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Cyclopolymerization of Amino Acid-Based Diynes and Properties of the Obtained Polymers. Chiral Recognition and Metal Ion Extraction

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Summary

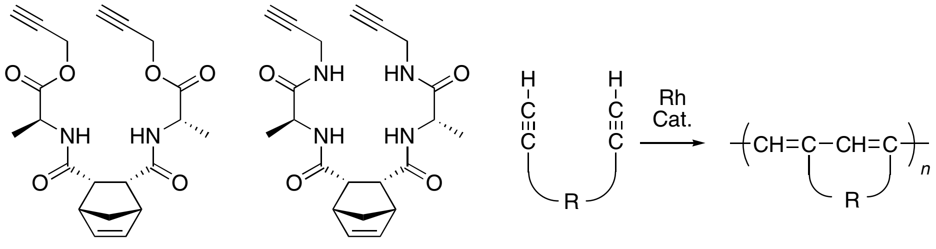
Cyclopolymerization of amino acid-derived novel dipropargyl ester and dipropargylamide was carried out using a rhodium catalyst. Polymers with cyclized structures were obtained under certain conditions. The dipropargylamide polymer exhibited a large specific rotation and an intense Cotton effect around 300 nm based on the chiral higher order structure. It adsorbed *N*-benzyloxycarbonyl-L-alanine more than the D-isomer, and extracted Li^+, Na^+, K^+, and Cs^+ from water phase into CH_2Cl_2 phase.

Introduction

Amino acids are constituents of proteins, typical biological polymers, and are not only biologically important but also are useful substances for chiral auxiliaries and building blocks in organic synthesis. Amino acid-based synthetic polymers show biocompatibility and biodegradability similarly to polypeptides. They are expected as drug delivery materials, chiral recognition materials, and polymer catalysts for asymmetric organic synthesis [1,2]. We have synthesized a series of amino acid-based polyacetylenes by the polymerization of the corresponding *N*-propargylamides catalyzed with a rhodium complex [3–14]. The formed polymers take a helical conformation in solution, whose sense, tightness, and stability depend on the structures of the amino acid pendants. Some of the polymers undergo helix-helix or helix-coil transition with external-stimuli such as solvent, heat, light, and pH. Intramolecular hydrogen bonding between the amide groups plays an important role in stabilizing the helical conformation [15].

Meanwhile, cyclopolymerization of bifunctional monomers is a powerful tool to obtain polymers carrying macrocycles adjacent to the polymer main chains [16–21]. They are applicable to molecular recognition materials, some of which can distinguish chiral compounds from the enantiomers [22]. Cyclopolymerization of diyne derivatives gathers much attention, because the formed π-conjugated polymers show interesting features including electrical, optical, and liquid crystalline properties [16].

The present article deals with polymerization of amino acid-based optically active novel diynes **1** and **2** (Scheme 1), and examination of the chiral recognition and metal-extracting properties of the formed polymers.



1 **2**

Scheme 1. Polymerization of **1** and **2**.

Experimental

Measurements

^{1}H and ^{13}C NMR spectra were recorded in chloroform-*d* ($CDCl_3$) on a JEOL EX-400 spectrometer. IR spectra were measured using a Shimadzu FTIR-8100 spectrophotometer. Elemental analysis was done at the Kyoto University Elemental Analysis Center. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-100 digital polarimeter with a sodium lamp as a light source. The number- and weight-average molecular weights (M_n and M_w) of polymers were determined by gel permeation chromatography (GPC) on a JASCO Gulliver system (PU-980, CO-965, RI-930, and UV-1570) equipped with polystyrene gel columns (Shodex columns K804, K805, and J806), using THF as an eluent at a flow rate of 1.0 mL/min, calibrated by polystyrene standards at 40 °C. CD and UV-vis spectra were measured in a quartz cell (thickness: 1 cm) using a JASCO J-800 spectropolarimeter.

