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Molecular Dynamics Simulation Study on Structural Transition of Temperature- responsive Poly(glycidyl ether)s with Different Side Chain End Structures

A Dissertation for the Degree of Doctor of Philosophy

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Hokkaido University

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Chapter 1

General Introduction

1.1 Thermoresponsive Polymers

Thermoresponsive polymers are stimulus-responsive polymers that change their solubility in water at a certain temperature. There are two types of temperature-responsive polymers: Lower Critical Solution Temperature (LCST) polymers that dissolve in water at low temperatures and become insoluble at high temperatures and Upper Critical Solution Temperature (UCST) polymers that are insoluble at low temperatures and soluble at high temperatures. In particular, LCST-type thermoresponsive polymers, which dissolve in water at low temperatures but become insolubilized and precipitate when heated above the Lower Critical Solution Temperature (LCST), are expected to be used in biomaterial fields including drug delivery [1] and tissue engineering [2].

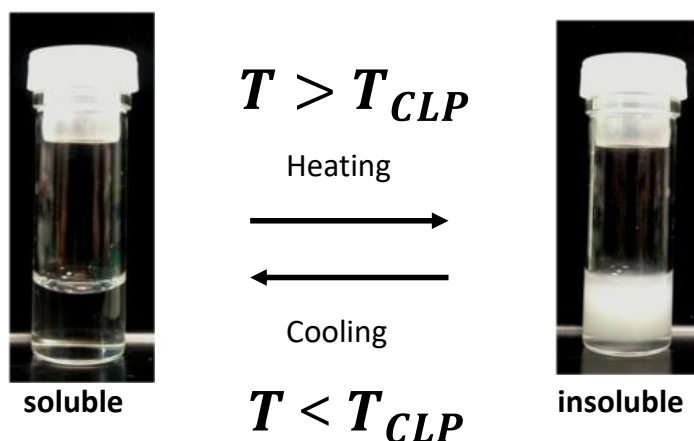


Figure 1-1. LCST-type phase transition of a thermoresponsive polymer in aqueous solution

As the LCST-type thermoresponsive polymers, poly(*N*-isopropylacrylamide) (PNIPAM)[3–6], poly(ethylene glycol) (PEG)[7], poly[poly(ethylene glycol) methyl ether methacrylate][8–10], poly(glycidyl ether) (PGE)[11–14], polyisocyanates[15], poly(*N,N*-diethylacrylamide)[16], poly(*N*-vinylcaprolactam)[17,18], and poly[2-(dimethylamino)ethyl methacrylate][19], etc. have been reported. As a mechanism of temperature responsiveness, polymer chains are hydrated by hydrogen bonding with water molecules and have a coil structure in polymer solutions at low temperatures. On the other hand, at high temperatures, the hydrogen bonds weaken and the polymer chains dehydrate to form a globule structure. The polymers with globule structures aggregate through hydrophobic interactions to form hydrophobic phases (Figure 1-2).

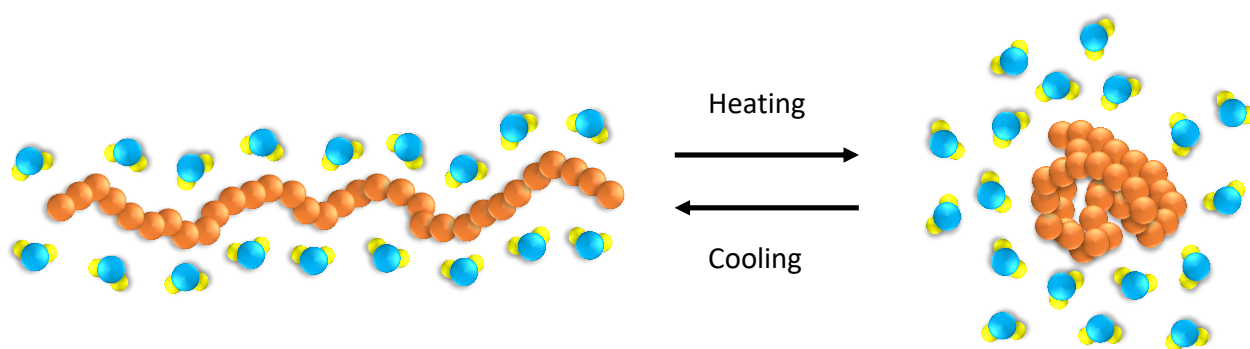


Figure 1-2. coil-globule phase transition of thermoresponsive polymer in aqueous solution

PNIPAM [3–6] is a representative temperature-responsive polymer that exhibits coil globule phase transition (Figure 1-3). Below the LCST temperature, the strong interaction between the amide groups of PNIPMA and water causes the polymer chain to dissolve and have a random coiled conformation.

As the temperature rises, the hydrogen bond between the amide group and water becomes unstable, and dehydration of the hydrophobic part occurs, causing the polymer chain to shrink to globule conformation. Furthermore, hydrophobic interactions cause globule aggregation and macroscopic phase separation. Thus, the phase separation phenomenon in aqueous polymer solutions is related to the structural transition of polymers, and it is important to clarify the polymer structures in response to temperature.

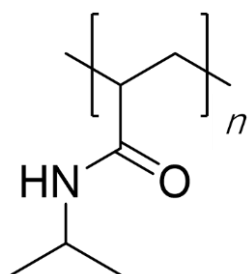


Figure 1-3. Chemical structure of poly(*N*-isopropylacrylamide)

The reason why PNIPAM can observe a clear coil globule conformational transition is that PNIPAM has both a proton donor and a proton acceptor due to the presence of an amide group which forms an intramolecular hydrogen bond above LCST temperature. On the other hand, poly(glycidyl ether), the LCST-type temperature-responsive polymer focused on in this study, has only proton acceptors with ether groups (Figure 1-4). Fundamental studies of structural transition in thermoresponsive polymers other than PNIPAM have not been well reported, and the relationship between polymer structure and temperature response in poly(glycidyl ether)s has not yet been fully investigated. In particular, it is not

clear whether the coil-globule structural transition occurs in poly(glycidyl ether)s with only proton acceptors.

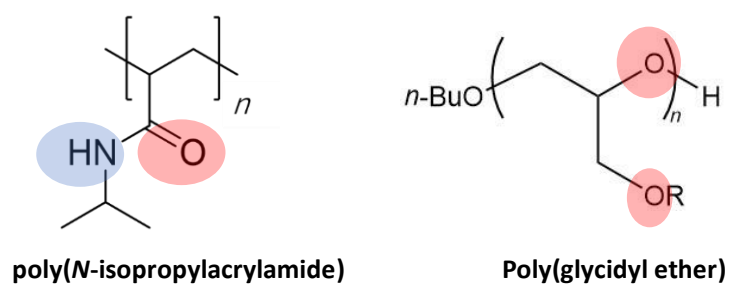


Figure 1-4. Chemical structure of poly(*N*-isopropylacrylamide) (left) and poly(glycidyl ether) (right). Blue means proton donor and red means proton acceptor.

1.2 poly(glycidyl ether)

Poly(glycidyl ether) (PGE) is one of the aliphatic polyethers and has been reported to have low toxicity, biological compatibility, and thermoresponsive properties [11–14]. LCST of PGE is strongly affected by the length [9] and structure [8,10] of the alkyl chain. Isono et al. have synthesized six types of PGEs with different side chain structures, and has reported that each of them exhibits different temperature responsiveness[14](Figure 1-5 and table 1-1).

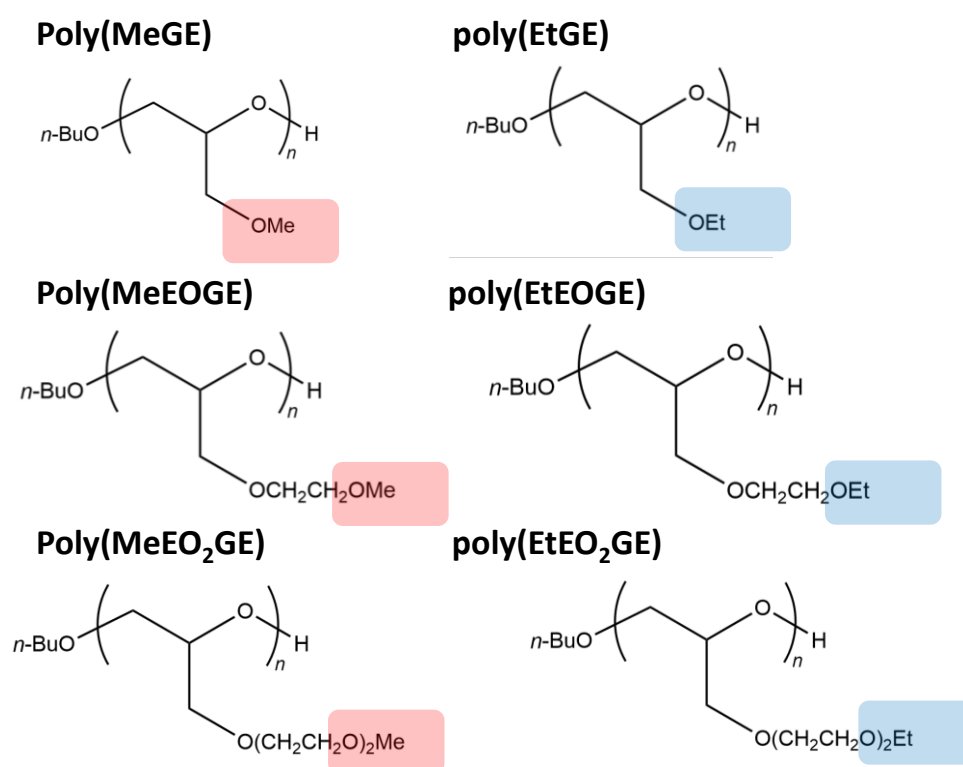


Figure 1-5. Chemical structure of six types of PGEs with different side chain structures.

Table 1-1. experimental T_{CLP} for 6 kinds of PGEs with different side chains structures

sample ID	Experimental T_{CLP} (K)
poly(MeGE) _{2.5k}	338.5
poly(EtGE) _{2.5k}	283.3
poly(MeEOGE) _{2.5k}	364.6
poly(EtEOGE) _{2.5k}	314.3
poly(MeEO ₂ GE) _{2.5k}	Not observed**
poly(EtEO ₂ GE) _{2.5k}	331.2

Isono et al. also reported that block copolymers of PGE, poly(MeEOGE), and poly(EtEOGE) with different side chain structures, each with the same degree of polymerization, exhibit very interesting temperature response[14]. Figure 1-6 shows the chemical structural formula of the polymer, and the results of turbidity measurement of the polymer. The turbidity measurement results show that the polymer is soluble in water at temperatures lower than 318 K, but insolubilization occurs from 318 K to around 327 K, dissolves again at 332 K, and becomes insoluble again above 335 K. Thus, PGE has the potential to create materials that exhibit various temperature responses by changing the side chain

structure or synthesizing block copolymers. However, the relationship between polymer structure and temperature response in PGE has not been adequately studied.

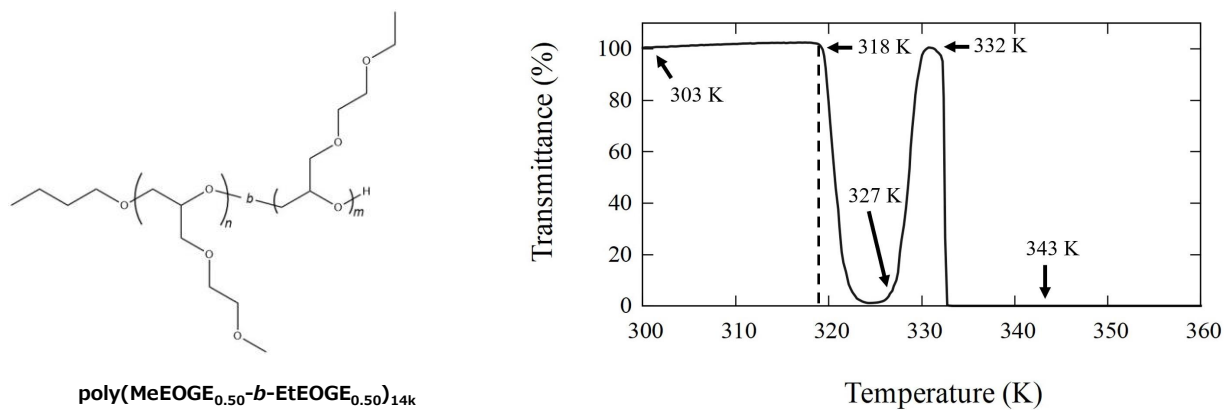


Figure 1-6. Chemical structure of PGE block copolymer (left) and transmittance curve for the aqueous solution of PGE block copolymer in turbidity measurement (right).

1.3 Molecular Dynamics (MD) Simulation

Molecular dynamics (MD) simulation is one of molecular simulation methods that uses a computer to numerically solve the equations of motion for individual atoms and molecules to track changes in position, velocity, and energy over time. MD simulations have been employed to understand the response mechanisms of some thermoresponsive polymers, including PNIPAM[20–22], PGE[23], PEG[24] and poly(*N*-vinylcaprolactam) (PVCL)[25–27]. In addition, there is a research on the hydrophobic behavior of carbon nanoparticles using MD simulation in the study of their water solubility[28]. AMBER (Assisted model building with energy refinement) is one of the world's most widely used software in the field of molecular dynamics. In this study, I performed MD simulations using AMBER 14 package [29]. A simple molecular dynamics simulation flow is shown in Figures 1-7.

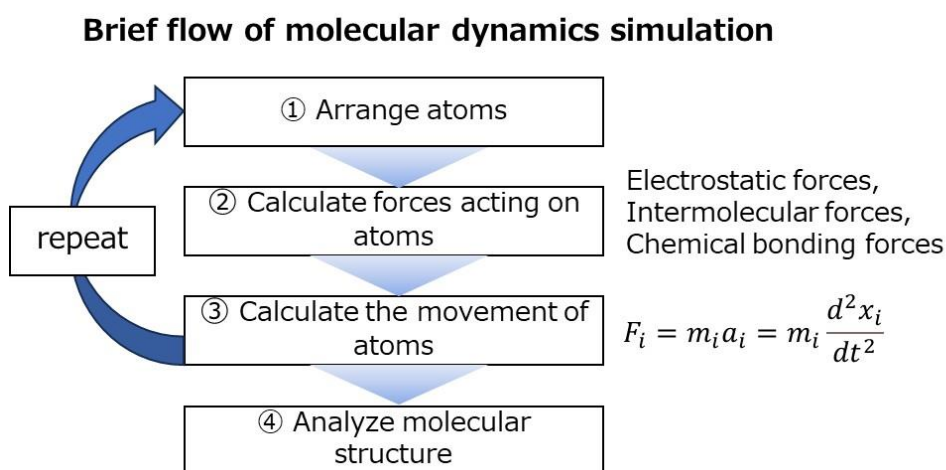


Figure 1-7. Brief flow of molecular dynamics simulation

In molecular dynamics simulation software such as AMBER, molecules follow classical mechanics, and each atom is treated as a mass point with mass m_i . The atoms are connected to each other like a kind of spring, and when they are stretched, contracted, or twisted, they tend to return to their original positions. In addition, since atoms have positive and negative charges, there are electrostatic forces generated from this and van der Waals forces that act when atoms are brought close together. In this way, the motion of atoms that move in response to forces from their surroundings follows Newton's equation of motion as shown in (1).

$$F_i = m_i a_i = m_i \frac{d^2 x_i}{dt^2} \quad (1)$$

The force acting on the atom i is F_i , and the atom's acceleration and mass are a_i and m_i , respectively. Since atoms move according to Newton's equation of motion, if the initial conditions; position x_i and velocity v_i of atom i at time 0, are known, the subsequent position and velocity of the atom can be determined. To solve Newton's equation of motion, the values of the forces acting on the atoms are needed. Originally, quantum mechanical calculations such as the molecular orbital method are required to precisely calculate the motion of molecules, but it is difficult for current computational chemistry to perform calculations on large systems such as biopolymers. Therefore, the mainstream method is to calculate forces from differentials based on classical mechanics, using approximate potentials that represent the potentials that express the forces acting between atoms

using a relatively simple system of functions. In MD calculations, these potential functions and their parameters are collectively called a force field. The functional form of the AMBER force field is shown in (2).

$$\begin{aligned}
 V_{\text{AMBER}} = & \sum_i^{n_{\text{bonds}}} b_i (r_i - r_{i,\text{eq}})^2 + \sum_i^{n_{\text{angles}}} a_i (\theta_i - \theta_{i,\text{eq}})^2 + \sum_i^{n_{\text{dihedrals}}} \sum_n^{n_{i,\text{max}}} (V_{i,n}/2) [1 + \cos(n\phi_i - \gamma_{i,n})] \\
 & + \sum_{i < j}^{n_{\text{atoms}}} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6} \right) + \sum_{i < j}^{n_{\text{atoms}}} \left(\frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \right), \quad (2)
 \end{aligned}$$

Although it is possible to simulate large-scale systems using various approximations, it is impossible to perform calculations on the order of 1 mol. Therefore, periodic boundary conditions are often used in normal calculations. The periodic boundary conditions are a set of boundary conditions that assumes a model in which virtual image cells are periodically arranged around the basic cell, which is actually performed by MD calculation. If an atom jumps out of a basic cell into a neighboring image cell, the same atom is considered to come in from the opposite image cell, and the system can be treated over a wider area simply by performing the calculation for the basic cell (Figure 1-8). MD simulations can handle large systems, and track changes individual atoms and molecules for position, velocity, and energy over time, so it is an effective method for investigating molecular structural changes.

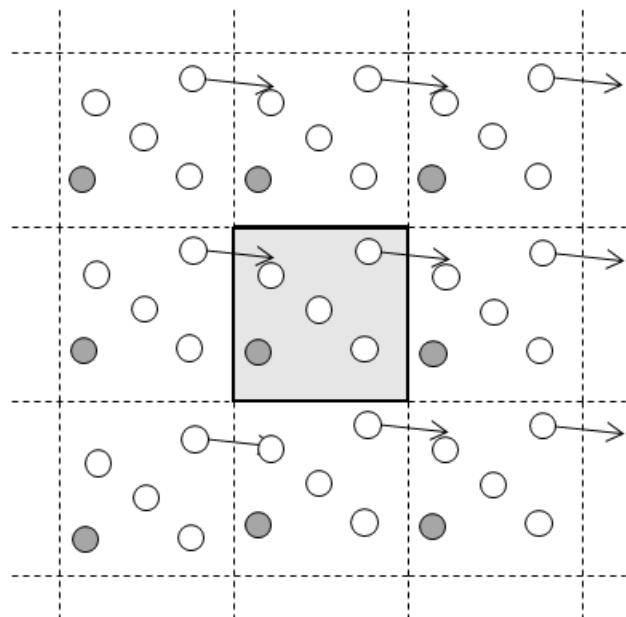


Figure 1-8. Schematic diagram of periodic boundary conditions. Basic cell (center) and image cells (around basic cell).

1.4 Objective and Outline of the Thesis

As described above, poly(glycidyl ether)s have attracted attention as biomaterials, including drug delivery, because they exhibit temperature responsiveness and are biocompatible. Studies have shown that the temperature response of poly(glycidyl ether)s is affected by the side chain structure and molecular weight. Isono et al. have already synthesized poly(glycidyl ether)s with various side chain structures and molecular weights and investigated their effects on temperature responsiveness, and experimentally demonstrated that the oligoethylene oxide side chain structure affects the temperature response. Furthermore, they reported that block copolymers of poly(glycidyl ether) with different side chain structures showed a very interesting temperature response: as temperature increased, they went from water-soluble to insoluble and then back to water-soluble and insoluble in water. However, the relationship between polymer structure and temperature response in poly(glycidyl ethers), especially the structural transition in temperature response, has not yet been adequately investigated. In addition, it is difficult to analyze the structure of individual polymers in experiments because many polymers get aggregated. Therefore, in this study, molecular dynamics (MD) simulations were used to study the temperature response and structural analysis of poly(glycidyl ether)s with different side chain end structures.

An outline of this thesis is as follows:

Chapter 2 describes temperature response of PGEs with oligooxyethylene side chains terminated with alkyl groups using MD simulations. I performed MD simulations of PGE with six different side chains terminated with alkyl groups in aqueous solutions to investigate the effects of side-chain structures on LCST-type phase transition. To investigate if the coil–globule structural transition occurs, I analyzed the R_g , which indicates the degree of polymer chain extension, and the $\bar{L}/L_{max}$, which indicates the degree of polymer shrinkage. Next, I focused on the RDF as another physical quantity that indicates the distribution of water molecules around the polymer and calculated the RDF for the oxygen atoms of waters measured from carbon atoms at the side-chain ends of the polymers.

Chapter 3 describes structural study of two polymer chains of poly((MeEOGE)-*b*-poly(EtEOGE)) thermoresponsive block copolymers using molecular dynamics simulations. I have performed MD simulation of one or two polymer chains of poly((MeEOGE)-*b*-poly(EtEOGE)) block copolymer in aqueous solutions and investigated structural transition of the block copolymer analyzing radius of gyration, snapshots, and eigen values of the moment of inertia tensor.

The concluding Chapter 4 summarized the temperature response and structural transition of thermoresponsive poly(glycidyl ether) with different side chain end structures using molecular dynamics simulations.

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Chapter 2

Temperature Response of Poly(glycidyl ether)s with Oligooxyethylene Side Chains Terminated with Alkyl Groups

2.1 Introduction

Thermoresponsive polymers with a lower critical solution temperature (LCST) are attracting significant research interest. These polymers exhibit structural changes in response to external temperature change; thus, they are exploited for many applications, including drug delivery. Among the LCST-type thermoresponsive polymers, including poly(*N*-isopropylacrylamide) (PNIPAM)[3,4], poly(ethylene glycol) (PEG)[7], poly[poly(ethylene glycol) methyl ether methacrylate][8–10], poly(glycidyl ether) (PGE)[11–14], polyisocyanates[15], poly(*N,N*-diethylacrylamide)[16], poly(*N*-vinylcaprolactam)[17,18], and poly[2-(dimethylamino)ethyl methacrylate][19], PGE is known for its low cost, handling ease, and nontoxicity; thus, many PGE derivatives are commercially available. Additionally, PGE is widely employed in biomedicine for drug delivery[30,31] and as a scaffold material for tissue engineering[32,33]. Studies have shown that the LCST of PGE is controlled by its molecular weight[13] and molecular structure[12,14], as well as the balance between hydrophilic and hydrophobic side chains[14,34].

For example, Watanabe et al. reported that poly(glycidyl methyl ether), poly(ethyl glycidyl ether), and poly(ethoxyethyl glycidyl ether) exhibited LCST-type phase transitions from 14.6°C to 57.7°C when the hydrophobicity of their side chains was reduced[34]. In addition, Isono et al. previously synthesized PGEs with various oligoxyethylene side chains terminated with an alkyl group and established that the LCSTs of poly(glycidyl methyl ether), poly(ethyl glycidyl ether), poly(2-

methoxyethyl glycidyl ether), poly(2-ethoxyethyl glycidyl ether), and poly(2-(2-ethoxyethyl)ethyl glycidyl ether) phase transitions increased from 10.3°C to 91.6°C with a decrease in the hydrophobicity of their oligooxyethylene side chains[14]. However, despite the application prospects of PGE as a promising thermoresponsive material, the relationship between its temperature responsivity and polymer structure has not been adequately studied.

Molecular dynamics (MD) simulations have been employed to understand the response mechanisms of some thermoresponsive polymers, including PNIPAM[20–22], PGE[23], PEG[24] and poly(*N*-vinylcaprolactam) (PVCL)[25–27]. In addition, there is a research on the hydrophobic behavior of carbon nanoparticles using MD simulation in the study of their water solubility[28]. Conventionally, PNIPAM undergoes a coil–globule transition by the recombination of the polymer–water hydrogen bonds with the intrapolymer hydrogen bonds[20–22]. Conversely, the mechanism of the coil–globule transition in PGE has not been clarified yet. From a thermodynamic standpoint, hydrogen bonds between polymer chains and water molecules contribute favorable enthalpies to the free energy of mixing, whereas bonds between water molecules and polymer chains, particularly hydrophobic hydration shells formed around hydrophobic groups, promote the ordering of water molecules. Therefore, they contribute negatively to the mixing entropy. At relatively high temperatures, the entropy term, TS , becomes predominant, and the free energy of mixing becomes positive, which accounts for the insolubility of the polymer. The coil–globule structural transition in PNIPAM has been

studied using MD simulations[20–22]. Also, Pica and Graziano reported that the solvent exclusion volume effect can be an indicator of the LCST phase transition[35,36]. PGE, which is actively studied in biomedicine, requires strict temperature control. If the LCST temperature can be predicted by MD simulations, the polymer structure can be designed according to the target temperature.

