

Mid-Infrared Spectroscopic Investigation of the Perfect Vitrification of Poly(ethylene glycol) Aqueous Solutions

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Abstract

Crystallization/recrystallization behaviors of poly(ethylene glycol) (PEG) aqueous solutions with water contents (W_C 's) of ~36–51 wt% were investigated by temperature-variable mid-infrared spectroscopy. At a W_C of 43.2 wt%, crystallization/recrystallization of water and PEG were not observed. At this specific W_C value (W_{CPV}), perfect vitrification occurred. Below and above the W_{CPV} value, crystallization/recrystallization behaviors changed drastically. The crystallization temperature below W_{CPV} (237 K) was ~10 K greater than that above W_{CPV} (226 K). Recrystallization above and below W_{CPV} occurred in one (213 K) and two (198 and 210 K) steps, respectively. These findings resulted from the difference in the (re)crystallization behaviors of water molecules associated with PEG chains with helical and random-coil conformations. These two types of water molecules might have limiting concentrations for their (re)crystallization, indicating that perfect vitrification might have occurred when the concentrations of the two types of water molecules were less than the limiting concentrations of their (re)crystallization.

1. Introduction

Poly(ethylene glycol) (PEG) $(-(OCH_2CH_2)_n-)$, also called poly(oxyethylene) (POE) or poly(ethylene oxide) (PEO), is a synthetic polymer with various unique properties and is one of the most extensively studied polymers. PEG is used not only for industrial, medical and cosmetic applications, such as lubricants in metal processing, matrices for medical reagents, and emulsifying agents, respectively, but also as a biocompatible material^{1–6} that strongly suppresses nonspecific protein adsorption and cell adhesion. The formation of a surface diffusion layer based on hydrated PEG chains has been proposed as the origin of the polymer's biocompatibility.^{7–11} The hydration structure of PEG chains has been of interest because of the extremely high water solubility of PEG; PEG is freely soluble in water, whereas PEG analogues such as poly(oxymethylene) $(-(OCH_2)_n-)$ and poly(propylene glycol) $(-(OCH_2CH(CH_3))_n-)$ are insoluble in water.¹² Many investigations to reveal the hydration structure of the PEG–water binary system have been carried out using various experimental and computational methods including viscosity measurements,^{13–15} quasielastic neutron scattering,^{16,17} nuclear magnetic resonance,¹⁸ Raman^{19–21} and infrared^{22–24} spectroscopies, and molecular-dynamics^{25–32} and density-functional-theory³³ simulations. In many of the cases cited here, the hydration structure has been discussed at and/or above 298 K, that is, in the liquid state.

Differential scanning calorimetry (DSC),^{34–41} on the other hand, has also been frequently used to investigate interactions between PEG and water molecules. Differing from the aforementioned methods, DSC analysis cannot be used to investigate the state of water and PEG in the liquid state but has revealed some unique thermal properties of the PEG–water binary system. It has provided evidence for a typical eutectic system, for the crystallization of water during heating, that is, recrystallization of water over a wide range of water content (W_C) values of 10–95 wt%, and for perfect vitrification at a specific W_C value. These phenomena depend strongly on the molecular weight of PEG and were observed for PEG molecules with molecular weights from 1000–2000. Over the course of nearly a decade, this recrystallization phenomenon (recrystallization of water) has received extensive attention in the field of biomaterials, although it has also been observed for various aqueous polymer solutions such as poly(*N*-vinyl pyrrolidone),⁴² ten different types of polysaccharides,^{43–45} and non-denatured proteins (bovine serum albumin⁴⁶ and cytochrome *c*⁴⁷). This attention was first triggered by a series of reports on the thermal properties of water sorbed on poly(2-methoxyethyl acrylate) (PMEA), which is a non-water-soluble polymer; recrystallization of water was observed for hydrated PMEA, which possesses a highly effective blood-compatible property (biocompatibility).^{48–50} The research group that reported this finding hypothesized that polymers demonstrating recrystallizability of water are biocompatible; conversely, recrystallizable water makes materials biocompatible. The fact that PMEA and PEG possess recrystallizable water and high biocompatibility has often been referenced to support this hypothesis, implying that the hydration structures of PMEA and PEG are the same. Confirmation of the hypothesis is unclear, but it is difficult to predicate it, because

recrystallizable water is also found with non-biocompatible polymers such as poly(methyl acrylate), poly(*n*-butyl methacrylate), poly(ethoxyethyl acrylate), poly(ethoxyethyl methacrylate), and polystyrene.⁵¹⁻⁵³

