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Article

RAFT Copolymerization of Glycerol-Derived Vinyl Ethers Possessing Acetal-Protected Diols for Biobased Hydrophilic and Thermoresponsive Polymers

Riko Kashima, Tomohiro Kubo, and Kotaro Satoh*

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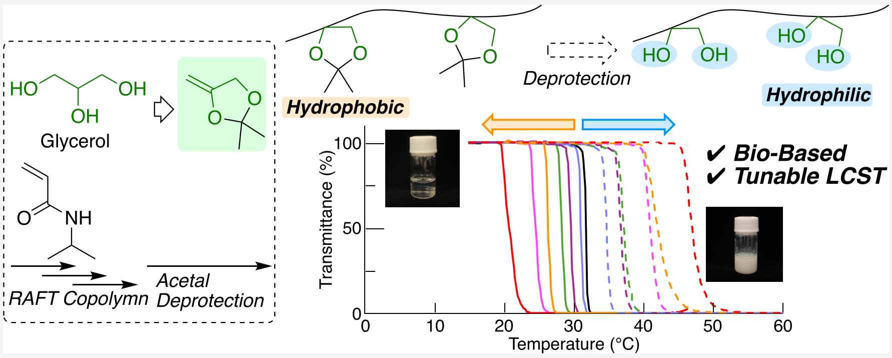

ABSTRACT: Here, we synthesized a vinyl ether with acetal-protected diols from glycerol and acetone. The glycerol-derived vinyl ether was copolymerized with common vinyl monomers, methyl acrylate (MA) and *N*-isopropylacrylamide (NIPAM), via the reversible addition−fragmentation chain transfer (RAFT) mechanism. Through the monomer reactivity ratio analysis, relatively high copolymerization reactivity was observed with MA, while for NIPAM copolymerization, the reactivity ratio changed slightly depending on the polymerization solvent. The acetal deprotection reaction following the copolymerization proceeded nearly quantitatively, yielding well-defined copolymers with glycerol-derived diol groups. For the NIPAM copolymers, the thermoresponsive behavior was investigated before and after deprotection, resulting in tunable cloud points ranging from 20 to 46 °C by incorporating just 10% of glycerol-derived monomers into poly(NIPAM).

■ INTRODUCTION

In recent years, the depletion of fossil resources has emerged as a critical environmental challenge. To establish a sustainable society from the viewpoint of carbon neutrality, increasing attention has been directed toward polymers derived from renewable resources, i.e., biobased polymers.[1−5] Among them, the vinyl polymerization of plant-derived monomers has garnered significant interest over the years, as numerous natural compounds possess or can be easily modified to have carbon−carbon double bonds.[6,7] Several reports on the synthesis of functional biobased polymers have been made by combining plant-derived vinyl monomers with controlled/living polymerization techniques.[8−10] The reversible addition−fragmentation chain transfer (RAFT) mechanism[11−13] is especially utilized owing to the facile procedure and versatility of monomers.[14−17] Even with nonhomopolymerizable monomers, for instance, electron-donating vinyl compounds, the radical copolymerization proceeds smoothly and can be controlled via the RAFT mechanism.[18] The RAFT copolymerization of maleimide and limonene, a biobased electron-donating monomer which rarely undergoes homopolymerization, afforded well-defined copolymers, and moreover, the unique copolymerization reactivity resulted in 1:2 sequence-regulated copolymers.[19]

Polymers with various functionalities, for example, hydrophilicity, are of significant interest in polymer chemistry as they enable the development of advanced functional materials.[20−22] A notable example is poly(*N*-isopropylacrylamide) (poly(NIPAM)),[23,24] a water-soluble polymer exhibiting thermoresponsive behavior in aqueous environments. Showing a lower critical phase transition (LCST) under aqueous conditions between 31 and 35 °C, poly(NIPAM) is highly attractive for applications in drug delivery systems and biosensors. The LCST temperature of poly(NIPAM) is reported to vary depending on tacticity,[25] distribution,[26] copolymerization,[27−29]

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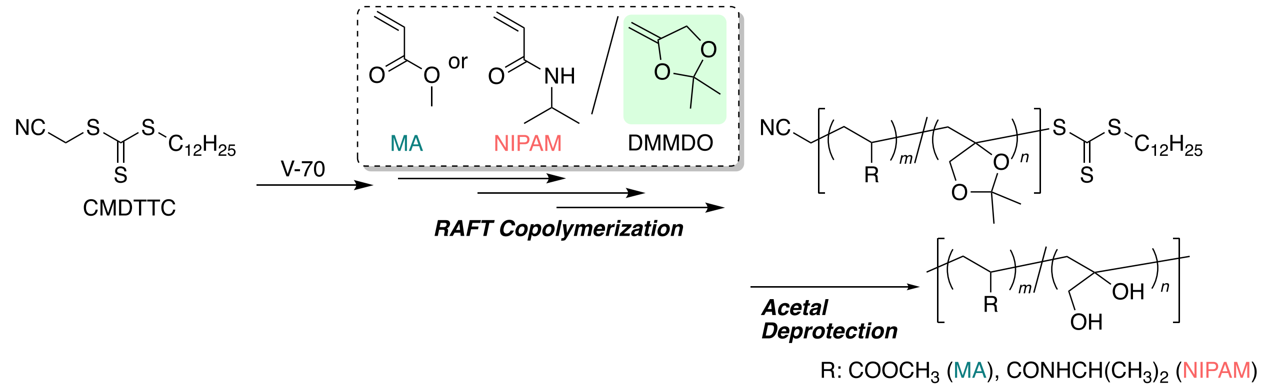
Scheme 1. RAFT Copolymerization of DMMDO with Common Vinyl Monomers (MA or NIPAM) and Acetal Deprotection



and terminal structure. In addition, the copolymerization of NIPAM with biobased cinnamic monomers has also been shown to effectively tune its thermoresponsive properties.[30]

Glycerol is a biomass-derived feedstock and recognized well for its high availability and low production cost.[31,32] Mainly obtained through the hydrolysis of plant oils, glycerol has recently been available on industrial scales as a byproduct of biodiesel fuel production. Owing to its three hydroxyl groups, glycerol serves as a versatile precursor for the synthesis of a broad range of value-added chemicals, including polymerizable monomers such as acrylic acid, lactides, and epoxides.[33,34] Polymers with various backbones, such as polyketones, polyethers, and polycarbonates, have been developed from glycerol precursors.[35,36] Degradable polymers have also been reported through the incorporation of glycerol-derived cyclic acetals into the polymer backbone.[37] Recently, we have reported the modification of glycerol into new vinyl ethers possessing acetal-protected diols by using various aldehydes as protecting agents.[38] Though this kind of vinyl ether derivative has been subjected to both radical and cationic ring-opening polymerization in the literatures,[39−42] we also investigated its radical copolymerization with common vinyl monomers and demonstrated their high copolymerization reactivity. Well-defined copolymers were successfully obtained by RAFT copolymerization with methyl acrylate (MA). Notably, subsequent deprotection of the acetal groups yielded diol functionalities derived from glycerol, and thereby, the copolymers showed significant hydrophilicity.

