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Design and Synthesis of Thermoresponsive Aliphatic Polyethers with Tunable Phase Transition Temperature

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Abstract

This paper describes the comprehensive study of the lower critical solution temperature (LCST)-type thermoresponsive properties of various poly(glycidyl ether) homopolymers, varying in their side chain structure, molecular weight, and main chain tacticity, as well as their copolymers, varying in the monomer composition and monomer sequence. For the initial screening, we prepared nine kinds of poly(glycidyl ether)s by the phosphazene base-catalyzed ring-opening polymerization of glycidyl methyl ether (MeGE), ethyl glycidyl ether (EtGE), glycidyl isopropyl ether (iPrGE), 2-methoxyethyl glycidyl ether (MeEOGE), 2-ethoxyethyl glycidyl ether (EtEOGE), 2-propoxyethyl glycidyl ether (PrEOGE), 2-(2-methoxyethoxy)ethyl glycidyl ether ($MeEO_2GE$), 2-(2-ethoxyethyl)ethyl glycidyl ether ($EtEO_2GE$), and 2-(2-(2-methoxyethoxy)ethoxy)ethyl glycidyl ether ($MeEO_3GE$). Among them, poly(MeGE), poly(EtGE), poly(MeEOGE), poly(EtEOGE), and poly($MeEO_2GE$) (M_n = ca. 5000 g mol^{-1}) were found to exhibit the LCST-type phase transition in water at 65.5 °C, 10.3 °C, 91.6 °C, 41.3 °C, and 58.2 °C, respectively. Although the molecular weight and main chain tacticity had little impact on the phase transition temperature, the side chain structure, i.e., the number of oxythylene units and terminal alkyl group, significantly affected the transition temperature. The statistical copolymers composed of MeEOGE and EtEOGE revealed that the transition temperature of the polymer can be desirably customized in between those of the homopolymers by varying the monomer composition. On the other hand, we found that the block

copolymer composed of MeEOGE and EtEOGE exhibited a complex thermoresponsive behavior due to its ability to form a micellar aggregate.

Introduction

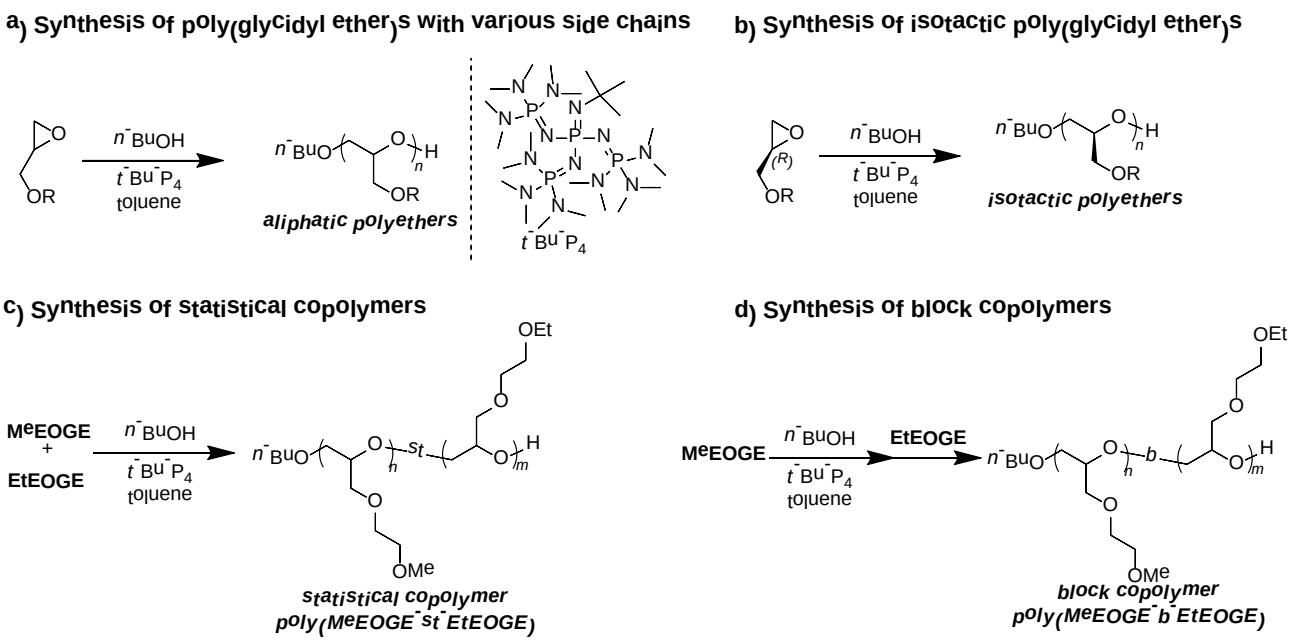
Aliphatic polyethers, which can be produced by the ring-opening polymerization (ROP) of epoxides, have been an important class of polymeric materials for use in a wide variety of application fields, including lubricants, emulsifiers, and raw materials for polyurethanes.[1] Apart from such conventional uses, the aliphatic polyethers have received a good deal of attention as a building block for the design of smart materials because of their low toxicity, biocompatibility, and thermoresponsive property.[2-6] Poly(ethylene oxide) (PEO) has been the most important one among the aliphatic polyethers and has been the focus of intense research investigations for constructing a wide variety of smart materials.[7-9] However, one drawback of the PEO, which is the absence of a functional group loading capacity on its main chain, makes it difficult to optimize the property and function of the smart materials. To overcome this inherent problem, the copolymerization of EO with various epoxide monomers has been intensively studied by several research groups, and this approach has successfully produced a wide variety of PEO derivatives with desirable stimuli responsive properties.[10-14] However, the experimental handling of EO is very problematic because of its gaseous characteristic, toxicity, and flammability. Furthermore, the copolymerization of EO and substituted epoxides sometimes results in producing blocky copolymers with the EO-rich segment near from the initiation end, because of the appreciable difference in their reactivities.[15] Therefore, exploring an alternative aliphatic polyether system as tunable thermoresponsive materials is of great importance.

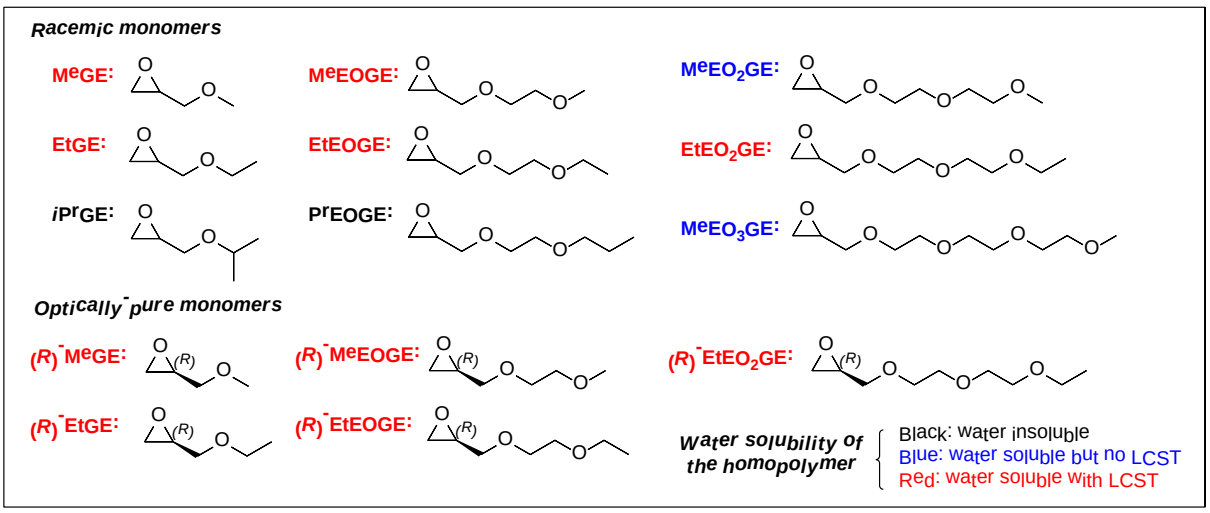
According to pioneering studies, some of the water-soluble aliphatic polyethers made of glycidyl ethers exhibit a lower critical solution temperature (LCST)-type phase transition in their aqueous solutions.[16-18] The LCST-type thermoresponsiveness is the most useful and important characteristic for the smart material design. For example, Watanabe et al. reported that poly(glycidyl methyl ether), poly(ethyl glycidyl ether), and poly(ethoxyethyl glycidyl ether) showed the LCST-type phase transition at 57.7, 14.6, and 40.0 °C, respectively, at which the polymers became insoluble in water.[19] In addition, Weinhart and Schmalz found that the LCST of the random copolymers made from glycidyl methyl ether and ethyl glycidyl ether can be optimized from 15 to 60 °C by the comonomer composition.[20] It should be emphasized that many of the glycidyl ether monomers are commercially available, and such monomers can be easily handled, unlike EO. Despite the potential benefits of the poly(glycidyl ether)s as the thermoresponsive material, a systematic study of the correlation between the thermoresponsive properties and polymer structures of the poly(glycidyl ether)s has not yet been reported. Such information should be of fundamental interest for the design of novel smart materials based on the poly(glycidyl ether)s.

