## INVITED ARTICLE

# Chiral interaction between aromatic aldehydes and a polymer bearing large chiral rings obtained by cyclopolymerization of bisacrylamide

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This paper describes the investigation of an interaction between chiral induction behavior and a chiral polymer obtained by cyclopolymerization of a bisacrylamide (1) prepared from α-pinene and acrylonitrile. Poly(1) can interact with aromatic aldehydes, as confirmed by infrared (IR), circular dichroism (CD), diffusion-ordered nuclear magnetic resonance spectroscopy (DOSY) and 1-D nuclear Overhauser effect difference (1-D NOE) measurements. The observed induced CD demonstrates that the chiral framework of poly(1) forced aldehydes to remain in chiral environments. IR, DOSY and 1-D NOE measurements on mixtures of poly(1) and aromatic aldehydes suggest that carbonyl groups interacted with the polymer.
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### INTRODUCTION

Chiral polymers have been used as stationary phases for chiral separation[1–10] and as templates for asymmetric reactions.[11–15] To achieve high performance with a chiral polymer, the polymer needs appropriate functional groups and a rigid structure. As a candidate, we designed a chiral polyacrylamide prepared through cyclopolymerization of a chiral bisacrylamide (1) (Scheme 1).[16] The monomer can easily be prepared by a one-step reaction of α-pinene and acrylonitrile.[17] The cyclopolymerization proceeds through the formation of 10- or 11-membered chiral rings. Although the structure of the rings has not been clarified completely by spectroscopic analyses, computational calculation suggested that the 11-membered ring formations are significantly predominant over 10-membered ring formations because of steric hindrance and the stability of propagating radicals. The details will be described elsewhere. In spite of the typically unfavorable large ring formation, this cyclopolymerization can yield soluble polymers bearing the desired cyclic units in quantitative yields. The selectivity of the cyclopolymerization without branching was confirmed by matrix-assisted laser desorption-ionization time of flight mass spectroscopy analysis of poly(1) obtained by reversible addition-fragmentation chain transfer (RAFT) polymerization, indicating that poly(1) has only one initiating and terminating group originating from the chain transfer agent. The circular dichroism (CD) spectra of the resulting polymers show Cotton effects originating from the amide moieties in chiral environments and suggest the potential application of poly(1) as a chiral polymer. The chiral rings in poly(1) contain chiral cyclic structures capable of straining the functional groups (that is, amide in this case) at chirally regulated spaces. The effectiveness of such designs has been proven by many studies on chiral recognition by polymers bearing both chiral cyclic structures and functional groups for intermolecular interactions.[18–21] For example, stationary phases based on poly(*trans*-1,2-cyclohexanediyl-bisacrylamide),[19] which has a dichiral cyclic structure with restricted configuration, can separate many enantiomers. Accordingly, we evaluated the chiral induction with poly(1) consisting of units containing a chiral bicyclic structure and two amide groups by nuclear magnetic resonance (NMR) and CD spectroscopic measurements. Diffusion-ordered nuclear magnetic resonance spectroscopy (DOSY) and 1-D nuclear Overhauser effect difference measurements were used for analysis of intermolecular interactions.[22–26]

### EXPERIMENTAL PROCEDURE

#### Materials

The bisacrylamide monomer (1)[17] was prepared according to the reported procedure. Poly(1) ($M_n$=5400, $M_w/M_n$=3.65) was prepared by free radical polymerization in *N,N*-dimethylformamide (0.12 M) according to the reported procedure.[16] The polymerization was conducted at 80 °C in a degassed sealed tube for 24 h in the presence of 2,2′-azobisisobutyronitrile ([1]₀/[AIBN]₀=70), and the polymer was isolated by precipitation into diethyl ether. 1,4-Dioxane was dried over sodium and distilled under a nitrogen atmosphere before use. Dichloromethane was dried over $CaH_2$ and distilled under a nitrogen atmosphere before use. Other reagents were used as received.