In this chapter, I performed MD simulations on six different types of side-chain structures investigated by Isono and Satoh et al[14]. and examined the effect of the number of oxyethylene units on the LCST. I found that the hydrophobic shell intensity of the sidechain terminal alkyl groups well correlated with LCST.

2.2 Computational Method

2.2.1 Initial structure of the polymers

Models of poly(glycidyl methyl ether) (poly(MeGE)), poly(ethyl glycidyl ether) (poly(EtGE)), poly(2-methoxyethyl glycidyl ether) (poly(MeEOGE)), poly(2-ethoxyethyl glycidyl ether) (poly(EtEOGE)), poly(2-(2-methoxyethoxy)ethyl glycidyl ether) (poly(MeEO₂GE)), and poly(2-(2-ethoxyethyl)ethyl glycidyl ether) (poly(EtEO₂GE)) were prepared by the random addition of monomers with *d* and *l* structures, mimicking the atacticity of the whole chain (Figure 2-1). These polymer structures were optimized by the molecular mechanics 2 (MM2) method included chem3D package of PerkinElmer. All the polymer molecular weights (MW) were set at ca. 2500, and 5000.

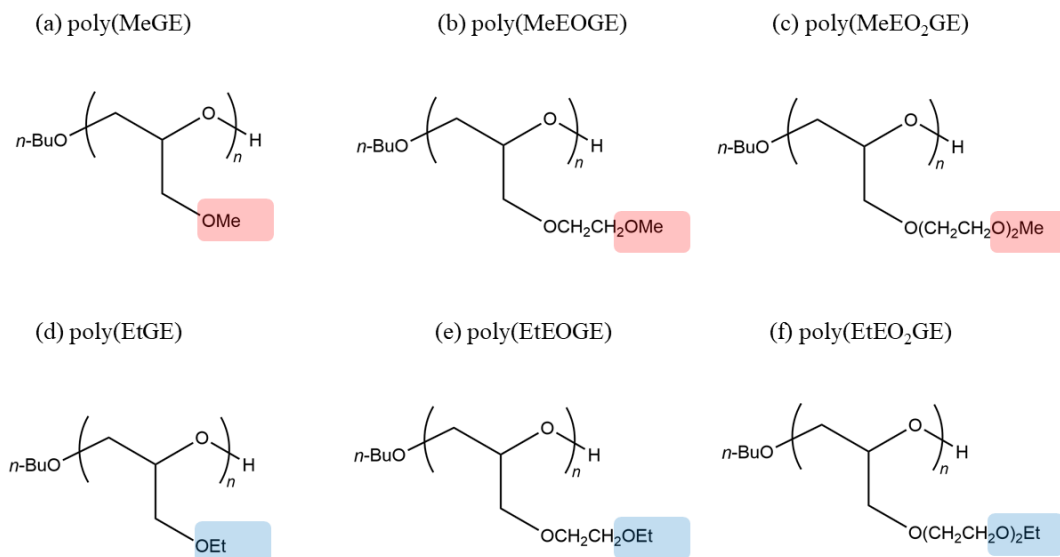


Figure 2-1. Chemical structures of (a) poly(MeGE), (b) poly(MeEOGE), (c) poly(MeEO₂GE), (d) poly(EtGE), (e) poly(EtEOGE), and (f) poly(EtEO₂GE).

2.2.2 Atomic charges and force fields

The atomic partial charges for the six polymer species were obtained through the AM1-BCC protocol[32, 33] implemented in the antechamber program[34] of AMBER 14. All other force-field parameters for the polymers were acquired using the general AMBER force field (GAFF)[39]. The GAFF was chosen because it has been demonstrated to be accurate for the simulation of most organic molecules. The detailed force field parameters are provided in gaff.dat[39].

2.2.3 Solvent water addition into a simulation box

Each polymer was centered in a cubic simulation box under periodic boundary conditions. Over 2000 TIP3P-modeled water molecules were added with a margin of 10 Å along each dimension in Table 2-1.

Table 2-1 Total number of water molecules and box length

sample ID	Total number of water molecules	box length
		Length, Width, Height (Å)
poly(MeGE) _{2.5k}	2321	44.7, 43.5, 52.7
poly(EtGE) _{2.5k}	2015	44.2, 41.9, 49.0
poly(MeEOGE) _{2.5k}	2012	42.1, 43.8, 49.0
poly(EtEOGE) _{2.5k}	2184	45.6, 47.1, 45.0
poly(MeEO ₂ GE) _{2.5k}	2297	44.5, 47.9, 47.0
poly(EtEO ₂ GE) _{2.5k}	2287	46.6, 44.4, 48.3
poly(MeGE) _{5k}	3182	49.9, 53.0, 52.7
poly(EtGE) _{5k}	3488	58.3, 52.9, 49.0
poly(MeEOGE) _{5k}	2471	48.8, 44.4, 50.1
poly(EtEOGE) _{5k}	2423	47.7, 47.1, 48.0
poly(MeEO ₂ GE) _{5k}	4213	46.7, 66.1, 56.4
poly(EtEO ₂ GE) _{5k}	3876	54.8, 51.6, 58.0

2.2.4 Energy minimization and temperature equilibration

The whole system consisted of a polymer, and the water molecules were energy-minimized and equilibrated with the sander program implemented in the AMBER system before the MD simulations. The energy minimization was performed in two steps. First, the solvent molecules were energy-minimized using the steepest decent method for 1000 steps and the conjugate gradient method for 1500 steps while keeping the solute molecular chains restrained with a force of 500 kcal mol⁻¹ Å⁻². Second, the restraint was eliminated, and the entire system including the polymer chain was energy-minimized

using the steepest decent method for 1000 steps and the conjugate gradient method for 1500 steps as in the first step.

Subsequently, the energy equilibration was performed in two steps. First, the system was gradually heated to an assigned temperature, 278, 300, 323, 343, and 368K, under constant volume boundary conditions for 10,000 steps, with a time step of 2 fs while maintaining the 10 kcal mol⁻¹ Å⁻² constraint on the solute polymer chains. In the second step, the restraint was removed, and the entire system was equilibrated under periodic boundary conditions at a constant pressure of 1 atm for 50,000 steps, with a time step of 2 fs while maintaining the specified temperature.

The Langevin method was employed for temperature control, and isotropic scaling was employed for pressure control. The SHAKE algorithm was applied to maintain constant hydrogen atom bond lengths. A cutoff length of 9.0 Å and particle mesh Ewald (PME) sums were applied for the electrostatic interactions.

2.2.5 MD simulation

After confirming the equilibrium of the whole system, MD simulations were performed for 20 ns or 100 ns, with a time step of 2 fs using a pmemd program of AMBER 14. All the MD simulations were conducted in NPT (number of molecules (N), pressure (P), and temperature (T) is conserved) ensembles to capture the dynamics and structural evolution of both the polymer and water molecules

at five different temperatures (278, 300, 323, 343, and 368 K). The simulations were carried out at atmospheric pressure (1 atm). The trajectories were outputted at 2.0 ps intervals.

2.3 Analysis Method

2.3.1 Radius of gyration

The structural evolution of each polymer was studied along the time course of the stored atomic trajectories by analyzing the radius of gyration (R_g). R_g , which is a measure of the extension degree of a polymer chain, was calculated using the equation below:

$$R_g^2 = \frac{1}{N} \sum_n \langle (\mathbf{R}_n - \mathbf{R}_c)^2 \rangle, \quad (1)$$

where $\mathbf{R}_c$ is the center of mass of the polymer chain, and N is the number of atoms included in the polymer chain. The sum for all the atoms in the chain was obtained.

2.3.2 Radial distribution function

The radial distribution function (RDF), $g(r)$, represents the number density of the particles existing in the spherical shells between distances r and $r + dr$ from a given reference particle. It can be expressed as

$$g(r) = \frac{\langle n(r) \rangle}{4\pi r^2 dr \rho}, \quad (2)$$

where $n(r)$ indicates the number of particles of the spherical shell at distances of r and $r + dr$ from the given reference particle. ρ is the average number density of the particles in the bulk condition.

The $g(r)$ function is zero when the interparticle distance, r , approaches zero because repulsive force prevents the atoms from closely approaching each other. Additionally, when distance r is infinite, the

local density in the shell is equivalent to the mean bulk density averaged over the whole volume; therefore, $g(r)$ is standardized to 1.

The RDF was calculated to determine the difference in the structural arrangements of the polymer atoms and water molecules at 278, 300, 323, 343, and 368 K. The RDFs around the carbon atom of the side chain and for the water–oxygen atom were carefully investigated for six different kinds of polymers.

2.4 results and Discussion

2.4.1 Temperature dependence of R_g

In PNIPAM, the LCST-type phase transition and coil–globule structural transitions are known to be correlated. The occurrence of the coil–globule structural transition can be determined using the R_g , which represents the degree of chain extension. Therefore, the temperature dependence of R_g was analyzed to observe the structural transition behaviors of poly(MeGE), poly(EtGE), poly(MeEOGE), poly(EtEOGE), poly(MeEO₂GE), and poly(EtEO₂GE). Five polymers other than poly(MeEO₂GE) have been reported to exhibit phase transitions[10]. In this chapter, MD simulations were performed with molecular weights of 2500 and 5000 for all polymers. The degrees of polymerization with molecular weights of 2500 for poly(MeGE), poly(EtGE), poly(MeEOGE), poly(EtEOGE), poly(MeEO₂GE), and poly(EtEO₂GE) were 28, 24, 19, 17, 14, 15, respectively. Also, the degrees of polymerization with molecular weights of 5000 for poly(MeGE), poly(EtGE), poly(MeEOGE), poly(EtEOGE), poly(MeEO₂GE), and poly(EtEO₂GE) were 55, 47, 37, 33, 27, 29, respectively. The averaged trajectories obtained from two MD simulations were employed for the analysis. Figures 2-2, 2-3, and 2-4 show the R_g distributions for six different kinds of polymers having molecular weights 2500 obtained with their time courses for 20 ns. The R_g distributions of poly(EtGE), poly(EtEOGE), and poly(EtEO₂GE) with ethyl terminal groups were relatively unimodal across the temperature range, whereas those of poly(MeGE) and poly(MeEOGE) with methyl terminal groups were multimodal or

broadened in the low to medium temperature range. Table 2-2 summarizes the peak values of the R_g distribution at each temperature and the corresponding experimental cloud point (CLP) values. The experimental CLP temperatures (T_{CLP}) are referenced from the results obtained using the molecular weight of ca. 5000[10]. Figure 2-5 and 2-6 shows the R_g peak values versus the temperatures in Table 2-2. No significant change was observed in the main peak values of R_g above and below T_{CLP} for any of the polymers. This suggests that the coil–globule structural transition was not a prerequisite for the LCST-type phase transition in the PGEs with oxyethylene units. For the standard deviation (SD), the PGE with side-chain ethyl groups tended to have a smaller SD value than those with side-chain methyl group. This implies that the PGE with ethyl groups at the side-chain ends are bulkier than those with methyl groups, and thus, the movement of the main-chain structure should be suppressed. Notably, the difference in the bulkiness of the terminal structure affected the distribution of R_g . Figure 2-7 shows snapshots of each polymer corresponding to the main peak values of R_g at temperatures below and above T_{CLP} . No clear coil–globule structural transitions were observed above and below T_{CLP} for any of the polymers, as evidenced by the analysis of R_g . It was difficult to observe structural transitions from the R_g distributions and snapshots for six different kinds of polymers having molecular weights 5000 obtained with their time courses for 100 ns in figures 2-8, 2-9, 2-10, and 2-11. The R_g distributions of polymers with molecular weight 5000 tended to have larger width than those with molecular weight 2500, which should be attributed to the greater fluctuations caused by doubling of molecular weight.

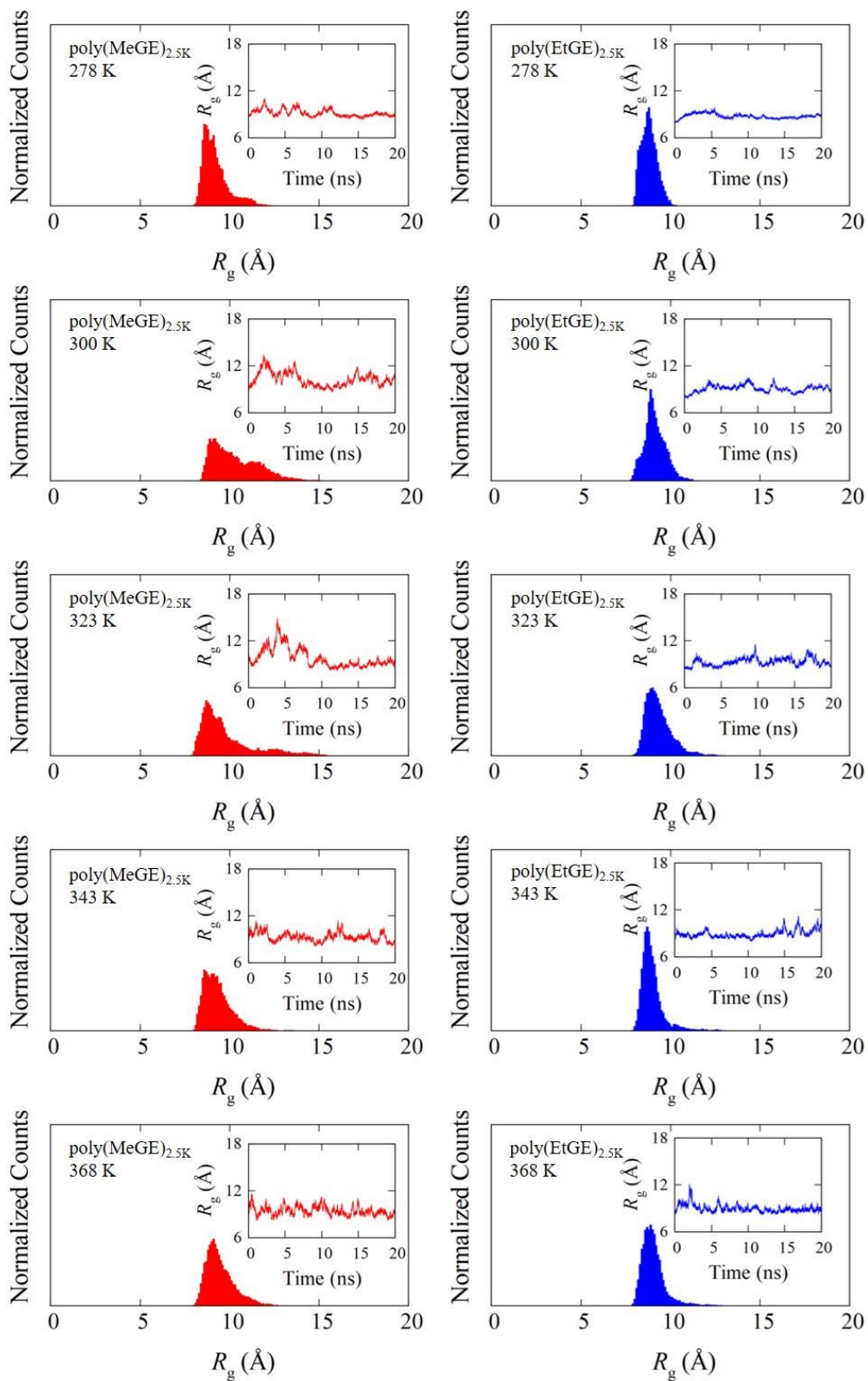


Figure 2-2. R_g distribution inserted for poly(MeGE)_{2.5K} (left) and poly(EtGE)_{2.5K} (right). The inset is the corresponding time dependence of R_g .

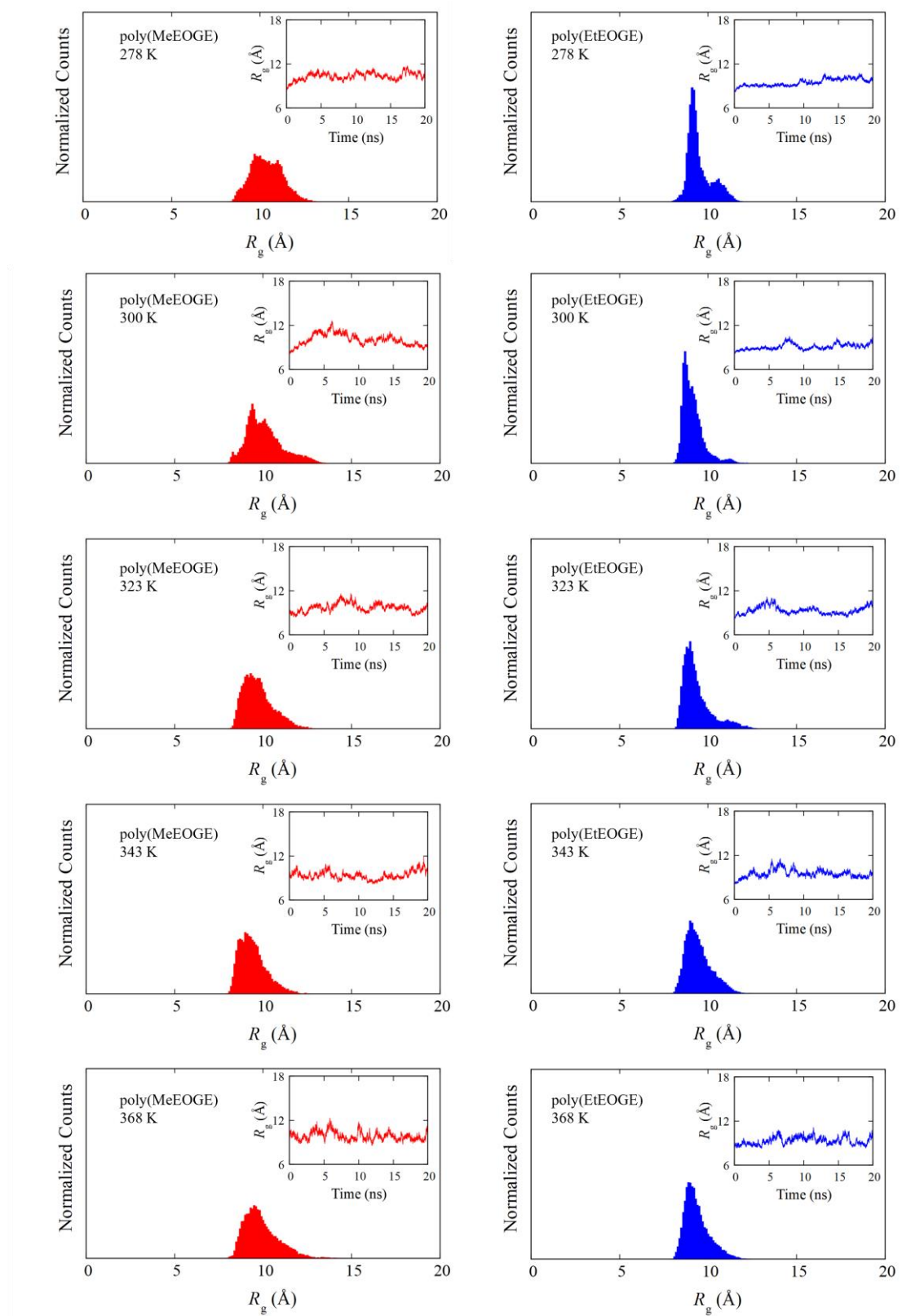


Figure 2-3. R_g distribution inserted for poly(MeEOGE)_{2.5k} (left) and poly(EtEOGE)_{2.5k} (right). The inset is the corresponding time dependence of R_g .

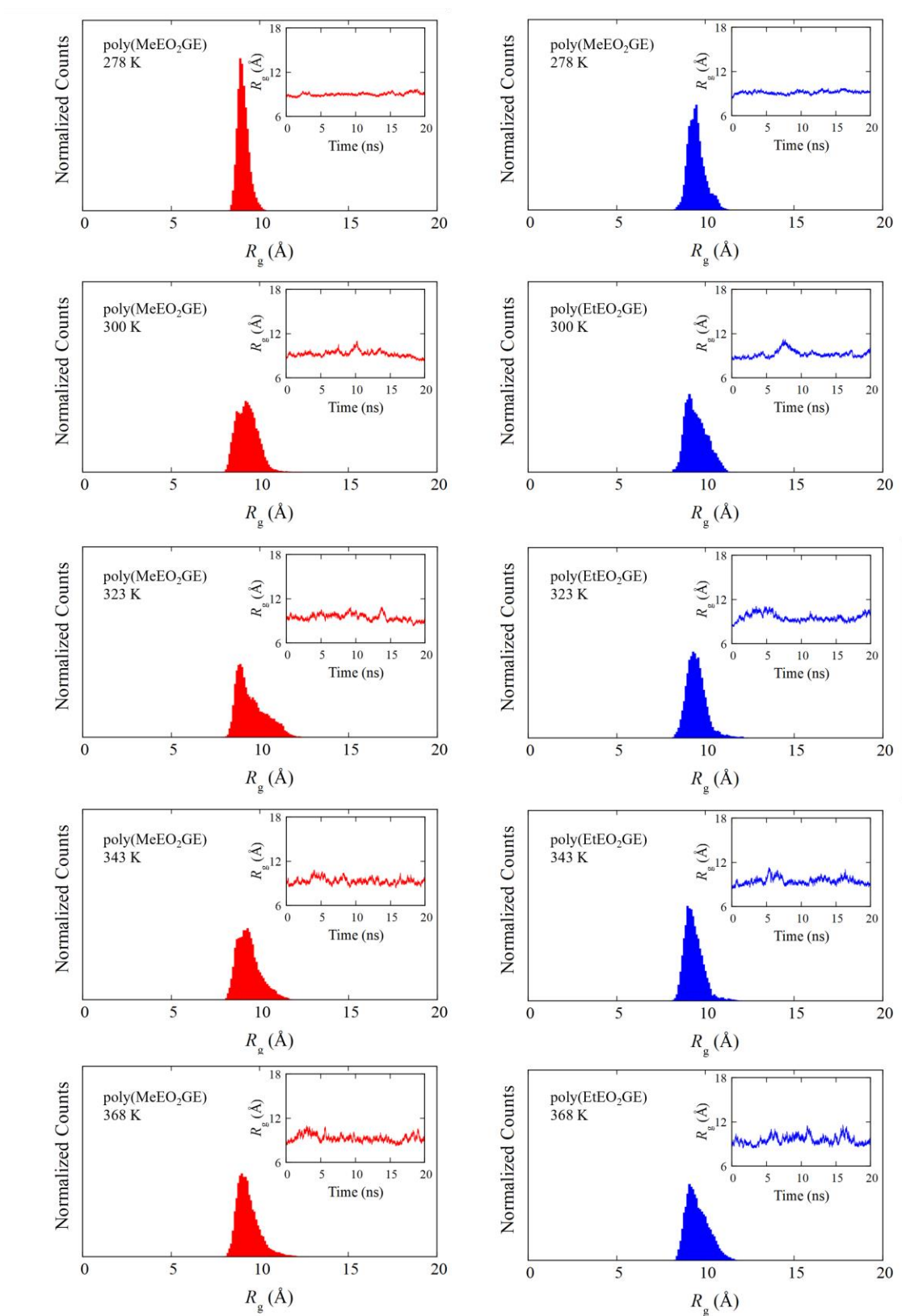


Figure 2-4. R_g distributions for poly(MeEO₂GE)_{2.5k} (left) and poly(EtEO₂GE)_{2.5k} (right). The inset is the corresponding time dependence of R_g .

Table 2-2 Calculated principal R_g peaks and experimental T_{CLP}

sample ID	Experimental T_{CLP} * (K)	$R_g / \text{\AA}$ (SD / $\text{\AA}$)				
		278 K	300 K	323 K	343 K	368 K
poly(MeGE) _{2.5k}	338.5	8.6 (0.5)	8.9 (0.9)	8.7 (1.2)	8.6 (0.6)	9.1 (0.6)
poly(EtGE) _{2.5k}	283.3	8.8 (0.3)	8.9 (0.5)	9.0 (0.5)	8.7 (0.5)	8.9 (0.5)
poly(MeEOGE) _{2.5k}	364.6	9.7 (0.5)	9.4 (0.8)	9.3 (0.6)	9.0 (0.6)	9.5 (0.6)
poly(EtEOGE) _{2.5k}	314.3	9.1 (0.5)	8.7 (0.4)	9.0 (0.5)	9.0 (0.6)	8.9 (0.5)
poly(MeEO ₂ GE) _{2.5k}	Not observed**	8.9 (0.2)	9.2 (0.4)	8.9 (0.4)	9.3 (0.4)	9.0 (0.5)
poly(EtEO ₂ GE) _{2.5k}	331.2	9.5 (0.2)	9.1 (0.5)	9.3 (0.5)	9.0 (0.5)	9.1 (0.6)

* Cloud point temperature observed by the turbidity measurements[14].

