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J. Kadokawa[a]; K. Tawa[a]; M. Suenaga[a]; Y. Kaneko[a]; M. Tabata[b]
[a] Department of Nano-structured and Advanced Materials, Graduate School of Science and Engineering, Korimoto, Kagoshima, Japan [b] Department of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo, Japan

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Polymerization and Copolymerization of a New *N*-Propargylamide Monomer Having a Pendant Galactose Residue to Produce Sugar-Carrying Poly(*N*-propargylamide)s

J. KADOKAWA,[1] K. TAWA,[1] M. SUENAGA,[1] Y. KANEKO,[1] AND M. TABATA[2]

[1]Department of Nano-structured and Advanced Materials, Graduate School of Science and Engineering, Korimoto, Kagoshima, Japan
[2]Department of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo, Japan

Rh-catalyzed polymerization of a new N-propargylamide monomer having a galactose residue was investigated. The polymerization proceeded in a mixed solvent of THF and water to produce the galactose-carrying poly(N-propargylamide) consisting of cis-isomer. The copolymerization of the monomer with the N-propargylamide having the alkyl chain was also carried out.

Keywords conjugated polymers, polyacetylenes, water-soluble polymers

Introduction

Research concerning conjugated polymers, such as polyacetylene, polypyrrole, and polyphenylene, has attracted much attention because of the various practical applications of their interesting electrical and optical properties (1). Moreover, the relative regular higher-ordered structures in the conjugated polymers have often been constructed due to the rigid-rod natures of their main-chains. Recently, polymerization of monosubstituted acetylene derivatives has been widely investigated using Rh complex catalysts (2), which enables stereoselectively to give the corresponding polyacetylenes of the *cis*-isomers.

On the other hand, polymers having sugar residues, i.e., "glycopolymers", have been interesting as new polymeric materials, because of their possible applications for biological functions based on specific molecular and cell recognition abilities (3). So far, a number of such glycopolymers have been synthesized, which are composed of various organic polymeric main chains combined with a variety of sugar-residues. For example, lactose–containing polystyrene was prepared to be useful for the culture substrate of hepatocytes with asialoglycoprotein receptors (4). In the polymer, the galactose residues of the lactose side chains probably act as an important role for the functions. However, it is

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Address correspondence to J. Kadokawa, Department of Nano-structured and Advanced Materials, Graduate School of Science and Engineering, Korimoto, Kagoshima 890-0065, Japan. Fax: (+81)99-285-3253; E-mail: kadokawa@eng.kagoshima-u.ac.jp

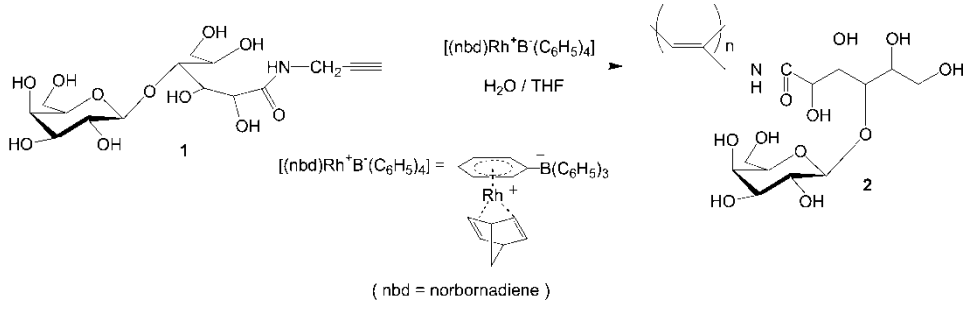
difficult for the glycopolymers to keep the three-dimensional arrays of the sugar-residues because of a flexible nature of the common polymer main-chains. It has been pointed out that the relative spatial compatibility of sugar-residues is important for molecular recognition in addition to their structural compatibility (5, 6). Controlling the three-dimensional arrays of sugar-residues in the glycopolymers would give the relative spatial compatibility, leading to recognition of specific cell receptors.