A decisive difference, furthermore, between the PEG–water and PMEA–water systems has been reported. Hung and Nishinari demonstrated that an aqueous solution of PEG with a molecular weight of 1540 had a specific W_C at which no crystallization and no recrystallization occurred, that is, at which perfect vitrification occurred. Figure 1 shows the recrystallization and fusion enthalpies of a PEG–water system with various W_C values measured via DSC. At a W_C of ~40 wt%, no recrystallization or fusion of PEG, no eutectic mixture (PEG–water), and no water were observed; it demonstrated perfect vitrification. In usual polymer–water systems, irrespective of their water solubilities, no (re)crystallization of water at lower W_C values can be easily understood from a physicochemical point of view. As expected, in all of the cases (including PEG) cited above, no (re)crystallization of water has been demonstrated at lower W_C values. Except for the PEG–water system, with an increase of W_C , the total amount of (re)crystallized water increased monotonously, as was easily predicted. As seen in Figure 1, on the other hand, the PEG–water system demonstrated the reappearance of a W_C at which no (re)crystallization of water occurred, while the total amount of (re)crystallized water increased. It is noteworthy that recrystallized water existed below and above the W_C at which perfect vitrification occurred. The reason for the occurrence of perfect vitrification has not been satisfactorily explained in the literature. If the hydration structure of recrystallizable water is assumed to be the same regardless of the type of polymer and W_C values as per the hypothesis mentioned above, it is difficult to explain this phenomenon.

Our recent study using a PEG aqueous solution with a W_C of 37.5 wt% revealed that the recrystallizable water in this solution had two different types of hydration structures and that their recrystallization temperatures were different.⁵⁴ The perfect vitrification of the PEG–water system was probably related to the existence of these two different types of hydration structure. In the present study, to reveal the cause of the perfect vitrification, the thermal properties of PEG aqueous solutions with various W_C values in the range ~36–51 wt% were investigated by temperature-variable Fourier-transform mid-infrared spectroscopy (TVFT-IR). Unlike calorimetric methods such as DSC, infrared (IR) spectroscopy probing a molecular vibration cannot detect heat fluxes in state changes of matter via temperature change but does provide information about molecular orientation and conformation in situ.

2. Experiments

Poly(ethylene glycol) dimethyl ether (PEG) (Aldrich) was purified via precipitation in ethanol–chloroform. The weight-average and number-average molecular weights of PEG were 2064 and 2036, respectively. The quality of water used in all experiments was Milli-Q grade (resistivity >18.2 M Ω ·cm). PEG aqueous solutions with seven different W_C values of 36.4, 38.6, 40.7, 43.3, 45.1, 46.1, and 50.9 wt% were prepared. Each W_C value is expressed as the percentage of the weight of water over the weight of the total solution.

Mid-IR spectra of the PEG aqueous solutions were recorded on a Spectrum One NTS (Perkin-Elmer) with a resolution of 4 cm⁻¹ and a scanning time of 20 s over a temperature (T) range of 298–170 K. The cooling rate was either 1.0 or 4.8 K·min⁻¹, and the heating rate was 1.0 K·min⁻¹. The temperature of the sample was controlled with an Optistate-DN cryostat (Oxford) connected to a model ITC601 T controller. An appropriate amount of PEG aqueous solution, typically 1 μ L, was placed between two sapphire substrates (13 mm in diameter and 1 mm in thickness), and the sapphire cell was hermetically sealed with indium. The cell length (thickness of the sample) was not determined, but it was confirmed that the maximum absorbance in the observed wavenumber range (4000–2500 cm⁻¹) was below 1 at room T .

3. Results

3.1. Room Temperature (Figure 2). Mid-IR spectra of PEG aqueous solutions with various W_C values at 298 K are shown in Figure 2. The spectral intensity was normalized at 2881 cm⁻¹ (Figure 2A).

3.1.1. PEG. Several components that overlapped with each other in the wavenumber range of 3000–2800 cm⁻¹ (Figure 2B) were C–H stretching vibrations of the PEG chain. Among them, the component at ~2918 cm⁻¹ was a C–H stretching vibration of PEG with a random-coil conformation, and the component at ~2881 cm⁻¹ was an overlapped one of the C–H stretching vibrations of PEG with random-coil and “*tgt*” conformations.¹⁶⁻²¹ For the *tgt* conformation, the sequence –O–CH₂–CH₂–O– had a trans (*t*) conformation about the –O–C– bond, a gauche (*g*) conformation about the –C–C– bond, and a *t* conformation about the –C–O– bond. The *tgt* conformation was a basic unit of a 7/2 helical segment formed in the crystalline solid PEG (dotted spectrum in Figure 2B). Following the literature on PEG aqueous solutions at room temperature, a portion of the PEG chain had the 7/2 helical conformation in the aqueous solution. A decrease in the ratio of absorbance at 2881 cm⁻¹ (A2881) and 2918 cm⁻¹ (A2918), that is, A2881/A2918, with W_C (Figure 2C) indicated a relative decrease of the helical PEG segment.

