

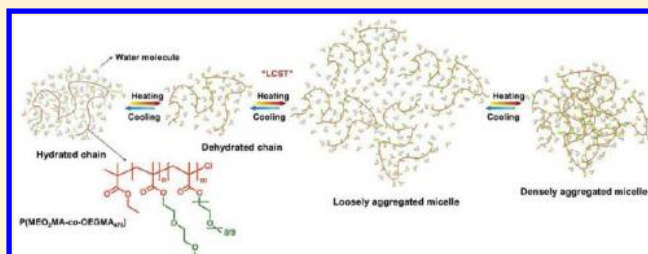
# On the Thermally Reversible Dynamic Hydration Behavior of Oligo(ethylene glycol) Methacrylate-Based Polymers in Water

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## S Supporting Information

**ABSTRACT:** Dynamic thermally reversible hydration behavior of a well-defined thermoresponsive copolymer P-(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) in D<sub>2</sub>O synthesized by ATRP random copolymerization of 2-(2-methoxyethoxy)ethyl methacrylate (MEO<sub>2</sub>MA) and oligo(ethylene glycol) methacrylate ( $M_n = 475$  g/mol) was studied by means of IR spectroscopy in combination with perturbation correlation moving window (PCMW) technique and two-dimensional correlation spectroscopy (2DCOS). Largely different from poly(*N*-isopropylacrylamide) (PNIPAM), P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) exhibits a sharp change below LCST and a gradual change above LCST due to the absence of strong intermolecular hydrogen bonding interactions between polymer chains, and the apparent phase transition is mainly arising from the multiple chain aggregation without a precontraction process of individual polymer chains. Additionally, the self-aggregation process of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) is found to be mainly dominated or driven by the conformation changes of oxyethylene side chains, which collapse first to get close to the hydrophobic backbones and then distort to expose hydrophilic ether oxygen groups to the “outer shell” of polymer chains as much as possible. On the other hand, PCMW easily determined the phase transition temperature to be ca. 32.5 °C during heating and ca. 31 °C during cooling as well as the transition temperature range to be 28.5–37 °C. 2DCOS was finally employed to discern the sequence order of all the group motions during heating and cooling. It is concluded that during the phase transition P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) chains successively experience “hydrated chains–dehydrated chains–loosely aggregated micelles–densely aggregated micelles” four consecutive conformation changes. The results were further confirmed by temperature-variable <sup>1</sup>H NMR analysis and molecular dynamics simulation.



## 1. INTRODUCTION

Synthetic polymers exhibiting a lower critical solution temperature (LCST) in water are very promising for the preparation of a wide variety of smart responsive materials such as biosensors, matrices for tissue engineering, and drug delivery carriers.<sup>1</sup> Among them, poly(*N*-isopropylacrylamide) (PNIPAM) with a LCST (~32 °C) close to physiological temperature has been by far mostly studied, which exhibits a thermally reversible coil-to-globule phase transition upon heating and cooling.<sup>2</sup> However, despite its wide popularity, PNIPAM is found to have several inherent disadvantages such as nonignorable hysteresis, producing toxic low-molecular-weight amines during hydrolysis and strong bioadhesion with proteins by cooperative hydrogen bonding interactions.<sup>3</sup> In recent years, a new family of thermal-responsive polymers based on oligo(ethylene glycol) (meth)acrylate (OEGMA) has been developed.<sup>4,5</sup> Similar to PNIPAM, the phase transition of OEGMA-based polymers (POEGMA) is reversible and relatively insensitive to environmental conditions such as concentration, ionic strength, pH, and chain length.<sup>6</sup> As poly(ethylene glycol) (PEG) side chains are uncharged, nontoxic, nonimmunogenic, and FDA-approved, POEGMA may probably become the mostly applied synthetic polymers in

biotechnology applications.<sup>7,8</sup> Owing to their excellent thermoresponsive and biocompatible properties, POEGMA has been widely used in the construction of functional polymers,<sup>9–12</sup> hydrogels<sup>13,14</sup> and microgels,<sup>5,15</sup> polymer brushes,<sup>16,17</sup> nanohybrid materials,<sup>18,19</sup> and bioactive surfaces.<sup>20,21</sup>

The thermoresponsive behavior of POEGMA can be precisely adjusted using a simple random copolymerization of OEG macromonomers of different chain lengths  $n$  (i.e., of different hydrophilicity but similar chemical nature) by living polymerization methods such as atom transfer radical polymerization (ATRP),<sup>22,23</sup> reversible addition–fragmentation chain transfer (RAFT) polymerization,<sup>24,25</sup> and anionic polymerization.<sup>26</sup> For instance, ATRP random copolymerization of 2-(2-methoxyethoxy)ethyl methacrylate (MEO<sub>2</sub>MA,  $n = 2$ ) and OEGMA ( $n = 8–9$ ,  $M_n = 475$  g/mol) leads to the formation of thermoresponsive copolymers P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) with LCST values varying from 26 to 90 °C by changing comonomer composition.<sup>22</sup> In analogy to PNIPAM,<sup>27,28</sup> the

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LCST-type behavior of POEGMA can also be regarded as the consequence of the competition between hydrophilic polymer–water interactions and hydrophobic polymer–polymer interactions. At room temperature, the polymer–water interactions are favorable to allow solubilization while above LCST hydrophobic polymer–polymer interactions are thermodynamically favored, resulting in the self-aggregation of POEGMA chains.<sup>4</sup> Up to now, plenty of researches have been devoted to study the thermoresponsive behavior of POEGMA. As Lutz et al. reported, the thermoresponsive behavior of POEGMA can also be related to a coil-to-globule phase transition. However, differing from PNIPAM whose collapsed state is stabilized by strong intramolecular and intermolecular N–H···O=C hydrogen bonds, there is no strong hydrogen bond donor in POEGMA chains but weaker van der Waals interactions. Therefore, the phase transition of POEGMA is well reversible, and no significant hysteresis of POEGMA can be observed.<sup>29</sup> The gelation capability of PMEO<sub>2</sub>MA aqueous solutions was also investigated by Liu et al., who found that compared to a good gelation capability of PNIPAM aqueous solutions due to more pronounced physical interactions, for PMEO<sub>2</sub>MA weak intermolecular interactions fail to result in gelling during heating.<sup>30</sup> Recently, Gibson et al. found that by mixing two POEGMA chains with different molecular weights two independent phase transitions would be observed due to a weak molecular weight dependence on its cloud point.<sup>31</sup> A similar phenomenon has also been observed in POEGMA block copolymers.<sup>32</sup> Liu and Tam et al. synthesized a well-defined random copolymer containing MEO<sub>2</sub>MA and a PEG macromonomer of long chain length ( $M_n = 2080$  g/mol) which exhibited an unusual thermally induced two-stage aggregation process.<sup>33</sup> Indeed, by altering the chain length of OEG side chains and chain architecture, POEGMA would show more interesting and diverse phase transition behaviors than other thermoresponsive polymers.