From the above viewpoints, the synthesis of sugar-containing conjugated polymers would be a promising research topic to control the three-dimensional arrays of sugar-residues affected by their regular higher-ordered structures, providing possible interesting and new type of biopolymeric materials. Previously, some works for production of sugar-containing conjugated polymers have been studied, examples of polythiophene (7), poly(*p*-phenylene ethynylene) (8), polyisocyanide (9), and polyaniline (10). The polyacetylenes having pendant sugar residues such as cyclodextrin and lactose were also synthesized (11, 12). In these studies, the poly(phenylacetylene) structure was employed as a main-chain, implying that the sugar residues were connected to the polyacetylene backbone through the phenylene groups. Since we have been interested in the effect of the sugar side-chains like the chirality toward the higher-ordered structures of the conjugated glycopolymers, in addition to controlling the three-dimensional arrays of the sugar residues, we are attempting to synthesize the polyacetylene derivatives which have the main-chain structures directly carrying the sugar residues. To prepare such structured polyacetylenes, we investigated the polymerization of a *N*-progargylamide monomer having a sugar residue, giving a new glyco-polyacetylene. Because the polymerization of the *N*-propargylamide monomers having various substituted groups using Rh catalyst have widely been reported to produce the corresponding poly(*N*-propargylamide) derivatives with *cis*-isomers (13). In this paper, we would like to report the polymerization of the *N*-propargylamide monomer (**1**) having a galactose residue using Rh catalyst to give the galactose-carrying poly(*N*-propargylamide) (**2**) (Scheme 1). Furthermore, copolymerizability of **1** was investigated by the copolymerization with *N*-propargylpentanamide (**3**) (Scheme 3).

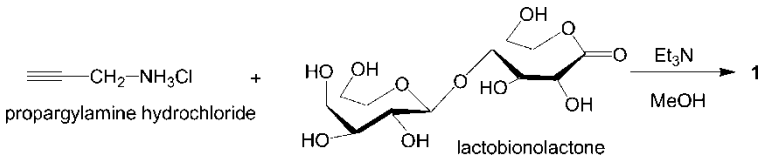
Experimental

Materials

Monomer **3** and catalyst, (nbd)$Rh^{+}B^{-}(C_6H_5)_4$, were prepared according to the literature (14, 15). THF of the polymerization solvent was purified by distillation. Other reagents and solvents were used without further purification.



Scheme 1. Polymerization of monomer **1**.



Scheme 2. Synthesis of monomer **1**.

Synthesis of Monomer 1

The synthesis of monomer **1** was carried out according to Scheme 2 (16). Lactobionolactone (16) (6.00 mmol) was first dissolved by slightly warming up in methanol, and propargylamine hydrochloride (9.60 mmol) and triethylamine (7.80 mmol) were added to the solution at room temperature. The mixture was stirred for 1 h, concentrated by evaporation, and dried under the reduced pressure. The residue was subjected by a column chromatography on silica gel using chloroform and methanol (3:1, vol/vol) as an eluent. For further purification of the monomer, the fractions containing the products were collected and concentrated under the reduced pressure until the solution became turbid. The precipitate was filtrated and dried *in vacuo* to give monomer **1** (3.43 mmol) in 57.2% yield. The structure of **1** was established by the following analytical data; ^{1}H-NMR (D_2O); δ 2.59 (t, $J = 2.6$ Hz, H-C≡C, 1 H), 3.56–4.00 (m, -C*H*(*O*-D-gal)-C*H*(OH)-C*H*$_2$OH, H2-H6 of D-gal, 10 H), 4.04 (m, ≡ CCH$_2$–, 2 H), 4.19 (t, $J = 3.0$ Hz, C(=O)CH(OH)C*H*(OH)-, 1 H), 4.43 (d, $J = 3.0$ Hz, C(=O)C*H*(OH)-, 1 H), 4.56 (d, $J = 7.2$ Hz, H1(β) of D-gal, 1 H); ^{13}C-NMR (D_2O); δ 28.9 (C*C*H$_2$-), 61.4, 62.3 (CH$_2$OH), 69.0 (H-C≡), 61.4, 62.3, 70.7–72.9, 75.7 (O=C-*C*H-*C*H-, -CH-CH$_2$OH, C2–C6 of D-gal), 79.8 (H-C≡*C*-), 81.1 (CH(*O*-D-gal)), 103.8 (C1 of D-gal), 174.5 (C=O).