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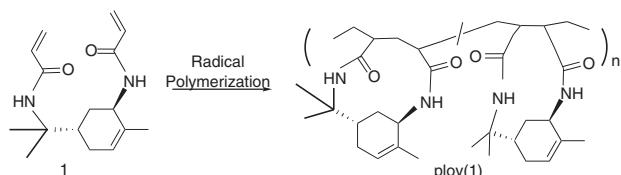E-mail: tendo@mol-eng.fuk.kindai.ac.jp

## Measurements

NMR spectroscopy measurements were determined using a JEOL ECX-400 instrument (JEOL, Tokyo, Japan) using tetramethylsilane as an internal standard at ambient temperatures (400 MHz for $^1$H and 100 MHz for $^{13}$C). The 1-D difference nuclear Overhauser effect measurements were determined at 35 °C with a relaxation delay of 2 s and an irradiation time of 0.2 s. Both parameters were optimized using arrayed experiments by changing the parameters with a step of 0.1 s. DOSY spectra were measured under the following conditions: 35 °C; diffusion time, 18–20 ms; duration of magnetic-field-gradient pulse, 1 ms; and relaxation delay, 8 s. Two-dimensional spectra were processed using the CONTIN method with Delta 4.3.4 software (JEOL). Ultraviolet visible spectra were measured using a JASCO V-550-DS instrument (Jasco, Tokyo, Japan). CD spectra were measured using a JASCO J-720 WI instrument at an ambient temperature (~25 °C). Molar ellipticity was calculated on the basis of molecular weight per unit. Fourier transfer infrared (IR) spectra were recorded using a Horiba FT-IR 210 instrument (Horiba, Kyoto, Japan) equipped with a SensIR Technologies DuraScope attenuated total reflectance accessory (SensIR Technologies, Danbury, CT, USA). The mixtures of equimolar amounts of poly(**1**) and aldehydes for IR spectrometry were prepared by drying the chloroform solutions of mixtures.

## RESULTS AND DISCUSSION

### CD spectroscopy analysis of mixtures of poly(**1**) and aromatic substrates

In the previous report, we demonstrated that poly(**1**) contains chiral structures, as confirmed by its CD spectrum in methanol.[16] We expected the hydrogen-bonding ability of the amide moieties in poly(**1**) to be important for interactions between poly(**1**) and substrates for chiral induction or chiral resolution. Accordingly,

