accompanied by significant amplification of the chirality followed by its memory, thus showing a characteristic ICD. The Cotton effect signs can be used to sense the chirality of chiral hydrocarbons (Figure 1). The present direct chirality-sensing method using CD differs from prior work by requiring no further chemical reactions and can enable the rapid detection of hardly detectable hidden chirality in chiral hydrocarbons and deuterated isotopomers and their absolute configurations together with their optical purities (% ee) can be determined.

As recently reported, poly-**1** is a quite unique helical polymer whose main-chain helicity and axial chirality of the biphenyl pendants can be induced in the solid state as well as in solution upon interaction with a nonracemic alcohol, *e.g.*, (*S*)-1-phenylethanol ((*S*)-**2**), thereby exhibiting split-type ICDs in the polymer chromophore regions.[12] Unlike previously reported dynamic helical poly(phenylacetylene)s with functional pendants, such as carboxy and amino groups,[13] the induced helical chirality and axial chirality of poly-**1** are automatically memorized after isolation of the polymer by complete removal of (*S*)-**2**.[14] In addition, subsequent immersion of the optically-active poly-**1** in the enantiomeric (*R*)-**2** causes a complete inversion of both the helical and axial chiralities that are also retained after isolation. Based on this unique switchable memory effect of poly-**1**, we succeeded in developing an unprecedented switchable chiral stationary phase (CSP) for HPLC, whose elution orders or enantioselectivity can be reversibly switched.[12,15]