Typical Procedure for Polymerization of 1

A typical polymerization procedure was as follows (run 3 in Table 1). Under argon, a solution of catalyst (0.0051 g, 0.010 mmol) in THF (1.8 mL) was added to a solution of **1** (0.079 g, 0.20 mmol) in water (0.20 mL) at 25°C and the mixture was stirred for

Table 1
Polymerization of **1** by Rh catalyst in THF-water solvent

Run	[Catalyst]/[1]	temp (°C)	Time (h)	Yield (%)[a]	M_n[b] M_w/M_n[b]	$[\alpha]_D$	(deg)[c]
1	0.02	25	6	0			
2	0.05	2	26	0			
3	0.05	25	0.25	48.4	10200	1.44	+86.0
4	0.05	25	1	66.2	12600	1.55	+80.8
5	0.05	50	0.25	65.4	9400	1.41	+73.1
6	0.1	25	0.25	41.8	10700	1.47	+63.5

[a]Methanol-insoluble fraction.
[b]Determined by GPC with water as eluent using pullulan standards.
[c]Measured by polarimetry in water, $c = 1.0$ g/dL at 25°.

15 min at that temperature. The resulting solution was poured into acetone (80 mL) to precipitate the product, which was isolated by filtration. The material was collected and treated with methanol for 5 h at reflux temperature. The insoluble fraction was filtered and dissolved in a small amount of water. The solution was poured into methanol (80 mL) to precipitate the polymeric product. The product was isolated by filtration and dried under the reduced pressure to give polymer **2** (0.038 g) in 48.4% yield. ^{1}H-NMR (D_2O); δ 3.0–4.1 (-C*H*(*O*-D-gal)-C*H*(OH)-CH_2OH, =CCH_{2-}, H2-H6 of D-gal, 12 H), 4.22 (C(=O)CH(OH)C*H*(OH)-, 1 H), 4.44 (C(=O)C*H*(OH)-, 1 H), 4.57 (H1(β) of D-gal, 1 H), 6.22 (-CH=C-, 1 H); ^{13}C-NMR (D_2O); δ 44.9 (=C*C*H_{2-}), 61.5, 62.3, 69.0–75.7 (O=C-*C*H-*C*H-, -CH-CH_2OH, C2–C6 of D-gal), 81.8 (CH(*O*-D-gal)), 103.8 (C1 of D-gal), 126.2 (-CH=), 136.7 (-CH=*C*-), 174.3 (C=O).

Typical Procedure for Copolymerization of 1 with 3

A typical copolymerization procedure was as follows (run 2 in Table 2). Under argon, a solution of **3** (0.019 g, 0.12 mmol) in THF (0.90 mL) and a solution of catalyst (0.0083 g, 0.016 mmol) in THF (0.90 mL) were added to a solution of **1** (0.079 g, 0.20 mmol) in water (0.20 mL) in this order at 30°C. After the mixture was stirred at that temperature for 120 min, the precipitated fraction was isolated by decantation and washed with a mixed solution of THF and water (9:1). The product was dried under the reduced pressure to give copolymer **4** (0.076 g) in 77.1% yield. ^{1}H-NMR (D_2O); δ 0.733 (CH_3), 1.14 ($CH_3CH_2CH_2$), 1.45 (CH_2CH_2C=O), 2.08 (CH_2C=O), 3.0–4.0 (-C*H*(*O*-D-gal)-C*H*(OH)-CH_2OH, =CCH_{2-}, H2-H6 of D-gal), 4.07 (C(=O)CH(OH)C*H*(OH)-), 4.28 (C(=O)C*H*(OH)-), 4.41 (H1(β) of D-gal), 6.06 (-CH=C-).

Measurements

NMR spectra were recorded on a JEOL ECA 600 spectrometer. Optical Rotations were measured with a Jasco P-1030 digital polarimeter. Gel permeation chromatographic (GPC) analyses were performed by using a TOSOH 8012 with RI detector under the following conditions: Shodex Asahipak GF-310HQ column with water as the eluent at a flow rate of 0.5 mL/min. The calibration curve was obtained using pullulan

Table 2
Copolymerization of **1** with **3** by Rh catalyst in THF-water solvent[a]

Run	Feed ratio ([1] : [3])	Yield (%)[b]	Unit ratio[c] ([1] : [3])	M_n[d]	M_w/M_n[d]	$[\alpha]_D$ (deg)[e]
1	1:0.20	84.2	1:0.15	5600	1.52	+68.9
2	1:0.60	77.1	1:0.26	5400	1.54	+71.2
3	1:1	68.7	1:0.39	4600	1.58	+55.6
4	1:1.5	58.1	1:0.44	7600	1.53	+54.0[f]

[a][catalyst]/[**1** + **3**] = 0.05, reaction temperature; 30°C, reaction time; 2 h.
[b]Precipitated fraction from reaction mixture.
[c]Determined by integrated ratio in the ^{1}H-NMR spectrum.
[d]Determined by GPC with water as eluent using pullulan standards.
[e]Measured by polarimetry in water, c = 1.0 g/dL at 25°C.
[f]c = 0.5 g/dL at 25°C.

standards. CD and UV-Vis spectra were measured in a quartz cell (thickness 1 cm) at room temperature using a Jasco J-820 spectropolarimeter and Shimadzu UV160A spectrophotometer, respectively.

