ORIGINAL ARTICLE

Cyclopolymerization of a bisacrylate through selective formation of a 19-membered ring

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Radical polymerization of a bisacrylate monomer *trans*-1,2-bisacryloyloxyethylcarbamoyloxycyclohexane proceeded via cyclopolymerization. The repeating unit consisted of a 19-membered ring structure. Notably, highly selective cyclopolymerization proceeded at a monomer concentration of 0.033 mol l⁻¹ and produced the corresponding polymer in high yield. The selectivity was validated by size-exclusion chromatography, and nuclear magnetic resonance and matrix-assisted laser desorption ionization time-of-flight mass spectroscopic analyses.

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INTRODUCTION

Cyclopolymerization facilitates preparation of polymers bearing cyclic structures, which serve as rigid skeletons for thermal and mechanical stability, templates for reactions and selective capturing of ions and molecules.^{1–4} For supramolecular applications, macrocycles larger than 12-membered rings are typically necessary, as indicated by the supramolecular chemistry of various low-molecular-weight hosts, such as crown ethers^{4–6} and cyclodextrins.^{7,8} Cyclopolymerization requires very high selectivity of cyclization to avoid crosslinking; hence, cyclopolymerization-producing macrocycles cannot be performed without specific design of monomers and/or polymerization methods. The simplest approach is polymerization under highly diluted conditions, in which, for example, various polymers bearing crown ether cavities have been prepared with bifunctional monomers bearing polyether spacers. However, the low concentration often limits the yields of polymers.^{4,9} Effective strategies for improvement of the cyclization tendency involve conformational orientation of two polymerization groups with cyclic structures^{10–21} or templates such as metal cations^{22,23} and selective alternating copolymerization.^{24,25} In the most common method, namely, the design of oriented monomers, additional constraints by steric hindrance^{12,13,19} and hydrogen bonding¹⁷ are effective in improving the cyclization tendency.

Among these methodologies, we focus on the design of oriented bifunctional monomers accessible via simple one-step reactions suitable for practical applications.^{15,17,20} A bismethacrylate monomer, BMCH (*trans*-1,2-bismethacryloyloxyethylcarbamoyloxycyclohexane), can be prepared via the reaction of 2-methacryloyloxyethylisocyanate and *trans*-1,2-cyclohexanediol. The radical polymerization of BMCH proceeded through the selective cyclopolymerization because of the orientation of the methacrylate moieties by the cyclohexane ring and the hydrogen bonding of the urethane groups and gave a polymer consisting of repeating 19-membered ring units.¹⁷ To expand the

applicability of this design, we prepared BACH (*trans*-1,2-bisacryloyloxyethylcarbamoyloxycyclohexane) as an acrylate analog of BMCH and explored its cyclopolymerization, giving a polymer composed of repeating units bearing a 19-membered ring.

EXPERIMENTAL PROCEDURE

Materials

2,2'-Azobisisobutyronitrile (AIBN) was recrystallized from methanol. 1,4-Dioxane was distilled over sodium under a nitrogen atmosphere. Dehydrated *N,N*-dimethyl formamide was stored under a nitrogen atmosphere. 2-Acryloyloxyethylisocyanate was supplied by Showa Denko (Tokyo, Japan). Other reagents were used as received.

Measurements

¹H (400 MHz) and ¹³C (100 MHz) nuclear magnetic resonance (NMR) spectra were measured on a JEOL (Tokyo, Japan) ECX-400 instrument using tetramethylsilane as an internal standard at ambient temperature in CDCl₃. Fourier-transform infrared spectra were measured on a Horiba (Kyoto, Japan) FT-210 instrument. Elemental analysis was performed on a Perkin-Elmer (Waltham, MA, USA) CHNS/O2400II analyzer. Size-exclusion chromatography measurements were performed on a Tosoh (Tokyo, Japan) DP-8020 pump system equipped with a Viscotek (Houston, TX, USA) TDA model 300 detector and polystyrene-gel tandem columns (Tosoh TSK gels GMHXL, G4000XL, G3000XL and G2500XL) using tetrahydrofuran (THF) as an eluent at 40 °C. Polystyrene standards were used for calibration. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectra were measured on a Bruker Daltonics (Billerica, MA, USA) ultrafleXtreme spectrometer using the linear mode. The acceleration voltage was 25 kV. The mass was calibrated with angiotensin II (1047.189 Da), angiotensin I (1297.486 Da), substance P (1348.642), bombesin (1620.860 Da), ACTH clip(1–17) (2097.427 Da), somatostatin-28 (3149.574 Da) and insulin (5734.508 Da). The sample solution was prepared by mixing the polymer solution in THF (10 mg ml⁻¹), dithranol in THF (10 mg ml⁻¹) and CF₃COONa in THF (1 mg ml⁻¹) in a 1/10/1