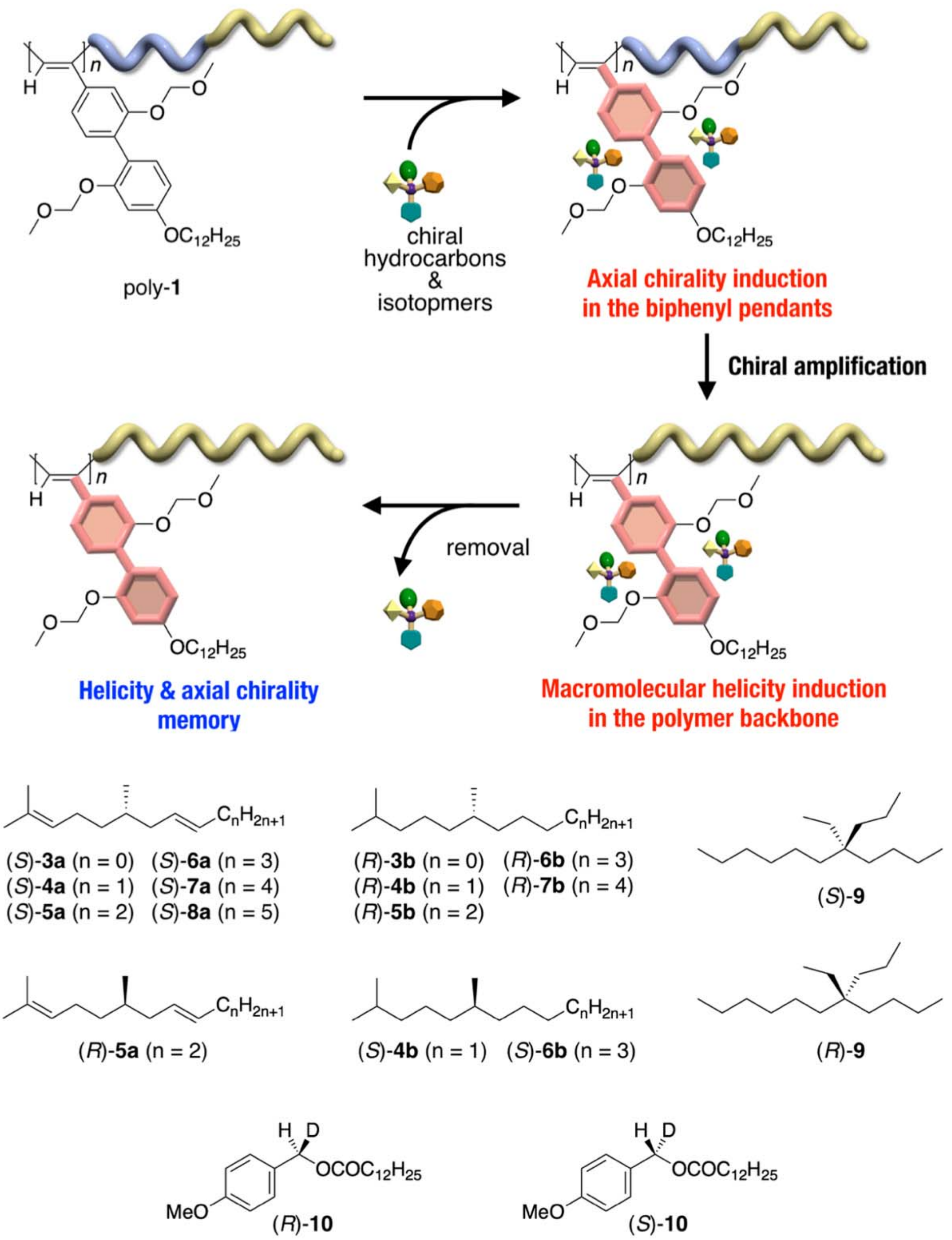


Figure 1. Schematic illustration of a sequential induction of axial chirality at the biphenyl pendants of poly-**1** and its macromolecular helicity accompanied by chiral amplification through noncovalent interactions with chiral tertiary (**3–8**) and quaternary (**9**) hydrocarbons, and chiral deuterated isotopomers (**10**) and subsequent memory of the induced axial chirality and helicity of poly-**1** after

complete removal of chiral hydrocarbons and isotopomers. The structures of chiral hydrocarbons and deuterated isotopomers are also shown.

RESULTS AND DISCUSSION

Since poly-**1** is soluble in various hydrocarbons, we measured the CD and absorption spectra of poly-**1** in various chiral unsaturated (**3a**–**8a**) and saturated (**3b**–**7b**) tertiary hydrocarbons as the solvents at –10 °C (Figure 2) and the ICD results are summarized in Table 1.[16] Interestingly, poly-**1** exhibited apparent ICDs in all the tested chiral hydrocarbons in the absorption region of the polymer backbone due to a preferred-handed helix formation of poly-**1**[12] in response to the chirality of the hydrocarbons despite the absence of functional groups capable of interacting with poly-**1**. Weak CH-π interactions between the biphenyl pendants and the chiral hydrocarbons[17] probably play a role in inducing an excess one-handed helix on poly-**1**. There is a clear tendency that the chiral unsaturated hydrocarbons always showed more intense ICDs than the chiral saturated hydrocarbons, and among the chiral hydrocarbons used, (*R*)- and (*S*)-**5a** induced the most intense ICDs of the mirror images (Figure 2a). Although there are a few reports of the chiroptical sensing of chiral hydrocarbons using dynamically racemic receptors or helical polymers by CD,[17a,18] they are limited to cyclic hydrocarbons, such as naturally-occurring monoterpenes,[19] except for one example.[18d] The chiroptical sensing of chiral acyclic hydrocarbons including **3**–**8** has not been reported, indicating that poly-**1** is indeed the most sensitive and useful synthetic receptor for the chiroptical sensing of chiral hydrocarbons.[20]