** The LCST-type phase transition was not observed at temperatures up to 374 K[14].

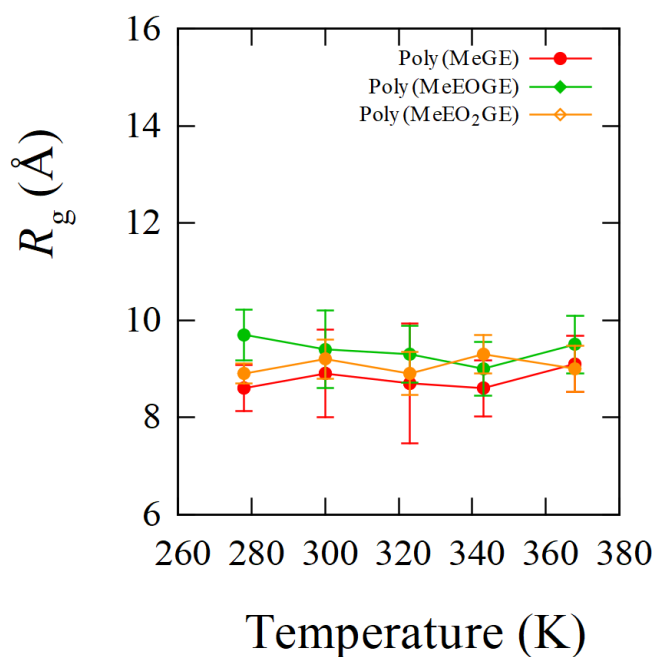


Figure 2-5. R_g peaks plotted versus temperatures for poly(MeGE)_{2.5k}, poly(MeEOGE)_{2.5k}, and poly(MeEO₂GE)_{2.5k} with error bars.

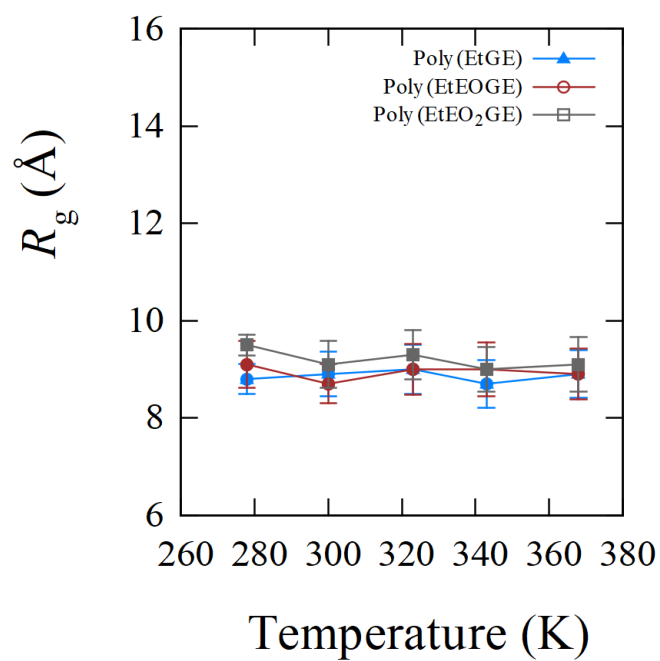


Figure 2-6. R_g peaks plotted versus temperatures for poly(EtGE)_{2.5k}, poly(EtEOGE)_{2.5k}, and poly(EtEO₂GE)_{2.5k} with error bars.

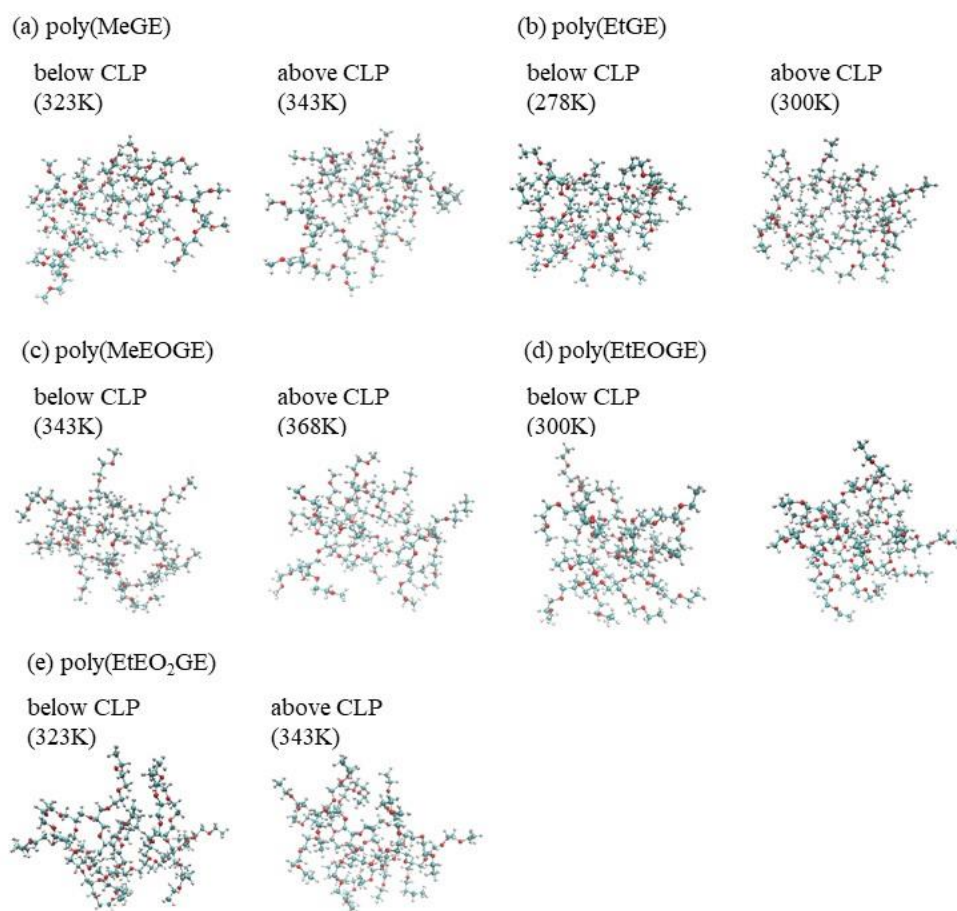


Figure 2-7. Snapshots of (a) poly(MeGE)_{2.5k}, (b) poly(EtGE)_{2.5k}, (c) poly(MeEOGE)_{2.5k}, (d) poly(EtEOGE)_{2.5k} and (e) poly(EtEO₂GE)_{2.5k} at the end of 20 ns below and above T_{CLP} . The carbon, oxygen, and hydrogen atoms of polymers are shown in green, red, and grey colors, respectively. Solvent water molecules have been omitted for clarity.

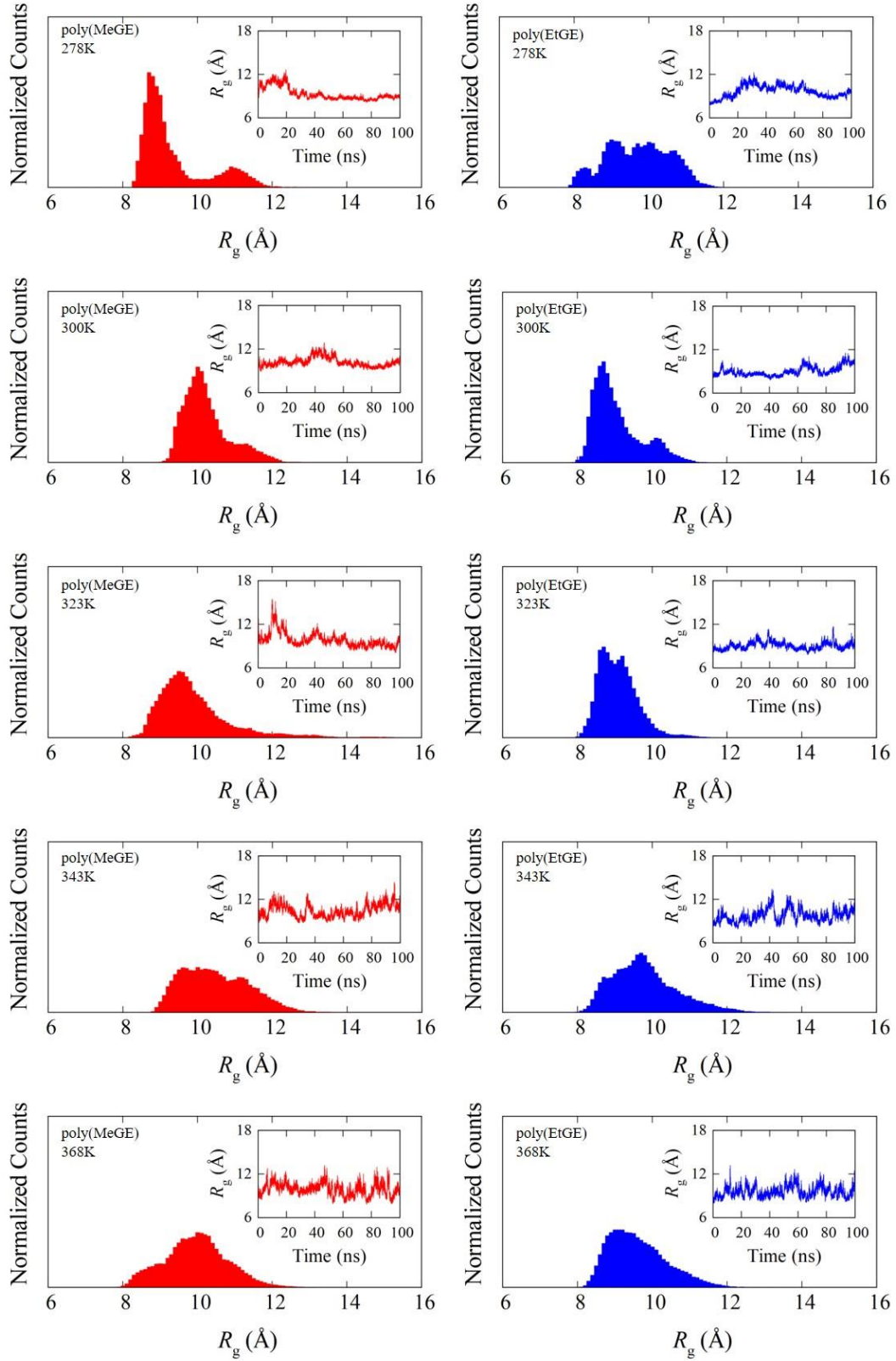


Figure 2-8. R_g distributions for poly(MeGE)_{5k} (left) and poly(EtGE)_{5k} (right). The inset is the corresponding time dependence of R_g .

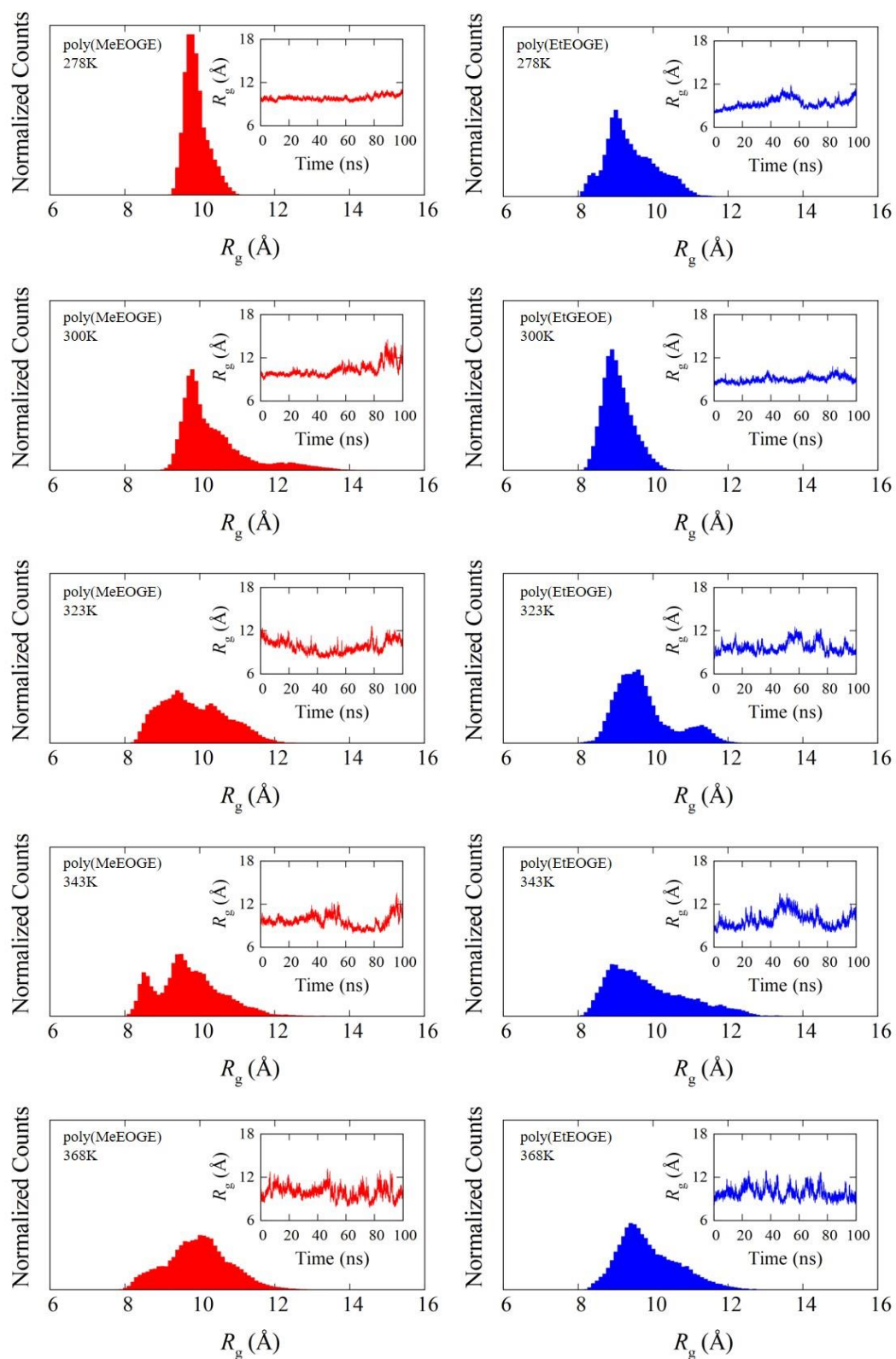


Figure 2-9. R_g distributions for poly(MeEOGE)_{5k} (left) and poly(EtEOGE)_{5k} (right). The inset is the corresponding time dependence of R_g .

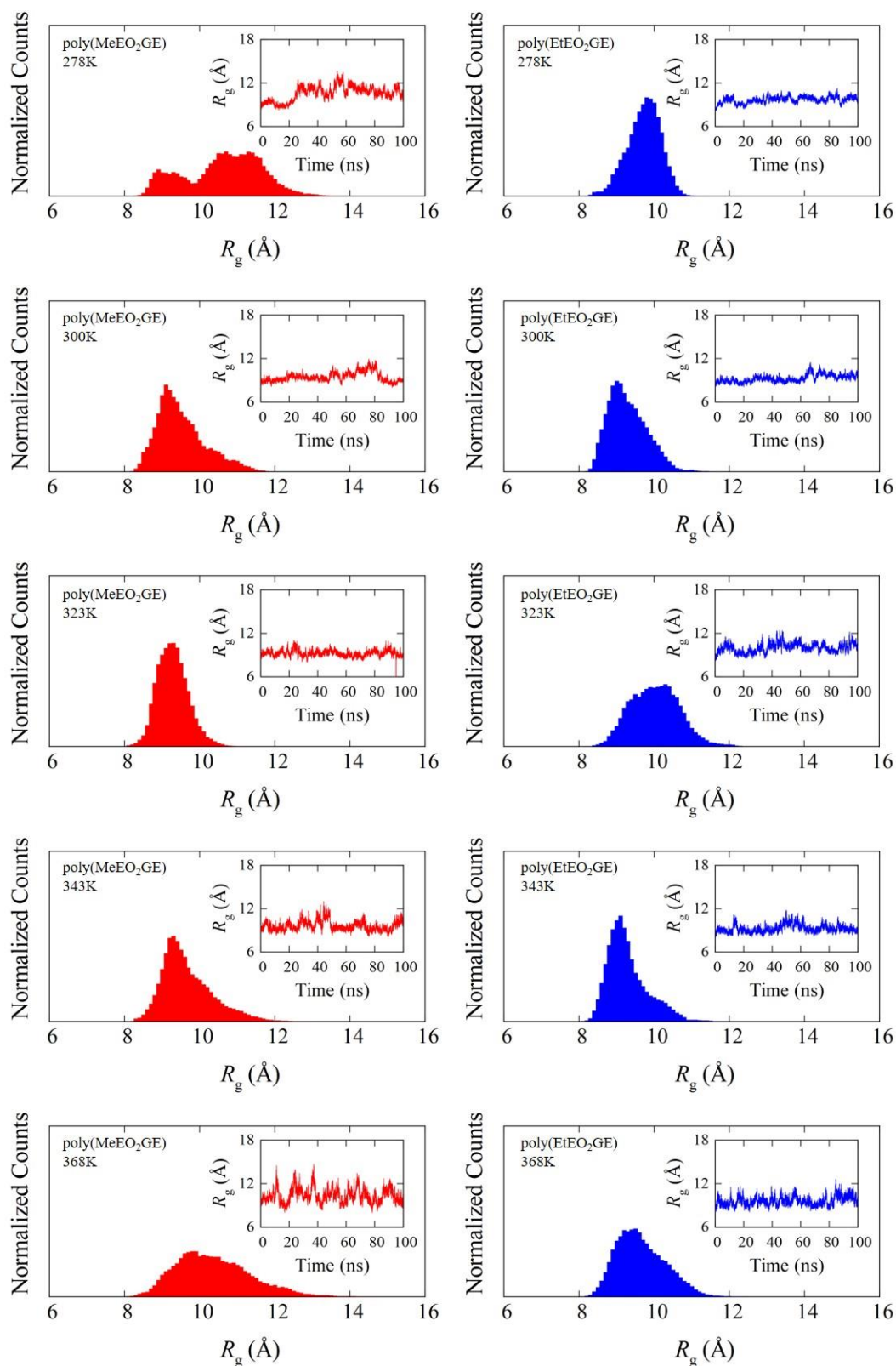


Figure 2-10. R_g distributions for poly(MeEO₂GE)_{5k} (left) and poly(EtEO₂GE)_{5k} (right). The inset is the corresponding time dependence of R_g .

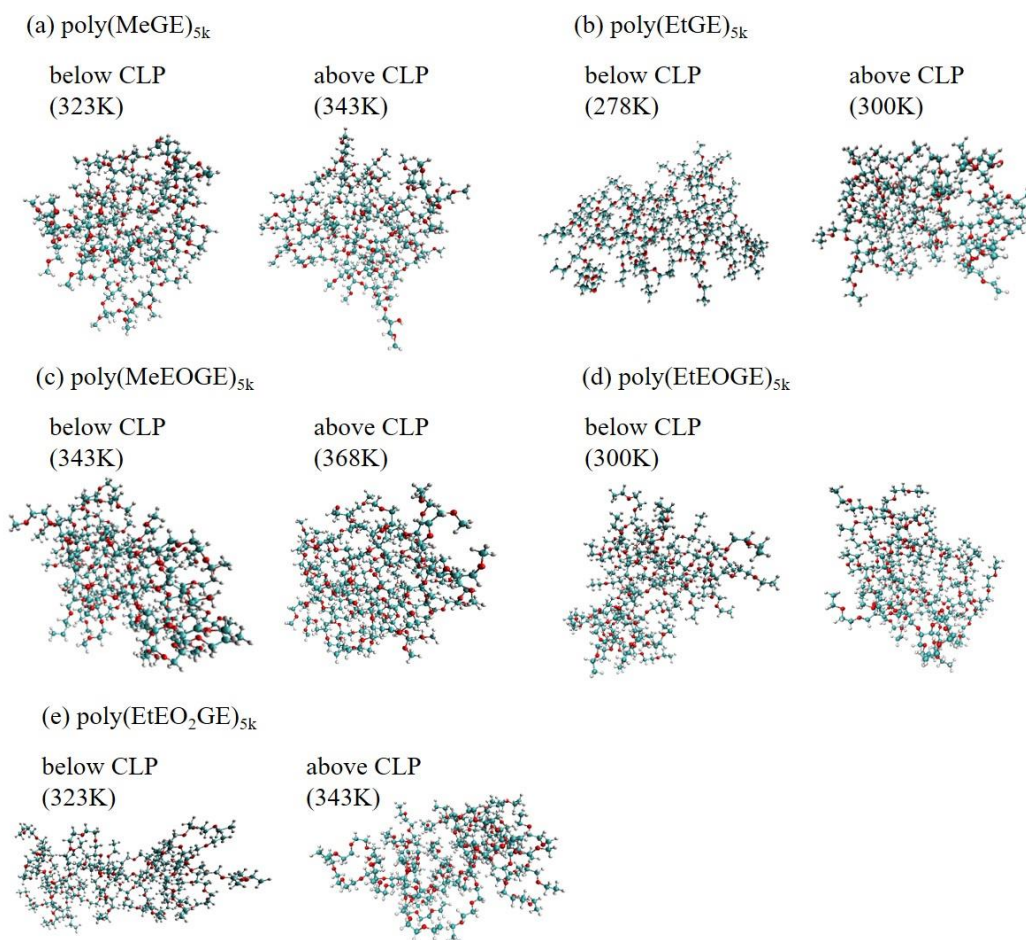


Figure 2-11. Snapshots of (a) poly(MeGE)_{5k}, (b) poly(EtGE)_{5k}, (c) poly(MeEOGE)_{5k}, (d) poly(EtEOGE)_{5k} and (e) poly(EtEO₂GE)_{5k} at the end of 20 ns below and above T_{CLP} . The carbon, oxygen, and hydrogen atoms of polymers are shown in green, red, and grey colors, respectively. Solvent water molecules have been omitted for clarity.

2.4.2 Degree of chain extensions and their fluctuations

To investigate whether the polymer is in the coil or globule state, the ratio of the maximum length of the main chain ($L_{\max}$) to the time average length ($\bar{L}$) obtained from the MD simulation performed with a molecular weight of 2500 was calculated. The time dependence and distribution of $\bar{L}$ for the six polymers are shown in Figures 2-12, 2-13, 2-14, 2-15, 2-16, and 2-17. For freely jointed chains or ideal chains with the degree of polymerization, N , the following equation holds:

$$\frac{\bar{L}}{L_{\max}} = \frac{1}{\sqrt{N}}. \quad (3)$$

If the ratio is larger than $1/\sqrt{N}$, the polymer can be roughly considered to be in the coil state, and if it is smaller, it can be considered to be in the globule state[40]. Table 2-3 summarizes the values of $\bar{L}/L_{\max}$ and $1/\sqrt{N}$ for all the polymers. For poly(MeGE) (28-mers) and poly(EtGE) (24-mers), which had relatively large degrees of polymerization, the values of $\bar{L}/L_{\max}$ were smaller than the corresponding $1/\sqrt{N}$ values in almost all temperature ranges, suggesting that they consistently adopted globule structures. Poly(MeEOGE) (19-mers) exhibited larger values of $\bar{L}/L_{\max}$ than $1/\sqrt{N}$ in all temperature ranges; thus, it could be considered to be consistently in the coil state. Conversely, poly(EtEOGE) (17-mers) exhibited smaller values of $\bar{L}/L_{\max}$ than $1/\sqrt{N}$ at 300, 323, and 343 K; thus, it was expected to be in the globule state. Poly(MeEO₂GE) (14-mers) and poly(EtEO₂GE) (15-mers) with relatively small degrees of polymerization exhibited larger values of $\bar{L}/L_{\max}$ than $1/\sqrt{N}$; thus, they were expected to be in the coil state in all temperature ranges. The coefficient of variation

(CV) was calculated to compare the fluctuation of $\bar{L}/L_{max}$ for the six polymers without the effect of different degrees of polymerization. The CV is the SD normalized by the mean value. It is a dimensionless number used to evaluate the relative relationship of the SDs among the data with different mean values. When the CV values between poly(MeGE) and poly(EtGE), poly(MeEOGE) and poly(EtEOGE), and poly(MeEO₂GE) and poly(EtEO₂GE) were compared, the polymer with the methyl group at the side-chain ends tended to exhibit higher values than those for the polymer with the ethyl group at the side-chain ends. According to the R_g measurement results, the magnitude of fluctuation was different between the methyl and ethyl side-chain ends; however, it was unclear whether the difference was due to the main chain or the side chain. This suggests that the polymer main-chain structure with the methyl group fluctuated more than that with the ethyl group. Table 2-4 shows the ratio of the maximum length of the main chain (L_{max}) to the temperature average length ($\langle \bar{L} \rangle_{temp}$), SD, and CV for the six polymers at five temperatures. Resultantly, except for poly(MeEO₂GE), the CV values of the polymers with terminal methyl groups were larger than those of the polymers with terminal ethyl groups. This indicates that the main-chain structural fluctuation of the polymer with terminal a methyl group on the side chain should be larger than that of the polymer with a terminal ethyl group on the side chain.