Materials

All the reagents in monomer synthesis were used as purchased without purification. (nbd)$Rh^+[\eta^6\text{-}C_6H_5B^-(C_6H_5)_3]$ (nbd = 2,5-norbornadiene) [23] and *N*-(*tert*-butoxycarbonyl)-L-alanine *N'*-propargylamide [3] were synthesized according to the literature. Solvents used for polymerization were distilled by the standard procedure.

*Synthesis of **1***

$SOCl_2$ (67 mL, 920 mmol) was added to a mixture of L-alanine (25 g, 280 mmol) and propargyl alcohol (200 mL, 3440 mmol) at -10 °C, and the resulting mixture was stirred at room temperature for 24 h. Residual propargyl alcohol was removed by evaporation, and the residue was purified by recrystallization from ether to obtain L-alanine propargyl ester hydrochloride. Yield 10 g (22%). Et_3N (15.4 g, 152 mmol) was added to a solution of L-alanine propargyl ester hydrochloride (4.98 g, 30.5 mmol) and *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (5.00 g, 30.5 mmol) in CH_2Cl_2, and the resulting mixture was stirred at room temperature overnight. After that, L-alanine propargyl ester (4.98 g, 30.5 mmol), 1-(3-dimethylaminopropyl)-3-

ethylcarbodiimide hydrochloride (EDC•HCl, 6.32 g, 33.0 mmol), and 4-(dimethylamino)pyridine (0.37 g, 3.00 mmol) were added to the mixture, and then Et_3N (3.03 g, 30.0 mmol) was added at 0 °C. After the reaction mixture was stirred at room temperature for 3 h, it was washed with 1 M HCl, saturated aq. $NaHCO_3$, and saturated aq. NaCl subsequently. The organic layer was dried over anhydrous $MgSO_4$, and concentrated by rotary evaporation. The residual mass was purified by silica gel column chromatography eluted with hexane/ethyl acetate = 5/1 (volume ratio) to obtain **1**. Yield 7.93 g, yield 65%. $[\alpha]_D = -11°$ (c = 0.1 g/dL, THF). IR (neat): 3287 ($\nu_{\equiv C\text{-}H}$), 2130 ($\nu_{C\equiv C}$), 1755, 1661, 1196, 1015 cm^{-1}. ^1H NMR (400 MHz, δ in ppm, $CDCl_3$): 1.38 (d, J=6.4 Hz, 6H), 1.48 (t, J=7.9 Hz, 1H), 1.82 (s, 1H), 2.49 (s, 2H), 3.15–3.16 (m, 2H), 3.27–3.30 (m, 2H), 4.45–4.66 (m, 2H), 4.68–4.72 (m, 4H), 6.45–6.50 (m, 2H), 6.67 (d, J=4.7 Hz, 1H), 6.72 (d, J=2.1 Hz, 1H). ^{13}C NMR (100 MHz, δ in ppm, $CDCl_3$): 18.25, 48.40, 49.12, 50.03, 52.02, 53.40, 76.11, 77.98, 136.42, 172.80, 173.27. Anal. Calcd for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00. Found: C, 62.80; H, 5.99; N, 6.84.