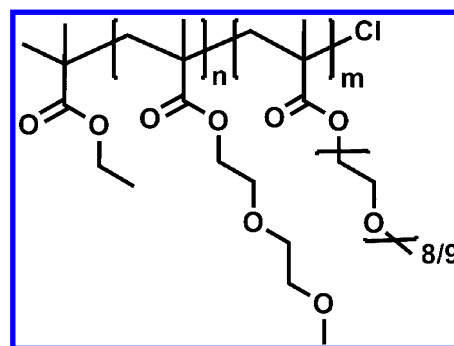
Vibrational spectroscopy was proved to be a quite useful method to observe changes in the hydration states of individual chemical groups of polymers, especially thermoresponsive polymers.<sup>34</sup> Comparing with common LCST-type polymers such as PNIPAM,<sup>27,28</sup> poly(*N*-vinylcaprolactam) (PVCL),<sup>35</sup> and poly(vinyl methyl ether) (PVME),<sup>36</sup> the vibrational spectroscopic investigations of the thermoresponsive behavior of POEGMA are still very limited. For example, Maeda et al. employed IR spectroscopy in combination with DFT calculation and confocal micro-Raman spectroscopy to study the hydration changes of C=O and C–H groups during the phase transition of PMEO<sub>2</sub>MA and found that both C=O and C–H groups are hydrated in PMEO<sub>2</sub>MA and free C=O groups exist in the polymers even at low polymer concentrations and below the phase separation temperature.<sup>37,38</sup> However, to the best of our knowledge, no integrated dynamic mechanism of the thermally induced phase transition of POEGMA during both heating and cooling processes has ever been clarified. Therefore, in this paper, we attempt to apply IR spectroscopy in combination with two spectral analysis methods—perturbation correlation moving window (PCMW) and two-dimensional correlation spectroscopy (2DCOS)—to illustrate the dynamic hydration behavior of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) (the mostly studied thermoresponsive POEGMA) during the thermally reversible phase transition upon a heating-and-cooling cycle. By PCMW and 2DCOS analysis, additional information on the specific order taking place corresponding to chain conformation changes

during phase transition would be extracted, which is very helpful for our further understanding the evolution mechanism of micelle formation of POEGMA.

## 2. EXPERIMENTAL SECTION

**2.1. Materials.** P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) was synthesized via atom transfer radical copolymerization of MEO<sub>2</sub>MA and OEGMA ( $n = 8–9$ ,  $M_n = 475$  g/mol) monomers according to previous reports.<sup>22</sup> Herein, the feed ratio of [OEGMA]/[MEO<sub>2</sub>MA] was fixed to 5:95, and the polymerization time was adjusted to 9 h. The number-average molecular weight ( $M_n$ ) and polydispersity index ( $PDI = M_w/M_n$ ) were determined by GPC measurements with monodisperse polystyrene as standard and THF as eluent phase at 35 °C. The resulting copolymer (chemical structure as shown in Scheme 1) has  $M_n = 1.30 \times 10^4$  g/mol

**Scheme 1. Chemical Structure of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>), Wherein  $m \approx 3$ ,  $n \approx 61$**



and  $PDI = 1.21$ . According to <sup>1</sup>H NMR measurements (in CDCl<sub>3</sub>), the molar fraction of OEGMA in the copolymer  $F_{\text{OEGMA}} = 0.045$ , which is nearly equal to the molar fraction of OEGMA in the initial comonomer feed ( $f_{\text{OEGMA}} = 0.05$ ). D<sub>2</sub>O was purchased from Cambridge Isotope Laboratories Inc. (D-99.9%). For <sup>1</sup>H NMR and FT-IR measurements, the concentration of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O was fixed to 10 wt %. P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) solution in D<sub>2</sub>O was placed at 4 °C for a week before <sup>1</sup>H NMR and FT-IR measurements to ensure complete dissolution.

**2.2. Instruments and Measurements.** The sample of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) solution for FT-IR measurements was prepared by being sealed between two CaF<sub>2</sub> tablets. All time-resolved FT-IR spectra at different temperatures were recorded on a Nicolet Nexus 470 spectrometer with a resolution of 4 cm<sup>−1</sup>, and 32 scans were available for an acceptable signal-to-noise ratio. Temperatures were manually controlled with an electronic cell holder at rates of ca. 0.3 °C/min with an increment of 0.5 °C. The neat P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) sample for FT-IR measurement was prepared by drop-casting on a KBr tablet from its THF solution. Raw spectra were baseline-corrected by the software Omnic, ver. 6.1a.

Calorimetric measurements of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O were performed on a Mettler-Toledo differential scanning calorimeter (DSC) thermal analyzer with varying scanning rates from 5 to 60 °C. The temperature-dependent average hydrodynamic radius ( $R_h$ ) measurements of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in H<sub>2</sub>O (0.1 and 1.0 mg/mL) were performed on a dynamic light scattering (DLS)—zetasizer nanosystem (Malvern) with an increment of 1 °C from 25 to 45 °C. Temperature-variable <sup>1</sup>H NMR spectra of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) and linear PNIPAM were recorded on Varian Mercury plus (400 MHz) spectrometer using D<sub>2</sub>O as solvent (concentration = 10 wt %) with an increment of 1 °C.

**2.3. Investigation Methods.** **2.3.1. Perturbation Correlation Moving Window (PCMW).** FT-IR spectra collected with an increment of 0.5 °C during heating and cooling were used to perform PCMW analysis. Primary data processing was carried out with the method Morita provided and further correlation calculation was performed using the software 2D Shige, ver. 1.3 (Shigeaki Morita, Kwansei-

Gakuin University, Japan, 2004–2005). The final contour maps were plotted by Origin program, ver. 8.5, with warm colors (red and yellow) defined as positive intensities and cool colors (blue) as negative ones. An appropriate window size ( $2m + 1 = 11$ ) was chosen to generate PCMW spectra with good quality.

**2.3.2. 2D Correlation Spectroscopy (2DCOS).** FT-IR spectra chosen from PCMW analysis were used to perform 2D correlation analysis. 2D correlation analysis was carried out using the same software 2D Shige ver. 1.3 (Shigeaki Morita, Kwansei-Gakuin University, Japan, 2004–2005) and was further plotted into the contour maps by Origin program ver. 8.5. In the contour maps, warm colors (red and yellow) are defined as positive intensities, while cool colors (blue) as negative ones.