In this work, we report the synthesis and polymerization of a new glycerol-derived cyclic vinyl ether using acetone as a protecting agent to protect two hydroxyl groups in glycerol. Namely, we aimed to readily synthesize a vinyl ether with an acetal protecting group, which will subsequently show a higher deprotection efficiency by designing 2,2-dimethyl-4-methylene-1,3-dioxolane (DMMDO). The RAFT copolymerization with common vinyl monomers, MA and NIPAM, and the following acetal deprotection was investigated (Scheme 1). The thermoresponsive behavior of the copolymers obtained from the copolymerization of DMMDO and NIPAM was studied at different feed ratios, as well as before and after deprotection, respectively.

■ EXPERIMENTAL SECTION

Materials. Glycerol (Wako, >99.0%), acetone (Wako, >99.5%), *p*-toluenesulfonic acid monohydrate (TCI, >98.0%), *p*-toluenesulfonyl chloride (TCI, >99.0%), triethylamine (Nacalai, >99.0%), potassium *tert*-butoxide (Sigma-Aldrich, >98.0%), ethyl acetate (Wako, >99.5%), methanol (Wako, >99.5%), cyanomethyl dodecyl trithiocarbonate (CMDTTC; Sigma-Aldrich, >98.0%), 2,2'-azobis(*N*-butyl-2-methylpropionamide) (VAm-110; Wako, >95.0%), and aq. HCl (Nacalai, 35−37.0%) were used as received. 1,2,3,4-Tetrahydronaphthalene (TCI, >97.0%) and methyl acrylate (MA; TCI, >99.0%) were distilled over calcium hydride under reduced pressure. *N*-Isopropylacrylamide (NIPAM) (TCI, >98.0%) was recrystallized from hexane and toluene. *N*,*N*-Dimethylformamide (DMF) (KANTO, >99.5%; H_2O <0.001%), toluene (KANTO, >99.5%; H_2O <0.001%), and THF (KANTO, >99.5%; H_2O <0.001%) were dried and deoxygenized by passage through columns of Glass Contour Solvent Systems before use. 2,2'-Azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70; Wako, >95.0%) was purified by washing with acetone at −15 °C and evaporated until dryness under reduced pressure.

Measurements. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECZ-400S spectrometer, operating at 400 and 100 MHz for ^{1}H and ^{13}C NMR, respectively. The number-average molecular weight (M_n) and molecular weight distribution (M_w/M_n) of the product polymers were determined by SEC in THF at 40 °C on two polystyrene gel columns [Tosoh Multipore HXL-M (7.8 mm i.d. × 30 cm) × 2; flow rate 1.0 mL min^{-1}] or in DMF containing 100 mM LiCl at 40 °C on two hydrophilic polymer gel columns [Tosoh α-M + α-3000 (7.8 mm i.d. × 30 cm); flow rate 1.0 mL min^{-1}] connected to a JASCO PU-2085 or PU-2080 precision pump (for THF SEC or DMF SEC, respectively) and a JASCO RI-2031 detector. The columns were calibrated against standard poly(methyl methacrylate) (Agilent Technologies; M_p = 500−1591000, M_w/M_n = 1.02−1.14). Glass transition temperature of the polymers was recorded by a DSC 250 differential scanning calorimeter (TA Instruments Inc.). Samples were first heated to 200 °C at 10 °C min^{-1}, equilibrated at this temperature for 5 min, and cooled to −100 °C at 10 °C min^{-1}. After being held at this temperature for 5 min, the samples were then reheated to 200 at 10 °C min^{-1}. All T_g values were obtained from the second scan after removal of the thermal history. Thermogravimetric analysis (TGA) was performed on a TGA 55 system (TA Instruments Inc.). The samples were equilibrated at 100 °C for 10 min and heated to 500 °C at 20 °C min^{-1} under a N_2 gas flow. The LCST was determined as the temperature at which the transmittance of a 500 nm light beam through the aqueous solution of the samples became lower than 90% (cloud point). The transmittance of a 10 mg/mL aqueous solution of the samples was measured by monitoring the transmittance through a 1 cm quarts sample cell during the heating and cooling process at the rate of 1.0 °C/min. The transmittance was recorded using a Shimadzu UV-2600i UV−vis spectrometer equipped with a S-1700 thermoelectric single cell holder.

Synthesis of 2,2-Dimethyl-4-Methylene-1,3-Dioxolane (DMMDO). 1,2-Isopropylidene glycerol (S1) and 2,2-dimethyl-4-tosyloxymethyl-1,3-dioxolane (S2) was synthesized according to literature.[1] 2,2-Dimethyl-4-tosyloxymethyl-1,3-dioxolane (217 g, 0.759 mol) and potassium *tert*-butoxide (255 g, 2.28 mol) was dissolved in DMF, respectively. Into the potassium *tert*-butoxide solution, 2,2-dimethyl-4-tosyloxymethyl-1,3-dioxolane (DMF solu-

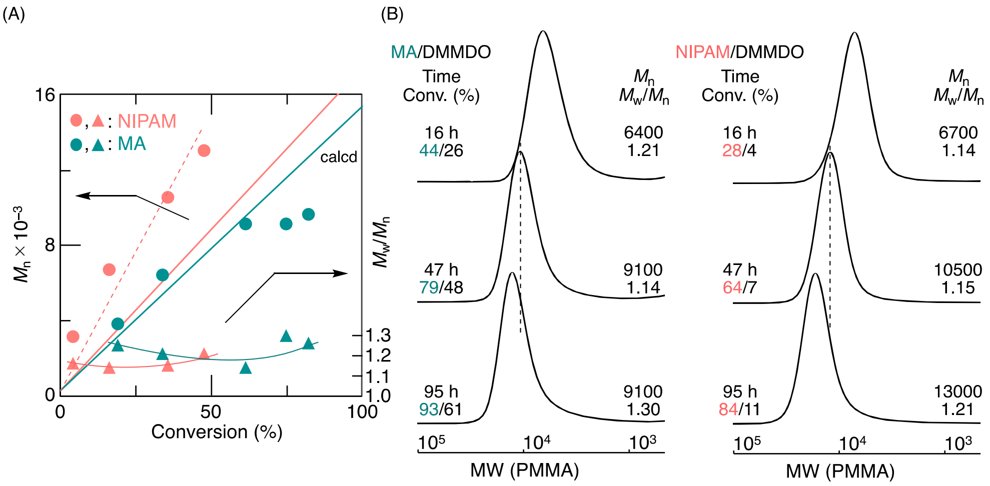


Figure 1. M_n and M_w/M_n values of the obtained copolymers vs total weight monomer conversion (A) and SEC curves (B) for the RAFT copolymerization of MA/DMMDO and NIPAM/DMMDO: [MA or NIPAM]$_0$/[DMMDO]$_0$/[CMDTTC]$_0$/[V-70]$_0$ = 1200/1200/16/4 mM at 20 °C.

tion) was added dropwise to the reaction mixture and was stirred for 30 min at 0 °C. Diethyl ether and water were added to stop the reaction. The organic layer was washed with brine and was concentrated by rotary evaporation. The crude compound was distilled under reduced pressure to yield 2,2-dimethyl-4-methylene-1,3-dioxolane as a clear liquid (27.5 g, 241 mmol, 32%). ^{1}H NMR ($CDCl_3$, r.t.): δ 4.51 (t, J = 1.6 Hz, 2H, CCH_2O), 4.28 (q, J = 2.1 Hz, 1H, $CH_2{=}C$), 3.85 (q, J = 1.7 Hz, 1H, $CH_2{=}C$), and 1.46 (s, 6H, $C(CH_3)_2$) ppm. ^{13}C NMR ($CDCl_3$, r.t.): δ 156.2 ($CH_2{=}C$), 111.9 ($O{-}C(CH_3)_2{-}O$), 77.7 ($CH_2{=}C$), 66.5 (CCH_2O), and 25.2 ($C(CH_3)_2$) ppm.