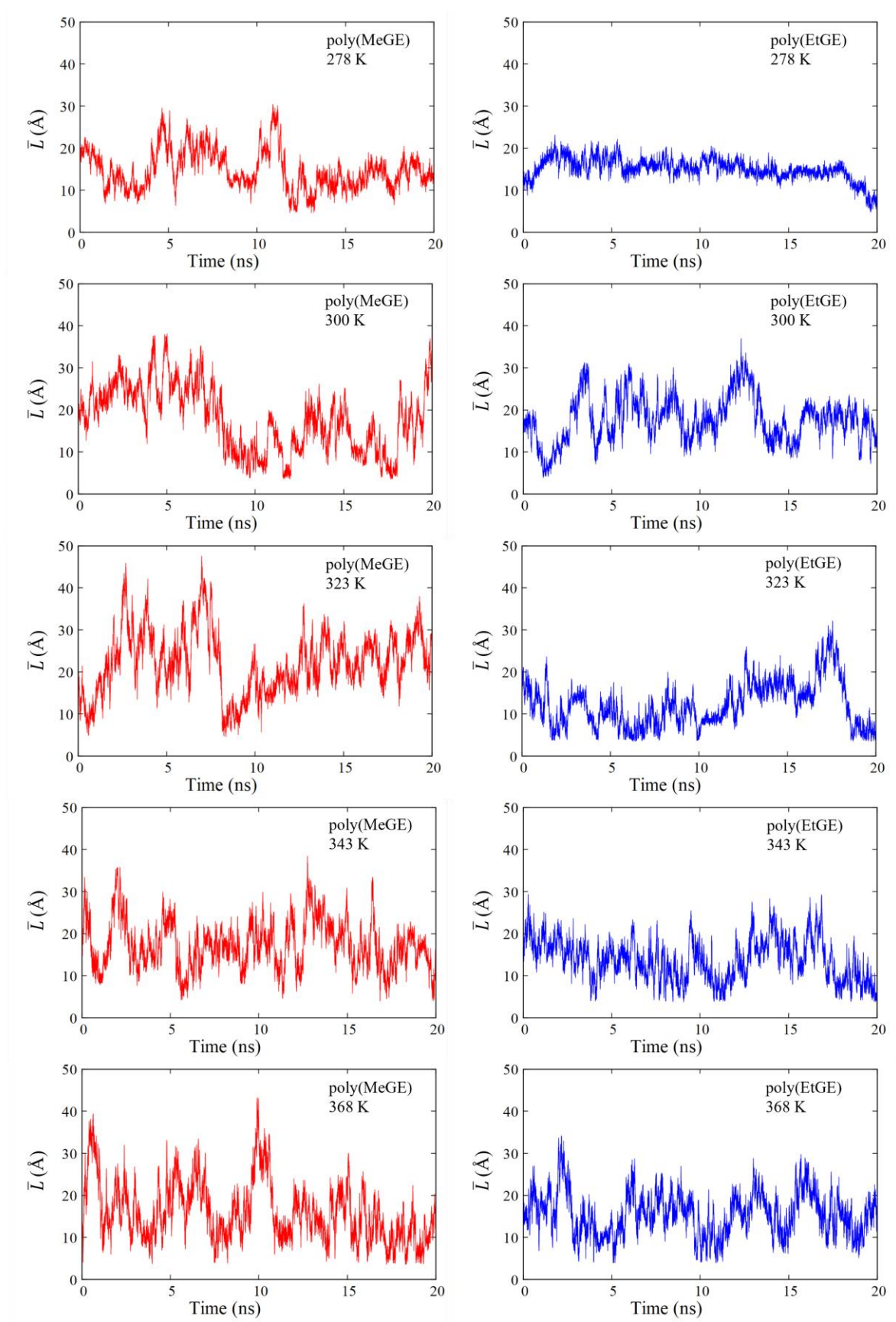


Figure 2-12. Time dependence of $\bar{L}$ for poly(MeGE)_{2.5k} (left) and poly(EtGE)_{2.5k} (right).

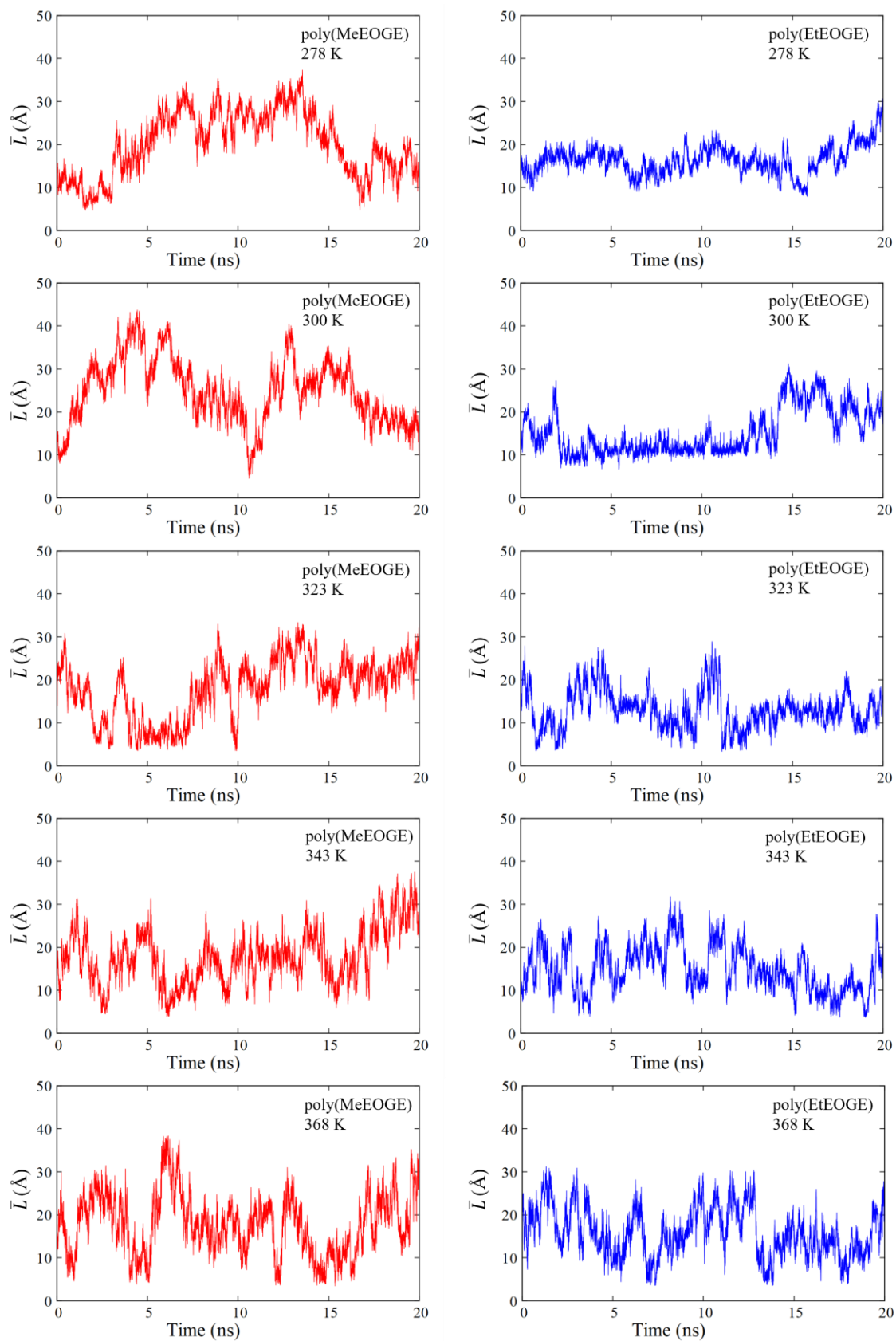


Figure 2-13. Time dependence of $\bar{L}$ for poly(MeEOGE)_{2.5k} (left) and poly(EtEOGE)_{2.5k} (right).

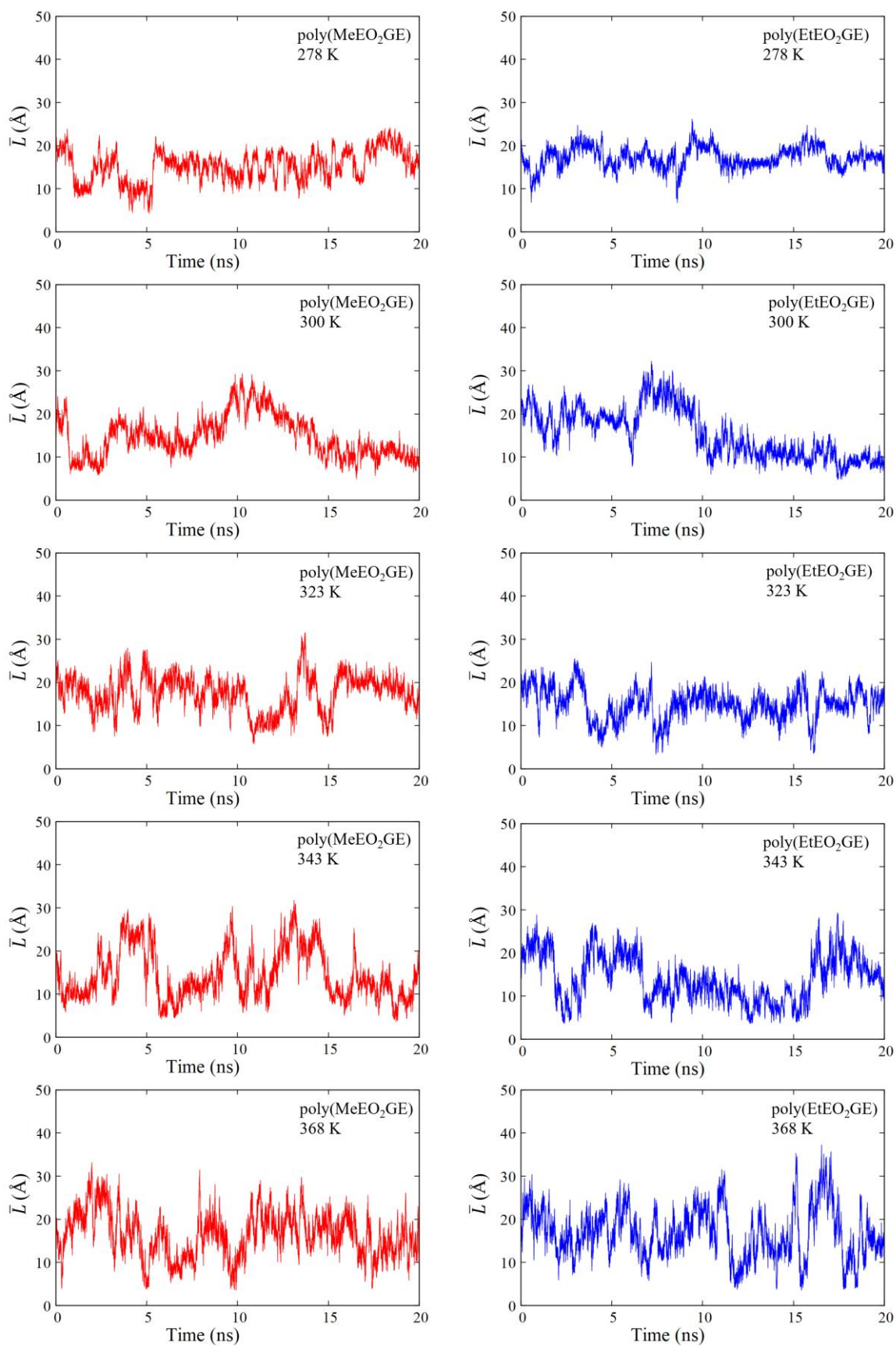


Figure 2-14. Time dependence of $\bar{L}$ for poly(MeEO₂GE)_{2.5k} (left) and poly(EtEO₂GE)_{2.5k} (right).

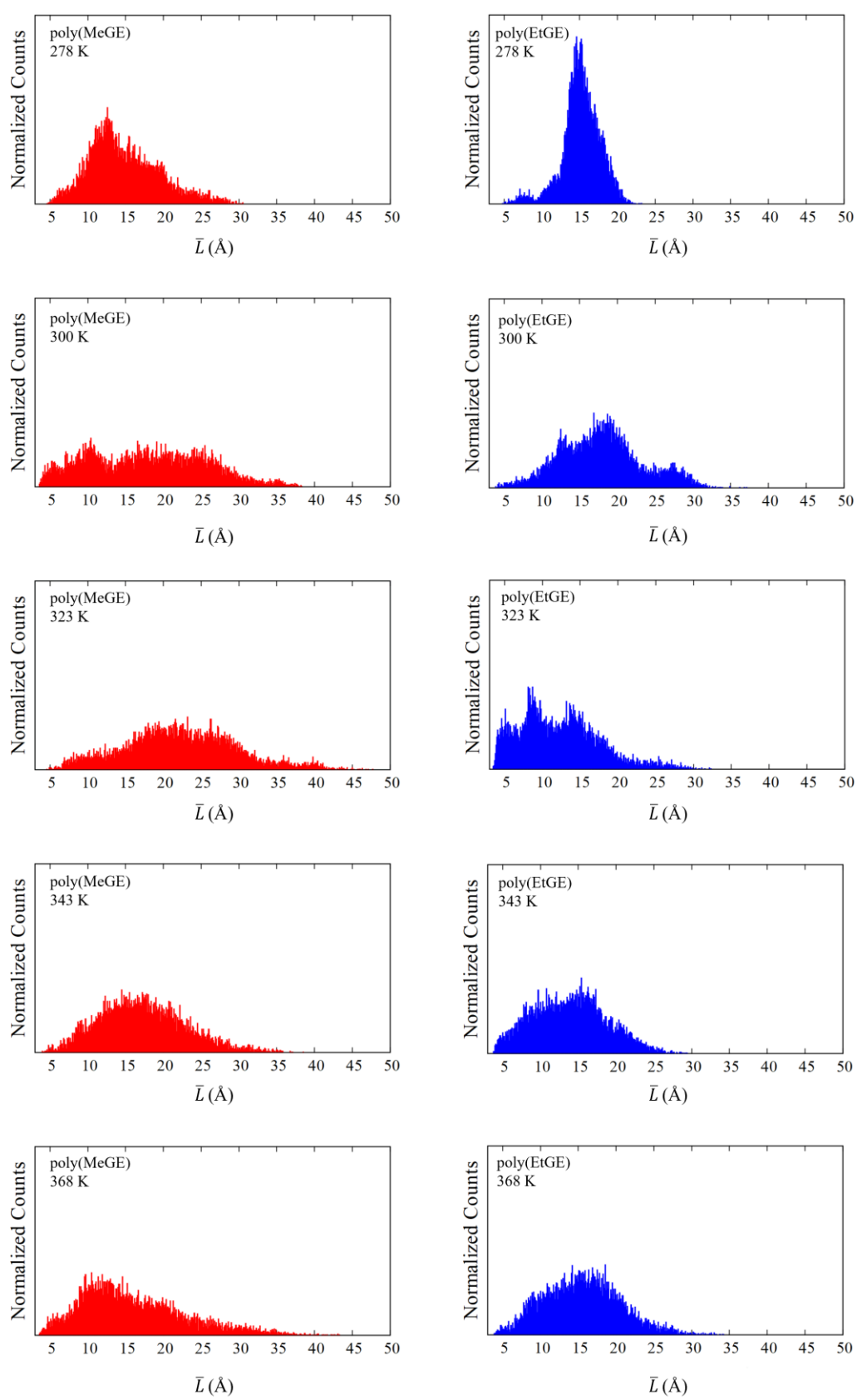


Figure 2-15. $\bar{L}$ distribution for poly(MeGE)_{2.5k} (left) and poly(EtGE)_{2.5k}.

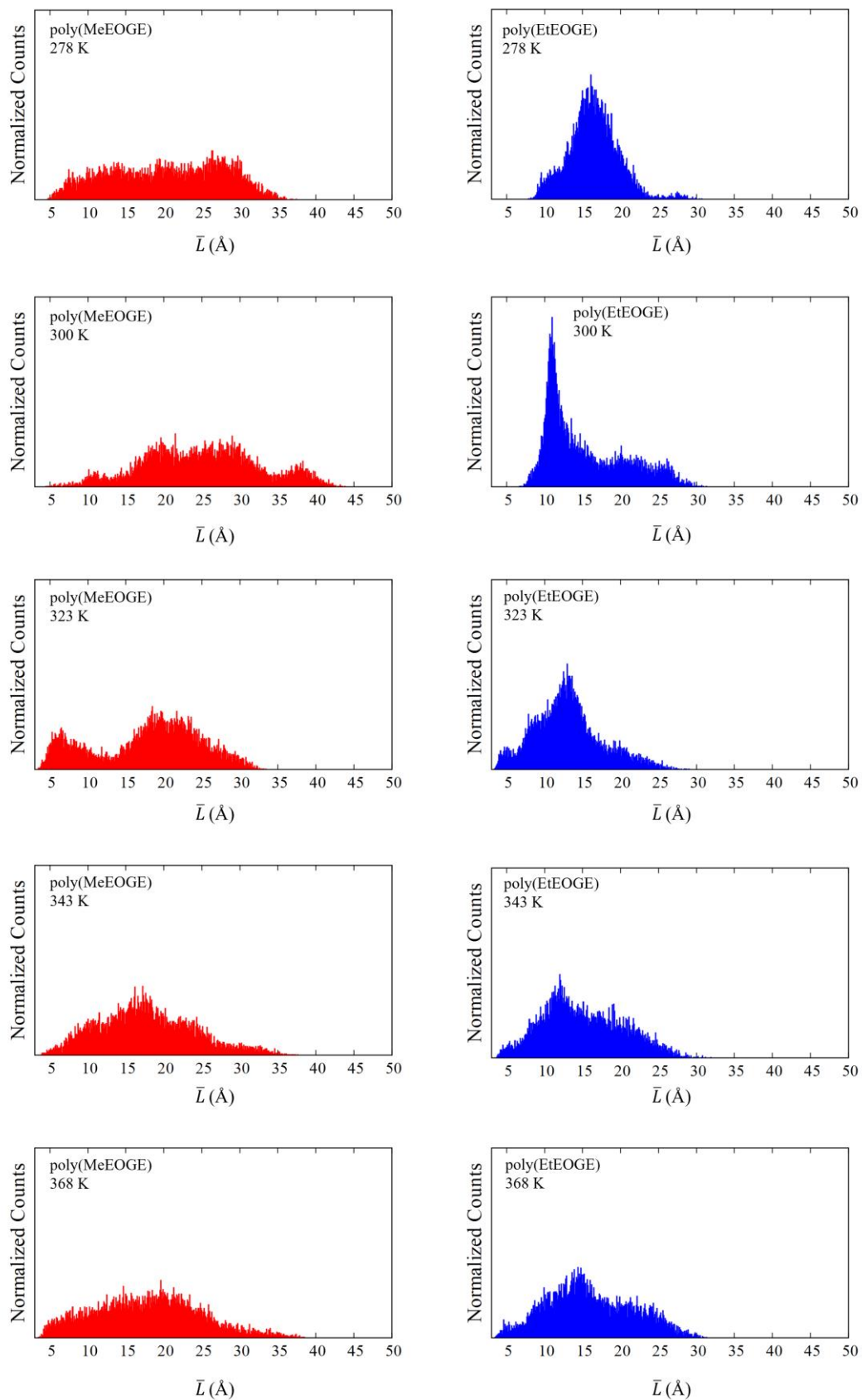


Figure 2-16. $\bar{L}$ distribution for poly(MeEOGE)_{2.5k} (left) and poly(EtEOGE)_{2.5k} (right).

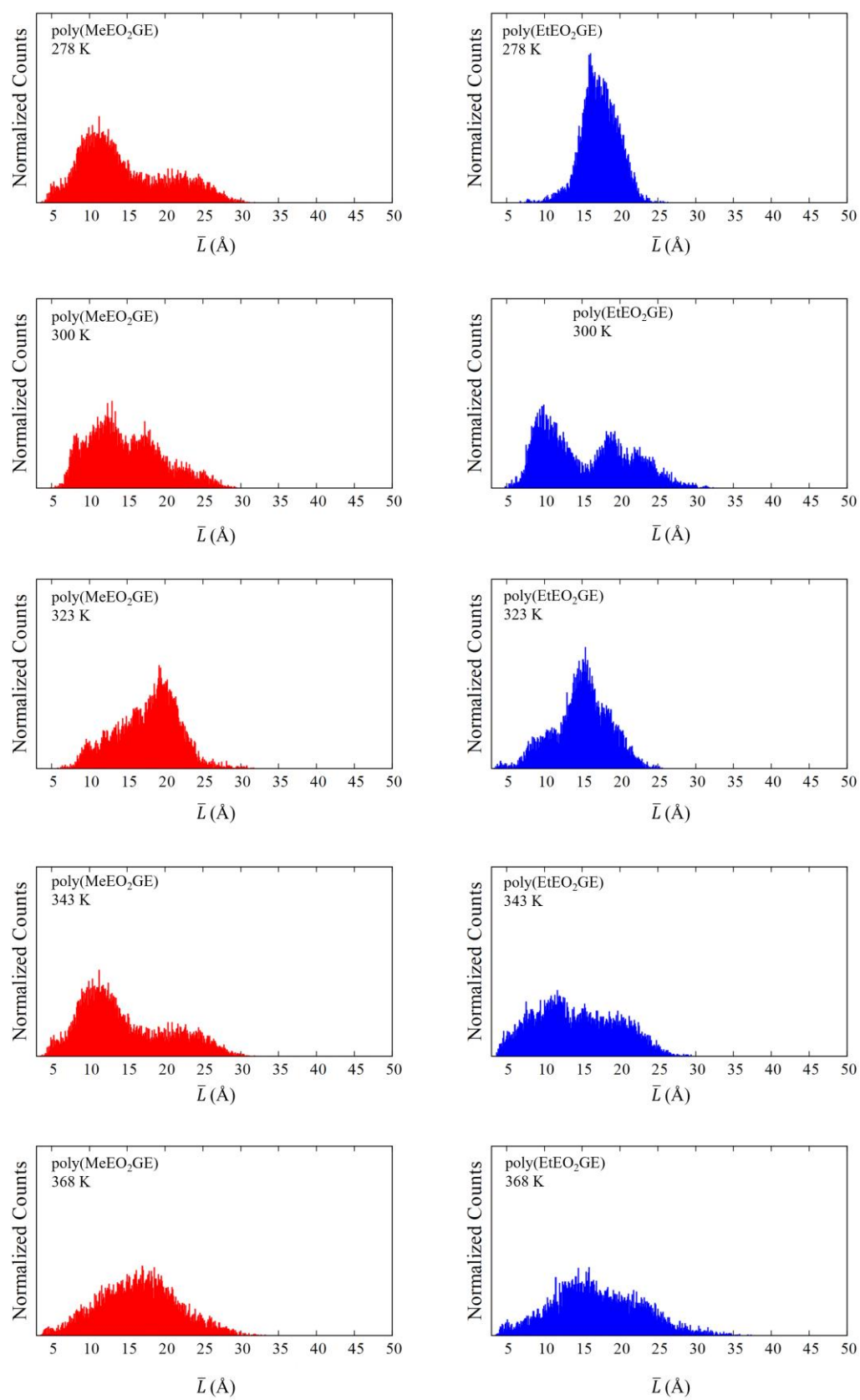


Figure 2-17. $\bar{L}$ distribution for poly(MeEO₂GE)_{2.5k} (left) and poly(EtEO₂GE)_{2.5k} (right).