In this article, we report a comprehensive investigation of the thermoresponsive properties of a series of well-defined poly(glycidyl ether) homopolymers, varying in side chain structure, molecular weight, and main chain tacticity, as well as the copolymers, varying in comonomer composition and monomer sequence (**Scheme 1**). To have a better understanding of the correlation between the side chain structure and thermoresponsive property, nine kinds of glycidyl ethers were

evaluated; i.e., glycidyl methyl ether (MeGE), ethyl glycidyl ether (EtGE), glycidyl isopropyl ether (iPrGE), 2-methoxyethyl glycidyl ether (MeEOGE), 2-ethoxyethyl glycidyl ether (EtEOGE), 2-propoxyethyl glycidyl ether (PrEOGE), 2-(2-methoxyethoxy)ethyl glycidyl ether ($MeEO_2GE$), 2-(2-ethoxyethyl)ethyl glycidyl ether ($EtEO_2GE$), and 2-(2-(2-methoxyethoxy)ethoxy)ethyl glycidyl ether ($MeEO_3GE$). The anionic ROP of the various glycidyl ethers was carried out using the combination of a phosphazene base catalyst (*t*-Bu-P_4) and alcohol initiator, which provided the corresponding poly(glycidyl ether)s with very narrow dispersities and predictable molecular weights.[21-23] The aqueous solutions of the well-defined poly(glycidyl ether)s were subjected to a turbidimetric measurement to provide information about the correlation between the thermoresponsive properties and polymer structures.

Scheme 1. Synthesis of thermoresponsive aliphatic polyethers via *t*-Bu-P_4-catalyzed ring-opening polymerization of various glycidyl ether monomers





Results and Discussion

Thermoresponsive Properties of Various Poly(glycidyl ether) Homopolymers. For the initial study, we investigated the water solubility and thermoresponsive characteristics of a series of aliphatic polyethers varying in side chain structure while fixing the chain end group (*n*-butoxy group for the α-chain end and hydroxyl group for the ω-chain end) and molecular weight, i.e., poly(MeGE), poly(EtGE), poly(*i*PrGE), poly(MeEOGE), poly(EtEOGE), poly(PrEOGE), poly($MeEO_2GE$), poly($EtEO_2GE$), and poly($MeEO_3GE$). In accordance with **Scheme 1a**, all the polyethers were prepared by the *t*-Bu-P_4-catalyzed anionic ROP of the corresponding glycidyl ether monomers using *n*-butanol (*n*-BuOH) as the initiator (**Tables 1** and S1). Here, the initial monomer-to-initiator ratio ($[M]_0/[n\text{-BuOH}]$) was varied in the range of 25 – 100 to produce the polyethers with various molecular weights. All the polymerizations proceeded with a quantitative monomer conversion (conv. >99%), giving the corresponding polyethers with the desired molecular weight ranging from 2000 to 14000 g mol^{-1}. The size exclusion chromatography (SEC) experiment was performed using the obtained products (**Figures 1,** S1 – S6), which demonstrated the narrow dispersity (M_w/M_n) value of less than 1.1. In addition, the ^{1}H NMR spectra exhibited signals due to the *n*-butoxy group, indicating that the obtained product definitely possessed an *n*-butoxy group at the α-chain end (Figure S7 – 11). **Table 1** lists the molecular characteristics of the polyethers possessing the LCST-type thermoresponsive property (*vide infra*).

Table 1. Synthesis and thermoresponsive property of poly(MeGE)$_{5k}$, poly(EtGE)$_{5k}$, poly(MeEOGE)$_{5k}$, poly(EtEOGE)$_{5k}$, and poly(EtEO$_2$GE)$_{5k}$ [a]

sample ID	$[M]_0$/ $[n$-BuOH$]_0$/ $[t$-Bu-P$_4]_0$	time (h)	$M_{n,theo}$ [b] (g mol^{-1})	$M_{n,NMR}$ [c] (g mol^{-1})	M_w/M_n [d]	T_{cp} (ºC) [e]
poly(MeGE)$_{5k}$	56/1/1	20	5010	4,940	1.03	65.5
poly(EtGE)$_{5k}$	50/1/3	20	5180	5,290	1.04	10.3
poly(MeEOGE)$_{5k}$	37/1/1	12	4960	4,860	1.05	91.6
poly(EtEOGE)$_{5k}$	34/1/1	12	5040	5,030	1.04	41.3
poly(EtEO$_2$GE)$_{5k}$	25/1/1	12	4830	4,930	1.06	58.2

[a] Polymerization condition: Ar atmosphere; solvent, toluene; initiator, *n*-BuOH; $[M]_0$ = 2.5 mol L^{-1}; temp., 27 °C; conv., >99%. [b] Calculated from ($[M]_0/[n$-BuOH$]_0$) × (conv.) × (M.W. of monomer) + (M.W. of initiator) [c] Determined by ^{1}H NMR in $CDCl_3$. [d] Determined by SEC in THF using polystyrene standards. [e] Determined by turbidimetric analysis for a 1 wt% aqueous polymer solution.

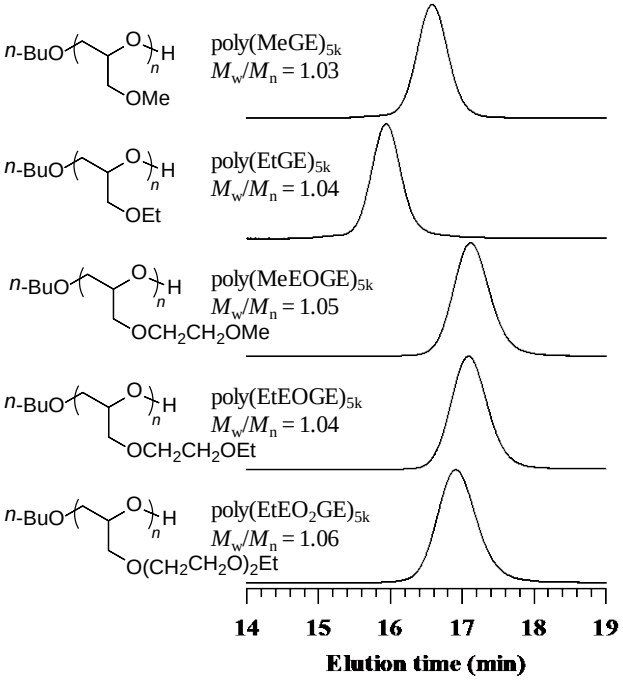


Figure 1. SEC traces of poly(MeGE)$_{5k}$, poly(EtGE)$_{5k}$, poly(MeEOGE)$_{5k}$, poly(EtEOGE)$_{5k}$, and poly(EtEO$_2$GE)$_{5k}$ (eluent, THF; flow rate, 1.0 mL min^{-1}).