3.1.2. Water. The mid-IR spectra of water in the PEG aqueous solutions had at least three components: two shoulders at 3520 and 3270 cm⁻¹ and a peak at 3430 cm⁻¹. Pure water (dotted spectrum in Figure 2A) also had at least these three components in its spectrum, but the three components differed from those of the PEG solutions: two shoulders at 3650 and 3240 cm⁻¹ and a peak at 3400 cm⁻¹. As seen in the spectra normalized over the high wavenumber region (Figure 2D), the relative intensity of the spectra in the low wavenumber region increased with W_C . The ratio of

integrated absorbance in the O–H stretching region (OH_{area} , 3700–3000 cm^{-1}) to that in the C–H stretching region (CH_{area} , 3000–2700 cm^{-1}) showed a slight quadratic increase with W_C (Figure 2E), suggesting that the number of water molecules hydrogen-bonded between other water molecules increased with the W_C . The numbers of water molecules per repeat unit of PEG (N_{water}) at the highest (50.9 wt%) and lowest (36.4 wt%) W_C values in this study were 2.54 and 0.399, respectively. Several studies showed that the number of bound water molecules per repeat unit of PEG was in the range of 1–4. If the term “bound water” indicates water molecules that strongly interacted with the PEG chain, it can be said that hydrogen bonds between water molecules existed but that no water interacted without the PEG chain. A molecular-dynamics simulation also showed no free water at $W_C < 50$ wt%.²⁵

3.2. Temperature dependence. For basic information concerning pure water, the temperature dependence of the spectrum of pure water is shown in Figure 3. The top and bottom panels of the figure show the temperature dependence of the spectrum of water and that of the absorbance at 3250 cm^{-1} (A3250), respectively, and the left and right panels show the results for the cooling and heating processes, respectively. At 251 K during cooling, the spectrum with a large width suddenly changed to one with a very sharp peak at ~ 3250 cm^{-1} . The opposite change was observed at 273 K during heating. The two changes indicated crystallization and fusion, respectively. The A3250 value at the two state changes sharply increased and decreased, respectively. The two state changes should be judged on the basis of changes in the spectra and A3250 values.

The results for PEG aqueous solutions in the temperature range of 298–170 K at W_C values of 38.6, 43.2, and 50.8 wt% are shown in Figures 4, 5, and 6, respectively. The spectra of the other W_C values are given in the Supporting Information. The results at W_C values of 38.6 wt% (Figure 4) and 50.8 wt% (Figure 6) are representative cases for those below and above a W_C of 43.2 wt%, respectively. Panels (A) and (B) in each figure show the spectra obtained at a cooling rates of 4.8 $\text{K}\cdot\text{min}^{-1}$ (rapid cooling) and 1.0 $\text{K}\cdot\text{min}^{-1}$ (slow cooling), respectively, and the top and bottom parts in each panel are spectra of the O–H stretching and C–H stretching regions, respectively. Panel (C) shows the temperature dependence of the value of A3250 (top) and that of A2881/A2918 (bottom). The left and right panels show the results of the cooling and heating processes, respectively.

3.2.1. $W_C < 43.2$ wt% (38.6 wt%, Figure 4). Irrespective of the cooling rate, the A2881/A2918 value increased following a saturation curve with cooling until ~ 240 K (bottom of Figure 4C). In the case of rapid cooling, a slight decrease in the A2881/A2918 value was observed below ~ 240 K, but a drastic change was not observed. In the case of slow cooling, on the other hand, a sharp increase of the value was observed, indicating crystallization of the PEG, and was confirmed by the similar shape of the spectrum to that of the crystalline solid PEG (bottom of Figure 4B). At the same T (~ 240 K), a sharp increase of the A3250 value was also observed (left top of Figure 4C). The spectra in the O–H stretching region below ~ 240 K were similar to the spectrum of ice (left top of Figure 4B), indicating ice formation. In the case of rapid cooling, the slight deviation from the change of the A3250 value (left top of Figure 4C) might indicate a small amount of ice formation, although an ice-like spectrum was not clearly observed (left top of Figure 4A).