Table 2-3. Calculated $\bar{L}/L_{max}$ at each temperature

polymer ID	temperature (K)	$\bar{L}/L_{max}$	$1/\sqrt{N}$	SD	CV
poly(MeGE) _{2.5k}	278	0.14	0.19	0.04	0.32
	300	0.17	0.19	0.07	0.43
	323	0.21	0.19	0.07	0.34
	343	0.16	0.19	0.05	0.33
	368	0.15	0.19	0.07	0.44
poly(EtGE) _{2.5k}	278	0.17	0.20	0.03	0.17
	300	0.20	0.20	0.06	0.31
	323	0.14	0.20	0.06	0.44
	343	0.15	0.20	0.05	0.35
	368	0.17	0.20	0.06	0.33
poly(MeEOGE) _{2.5k}	278	0.28	0.23	0.10	0.37
	300	0.34	0.23	0.10	0.30
	323	0.25	0.23	0.10	0.39
	343	0.24	0.23	0.09	0.36
	368	0.25	0.23	0.10	0.39
poly(EtEOGE) _{2.5k}	278	0.25	0.24	0.05	0.20
	300	0.23	0.24	0.08	0.35
	323	0.20	0.24	0.07	0.34
	343	0.23	0.24	0.08	0.35
	368	0.24	0.24	0.09	0.35
poly(MeEO ₂ GE) _{2.5k}	278	0.28	0.27	0.07	0.24
	300	0.27	0.27	0.09	0.33
	323	0.32	0.27	0.08	0.24
	343	0.27	0.27	0.11	0.40
	368	0.30	0.27	0.10	0.32
poly(EtEO ₂ GE) _{2.5k}	278	0.34	0.26	0.05	0.14
	300	0.30	0.26	0.11	0.37
	323	0.29	0.26	0.07	0.25
	343	0.28	0.26	0.11	0.38
	368	0.33	0.26	0.12	0.35

Table 2-4. Calculated $\langle \bar{L} \rangle_{temp}/L_{max}$ with their SD, and CV

polymer ID	$\langle \bar{L} \rangle_{temp}/L_{max}$	SD	CV
poly(MeGE) _{2.5k}	0.17	0.027	0.159
poly(EtGE) _{2.5k}	0.16	0.023	0.140
poly(MeEOGE) _{2.5k}	0.27	0.043	0.158
poly(EtEOGE) _{2.5k}	0.23	0.020	0.085
poly(MeEO ₂ GE) _{2.5k}	0.29	0.024	0.082
poly(EtEO ₂ GE) _{2.5k}	0.31	0.026	0.084

It has been reported that the T_{CLP} of poly(MeEOGE) decreases as the molecular weight increases[14]. The $\bar{L}/L_{max}$ values of poly(MeEOGE) for molecular weights of 1250 and 5000 were calculated, and the polymer-chain extension was investigated. Table 2-5 summarizes the results of the $\bar{L}/L_{max}$ and $1/\sqrt{N}$ calculations for poly(MeEOGE) with molecular weights of 1250, 2500, and 5000. As the molecular weight increased, the value of $\bar{L}/L_{max}$ tended to decrease. For the molecular weight of 1250, the values of $\bar{L}/L_{max}$ were larger than the corresponding $1/\sqrt{N}$ values in all temperature regions except for 278 K. This indicated that poly(MeEOGE) with a molecular weight of 1250 exhibited a coil structure. For the molecular weight of 5000, the values of $\bar{L}/L_{max}$ were smaller than the $1/\sqrt{N}$ values in all temperature regions, indicating that the poly(MeEOGE) with a molecular weight of 5000 had a globule structure. A similar tendency was observed for poly(EtEOGE) (Table 2-6). These results suggested that the smaller the degree of polymerization of PGE, the lower the probability that it exhibits the coil structure, and the larger the degree of polymerization, the higher the

probability that it exhibits the globule structure. The larger the degree of polymerization of poly(MeEOGE), the higher its tendency to adopt the globule structure. This implies that the change from the coil to the globule state with increasing molecular weight was related to the change in the T_{CLP} . This relation will be explained by RDF analysis.

Table 2-5. Calculated $\bar{L}/L_{max}$ of poly(MeEOGE) for molecular weights of 1250, 2500, and 5000

polymer ID	temperature (K)	$\bar{L}/L_{max}$	$1/\sqrt{N}$	SD	CV
poly(MeEOGE) _{1.25k}	278	0.30	0.33	0.11	0.36
	300	0.43	0.33	0.05	0.12
	323	0.35	0.33	0.14	0.40
	343	0.37	0.33	0.12	0.32
	368	0.38	0.33	0.13	0.34
poly(MeEOGE) _{2.5k}	278	0.28	0.23	0.10	0.37
	300	0.34	0.23	0.10	0.30
	323	0.25	0.23	0.10	0.39
	343	0.24	0.23	0.09	0.36
	368	0.25	0.23	0.10	0.39
poly(MeEOGE) _{5k}	278	0.07	0.16	0.02	0.31
	300	0.11	0.16	0.01	0.12
	323	0.08	0.16	0.02	0.27
	343	0.15	0.16	0.03	0.20
	368	0.11	0.16	0.04	0.37

Table 2-6 Calculated $\bar{L}/L_{\max}$ of poly(EtEOGE) for molecular weights of 1250, 2500, and 5000

polymer ID	temperature (K)	$\bar{L}/L_{\max}$	$1/\sqrt{N}$	SD	CV
poly(EtEOGE) _{1.25k}	278	0.41	0.35	0.12	0.30
	300	0.33	0.35	0.12	0.37
	323	0.35	0.35	0.11	0.32
	343	0.40	0.35	0.15	0.37
	368	0.41	0.35	0.14	0.35
poly(EtEOGE) _{2.5k}	278	0.25	0.24	0.05	0.20
	300	0.23	0.24	0.08	0.35
	323	0.20	0.24	0.07	0.34
	343	0.23	0.24	0.08	0.35
	368	0.24	0.24	0.09	0.35
poly(EtEOGE) _{5k}	278	0.22	0.17	0.05	0.23
	300	0.14	0.17	0.04	0.31
	323	0.12	0.17	0.04	0.36
	343	0.14	0.17	0.06	0.44
	368	0.15	0.17	0.05	0.32

2.4.3 The side-chain lengths and their fluctuations

The results of the $\bar{L}/L_{\max}$ calculations suggested that the main-chain structure of PGE with methyl terminal groups fluctuated more than that of the PGE with ethyl terminal groups at the side-chain ends. To further investigate if the fluctuation of the side-chain structure affects the polymer fluctuation, the side-chain lengths (i.e., the lengths between the main-chain carbon atom and the side-chain terminal carbon atom) of six polymers with molecular weights 2500 were obtained using the time-averaged values of the side-chain length in the MD simulations. Table 2-7 summarizes the time-averaged side-chain lengths, and their temperature-averaged values, SDs, and CVs, as well as the calculated side-

chain lengths at each temperature, are shown in Table 2-8. Comparing the CV values, when the side chain was short, as in poly(MeGE) and poly(EtGE), no difference in the magnitude of the fluctuations was observed. However, when the side chain was long, as in poly(MeEOGE), poly(EtEOGE), poly(MeEO₂GE), and poly(EtEO₂GE), the PGE with the methyl group exhibited a higher magnitude of fluctuation in the side-chain structure than those with ethyl group. This suggested that the fluctuation of the side-chain structure affected the fluctuation of the polymer structure.

Table 2-7. Time-averaged side chain lengths and their fluctuations

sample ID	Time averaged side chain length (Å)					Temperature averaged side chain length (Å)	SD (Å)	CV
	278K	300K	323K	343K	368K			
poly(MeGE) _{2.5k}	3.70	3.70	3.69	3.67	3.66	3.68	0.017	0.005
poly(EtGE) _{2.5k}	4.74	4.72	4.70	4.69	4.68	4.71	0.023	0.005
poly(MeEOGE) _{2.5k}	6.30	6.24	6.20	6.16	6.13	6.21	0.068	0.011
poly(EtEOGE) _{2.5k}	7.06	7.01	7.08	7.11	7.00	7.05	0.047	0.007
poly(MeEO ₂ GE) _{2.5k}	8.08	8.00	8.08	8.01	7.97	8.03	0.048	0.006
poly(EtEO ₂ GE) _{2.5k}	8.54	8.54	8.49	8.56	8.55	8.54	0.024	0.003

Table 2-8. Calculated side chain lengths at each temperature

polymer ID	temperature (K)	side chain lengths (Å)	SD	CV
poly(MeGE) _{2.5k}	278	3.70	0.04	0.010
	300	3.70	0.04	0.010
	323	3.69	0.04	0.012
	343	3.67	0.04	0.012
	368	3.66	0.04	0.012
poly(EtGE) _{2.5k}	278	4.74	0.04	0.009
	300	4.72	0.04	0.009
	323	4.70	0.05	0.010
	343	4.69	0.05	0.010
	368	4.68	0.05	0.011
poly(MeEOGE) _{2.5k}	278	6.30	0.11	0.018
	300	6.24	0.12	0.020
	323	6.20	0.14	0.022
	343	6.16	0.14	0.023
	368	6.13	0.15	0.025
poly(EtEOGE) _{2.5k}	278	7.06	0.24	0.034
	300	7.01	0.27	0.038
	323	7.08	0.28	0.039
	343	7.11	0.29	0.040
	368	7.00	0.30	0.043
poly(MeEO2GE) _{2.5k}	278	8.08	0.25	0.031
	300	8.00	0.27	0.034
	323	8.08	0.29	0.035
	343	8.01	0.30	0.038
	368	7.97	0.32	0.040
poly(EtEO2GE) _{2.5k}	278	8.54	0.38	0.044
	300	8.54	0.39	0.045
	323	8.49	0.40	0.047
	343	8.56	0.40	0.047
	368	8.55	0.40	0.047

2.4.4 RDF of hydrophobic solvation

Since the structural transition corresponding to the LCST-type phase transition was not observed by R_g analysis, an alternative physical quantity that reflects CLP was investigated. The RDF is utilized to explore the local order of water molecules surrounding polymers. Therefore, the RDF for the oxygen atoms of waters with polymers having carbon atoms at the side-chain ends was investigated. All the results are based on the average values obtained from two MD simulations conducted with a molecular weight 2500. Figure 2-18 shows the water–oxygen RDF measured using the carbon atoms at all the side-chain ends of poly(MeGE), poly(EtGE), poly(MeEOGE), poly(EtEOGE), poly(MeEO₂GE), and poly(EtEO₂GE) at 278, 300, 323, 343, and 368 K. The first peaks in the water–oxygen RDF spectra were observed at around 3.6 Å for all polymers; thus, the first hydrophobic hydration shells are formed at 3.6 Å from carbon atoms at the side-chain ends. Thereafter, the temperature dependence of the peak intensity in the first hydrophobic hydration shell was investigated. As shown in Figure 2-19, the peak intensity of the hydrophobic hydration shell decreased during the heating process. Furthermore, the crossing point temperature (T_{CRP}) at which the peak intensity decreased below $g(r) = 1.0$ was analyzed for the six types of polymers. The T_{CRP} values are summarized together with the T_{CLP} values reported in the experiments[14] in Table 2-9. The T_{CRP} values for poly(MeGE), poly(EtGE), poly(MeEOGE), poly(EtEOGE), and poly(EtEO₂GE) appeared at 326, 291, 349, 334, and 348 K, respectively, and they were close to the experimental T_{CLP} values. These results indicated that the

hydrophobic hydration shell strength at the end of the polymer side chain correlated with T_{CLP} . By examining the side-chain end structures, I established that the T_{CRP} obtained by simulation for poly(MeGE) and poly(MeEOGE) with methyl side-chain ends were lower than the experimentally obtained T_{CLP} values. Conversely, the T_{CRP} obtained by simulation for poly(EtGE), poly(EtEOGE), and poly(EtEO₂GE) with ethyl side-chain ends were higher than the experimentally obtained T_{CLP} values. In this study, MD simulations were performed with a single polymer chain, and the T_{CRP} should be higher than the experimental T_{CLP} because the polymer concentration in the MD simulation is lower than that in the actual experiment. In the experiments, T_{CLP} tends to increase as the concentration of the polymer solution decreases. This is because the collision frequency between the polymers is reduced, and aggregation is less likely to occur. Contrarily, for the PGE with methyl groups at the side-chain ends, T_{CRP} was lower than T_{CLP} . This relationship is plotted in Figure 2-20. The PGE with methyl terminal groups exhibited large fluctuations in the main-chain and side-chain structures, as evidenced by the results of R_g , $\bar{L}/L_{max}$, and time-averaged side-chain length measurements. Therefore, it is expected that water molecules enter the gaps between the adjacent side chains of the PGE with hydrophobic methyl groups, the proportion of the side-chain end occupying the polymer surface decreases, and the proportion of the hydrophilic ether part occupying the polymer surface increases (Figure 2-21). T_{CRP} only reflects the aqueous environment at the end of the side

chain and not the entire polymer surface. This suggests that the T_{CRP} of the PGE with methyl groups at the side-chain ends was lower than the T_{CLP} .

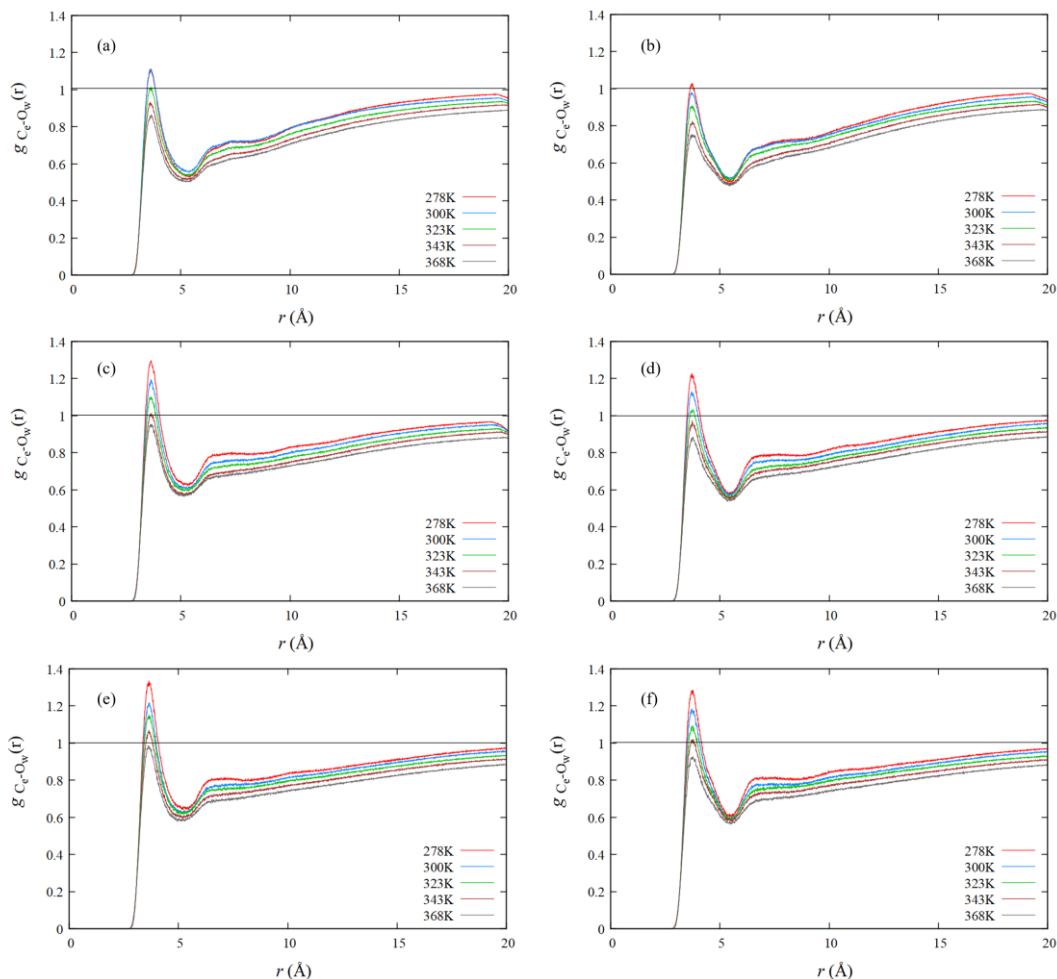


Figure 2-18. RDFs of (a) poly(MeGE)_{2.5k}, (b) poly(EtGE)_{2.5k}, (c) poly(MeEOGE)_{2.5k}, (d) poly(EtEOGE)_{2.5k}, (e) poly(MeEO₂GE)_{2.5k}, and (f) poly(EtEO₂GE)_{2.5k} for O atoms of water measured from C atoms at the sideside chain ends.

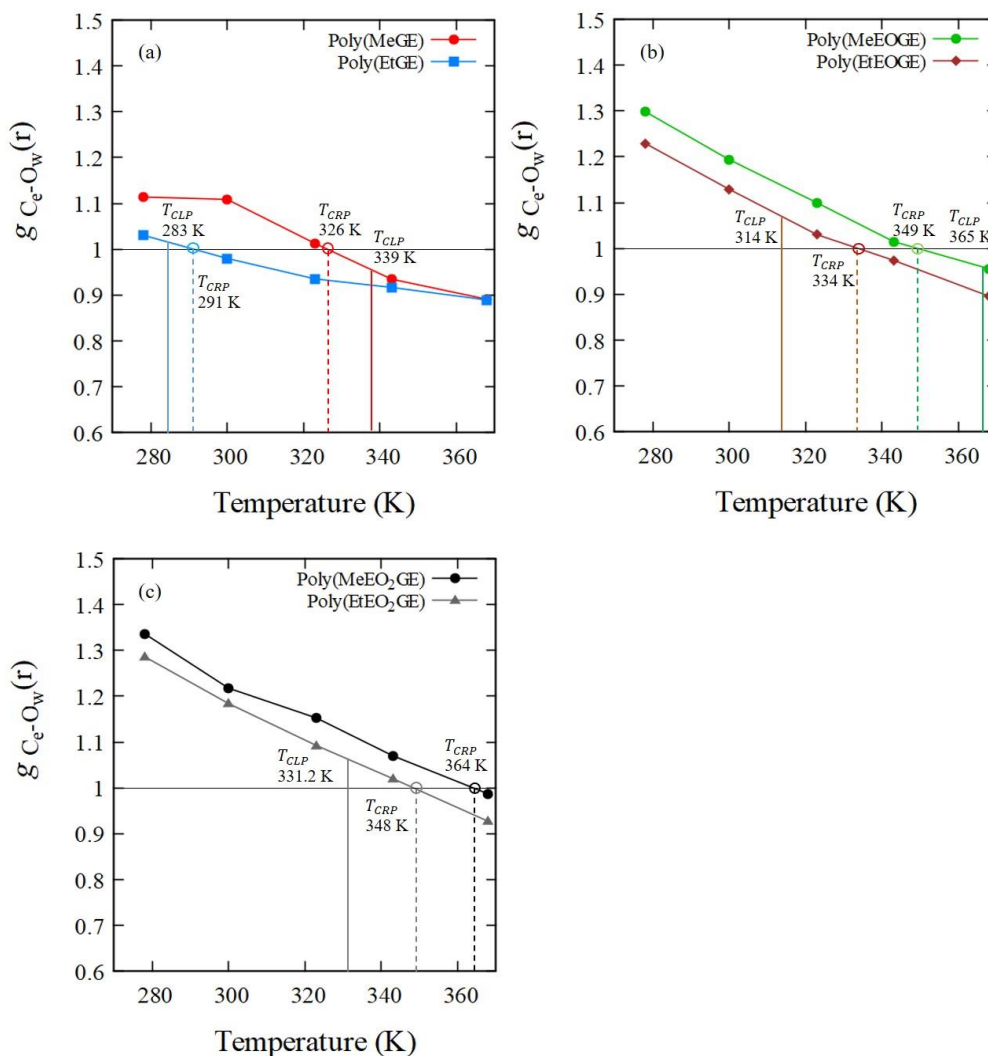


Figure 2-19. Temperature response of the 1st peak intensity in the RDFs of O atoms (water) observed from C atoms at the side chain ends, (a) poly(MeGE)_{2.5k} and poly(EtGE)_{2.5k}, (b) poly(MeEOGE)_{2.5k} and poly(EtEOGE)_{2.5k}, and (c) poly(MeEO₂GE)_{2.5k}, and poly(EtEO₂GE)_{2.5k}.

The solid line shows T_{CLP} and broken line shows T_{CRP} .

Table 2-9. Calculated T_{CRP} vs experimental T_{CLP}

Sample ID	Calc. T_{CRP} (K)	Exp. T_{CLP} (K)	$T_{CRP} - T_{CLP}$ (K)
poly(MeGE) _{2.5k}	326	339	-13
poly(EtGE) _{2.5k}	291	283	+8
poly(MeEOGE) _{2.5k}	349	365	-16
poly(EtEOGE) _{2.5k}	334	314	+20
poly(MeEO ₂ GE) _{2.5k}	364	N.D.	
poly(EtEO ₂ GE) _{2.5k}	348	331	+17

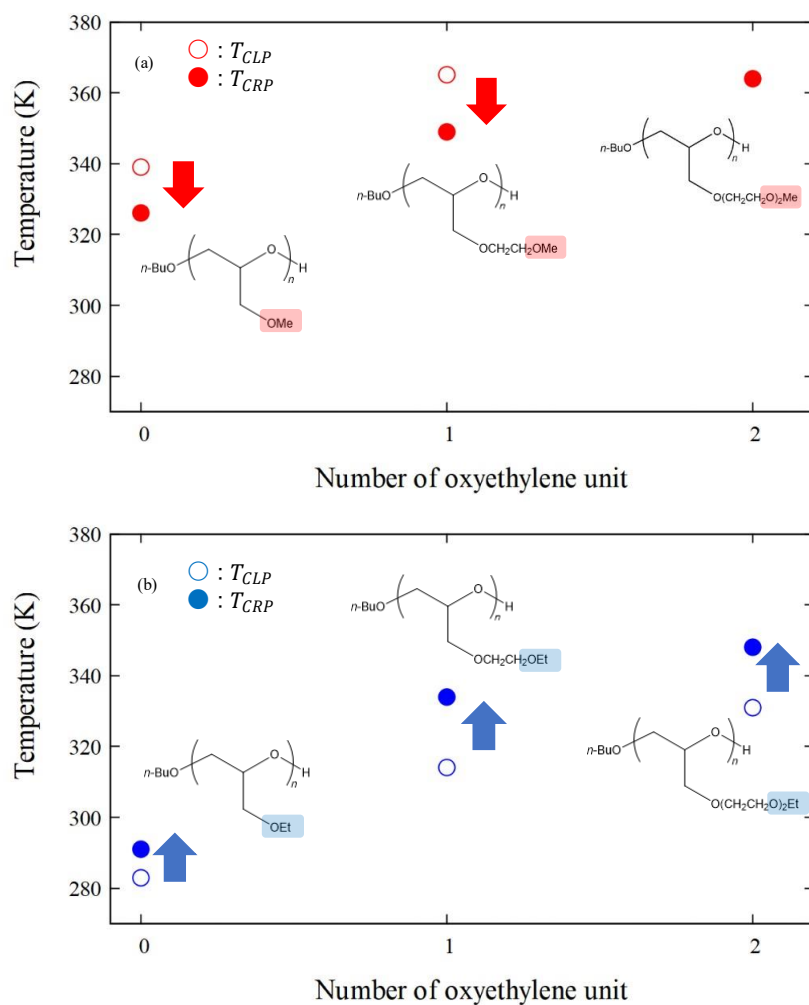


Figure 2-20. Plots of T_{CRP} and T_{CLP} vs number of oxyethylene units for methyl terminated poly(Me(EO)_nGE) (a) and ethyl terminated poly(Et(EO)_nGE) (b). Open and filled circle correspond to T_{CLP} and T_{CRP} , respectively.

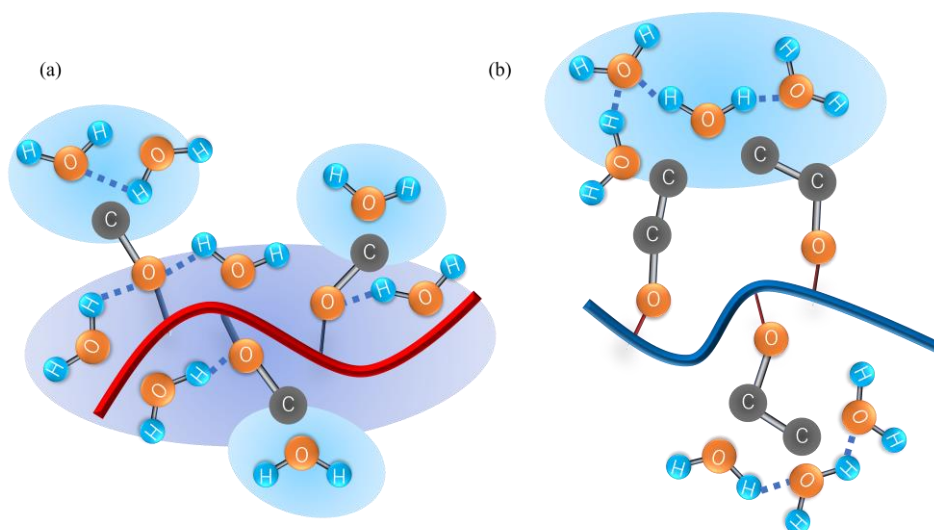


Figure 2-21. Schematic illustration of (a) poly(Me(EO)_nGE), and (b) poly(Et(EO)_nGE) in water

In addition, to investigate if the molecular weight affects the RDF, the T_{CRP} values for poly(MeEOGE) and poly (EtEOGE) with molecular weights of 1500, 2500, and 5000 were analyzed. Figure 2-22 shows that as the molecular weight increased, T_{CRP} decreased. It has been reported that the phase-transition temperature of poly(MeEOGE) tends to decrease with increasing molecular weight[14], and a similar result was observed in my T_{CRP} analysis in the MD calculations. This suggests that as the molecular weight increased, the hydrophobicity of the polymer surface increased because of the hydrophobic side chain, resulting in a decrease in T_{CLP} .