Among the nine kinds of aliphatic polyethers, poly(MeGE), poly(EtGE), poly(MeEOGE), poly(EtEOGE), poly(MeEO$_2$GE), poly(EtEO$_2$GE), and poly(MeEO$_3$GE) were found to be soluble in pure water at room temperature or even at a lower temperature. The aqueous solutions of poly(MeGE), poly(EtGE), poly(MeEOGE), poly(EtEOGE), and poly(EtEO$_2$GE) were found to become opaque upon heating, suggesting the LCST-type phase transition. On the other hand, poly(MeEO$_2$GE) and poly(MeEO$_3$GE) were completely soluble in water and did not show any LCST-type phase transition even at 95 °C. It should be noted that polyacrylates and polymethacylate possessing diethylene and triethylene glycol monomethyl ether side chains showed an LCTS-type phase transition in water,[24,25] which is in sharp contrast to the results of poly(MeEO$_2$GE) and poly(MeEO$_3$GE). The absence of the LCST phase transition in these polymers is attributable to the very strong hydrophilicity originating from the PEO backbone. In addition, the presence of the methyl side chain terminal, instead of ethyl or longer alkyl ones, also contributed the absence of the LCST phase transitions in these polymers.

The cloud point (T_{cp}) for the five kinds of thermoresponsive polyethers with the $M_{n,NMR}$ of ca. 5000 g mol^{-1} was then examined by the variable-temperature UV absorption measurement for the 1 wt% aqueous solution (**Figure 2a**). In all cases, a very sharp decrease in the transmittance was observed upon heating, from which the T_{cp} value can be determined. Here, the T_{cp} was defined as the temperature at which the transmittance of the solution reached 50% (at λ = 500 nm). As listed in

Table 1, the T_{cp} of the polyethers was observed in the temperature range of 10.3 – 91.6 °C and increased in the following order: poly(EtGE) (10.3 °C) < poly(EtEOGE) (41.3 °C) < poly($EtEO_2GE$) (58.2 °C) < poly(MeGE) (65.5 °C) < poly(MeEOGE) (91.6 °C). Thus, the polyether system is capable of performing a thermoresponsive event over a wide temperature range. We found that the phase transition is reversible with a negligible hysteresis. As shown in **Figure 2a**, the transmittance of each solution recovered to 100% upon cooling. Therefore, the hysteresis for the polyether system is highly suppressed unlike the phase transition of poly(*N*-isopropylacrylamide) (PNIPAM).[26] The suppressed hysteresis in the polyethers should be attributed to the absence of the amide group which causes additional inter- and intramolecular hydrogen binding formations in the globule state. It was also found that the molecular weight had little effect on the T_{cp} value of the polyethers (**Figure 2b**). The T_{cp} values of a series of polyethers with varied molecular weights are listed in Table S1 along with their molecular characteristics. For poly(MeGE) and poly(MeEOGE), the T_{cp} value slightly decreased with the increasing molecular weight and finally converged at a certain temperature. Such a tendency had been commonly observed for a wide variety of thermoresponsive polymers and can be explained by the contributions from the end group polarity as well as the local concentration. On the other hand, the other thermoresponsive polyethers did not show any significant change in the LCST upon an increase in their molecular weight.

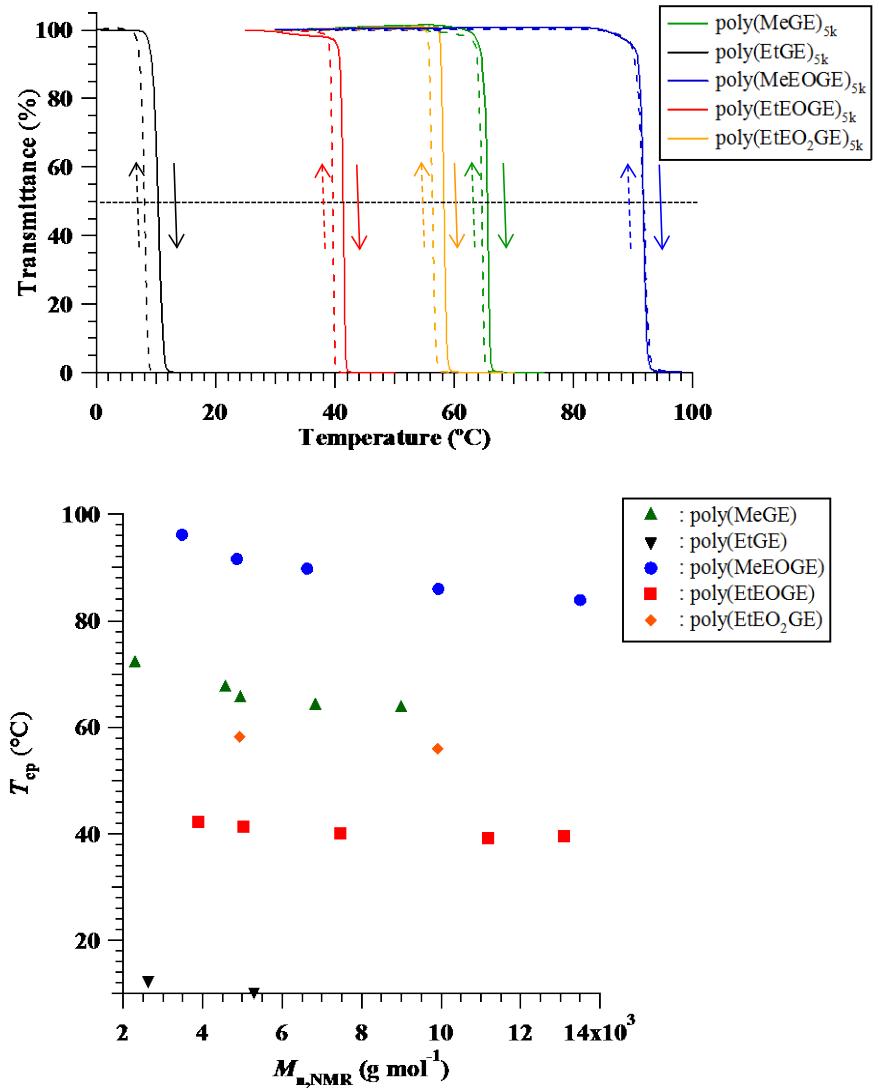


Figure 2. (a) Transmittance curves for 1 wt% aqueous solutions of poly(MeGE)$_{5k}$ (green), poly(EtGE)$_{5k}$ (black), poly(MeEOGE)$_{5k}$ (blue), poly(EtEOGE)$_{5k}$ (red), and poly(EtEO$_2$GE)$_{5k}$ (orange) during the heating (solid line) or cooling (dotted line) process. (b) Dependence of T_{cp} on the $M_{n,NMR}$ for poly(MeGE)s (green), poly(EtGE)s (black), poly(MeEOGE)s (blue), poly(EtEOGE)s (red), and poly(EtEO$_2$GE)s (orange).

It is very important to understand the correlation between the polymer structure and LCST for the rational design of aliphatic polyether-based novel thermoresponsive materials. To gain insight into the structure-T_{cp} relationship, the T_{cp} value was plotted versus the number of oxyethylene units on the side chain, as shown in **Figure 3**. For comparison, the T_{cp} data for the poly(acrylate)s and

poly(methacrylate)s carrying the oligo(ethylene glycol) (OEG) side chain are also included in **Figure 3**.[27,28] There is a general tendency that the increase in the number of oxyethylenes unit results in an increase in the T_{cp} value, and one oxyethylene unit increased the T_{cp} by ca. 25 °C. A similar tendency was observed in the OEG-functionalized poly(acrylate)s and poly(methacrylate)s, as can be seen in **Figure 3**. It should be mentioned that the T_{cp} values for the polyether system are much higher than those of the OEG-functionalized poly(acrylate)s and poly(methacrylate)s. This observation suggested that the increase in the hydrophobicity of the main chain led to lowering of the T_{cp} value. In the case of aliphatic polyethers, both the main chain and side chain are made of hydrophilic oxyethylene units, which endowed them with a higher T_{cp}, and thus LCST, than any other kinds of OEG-functionalized thermoresponsive polymers.