RAFT Copolymerization. RAFT copolymerization was carried out by a syringe technique under dry nitrogen in sealed glass tubes. A typical example for polymerization of DMMDO and MA with CMDTTC as a RAFT agent in the presence of V-70 is given below: DMMDO (1.18 mL, 9.60 mmol), MA (0.86 mL, 9.60 mmol), CMDTTC (0.640 mL of 200 mM solution in toluene, 0.128 mmol), V-70 (9.8 mg, 0.0320 mmol), 1,2,3,4-tetrahydronaphthalene (0.200 mL) as an internal standard, and toluene were placed in a 25 mL round-bottomed flask equipped with a three-way stopcock at 0 °C. The total volume of the reaction mixture was 8.0 mL. Immediately after mixing, the solution was evenly charged in eight glass tubes, and the tubes were sealed by a flame under a nitrogen atmosphere. The tubes were immersed in a thermostatic water bath at 20 °C. In predetermined intervals, the polymerization was terminated by cooling the reaction mixtures to −78 °C. Monomer conversion was determined from the concentration of residual monomer measured by ^{1}H NMR with 1,2,3,4-tetrahydronaphthalene as an internal standard (e.g., 47 h, DMMDO/MA = 48/79%). Total weight monomer conversion was calculated using the following formula: $[(M_1\ MW) \times ([M_1]_0/[RAFT]_0) \times (M_1\ conv.) + (DMMDO\ MW) \times ([DMMDO]_0/[RAFT]_0) \times (DMMDO\ conv.)]/[(M_1\ MW) \times ([M_1]_0/[RAFT]_0) \times 100 + (DMMDO\ MW) \times ([DMMDO]_0/[RAFT]_0) \times 100]$. The quenched reaction solutions were evaporated to dryness to give poly(MA-*co*-DMMDO) (M_n = 9100, M_w/M_n = 1.14). The obtained polymer was purified by preparative size-exclusion chromatography (SEC) for ^{1}H NMR analysis.

Deprotection of Acetal Groups. The acetal-containing copolymers were converted into polymers with diol units by acetal deprotection under acidic conditions. A typical example is given below: the obtained P(MA-*co*-DMMDO) (0.420 g, M_n = 8300, M_w/M_n = 1.17) was dissolved in THF (11.2 mL) and H_2O (1.06 mL), followed by the addition of 35−37.0% aq. HCl (1.73 mL of 1 M in water, 1.73 mmol) at 50 °C. After stirring for 45 h, aq. conc. $NaHCO_3$ was added into the mixture until the solution turned basic. The solution was dialyzed in water and then freeze-dried to afford a polymer with diol units.

RESULTS AND DISCUSSION

RAFT Copolymerization of DMMDO with Acrylates and Acrylamides. Using glycerol and acetone as starting materials, DMMDO was synthesized in three steps (Scheme S1). Two of glycerol's hydroxyl groups were selectively protected through the formation of an acetal linkage using acetone as the protecting agent. After treating the residual hydroxyl group with tosyl chloride, the E2 elimination reaction was carried out using potassium *tert*-butoxide as a strong base. The characterization of the obtained product was conducted using ^{1}H NMR analysis to confirm the synthesis of DMMDO (Figures S1 and S2).

The RAFT copolymerization of DMMDO was investigated with a common vinyl monomer, MA. The copolymerization was carried out using a low temperature azo initiator 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) and cyanomethyl dodecyl trithiocarbonate (CMDTTC) as the RAFT agent at 20 °C. The RAFT copolymerization of DMMDO with MA proceeded smoothly, and the conversion of MA reached over 90% in 95 h (Figure S3). The molecular weight distribution (M_w/M_n) remained low (~1.20), and the number-average molecular weight (M_n) of the obtained copolymers increased linearly as the monomers were consumed, although it slowly deviated at the later stage of polymerization (Figure 1).

The RAFT copolymerization was then investigated by using NIPAM as a comonomer. For the copolymerization of DMMDO with NIPAM, the solubility of NIPAM-rich copolymers in toluene was low, so ethyl acetate was employed as the solvent. The copolymerization proceeded smoothly, although the conversion of DMMDO was lower compared to the copolymerization with MA (Figure S4). The M_w/M_n was below 1.21 throughout the polymerization, and the M_n of the obtained copolymers increased linearly against conversion (Figure 1). The M_ns for poly(NIPAM-*co*-DMMDO) were higher than the calculated values assuming one copolymer chain is generated from one RAFT molecule likely due to the difference in hydrodynamic volumes between standard poly(methyl methacrylate) and the obtained copolymers.

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Table 1. RAFT Copolymerization of DMMDO with MA and NIPAM

entry	M_1	$[M_1]_0/[DMMDO]_0$	time (h)	conv.[c] (%) M_1/DMMDO	M_n (calcd)	M_n (NMR)	M_n[d] (SEC)	M_w/M_n	m/n (calcd)	m/n[e] (NMR)
1[a]	MA	1500/1500	52	80/53	10000	10100	10400	1.15	60/40	60/40
2[a]	MA	1000/2000	96	98/45	9300	12200	8200	1.17	56/44	52/48
3[a]	MA	2700/300	52	86/89	11800	12200	12600	1.10	90/10	88/12
4[b]	NIPAM	1200/1200	47	64/7	6400	6500	12300	1.08	90/10	87/13
5[b]	NIPAM	800/1600	120	86/9	6200	8000	9900	1.12	82/18	83/17
6[b]	NIPAM	1600/800	48	68/9	8500	10500	15200	1.09	93.7/6.3	94.3/5.7
7[b]	NIPAM	1800/600	48	61/8	8400	9200	15200	1.10	95.7/4.3	95.9/4.1
8[b]	NIPAM	2000/400	48	73/16	11000	10700	19100	1.10	95.9/4.1	96.6/3.4
9[b]	NIPAM	2160/240	48	80/15	12800	11000	21700	1.09	97.9/2.1	98.3/1.7
10[b]	NIPAM	2280/120	48	83/15	13800	11000	23700	1.08	99.0/1.0	99.2/0.8

[a] Polymerization conditions: $[CMDTTC]_0/[V\text{-}70]_0 = 20/5$ mM at 20 °C in toluene. [b] Polymerization conditions: $[CMDTTC]_0/[V\text{-}70]_0 = 16/4$ mM at 20 °C in ethyl acetate. [c] Determined by ^{1}H NMR of the reaction mixture. [d] Determined by SEC. [e] Determined by ^{1}H NMR of the obtained polymer.