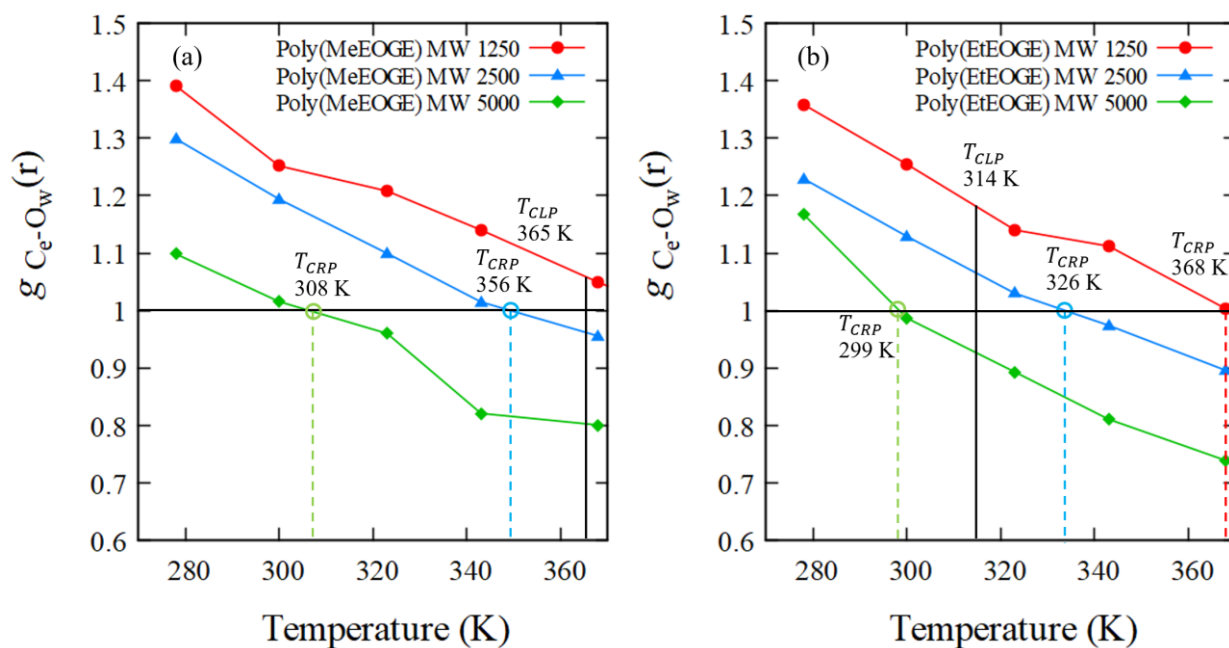


Figure 2-22. Temperature response of the 1st peak intensity in the RDFs of O atoms (water) observed from C atoms at the side chain ends in poly (MeEOGE) and poly(EtEOGE) for MW 1250, 2500 and 5000. The solid line shows T_{CLP} and broken line shows T_{CRP} .

2.4.5 Numbers of hydrogen bonds between the polymer and water molecules

In 2.4.4, the hydrophobic hydration shells were analyzed, after which the hydrogen bonds between the polymer oxygen atoms and water molecules were investigated to determine the contribution of the hydrophilic ether oxygen to the LCTS-type phase transition. The average number of hydrogen bonds between the oxygen atoms in the main chains or the side chains and the hydrogen atoms in water are listed in Table 2-10. Figures 2-23 and 2-24 show the average numbers of hydrogen bonds between the

polymer and water molecules in the main-chain oxygen atoms or the side-chain oxygen atoms per oxygen in the polymer residue, $\langle N_{main\ chain\ HB} \rangle$, or $\langle N_{side\ chain\ HB} \rangle$, versus temperature. The average numbers of hydrogen bonds between the polymer and water molecules in the main-chain oxygen atoms tend to decrease as the temperature increases for all polymers, and similar results were obtained for the side-chain oxygen atoms. In addition, the average number of hydrogen bonds between the water and oxygen atoms in the side chain tended to be higher than that of the bonds between the water and oxygen atoms in the main chain.

Furthermore, a relatively large decrease in the number of hydrogen bonds around T_{CLP} or T_{CRP} was observed. Although not shown in the table 2-10, the average number of hydrogen bonds between the intrapolymer was almost zero at any temperature for all polymers. The average numbers of hydrogen bonds within an intrapolymer are shown in Table 2-11. This suggests that the recombination of intrapolymer hydrogen bonds and polymer–water hydrogen bonds for the OEO ether group of the PGE side chain had not occurred. N-substituted acrylamide-based polymers, such as PNIPAM, have amide groups with a proton donor and acceptor, and they promote the recombination of hydrogen bonds between an intrapolymer and between polymer and water molecules[6,41]. However, since PGE has ether groups with only a proton acceptor, the hydrogen bonds between the intrapolymer should be weak; therefore, no hydrogen-bond recombination was observed. In addition, it has been reported that hydrogen bonding does not affect the LCST-type transition in poly(oligo(ethylene glycol)methyl ether

methacrylate) with an ether group[42]. This suggests that the weak hydrogen bonding in the PGE with ether groups led to the absence of a clear coil–globule structural transition.

Table 2-10. Average numbers of hydrogen bonds between polymer and water calculated over 20 ns at 278, 300, 323, 343, and 368 K.

sample ID	T_{CLP} (K)	Average number of polymer - water HBs in main chain O atoms, (per oxygen in polymer residue)					Average number of polymer - water HBs in side chain O atoms, (per oxygen in polymer residue)				
		278 K	300 K	323 K	343 K	368 K	278 K	300 K	323 K	343 K	368 K
poly(MeGE) _{2.5k}	338.5	0.31	0.29	0.25	0.23	0.19	0.41	0.42	0.34	0.32	0.27
poly(EtGE) _{2.5k}	283.3	0.30	0.26	0.24	0.21	0.19	0.44	0.36	0.31	0.25	0.24
poly(MeEOGE) _{2.5k}	364.6	0.34	0.31	0.27	0.20	0.23	0.48	0.44	0.40	0.29	0.34
poly(EtEOGE) _{2.5k}	314.3	0.33	0.27	0.23	0.23	0.18	0.56	0.47	0.38	0.37	0.29
poly(MeEO ₂ GE) _{2.5k}	N.D.	0.39	0.27	0.25	0.28	0.21	0.46	0.38	0.42	0.39	0.32
poly(EtEO ₂ GE) _{2.5k}	331.2	0.35	0.29	0.28	0.26	0.22	0.45	0.37	0.36	0.35	0.29

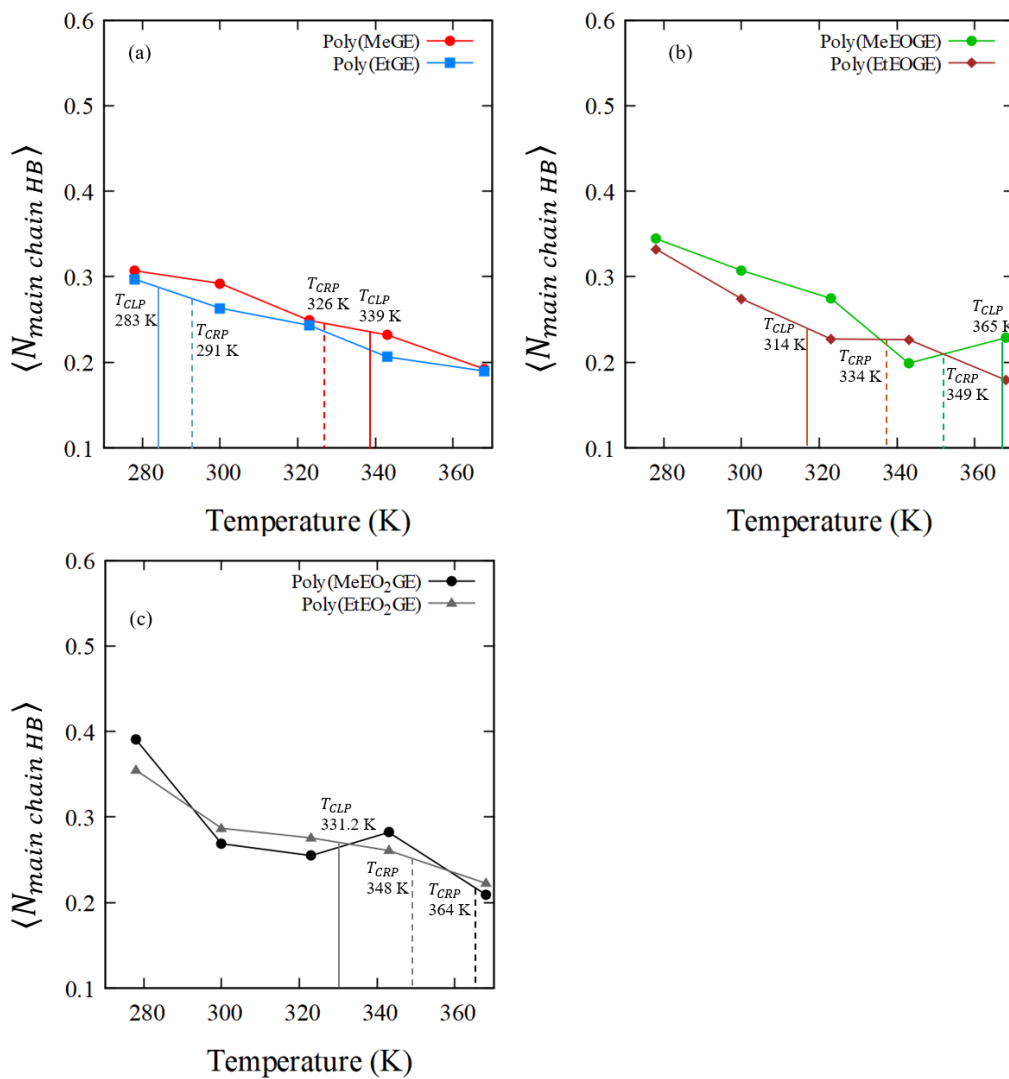


Figure 2-23. $\langle N_{main\ chain\ HB} \rangle$ of (a) poly(MeGE)_{2.5k} and poly(EtGE)_{2.5k}, (b) poly(MeEOGE)_{2.5k} and poly(EtEOGE)_{2.5k}, and (c) poly(MeEO₂GE)_{2.5k}, and poly(EtEO₂GE)_{2.5k}. They are normalized per oxygen in polymer residue. The solid line shows T_{CLP} and broken line shows T_{CRP} .

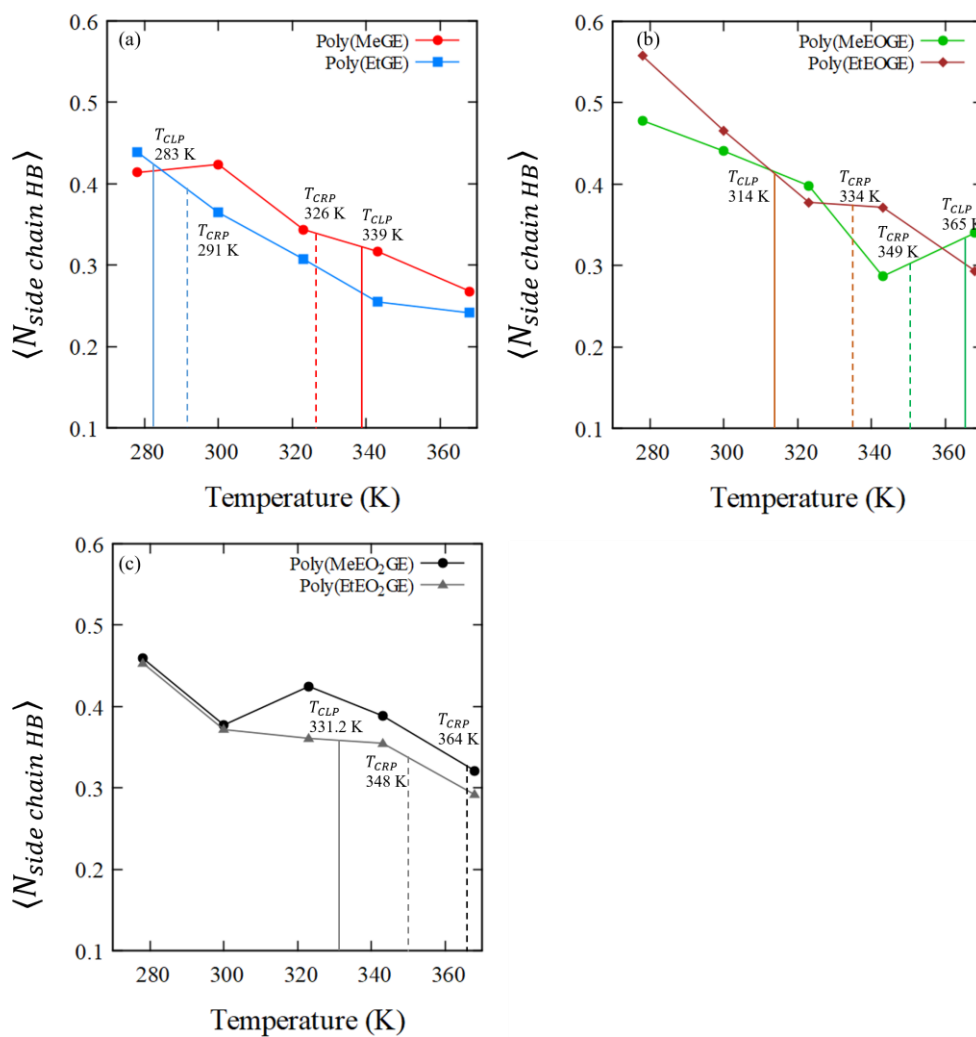


Figure 2-24. $\langle N_{side\ chain\ HB} \rangle$ of (a) poly(MeGE)_{2.5k} and poly(EtGE)_{2.5k}, (b) poly(MeEOGE)_{2.5k} and poly(EtEOGE)_{2.5k}, and (c) poly(MeEO₂GE)_{2.5k}, and poly(EtEO₂GE)_{2.5k}. They are normalized per oxygen in polymer residue. The solid line shows T_{CLP} and broken line shows T_{CRP} .

Table 2-11. Average numbers of hydrogen bonds within an intra-polymer calculated over 20 ns at 278K, 300K, 323K, 343K, and 368K

polymer	LCST (K)	Average number of intra-polymers HBs in all O atoms, (per oxygen in polymer residue)				
		278 K	300 K	323 K	343 K	368 K
poly(MeGE) _{2.5k}	338.5	0.005	0.002	0.002	0.002	0.001
poly(EtGE) _{2.5k}	283.3	0.004	0.002	0.002	0.002	0.002
poly(MeEOGE) _{2.5k}	364.6	0.003	0.002	0.002	0.002	0.002
poly(EtEOGE) _{2.5k}	314.3	0.003	0.003	0.003	0.002	0.002
poly(MeEO ₂ GE) _{2.5k}	N.D.	0.002	0.002	0.002	0.002	0.002
poly(EtEO ₂ GE) _{2.5k}	331.2	0.002	0.002	0.003	0.003	0.002

2.5 Conclusions

In this study, I performed MD simulations of PGE with six different oligooxyethylene side chains terminated with alkyl groups in aqueous solutions to investigate the effects of side-chain structures on LCST-type phase transition. To investigate if the coil–globule structural transition occurs, I analyzed the R_g , which indicates the degree of polymer chain extension, and the $\bar{L}/L_{max}$, which indicates the degree of polymer shrinkage. Comparing the SD of R_g and the CV values of $\bar{L}/L_{max}$ and the side-chain lengths for the six polymers, the PGE with a methyl group at the end of the side chain revealed larger values than the PGE with an ethyl group, suggesting that the PGE with terminal methyl groups on the side chain has larger fluctuations both in the main and side chains than the PGE with terminal ethyl groups on the side-chain. Although, I did not observe clear coil–globule structural transition in any PGEs, I found that as the degree of polymerization increased, the globule structure became easier to obtain. To investigate if the coil-globule transition occurs in more detail, I will analyze the eigenvalues of the radius of the gyration tensor in my future study.

Next, I focused on the RDF as another physical quantity that indicates the distribution of water molecules around the polymer and calculated the RDF for the oxygen atoms of waters measured from carbon atoms at the side-chain ends of the polymers. The result showed that hydrophobic hydration shells were formed around 3.6 Å from the carbon atoms at the end of the polymer side chains in all six polymers. I investigated the temperature dependence of the peak intensity of the hydrophobic

hydration shells and found that the crossing point temperatures (T_{CRP}) at which the peak intensity was below $g(r) = 1.0$ were close to the CLP temperatures (T_{CLP}) obtained in the experiments[14] for all polymers. The phase-transition temperature of the PGE was correlated with the intensity of the primary hydrophobic hydration shell of the side-chain terminal alkyl carbon. Furthermore, the T_{CRP} of the PGE with terminal methyl groups on the side chain was lower than the experimental T_{CLP} , while the T_{CRP} for the PGE with terminal ethyl groups on the side chain was higher than the experimental T_{CLP} . In this work, I performed MD simulations with a single polymer chain; therefore, the T_{CRP} should be higher than the experimental T_{CLP} because the polymer concentration is lower than that in the actual experiment. I consider that the magnitude of the polymer fluctuation affects the relationship between the T_{CRP} and the T_{CLP} . In other words, since the PGE with terminal methyl groups on the side chain tends to have larger polymer fluctuation than the PGE with terminal ethyl groups on the side chain, as evidenced by the results of R_g , $\bar{L}/L_{max}$, and time-averaged side-chain length measurements, I assume that water molecules entered the gaps between the adjacent side chains of PGE with hydrophobic methyl groups. Consequently, the proportion of the hydrophilic ether part occupying the polymer surface increased. Thus, the T_{CRP} of PGE with methyl groups at the side-chain ends was lower than the T_{CLP} value. In the future, I will expand my research to encompass multiple polymer chains to investigate interpolymer interactions.

2.6 References and Notes

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Chapter 3

***Structural study of two polymer chains of
poly((MeEOGE)-b-poly(EtEOGE))
thermoreponsive block copolymers using
molecular dynamics simulations***

3.1 Introduction

Block copolymers are polymers consisting of two types of polymers linked by covalent bonds, and are attracting attention as self-assembling materials that can express various nanostructures depending on their physicochemical properties [1–5]. In particular, temperature-responsive block copolymers have a lot of applications including biomaterials, such as development in Drug Delivery System (DDS)[6–11], and are one of the important materials in soft materials science. Among temperature-responsive polymers, block copolymers of poly(glycidyl ether) (PGE) are expected to be used as biomaterials, mainly in DDS and cell sheet engineering [12–17].

Isono et al. reported temperature responsiveness of block copolymers of poly(2-methoxyethyl glycidyl ether)(poly(MeEOGE)) and poly(2-ethoxyethyl glycidyl ether)(poly(EtEOGE)) [18], and observed an interesting thermoresponsive properties in the block copolymer composed of poly(MeEOGE) and poly(EtEOGE) with same degree of polymerization (poly(MeEOGE)_{0.50}-*b*-poly(EtEOGE)_{0.50})_{14k}; poly(MeEOGE)_{0.50}-*b*-poly(EtEOGE)_{0.50})_{14k} was water-soluble at low temperatures, but as raising temperature, UV-absorption (turbidity) measurements showed that the block copolymer were insolubilized at around 323 K, and water-soluble again at around 330 K, then insolubilized in water again when heated above 333 K (figure 3-1). The dynamic light scattering (DLS) results showed that the hydrodynamic diameter (D_h) of the polymer was 60 nm at 303 K, increased to 227 nm at 327 K, and decreased to 11 nm at 332 K, and then increased to 822

nm at 343 K[18]. These results suggested that poly(MeEOGE_{0.50}-*b*-poly(EtEOGE_{0.50})_{14k} had a core-shell micelle structure at 303 K, and the micelles aggregated at 327 K. The core part shrunk and the micelle structures were rearranged at 332K, and finally the shrunken micelle structures aggregated and precipitate out at 343 K. However, the relationship between polymer structures and inter-polymer interactions at each temperature have not yet been clarified. It is important to analyze the correlation between each polymer structure and polymer aggregates of block copolymers for future material design. It is difficult to observe the structure of each polymer chain one by one in experiments because many block copolymers get aggregated in experiments.

Molecular dynamics (MD) simulations have been employed to understand the structural transition of temperature-responsive polymers[19–30]. Also, it is possible to selectively create only one polymer chain or two polymer chains and study structural analysis in MD simulations. Examining the relationship between each polymer structure and temperature is important in understanding the micelle structure or random aggregates. For example, García et al. performed MD simulation for two polymer chains of poly(*N*-isopropylacrylamide) in aqueous solution and reported structural transition in temperature response [19]. Mizutani et al. conducted MD simulations for two polymer chains of poly(methyl tri(ethylene oxide) isocyanate) and poly(ethyl tri(ethylene oxide) isocyanate), and found that poly(methyl tri(ethylene oxide) isocyanate) formed parallel dimers and metastable T-shape dimers at 343 K which was slightly below the LCST [20]. From the above, I consider that it is possible to

capture detailed polymer structural transition on a small scale by performing MD simulation for two polymer chains.

In this study, I performed MD simulations for two polymer chains of block copolymer of poly(MeEOGE) and poly(EtEOGE) which had the same degree of polymerization from 303 K to 368 K. I investigated the temperature response of polymer structures in detail analyzing R_g distribution and eigenvalues of the moment of inertia tensor distribution, then observed the linear-to-U-type polymer structural transition, which supports the unique experimental temperature response of block copolymer of poly(MeEOGE-*b*-EtEOGE) [18].

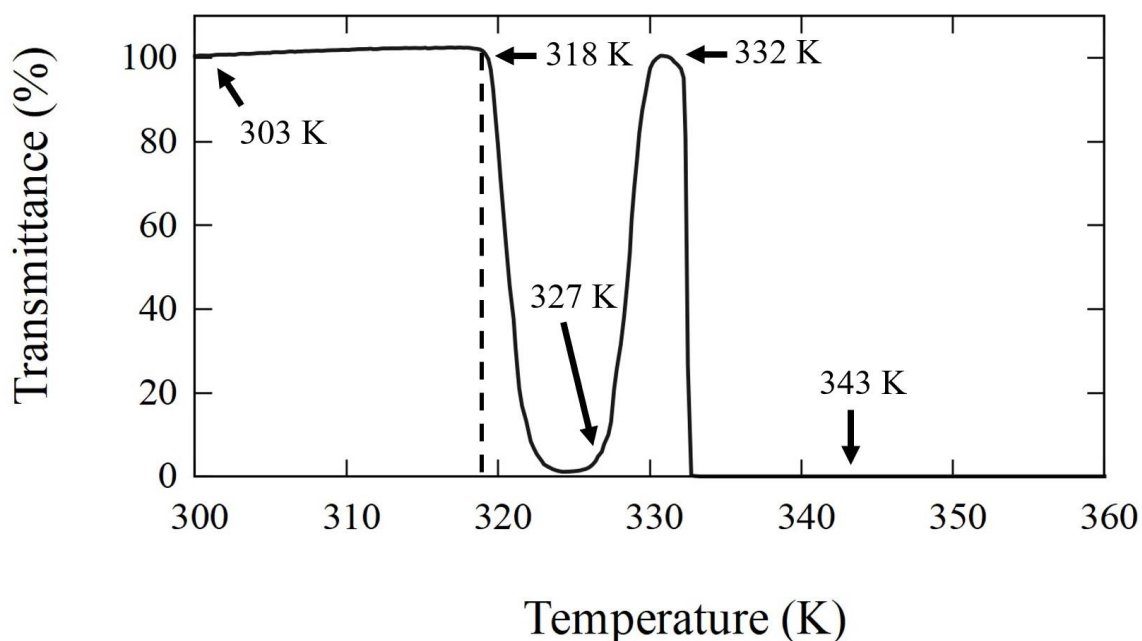


Figure 3-1. Transmittance curve for the aqueous solution of poly(MeEOGE_{0.50}-*b*-EtEOGE_{0.50})_{14k}.

3.2 Computational Method

Molecular modeling of block copolymer of poly(2-methoxyethyl glycidyl ether) (poly(MeEOGE)) and poly(2-ethoxyethyl glycidyl ether) (poly(EtEOGE)) (poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k}) (Figure 3-2) was carried out using Winmostar V.9.4.0[31]. The degrees of polymerization of poly(MeEOGE) and poly(EtEOGE) were both set to 9 to be close to those of my previous MD study on the homopolymers of poly(MeEOGE) and poly(EtEOGE) reported by Terada and Sato et al[32]. Also, to investigate the structure of higher molecular weight, poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k} with degree of polymerization of 15 was also prepared. The two polymer chains were placed 20 to 40 Å apart as an initial arrangement by using the Xleap tool of the AMBER 14 package[33].