volume ratio. A 1 μ l aliquot of the solution was dropped on a measurement plate and was dried at room temperature in the dark.

Synthesis of BACH

To a 100-ml two-necked flask equipped with a dropping funnel and a three-way cock, *trans*-1,2-cyclohexanediol (2.32 g, 20.0 mmol) was added, and the flask was filled with nitrogen. Next, dichloromethane (40 ml) and dibutyltin dilaurate (11.8 μ l, 20 μ mol) were added. A dichloromethane (4.0 ml) solution of 2-acryloyloxyethylisocyanate (5.93 g, 42.0 mmol) was added dropwise from the dropping funnel, and the mixture was stirred at 30 $^{\circ}$ C for 24 h under a nitrogen atmosphere. After the reaction, diethyl ether and brine were added, and the organic layer was dried over $MgSO_4$. Volatile substances were evaporated, and the residue was subjected to silica gel column chromatography eluted with chloroform. Crude BACH was purified via recrystallization from a mixed solvent of diethyl ether and hexane to obtain white crystals of BACH (3.78 g, 9.48 mmol, 47.4%).

Melting point = 67.5–68.0 $^{\circ}$ C. 1H NMR (δ in p.p.m.): 1.20–1.48 and 1.62–1.80 (4H, br, $-CH_2(CH_2)_2CH_2-$), 1.20–1.48 and 2.00–2.18 (4H, br, $-CH_2(CH_2)_2CH_2-$), 3.34–3.56 (4H, br, $-COOCH_2CH_2NH-$), 4.10–4.30 (4H, t, $J=5.5$ Hz, $-COOCH_2CH_2NH-$), 4.60–4.80 (2H, br, $-NHCOOCH-$), 4.98–5.12 (2H, br, $-NH-$), 5.88 (2H, dd, $J=1.1$ and 10.8 Hz, $CH_2=CH-$), 6.14 (2H, dd, $J=10.6$ and 17.5 Hz, $CH_2=CH-$), 6.41 (2H, dd, $J=1.1$ and 17.5 Hz, $CH_2=CH-$). ^{13}C NMR (δ in p.p.m.): 23.5 ($-CH_2(CH_2)_2CH_2-$), 30.6 ($-CH_2(CH_2)_2CH_2-$), 39.9 ($-COOCH_2CH_2NH-$), 63.5 ($-COOCH_2CH_2NH-$), 74.3 ($-COOCH-$), 127.9 ($CH_2=CH-$), 131.3 ($CH_2=CH-$), 155.6 ($-CC(=O)NH-$), 165.9 ($CH_2=CHC(=O)-$). IR (KBr, cm^{-1}): 1683 (C=O in urethane), 1720 (C=O in ester), 3290 (NH). EA: calcd C, 54.26; H, 6.58; N, 7.03; found C, 54.30; H, 6.62; N, 7.01.

Polymerization of BACH (typical procedure)

BACH (99.6 mg, 250 μ mol) and AIBN (410 μ g, 2.5 μ mol) were added to a glass tube. After the tube was degassed and filled with nitrogen, 1,4-dioxane (3.0 ml) was added. Then, the tube was cooled with liquid nitrogen, degassed and sealed.

Scheme 1 Radical polymerization of BACH (*trans*-1,2-bisacryloyloxyethylcarbamoyloxycyclohexane).