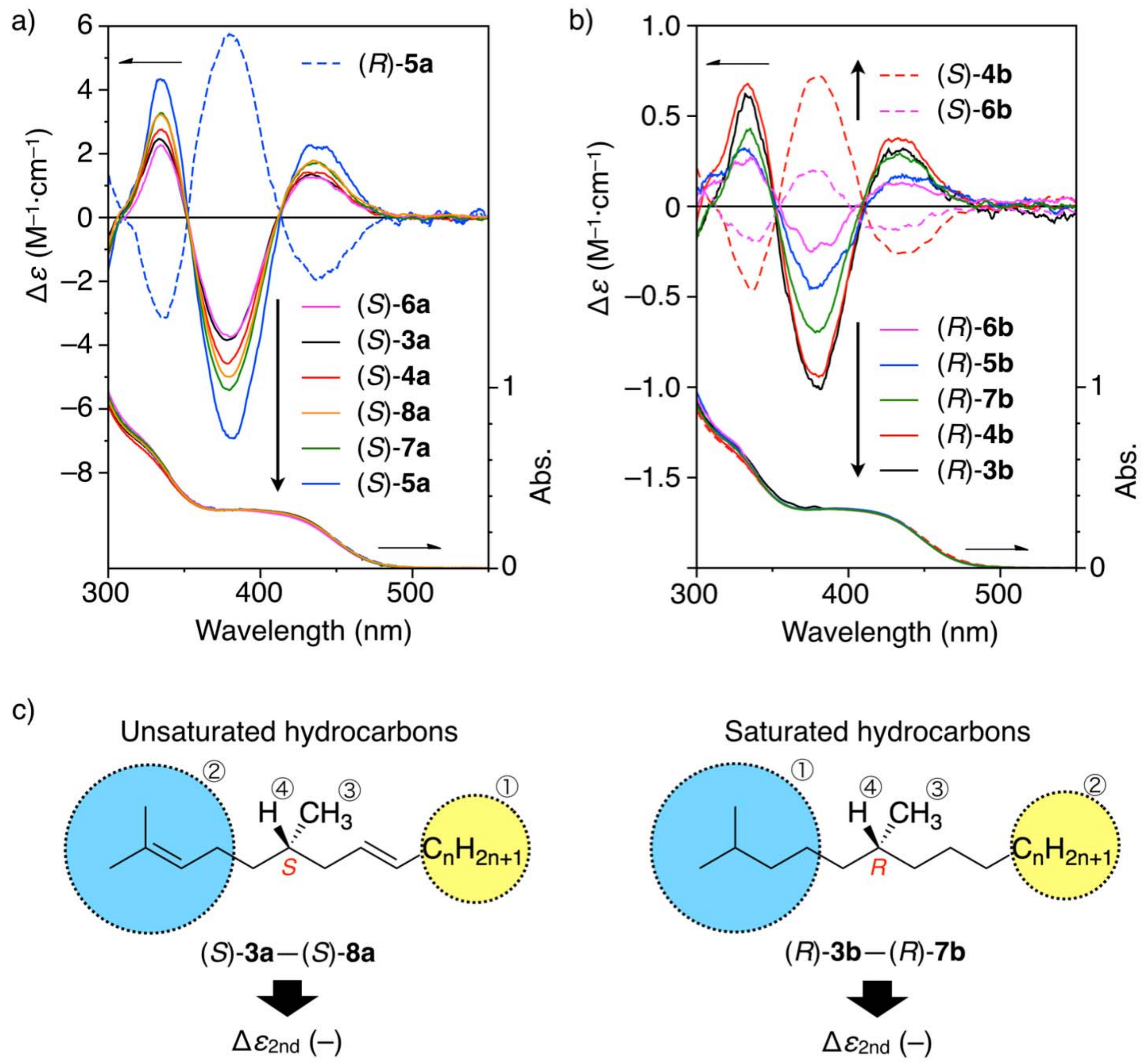


Figure 2. CD and absorption spectra of poly-**1** (1.0 mM) in optically-active unsaturated (**3a**–**8a**) (a) and saturated tertiary hydrocarbons (**3b**–**7b**) (b) measured at –10 °C after heating at 50 °C for 5 h. (c) The relationships between the sign of the second Cotton effect ($\Delta\varepsilon_{2nd}$) and the absolute configurations of unsaturated ((*S*)-**3a**–(*S*)-**8a**) (left) and saturated ((*R*)-**3b**–(*R*)-**7b**) (right) tertiary hydrocarbons. The substituents with blue circles are more bulky than those with yellow circles. The priority sequences are also shown.