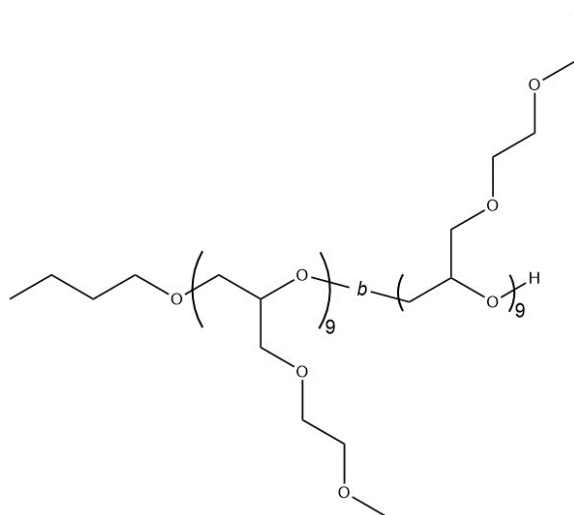


Figure 3-2. Chemical structure of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k}

The atomic partial charges for the polymers were obtained through the AM1-BCC protocol [34,35] implemented in the antechamber program [36] of AMBER 14. All the force-field parameters for the polymers in eq. (1) were acquired using the general AMBER force field (GAFF) version 1.7[36]. The GAFF was chosen because it has been demonstrated to be accurate for the simulation of most organic molecules. The detailed force field parameters are provided in gaff.dat[36].

Each polymer was centered in a cubic simulation box under periodic boundary conditions. Approximately, 3000 TIP3P-modeled water molecules were added with a margin of 10 Å along each dimension in Table 3-1.

Table 3-1 Total number of water molecules and box length

sample ID	Total number of water molecules	box length
		Length, Width, Height (Å)
poly(MeEOGE ₉ - <i>b</i> -EtEOGE ₉) _{2.5k}	2717	44.6, 55.2, 48.3
poly(MeEOGE ₁₅ - <i>b</i> -EtEOGE ₁₅) _{4.2k}	3282	47.7, 54.0, 55.4

The whole system consisted of one or two polymers solvated by water molecules were energy-minimized and equilibrated with the sander program implemented in the AMBER system before the MD simulations. The energy minimization was performed in two steps. First, the solvent molecules

were energy-minimized using the steepest decent method for 1000 steps and the conjugate gradient method for 1500 steps while keeping the solute molecular chains restrained with a force of 500 kcal mol⁻¹ Å⁻². Second, the restraint was eliminated, and the entire system, including the polymer chain, was energy-minimized using the steepest decent method for 1000 steps and the conjugate gradient method for 1500 steps as in the first step. Subsequently, the energy elevation followed by equilibration was performed in two steps. First, the system was gradually heated to an assigned temperature, 303, 318, 323, 333, 348, or 368 K, under constant volume boundary conditions for 10,000 steps, with a time step of 2 fs while maintaining the 10 kcal mol⁻¹ Å⁻² constraint on the solute polymer chains. In the second step, the restraint was removed, and the entire system was equilibrated under periodic boundary conditions at a constant pressure of 1 atm for 50,000 steps, with a time step of 2 fs while maintaining the specified temperature. The Langevin method was employed for temperature control, and isotropic scaling was employed for pressure control. The SHAKE algorithm was applied to maintain constant hydrogen atom bond lengths. A cutoff length of 12 Å and particle mesh Ewald (PME) sums were applied for the electrostatic interactions. After confirming the equilibrium of the whole system, MD simulations were performed for 100 ns or 150 ns, with a time step of 2 fs using a pmemd program of AMBER 14. All the MD simulations were conducted in NPT (number of molecules (N), pressure (P), and temperature (T) are conserved) ensembles to capture the dynamics and structural evolution of both the polymer and water molecules at six different temperatures (303, 318, 323, 333, 348, or 368 K).

The simulations were carried out at atmospheric pressure (1 atm). The trajectories were outputted at 2.0 ps intervals.

3.3 Analysis Method

3.3.1 Radius of Gyration

The structural evolution of each block copolymer as well as two block-polymer chain association structure was studied along the time course of the stored atomic trajectories by analyzing the radius of gyration (R_g). R_g , which is a measure of the extension degree of a polymer chain, was calculated using the eq. (2) below:

$$R_g^2 = \frac{1}{N} \sum_n \langle (R_n - R_c)^2 \rangle, \quad (1)$$

where R_c is the center of mass of one polymer chain or two polymer chain, and N is the number of atoms included in the polymer chains.

3.3.2 Eigen values of the moment of inertia tensor

To further differentiate polymer's molecular conformations, the diagonalized moment of inertia tensor of polymers was calculated[37].

$$I = \lambda_1^2 + \lambda_2^2 + \lambda_3^2 \quad (2)$$

3.3.3 Radial Distribution Function

The radial distribution function (RDF), $g(r)$, represents the number density of the particles existing in the spherical shells between distances r and $r + dr$ from a given reference particle. It can be expressed as:

$$g(r) = \frac{\langle n(r) \rangle}{4\pi r^2 dr \rho}, \quad (3)$$

where $n(r)$ indicates the number of particles of the spherical shell at distances of r and $r + dr$ from the given reference particle. ρ is the average number density of the particles in the bulk condition. The $g(r)$ function is zero when the interparticle distance, r , approaches zero because repulsive force prevents the atoms from closely approaching each other. Additionally, when distance r is infinite, the local density in the shell is equivalent to the mean bulk density averaged over the whole volume; therefore, $g(r)$ is standardized to 1.

The RDF was calculated to determine the difference in the structural arrangements of the polymer atoms and water molecules at 288, 303, 318, 323, 333, 348 or 368 K. The RDFs around the carbon atom of the side chain and for the water–oxygen atom were carefully investigated for poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} and poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k}.

3.4 Results and Discussion

As a first step, the temperature dependence of one polymer chain's R_g was analyzed to observe the structural transition behaviors of poly (MeEOGE₉-*b*-EtEOGE₉)_{2.5k}. Figure 3-3 shows the R_g distributions for one polymer chain of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} and representative snapshots at five different temperatures. The main peak values of the R_g distributions for the block copolymer were around 14 Å at 303 K, 318 K, 323 K, and 333 K, while shifted to 10 ~ 11 Å at 348 K. The polymer structure corresponding to around 14 Å peak value was a linear structure with poly(EtEOGE) and poly(MeEOGE) repelling each other. On the other hand, the polymer structure corresponding to around 11 Å peak value had a U-shaped structure in which poly (EtEOGE) and poly (MeEOGE) attract each other. Figure 3-4 shows magnified views of snapshots of linear and U-type structures at the main peak for one polymer chain of poly(MeEOGE₉-EtEOGE₉)_{2.5k} at 318K and 348 K. The structural transition of the block polymer from linear to U-shaped occurred between 333 K and 348 K. Furthermore, the main peak values of the R_g distribution of poly (MeEOGE) and poly (EtEOGE) homopolymers with the same molecular weight were approximately 9 Å at any temperature from 278 K to 368 K in chapter 2 (figure 2-3)[32], indicating that the R_g main peak values of the block copolymers were larger than those of the homopolymers. The chi (χ) parameter is an interaction parameter that represents the compatibility of polymer and solvent. The increase in elongation of the block copolymer when compared to the homopolymer should be caused by

repulsion due to the difference in the χ values of poly(EtEOGE) and poly(MeEOGE). In block copolymers, poly(MeEOGE) and poly(EtEOGE) have different solubility in water at low temperatures, and χ parameters differ between poly(MeEOGE) and poly(EtEOGE), so it suggests that they repel each other and form linear structures. At high temperatures, both poly(MeEOGE) and poly(EtEOGE) become less soluble in water, resulting in a U-shaped structure due to hydrophobic interactions. Homopolymers have no difference in solubility in water and no difference in χ parameter even at low temperatures, so it suggests that they have U-shaped structures close to an agglomerated structures at both high and low temperatures. Elongated and straightened structures of the block polymer may contribute to ease of micelle structure formation observed by DLS measurements of my previous study[18].

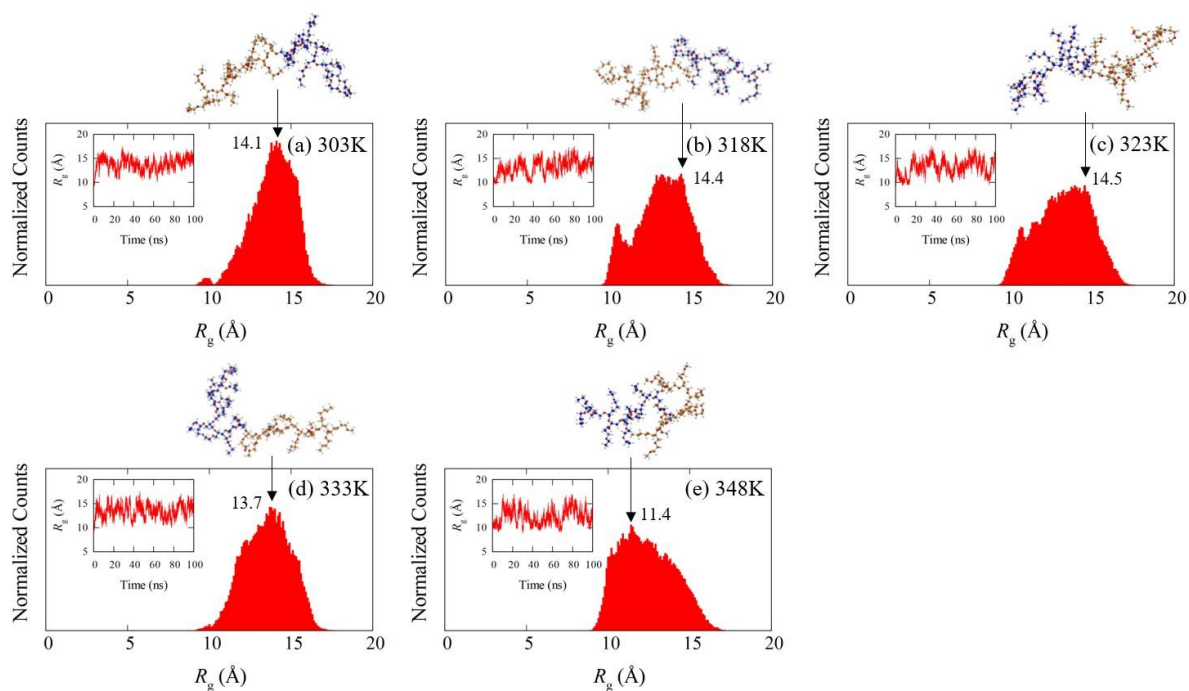
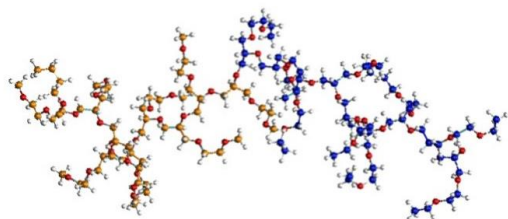


Figure 3-3. R_g distributions for one polymer chain of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} at (a) 303 K, (b) 318 K, (c) 323 K, (d) 333 K, and (e) 348 K. The inset is the corresponding time dependence of R_g . Representative snapshots are taken at specific times indicated by the arrows. The orange atoms are carbons of the polymer with methyl terminal groups, the blue atoms are carbons of the polymer with ethyl terminal groups, the red and white atoms are oxygen and hydrogen.

(a) 318 K



(b) 348 K

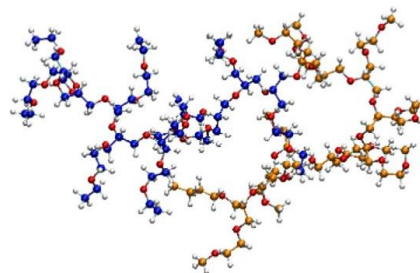


Figure 3-4. Representative snapshots for one polymer chain of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} at (a) 318K and (b) 348 K. The orange atoms are carbons of the polymers with methyl terminal groups, the blue atoms are carbons of the polymers with ethyl terminal groups, the red and white atoms are oxygen and hydrogen.

To investigate the degree of expansion of the block polymer chain, the end-to-end distances of block copolymer were calculated. Figure 3-5 shows the distribution of end-to-end distances for poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} at 318 K and 348 K. The main peak value of the distribution was 40 Å at 318 K, and decreased to 25~26 Å at 348 K; the end-to-end distance at high temperatures was about half that at low temperatures. It suggests that linear structure transitions to U-shaped structure as the temperature increased.

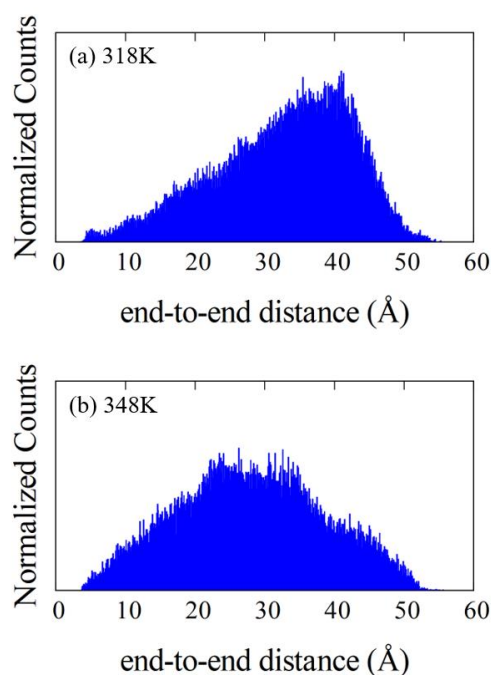


Figure 3-5. The distribution of end-to-end distances for poly(MeEOGE9-*b*-EtEOGE9)_{2.5k} at (a) 318 K and (b) 348 K.

To investigate the aggregation and dissociation phenomena of block copolymers in detail, MD simulations were performed on two polymer chains of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} and the R_g distributions were analyzed. Figure 3-6 shows the R_g distributions for two polymer chains of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} measured from the center of gravity of the two chains, and representative snapshots at six different temperatures. At 303 K, only dissociated species of two polymer chains with the peak values greater than 20 Å were observed. This corresponds well with the experimental result that the block polymers were water-soluble in the UV-absorption

measurements[18](figure 3-1). The R_g distribution was relatively unimodal at 318 K with the main peak value located at 18 Å. The snapshots showed that the two polymer chains had linear structures, and the two polymers with terminal ethyl groups were close to each other at 318 K in Figure 3-7. these results indicate that the PGE block copolymer had core-shell micelles with poly(EtEOGE) as the core formed by linear polymers. At 323 K, the main peaks were observed at 13 Å and 17 Å, and the R_g distribution was broadened above 20 Å. It suggested that aggregated micellar structures were formed, and should be reasonable considering the experimental result that the block copolymer became insoluble at 327 K in the UV-absorption measurements [18]. Next, the main peak value decreased from 17 Å to 15 Å at 333 K, and dissociated species of two polymer chains which had U-shaped structures were observed in the snapshot at 15 Å in Figure 3-7. This suggests that increasing the temperature destabilized the micelle structures and the polymers were dissociated, and it is consistent with the experimental result that the block copolymers were dissolved at 332 K in the UV-absorption measurements[18]. The main peak value was 14 Å at 348 K; a cohesive structure was observed in the snapshot of the main peak in Figure 3-7. It implies that the dissociated polymers aggregated again at 348 K. Considering the experimental result that the transmittance became 0% above 333 K in the UV-absorption measurements from the experimental results[18], it suggests that the aggregated polymers precipitated out at 348 K. Figure 3-8 and 3-9 shows the R_g

distributions and snapshots for poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k}, and these results were similar to those of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k}

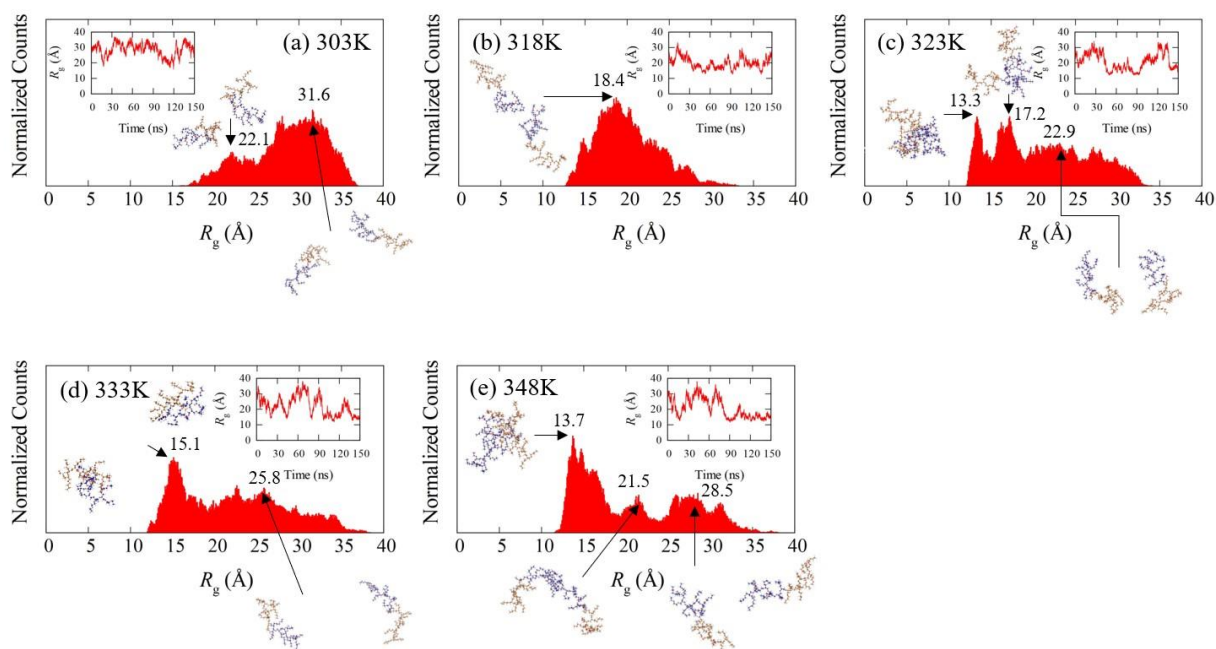
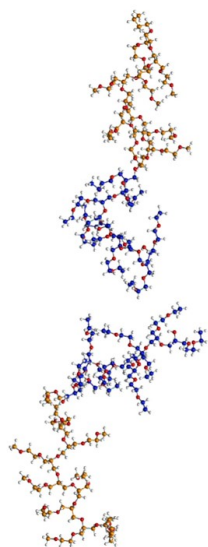


Figure 3-6. R_g distributions for two polymer chains of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} at (a) 303 K, (b) 318 K, (c) 323 K, (d) 333 K, and (e) 348 K. The inset is the corresponding time dependence of R_g . Representative snapshots are taken at specific times indicated by the arrows. The orange atoms are carbons of the polymers with methyl terminal groups, the blue atoms are carbons of the polymers with ethyl terminal groups, the red and white atoms are oxygen and hydrogen.

(a) 318 K



(b) 333 K



(c) 348 K

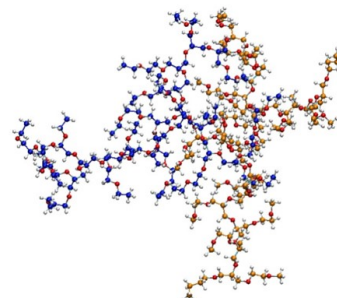


Figure 3-7. Representative snapshots at main peak for two polymer chains of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} at (a) 318 K, (b) 333 K, and (c) 348 K. The orange atoms are carbons of the polymers with methyl terminal groups, the blue atoms are carbons of the polymers with ethyl terminal groups, the red and white atoms are oxygen and hydrogen.

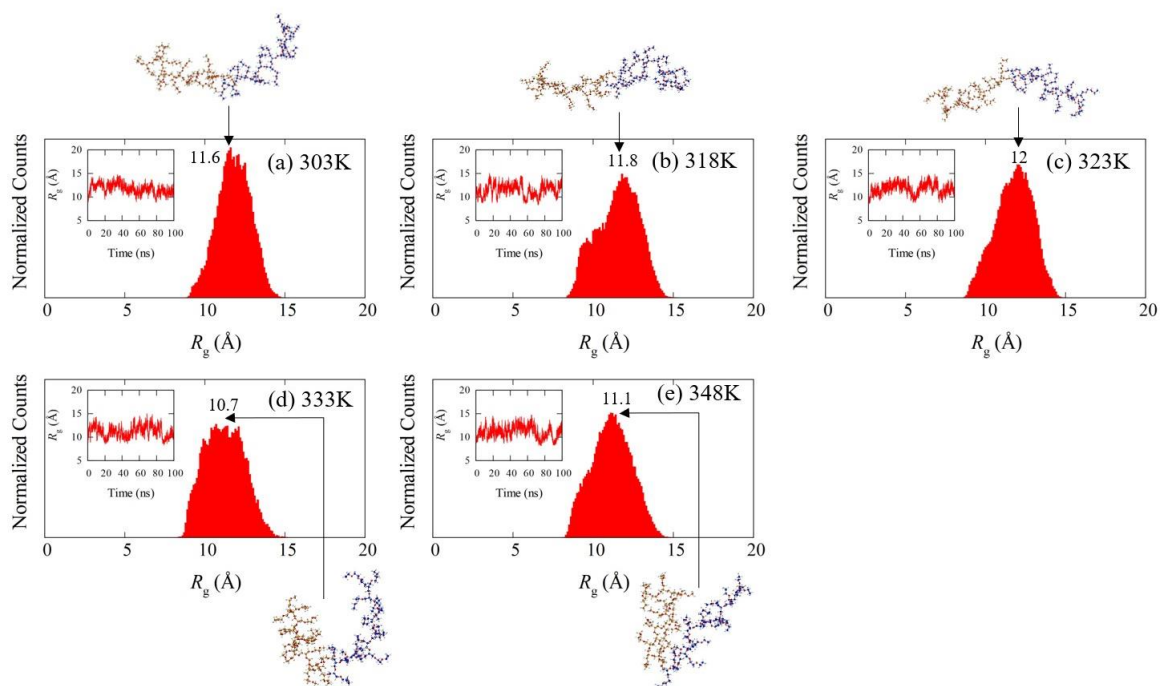


Figure 3-8. R_g distributions for one polymer chain of poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k} at (a) 303 K, (b) 318 K, (c) 323 K, (d) 333 K, and (e) 348 K. The inset is the corresponding time dependence of R_g . Representative snapshots are taken at specific times indicated by the arrows. The orange atoms are carbons of the polymers with methyl terminal groups, the blue atoms are carbons of the polymers with ethyl terminal groups, the red and white atoms are oxygen and hydrogen.

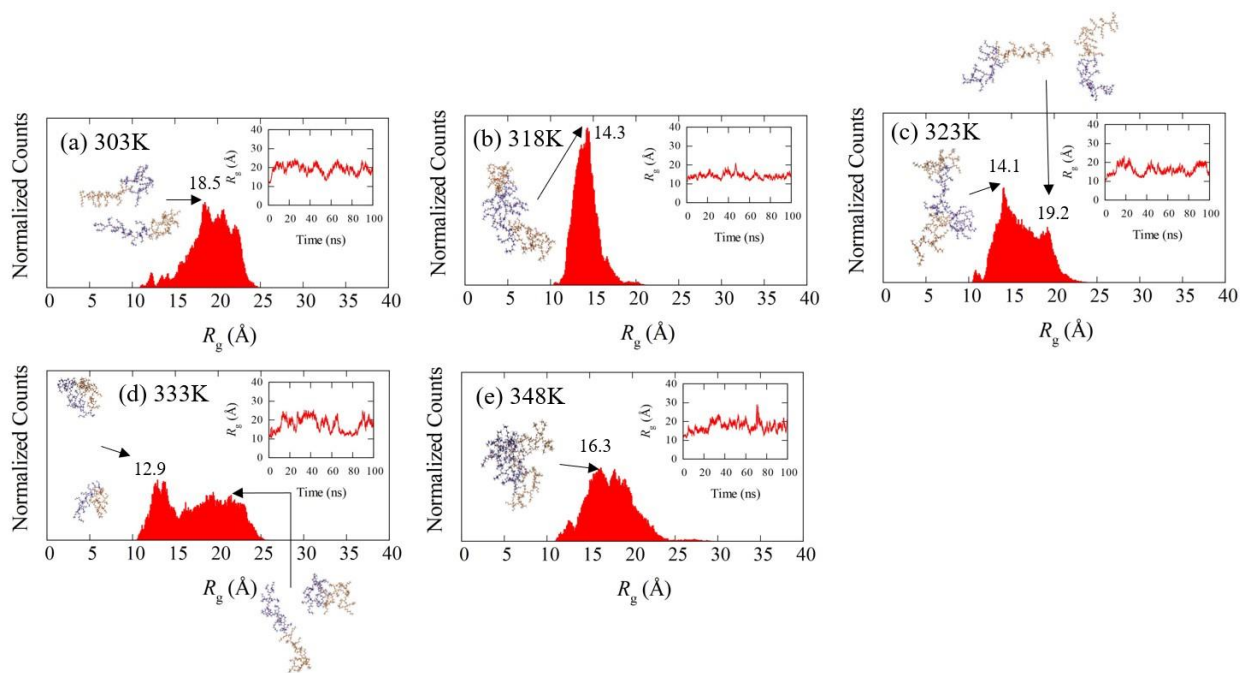


Figure 3-9. R_g distributions for two polymer chains of poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k} at (a) 303 K, (b) 318 K, (c) 323 K, (d) 333 K, and (e) 348 K. The inset is the corresponding time dependence of R_g . Representative snapshots are taken at specific times indicated by the arrows. The orange atoms are carbons of the polymers with methyl terminal groups, the blue atoms are carbons of the polymers with ethyl terminal groups, the red and white atoms are oxygen and hydrogen.