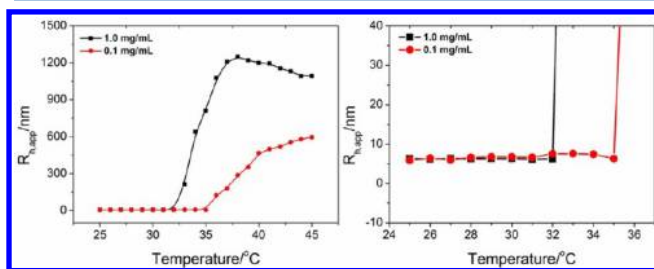
**2.3.3. Molecular Dynamics Simulation.** Molecular dynamics simulation was performed on the software package Materials Studio ver. 5.0 (Accelrys Inc., San Diego, CA, 2001–2009). A model compound, 2-(2-methoxyethoxy)ethyl 3-methyl-3-pentanoate (MEO<sub>2</sub>MPa), was used for the construction of an amorphous cell with water molecules. The geometry optimization and molecular dynamics run were accounted by the COMPASS force field, which was implemented in the Discover and Forcite modules. The hydrogen bonding energy calculation was carried out by the Drieding force field implemented in the Forcite module.

### 3. RESULTS AND DISCUSSION

**3.1. DLS and Calorimetric Measurements.** P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) was synthesized via atom transfer radical copolymerization of MEO<sub>2</sub>MA and OEGMA ( $n = 8–9$ ,  $M_n = 475$  g/mol) monomers in ethanol to obtain a chain-to-chain statistical copolymer. As Lutz reported,<sup>22</sup> the LCST of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) can be precisely predicted from the theoretical average number of OEGMA units per chain ( $DP_{\text{OEGMA}}$ ) by eq 1 as follows:

$$\text{LCST} = 28 + 1.04DP_{\text{OEGMA}} \quad (1)$$

As shown in Scheme 1,  $DP_{\text{OEGMA}} = m \approx 3$ . Thus, the LCST of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) we synthesized can be estimated to be 31.1 °C, very close to the LCST value of PNIPAM. The LCST of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) can also be determined by DLS and calorimetric measurements. The temperature-dependent average hydrodynamic radius ( $R_h$ ) curves of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) at the concentration of 0.1 and 1.0 mg/mL are presented in Figure 1.

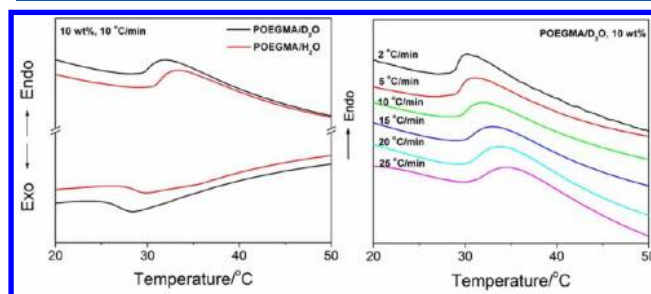


**Figure 1.** DLS measurements of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) at the concentration of 0.1 and 1.0 mg/mL from 25 to 45 °C. The right figure is the enlarged image at low temperatures.

As expected,  $R_h$  exhibits an abrupt increase at 35 and 32 °C for 0.1 and 1.0 mg/mL, consistent with the predicted value. In accordance with previous report, the LCST of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) is a little concentration dependent, suggesting that the transition must involve multiple polymer chains aggregating together; i.e., the polymer chains do not “find” each other as quickly in dilute solution, and hence the apparent LCST with a constant heating rate is increased.<sup>39</sup> It can also be confirmed

from the  $R_h$  changes after the phase transition at different concentrations. At the relatively dilute solution (0.1 mg/mL), the  $R_h$  continuously increase from 460 nm at 40 °C to 600 nm at 45 °C, corresponding to the size growth of micelles formed by binding more P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) chains. However, at 1.0 mg/mL, the size of the formed micelles is relatively stable, but with a slight decrease from 1250 nm at 38 °C to 1100 nm at 45 °C. It reveals that P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) chains would continuously expel water molecules or dehydrate even after the phase transition, which is largely different from PNIPAM<sup>40</sup> but something like PVCL.<sup>35</sup> It should also be worth noting that before the phase transition the average size of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) unimers is nearly unchanged or very slightly decreased. In contrary to a precontraction process of individual polymer chains before the phase transition usually found in PNIPAM-based polymers,<sup>41,42</sup> the coil of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) does not collapse (mainly by the distortion of backbones) into a crumpled structure at low temperatures. In other words, the apparent phase transition of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) chains may be individually arising from the multiple chain aggregation.

DSC heating and cooling curves of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) (10 wt %) in D<sub>2</sub>O and H<sub>2</sub>O at 10 °C/min as well as the heating curves at different scanning rates are presented in Figure 2. The transition temperature obtained

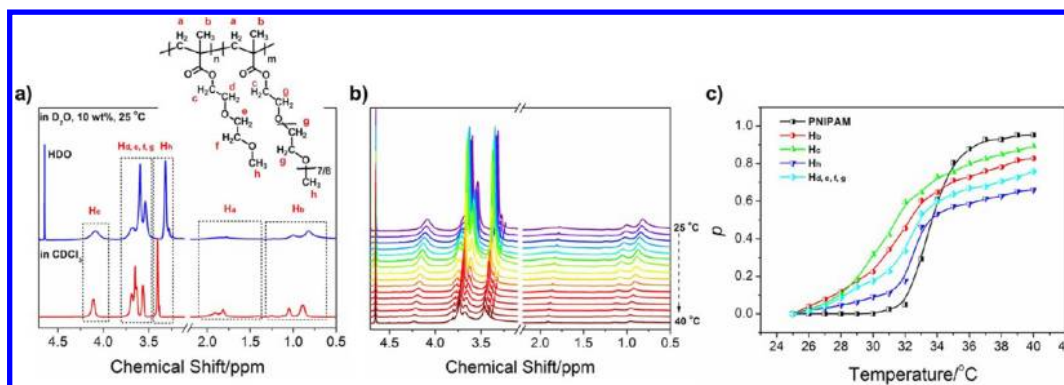


**Figure 2.** Left: DSC heating and cooling curves of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) (10 wt %) in D<sub>2</sub>O and H<sub>2</sub>O at 10 °C/min. Right: DSC heating curves P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) (10 wt %) in D<sub>2</sub>O at different scanning rates.