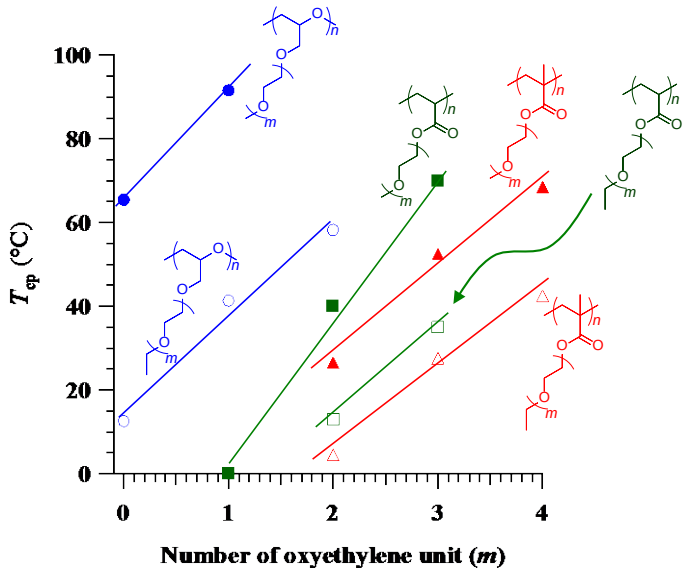


Figure 3. Relationship between the cloud points (T_{cp}) and number of oxyethylene units on the side chain (*m*) for the aqueous solutions of poly(MeGE), poly(EtGE), poly(MeEOGE), poly(EtEOGE), and poly($EtEO_2GE$). For comparison purposes, the T_{cp}s (or LCSTs) of the thermoresponsive poly(acrylate)s and poly(methacrylate)s carrying oligo(oxyethylene) side chain are also plotted.[27,28]

When compared among the polyethers having the methyl and ethyl side chain terminals, the T_{cp} value for the methyl ether polymers was ca. 50 °C higher than that of the corresponding ethyl ethers. This clearly suggested that the introduction of the hydrophobic group at the side chain terminal has a significant impact on the LCST. Aoshima et al.[29] and Ishizone et al.[30] also determined the significant role in the side chain terminal structure on the LCST of the poly(vinyl ether)s and poly(methacrylate)s. Such a simple correlation between the side chain structure and T_{cp} value could be helpful for designing thermoresponsive aliphatic polyethers with the desired phase transition temperature.

Thermoresponsive Properties of Isotactic Poly(glycidyl ether)s. Next, the thermoresponsive properties of the isotactic polyethers were investigated using the same technique as previously

described. As reported in our previous paper, the *t*-Bu-P_4-catalyzed ROP of the optically-pure epoxide monomer afford the corresponding isotactic polymers without stereoinversion.[31] Thus, we prepared the optically-pure glycidyl ether monomers, i.e, (*R*)-MeGE, (*R*)-EtGE, (*R*)-MeEOGE, (*R*)-EtEOGE, and (*R*)-EtEO_2GE, by reacting the corresponding alcohols with (*S*)-epichlorohydrin (*ee* <99%) in the presence of BF_3-Et_2O to produce the corresponding chlorohydrins and subsequent ring closure reaction under basic conditions (Scheme S1). The chiral HPLC analysis proved that all the obtained monomers were sufficiently pure with the enantiomeric excess (*ee*) of >95% (Figure S12). The *t*-Bu-P_4-catalyzed ROP of the optically-active monomers with the *n*-BuOH initiator successfully afforded the corresponding optically-active polyethers (Table S2), i.e., poly[(*R*)-MeGE]$_{9k}$ ($M_{n,NMR}$ = 8990 g mol^{-1}, M_w/M_n = 1.04, $[\alpha]_D$ = -35.7 °), poly[(*R*)-EtGE]$_{5k}$ ($M_{n,NMR}$ = 5430 g mol^{-1}, M_w/M_n = 1.04, $[\alpha]_D$ = -26.3 °), poly[(*R*)-MeEOGE]$_{13k}$ ($M_{n,NMR}$ = 13000 g mol^{-1}, M_w/M_n = 1.05, $[\alpha]_D$ = -20.5 °), poly[(*R*)-EtEOGE]$_{15k}$ ($M_{n,NMR}$ = 15100 g mol^{-1}, M_w/M_n = 1.07, $[\alpha]_D$ = -21.0 °), and poly[(*R*)-EtEO_2GE]$_{10k}$ ($M_{n,NMR}$ = 9640 g mol^{-1}, M_w/M_n = 1.05, $[\alpha]_D$ = -14.3 °), with narrow M_w/M_n value of less than 1.1 (Figure S13). The specific rotation value of these products was in the range of -14.3 – -35.7 °. To obtain further information about the main chain tacticity, a ^{13}C NMR analysis was performed on the obtained products. As a representative example, a comparison between the ^{13}C NMR spectra of the atactic and isotactic poly(MeEOGE)s is depicted in **Figure 4**. The ^{13}C NMR spectra of the optically-active polyethers showed only one signal due to the *ii* triad for the main chain methin carbon at around 79 ppm, while the corresponding atactic counterparts exhibited three signals

assignable to the *ii*, *is*/*si*, and *ss* triads with an approximately 1:2:1 integral ratio (Figures S14 – S18). These results implied that the polymerizations proceeded without the racemization of the stereocenter. Therefore, we have succeeded in the preparation of the isotactic version of the thermoresponsive aliphatic polyethers.

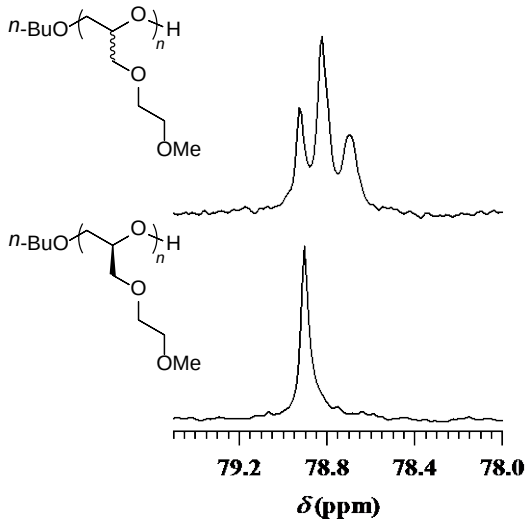


Figure 4. ^{13}C NMR spectra of the main chain methin carbon region for poly(MeEOGE)$_{14k}$ and poly[(*R*)-MeEOGE]$_{13k}$ in $CDCl_3$ (400 MHz).

We next examined the thermoresponsive behavior of the isotactic polyethers and compared them to the corresponding atactic counterparts (**Figure 5**). Table S3 summarizes the molecular characteristics and thermoresponsive behaviors of the atactic and isotactic polyethers with comparable molecular weights. All the isotactic polyethers indeed exhibited the LCST-type phase transition, and the T_{cp} value for the isotactic ones tended to become slightly higher than that of the corresponding atactic counterparts. For example, the T_{cp} value of poly[(*R*)-MeGE]$_{9k}$ was determined

to be 62.7°C, while poly(MeGE)$_{9k}$ exhibited the T_{cp} at 63.6 °C. At this stage, however, it is difficult to exclude the effect of the difference in the molecular weights among the isotactic and atactic samples. Therefore, we tentatively concluded that the main chain tacticity has a negligible impact on both the phase transition temperature and phase separation mechanism of the aliphatic polyethers.[32] This observation is in stark contrast to the tacticity-dependent thermoresponsive behaviors of the PNIPAMs.[33] Ishizone et al. also reported that a small difference in the main chain taciticity of the OEG-functionalized polymethacrylates also affects its LCST.[34] The reduced impact of the tacticity on the thermoresponsive polyethers should be attributed to the highly flexible nature of the polyether main chain as well as the absence of the hydrogen bond-forming functional group.