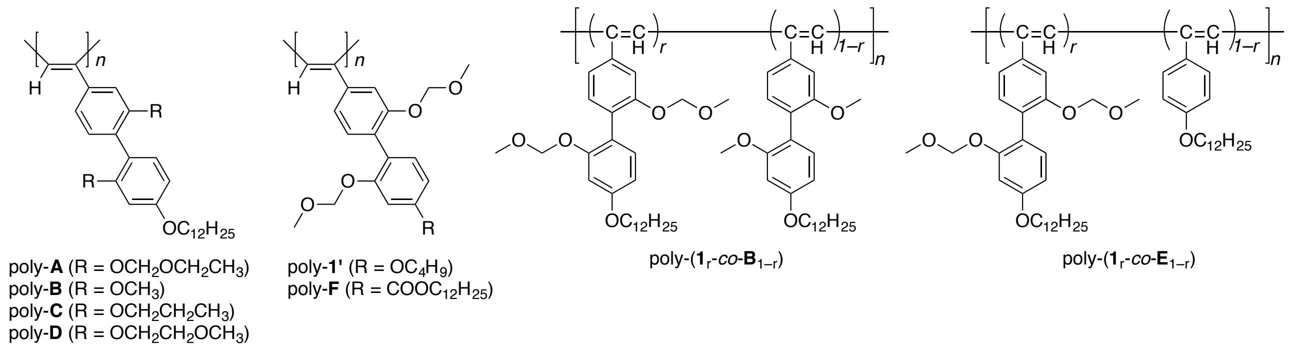
As shown in Table 1, there is a good correlation between the Cotton effect signs and the absolute configurations of chiral tertiary unsaturated and saturated hydrocarbons (**3a**–**8a**, **3b**–**7b**). The relationships between the Cotton effect signs and the absolute configurations of chiral tertiary hydrocarbons (**3a**–**8a**, **3b**–**7b**) can be generalized as follows. As shown in Figure 2c, the helical sense of poly-**1** preferentially induced by the chiral unsaturated (**3a**–**8a**) and saturated (**3b**–**7b**) tertiary hydrocarbons appears to be governed by the steric difference in the bulkiness between the two alkenyl or alkyl substituents on the stereogenic centers, respectively. The more bulky branched 4-methyl-3-pentenyl groups (**3a**–**8a**) and the 4-methylpentyl groups (**3b**–**7b**) (Figure 2c) most likely serve as a stereodemanding substituent. Therefore, the (*S*)-**3a**–**8a** and (*R*)-**3b**–**7b** induced the same right-handed helicity in poly-**1**[12] to show ICDs with the same Cotton effect signs, which clearly revealed that the absolute configurations of a series of chiral tertiary hydrocarbons can be determined by poly-**1**.[21]

Table 1. Signs and Difference in Exciton Coefficient of the Second Cotton ($\Delta\varepsilon_{2nd}$) for Poly-1 in Various Optically-Active Tertiary Hydrocarbons (3–8)[a]

run	chiral hydrocarbon	second Cotton		
		sign	$\Delta\varepsilon$ [$M^{-1}cm^{-1}$]	(λ [nm])
1	(*S*)-**3a**	–	3.84	(378)
2	(*S*)-**4a**	–	4.58	(379)
3	(*S*)-**5a**	–	6.92	(380)
4	(*R*)-**5a**	+	5.75	(380)
5	(*S*)-**6a**	–	3.75	(380)
6	(*S*)-**7a**	–	5.41	(380)
7	(*S*)-**8a**	–	4.73	(379)
8	(*R*)-**3b**	–	1.01	(382)
9	(*R*)-**4b**	–	0.93	(379)
10	(*S*)-**4b**	+	0.74	(382)
11	(*R*)-**5b**	–	0.46	(375)
12	(*R*)-**6b**	–	0.25	(375)
13	(*S*)-**6b**	+	0.20	(375)
14	(*R*)-**7b**	–	0.70	(378)

[a] Measured at –10 °C after heating at 50 °C for 5 h. [poly-**1**] = 1.0 mM.

Chart 1. Structures of Homopolymers (poly-A–poly-D, poly-F, and poly-1') and Copolymers (poly-(1_r-*co*-B_{1-r}), poly-(1_r-*co*-E_{1-r}))