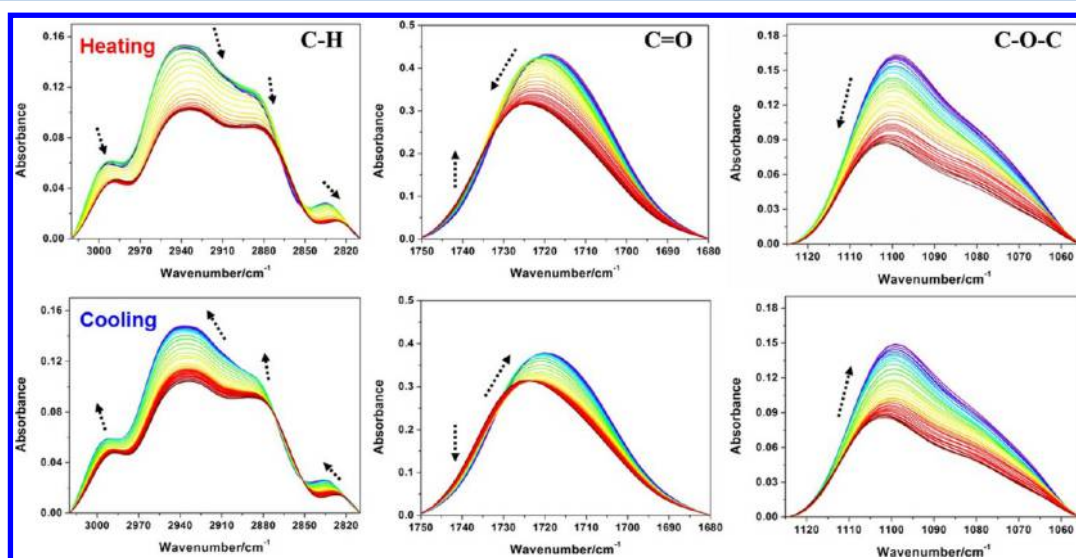
from DSC is also in good conformity with the predicted LCST value and that from DLS measurements. At a relatively high scanning rate, P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) shows a slight hysteresis ( $\sim 2.6$  °C) during a heating-and-cooling cycle, which should be caused by much slower chain aggregation and disaggregation than external temperature changes. However, the hysteresis is weaker than PNIPAM ( $\sim 3.5$  °C)<sup>28</sup> under the same scanning conditions, perhaps attributing from the absence of strong intramolecular and intermolecular hydrogen bonding interactions. Additionally, the LCST-type phase transition of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) exhibits a strong dependence on the scanning rates. That is, a faster scanning rate leads to a higher transition temperature, indicating that the phase transition of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) is mainly dominated by interchain aggregation.<sup>43</sup>

It is interesting to find that the transition temperature of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) in D<sub>2</sub>O is slightly lower ( $\sim 1.4$  °C) than that in H<sub>2</sub>O, and both heating and cooling DSC curves are broad (more than 15 °C) and markedly asymmetric with a sharp change below LCST and a gradual change above LCST. The latter can also be observed in previous researches.<sup>37–39</sup> Both the two features are largely different





**Figure 3.** (a) <sup>1</sup>H NMR spectra of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O (10 wt %, 25 °C) and CDCl<sub>3</sub> and the spectral assignment of main resonances. (b) Normalized temperature-variable <sup>1</sup>H NMR spectra of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O (10 wt %) from 25 to 40 °C with an increment of 1 °C. (c) Temperature dependences of phase separated fraction *p* for different proton types of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) and −CH(CH<sub>3</sub>)<sub>2</sub> of PNIPAM in D<sub>2</sub>O.



**Figure 4.** Temperature-dependent FT-IR spectra of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O (10 wt %) during heating and cooling between 24 and 42 °C in the regions 3020–2810, 1750–1680, and 1125–1055 cm<sup>-1</sup>. The temperature increment is 0.5 °C, and only a 1 °C interval is shown here for clarity.

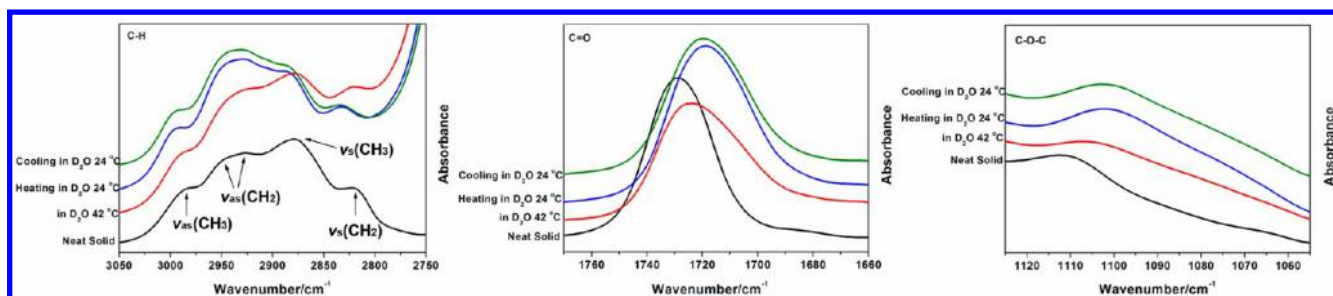
from PNIPAM<sup>27,43</sup> but very similar to PVCL which is also lacking of strong self-associated hydrogen bonding.<sup>35,44</sup> However, none of the previous reports can explain well the two distinct enthalpy changes of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) at the molecular level below and above LCST, which may be the key to understanding the dynamic nature of the phase transition of POEGMA in water.