Table 1 Radical polymerization of BACH

Run	Conc. (mol l ⁻¹)	Conv. (%) ^a	Yield (%)		M_n (M_w/M_n) ^b	
			Soluble ^c	Insoluble ^d	RI	RALLS
1	0.033	91	78	0	3100 (1.37)	3700 (1.22)
2	0.063	96	83	0	6400 (1.93)	7800 (2.28)
3	0.083	97	88	0	8200 (2.27)	8400 (3.37)
4	0.125	97	85	0	14800 (4.25)	34700 (7.69)
5	0.400	>99	0	>99		

Abbreviations: BACH, *trans*-1,2-bisacryloyloxyethylcarbamoyloxycyclohexane; M_n , number-average molecular weight; M_w , weight-average molecular weight; 1H NMR, 1H nuclear magnetic resonance; SEC, size-exclusion chromatography; THF, tetrahydrofuran.

^aDetermined by 1H NMR spectrometry (400 MHz, $CDCl_3$).

^bEstimated by SEC (THF, polystyrene standard).

^cIsolated yield after precipitation with diethyl ether.

^dIsolated yield after Soxhlet extraction with THF.

The mixture was stirred at 60 $^{\circ}$ C for 24 h. The resulting polymer was isolated by precipitation with an excess amount of diethyl ether (87.3 mg, 87.6%).

1H NMR (δ in p.p.m.): 0.80–2.80 (14H, $-CH_2CH(COOR)-$, $-CH_2(CH_2)_2CH_2-$), 2.90–3.82 (4H, br, $-COOCH_2CH_2NH-$), 3.82–4.95 (6H, $-COOCH_2CH_2NH-$, $-NHCOOCH-$), 4.95–6.80 (2H, br, $-NH-$). ^{13}C NMR (δ in p.p.m.): 23.2–24.6 ($-CH_2(CH_2)_2CH_2-$), 30.5–32.2 ($-CH_2(CH_2)_2CH_2-$), 32.1–38.5 ($-CH_2CH(COOR)-$), 38.5–44.0 ($-CH_2CH(COOR)-$, $-COOCH_2CH_2NH-$), 62.0–66.8 ($-COOCH_2CH_2NH-$), 74.0–76.2 ($-COOCH-$), 155.8–157.6 ($-CC(=O)NH-$), 174.0–176.8 ($CH_2=CHC(=O)-$). IR (KBr, cm^{-1}): 1626 (C=O in urethane), 1723 (C=O in ester) and 3422 (NH).

RESULTS AND DISCUSSION

Radical polymerization of BACH

The diacrylate monomer BACH was prepared via the reaction of 2-acryloyloxyethylisocyanate and *trans*-1,2-cyclohexanediol in a manner similar to that of the analogous dimethacrylate monomer BMCH. The 1H NMR signal assigned to the NH group appeared at the identical chemical shift,¹⁷ suggesting that the conformation taken by BACH for ring closing is identical to that taken by BMCH. The structure was validated by the NMR spectroscopic and elemental analyses.

Figure 1 Refractive index (RI) and right angle laser light scattering (RALLS)-detected size-exclusion chromatography (SEC) profiles of poly-BACH (*trans*-1,2-bisacryloyloxyethylcarbamoyloxycyclohexane) obtained under various concentrations (2,2'-azobisisobutyronitrile (AIBN) = 1 mol%, 60 $^{\circ}$ C, 24 h, degassed sealed tube). A full color version of this figure is available at *Polymer Journal* online.

BACH was polymerized at 60 °C in 1,4-dioxane under various concentrations using AIBN (1 mol% to BACH) as an initiator in degassed and sealed tubes (Scheme 1 and Table 1). Polymerization conducted under concentrations below 0.125 mol l⁻¹ gave soluble products in high yields (runs 1–4), but polymerization conducted at 0.400 mol l⁻¹ was insoluble in any common solvents (run 5). This tendency is almost identical to the polymerization of BMCH, which yielded soluble and insoluble products at 0.082 and 0.200 mol l⁻¹, respectively.¹⁷ The number-average molecular weight (M_n) of the polymers and the yields were lower compared with those of poly-BMCH obtained under analogous conditions. The M_n values increased with the concentration, but the polydispersity indices (M_w/M_n) also increased. This behavior implies that a higher concentration leads not only to smooth propagation but also undesired branching. The branching behavior was evaluated by size-exclusion chromatography profiles detected by refractive index and right angle laser light scattering (RALLS). The refractive index and RALLS profiles of the polymer obtained in run 1 have similar shapes, indicating that the polymer contains negligible branching (Figure 1). The shoulders of the refractive index profiles at the higher-molecular-weight region became clearer with the increase of the concentration, and the RALLS profiles shifted to significantly lower elution volume regions. This result supports that the highly selective cyclopolymerization proceeded under appropriately diluted conditions.