The structures of the polymers obtained from the RAFT copolymerization of DMMDO with MA and NIPAM were evaluated by ^{1}H NMR spectroscopy. Broad signals from both repeating units were observed along with small peaks corresponding to the terminal RAFT group (Figures S5 and S10). For both copolymers, characteristic peaks of the methyl groups on the acetal position of DMMDO were observed at 1.2−1.4 ppm. The incorporation ratio of DMMDO was calculated using the dimethyl protons (f) of DMMDO and the peak of the methyl proton (c) of the MA unit along with the methylene protons of the dioxolane skeleton (e) at 3.5−3.9 ppm for poly(MA-*co*-DMMDO). For poly(NIPAM-*co*-DMMDO), the methylene protons of the dioxolane skeleton (g) at 3.4−3.8 ppm and the peak of the proton next to the amide group (d) at 3.8−4.2 ppm were used to determine the ratios. The incorporation ratios determined from the ^{1}H NMR spectra matched well with the ratios calculated from the monomer feed ratio and conversion in each case. Additionally, the molecular weights obtained from the characteristic peaks of DMMDO and MA/NIPAM as well as the terminal RAFT group (x) were close to the theoretical value. From ^{13}C NMR spectra analysis, the copolymerization was confirmed to have proceeded without ring-opening of DMMDO (Figures S6 and S11). Ring-opening has been reported to occur under high polymerization temperatures,[41,42] and the ring-opening of DMMDO was also observed at 110 °C (Figure S8). Thus, by polymerizing 2-substituted-4-methylene-1,3-dioxolanes under low temperatures, copolymers with ring-retained structures could be obtained.

The copolymerization was further explored by changing the copolymerization conditions. Varying the monomer feed ratio of MA/DMMDO or NIPAM/DMMDO resulted in copolymers with different DMMDO incorporation ratios (Table 1). For the RAFT copolymerization of DMMDO and MA, the incorporation ratio of DMMDO reached up to 48% by tuning the monomer feed ratio $[MA]_0/[DMMDO]_0$ to 1/2 equiv, indicating the relatively high copolymerization reactivity of DMMDO with acrylates. Additionally, copolymers with various molecular weights were obtained by changing the feed ratio of monomers to the RAFT agent (Table S1). Therefore, the RAFT copolymerization of DMMDO with acrylates and acrylamides afforded well-defined copolymers with tunable incorporation ratios and molecular weights.

Monomer Reactivity Ratios. The copolymerization behavior was further evaluated by determining traditional monomer reactivity ratios using the Kelen-Tüdös method and the Meyer-Lowry method.[43,44] The r_1 and r_2 values determined from the Kelen-Tüdös method when copolymerizing DMMDO with MA were <0.01 and 0.77, respectively (Table S2, Figures 2A and S12). These values were close to the monomer reactivity ratios of glycerol-derived cyclic vinyl ethers with different substituents at the acetal position (n-butyl, cyclohexyl, and phenyl) and MA (Table S2).[30] Thus, the copolymerization behavior of glycerol-derived cyclic vinyl ethers and MA showed similar reactivity regardless of the pendant groups, as was the case for RAFT copolymerization.

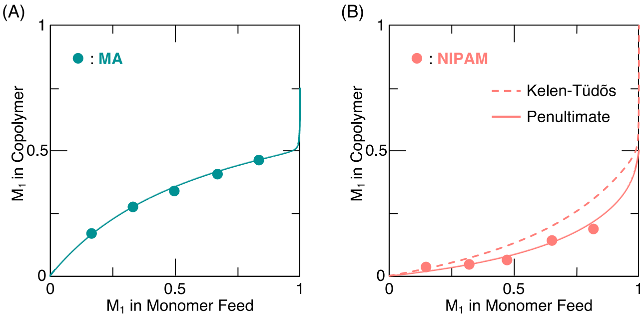

Figure 2. Copolymer composition curves for the copolymerization of DMMDO with MA in toluene (A) and NIPAM in ethyl acetate (B): $[MA \text{ or } NIPAM]_0 + [DMMDO]_0 = 2000$ mM, $[V\text{-}70]_0 = 20$ mM.

For the copolymerization of DMMDO and NIPAM, the monomer reactivity ratios showed a solvent dependence (Table 2). The solvent effect on radical copolymerization of acrylates, methacrylates and acrylamides has been reported;[45−47] thus, the reactivity ratios were investigated in detail using different solvents. Employing toluene and ethyl acetate as the solvent, the copolymer composition curves determined from the Kelen-Tüdös method deviated from the experimental data, particularly at higher feed ratios of DMMDO (Figures 2B and S13). Hence, the penultimate model[48] was tested, and the composition curves were found to fit well in this case (Scheme 2). When using DMF and methanol, the r_1 and r_2 values from the Kelen-Tüdös method fitted the experimental plots better than toluene and ethyl acetate and showed similar values to those determined applying the Meyer-Lowry method from the RAFT copolymerization results. This difference depending on solvent is probably because the NIPAM molecules' amide groups can form hydrogen bonding with other amide groups in toluene and ethyl acetate, increasing the selectivity of NIPAM−

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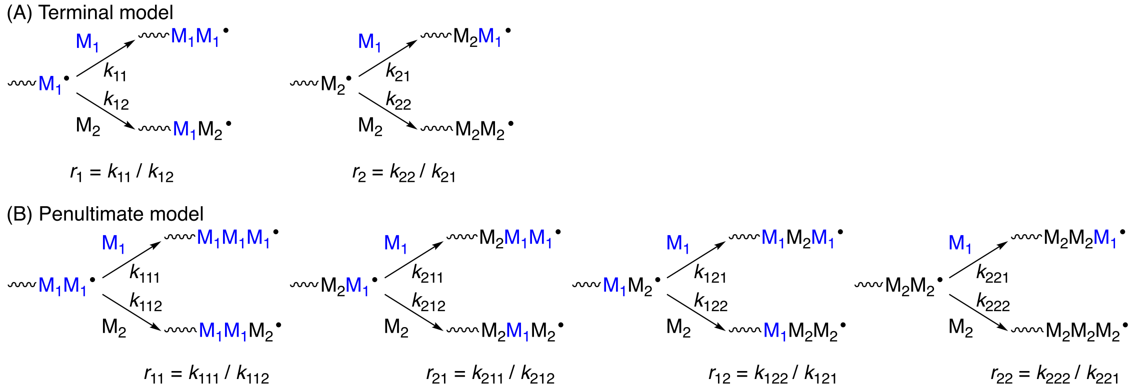
Table 2. Monomer Reactivity Ratios of DMMDO/MA and DMMDO/NIPAM

				Meyer-Lowry[a,b]		Penultimate[b]		
entry	M_1	M_2	solvent	r_1	r_2	$r_{11} = r_{21}$	r_{12}	r_{22}
1	DMMDO	MA	toluene	0.01	0.60	<0.01	1	0.60
2	DMMDO	NIPAM	toluene	0.01	3.0	<0.01	60	3.0
3	DMMDO	NIPAM	ethyl acetate	0.01	6.6	<0.01	50	8.0
4	DMMDO	NIPAM	DMF	0.01	4.0	<0.01	30	4.0
5	DMMDO	NIPAM	methanol	0.01	2.0	<0.01	10	2.4

[a] Polymerization conditions: $[M_1]_0/[MA]_0/[CMDTTC]_0/[V\text{-}70]_0$ = 2000/1000/20/5 mM for entry 1 and $[M_1]_0/[NIPAM]_0/[CMDTTC]_0/[V\text{-}70]_0$ = 2000/400/16/4 mM for entries 2−5 at 20 °C. [b] Optimized by fitting the data.