To further differentiate polymer's molecular structure and configurations, the eigen values of the moment of inertia tensor measured from the center of gravity of the two polymer chains of poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k} were analyzed. Figure 3-10 shows the λ_1 distribution results at 303 K, 318 K, 323 K, 333 K, and 348 K, and figure 3-11 shows the λ_2 , and λ_3 distributions. The λ_1 distribution was broad and the main peak position was approximately 270 amu Å² at 303 K, which was very large compared to other temperatures. This suggests that the two polymer chains have dissociated each other. Then, the main peak decreased to 129 amu Å² and the λ_1 distribution narrowed at 318 K, indicating that the polymers got close to each other. Considering the results of R_g analysis, this implies that the polymers formed micelle structures. When the temperature was raised to 323 K, the λ_1 main peak (129 amu Å²) remained the same at 318 K, but the broad band appears at 200 ~ 300 amu Å². At 333 K, the λ_1 distribution was further broadened to larger values (300 ~ 500 amu Å²). This large λ_1 distribution broadening indicates that the two block copolymers were dissociated each other, leading to the collapse of micelle structure. The λ_1 distribution narrowed at 348 K, suggesting that the two polymers aggregated each other. From the above, the eigen values of the moment of inertia tensor results showed the similar phenomenon to the R_g analysis and experimental results. Figure 3-12 shows the eigen values of the moment inertia tensor distribution for poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k}, and similar results were observed with poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k}.

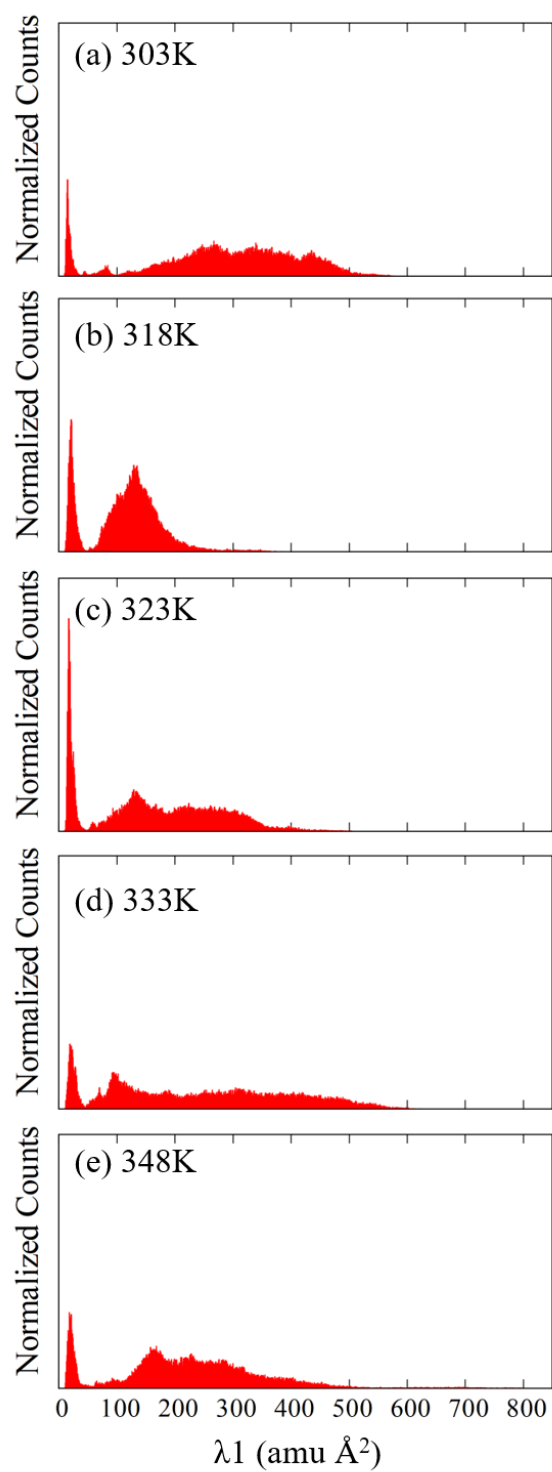


Figure 3-10. Principal λ_1 eigenvalue of the moment of inertia tensor distribution for two polymer chains of poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k} at (a) 303 K, (b) 318 K, (c) 323 K, (d) 333 K, and (e) 348 K.

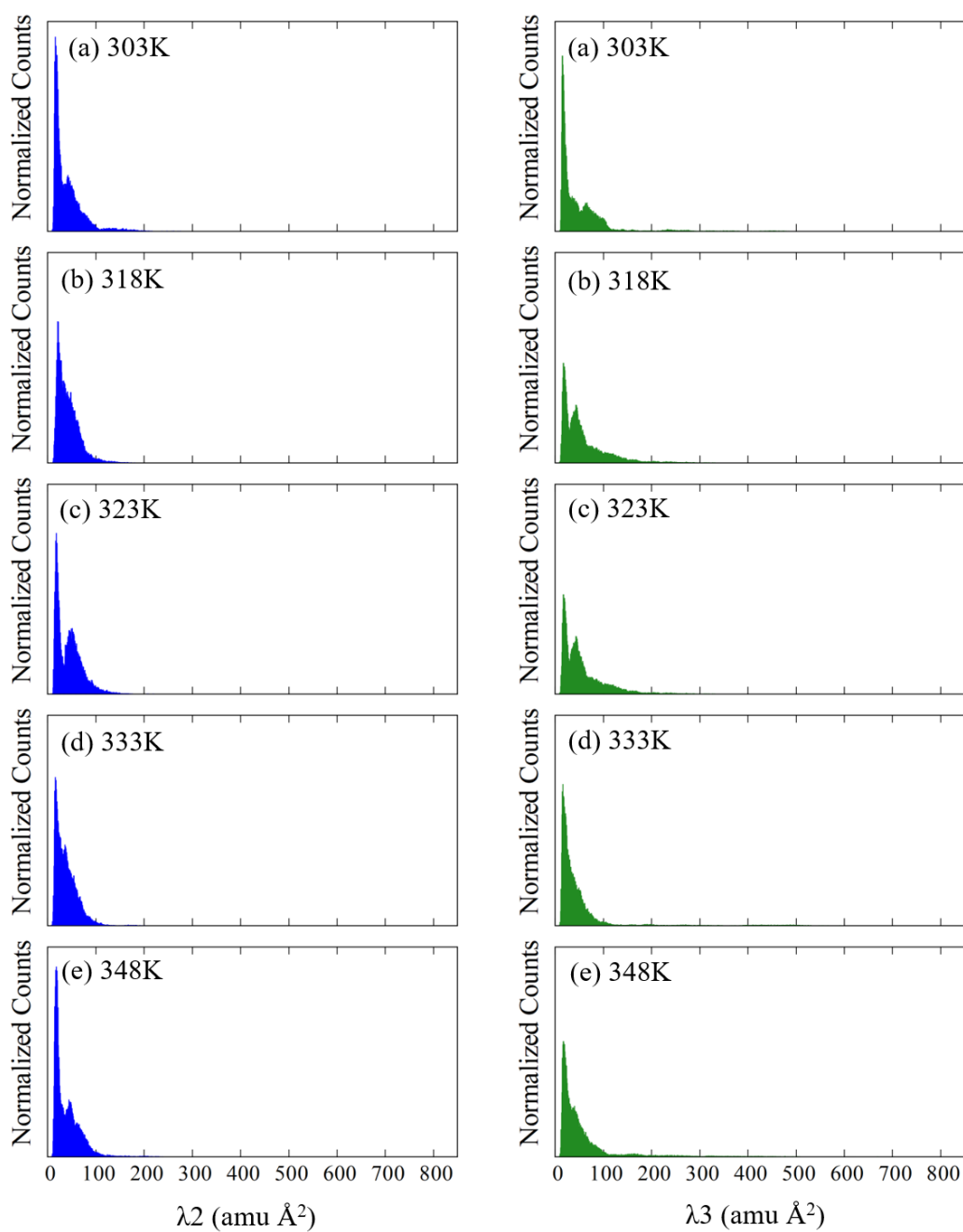


Figure 3-11. Two eigenvalues (λ_2 and λ_3) of the moment of inertia tensor distribution for two polymer chains of poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k} at (a) 303 K, (b) 318 K, (c) 323 K, (d) 333 K, and (e) 348 K. λ_2 : left, λ_3 : right.

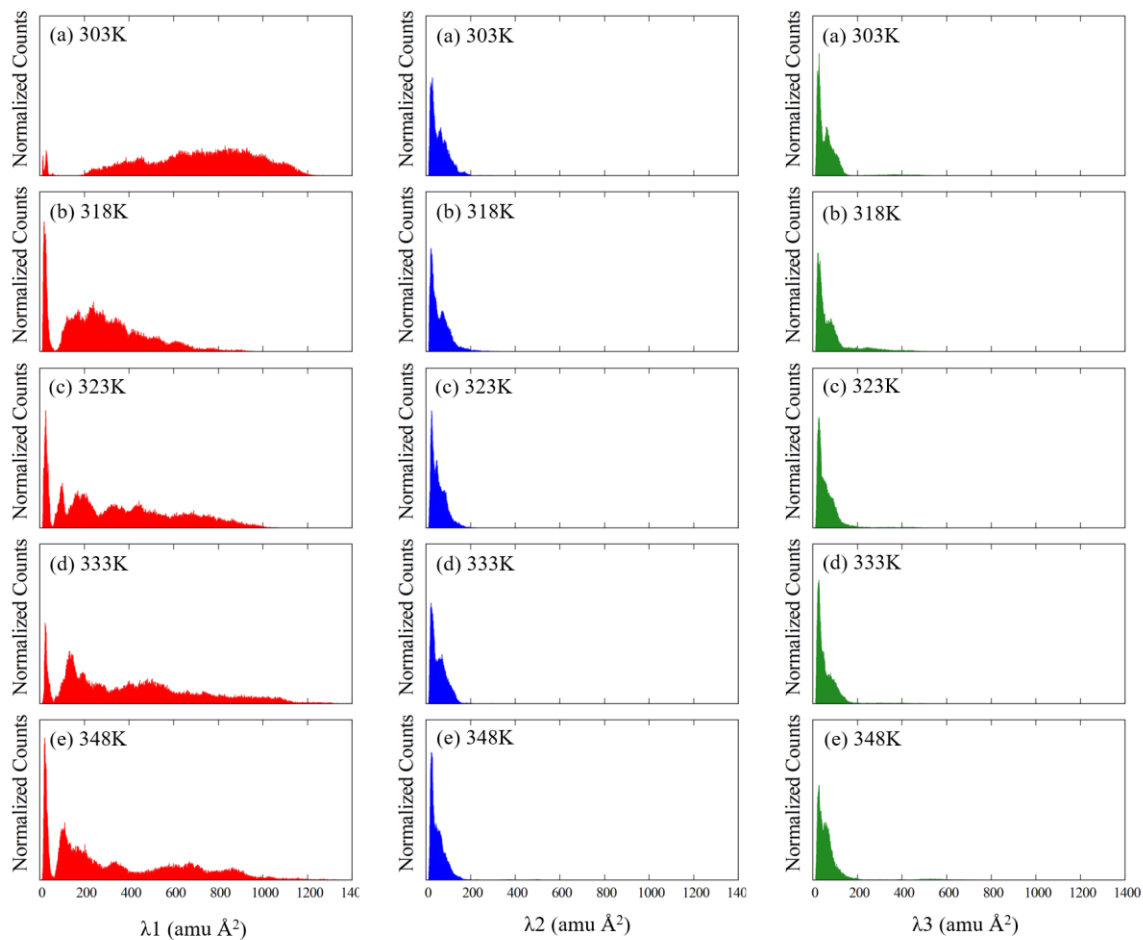


Figure 3-12. Three eigenvalues (λ_1 , λ_2 and λ_3) of the moment of inertia tensor distribution for two polymer chains of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} at (a) 303 K, (b) 318 K, (c) 323 K, (d) 333 K, and (e) 348 K. Red is λ_1 , blue is λ_2 , and green is λ_3 .

To investigate the effect of temperature on the water molecules surrounding the polymer chains, the RDF of the water oxygen atoms measured from carbon atoms at the side chain ends of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} and poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k} was analyzed. Figure 3-13 shows the water-oxygen RDF measured using the carbon atoms at all the sidechain ends of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} and poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k} at 288 K, 303 K, 318K, 323 K, 333 K, 348 K, and 368 K respectively. The first peaks in the water–oxygen RDF spectra were observed at around 3.6 Å for poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} and poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k}, indicating that the first hydrophobic hydration shells formed at 3.6 Å from carbon atoms at the side-chain ends. For the peaks of the first hydrophobic hydration shell of poly(MeEOGE₉-EtEOGE₉)_{2.5k} and poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k}, both peak intensities decreased with the increasing temperature. It suggests that as the temperature raised, the hydrophobicity of the alkyl ends of the side chains covering the polymer surface increased and became insoluble. Figure 3-14 shows the peak intensity of the hydrophobic hydration shell decreased during the heating process. My previous paper reported that the crossing point temperatures (T_{CRP}) at which the peak intensity was below $g(r) = 1.0$ were close to the cloud point temperature (T_{CLP}) obtained in the experiments[32]. T_{CRP} for poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k} appeared at 347 K, which was close to the experimental value of random aggregation at 343 K[18].

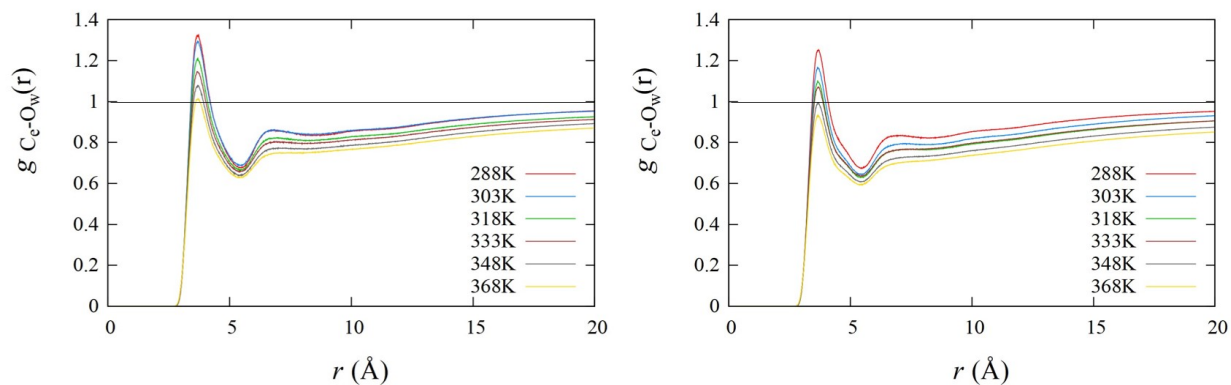


Figure 3-13. RDF of poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} (left) and poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k} (right) for O atoms of water measured from C atoms at the side-chain ends.

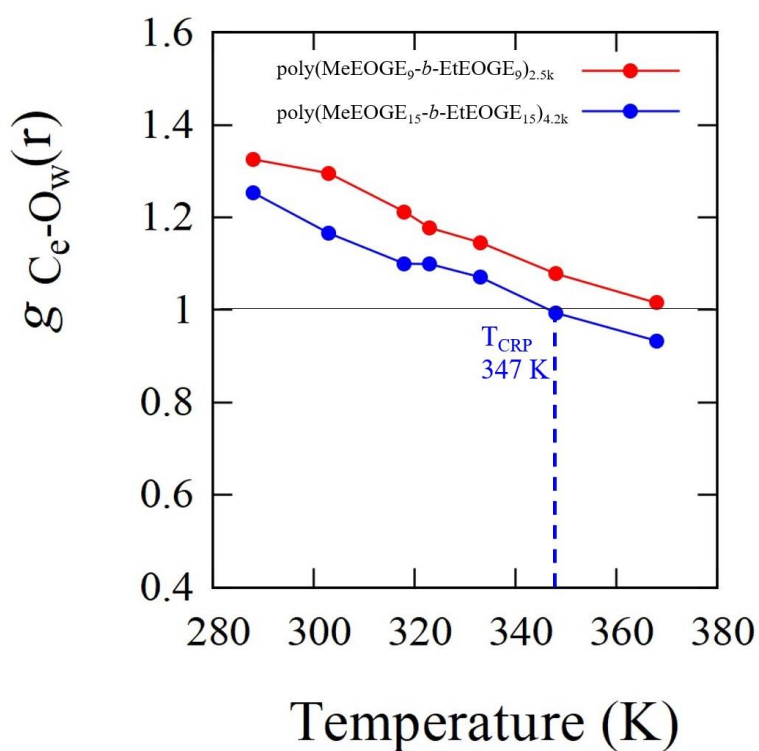


Figure 3-14. Temperature response of the first peak intensity in the RDFs of O atoms (water) observed from C atoms at the side-chain ends. The red line and blue line are poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} and poly(MeEOGE₁₅-*b*-EtEOGE₁₅)_{4.2k}.

Combining the R_g analysis, snapshot, and the eigenvalue of the moment of inertia tensor, and RDF results obtained from the MD simulations with the experimental results, a plausible relationship between polymer structure and phase transition with increasing temperature is summarized in Figure 3-15. The polymers had linear-shaped structures and were dissolved in water at 303 K, then formed core-shell micelle structures retaining still linear-shaped structures and remained water-soluble at 318 K. As the temperature increased to 327 K, the micelles aggregated and became insoluble. Once they showed water-soluble in the UV-absorption measurements around 332 K, it indicates that each block polymer transitioned to U-shaped structures and the agglomerated micelles structures were destroyed. The experimental results of the UV-absorption measurements showed that the polymers were insoluble at 343 K, which suggested that U-shaped polymers aggregated randomly and then precipitated out.

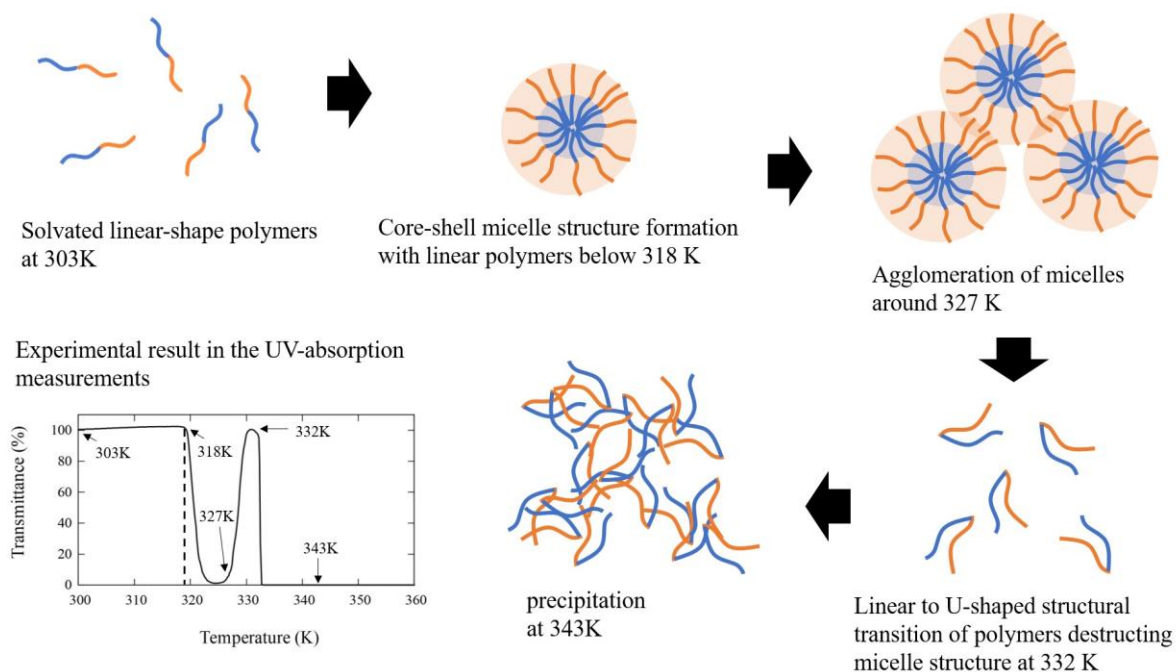


Figure 3-15. Schematic illustration of possible structural transitions for poly(MeEOGE₉-*b*-EtEOGE₉)_{2.5k} upon heating. Orange lines means the polymers with methyl terminal groups, and blue lines means the polymers with ethyl terminal groups.

3.5 Conclusion

In this chapter, I have performed MD simulation of one or two polymer chains of poly(glycidyl ether) block copolymer in aqueous solutions and newly found the linear-to-U-shaped structural transition of each polymer chain with increasing temperature from the R_g distribution analysis, snapshots. The block copolymer had linear-shaped structure at 303 K, and formed core-shell micelle structure at 318 K, then the micelle aggregated at 323 K, the micelle collapsed, and the linear-shaped polymer structure transitioned to U-shaped structure at 333 K, and U-shaped polymers, which was soluble at 333 K, aggregated and precipitated at 348 K. These results from the MD simulations of two-polymer chains corresponded to the experimental complex temperature response and provided the basis for the understanding of intermolecular arrangement of many polymers.

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Chapter 4

Conclusions

In this thesis, the author describes temperature response and structural transition of thermoresponsive poly(glycidyl ether) with different side chain end structures using molecular dynamics simulations. Comparing homopolymers and block copolymers of poly(glycidyl ether) with similar degree of polymerization, clear structural transition was not observed in the homopolymers, but the linear to U-shaped structural transition was observed in the block copolymers. Furthermore, MD simulations of two-polymer chains allowed me to observe not only the polymer structure but also the separation and aggregation of the two-polymers. In addition, I found that the phase transition temperature of poly(glycidyl ether)s was correlate with the strength of the first hydrophobic hydration shell of the carbon atom of the side chain terminal alkyl group. Therefore, I believe that this investigation provides the basis for the understanding of the structural transition of the temperature-responsive polymers. This research will help molecular design of temperature-responsive polymers with targeted cloud point temperature and pave the way for a successful social implementation of functional temperature-responsive polymers for biomaterials including drug delivery system, cell sheet engineering and so on.

A summary of this thesis is as follows:

In chapter 2, I have found that the PGE with terminal methyl groups on the side chain has larger fluctuations both in the main and side chains than the PGE with terminal ethyl groups on the side-chain comparing the SD of R_g and the CV values of $\bar{L}/L_{max}$ and the side-chain lengths for the six polymers. Although, I did not observe clear coil–globule structural transition in any PGEs, I found that as the degree of polymerization increased, the globule structure became easier to obtain. The results of the radial distribution function showed that the temperature at which the peak is at $g(r) = 1$ (T_{CRP}) is close to the experimental cloud point temperature (T_{CLP}). The phase-transition temperature of the PGE should be correlated with the intensity of the primary hydrophobic hydration shell of the side-chain terminal alkyl carbon. The T_{CRP} of PGEs with methyl group at the end of the side chain tended to be lower than T_{CLP} , while the T_{CRP} of PGEs with ethyl groups at the end of the side chain was higher than T_{CLP} . A possible reason for this result is that PGEs with methyl groups in the side chain end structure have large fluctuations in the main chain and side chains, and the proportion of hydrophobic methyl groups on the polymer surface decreases and the proportion of hydrophilic ether groups increases as water molecules enter the gaps between the side chains.

In chapter 3, I have newly found the linear-to-U-shaped structural transition of each polymer chain with increasing temperature from the R_g distribution analysis, snapshots. The block copolymer had linear-shaped structure at 303 K, and formed core-shell micelle structure at 318 K, then the micelle aggregated at 323 K, the micelle collapsed, and the linear-shaped polymer structure transitioned to U-shaped structure at 333 K, and U-shaped polymers, which was soluble at 333 K, aggregated and precipitated at 348 K. These results from the MD simulations of two-polymer chains corresponded to the experimental complex temperature response and provided the basis for the understanding of intermolecular arrangement of many polymers.