Synthesis of ***2***

Trifluoroacetic acid (TFA, 50 mL, 673 mmol) was added to a solution of *N*-(*tert*-butoxycarbonyl)-L-alanine *N'*-propargylamide (19.9 g, 88.2 mmol) in CH_2Cl_2 (250 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. Then, TFA was evaporated off under a reduced pressure to obtain crude L-alanine *N'*-propargylamide•TFA salt. Monomer **2** was synthesized by the reaction of *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride with crude L-alanine *N'*-propargylamide•TFA salt in a manner similar to **1**. It was purified by silica gel column chromatography eluted with ethyl acetate/ethanol = 1/1 (volume ratio). Yield 28%. $[\alpha]_D = -26°$ (c = 0.1 g/dL, THF). IR (neat): 3258 ($\nu_{\equiv C\text{-}H}$), 2122 ($\nu_{C\equiv C}$), 1701, 1659, 1541, 1202 cm^{-1}. ^1H NMR (400 MHz, δ in ppm, $CDCl_3$): 1.47 (d, J=5.2 Hz, 6H), 1.66–1.75 (m, 2H), 2.26 (s, 2H), 3.33–3.34 (m, 2H), 3.45 (broad s, 2H), 4.02–4.07 (m, 4H), 4.62 (q, J=2.2 Hz, 2H), 6.04 (s, 1H), 6.21 (d, J=2.4 Hz, 1H), 6.25 (d, J=2.4 Hz, 2H), 7.26 (broad s, 2H). ^{13}C NMR (100 MHz, δ in ppm, $CDCl_3$): 14.52, 29.73, 46.07, 49.73, 52.70, 72.37, 77.34, 79.18, 135.00, 168.65, 177.35. Anal. Calcd for $C_{21}H_{26}N_4O_4$: C, 63.30; H, 6.58, N; 14.06. Found: C, 63.12; H, 6.51; N, 14.21.

Polymerization

All the polymerizations were carried out in a glass tube equipped with a three-way stopcock under nitrogen. $(nbd)Rh^+[\eta^6\text{-}C_6H_5B^-(C_6H_5)_3]$ was added to a solution of a monomer in an appropriate solvent, and the resulting mixture was vigorously stirred. It was kept in a water bath at 30 °C for a set period. The resulting mixture was poured into a large amount of hexane to precipitate a polymer. When *N,N*-dimethylformamide (DMF) was used as the polymerization solvent, ether was used instead of hexane. The polymer precipitated was separated by filtration using a membrane filter (ADVANTEC H100A047A), and dried under reduced pressure.

Spectroscopic Data of the Polymers

Poly(**1**) IR (KBr): 1742, 1655, 1526, 1456, 750 cm^{-1}. ^1H–NMR (400 MHz, δ in ppm, $CDCl_3$): 0.99–1.36 (m), 3.13–3.17 (m), 4.48–4.50 (m), 4.72–4.79 (m), 6.45–6.52 (m), 6.62–6.68 (m). Poly(**2**) IR (KBr): 2964, 1701, 1623, 1527, 1385 cm^{-1}. ^{1}H NMR (400 MHz, δ in ppm, $CDCl_3$): 0.90 (broad s), 1.35 (broad s), 1.87 (broad s), 3.33 (broad s), 3.84 (broad s), 4.59 (broad s), 6.08 (broad s), 7.28 (broad s).

Chiral Recognition

Poly(**2**) (20 mg) was placed in a glass tube. The polymer was washed with a solution (1 mL) of hexane/2-propanol (80:20, volume ratio) three times. A solution (100 μL) of an adsorbate (10 g/L) and hexylbenzene (20 g/L) in hexane/2-propanol (80:20, volume ratio) to the polymer, and the resulting mixture was allowed to stand for 4 h. The aliquot (20 μL) of the solution was analyzed by HPLC with UV detection, eluted with THF. The residual amount of adsorbate was determined by the peak area ratio between the adsorbate and hexylbenzene before and after the experiment.

Extraction of Metal Ion

A solution (5 mL) of poly(**2**) (4.02×10^{-4} M) in CH_2Cl_2, and a solution (5 mL) of picric acid (8.82×10^{-5} M) and a metal hydroxide ($0.83–1.00 \times 10^{-3}$ M) in water were vigorously stirred at room temperature for 5 min. The UV-spectrum of the water phase was measured to determine the concentration of picric acid, and the amount of metal picrate extracted from water phase into CH_2Cl_2 phase was calculated.

Results and discussion

Table 1 summarizes the conditions and results of the polymerizations of diyne monomers **1** and **2** catalyzed with $(nbd)Rh^+[\eta^6\text{-}C_6H_5B^-(C_6H_5)_3]$ in CH_2Cl_2, THF, and DMF. When the polymerization of **1** was carried out in CH_2Cl_2 and THF with the initial monomer concentration ($[M]_0$) ≥ 0.05 M, solvent-insoluble gels were obtained (runs 2, 4, and 5). It is supposed that crosslinking reaction of the bifunctional monomer took place under these conditions. On the other hand, solvent-soluble products were obtained by lowering $[M]_0$ to 0.02 M, but the M_n was as low as 500 (runs 1 and 3). When the polymerization of **1** was carried out in DMF, solvent-soluble products were obtained irrespective of $[M]_0$, but the M_n was low in every case (runs 6–8). When the polymerization of **2** was carried out in CH_2Cl_2 with $[M]_0 = 0.1$ M for 24 h, a solvent-soluble polymer with the M_n of 15000 was successfully obtained (run 11). Decrease of $[M]_0$ and time resulted in decrease of the polymer yield and M_n (runs 9 and 10). Both amino acid-derived propargyl ester and *N*-propargylamide exhibit sufficient polymerizability when the Rh complex is used as a catalyst [3]. Monomer **2** possibly forms intramolecular hydrogen bonding between the two *N*-propargylamide moieties, which leads to the conformation favorable for cyclopolymerization. On the other hand, one cannot expect such effect in the polymerization of **1**. It seems that no intramolecular interaction around the propargyl groups resulted in gel formation in the polymerization of **1**.

The structures of the polymers were examined by ^{1}H NMR and IR spectroscopies [24]. No signal and absorption based on the ethynyl group were observed in the spectra of the polymers, which indicates that the ethynyl groups quantitatively converted. Judging from the good solubility and single modal GPC traces of poly(**2**), it can be considered that no gelation but cyclopolymerization took place to give the polymers with moderate molecular weights under the conditions in runs 9, 11, and 12, whose structure is illustrated in Scheme 1. It is likely that poly(**1**) obtained in runs 1, 3, and 6–8 is also a cyclized polymer, but the molecular weight was low compared to poly(**2**). As listed in Table 1, poly(**2**) exhibited much larger $[\alpha]_D$ than that of **2** ($[\alpha]_D$ = –26°). Poly(**2**) showed an intense Cotton effect in the CD spectrum around 300 nm, presumably based on the conjugated polyactylene backbone (Figure 1). Poly(**2**) seems to take a chiral higher order structure such as a helix with predominantly one-handed screw sense.

Table 1. Polymerization of **1** and **2**[a].

Run	Monomer	Solvent	Conc (M)	Time (h)	Yield[b] (%)	M_n[c]	M_w/M_n[c]	$[\alpha]_D$[d] (°)
1	**1**	CH_2Cl_2	0.02	24	62	500	1.32	+8.8
2	**1**	CH_2Cl_2	0.2	24	quant	gel		
3	**1**	THF	0.02	24	60	500	1.52	
4	**1**	THF	0.05	24	73	gel		
5	**1**	THF	0.1	24	81	gel		
6	**1**	DMF	0.02	24	8	400	1.65	
7	**1**	DMF	0.05	24	31	700	1.35	
8	**1**	DMF	0.1	24	16	500	1.41	
9	**2**	CH_2Cl_2	0.08	24	45	3700	1.19	-284
10	**2**	CH_2Cl_2	0.1	1	55	300	1.12	
11	**2**	CH_2Cl_2	0.1	24	91	15000	1.56	-352
12	**2**	THF	0.1	24	68	8000	1.78	

[a] Conditions: catalyst (nbd)Rh$^+$[η^6-$C_6H_5B^-(C_6H_5)_3$], $[M]_0/[cat] = 50$, 30 °C. [b] Hexane- or ether-insoluble part. [c] Determined by GPC (THF, PSt). [d] Measured by polarimetry in THF at r.t., c = 0.1 g/dL.

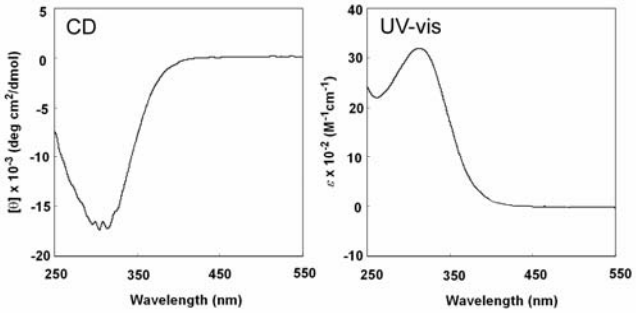


Figure 1. CD and UV-vis spectra of poly(**2**) measured in THF.

We next examined the chiral recognition ability of poly(**2**). *N*-Benzyloxycarbonyl L- and D-alanines (Z-L-Ala-OH and Z-D-Ala-OH) and the methyl esters (Z-L-Ala-OMe and Z-D-Ala-OMe) were used as adsorbates. As summarized in Table 2 [25], poly(**2**) adsorbed Z-L-Ala-OH much more than Z-D-Ala-OH. On the other hand, poly(**2**) exhibited no such apparent selectivity toward Z-L-Ala-OMe and Z-D-Ala-OMe. We measured the CD spectrum of poly(**2**) in the presence of Z-L-Ala-OH to find that the spectroscopic pattern slightly changed compared to the case in the absence of Z- L-Ala-OH. It seems that the interaction exists between the polymer and Z-L-Ala-OH, but it is not strong.

Table 2. Adsorption of L-and D-alanine derivatives to poly(**2**).

Adsorbate	Ratio of Adsorption[a] (%)
Z-L-Ala-OH	63
Z-D-Ala-OH	7
Z-L-Ala-OMe	50
Z-D-Ala-OMe	60

[a] $[1 - ([\text{adsorbate}]_{\text{after}} / [\text{hexylbenzene}]_{\text{after}}) / ([\text{adsorbate}]_{\text{before}} / [\text{hexylbenzene}]_{\text{before}})] \times 100$. The concentrations of adsorbates and hexylbenzene (internal standard) were determined by HPLC.

Extraction of metal ion from water is an issue of great importance in environmental chemistry. A wide variety of polymers carrying metal-coordinating groups have been examined for this purpose, which include sulfoxyl, carboxyl, ammonium, amino, hydroxyl, ester, ether, and amide-containing polymers [26,27]. The polymers in the present study are expected to show metal-extraction ability, because the cyclic structures containing amide groups possibly coordinate metals. We examined the extraction of several metal ions using poly(**2**). Metal hydroxides were dissolved in water, and the degree of extraction was estimated by the decrease of picric acid in the water phase. As summarized in Table 3, poly(**2**) extracted Li^+, Na^+, K^+, and Cs^+ as the corresponding picrate from the water phase. Li^+ was extracted most efficiently among the metal ions examined, presumably because the small ionic radius matched the size of binding site of the polymer.

Table 3. Extraction of metal picrates with poly(**2**) from water phase into CH_2Cl_2 phase.

Metal Ion	Degree of Extraction[a] (%)	Metal Ion	Degree of Extraction[a] (%)
Li^+	8.6	Cs^+	3.6
Na^+	1.2	Ca^{2+}	< 1
K^+	5.9	Ba^{2+}	< 1
Rb^+	< 1		

[a] Determined by UV-vis absorption at 354 nm based on metal picrate, which remained in water phase. [picric acid] = 8.82×10^{-5} M, [metal hydroxide] = $0.83–1.00 \times 10^{-3}$ M, [poly(**2**)] = 4.02×10^{-4} M/repeating unit.

In summary, we demonstrated the rhodium-catalyzed cyclopolymerization of novel dipropargyl ester and dipropargylamide **1** and **2**. Polymers with cyclized structures were successfully obtained when the polymerization was carried out under diluted conditions. Poly(**2**) was supposed to take a higher order structure, and it exhibited chiral recognition and metal ion-extracting abilities.

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