**3.2. Temperature-Variable <sup>1</sup>H NMR Analysis.** To quantitatively describe the phase transition degree of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>), we performed temperature-variable <sup>1</sup>H NMR measurement, as shown in Figure 3. Nearly all the proton types in P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) can be observed in <sup>1</sup>H NMR spectra in both D<sub>2</sub>O and CDCl<sub>3</sub> with the assignment labeled in Figure 3a. It is noted that the <sup>1</sup>H NMR spectrum in D<sub>2</sub>O slightly differs from that in CDCl<sub>3</sub>. In CDCl<sub>3</sub>, all the protons of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) exhibit sharp and intense signals, indicating that the copolymer is uniformly molecularly dissolved, which can be used to calculate the molar fraction of OEGMA in the copolymer. However, in D<sub>2</sub>O, the resonant peaks corresponding to oxyethylene side chains (H<sub>d,e,f,g</sub> and H<sub>h</sub>) remain sharp, but the intensities of the peaks attributing from the backbone (H<sub>a</sub> and H<sub>b</sub>) and protons in

proximity to the backbone (H<sub>c</sub>) are considerably reduced and broadened. It reveals that the hydration of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O is not uniform with more water molecules surrounding the hydrophilic side chains and less water molecules around the backbone.<sup>29</sup> Figure 3b shows the temperature-dependent <sup>1</sup>H NMR spectra of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O (10 wt %) from 25 to 40 °C. The normalization was performed according to the integrated intensity of HDO peak from the solvent. While the HDO peak does not shift over the whole temperature range of 25–40 °C, all the other peaks corresponding to the copolymer shift toward lower field along with a drastic intensity decrease with rising temperature, which is similar to the case of PNIPAM.<sup>45,46</sup> Obviously, the signals of protons in and close to the backbone of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) become hardly detectable after the phase transition, and only the proton signals from the hydrophilic side chains (still soluble and mobile structures) in the surface of micelles can be detected.

We employed the phase separation fraction *p* to characterize the degree of phase transition, where *p* is defined as

$$p = 1 - (I/I_0) \quad (2)$$



**Figure 5.** Spectral comparison of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) in D<sub>2</sub>O (10 wt %) at 24 and 42 °C during heating and cooling and neat P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) sample.

In eq 2,  $I$  and  $I_0$  are the normalized integrated intensities of a selected resonant peak at a specified temperature and at 25 °C, respectively.<sup>47,48</sup> We plotted the temperature dependences of the phase separation fraction  $p$  for different proton types of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) and  $-\text{CH}(\text{CH}_3)_2$  of PNIPAM in D<sub>2</sub>O for comparison as presented in Figure 3c. The temperature-variable <sup>1</sup>H NMR spectra and corresponding assignment of PNIPAM in D<sub>2</sub>O (10 wt %) are shown in Figure S1. It is observed that the phase separation degree of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) is rather lower than that of PNIPAM, especially just after the phase transition at 34 °C with phase separation degrees of only 0.5–0.7 dependent on different proton types, while PNIPAM shows a phase separation degree of ca. 0.93 after the phase transition at 37 °C. Continuously increasing the temperature would raise the phase separation degree to a much higher value, corresponding to the gradual change above LCST as we observed in DLS and calorimetric measurements.

Additionally, judging from the temperature-dependent phase separation curves in Figure 3c, we can find that the protons in and close to the backbone ( $H_b$  and  $H_c$ ) have a higher phase separation degree than oxyethylene side chains ( $H_{d,e,f,g}$  and  $H_h$ ). The lower phase separation degree of oxyethylene side chains can be attributed to a relatively weak dehydration (both hydrophilic in the unimer and micelle) during the phase transition. It is worth noting that despite the absence of a precontraction process as we stated in DLS analysis, P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) chains exhibit a nearly simultaneous dehydration process (especially for  $H_b$ ,  $H_c$  and  $H_{d,e,f,g}$ ) before the phase transition. It suggests that the dehydration of C–H groups (mainly in side chains) may be the key to the self-aggregation process of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>).

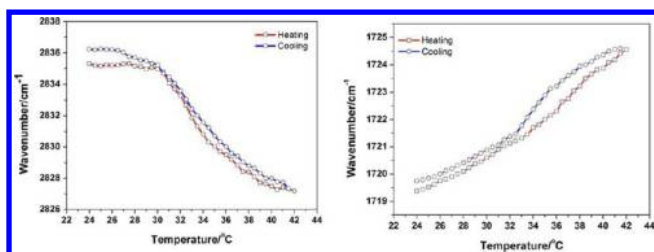
**3.3. Conventional IR Analysis.** To further elucidate the dynamic mechanism of the thermoresponsive behavior, we performed temperature-dependent FT-IR measurements of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) in D<sub>2</sub>O (10 wt %) during a heating-and-cooling cycle between 24 and 42 °C, as shown in Figure 4. It should be noted that we used D<sub>2</sub>O instead of H<sub>2</sub>O as the solvent here in order to eliminate the overlap of  $\delta(\text{O}-\text{H})$  band of H<sub>2</sub>O around 1640 cm<sup>−1</sup> with  $\nu(\text{C}=\text{O})$  of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) as well as the broad  $\nu(\text{O}-\text{H})$  band of H<sub>2</sub>O around 3300 cm<sup>−1</sup> with  $\nu(\text{C}-\text{H})$  bands.<sup>27,28</sup> As shown in Figure 2, the transition temperature of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) in D<sub>2</sub>O is only slightly lower than that in H<sub>2</sub>O. Thus, the deuterium isotope effect does not cause obvious changes on the phase transition behavior of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>).

Here, we mainly focus on three spectral regions: C–H stretching region (3020–2810 cm<sup>−1</sup>), C=O stretching region (1750–1680 cm<sup>−1</sup>), and C–O–C stretching region (1125–

1055 cm<sup>−1</sup>). Then we can trace nearly all the group motions of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) during the phase transition. From Figure 4, we can find that during heating all the C–H stretching bands shift to lower frequency, indicating the gradual dehydration of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) backbones and side chains. It is believed that water clathrates exist around the hydrophobic moieties of water-soluble polymers where water molecules have a well-ordered structure.<sup>49</sup> The higher the number of water molecules surrounding C–H groups is, the higher the vibrational frequency is.<sup>50</sup> During heating the main bands of both C=O and C–O–C groups shift to higher frequency, suggesting the dehydration of hydrophobic ester linkages and the abruption of hydrogen bonds between ether oxygen groups and water. It should be noted that the slight emerging of C=O stretching around 1740 cm<sup>−1</sup> during heating does not correspond to a new peak according to the second-derivative curves but should result from a gradual blue shift of the band around 1720 cm<sup>−1</sup>. During cooling the case is just the opposite of that in the heating process.

To discern the effect of hydration on the frequency of C–H, C=O, and C–O–C stretching bands, spectral comparison of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) in D<sub>2</sub>O at 24 and 42 °C during heating and cooling and neat P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) sample has been presented in Figure 5. Since neat P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) cannot form hydrophobic hydration and hydrogen bonds due to the absence of hydrogen bond donor, we can ascribe the C–H, C=O, and C–O–C groups to be free of water and hydrogen bonds, respectively. It is noted that after the phase transition (42 °C) C–H groups of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) are nearly completely free of water while C=O and C–O–C groups are still partially hydrated or hydrogen bonded, in accordance with previous reports.<sup>37,38</sup> In a sense, the conformation changes of C–H groups (mainly in side chains) seems to dominate the self-aggregation process of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>), consistent with above <sup>1</sup>H NMR analysis. After a heating-and-cooling cycle, all the frequencies of main bands can revert to the original position, indicating the good thermal reversibility of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>).