During heating, in the case of the sample treated by slow cooling (Figure 4B), the temperature at which steep changes were observed was ~ 260 K and differed from that during cooling (240 K), but the changes of the spectrum and the values of A3250 and A2881/A2918 were the same as those of the cooling process in the opposite direction. In the case of the sample prepared by rapid cooling, steep increases in the values of A3250 and A2885/A2918 were observed in the temperature range of 198–220 K (right bottom of Figure 4C), indicating recrystallizations of both water and PEG. The difference from crystallization was a two-step event, and a detailed discussion of this two-step recrystallization has been reported previously.⁵⁴ In brief, the increase in A3250 in the low-temperature range of 198–210 K was comparable to that in the high temperature range of 210–220 K, whereas the increase in A2881/A2918 in the lower temperature range was approximately three-times less than that in the higher temperature range. This indicates that the water molecules that crystallized in the lower and higher temperature ranges corresponded to water molecules associated with the PEG chains with helical and random-coil conformations, respectively. The former and latter water molecules are called “type-H” and “type-R” water molecules, respectively. Above ~ 230 K, the observed changes were the same, irrespective of the cooling rate; the values of A3250 and A2885/A2918 decreased steeply at ~ 260 K and then returned to their initial values.

3.2.2. $W_C = 43.2$ wt% (Figure 5). The spectral changes of the samples treated by both slow cooling and rapid cooling were almost the same, and the comparable panel (B) is therefore omitted. As seen in the spectra, in the observed temperature range, an ice-like spectrum was not observed in either the cooling or heating process. The values of A3250 and A2881/A2918 also did not show steep or stepped changes, such as would suggest state changes of water and PEG (crystallization and recrystallization). This phenomenon was a perfect vitrification, that is, neither crystallization nor recrystallization occurred. The other difference from the samples below a W_C of 43.2 wt% was the change of A2885/A2918 with cooling; the value at a W_C of 43.2 wt% decreased (left bottom of Figure 5C), whereas those below a W_C of 43.2 wt% increased (left bottom of Figure 5C).

3.2.3. $W_C > 43.2$ wt% (50.8 wt%, Figure 6). Spectral changes at both rapid cooling and slow cooling were similar to those at W_C values of 43.2 wt% and 38.6 wt%, respectively, and the comparable panels (A) and (B) are therefore omitted. In the cooling process, no ice-like spectra were clearly observed. For the slow cooling, however, a

stepped increase in the A3250 value was observed at ~ 230 K, suggesting crystallization of a small amount of water molecules. The A2881/A2918 value increased synchronously with A3250, indicating crystallization of PEG. A gradual change in the values of A3250 and A2881/A2918 in the observed temperature range for rapid cooling indicated no crystallization of water or PEG, that is, vitrification. A steep increase in both the values of A3250 and A2881/A2918 in the heating process was observed at ~ 220 K, indicating recrystallization of both water and PEG. Recrystallization above a W_C of 43.2 wt% was a one-step event, unlike that of solutions with a W_C below 43.2 wt%.

4. Discussion

The state changes of water and PEG via temperature perturbation observed spectroscopically are summarized in Table 1. Except for a solution with a W_C of 43.2 wt%, crystallization and/or recrystallization (and fusion) occurred for both water and PEG. Perfect vitrification was observed at a W_C of 43.2 wt%. This specific W_C is expressed as “ W_{CPV} ” hereafter. The crystallization T (~ 237 K) below W_{CPV} was ~ 10 K greater than that above W_{CPV} (~ 226 K). The two-step recrystallization was not observed above W_{CPV} , and their recrystallization T values (~ 213 K) were similar to the T value of the two-step recrystallization below W_{CPV} (~ 210 K). DSC measurements also demonstrated perfect vitrification at a specific W_C , two-step recrystallization in the lower W_C range, and difference in the T values of each state change that depended on W_C .^{34–37} Some questions, however, have remained. How can the difference in crystallization T values below and above W_{CPV} be explained? What is the difference between the one-step and two-step recrystallization processes above and below W_{CPV} , respectively? Why does perfect vitrification occur at this specific W_C ?

The state changes via temperature perturbation observed spectroscopically, except for crystallization, recrystallization, and fusion, were related to the relative amount of the helical segment of PEG (the value of A2881/A2918); the amount (the value) at $W_C \geq W_{CPV}$ decreased and that at $W_C < W_{CPV}$ increased (Table 1). It can be said that at the former and latter W_C ranges, the amounts of type-H water molecules decreased and increased with cooling, respectively. If it can be assumed that type-H and type-R water molecules had limiting concentrations for their (re)crystallization, this assumption could provide plausible explanations for the questions listed above.