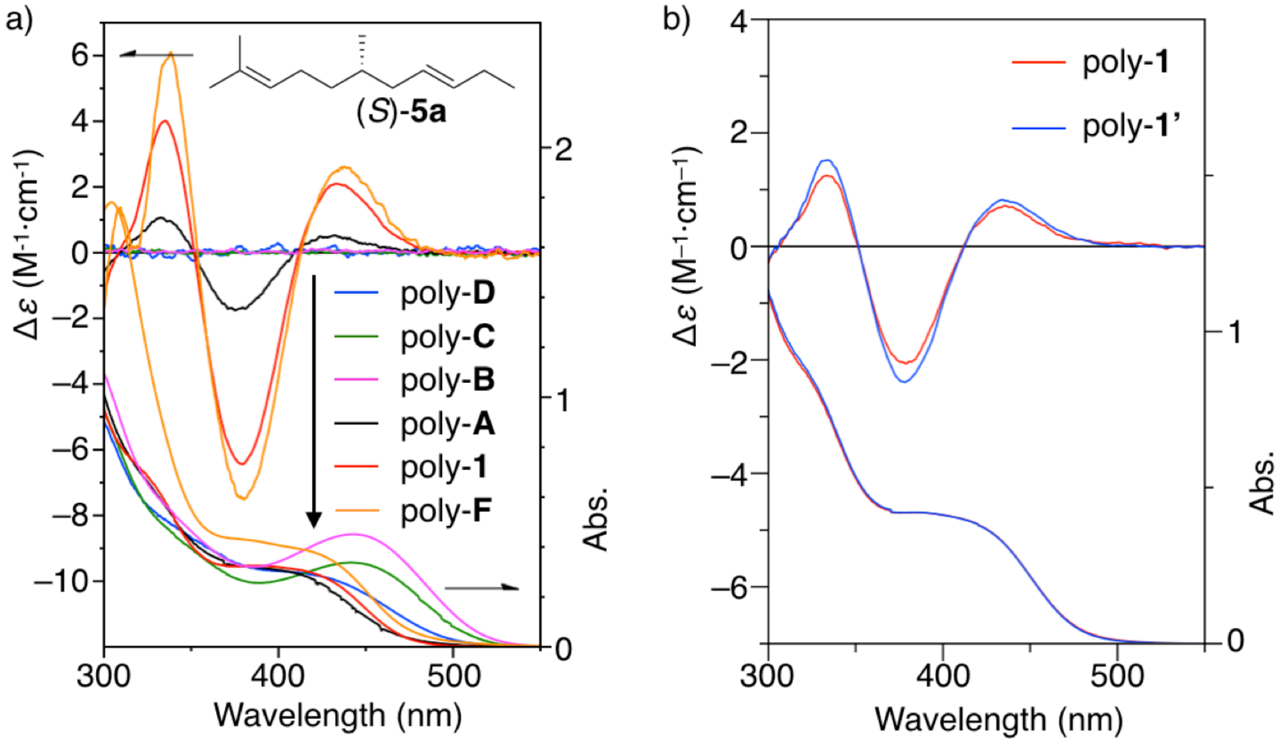


Figure 3. CD and absorption spectra of poly-**1**, poly-**A**–poly-**D**, and poly-**F** in (*S*)-**5a** measured at –10 °C after annealing at 50 °C for 5 h (poly-**1**, poly-**A**–poly-**D**) and 18 h (poly-**F**) (a) and those of poly-**1** (red line) and poly-**1'** (blue line) in (*S*)-**5a**/toluene (2/1, v/v) at 25 °C after annealing at 50 °C for 1 h (b). [polymer] = 1.0 mM.

The effect of the substituents at the 4'-position as well as the 2,2'-positions of the biphenyl pendants of poly-**1** on the observed high chiroptical sensing ability toward chiral hydrocarbons was then investigated. Among the analogous homopolymers (poly-**A**-poly-**D**) possessing alkoxy groups different from the methoxymethoxy (MOM) groups at the 2,2'-positions of the biphenyl pendants, such as the ethoxymethoxy, methoxy, propoxy, and methoxyethoxy groups, respectively (Chart 1), only poly-**A** bearing ethoxymethoxy groups showed a clear ICD, but its intensity was about one-third that observed in poly-**1** in (*S*)-**5a** (Figure 3a). Poly-**1** derivatives with a short butoxy chain (poly-**1'**) and a dodecyloxycarbonyl group at the 4'-position (poly-**F**)[22] instead of the dodecyloxy group in poly-**1** were also prepared and their CD spectra were measured in the presence of (*S*)-**5a** (Figure 3a,b), which revealed that the effect of the chain-length of the alkoxy group and an ester group at the 4'-position of the biphenyl pendants of poly-**1** on the chirality-sensing toward (*S*)-**5a** is not significant.