Scheme 2. Terminal Model (A) and Penultimate Model (B) for Copolymerization of Monomer M_1 and M_2



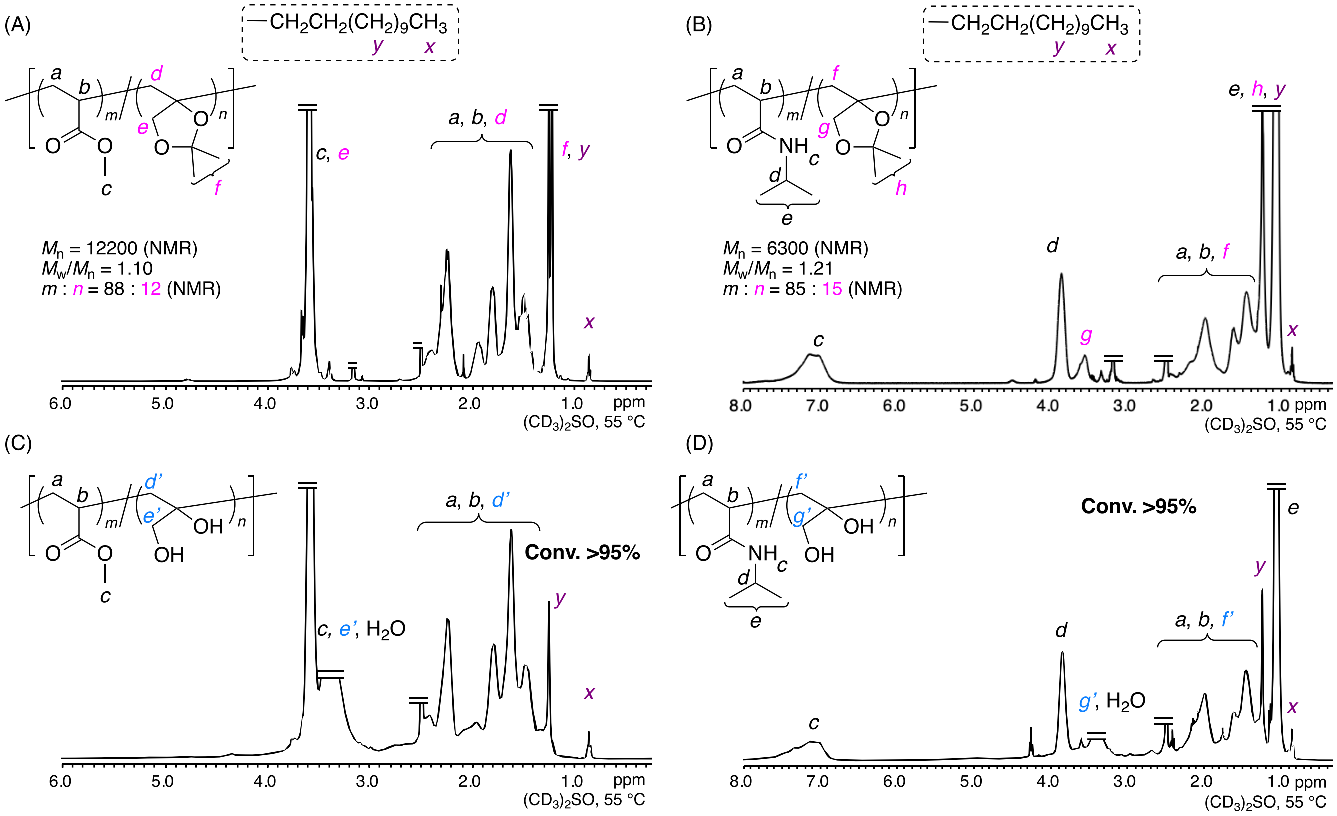


Figure 3. ^{1}H NMR spectra of poly(MA-*co*-DMMDO) (A), poly(NIPAM-*co*-DMMDO) (B), deprotected poly(MA-*co*-DMMDO) (C), and deprotected poly(NIPAM-*co*-DMMDO) (D): $[-OC(CH_3)_2O-]_0/[HCl]_0$ = 100/100 mM (for poly(MA-*co*-DMMDO)) or 150/150 mM (for poly(NIPAM-*co*-DMMDO)) in THF/H_2O (80/20 vol %) at 50 °C.

NIPAM sequences. The formation of hydrogen bonding triggers NIPAM−NIPAM diads, as the propagating NIPAM's amide can form hydrogen bonding with the consecutive NIPAM, making the r_{12} value higher. After a NIPAM−NIPAM sequence, hydrogen bonding has already formed, lowering the selectivity of the next monomer with a lower r_{22}.

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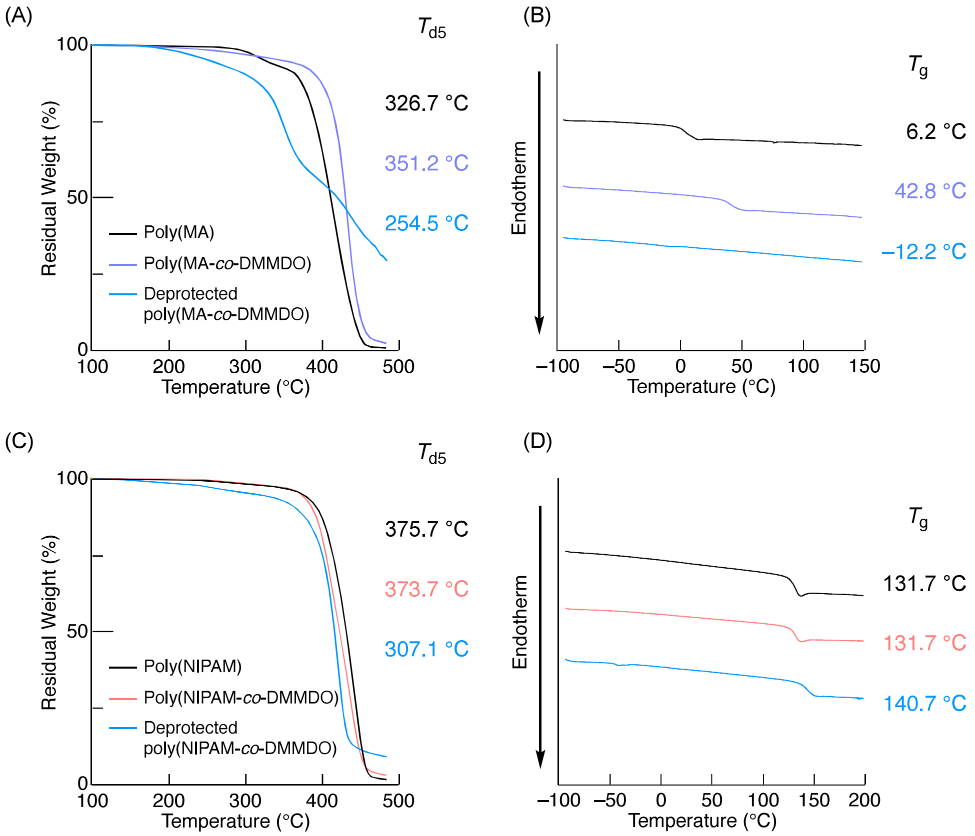

Figure 4. TGA (A) and DSC curves (B) of poly(MA-*co*-DMMDO) (M_n = 11100 (NMR), M_w/M_n = 1.17, 40% DMMDO incorporation, Table S1 entry 2), and TGA (C) and DSC curves (D) of poly(NIPAM-*co*-DMMDO) (M_n = 9200 (NMR), M_w/M_n = 1.08, 9% DMMDO incorporation, under the same conditions as Table 1, entry 6).