Results and Discussion

Polymerization of 1

When we briefly examined the polymerization of **1** under some conditions, the reaction proceeded smoothly at around 25–50°C using (nbd)$Rh^{+}B^{-}(C_6H_5)_4$ as the catalyst in a mixed solvent of THF and water (9:1, vol/vol). This result showed that the polymerization took place without protection of the sugar hydroxy groups in aqueous solvent. However, the ^{1}H-NMR spectrum (D_2O) of the acetone-insoluble fraction of the product indicated formation of not only the polymeric material, but also some aromatic compound. Although the structure of this side product has not yet been clear, one of the possible structures for it is a cyclic trimer, which can be formed by the cyclization of **1**. The side product was separated off by the treatment with methanol at reflux temperature, followed by reprecipitation, to isolate the polymer. The purified polymer was soluble in water, but insoluble in any organic solvents. The structure of the product polymer was confirmed by the ^{1}H-and ^{13}C-NMR spectra measured in D_2O solvent. The assignments of the NMR signals were determined by reference to the previous literature (6, 16, 17).

Figure 1 shows the ^{1}H-NMR spectrum (D_2O) of the polymer. In addition to signals due to the sugar and the methylene (═CC*H*$_2$NHC═O) protons, a signal **a** ascribed to the main-chain proton of -CH═C- is observed at δ 6.22. The chemical shift of this signal realistically corresponds to the *cis*-isomer and the integrated ratio of this *cis*-signal **a** to the signal **b** due to the H1 of the galactose residues is ca. 1:1. Furthermore, there is no signal due to *trans*-isomer at the lower magnetic field than the *cis*-signal. The NMR data support the structure **2** of the product polymer, which is mainly composed of *cis*-isomer.

The ^{13}C-NMR spectrum of the same sample is shown in Figure 2. The four signals **h**, **c**, **b**, and **a** assigned to the poly(*N*-propargylamide) structure of *cis*-isomer are observed at δ 44.9 (═C*C*H$_2$-), 126.2 (-CH═), 136.7 (-CH═*C*-), and 174.3 (C═O), respectively, in addition to the sugar signals. These ^{13}C-NMR data also support the structure **2**.

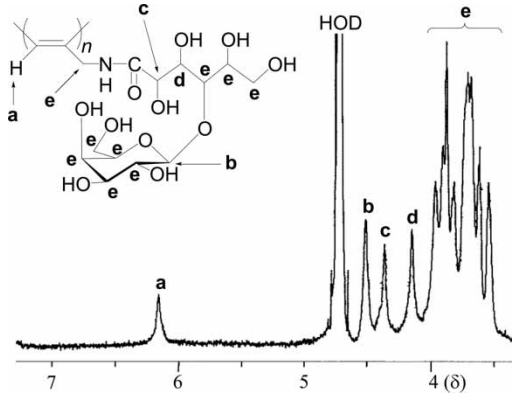


Figure 1. ^{1}H-NMR spectrum of product polymer **2** (D_2O)

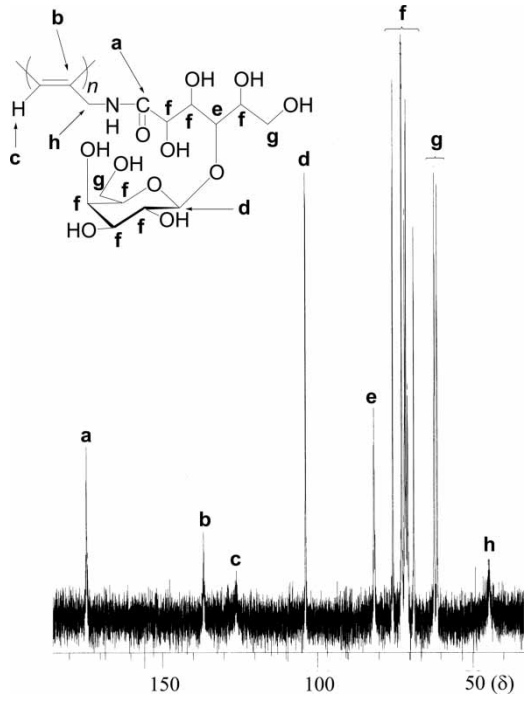


Figure 2. ^{13}C-NMR spectrum of product polymer **2** (D_2O).