Moreover, the ICD intensity of the copolymers poly-($\mathbf{1}_{r}$-*co*-$\mathbf{B}_{1-r}$) and poly-($\mathbf{1}_{r}$-*co*-$\mathbf{E}_{1-r}$) in (*S*)-**5a** at –10 °C significantly decreased with an increase in the content of **B** and (4-dodecyloxyphenyl)acetylene (**E**) units in the copolymers, and the copolymers composed of more than 20 mol% **B** and **E** units exhibited no ICD (Figure S7). These results revealed that cooperative close interactions between the neighboring biphenyl pendants with the alkoxymethoxy groups along the helical polymer backbone play a crucial role, which enables direct chiroptical detection of otherwise undetectable chirality of chiral hydrocarbons through an induction of non-racemic helicity in poly-**1** with a high sensitivity. We assume that the chiral information of the chiral hydrocarbons first transfers to the axial chirality in the biphenyl pendants, and subsequently, the induced axially twisted conformation with a slight excess of a one-handed twist-sense would be further amplified in the polymer backbone as an excess helical sense.[12,22] Obviously, we need further studies to propose a plausible mechanism of the helicity induction in poly-**1** followed by its helicity memory upon interacting with chiral compounds.

A notable feature of the noncovalent helicity induction and subsequent memory of the helicity of poly-**1** after isolation[12] enables the chirality detection of an extremely small amount of chiral hydrocarbons. For example, a solution of poly-**1** (0.46 mg) dissolved in 30 μL of (*R*)-**5a** followed by heating at 50 °C for 5 h, through which a preferred-handed helicity was induced and automatically memorized, then diluted with *n*-hexane (870 μL) ([poly-**1**] = 1.0 mM, [(*R*)-**5a**]/[poly-**1**] = 200) (Figure 4a) exhibited an ICD as intense as that of poly-**1** dissolved in 300 μL of (*R*)-**5a** ([poly-**1**] = 1.0 mM) after annealing at 50 °C for 5 h (Figure 4b).[23] In contrast, when poly-**1** was first dissolved in *n*-hexane (870 μL) followed by the addition of 30 μL of (*R*)-**5a** ([poly-**1**] = 1.0 mM), the poly-**1** showed a very weak ICD after heating the solution at 50 °C for 5 h due to a weak bimolecular interaction in the dilute solution (Figure 4c).