We additionally examine the temperature-dependent frequency shifts of the two bands around 2837 and 1720 cm<sup>−1</sup> corresponding to  $\nu_s(\text{CH}_2)$  ( $-\text{OCH}_2\text{CH}_2\text{O}-$ ) and  $\nu(\text{C}=\text{O})$ , whose peak positions can be easily determined, as shown in Figure 6. Obviously, the frequency shifting tendency of both the two bands exhibits an asymmetric sigmoid curve with a sharp shift below LCST but a gradual shift above LCST, which is also in good conformity with DSC observations. Note that PNIPAM has the frequency nearly unchanged both before and after phase transition (typical symmetric sigmoid curve);<sup>28</sup> this proves that P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) has a reduced



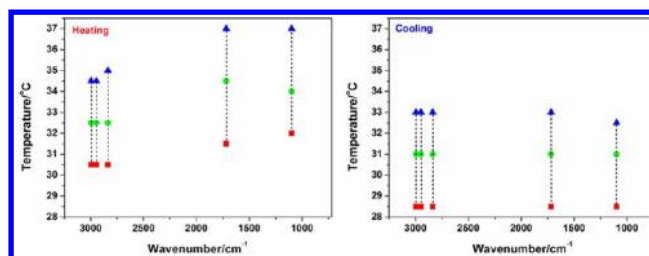
**Figure 6.** Temperature-dependent frequency shifts of  $\nu_s(\text{CH}_2)$  ( $-\text{OCH}_2\text{CH}_2\text{O}-$ ) and  $\nu(\text{C}=\text{O})$  during heating and cooling, respectively.

magnitude of conformation changes compared to PNIPAM, which may indicate a distinct phase transition mechanism. From Figure 6 we can also find that especially for C–H groups the heating curve and the cooling curve almost coincide, indicating a relatively weak hysteresis and good thermal reversibility of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>).

As for the asymmetric sigmoid curves in Figure 6, it is hard to accurately determine the transition temperatures during heating and cooling, even for our often-used Boltzmann fitting method.<sup>42</sup> Thus, a PCMW technique was employed to help in the determination of phase transition temperatures and ranges.

**3.4. Perturbation Correlation Moving Window.** PCMW is a newly developed technique, whose basic principles can date back to conventional moving window proposed by Thomas et al.,<sup>51</sup> and later in 2006 Morita et al.<sup>52</sup> improved this technique to much wider applicability through introducing the perturbation variable into correlation equation. Except for its original ability in determining transition points as conventional moving window did, PCMW can additionally monitor complicated spectral variations along the perturbation direction.

Figure 7 presents PCMW synchronous and asynchronous spectra of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O during heating and cooling between 24 and 42 °C, respectively. For convenience, we plotted all the points read from PCMW synchronous and asynchronous spectra in Figure 8. PCMW synchronous spectra are very helpful to find transition points. Thus, on average, for all the C–H, C=O, and C–O–C bands, we have LCST to be ca. 32.5 °C during heating and ca. 31 °C during cooling, in accordance with above DLS, DSC, and predicted values. However, different groups have apparently different responding temperatures. During heating C–H

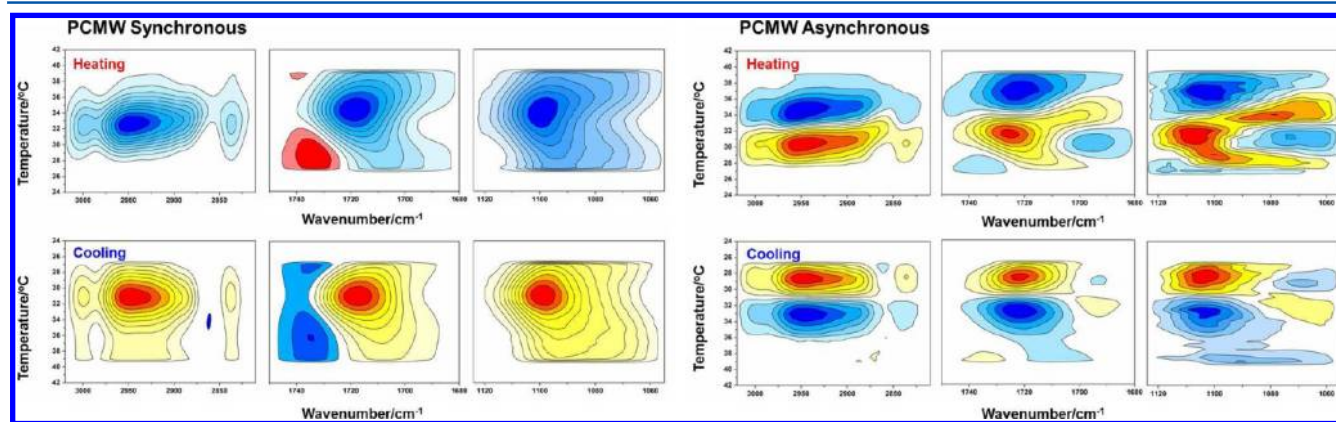


**Figure 8.** Corresponding transition temperatures and transition temperature regions of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O (10 wt %) during heating and cooling read from PCMW synchronous and asynchronous spectra.

groups have the earliest response than C–O–C groups followed by C=O groups with a slowest response, while during cooling all the three groups respond simultaneously. It reveals that the conformation changes of side chains should be the driving force of the self-aggregation process of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) while for the self-disaggregation process during cooling all the moieties of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) chains have a relatively cooperative response.