Table 1 shows the selected results of the polymerization in a mixed solvent of THF and water. The polymerization took place using the catalyst of 5–10 mol% for the monomer at 25–50°C (run 3–6). The longer reaction time and higher temperature gave the polymers in higher yields (run 4 and 5). However, the polymerization did not proceed in the presence of the less amount of the catalyst than 5 mol% or at the temperature below 25°C even under the conditions of the longer reaction times (run 1 and 2). The M_n values were estimated by GPC measurement with water as the eluent using pullulan standards to be 9400–12600 with polydispersities of ca. 1.5. The optical rotations of the obtained polymers (+73.1–86.0°) were larger than those of **1** (+36.4°).

Figure 3 shows the CD and UV-Vis spectra of the polymer **2** in water at room temperature. In the CD spectrum, the positive Cotton effect is observed at 330 nm,

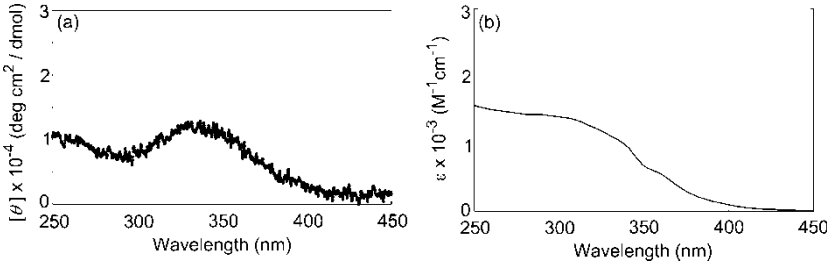


Figure 3. CD and UV-Vis spectra ((a) and (b) respectively) of product polymer **2** in water at room temperature ($c = 0.20$ mmol/L).

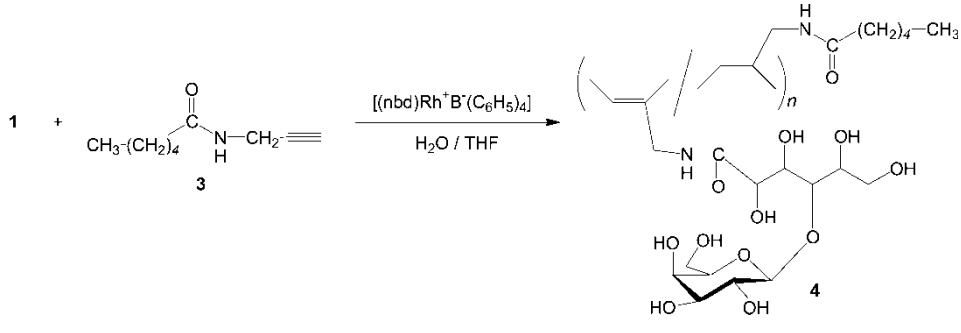
corresponding to the main-chain UV-Vis absorption. This indicates possibility for formation of a one-handed helical conformation in the main-chain of the polymer **2**. The detailed conformational study using the CD and UV-Vis spectroscopic methods under the various conditions is now in progress in our research group.

Copolymerization of 1 with 3

The copolymerizability of **1** was investigated by the copolymerization with the hydrophobic *N*-propargylamide monomer **3** (Scheme 3). The resulting polymers can be expected to have an amphiphilic nature and be soluble in organic solvents, depending on the composition of the hydrophilic unit **1** with the hydrophobic unit **3**. The reaction was carried out in the various feed ratios of **1** to **3** under the similar conditions to those of the homopolymerization of **1** as described above. The copolymerization required the longer reaction time to consume the monomers compared with the homopolymerization. The product was gradually precipitated from the reaction solution with the progress of the polymerization. Thus precipitated material was isolated by decantation or centrifugation and dried under reduced pressure to give the copolymer. Thus, the isolated copolymers did not contain the side products and had the enough purities without further purification procedures.