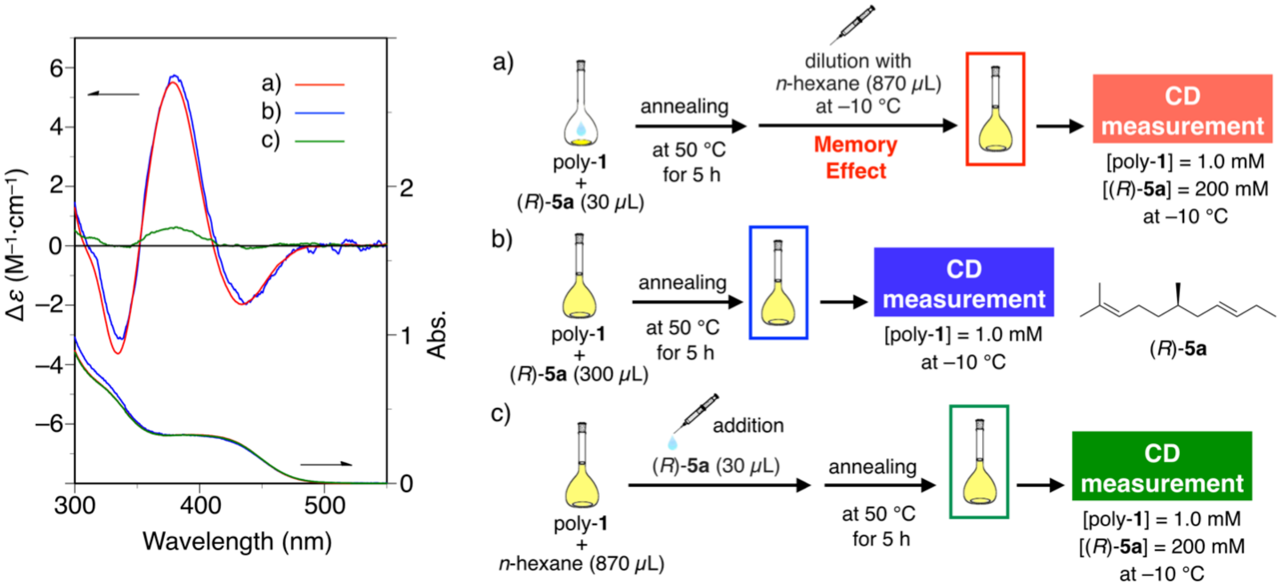


Figure 4. CD and absorption spectra of poly-**1** dissolved in 30 μL of (*R*)-**5a** followed by heating at 50 °C for 5 h, and then diluted with *n*-hexane (870 μL) ([poly-**1**] = 1.0 mM, [(*R*)-**5a**]/[poly-**1**] = 200) (a), those dissolved in 300 μL of (*R*)-**5a** ([poly-**1**] = 1.0 mM) after heating at 50 °C for 5 h (b), and those dissolved in *n*-hexane (870 μL) with (*R*)-**5a** (30 μL) after heating at 50 °C for 5 h ([poly-**1**] = 1.0 mM, [(*R*)-**5a**]/[poly-**1**] = 200) (c). All CD and absorption spectra were measured at –10 °C.

We next investigated whether poly-**1** could respond to the hardly detectable chirality of the cryptochiral quaternary hydrocarbon **9**. Based on the noncovalent helicity induction and subsequent memory strategy, poly-**1** was first dissolved in tiny amounts of (*S*)- and (*R*)-**9** (30 μL) and each solution was heated at 50 °C for 5 h followed by standing at 25 °C for 5 days, then diluted with *n*-hexane at –10 °C to measure the CD spectra. As shown in Figure 5a, poly-**1** showed weak, but perfect mirror image ICDs after helicity induction with the (*S*)- and (*R*)-**9** followed by the helicity memory. Furthermore, poly-**1** could also detect the minute chirality of the deuterated isotopomers, such as (*S*)- and (*R*)-**10**, and exhibited mirror image ICDs (Figure 5b).[24,25] As a consequence, the hardly detectable hidden chirality of a saturated quaternary hydrocarbon and deuterated isotopomers, which have never been detected by conventional optical spectroscopic methods, has been, for the first time, directly visualized by CD spectroscopy using the helical polyacetylene as a powerful chirality sensor.

Because of the extremely high sensitivity of the polyacetylene toward the minute chirality resulting from a unique memory effect through significant amplification of the chirality, the chiroptical sensing and further determination of the absolute configurations of a series of chiral saturated and unsaturated tertiary hydrocarbons and chiral deuterated isotopomers will be also possible. The present system described here may have further application in the study of other chiral compounds with hidden chiralities derived from other isotope substitutions, such as carbon (^{13}C/^{12}C) and oxygen (^{18}O/^{16}O).[26]