**Scheme 1** Radical polymerization of a chiral bisacrylamide (**1**).

we measured the CD spectra of poly(**1**) in 1,4-dioxane (Figure 1a). Poly(**1**) obtained by free radical polymerization was used because the visible absorption of the terminal pyrrole dithiocarbamate moieties in poly(**1**) obtained by reversible addition-fragmentation chain transfer polymerization makes the CD spectroscopic analysis difficult. The NMR spectra of the polymer used were identical to those of the polymer obtained by selective reversible addition-fragmentation chain transfer cyclopolymerization. This result suggests that the ring-closing efficiency of the polymer used is also quantitative. The Cotton effect of poly(**1**) is very weak in 1,4-dioxane. The very weak and positive signal at 220–240 nm is assignable to the n–π* transition of the carbonyl group in the amide, and no significant Cotton effect was observed at longer wavelengths (Figure 1). Accordingly, we choose aromatic aldehydes with absorptions at a longer wavelength region as guests. We measured the CD spectra of equimolar mixtures of poly(**1**) and achiral aromatic aldehydes in 1,4-dioxane to discover compounds capable of interacting with poly(**1**). The mixtures containing aldehydes showed clear negative CD signals (Figure 1), whereas the mixture containing phenol showed a CD spectra identical to that of the solution of poly(**1**). The CD signals observed in the wavelength region longer than 240 nm are attributable to the induced CD of achiral aromatic aldehydes by poly(**1**), with an absorption spectrum cutoff of approximately 240 nm. This result clearly demonstrates that p-methoxybenzaldehyde and 2-naphthaldehyde were forced to remain in chiral environments by poly(**1**). The CD spectra of the mixtures containing benzaldehyde and p-trifluoromethylbenzaldehyde showed Cotton effects at 220–250 nm, in which the absorptions of carbonyl groups in both amide and aldehyde moieties are present. Although we could not conclude that the observed Cotton effects originated from the chiral induction of the aldehyde groups or the changed chiral environments of poly(**1**), the appearance of Cotton effects supports the presence of interactions between aldehydes and poly(**1**), by which chiral induction or a conformational change in poly(**1**) occurred. Radical copolymerization of 1 and N-vinylcarbazole provides an alternating copolymer. Its CD spectrum in 1,4-dioxane shows negative CD signals at 230–250 nm, the shape of which resembles the CD signal of the mixture of poly(1) and benzaldehyde. Details of the alternating
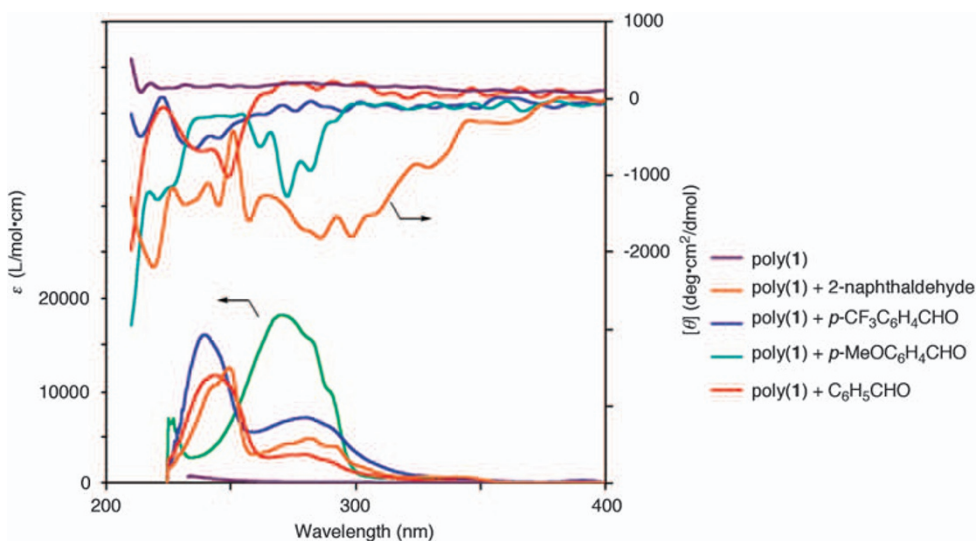
**Figure 1** Circular dichroism (CD) and ultraviolet visible spectra of poly(**1**); the mixture containing poly(**1**) and p-methoxybenzaldehyde; the mixture containing poly(**1**) and benzaldehyde; the mixture containing poly(**1**) and p-trifluoromethylbenzaldehyde; and the mixture containing poly(**1**) and 2-naphthaldehyde in 1,4-dioxane (0.5 mg ml$^{-1}$ of poly(**1**), [aldehyde]/[poly(**1**) unit]=1.0).

polymerization behavior and the CD spectrometry study will be described elsewhere. If the observed Cotton effects are induced CD, the absence of CD signals at longer wavelengths may be attributed to the weaker steric regulation (as discussed later).

The effect of the electron density of carbonyl groups was evaluated by IR spectrometry. The absorption of the amide I C=O stretching vibration of poly(**1**) was observed at $1644 \, cm^{-1}$, which is a very low wavenumber for a secondary amide and implies the strong hydrogen bonding between the amide moieties. The absorption shifted toward the higher wave number region with the addition of equimolar amounts of the aldehyde; that is, the absorptions were observed at 1646, 1650 and 1650–1660 by the addition of *p*-trifluoromethylbenz-aldehyde, benzaldehyde and *p*-methoxybenzaldehyde, respectively. The absorption of the amide group in the presence of *p*-methoxy-benzaldehyde overlapped with the absorption of the aldehyde group originally observed at $1681 \, cm^{-1}$, and we could not determine the exact absorption maximum of the absorption of the amide groups. The higher wavenumber shifts demonstrated the weakened hydrogen bonding between the amide groups in poly(**1**). By contrast, the absorption of the C=O stretching vibration of the aldehyde moieties shifted to a lower wave number. Although the absorption of *p*-methoxybenzaldehyde overlapped the absorption of poly(**1**), the estimated low wave number shift was between $-7$ and $-12 \, cm^{-1}$. The shifts of benzaldehyde and *p*-trifluoromethylbenzaldehyde were $-8 \, cm^{-1}$. This result supports the aforementioned presumption that the Lewis basic C=O groups in aldehydes interacted with amide protons. The release of the carbonyl groups in amide groups because of hydrogen bonding signifies that amide protons changed their electron-donating carbonyl groups from those in amide groups to those in aldehyde groups as the electron density increased.