Structure of poly-BACH

The structure of poly-BACH was elucidated by NMR and MALDI-TOF mass spectroscopy. Figure 2 shows the ¹H and ¹³C NMR spectra of poly-BACH obtained in run 1 in Table 1. All signals are assignable to the plausible structure, and the spectra are almost analogous to those of poly-BMCH.¹⁷ Signals assignable to the acrylate moieties were not detected in either spectrum (i.e., the dd signals at 5.88–6.41 p.p.m. for ¹H NMR and signals at 128 and 131 p.p.m. for ¹³C NMR). The clearly split signals of the methylene protons in both the formed ring (d and e) and the cyclohexane ring (i and j) suggest the constrained conformation by the ring structures. The efficient cyclization was confirmed by the ¹H NMR spectrum of the polymer obtained at low conversion. For example, the polymer obtained in an early stage (0.083 M, 30 min, conversion = 53%) contains a negligible amount of the acrylate moieties (1.3%) (Supplementary Figure S1). The ¹H NMR spectrum of the polymer obtained in *N,N*-dimethyl formamide contained trace signals of the acrylate moieties (1–2%), suggesting the importance of the intramolecular hydrogen bonding of the urethane structure aligning the two acrylate moieties toward the same direction in a manner similar to that of BMCH (Supplementary Figure S2).¹⁷

The MALDI-TOF mass spectrum of poly-BACH obtained in run 1 in Table 1 is shown in Figure 3. Two series of the peaks with a difference of 398 Da, which corresponds with the molecular weight of BACH, were observed. The intensity of the signals in the stronger series is ~30 times stronger than that of the signals in the weaker series. The simple spectrum indicates that most of the poly-BACH chains have the same initiating and terminating structures that originate from the selective cyclopolymerization. The peak with m/z = 3297.6 Da is assignable to the octamer of BACH ($398.40 \times 8 = 3187.2$). This spectrum was measured in the presence of CF₃COONa as an ionization agent, and the peaks observed are ionized by Na⁺. The remaining mass, namely, 87.4 Da, does not match with the initiating and terminating structures originated from the radical from AIBN and the proton (70 Da). This mass corresponds with the possible terminal structure originating from the solvent

Figure 2 ¹H (400 MHz) and ¹³C (100 MHz) nuclear magnetic resonance (NMR) spectra of poly-BACH (*trans*-1,2-bisacryloyloxyethylcarbamoyloxycyclohexane) obtained in run 1 in Table 1 (CDCl₃, room temperature (rt)). Asterisks indicate the signal of the remaining 1,4-dioxane.

Figure 3 Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrum of poly-BACH (*trans*-1,2-bisacryloyloxyethylcarbamoyloxycyclohexane) obtained in run 1 in Table 1.

1,4-dioxane (88.1 Da) and suggests the initiation from the radical produced via hydrogen abstraction from 1,4-dioxane. The MALDI-TOF mass spectrum of the polymer obtained in *N,N*-dimethyl formamide also shows the efficient cyclization and the initiation from *N,N*-dimethyl formamide (Supplementary Figure S3). This MALDI-TOF mass spectroscopic analysis supports the well-defined structure produced via highly selective cyclopolymerization. If the polymerization was accompanied by intermolecular branching, the resulting chain would have multiple initiating and terminating groups that result in another series of the peaks. The minor series of the signals implies a trace degree of an unexpected reaction, whereas we could not identify the structure. The masses do not match with the polymers bearing two initiating and terminating structures.

CONCLUSIONS

Radical polymerization of a bisacrylate monomer BACH proceeded via selective cyclopolymerization to give 19-membered rings under appropriate conditions. The high yield and the selective cyclopolymerization, which is typically inconsistent, may be achieved by designing the monomer structure to align the two acrylate moieties to a conformation suitable to cyclopolymerization. The facile one-step method for preparation of the monomer is also an advantage of this cyclopolymerization. We are now searching for applications of this polymer depending on the characteristic large ring structure.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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