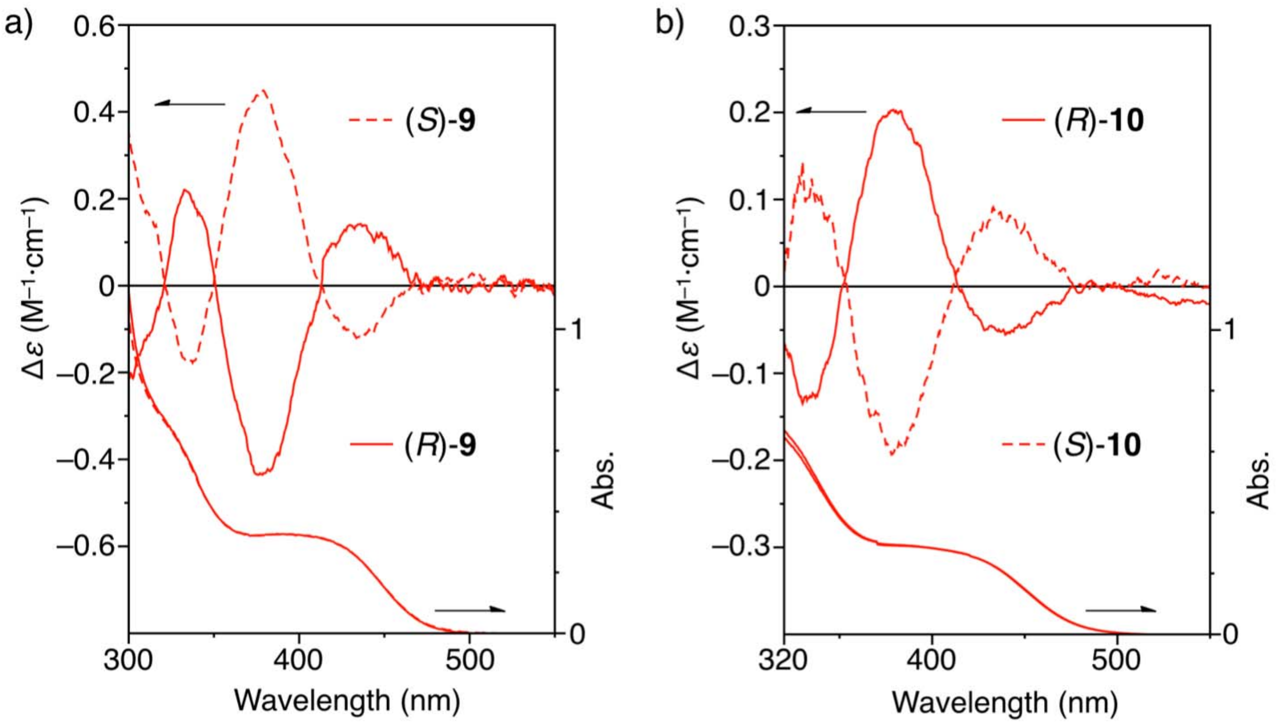


Figure 5. CD and absorption spectra of poly-**1** (1.0 mM) dissolved in cryptochiral **9** (30 μL) followed by heating at 50 °C for 5 h and standing at 25 °C for 5 days, and then diluted with *n*-hexane (870 μL) (a) and those dissolved in isotopically chiral **10** (30 μL) followed by standing at 25 °C for 24 h and then diluted with *n*-hexane (870 μL) at –10 °C (b). All CD and absorption spectra were measured at –10 °C.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:.

Experimental procedures, characterizations of polymers, copolymers, and chiral compounds, and additional spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank R. Ishidate (Kanazawa University) for his help in the synthesis of poly-**1'** and poly-**F**. This work was supported in part by JSPS KAKENHI (Grants-in-Aid for Scientific Research (B), no. 16H04154 (K.M.) and Grant-in-Aid for Scientific Research (S), no. 25220804 (E.Y.)) and by the Nanotechnology Platform Program (Molecule and Material Synthesis) of the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

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(19) Poly-**1** also responded to the chirality of monoterpenes, such as (*R*)-limonene ((*R*)-**12**) and (1*R*)-α-pinene ((1*R*)-**13**), thus exhibiting similar ICDs in their patterns (Figure S5).

(20) The chiral discrimination of chiral saturated tertiary alkanes (**3b–7b**) has also been achieved by Soai's asymmetric autocatalysis.[11]

(21) It should be noted that almost linear relationships between the enantiomeric excess (ee) of **4b** or **5a** and the ICD values of poly-**1** were observed (Figure S6), although the CD values of poly-**1** showed a strong positive nonlinear relationship with respect to the ee of **2** as previously reported.[12] This is probably because the interaction of poly-**1** with chiral hydrocarbons **4b** and **5a** is very weak. These linear relationships allow us to use poly-**1** to determine the ee of chiral hydrocarbons.

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(23) Poly-**1** dissolved in 3 μL of (*R*)-**5a** exhibited an ICD as intense as that in 30 μL of (*R*)-**5a**.

(24) Poly-**1** also detected the chirality of the isotopically chiral alcohol **11** (Figure S9) and showed mirror image ICDs in the presence of (*R*)- and (*S*)-**11** in toluene (2/10, v/v) after standing at 25 °C for 5 h. Toluene was used as the solvent because poly-**1** was insoluble in **11**.

(25) Poly-**1** also showed ICDs with chiral secondary alcohols ((*S*)-**14** and (*S*)-**15**) and a chiral secondary amine ((*S*)-**16**) (Figure S10) and the Cotton effect signs are the same when their absolute configurations are the same (Table S3).

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Graphics for TOC: