

Synthesis of Poly[*N*-(4-ethynylbenzyl)ephedrine] and Its Use as a Polymeric Catalyst for Enantioselective Addition of Dialkylzincs to Benzaldehyde

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ABSTRACT: A novel, optically active, *cis-transoidal* polyacetylene, poly[*N*-(4-ethynylbenzyl)ephedrine] (poly-4b) was prepared and interactions with chiral acids were examined by means of circular dichroism (CD) spectroscopy. The intensity of induced CD of the polymer decreased with an increase in the concentration of (*R*)- or (*S*)-mandelic acid. However, significant differences between the induced CD changes in the presence of (*R*)- or (*S*)-mandelic acid were not found in the complexation. Poly-4b was used as an optically active catalyst for enantioselective addition of benzaldehyde with dialkylzincs. Enantiomeric excess of 1-phenylethanol obtained was 30–49%.

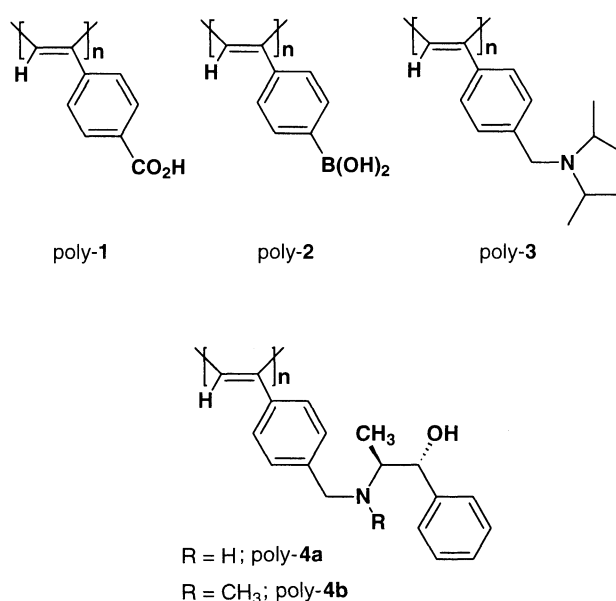
KEY WORDS: Optically Active Polymer / Polyacetylene / Helix / Circular Dichroism / Asymmetric Synthesis / Chiral Recognition /

Optically active polymers have aroused wide interest from synthetic, structural, and functional viewpoints,¹ since most naturally occurring polymers are optically active and show characteristic functionalities in living systems. Therefore, a number of optically active polymers have been synthesized so far, not only to mimic nature, but also to develop new chiral materials. Among them, optically active, helical polymers are particularly interesting. Polyisocyanides,^{1b,2} polychlorals,^{1d,3} polyisocyanates,^{1c,4} poly(2,3-quinoxaline)s,⁵ and poly(triaryl-methyl methacrylate)s^{1a,6} belong to this category and optically active, one-handed helical polymers have been prepared either by the polymerization of optically active monomers or by the asymmetric polymerization of the corresponding achiral monomers with chiral catalysts or initiators. Bulky side groups of the polymers contribute to maintain the one-handed helical conformation even in solution except for polyisocyanates. In sharp contrast, the helical structures of polyisocyanates are dynamic in nature and equilibrium exists in solution between both helices separated by the helix reversal points that move along the polymer backbone. However, the helix inversion barriers of polyisocyanates are very low, and therefore, optically active polyisocyanates with a prevailing one-handed helix can be obtained through anionic polymerization of optically active isocyanates or copolymerization of achiral isocyanates with a small amount of an optically active isocyanate.^{1c,4}

We recently found that stereoregular, *cis-transoidal* poly(phenylacetylene) derivatives bearing various functional groups such as, poly((4-carboxyphenyl)acetylene) (poly-1),⁷ poly((4-dihydroxyborophenyl)acetylene) (poly-2),⁸ and poly((4-*N,N*-diisopropylaminomethylphenyl)acetylene) (poly-3)⁹ form an induced helical structure upon complexation with optically active compounds capable of interacting with the functional groups of the polyphenylacetylenes. The complexes show an induced circular dichroism (ICD) in the UV—visible region, probably due to the prevailing one-handed helix formation of the polymers upon complexation with optically active compounds. The Cotton effect signs of ICDs corresponding to the helical sense can be used as a probe for the chirality assignment of chiral molecules. We

also found a unique helix—helix transition of optically active poly[(1*R*,2*S*)-*N*-(4-ethynylbenzyl)norephedrine] (poly-4a) induced by diastereomeric complexation with chiral acids.¹⁰ The binding with chiral acids having an (*R*) configuration induced a dramatic change in the ICD of the polymer in solution due to a helix—helix transition, while the CD spectrum of poly-4a hardly changed even in the presence of excess (*S*) acids. The helix—sense of poly-4a can be controlled by the addition of chiral acids and the changes in the ICD may be used as a probe for the chirality assignments of the acids. This may be the first example of a helix—helix transition induced by external, chiral stimuli through diastereomeric acid-base interactions.

In this study, we prepared an *N*-methylated analogous polymer, poly[(1*R*,2*S*)-*N*-(4-ethynylbenzyl)ephedrine] (poly-4b) and examined the interactions with chiral acids by means of CD spectroscopy. We also used poly-4b as an optically active, helical polymeric catalyst for asymmetric synthesis, since the complexes of ephedrine derivatives with dialkylzincs have been used as highly enantioselective reagents to aldehydes.¹¹



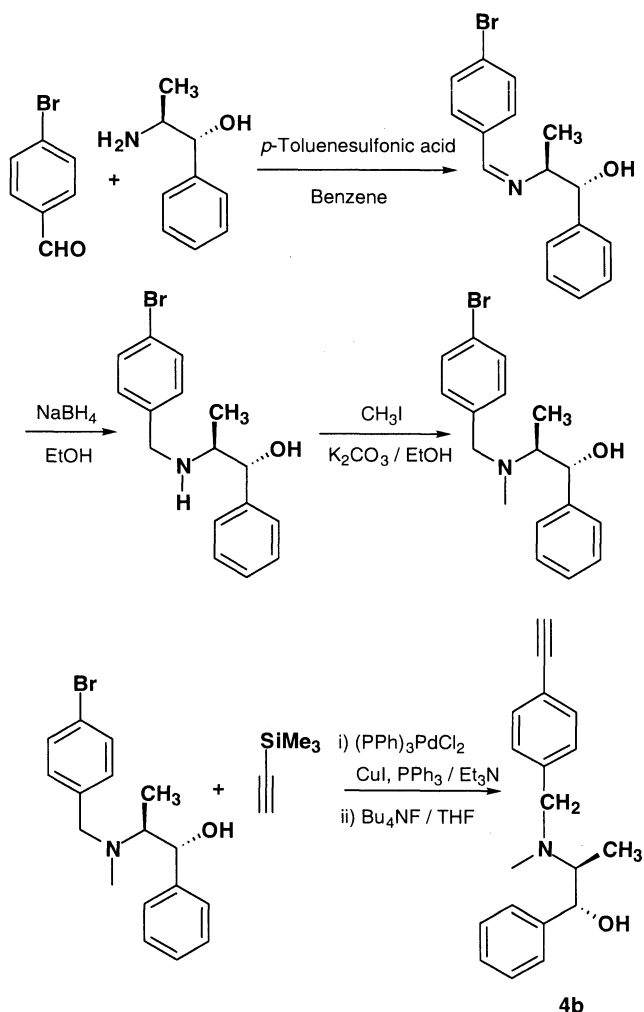
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EXPERIMENTAL

Materials

Tetrahydrofuran (THF) was dried over sodium benzophenone ketyl and distilled onto LiAlH_4 under nitrogen. Benzene was distilled from sodium benzophenone ketyl under nitrogen. These solvents were distilled under high vacuum just before use. Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were dried over calcium hydride and distilled under reduced pressure. Acetonitrile and chloroform were dried over calcium hydride and distilled. These solvents were stored under nitrogen over molecular sieves 4\AA (Nacalai Tesque). CDCl_3 (99.8 atom %D, Nacalai Tesque) was dried over molecular sieves 4\AA and stored under nitrogen. All solvents used for measurements of CD and NMR spectra were purged with argon prior to use. Benzaldehyde (Kishida, Japan) was dried over molecular sieves 4\AA and distilled.

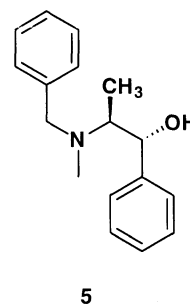
Bis(triphenylphosphine)palladium dichloride, [(norbornadiene)rhodium(I) chloride] $_2$ [$\text{Rh}(\text{nbd})\text{Cl}$] $_2$, dimethylzinc and diethylzinc in hexane (1.0 M) were purchased from Aldrich and used as received. 4-Bromobenzaldehyde, tetrabutylammonium fluoride (1.0 M in THF), and (-)-(1*R*,2*S*)-norephedrine were obtained from Tokyo Kasei (Japan). Triphenylphosphine and copper(I) iodide were from Kishida (Osaka, Japan). (Trimethylsilyl)acetylene was kindly supplied from Shinetsu Chemical (Tokyo, Japan). Optically active carboxylic acids were available from Aldrich or Tokyo Kasei.

*N*-(4-Ethynylbenzyl)ephedrine (**4b**)

Monomer **4b** was prepared from *N*-(4-bromobenzyl)norephedrine in a similar method used for the synthesis of **4a**¹⁰ as outlined below. *N*-Methylation of *N*-(4-bromobenzyl)norephedrine was carried out using iodomethane in the presence of potassium carbonate in dry ethanol according to the usual method. The coupling of (trimethylsilyl)acetylene to *N*-(4-bromobenzyl)ephedrine (17.6 g, 55 mmol) with a palladium catalyst, followed by desilylation of the trimethylsilyl protecting group, gave monomer **4b**. Purification by silica gel chromatography using hexane—ether (1/1, v/v) and hexane—ether (1/2, v/v) as eluent gave a slightly yellow viscous oil (23% yield); $[\alpha]_{\text{D}}^{25} +26.1^\circ$ (DMSO, $c = 1.0 \text{ g dl}^{-1}$). IR (KBr): 3410 ($\nu_{\text{NH,OH}}$), 3294 ($\nu_{\equiv\text{CH}}$), 2107 ($\nu_{\text{C}\equiv\text{C}}$); ^1H NMR (CDCl_3): δ 1.00 (d, CH_3 , 3H), 2.17 (s, *N*- CH_3 , 3H), 2.90 (m, CH, 1H), 3.05 (s, $\equiv\text{CH}$, 1H), 3.58 (s, CH_2 , 2H), 4.84 (d, CH, 1H), 7.12—7.43 (m, aromatic, 9H). Anal. Calcd for ($\text{C}_{19}\text{H}_{21}\text{NO}$): C, 81.68%; H, 7.58%; N, 5.01%. Found: C, 81.60%; H, 7.74%; N, 5.16%.

N-(4-Benzyl)ephedrine (**5**)

This model compound was prepared by the same method used for the synthesis of **4b** from *N*-(4-benzyl)norephedrine in 56% yield; mp 44.5—45.3°C; $[\alpha]_{\text{D}}^{25} -31.6^\circ$ (CHCl_3 , $c = 0.11 \text{ g dl}^{-1}$). ^1H NMR (CDCl_3): δ 0.99 (d, CH_3 , 3H), 2.19 (s, *N*- CH_3 , 3H), 2.91—2.96 (m, CH, 1H), 3.62 (q, CH_2 , 2H), 4.89 (d, CH, 1H), 7.23—7.34 (m, aromatic, 10H). Anal. Calcd for ($\text{C}_{17}\text{H}_{21}\text{NO}$): C, 79.96%; H, 8.29%; N, 5.49%. Found: C, 79.96%; H, 8.30%; N, 5.50%.