### NMR spectroscopy analysis of interactions between poly(**1**) and aromatic aldehydes

The interactions between poly(**1**) and benzaldehyde derivatives were evaluated by NMR spectroscopic analysis. First, 1-D nuclear Over-hauser effect measurements were determined for the mixtures of

poly(**1**) and aldehydes (0.9 equivalent with respect to the unit of poly(**1**)). Irradiation at 5.6 p.p.m., at which the signal of the alkene proton in poly(**1**) is observed, resulted in decreased intensities of the aromatic aldehydes. The signal intensities depended on the electron donating abilities of substituents, agreeing well with the intensities of induced CD signals (Table 1). The higher intensities can be correlated to the closer distances between the corresponding protons and poly(**1**). In all cases, the relative intensities are higher as the protons are closer to the aldehyde moieties. This result also confirms that aldehydes interacted with poly(**1**) by their carbonyl groups.

We attributed the significantly higher signal intensities in the case of *p*-methoxybenzaldehyde to an interaction stronger than that of others. A stronger interaction can lead to a greater strain of the aldehyde, which restricts the rotation between aldehyde moieties and the aromatic ring. The weaker interactions between aromatic aldehydes, benzaldehyde and *p*-trifluoromethylbenzaldehyde in this study and poly(**1**) resulted in a weaker rotational restriction. We attributed the absence of CD signals at longer wavelengths in the mixtures contain-ing these aldehydes to the longer distances between poly(**1**) and these

**Table 1 Relative intensities of protons of aromatic aldehydes in the 1-D nuclear Overhauser effect measurement of the mixtures of poly(1) and aromatic aldehydes in CDCl$_3$ at 35 °C**

| | *Relative intensity*[a] | | | |
|---|---|---|---|---|
| *aldehyde* | R—⬡—CHO | R—⬡—CHO (H) | R—⬡—CHO (H) | **R**—⬡—CHO |
| MeO—⬡—CHO | 0.171 | 0.140 | 0.123 | 0.095 |
| ⬡—CHO | 0.016 | 0.016 | 0.015 | 0.015 |
| F$_3$C—⬡—CHO | 0.0090 | 0.0085 | 0.0007 | — |

[a]Relative intensities per one hydrogen atom with respect to the signal intensity of the peak at 5.6 p.p.m.
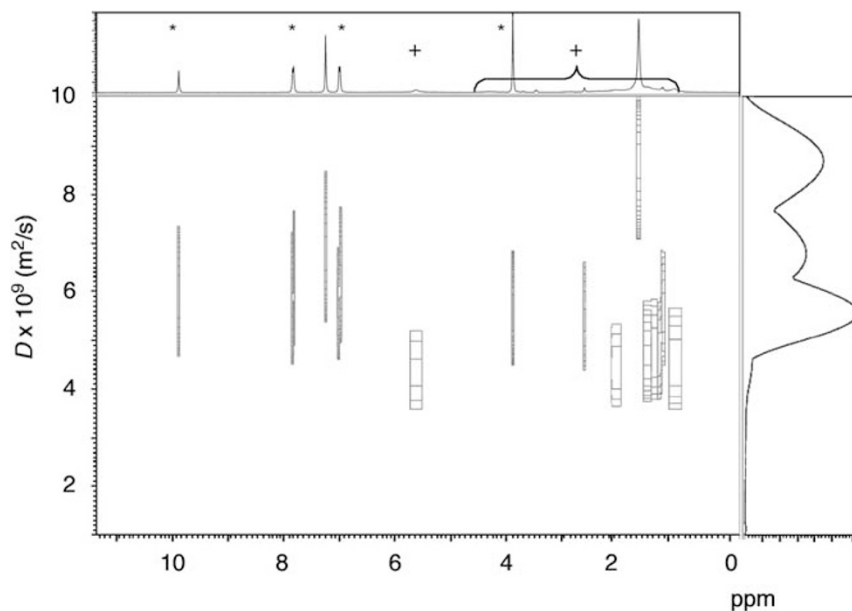


**Figure 2** Diffusion-ordered nuclear magnetic resonance spectroscopy spectra of the mixture of poly(**1**) ($6 \, mmol \, l^{-1}$) and *p*-methoxybenzaldehyde ($6 \, mmol \, l^{-1}$) in CDCl$_3$ at 35 °C. The asterisks and plus marks in the 1-D $^1$H nuclear magnetic resonance spectra indicate the signals of *p*-methoxybenzaldehyde and poly(**1**), respectively.

**Table 2 Diffusion coefficients of aromatic aldehydes and poly(1) in CDCl₃ at 35 °C (6 mmol l⁻¹ each)[a]**

| | $D_{poly(1)}$ $(m^2 s^{-1})$[b] | $D_{ArCHO}$ $(m^2 s^{-1})$[c] | $D_{ArCHO}/D_{poly(1)}$ |
|---|---|---|---|
| $p$-MeOC₆H₄CHO | $4.7 \times 10^{-9}$ | $6.2 \times 10^{-9}$ | 1.3 |
| C₆H₅CHO | $4.2 \times 10^{-9}$ | $7.7 \times 10^{-9}$ | 1.8 |
| $p$-CF₃C₆H₄CHO | $3.4 \times 10^{-9}$ | $7.5 \times 10^{-9}$ | 2.2 |

[a]The diffusion constants involve inherent errors of $\pm 0.2 \times 10^{-9}\,m^2\,s^{-1}$.
[b]Calculated on the basis of the signal at 5.4 p.p.m.
[c]Calculated on the basis of the signal assigned to the –C*H*O moieties.

aldehydes. The IR and NMR measurements suggested hydrogen bonding between the NH groups in poly(1) and the carbonyl groups in aldehydes, whereas the dipole–dipole interaction between the carbonyl groups in poly(1) and aldehydes also contributes to the interaction between the amide and aldehyde moieties. Other possible interactions are the π–π interaction between the double bond moieties in poly(1) and the aromatic rings in aldehydes and hydrophobic interactions. The NOE experiment suggested that the contributions of these interactions are weak.

The effect of the intermolecular interaction on diffusion behavior was also evaluated using DOSY experiments on the basis of the assumption that the strong intermolecular interactions cause the diffusion of poly(1) and aldehydes to be similar (Figure 2). Experiments were conducted using CDCl₃ solutions containing equimolar amounts of aldehydes and poly(1) units ($\sim$6 mmol l⁻¹ each) at 35 °C. The DOSY spectrum of the mixture containing poly(1) and $p$-methoxybenzaldehyde shows that each component diffused at $4.7 \times 10^{-9}$ and $6.2 \times 10^{-9}\,m^2\,s^{-1}$, and these diffusion coefficients indicate that $p$-methoxybenzaldehyde diffused slightly faster. The diffusion coefficient of poly(1) in the mixture is higher than that of poly (1) in the CDCl₃ solution without additives ($\sim$9–10×10⁻¹⁰ m² s⁻¹). We attributed the faster diffusion of poly(1) with $p$-methoxybenzaldehyde to the increased mobility of poly(1) because of interactions that weaken the inter- and/or intramolecular hydrogen bonding between different poly(1) units. The DOSY spectra of the mixtures containing poly(1) and other aldehydes indicate that aldehydes diffused faster than poly(1) with a decreasing electron density of aldehyde moieties. This behavior also supports the assertion that the interactions between aldehydes and poly(1) depend on the electron density of carbonyl groups (Table 2).

## CONCLUSIONS

The chiral polyacrylamide obtained by cyclopolymerization of **1** interacted with Lewis-basic aromatic compounds. The interacting aromatic aldehydes remained in chiral environments, as confirmed by the induced or changed CD signals, whereas phenol did not interact with poly(1). The hydrogen bonding between the protons of amide groups in poly(1) and the carbonyl groups in aldehydes proved to be the most important factor for the interaction. This unique behavior implies the possibility that poly(1) can serve as a chiral template or as a chiral separator.

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