The crystallization T below W_{CPV} was ~ 10 K greater than that above W_{CPV} . Our previous study demonstrated that during two-step recrystallization, type-H water molecules recrystallized at a lower T (~ 198 K) than did type-R water molecules (~ 210 K), indicating that the interaction of the former with the PEG chains was weaker than that of the latter. In the cooling process, the type-H water molecules might have crystallized at a higher T than did the type-R water molecules.⁵⁰ If the concentration of type-H water molecules was less than the limiting concentration for their crystallization, the crystallization T might have been dominated by type-R water molecules. Below W_{CPV} , the relative amount of the helical segment steeply increased with cooling, resulting in an increase in the amount of type-H water molecules. These type-H water molecules were considered to be crystallized. However, two-step crystallization (such as recrystallization) expected from crystallization of type-R water molecules was not observed. Crystallization of type-H water molecules should include a phase separation with the formation of a crystalline solid PEG. Differing from an intramolecular conformational transition such as the coil-to-helix transition, the phase separation should be accompanied by a dynamic (macroscopic) molecular diffusion/rearrangement. This dynamic transition likely triggers the coil-to-helix transition of the remaining random-coil segments. As a result, during crystallization of type-H water molecules, the amount of type-R water molecules decreased and their crystallization was not observed.

Recrystallization above and below W_{CPV} occurred in one and two steps, respectively. As mentioned repeatedly, during the two-step recrystallization, type-H and type-R water molecules recrystallized in the first (198 K) and second (210 K) steps, respectively. This phenomenon conflicts with the aforementioned discussion of crystallization; if the discussion could be adapted to the recrystallization phenomenon, recrystallization should occur in one step. This discrepancy can be explained by considering that the glass transition T (T_g) of the hydrated helical segment was less than that of the hydrated random-coil segment. At the T at which type-H water molecules recrystallized, the motion of type-R water molecules in a glassy state might be restricted, and their recrystallization, which requires molecular diffusion/rearrangement, could not occur. This conclusion is consistent with the fact that the recrystallization T values (198 K and 210 K) were sufficiently less than the crystallization T values (237 K and 226 K). This consideration, however, is not sufficient to explain the perfect vitrification.

Perfect vitrification was observed at a W_C of 43.2 wt% (W_{CPV}). Based on the aforementioned assumption—that the type-H and the type-R water molecules had limiting concentrations for their (re)crystallization—an explanation for the perfect vitrification should be easily obtained. At W_{CPV} , both the concentrations of type-H and type-R water molecules were less than their limiting concentrations. However, such a result meant that at $W_C < W_{CPV}$, the concentration of type-R water molecules should have been less than their limiting concentration and, therefore, one-step recrystallization at $W_C < W_{CPV}$ should have occurred. This is clearly inconsistent with the actual experimental results. This discrepancy might be solved by considering the local concentration. Recrystallization of type-H water molecules and PEG resulted from the phase separation of ice and solid PEG. At the same time, this phase separation also indicated phase separation of the hydrated random-coil chains of PEG, including the type-R water molecules, namely, the local concentration of type-R water molecules was increased, meaning that the type-R water molecules could be recrystallized above the T_g of the hydrated random-coil domain.

5. Conclusion

Temperature-variable measurements of the mid-IR spectra of PEG aqueous solutions with various W_C values demonstrated the existence of a specific W_C , 43.2 wt%, at which no (re)crystallization of water or PEG in a temperature range of 298–170 K occurred: perfect vitrification. At the other W_C values, vitrification during cooling was observed, but a large amount of recrystallization (devitrification) also occurred. These phenomena were caused by the existence of two types of water molecules that were associated with the PEG chains with helical and random-coil segments. The assumption that the two types of water molecules might have limiting concentrations for their (re)crystallization provided a plausible explanation for the perfect vitrification.

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Supporting Information Available. T dependence of spectra of the PEG aqueous solutions with water contents of 36.4, 40.7, 43.2, 45.1, 46.1, and 50.9 wt%. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Table 1. Crystallization, recrystallization, and melting temperatures.

W_c / wt%	Crystallization / K		Recrystallization / K		Melting / K		Change direction of A2881/A2918 during cooling to 250 K
	Water	PEG	Water	PEG	Water	PEG	
<43.2	237		198 (210)	210 (198)	260		Increase
=43.2	<i>N.D.</i>			<i>N.D.</i>	<i>N.D.</i>		Decrease
>43.2	226		213		260		Decrease

N.D.: Not detected.