Polymerization

Polymerization was carried out in a dry glass ampoule under a dry nitrogen atmosphere using [$\text{Rh}(\text{nbd})\text{Cl}$] $_2$ as a catalyst. Monomer **4b** (0.88 g, 3.1 mmol) was placed in a dry ampoule, which was then evacuated on a vacuum line and flushed with dry nitrogen. After this evacuation—flush procedure was repeated three times, a three-way stopcock was attached to the ampoule, and THF was added with a syringe. To this was added a solution of [$\text{Rh}(\text{nbd})\text{Cl}$] $_2$ in THF at 30°C. The concentrations of the monomer and the rhodium catalyst were 0.5 M and 0.005 M, respectively. After 3.5 h, the resulting polymer (poly-**4b**) was precipitated into a large amount of methanol, collected by centrifugation, and dried in vacuo at 50 °C for 2 h (0.84 g, 95% yield).

Spectroscopic data of poly-**4b**. $[\alpha]_{\text{D}}^{25} -37^\circ$ (DMSO, $c = 0.1 \text{ g dl}^{-1}$). IR (KBr): 3442 (ν_{OH}); ^1H NMR (CDCl_3): δ 0.83 (d, CH_3 , 3H), 1.95 (s, *N*- CH_3 , 3H), 2.72 (m, CH, 1H), 3.42 (s, CH_2 , 2H), 4.79 (d, CH, 1H), 5.85 (s, $\equiv\text{CH}$, 1H), 6.65—7.18 (m, aromatic, 9H). Anal. Calcd for ($\text{C}_{19}\text{H}_{21}\text{NO}$) $_n$: C, 81.68%; H, 7.58%; N, 5.01%. Found: C, 81.65%; H, 7.48%; N, 4.95%.

General Procedure for the Reaction of Benzaldehyde with Diethylzinc Catalyzed by Poly-4b

Poly-4b was reprecipitated from CHCl_3 to hexane before use. To a Schlenk flask was added hexane (2.5 ml), poly-4b (27.5 mg, 0.098 mmol monomer units), and benzaldehyde (0.10 ml, 0.98 mmol) under nitrogen at 0°C . Diethylzinc (2.1 ml, 2.1 mmol) in hexane (1.0 M) was then added dropwisely to the suspension solution under stirring. After 24 h at 0°C , the reaction was quenched by the addition of 1M NH_4Cl (ca. 10 ml) and the aqueous layer was extracted with diethyl ether (15 ml x 3). The organic layer was dried over Na_2SO_4 or MgSO_4 . The yield was determined by ^1H NMR of the crude product containing 1-phenylpropanol, benzaldehyde, and a small amount of benzylalcohol as a by-product. The crude product was chromatographed on silica gel with hexane—ethyl acetate (1/1, v/v) as the eluent to afford the product, 1-phenylpropanol as a colorless liquid. The ee of 1-phenylpropanol was determined with a chiral HPLC column, Chiralcel OD (Daicel, 25 cm x 4.6 mm i.d.), using hexane—2-propanol (99 / 1) as the eluent at the flow rate of 1.0 ml min^{-1} : $t_R = 20$, $t_S = 25$ min.

Instruments

Melting points were measured on a Büchi melting point apparatus and are uncorrected. NMR spectra were measured on a Varian VXR-500S or Varian Gemini 400 NMR spectrometer using TMS as the internal standard. IR spectra were recorded using a Jasco Fourier Transform IR-7000 spectrophotometer with a Jasco PTL-396 data processor. Absorption spectra were taken on a Jasco Ubest-55 spectrophotometer. CD spectra were measured in a 0.05 cm quartz cell unless otherwise noted using a Jasco J-720 L spectropolarimeter. HPLC experiments were performed on a Jasco PU-980 chromatograph equipped with a UV (Jasco 875-UV) and a polarimetric (Jasco OR-990) detectors.

CD Titration

The concentration of poly-4b was calculated based on monomer units. A 5 mg / 5 ml solution of poly-4b (3.9 mM) in DMSO or chloroform was prepared in a 5 ml flask equipped with a stopcock and the initial absorption and CD spectra were recorded using a 0.05 cm quartz cell. Aliquots amounting 2 ml of the poly-4b solution were transferred to two flasks equipped with a stopcock. Increasing amounts of (R)- or (S)-acid were directly added to the flasks, and the absorption and CD spectra were taken for each addition of the acid.

RESULTS AND DISCUSSION

Synthesis of Poly-4b and Interaction with Chiral Acids

Poly-4b was quantitatively obtained by the polymerization of 4b with $[\text{Rh}(\text{nbd})\text{Cl}]_2$ in THF at 30°C . The resulting yellow polymer was soluble in DMSO, chloroform, and THF, and partially soluble in toluene and benzene. The molecular weight (M_n) of poly-4b was estimated to be 1.0×10^5 as determined by GPC using DMSO as the eluent. The ^1H NMR spectrum of poly-4b in CDCl_3 showed a sharp singlet centered at 5.85 ppm, due to the main chain proton, indicating that the polymer possesses a highly *cis-transoidal*, stereoregular structure.¹³

CD spectra of poly-4b in the presence of optically active acids including mandelic acid (6), 1-phenylpropionic acid (7),

and 1-phenylbutanoic acid (8) were measured in order to investigate the possibility if the polymer responds to chiral acids, thus showing a characteristic ICD change (helix—helix transition) as seen in the case of poly-4a. Figure 1 shows the changes in the ICD of poly-4b in the presence of (R)-6 in dry DMSO. The ICD patterns of poly-4a and poly-4b were reversed in DMSO. The reason is not clear at present, but the change in hydrogen bonding ability of poly-4b due to the substituted *N*-methyl group may be critical for the formation of a helical structure with an opposite helix—sense. The intensity of ICD decreased with an increase in the concentration of (R)-6. These changes in the ICDs were accompanied by slight changes in the UV—visible absorption spectra; a peak around 400 nm in the UV—visible spectrum of poly-4b slightly shifted to a longer wavelength by ca. 10 nm in the presence of 100—fold 6. Similar ICD changes of poly-4b were also observed in the presence of excess (S)-6. However, in contrast with poly-4a,¹⁰ significant differences between the ICD changes in the presence of (R)- or (S)-6 and a helix—helix transition were not found in the complexation of poly-4b with (R)- or (S)-6. In DMSO, the CD spectra of poly-4b hardly changed even in the presence of 100—fold (R)- or (S)-7. Relatively weaker basicity of the *N*-substituted ephedrine residue (tertiary amine) of poly-4b than that of the *N*-substituted norephedrine residues (secondary amine) of poly-4a must be responsible for the different response to chiral acids.⁷

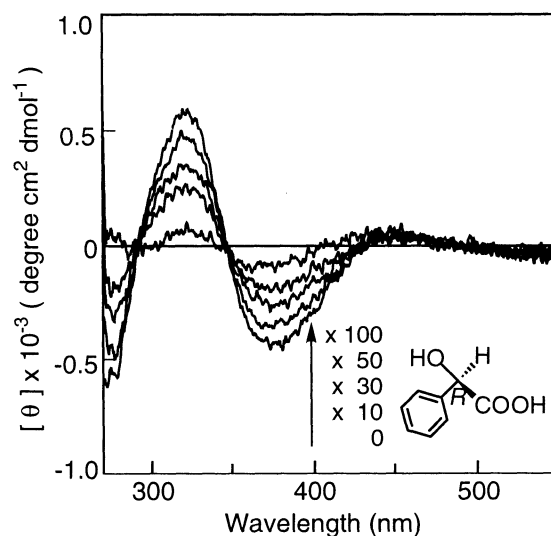
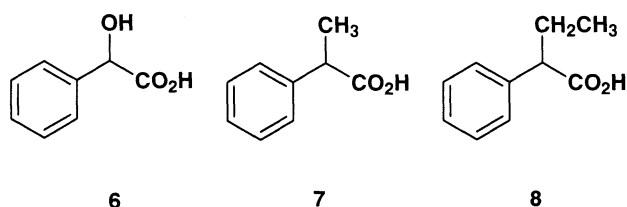


Figure 1. CD spectral changes of poly-4b with (R)- or (S)-mandelic acid (6) in DMSO.