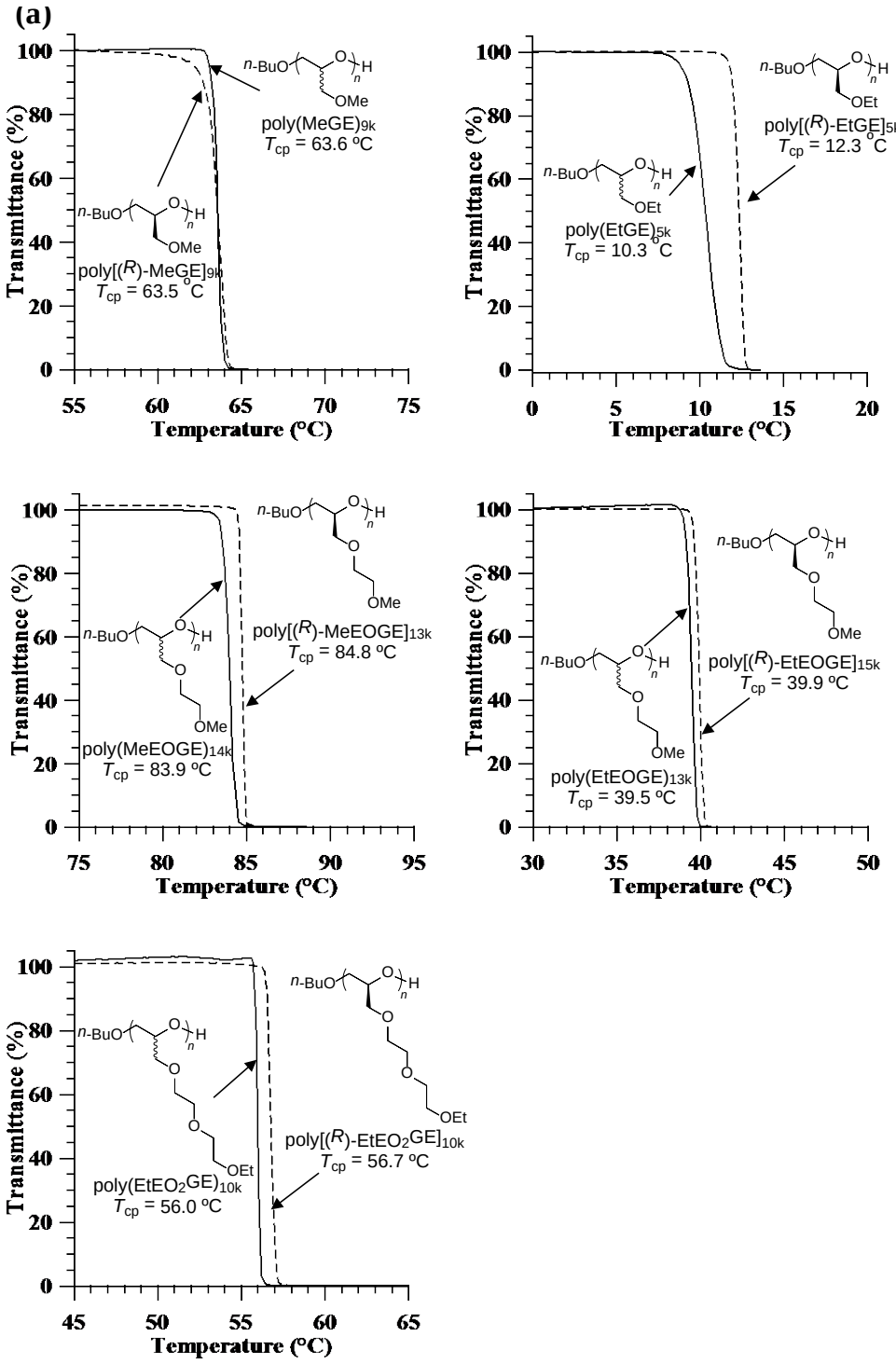


Figure 5. Comparison between the transmittance curves for 1 wt% aqueous solutions of atactic (solid line) and isotactic (broken line) (a) poly(MeGE)s, (b) poly(EtGE)s, (c) poly(MeEOGE)s, (d) poly(EtEOGE)s, and (e) poly($EtEO_2GE$)s.

Tuning of Thermoresponsive Properties by Statistical Copolymerization. Random (or

statistical) copolymerization had been generally employed to modify the thermoresponsive properties by incorporating either hydrophilic or hydrophobic comonomers. For example, Weinhart recently reported that the copolymerization of MeGE and EtGE occurred in a random fashion, and the resultant copolyether with a 1:3 monomer composition demonstrated an LCST near the human body temperature.[20] We have synthesized a series of copolyethers consisting of MeEOGE and EtEOGE with various monomer compositions aimed at gaining a correlation between the monomer composition and T_{cp} as well as to achieve a precise control over the thermoresponsive temperature over a wide temperature range.

The *t*-Bu-P_4-catalyzed ring-opening copolymerizations of MeEOGE and EtEOGE with various feed ratios were performed using *n*-BuOH as the initiator to produce a series of statistical copolymers with varying total molecular weights as well as the monomer composition (**Scheme 1c** and **Table 2)**. We first examined the copolymerizations with the $[MeEOGE]_0/[EtEOGE]_0/[n\text{-BuOH}]_0$ ratios of 6/19/1, 13/13/1, and 19/6/1. Both monomers were quantitatively consumed within 12 h, giving the statistical copolymers, i.e., poly(MeEOGE-*st*-EtEOGE)$_{4k}$s, with the $M_{n,NMR}$ value of 3600 – 3770 g mol^{-1} (DP = ca. 25). The mole fraction of MeEOGE in the obtained copolymers (F_{MeEOGE}) was evaluated by ^{1}H NMR and was found to be 0.24 for poly(MeEOGE$_{0.24}$-*st*-EtEOGE$_{0.76}$)$_{4k}$, 0.51 for poly(MeEOGE$_{0.51}$-*st*-EtEOGE$_{0.49}$)$_{4k}$, and 0.75 for poly(MeEOGE$_{0.75}$-*st*-EtEOGE$_{0.25}$)$_{4k}$ (Figure S20). In a similar manner, a series of poly(MeEOGE-*st*-EtEOGE)s with the $M_{n,NMR}$ values of ca. 7000 g mol^{-1} (DP = ca. 50; poly(MeEOGE-*st*-EtEOGE)$_{7k}$s) and 14000 g mol^{-1} (DP = ca. 75;

poly(MeEOGE-*st*-EtEOGE)$_{14k}$s) were prepared by varying the [MeEOGE]$_0$/[EtEOGE]$_0$/[*n*-BuOH]$_0$ ratio. Importantly, the monomer feed ratio did not affect the M_w/M_n values of the resultant copolymer and the M_w/M_n value was found in the range of 1.03 – 1.06 (Figure S21).

Table 2. Statistical copolymerization of MeEOGE and EtEOGE [a]

polymer	[MeEOGE]$_0$/ [EtEOGE]$_0$/ [*n*-BuOH]$_0$	time (h)	$M_{n,NMR}$ [b] (g mol^{-1})	M_w/M_n [c]	F_{MeEOGE} [d]	T_{cp} [e] (°C)
poly(MeEOGE$_{0.24}$-*st*-EtEOGE$_{0.76}$)$_{4k}$	6/19/1	12	3,770	1.06	0.24	47.6
poly(MeEOGE$_{0.51}$-*st*- EtEOGE$_{0.49}$)$_{4k}$	13/13/1	12	3,680	1.06	0.51	57.6
poly(MeEOGE$_{0.75}$-*st*- EtEOGE$_{0.25}$)$_{4k}$	19/6/1	12	3,600	1.06	0.75	71.6
poly(MeEOGE$_{0.25}$-*st*- EtEOGE$_{0.75}$)$_{7k}$	13/37/1	20	7,270	1.03	0.25	48.2
poly(MeEOGE$_{0.51}$-*st*- EtEOGE$_{0.49}$)$_{7k}$	25/25/1	20	7,080	1.04	0.51	57.9
poly(MeEOGE$_{0.75}$-*st*- EtEOGE$_{0.25}$)$_{7k}$	37/13/1	20	6,900	1.04	0.75	69.8
poly(MeEOGE$_{0.25}$-*st*- EtEOGE$_{0.75}$)$_{14k}$	25/75/1	24	14,400	1.04	0.25	46.9
poly(MeEOGE$_{0.50}$-*st*- EtEOGE$_{0.50}$)$_{14k}$	50/50/1	24	13,700	1.04	0.50	56.0
poly(MeEOGE$_{0.74}$-*st*- EtEOGE$_{0.26}$)$_{14k}$	75/25/1	24	14,300	1.04	0.74	66.9

[a] Polymerization condition: Ar atmosphere; solvent, toluene; initiator, *n*-BuOH; [*n*-BuOH]$_0$/[*t*-Bu-P$_4$]$_0$ = 1/1; [MeEOGE + EtEOGE]$_0$ = 2.5 mol L^{-1}; temp., 27 °C; conv. of each monomer, >99%. [b] Determined by ^{1}H NMR in $CDCl_3$. [c] Determined by SEC in THF using polystyrene standards. [d] Mole fraction of MeEOGE in the copolymer (F_{MeEOGE}) was determined by ^{1}H NMR. [e] Determined by turbidimetric analysis for a 1 wt% aqueous polymer solution.