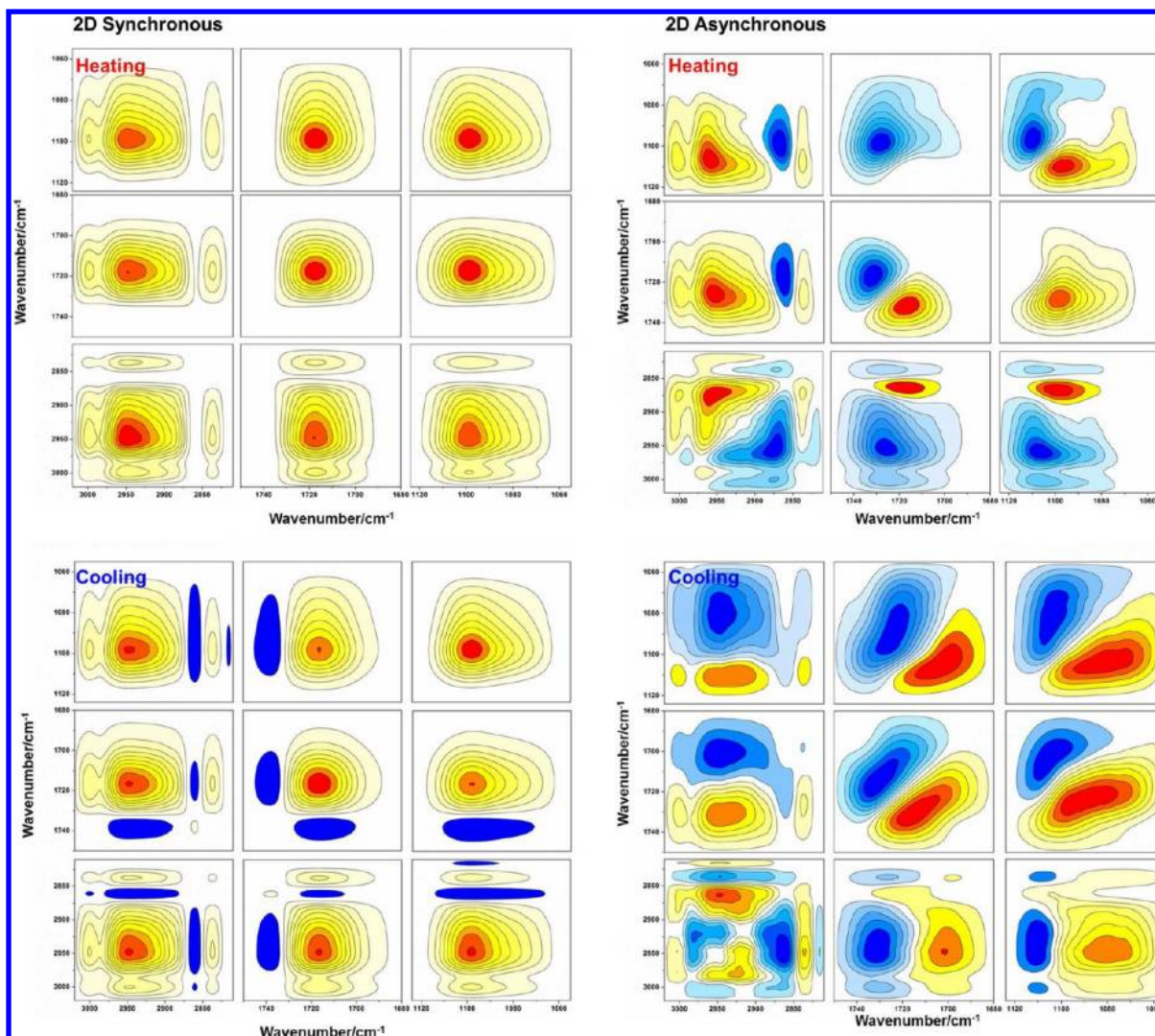
In addition to determining transition points, PCMW can also monitor the spectral variations along temperature perturbation combining the signs of synchronous and asynchronous spectra by the following rules: positive synchronous correlation represents spectral intensity increasing, while negative one represents decreasing; positive asynchronous correlation can be observed for a convex spectral intensity variation while negative one can be observed for a concave variation.<sup>52</sup> On the basis of this point, we can ascertain that all the C–H, C=O, and C–O–C main bands of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) show anti-S-shaped spectral changes, consistent with above conventional IR analysis. The transition temperature region can also be determined by the peaks in asynchronous spectra which are all turning points of the sigmoid curves, as shown in Figure 8. Then we can conclude that P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) experiences phase transition in D<sub>2</sub>O mainly between 30.5 and 37 °C during heating and between 28.5 and 33 °C during cooling. This served as an important basis for the segmental mode of the following 2DCOS analysis.

**3.5. Two-Dimensional Correlation Analysis.** 2DCOS is a mathematical method whose basic principles were first proposed by Noda in 1986.<sup>53</sup> Up to the present, 2DCOS has been widely used to study spectral variations of different



**Figure 7.** PCMW synchronous and asynchronous spectra of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O (10 wt %) during heating and cooling between 24 and 42 °C, respectively, wherein warm colors (red and yellow) are defined as positive intensities, while cool colors (blue) as negative ones.





**Figure 9.** 2DCOS synchronous and asynchronous spectra of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O (10 wt %) during heating and cooling, respectively, wherein warm colors (red and yellow) are defined as positive intensities, while cool colors (blue) as negative ones.

chemical species under various external perturbations (e.g., temperature, pressure, concentration, time, electromagnetic, etc.).<sup>54</sup> Because of the different response of different species to external variable, additional useful information about molecular motions or conformational changes can be extracted which cannot be obtained straight from conventional 1D spectra.

On the basis of the phase transition evolving regions obtained from PCMW, we chose all the spectra of P-(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) between 28.5 and 37 °C to perform 2DCOS analysis, as shown in Figure 9. 2D synchronous spectra reflect simultaneous changes between two given wavenumbers. For instance, nearly all the bands during heating have positive cross-peaks, indicating that they have similar response of spectral intensities to temperature perturbation; that is, all decrease during heating determined from raw spectra. On the other hand, it should be noted that several small bands showing spectral intensities a slight decrease during cooling are not real peaks, but arising from the large peak shift of neighbor bands such as the emerging of the band around 1740 cm<sup>-1</sup> as we stated before.

2D asynchronous spectra can significantly enhance the spectral resolution. In Figure 9 many subtle bands such as the bands at 2978 and 1732 cm<sup>-1</sup> attributed from  $\nu_{\text{as}}(\text{CH}_3)$ -

(backbone) and  $\nu(\text{C}=\text{O})$ (dehydrated) as well as four C–O–C splitting bands at 1111, 1103, 1095, and 1080 cm<sup>-1</sup> have been identified. For the convenience of discussion, all the bands found in asynchronous spectra and their corresponding assignments have been presented in Table 1. Note that both comonomers of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) are of the same kind (i.e., both contain a PEG segment and a methacrylate moiety). Thus, chemically speaking, the random copolymer can be considered as a homopolymer,<sup>4</sup> and we did not distinguish them from IR spectral assignments.