The ^{1}H-NMR spectrum of the product was shown in Figure 4. The both the signals due to the sugar protons and the alkyl protons are observed, indicating that the copolymerization of **1** with **3** proceeded to give the corresponding copolymer **4**. Furthermore, the structure of *cis*-isomer was supported by observation of the main-chain signal at δ 6.06. The unit ratio of the copolymer was calculated by the integrated ratio of the signals **b** and **c** to the methyl signal **i**.

The selected results of the copolymerization are listed in Table 2. The copolymerization proceeded in various feed ratios to give the corresponding copolymers in relatively high yields. The ratios of the units **3** in the copolymers increased with increasing the molar ratios of **3** in the feeds. However, the contents of the units **3** in the copolymers were always lower than those in the feeds. This is probably because that the fractions consisting of the relative higher contents of the units **3** were not precipitated from the reaction mixtures, and thus, which were lost during the isolation procedures. The M_n values were estimated by GPC measurement with water as the eluent to be 4600–7600 with polydispersities of ca. 1.5. The optical rotations of the obtained copolymers with the higher contents of the sugar residues (run 1 and 2) were larger than those with the lower contents of the sugar residues (run 3 and 4).



Scheme 3.

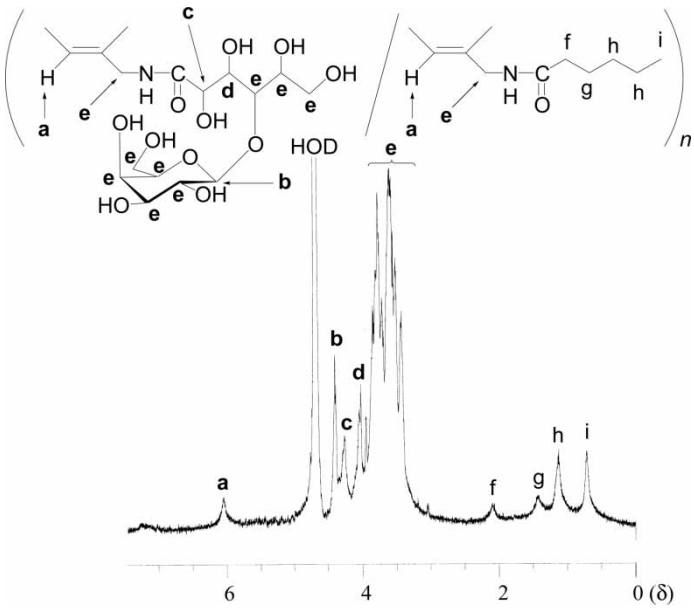


Figure 4. ^{1}H-NMR spectrum of product copolymer **4** obtained under the conditions of run 4 in Table 2 (D_2O).

The solubilities of copolymers **4** were listed in Table 3 in comparison with those of homopolymer **2**. As shown in this table, the copolymers were soluble in water and DMSO. In addition, the copolymers tend to be soluble in DMF, depending on the contents of the units **3** (run 2-4 in Table 2), but insoluble in other organic solvents such as methanol and chloroform.

Conclusion

We have synthesized the galactose-carrying poly(*N*-propargylamide) (**2**) by the polymerization of **1** using Rh catalyst. The polymerization proceeded by (nbd)$Rh^{+}B^{-}(C_6H_5)_4$ (5–10 mmol % for **1**) as the catalyst in a mixed solvent of THF and water (9:1) at 25–50°C. The isolated polymer had the structure **2** consisting of *cis*-isomer and was soluble in water. The copolymerization of **1** with the other *N*-propargylamide monomer

Table 3
Solubilities of **2** and **4** in various solvent[a]

Samples	Water	Methanol	DMSO	DMF	Chloroform
2	+	−	−	−	−
4 (run 1)	+	−	+	−	−
4 (run 2)	+	−	+	+−	−
4 (run 3)	+	−	+	+	−
4 (run 4)	+	−	+	+	−

[a]+: soluble, −: insoluble, +−: partly soluble.

3 took place under the similar conditions. The resulting copolymers were soluble in not only water but also DMSO. The present polymerization manner using the sugar-carrying *N*-propargylamide monomers will be applied to the synthesis of the polyacetylenes having various pendant sugar residues and glyco-chains in the future. A series of these glycopolymers can be expected for the applications to the recognition of specific cell receptors.

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