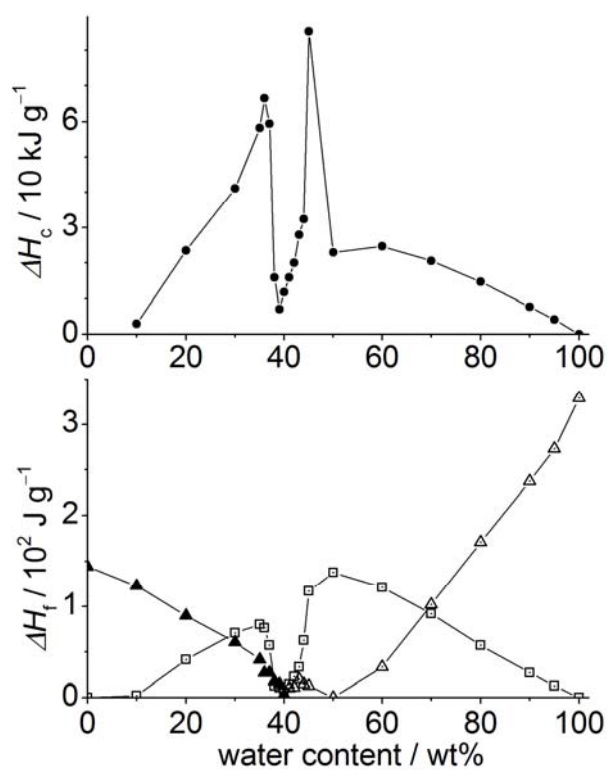


Figure 1. Recrystallization enthalpies (●) and fusion enthalpies of PEG (▲), a eutectic mixture of PEG–water (□), and water (△) observed for PEG aqueous solutions with various W_C values, determined by DSC measurements. The molecular weight of PEG was 1540. The figure was redrawn from the work of Huang et al.³⁶