Figure 6a displays the representative transmittance curves for the statistical copolymers along with their corresponding homopolymers. The aqueous solutions of the statistical copolymers also exhibited a very sharp phase transition upon heating. The T_{cp} value of the copolymers and homopolymers was plotted as a function of F_{MeEOGE}, as shown in **Figure 6b**. The copolymers exhibited a phase transition between the T_{cp} of the parent homopolymers and the T_{cp} increased with

the increasing F_{MEGE}, as expected. The molecular weight of the copolymer had little effect on the thermoresponsive behaviors. It can be reasonably expected that any combination of two different monomers can produce the thermoresponsive copolymers with a desirable T_{cp} between the two parent homopolymers. These results confirmed that the statistical copolymerization is one of the effective strategies for the fine-tuning of the LCST of the thermoresponsive aliphatic polyethers.

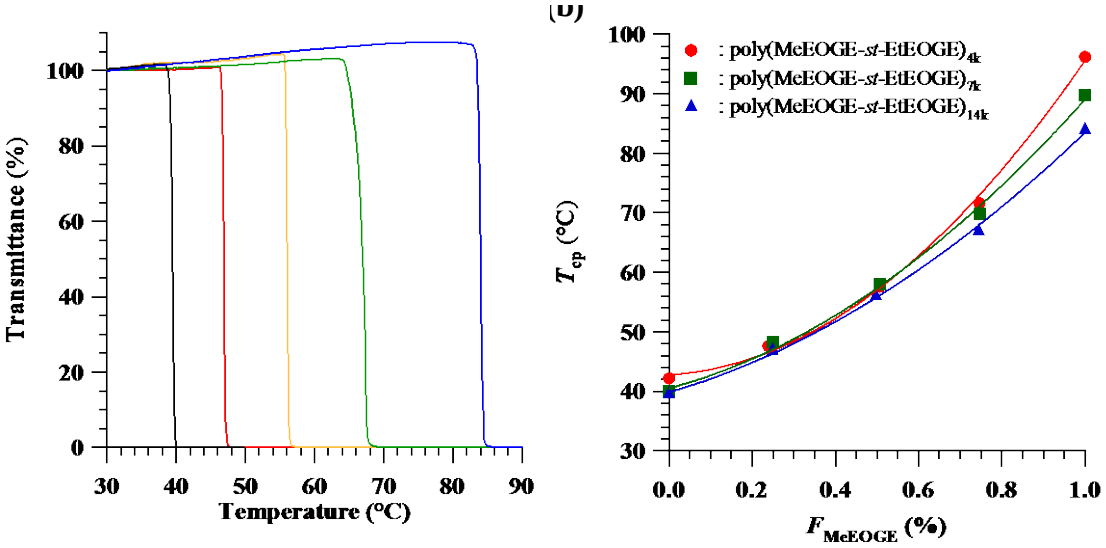


Figure 6. (a) Transmittance curves for 1 wt% aqueous solutions of poly(EtEOGE)$_{13k}$ (black line), poly(MeEOGE$_{0.25}$-*st*-EtEOGE$_{0.75}$)$_{14k}$ (red line), poly(MeEOGE$_{0.50}$-*st*- EtEOGE$_{0.50}$)$_{14k}$ (yellow line), poly(MeEOGE$_{0.74}$-*st*- EtEOGE$_{0.26}$)$_{14k}$ (green line), and poly(MeEOGE)$_{13k}$ (blue line). (b) Dependence of T_{cp} on the mole fraction of MeEOGE (F_{MeEOGE}) in the statistical copolymer.

Tuning of Thermoresponsive Properties by Block Copolymerization. We finally investigated the thermoresponsive behaviors of the BCPs consisting of MeEOGE and EtEOGE in order to gain an insight into the effect of the monomer sequence. In our previous studies, the *t*-Bu-P$_4$-catalyzed ROP was demonstrated to be an excellent way to synthesize the well-defined block copolymers of the

glycidyl ethers.[22,23,31] Thus, we conducted the sequential block copolymeization of MeEOGE followed by EtEOGE using the *t*-Bu-P_4/*n*-BuOH system with the $[MeEOGE]_0/[EtEOGE]_0/[n\text{-BuOH}]_0$ ratio of 25/75/1, 50/50/1, and 75/25/1 to afford a series of poly(MeEOGE-*b*-EtEOGE) having variosu F_{MEGE} values (**Scheme 1d** and **Table 3**). As the first stage of the block copolymerization, the *t*-Bu-P_4-catalyzed ROP of MeEOGE with the $[MeEOGE]_0/[n\text{-BuOH}]_0/[t\text{-Bu-P}_4]_0$ ratio of 25/1/1 was carried for 20 h. The ^{1}H NMR and SEC analyses of an aliquot of the polymerization mixture revealed the full monomer conversion and confirmed the formation of a living poly(MeEOGE) oxyanion with the $M_{n,NMR}$ of 4050 g mol^{-1} and M_w/M_n of 1.06. The block copolymerization was then started by adding 75 equivalents of EtEOGE with respect to the *n*-BuOH used for the first polymerization. After a 24-h polymerization, the quantitative consumption of EtEOGE was observed by ^{1}H NMR. In addition, the obtained copolymer showed proton signals corresponding to both the poly(MeEOGE) and poly(EtEOGE), and the F_{MeEOGE} and $M_{n,NMR}$ were calculated to be 0.24 and 11800 g mol^{-1}, respectively. Moreover, the SEC trace of the final product shifted to the higher molecular weight region as compared to that of the poly(MeEOGE) obtained by the first polymerization (**Figure 7**). Although a small shoulder peak was visible in the SEC trace of **Figure 7b** at the lower molecular weight regions, possibly due to the dead poly(MeEOGE) chain, such a tiny amount of (~10%) impurity seems not to affect the overall polymer properties. Indeed, the M_w/M_n value of 1.06 including the shoulder peak is still very narrow. These results confirmed the successful block copolymerization to yield

poly(MeEOGE$_{0.24}$-*b*-EtEOGE$_{0.76}$)$_{18k}$ with the predicted F_{MeEOGE}. In a similar manner, well-defined BCPs with the F_{MeEOGE} values of 0.50 and 0.75, i.e., poly(MeEOGE$_{0.50}$-*b*-EtEOGE$_{0.50}$)$_{14k}$ and poly(MeEOGE$_{0.75}$-*b*-EtEOGE$_{0.25}$)$_{14k}$, were also prepared.

Table 3. Block copolymerization of MeEOGE and EtEOGE [a]

polymer	monomer feed		[MeEOGE]$_0$/[EtEOGE]$_0$/[*n*-BuOH]$_0$	$M_{n,NMR}$ [b] (g mol^{-1})	M_w/M_n [c]	F_{MeEOGE} [d]
poly(MeEOGE$_{0.24}$-*b*-EtEOGE$_{0.76}$)$_{18k}$	1st	MeEOGE	25/75/1	4,050	1.06	0.24
	2nd	EtEOGE		17,900	1.05	
poly(MeEOGE$_{0.50}$-*b*- EtEOGE$_{0.50}$)$_{14k}$	1st	MeEOGE	50/50/1	6,560	1.05	0.50
	2nd	EtEOGE		13,600	1.06	
poly(MeEOGE$_{0.75}$-*b*- EtEOGE$_{0.25}$)$_{14k}$	1st	MeEOGE	75/25/1	10,400	1.04	0.75
	2nd	EtEOGE		14,200	1.06	

[a] Polymerization condition: Ar atmosphere; solvent, toluene; initiator, *n*-BuOH; [*n*-BuOH]$_0$/[*t*-Bu-P$_4$]$_0$ = 1/1; [MeEOGE]$_0$ = 2.5 mol L^{-1}; temp., 27 °C; conv. for each step, >99%. [b] Determined by ^{1}H NMR in CDCl$_3$. [c] Determined by SEC in THF using polystyrene standards. [d] Mole fraction of MeEOGE in the copolymer (F_{MeEOGE}) was determined by ^{1}H NMR.