Acetal Deprotection and Polymer Analysis. Poly(MA-*co*-DMMDO) and poly(NIPAM-*co*-DMMDO) were each treated with an acid to deprotect the acetal linkages. By cleaving the acetal protecting groups, diols that originated from glycerol will be incorporated into the main chain, adding hydrophilicity to the copolymers. Each copolymer was treated with HCl in THF/H_2O (80/20 vol %) at 50 °C. From ^{1}H NMR spectrum analysis, the nearly quantitative deprotection was confirmed by the significant decrease of the peaks for the dimethyl protons at 1.2−1.4 ppm (Figure 3). In addition, the peak of the quaternary carbon at the acetal position could no longer be observed from the ^{13}C NMR spectrum, verifying the high deprotection ratio (Figure S15 and S16). This result shows the deprotection of glycerol-derived cyclic vinyl ether with dimethyl groups at the acetal position is more effective than that of the previously reported monomer with phenyl groups.[30] As the deprotection of poly(MA-*co*-DMMDO) proceeds, acetone is released. Since the deprotection is an equilibrium reaction, the elimination of acetone from the reaction solution at 50 °C most likely resulted in higher deprotection ratios for the case of DMMDO.

The thermal properties of obtained poly(MA-*co*-DMMDO) and poly(NIPAM-*co*-DMMDO) before and after deprotection were analyzed by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). From TGA analysis, poly(MA-*co*-DMMDO) showed a decomposition temperature at 5% weight loss (T_{d5}) of 351 °C and decomposed in one step (Figure 4A), indicating that the five-membered acetal of DMMDO has relatively high thermal stability and decomposes without acetal elimination. From DSC analysis, the T_g increased to 42.8 °C, due to the incorporation of a cyclic structure into poly(MA) (Figure 4B). After deprotecting the acetal linkage in poly(MA-*co*-DMMDO), the T_{d5} and T_g decreased to 255 and −12.2 °C, respectively, likely due to the loss of the cyclic structure through deprotection. Thermal analysis was also evaluated for the NIPAM copolymers. For poly(NIPAM-*co*-DMMDO), T_{d5} and T_g showed almost identical values to poly(NIPAM), indicating that the small incorporation of DMMDO does not affect the thermal properties (Figure 4C,D). Although the decomposition temperature decreased slightly after deprotection, T_{d5} was still over 300 °C, showing high thermal stability.

Thermoresponsive Properties of Poly(NIPAM-*co*-DMMDO). Finally, the LCST behavior was studied by changing the incorporation ratio of DMMDO in poly(NIPAM) (Table 3). Copolymers with around 1 to 13% of DMMDO incorporation, and M_n of 6500−11000 were synthesized respectively by changing the monomer feed ratio in the RAFT copolymerization of DMMDO and NIPAM. Upon heating the 10 mg/mL aqueous solutions, all the copolymers became insoluble in water at certain temperatures, causing the solution to turn cloudy. While the poly(NIPAM-*co*-DMMDO) curves showed a relatively sharp transition, the transitions of the curves for the deprotected polymers were slightly dulled. As the ratio of hydrophobic DMMDO increased, the cloud point became lower, showing a cloud point at 19.8 °C with 13% DMMDO incorporation (Figure 5A). After the deprotection of the acetal groups, the hydrophilicity is expected to increase, as the copolymers possess glycerol-derived diols. As predicted, the cloud point of

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Table 3. Cloud Points[a] of Poly(NIPAM-*co*-DMMDO) and Copolymers after Acetal Deprotection

entry	DMMDO incorporation (%)	M_n[b] (NMR)	M_w/M_n	cloud point[a] (°C) before deprotection	cloud point[a] (°C) after deprotection
1	0	8500	1.14	31.4	
2	0.8	11000	1.08	30.7	34.1
3	1.7	11000	1.09	29.1	36.0
4	3.4	10700	1.10	27.9	36.4
5	4.1	9200	1.10	26.0	40.4
6	5.7	10500	1.09	24.0	40.0
7	13	6500	1.08	19.8	45.8

[a] Cloud point was determined by the temperature at which the transmittance (λ = 500 nm) of aqueous solution reaches 90%. [b] Determined by ^{1}H NMR of the obtained polymer.

the deprotected copolymers all increased (Figure 5B). As the ratio of glycerol-derived diols, i.e., DMMDO ratio, increased, the cloud points showed higher values. These results indicate that the higher incorporation of DMMDO lead to lower cloud points for protected copolymers, and higher cloud points for deprotected polymers, showing a relatively linear trend (Figure S19). Additionally, by conducting the transmittance measurements upon heating and cooling, a hysteresis behavior was observed, as is reported for poly(NIPAM) (Figure S20).[49,50] Overall, polymers with widely varying cloud points can be obtained, depending on the DMMDO incorporation rate and the presence or absence of acetal groups.

■ CONCLUSION

From the simple reaction of glycerol, a renewable resource, with acetone, a cyclic vinyl ether was synthesized. Their RAFT copolymerization with MA and NIPAM was conducted, and well-defined copolymers with various molecular weights and DMMDO incorporation were synthesized. The monomer reactivity ratios were determined using both the terminal and penultimate model. Relatively high copolymerization reactivity with MA was confirmed, and in the case of NIPAM, the ratios showed a solvent dependence. The nearly quantitative deprotection of acetal groups afforded functional copolymers with diols derived from glycerol. For the copolymers with NIPAM, their LCST behavior was evaluated to find out the cloud point of copolymers can simply be tuned through different DMMDO incorporation ratios and before and after deprotection. Given that the cloud points of the synthesized biobased thermoresponsive copolymers can be precisely tuned to temperatures near physiological temperature, these materials show potential applications such as drug-delivery systems and tissue engineering scaffold in biomedical fields.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.5c01401.

Experimental section, supplementary figures, schemes, and tables (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Kotaro Satoh – *Department of Chemical Science and Engineering, Institute of Science Tokyo, Meguro-ku, Tokyo 152-8550, Japan;* orcid.org/0000-0002-3105-4592; Email: satoh@mct.isct.ac.jp

Authors

Riko Kashima – *Department of Chemical Science and Engineering, Institute of Science Tokyo, Meguro-ku, Tokyo 152-8550, Japan*

Tomohiro Kubo – *Department of Chemical Science and Engineering, Institute of Science Tokyo, Meguro-ku, Tokyo 152-8550, Japan;* orcid.org/0000-0003-3913-5845

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.macromol.5c01401

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Haque, F. M.; Ishibashi, J. S. A.; Lidston, C. A L.; Shao, H.; Bates, F. S.; Chang, A. B.; Coates, G. W.; Cramer, C. J.; Dauenhauer, P. J.; Dichtel, W. R.; Ellison, C. J.; Gormong, E. A.; Hamachi, L. S.;

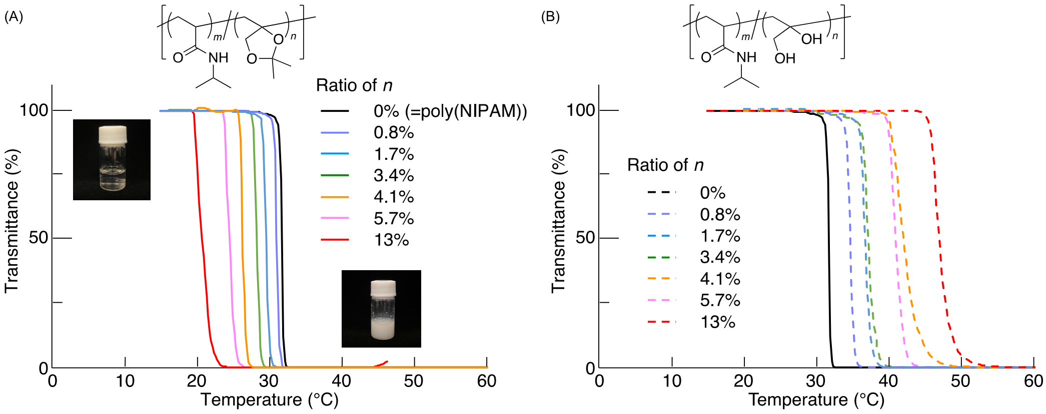

Figure 5. Temperature dependence of the aqueous solutions of the obtained copolymers before (A) and after (B) deprotection with various DMMDO incorporation ratios. Conditions: concentration = 10 mg/mL, heating rate = 1.0 °C/min.