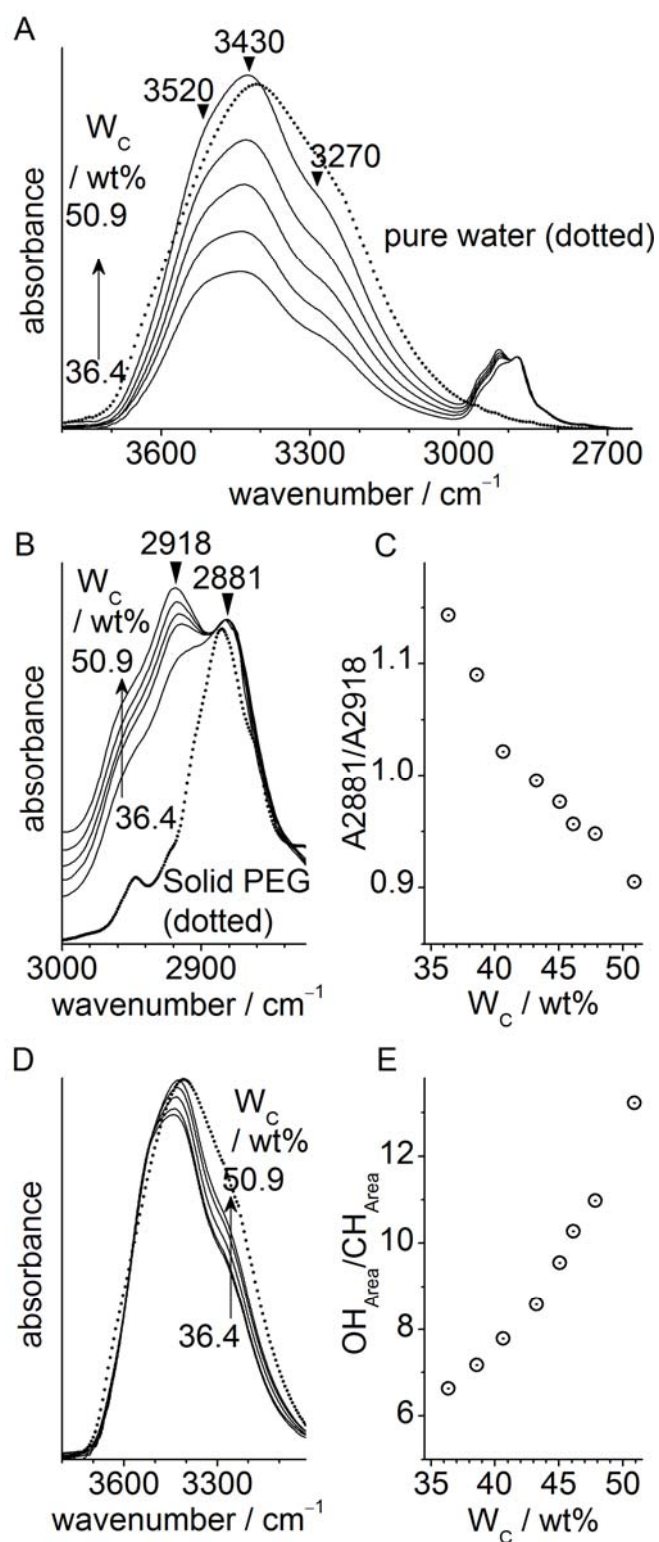


Figure 2. Mid-IR spectra of PEG aqueous solutions with various water contents (W_C) at 298 K. (A) Selected spectra in the wavenumber range of 3800-2650 cm^{-1} . Spectral intensity was normalized at 2885 cm^{-1} . (B) Spectra of the C-H stretching region (3000-2800 cm^{-1}). (C) W_C dependence of the A_{2881}/A_{2918} value. (D) Spectra of the O-H stretching region (3800-3000 cm^{-1}). The spectral intensity was normalized over the high wavenumber region. (E) W_C dependence of the $\text{OH}_{\text{Area}}/\text{CH}_{\text{Area}}$ value.

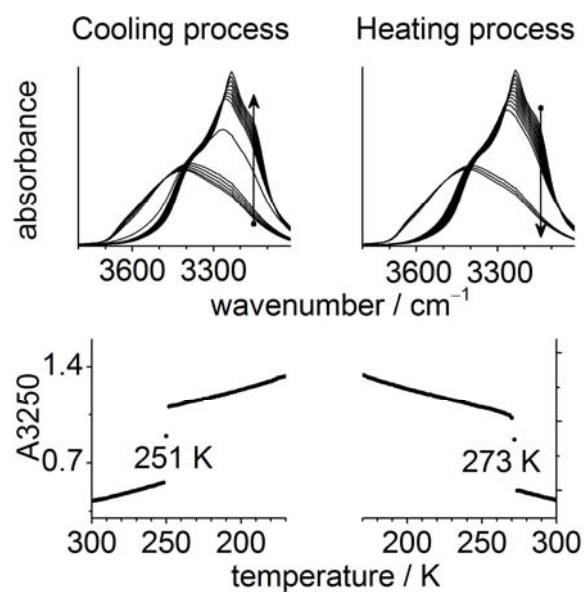


Figure 3. Temperature dependence of the mid-IR spectra (top) and A₃₂₅₀ value (bottom) of pure water. Left and right panels show the results of cooling and heating processes, respectively.