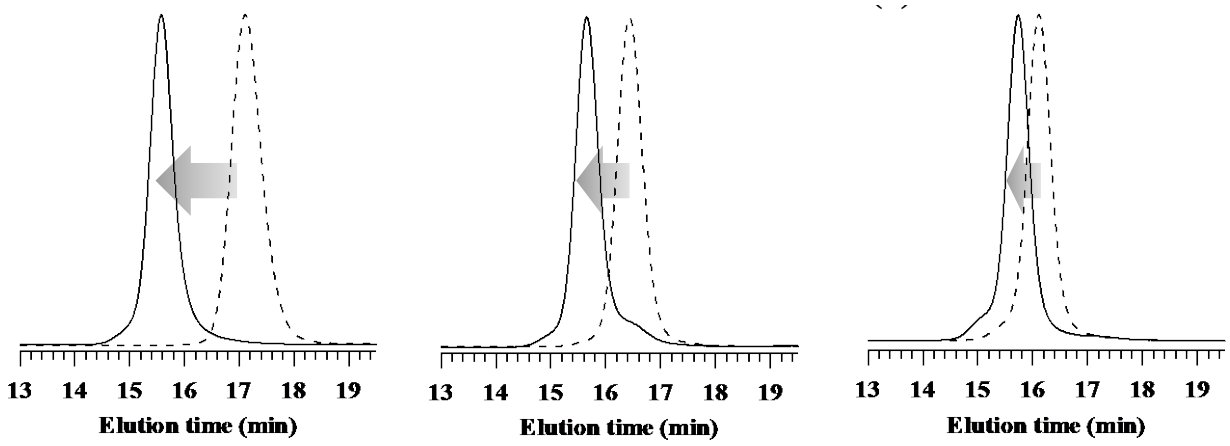


Figure 7. SEC traces of (a) poly(MeEOGE$_{0.24}$-*b*-EtEOGE$_{0.76}$)$_{18k}$, (b) poly(MeEOGE$_{0.50}$-*b*-EtEOGE$_{0.50}$)$_{14k}$, and (c) poly(MeEOGE$_{0.75}$-*b*-EtEOGE$_{0.25}$)$_{14k}$ (eluent, THF; flow rate, 1.0 mL min^{-1}). The broken lines indicate the poly(MeEOGE)s prepared by the first

polymerization.

The thermoresponsive behavior of the BCPs was then evaluated by variable-temperature UV absorption measurements. **Figure 8a** depicts the temperature-dependent transmittance curves for poly(MeEOGE$_{0.24}$-*b*-EtEOGE$_{0.76}$)$_{18k}$ and poly(MeEOGE$_{0.75}$-*b*-EtEOGE$_{0.25}$)$_{14k}$. For these two BCPs, an LCST-type phase transition was observed upon heating and the T_{cp} value was similar to that of the corresponding statistical copolymers with the comparable F_{MEGE}: 41.7 °C for poly(MeEOGE$_{0.24}$-*b*-EtEOGE$_{0.76}$)$_{18k}$ and 61.0 °C for poly(MeEOGE$_{0.75}$-*b*-EtEOGE$_{0.25}$)$_{14k}$. This suggests that the T_{cp} value is basically dominated by the monomer composition but not by the monomer sequence.

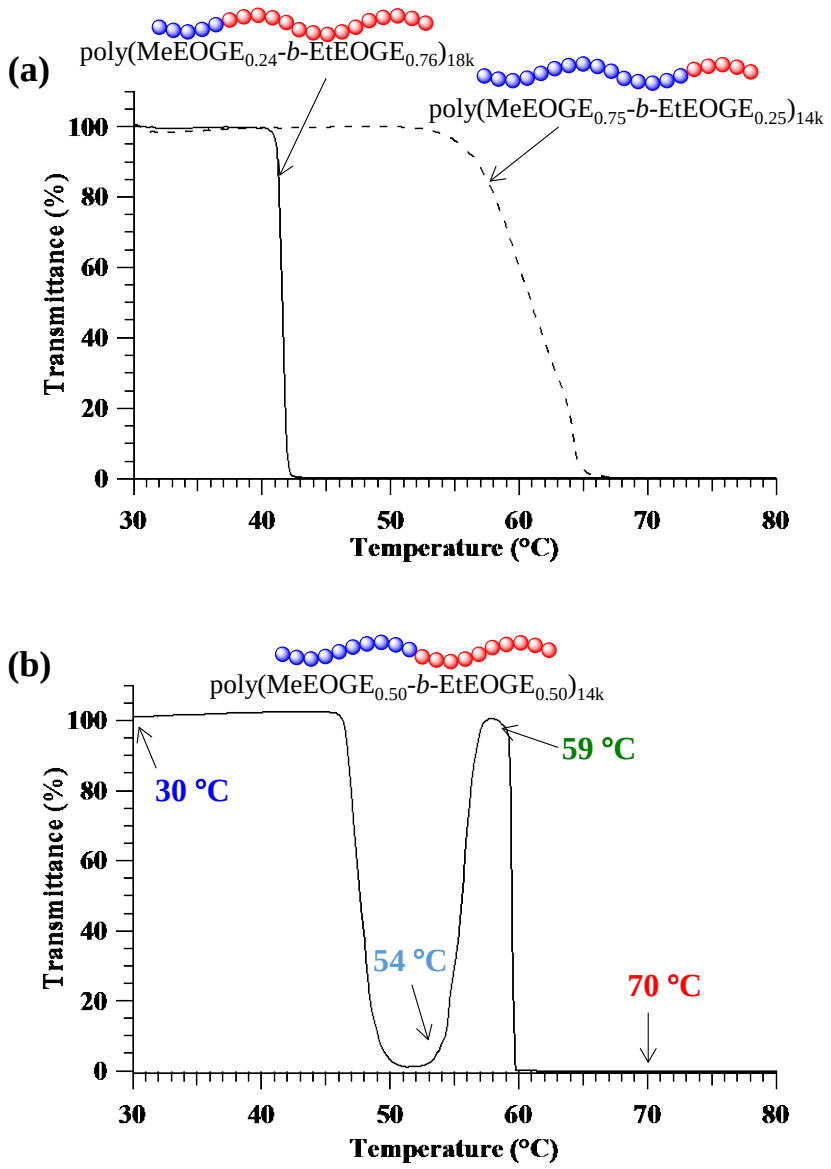


Figure 8. (a) Transmittance curves for the 1 wt% aqueous solutions of poly(MeEOGE$_{0.24}$-*b*-EtEOGE$_{0.76}$)$_{18k}$ (solid line) and poly(MeEOGE$_{0.75}$-*b*-EtEOGE$_{0.25}$)$_{14k}$ (broken line). (b) Transmittance curve for the aqueous solution of poly(MeEOGE$_{0.50}$-*b*-EtEOGE$_{0.50}$)$_{14k}$.

On the other hand, an aqueous solution of poly(MeEOGE$_{0.50}$-*b*-EtEOGE$_{0.50}$)$_{14k}$ showed an interesting phase behavior (**Figure 8b**); the solution became opaque at around 50 °C, but further heating made the solution being clear at around 57 °C. The solution again became opaque by heating above 60 °C. Thus, we found that the monomer sequence had a significant impact on the

thermoresponsive behaviors of aliphatic polyethers only when the two blocks have almost the same chain length. In order to further determine this the interesting phase behavior, dynamic light scattering (DLS) measurements were performed on the poly(MeEOGE$_{0.50}$-*b*-EtEOGE$_{0.50}$)$_{14k}$ solution at 30, 54, 59, and 70 °C to gain an insight into the hydrodynamic diameter (D_h) of the polymer at each stage of the phase transition (**Figure 9a**). A monomodal particle size distribution with the D_h of ca. 55 nm was observed at 30 °C, which implied the formation of a micellar aggregate before the heating. Given that the hydrodynamic radius (D_h/2) is comparable to the fully extended chain length (36 nm),[35] poly(MeEOGE$_{0.50}$-*b*-EtEOGE$_{0.50}$)$_{14k}$ most likely formed a regular core-shell micelle rather than the vesicle or large compound micelle. The significant difference in the water miscibility between the poly(EtEOGE) and poly(MeEOGE) segments led to forming the core-shell micellar aggregate. Considering the fact that poly(EtEOGE) has a lower LCST than poly(MeEOGE), the core and shell of the micellar aggregate should be attributed to poly(EtEOGE) and poly(MeEOGE), respectively (**Figure 9b**). The particle size distribution at 54 °C demonstrated that the D_h increased to ca. 220 nm. This confirmed that the micellar aggregate was agglomerated into larger particles due to the dehydration of the poly(EtEOGE) segment. Interestingly, the D_h drastically decreased to ca. 11 nm when the solution temperature increased to 59 °C. This suggested that the large agglomerated particles were decomposed and rearranged into smaller micellar aggregates consisting of shrunken poly(EtEOGE) as the core and poly(MeEOGE) as the shell, in which the poly(MeEOGE) segment was still hydrated because of its higher LCST. The particle size distribution at 70 °C showed the

presence of large particles with the D_h of ca. 822 nm, indicating that the poly(MeEOGE) segment was also dehydrated and the micellar aggregate then precipitated out.