Hoye, T. R.; Jin, M.; Kalow, J. A.; Kim, H. J.; Kumar, G.; LaSalle, C. J.; Liffland, S.; Lipinski, B. M.; Pang, Y.; Parveen, R.; Peng, X.; Popowski, Y.; Prebihalo, E. A.; Reddi, Y.; Reineke, T. M.; Sheppard, D. T.; Swartz, J. L.; Tolman, W. B.; Vlaisavljevich, B.; Wissinger, J.; Xu, S.; Hillmyer, M. A. Defining the Macromolecules of Tomorrow through Synergistic Sustainable Polymer Research. *Chem. Rev.* **2022**, *122*, 6322−6373.

(2) Zhu, Y.; Romain, C.; Williams, C. K. Sustainable Polymers from Renewable Resources. *Nature* **2016**, *540*, 354−362.

(3) Hayes, G.; Laurel, M.; MacKinnon, D.; Zhao, T.; Houck, H. A.; Becer, C. R. Polymers without Petrochemicals: Sustainable Routes to Conventional Monomers. *Chem. Rev.* **2023**, *123*, 2609−2734.

(4) Schuttner, S.; Krappel, M.; Koziol, M.; Marquart, L.; Schneider, I.; Sottmann, T.; Frey, H. Anionic Ring-Opening Copolymerization of Farnesyl Glycidyl Ether: Fast Access to Terpenoid-Derived Amphiphilic Polyether Architectures. *Macromolecules* **2023**, *56*, 6928−6940.

(5) Song, Y.; Ji, X.; Dong, M.; Li, R.; Lin, Y.-N.; Wang, H.; Wooley, K. L. Advancing the Development of Highly-Functionalizable Glucose-Based Polycarbonates by Tuning of the Glass Transition Temperature. *J. Am. Chem. Soc.* **2018**, *140*, 16053−16057.

(6) Satoh, K. Controlled/Living Polymerization of Renewable Vinyl Monomers into Bio-Based Polymers. *Polym. J.* **2015**, *47*, 527−536.

(7) Veith, C.; Diot-Néant, F.; Miller, S. A.; Allais, F. Synthesis and Polymerization of Bio-Based Acrylates: A Review. *Polym. Chem.* **2020**, *11*, 7452−7470.

(8) Matsuda, M.; Satoh, K.; Kamigaito, M. Periodically Functionalized and Grafted Copolymers via 1:2-Sequence-Regulated Radical Copolymerization of Naturally Occurring Functional Limonene and Maleimide Derivatives. *Macromolecules* **2013**, *46*, 5473−5482.

(9) Shin, J.; Lee, Y.; Tolman, W. B.; Hillmyer, M. A. Thermoplastic Elastomers Derived from Menthide and Tulipalin A. *Biomacromolecules* **2012**, *13*, 3833−3840.

(10) Nishida, T.; Satoh, K.; Tamura, M.; Li, Y.; Tomishige, K.; Kamigaito, M. Model and Terpenoid-Derived exo-Methylene Six-Membered Conjugated Dienes: Comprehensive Studies on Cationic and Radical Polymerizations of Substituted 3-Methylenecyclohexenes. *Macromolecules* **2022**, *55*, 2300−2309.

(11) Moad, G.; Rizzardo, E.; Thang, S. H. Living Radical Polymerization by the RAFT process. *Aust. J. Chem.* **2005**, *58*, 379−410.

(12) McKenzie, T. G.; Fu, Q.; Uchiyama, M.; Satoh, K.; Xu, J.; Boyer, C.; Kamigaito, M.; Qiao, G. G. Beyond Traditional RAFT: Alternative Activation of Thiocarbonylthio Compounds for Controlled Polymerization. *Adv. Sci.* **2016**, *3*, 1500394.

(13) Perrier, S. 50th Anniversary Perspective: RAFT Polymerization-A User Guide. *Macromolecules* **2017**, *50*, 7433−7447.

(14) Li, W.; Chen, G.; Zhang, Y.; Ding, J.; Liu, J.; Wang, R.; Shi, D.; Lei, W.; Zhang, L. Precision Synthesis of a Biobased Myrcene Thermoplastic Elastomer by Using an Amphiphilic Macro-RAFT Agent via Emulsion Polymerization in Aqueous Medium. *Polym. Chem.* **2024**, *15*, 2992−3002.

(15) Boner, S.; Parkatzidis, K.; Watuthanthrige, N. D. A.; Anastasaki, A. RAFT Polymerization of Renewable Monomers with Dithiobenzoates: Effect of Z-Group Substituents and Reaction Conditions. *Eur. Polym. J.* **2024**, *205*, 112721.

(16) Satoh, K.; Lee, D.-H.; Nagai, K.; Kamigaito, M. Precision Synthesis of Bio-Based Acrylic Thermoplastic Elastomer by RAFT Polymerization of Itaconic Acid Derivatives. *Macromol. Rapid Commun.* **2014**, *35*, 161−167.

(17) Tanizaki, S.; Kubo, T.; Bito, Y.; Mori, S.; Aoki, H.; Satoh, K. Development of a Bio-Based Adhesive by Polymerization of Boc-Protected Vinyl Catechol Derived from Caffeic Acid. *RSC Sustain.* **2025**, *3*, 1714−1720.

(18) Satoh, K.; Hashimoto, H.; Kumagai, S.; Aoshima, H.; Uchiyama, M.; Ishibashi, R.; Fujiki, Y.; Kamigaito, M. One-Shot Controlled/Living Copolymerization for Various Comonomer Sequence Distributions via Dual Radical and Cationic Active Species from RAFT Terminals. *Polym. Chem.* **2017**, *8*, 5002−5011.

(19) Satoh, K.; Matsuda, M.; Nagai, K.; Kamigaito, M. AAB-Sequence Living Radical Chain Copolymerization of Naturally Occurring Limonene with Maleimide: An End-to-End Sequence-Regulated Copolymer. *J. Am. Chem. Soc.* **2010**, *132*, 10003−10005.

(20) *Polyvinyl Alcohol Developments*, 2nd ed.; Finch, C. A., Ed.; Wiley: Chichester, 1992.

(21) Bayliss, N.; Schmidt, B. V. K. J. Hydrophilic Polymers: Current Trends and Visions for the Future. *Prog. Polym. Sci.* **2023**, *147*, 101753.

(22) Kadajji, V. G.; Betageri, G. V. Water Soluble Polymers for Pharmaceutical Applications. *Polymers* **2011**, *3*, 1972−2009.