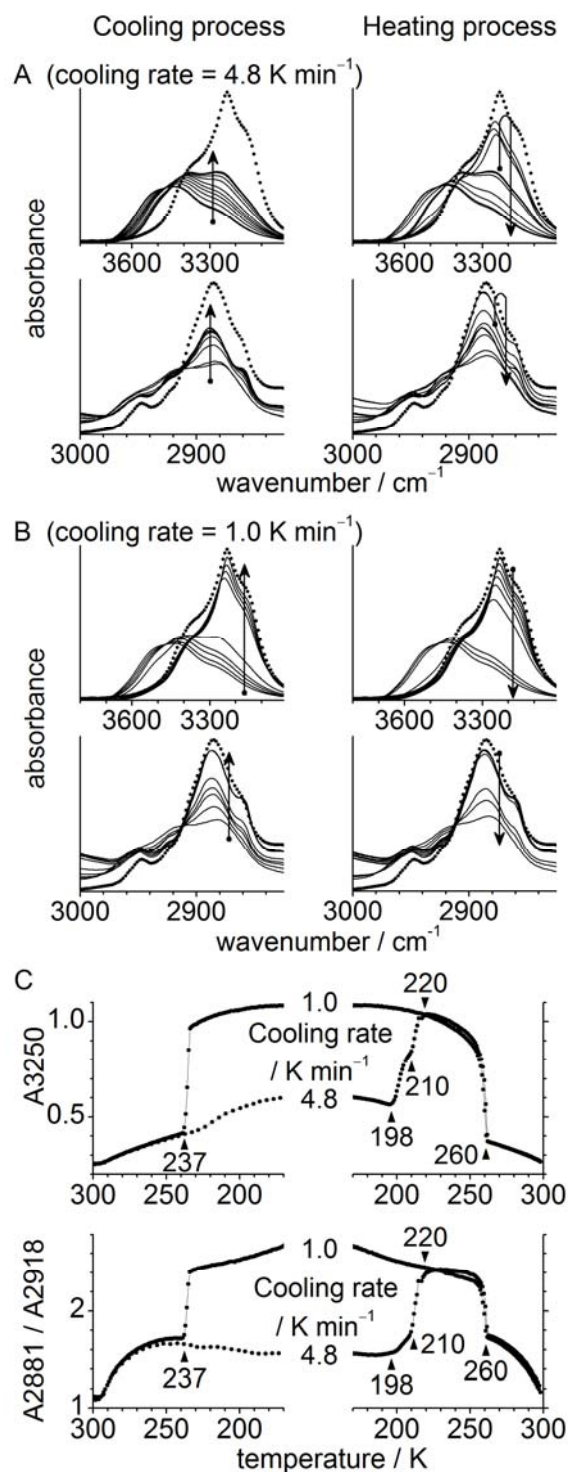


Figure 4. Temperature dependence of the mid-IR spectra of a PEG aqueous solution with a W_C of 38.6 wt%. (A) Spectra with a cooling rate of $4.8 \text{ K} \cdot \text{min}^{-1}$. (B) Spectra with a cooling rate of $1.0 \text{ K} \cdot \text{min}^{-1}$. (C) Temperature dependence of A_{3250} value (top) and that of A_{2881}/A_{2918} value (bottom). The top and bottom panels of (A) and (B) are spectra of the O–H stretching and C–H stretching regions, respectively. The left and right parts of each panel are results of the cooling and heating processes, respectively.

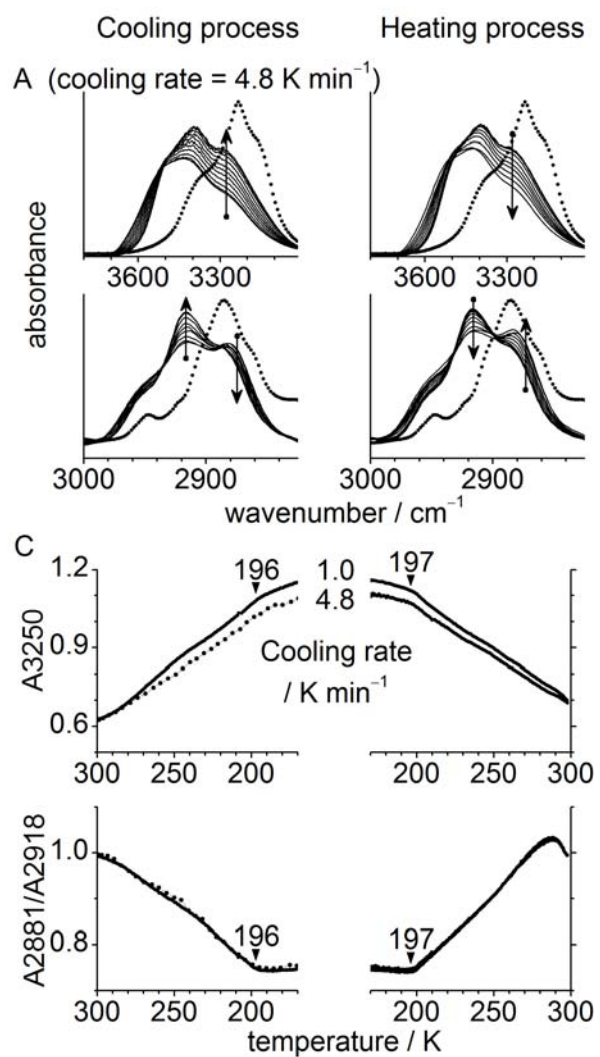


Figure 5. Temperature dependence of the mid-IR spectra of a PEG aqueous solution with a W_C of 43.2 wt%. The details are the same as those in Figure 4, though (B) is omitted.

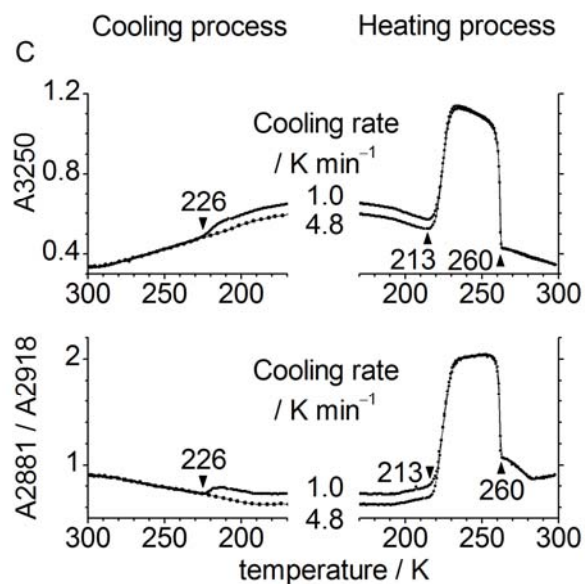


Figure 6. Temperature dependence of the mid-IR spectra of a PEG aqueous solution with a W_C of 50.9 wt%. The details are the same as those in Figure 4, though (A) and (B) are omitted.

TOC