In chloroform, however, poly-4b exhibited a helix—helix transition upon complexation with a relatively small amount of chiral carboxylic acids such as 7 and 8, although both enantiomers of the chiral acids gave rise to the transition independent of the absolute configuration. A similar helix—helix transition was observed in the complexation of

poly-**4a** with **7** and **8**.¹⁰ However, in these cases only acids with an *R* configuration brought about the helix—helix transition. In polar DMSO, ion association between poly-**4** and carboxylic acids is weak and a hydrogen bonded ion-pair may be predominant, and large excess acids may be necessary to bring about the helix—helix transition, while in less polar chloroform, ion association might be strong enough to give rise to the helix—helix transition with small amount of acids.

Asymmetric Alkylation of Benzaldehyde with the Complexes of Poly-**4b** and **5** with Dialkylzincs

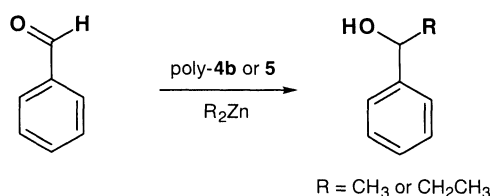
Poly-**4b** was used as an optically active catalyst for enantioselective addition of dialkylzincs to benzaldehyde, since the complexes of monomeric ephedrine derivatives and polystyrene—bound *N*-alkylnorephedrine with dialkylzincs have been known as highly enantioselective reagents to aldehydes.¹¹ We anticipated that poly-**4b** might show better enantioselectivity than the corresponding monomeric catalyst because poly-**4b** has a predominantly one—handed helical structure which may improve the enantioselectivity.¹⁴ Table I shows the results of the enantioselective addition of dialkylzincs to benzaldehyde using poly-**4b** and the model compound **5** as catalysts.

Table I. Enantioselective addition of R₂Zn to benzaldehyde using poly-**4b** and **5** as catalysts

Run	Catalyst ^a	R	Temp °C	Time h	Yield ^b %	%ee ^c	Confign
1	Poly- 4b	Et	25	24	88	45	R
2	5	Et	25	24	100	80	R
3	no	Et	25	24	53	0	—
4	Poly- 4b	Et	30	2	59	47	R
5	Poly- 4b ^d	Et	30	2	80	49	R
6	5	Et	30	2	98	80	R
7	no	Et	30	2	10	0	—
8	Poly- 4b	Et	0	6	27	30	R
9	5	Et	0	6	95	80	R
10	no	Et	0	6	8	0	—
11	Poly- 4b ^e	Me	30	42	84	9	R
12	5	Me	30	42	60	28	R
13	no	Me	30	42	9	0	—

^a Reactions were run in hexane in the presence of 10 mol% of chiral catalysts. ^b Determined by ¹H NMR. ^c Determined by chiral HPLC analysis using a chiral column (Chiralcel OD); UV detector (254 nm); eluent, *n*-hexane / 2-propanol 99:1 (v/v); flow rate, 1.0 ml min⁻¹.

^d Reaction was carried out in the presence of 30 mol% of chiral catalysts. ^e Reaction was carried out in the presence of 20 mol% of chiral catalyst.



Enantiomeric excess of 1-phenylethanol obtained by the reaction of benzaldehyde with diethylzinc in the presence of catalytic amount of poly-**4b** was 30—49%, while **5** exhibited better enantioselectivity (up to 80%ee). Soai and coworkers reported that the catalysts derived from polystyrene-bound *N*-substituted ephedrine afforded 1-phenylethanol of up to 89%ee.^{11b} These results indicate that the helical chirality of poly-**4b** may bring about a negative effect in the present asymmetric reaction. Further applications of the catalyst to other asymmetric reactions are in progress.

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