(23) Schild, H. G. Poly(N-Isopropylacrylamide): Experiment, Theory and Application. *Prog. Polym. Sci.* **1992**, *17*, 163−249.

(24) Xia, Y.; Yin, X.; Burke, N. A. D.; Stöver, H. D. H. Thermal Response of Narrow-Disperse Poly(N-isopropylacrylamide) Prepared by Atom Transfer Radical Polymerization. *Macromolecules* **2005**, *38*, 5937−5943.

(25) Ray, B.; Isobe, Y.; Matsumoto, K.; Habaue, S.; Okamoto, Y.; Kamigaito, M.; Sawamoto, M. RAFT Polymerization of *N*-Isopropylacrylamide in the Absence and Presence of Y(OTf)3: Simultaneous Control of Molecular Weight and Tacticity. *Macromolecules* **2004**, *37*, 1702−1710.

(26) Tong, S.; Zeng, F.; Zheng, X.; Sato, T. Inverse Molecular Weight Dependence of Cloud Points for Aqueous Poly(N-isopropylacrylamide) Solutions. *Macromolecules* **1999**, *32*, 4488−4490.

(27) Abdelaty, M. S. A.; Kuckling, D. Poly(*N*-isopropyl acrylamide-*co*-vanillin acrylate) Dual Responsive Functional Copolymers for Grafting Biomolecules by Schiff's Base Click Reaction. *Open J. Org. Polym. Mater.* **2018**, *8*, 15−32.

(28) Rzaev, Z. M. O.; Dincer, S.; Piskin, E. Functional Copolymers of N-Isopropylacrylamide for Bioengineering Applications. *Prog. Polym. Sci.* **2007**, *32*, 534−595.

(29) Dimitrov, I.; Trzebicka, B.; Müller, A. H. E.; Dworak, A.; Tsvetanov, C. B. Thermosensitive Water-Soluble Copolymers with Doubly Responsive Reversibly Interacting Entities. *Prog. Polym. Sci.* **2007**, *32*, 1275−1343.

(30) Terao, Y.; Satoh, K.; Kamigaito, M. Controlled Radical Copolymerization of Cinnamic Derivatives as Renewable Vinyl Monomers with Both Acrylic and Styrenic Substituents: Reactivity, Regioselectivity, Properties, and Functions. *Biomacromolecules* **2019**, *20*, 192−203.

(31) Gandini, A.; Lacerda, T. M.; Carvalho, A. J. F.; Trovatti, E. Progress of Polymers from Renewable Resources: Furans, Vegetable Oils, and Polysaccharides. *Chem. Rev.* **2016**, *116*, 1637−1669.

(32) Attarbachi, T.; Kingsley, M. D.; Spallina, V. New Trends on Crude Glycerol Purification: A Review. *Fuel* **2023**, *340*, 127485.

(33) Hejna, A.; Kosmela, P.; Formela, K.; Piszczyk, Ł.; Haponiuk, J. T. Potential Applications of Crude Glycerol in Polymer Technology-Current State and Perspectives. *Renew, Sustain. Energy Rev.* **2016**, *66*, 449−475.

(34) Sunder, A.; Hanselmann, R.; Frey, H.; Mulhaupt, R. Controlled Synthesis of Hyperbranched Polyglycerols by Ring-Opening Multibranching Polymerization. *Macromolecules* **1999**, *32*, 4240−4246.

(35) Zhang, H.; Grinstaff, M. W. Recent Advances in Glycerol Polymers: Chemistry and Biomedical Applications. *Macromol. Rapid Commun.* **2014**, *35*, 1906−1924.

(36) Rokicki, G.; Rakoczy, P.; Parzuchowski, P.; Sobiecki, M. Hyperbranched Aliphatic Polyethers Obtained from Environmentally Benign Monomer: Glycerol Carbonate. *Green. Chem.* **2005**, *7*, 529−539.

(37) Lingier, S.; Spiesschaert, Y.; Dhanis, B.; De Wildeman, S.; Du Prez, F. E. Rigid Polyurethanes, Polyesters, and Polycarbonates from Renewable Ketal Monomers. *Macromolecules* **2017**, *50*, 5346−5352.

(38) Kashima, R.; Kajita, A.; Kubo, T.; Kamigaito, M.; Satoh, K. Hydrophilic Bio-Based Polymers by Radical Copolymerization of Cyclic Vinyl Ethers Derived from Glycerol. *Chem. Commun.* **2022**, *58*, 8766−8769.

(39) Goodman, M.; Abe, A. Coupled Vinyl and Acetal Ring-Opening Polymerization. *J. Polym. Sci,. Part A: Gen. Pap.* **1964**, *2*, 3471−3490.

(40) Tardy, A.; Nicolas, J.; Gigmes, D.; Lefay, C.; Guillaneuf, Y. Radical Ring-Opening Polymerization: Scope, Limitations, and Application to (Bio)Degradable Materials. *Chem. Rev.* **2017**, *117*, 1319−1406.

(41) Hiraguri, Y.; Endo, T. Novel Synthesis of a Polyketone via Radical Ring-Opening Polymerization of 2,2-Diphenyl-4-Methylene-l,3-Dioxolane. *J. Am. Chem. Soc.* **1987**, *109*, 3779−3780.

(42) Pan, C.-Y.; Wu, Z.; Bailey, W. J. Preparation and Polymerization of 2-Phenyl-4-methylene-1,3-dioxolane. *J. Polym. Sci.; Part C: Polym. Lett.* **1987**, *25*, 243−248.

(43) Lynd, N. A.; Ferrier, R. C., Jr; Beckingham, B. S. Recommendation for Accurate Experimental Determination of Reactivity Ratios in Chain Copolymerization. *Macromolecules* **2019**, *52*, 2277−2285.

(44) Meyer, V. E.; Lowry, G. G. Integral and Differential Binary Copolymerization Equations. *J. Polym. Sci., Part A: Gen. Pap.* **1965**, *3*, 2843−2851.

(45) Ito, T.; Otsu, T. Solvent Effect in Radical Copolymerization of Methyl Methacrylate with Styrene. *J. Macromol. Sci., Part A: Chem.* **1969**, *3*, 197−203.

(46) Minsk, L. M.; Kotlarchik, C.; Darlak, R. S. Effect of Solvents Upon the Copolymerization of Acrylamide and Styrene. *J. Polym. Sci., Part A: Polym. Chem.* **1973**, *11*, 353−365.

(47) Saini, G.; Leoni, A.; Franco, S. Solvent Effects in Radical Copolymerization III. Methacrylamide. *Makromol. Chem.* **1971**, *147*, 213−218.

(48) Barson, C. A.; Fenn, D. R. A Method for Determining Reactivity Ratios when Copolymerizations are Influenced by the Penultimate Group Effects of Both Monomers. *Eur. Polym. J.* **1989**, *25*, 719−720.

(49) Roy, D.; Brooks, W. L. A.; Sumerlin, B. S. New Directions in Thermoresponsive Polymers. *Chem. Soc. Rev.* **2013**, *42*, 7214−7243.

(50) Wang, X.; Qiu, X.; Wu, C. Comparison of the Coil-to-Globule and the Globule-to-Coil Transitions of a Single Poly(*N*-Isopropylacrylamide) Homopolymer Chain in Water. *Macromolecules* **1998**, *31*, 2972−2976.