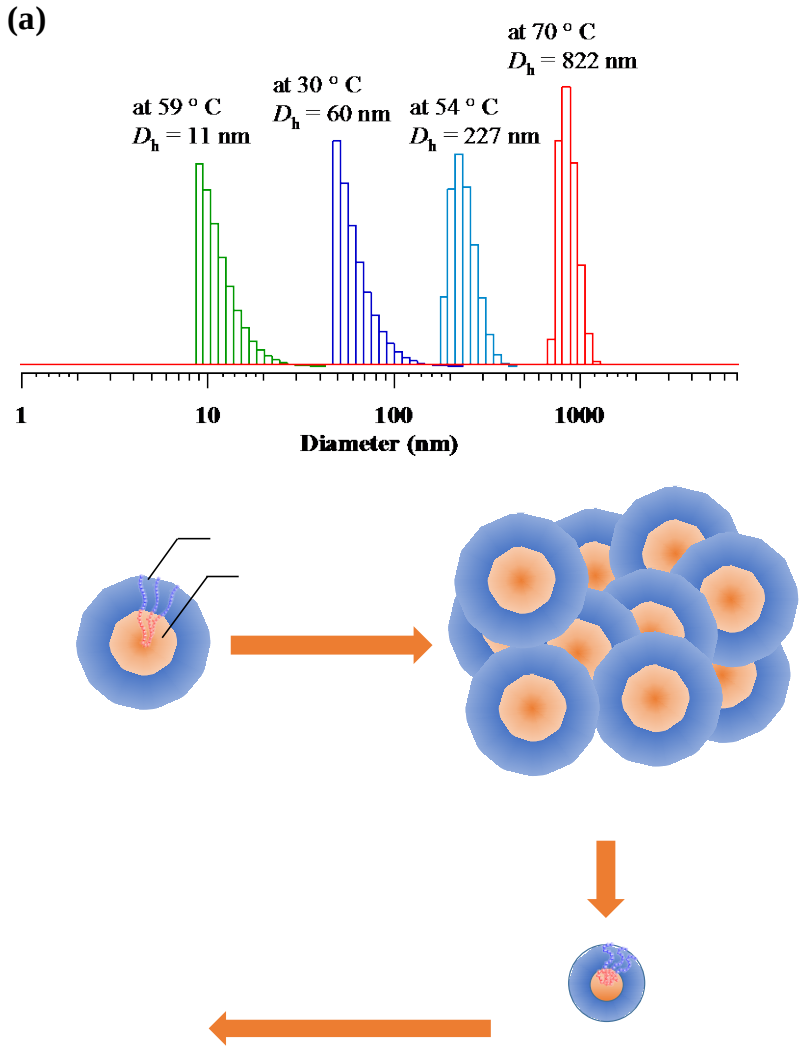


Figure 9. (a) Number-average particle size distributions for the aqueous solution of poly(MeEOGE$_{0.50}$-*b*-EtEOGE$_{0.50}$)$_{14k}$ at 30, 54, 59, and 70 °C determined by DLS. All the measurements were performed using a 1 wt% aqueous solution. (b) Possible mechanism for the complexed phase behavior observed in the aqueous solution of poly(MeEOGE$_{0.50}$-*b*-EtEOGE$_{0.50}$)$_{14k}$ upon heating.

In contrast to the case of poly(MeEOGE$_{0.50}$-*b*-EtEOGE$_{0.50}$)$_{14k}$, the DLS analysis of the aqueous solutions of poly(MeEOGE$_{0.24}$-*b*-EtEOGE$_{0.76}$)$_{18k}$ and poly(MeEOGE$_{0.75}$-*b*-EtEOGE$_{0.25}$)$_{14k}$ at 30 °C did not show any evidence of micellar aggregate formation. Both solutions exhibited a monomodal particle size distribution with the D_h value of less than 5 nm, which should be attributed to the molecularly-dissolved single polymer chain (Figure S22). These DLS studies revealed that the specific phase behavior observed in poly(MeEOGE$_{0.50}$-*b*-EtEOGE$_{0.50}$)$_{14k}$ originated from its capability of forming a micellar aggregate in water below the LCST. Thus, we can conclude that the micellar aggregate formation can enrich the phase behaviors of the thermoresponsive aliphatic polyethers.

Conclusion

We have synthesized a series of aliphatic polyethers having various side chain structures by the *t*-Bu-P$_4$-catalyzed ROP of commercially-available or readily-accessible glycidyl ether monomers. Due to the living nature of the present polymerization system, well-defined and narrowly-dispersed aliphatic polyethers were easily obtained in one-step. With the well-defined polyethers in hand, we have found a simple correlation between the thermoresponsive behaviors and polymer structures. Thus, a thermoresponsive polyether with a desirable transition temperature can be designed by either selecting the side chain structure or optimizing the comonomer composition. Furthermore, we found that the BCP composed of two different glycidyl ether monomers exhibited interesting

thermoresponsive properties due to its ability to form a micellar aggregate. Considering the fact that the PEO-based polymers have been used as biocompatible materials, the thermoresponsive polyethers are of high interest for applications in the biomedical, pharmaceutical, and environmental fields. Overall, we have demonstrated the structure-thermoresponsive property relationship in the aliphatic polyethers by using the *t*-Bu-P_4-catalyzed ROP system, which will significantly contribute to the macromolecular design of smart materials for biomedical, pharmaceutical, and environmental applications.

Acknowledgements

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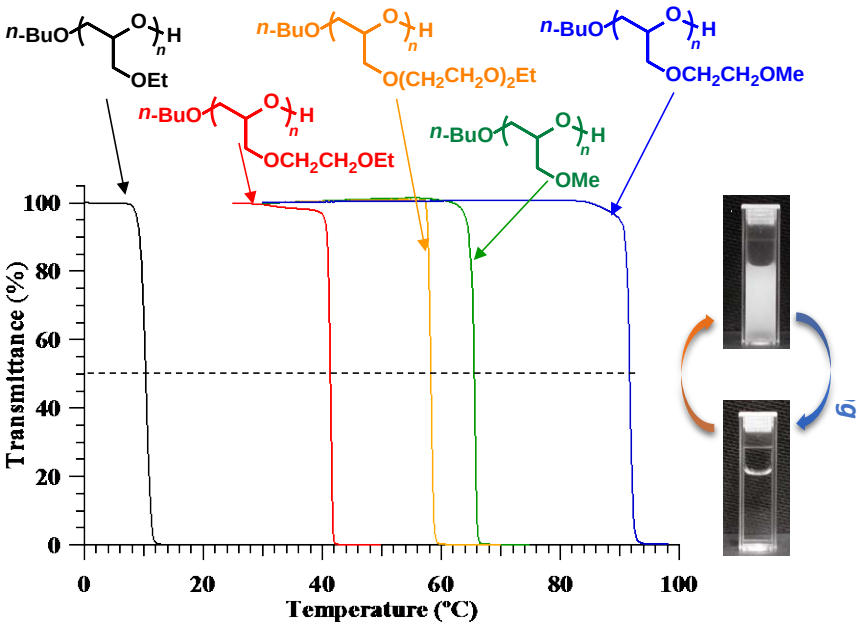
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35. When the total degree of polymerization and a monomer unit length are assumed to be 100 and 0.0358 nm, respectively, the fully extended chain length can be calculated to be 36 nm.

Table of Contents Entry

Design and Synthesis of Thermoresponsive Aliphatic Polyethers with Tunable Phase Transition Temperature

Takuya Isono, Kana Miyachi, Yusuke Satoh, Shin-ichiro Sato, Toyoji Kakuchi, Toshifumi Satoh



A comprehensive study of the synthesis and LCST-type thermoresponsive properties of poly(glycidyl ether) homopolymers and their copolymers is described.