Except for enhancing spectral resolution, 2DCOS can also discern the specific order taking place under external perturbation. The judging rule can be summarized as Noda's rule—that is, if the cross-peaks ( $\nu_1$ ,  $\nu_2$ , and assume  $\nu_1 > \nu_2$ ) in synchronous and asynchronous spectra have the same sign, the change at  $\nu_1$  may occur prior to that of  $\nu_2$ , and vice versa. As space is limited, the determination details of sequential orders have been presented in the Supporting Information, and only the final specific order for the heating process of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O is given as follows ( $\rightarrow$  means prior to or earlier than): 2954 cm<sup>-1</sup>  $\rightarrow$  3000 cm<sup>-1</sup>  $\rightarrow$  2837 cm<sup>-1</sup>  $\rightarrow$  2989 cm<sup>-1</sup>  $\rightarrow$  1095 cm<sup>-1</sup>  $\rightarrow$  2821 cm<sup>-1</sup>  $\rightarrow$  1716 cm<sup>-1</sup>  $\rightarrow$  1111 cm<sup>-1</sup>  $\rightarrow$  2873 cm<sup>-1</sup>  $\rightarrow$  1732 cm<sup>-1</sup>, or  $\nu_{\text{as}}(\text{CH}_2)$ -

**Table 1.** Tentative Band Assignments of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O According to 2DCOS Results<sup>36–38</sup>

wavenumber/cm <sup>-1</sup>	assignment
3000	$\nu_{\text{as}}(\text{CH}_3)(-\text{OCH}_3)(\text{dehydrated})$
2989	$\nu_{\text{as}}(\text{CH}_3)(-\text{OCH}_3)(\text{hydrated})$
2978	$\nu_{\text{as}}(\text{CH}_3)(\text{backbone})$
2954	$\nu_{\text{as}}(\text{CH}_2)(-\text{OCH}_2\text{CH}_2\text{O}-)(\text{dehydrated})$
2947	$\nu_{\text{as}}(\text{CH}_2)(-\text{OCH}_2\text{CH}_2\text{O}-)(\text{hydrated})$
2922	$\nu_{\text{as}}(\text{CH}_2)(\text{backbone})$
2889	$\nu_{\text{s}}(\text{CH}_3)(-\text{OCH}_3)(\text{dehydrated})$
2862	$\nu_{\text{s}}(\text{CH}_3)(-\text{OCH}_3)(\text{hydrated})$
2837	$\nu_{\text{s}}(\text{CH}_2)(-\text{OCH}_2\text{CH}_2\text{O}-)(\text{dehydrated})$
2821	$\nu_{\text{s}}(\text{CH}_2)(-\text{OCH}_2\text{CH}_2\text{O}-)(\text{hydrated})$
1732	$\nu(\text{C=O})(\text{dehydrated})$
1716	$\nu(\text{C=O})(\text{hydrated})$
1111, 1103	$\nu(\text{C-O-C})(\text{dehydrated})$
1095, 1080	$\nu(\text{C-O-C})(\text{hydrated})$

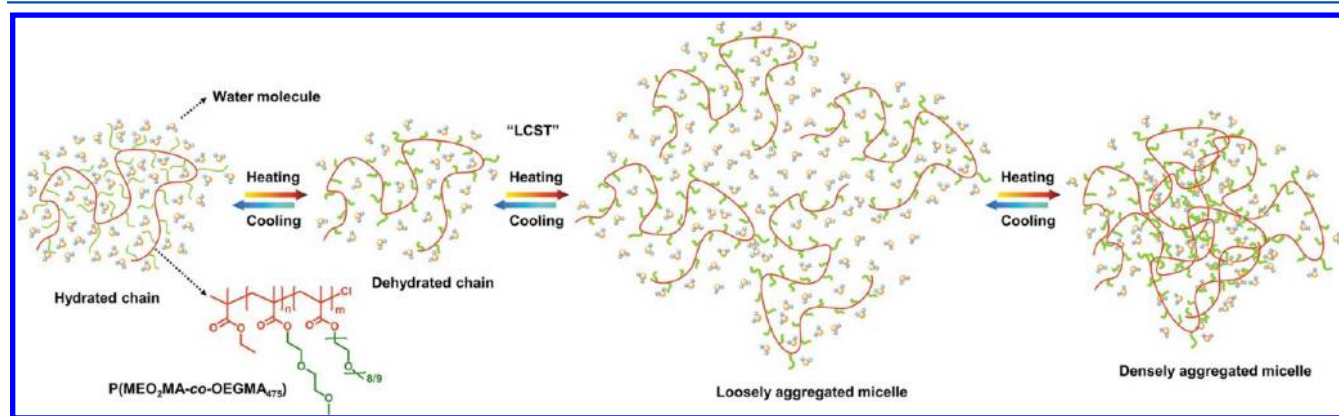
$(-\text{OCH}_2\text{CH}_2\text{O}-)(\text{dehydrated}) \rightarrow \nu_{\text{as}}(\text{CH}_3)(-\text{OCH}_3)(\text{dehydrated}) \rightarrow \nu_{\text{s}}(\text{CH}_2)(-\text{OCH}_2\text{CH}_2\text{O}-)(\text{dehydrated}) \rightarrow \nu_{\text{as}}(\text{CH}_3)(-\text{OCH}_3)(\text{hydrated}) \rightarrow \nu(\text{C-O-C})(\text{hydrated}) \rightarrow \nu_{\text{s}}(\text{CH}_2)(-\text{OCH}_2\text{CH}_2\text{O}-)(\text{hydrated}) \rightarrow \nu(\text{C=O})(\text{hydrated}) \rightarrow \nu(\text{C-O-C})(\text{dehydrated}) \rightarrow \nu_{\text{s}}(\text{CH}_3)(-\text{OCH}_3) \rightarrow \nu(\text{C=O})(\text{dehydrated})$ . Wherein, the band at 2873 cm<sup>-1</sup> is the overlapped peak of the bands at 2889 and 2862 cm<sup>-1</sup> (Table 1).

Without considering the differences in stretching modes, the sequence can be described as  $-\text{OCH}_2\text{CH}_2\text{O}- \rightarrow -\text{OCH}_3 \rightarrow \text{C-O-C} \rightarrow \text{C=O}$ . This sequence is in good conformity with the results obtained from PCMW. It reveals that during heating the dehydration of hydrophilic side chains takes place before the dehydration of hydrophobic carbonyl groups and backbones, and the conformation changes of C-H groups in side chains have a more significant effect on the phase transition than the abruption of hydrogen bonds between ether oxygen groups and water molecules. In other words, the driving force of the self-aggregation process of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) should be the dehydration of side chains. Obviously, the conformation changes of oxyethylene side chain groups along with the dehydration process play a key role in the formation of micelles as the starting point.

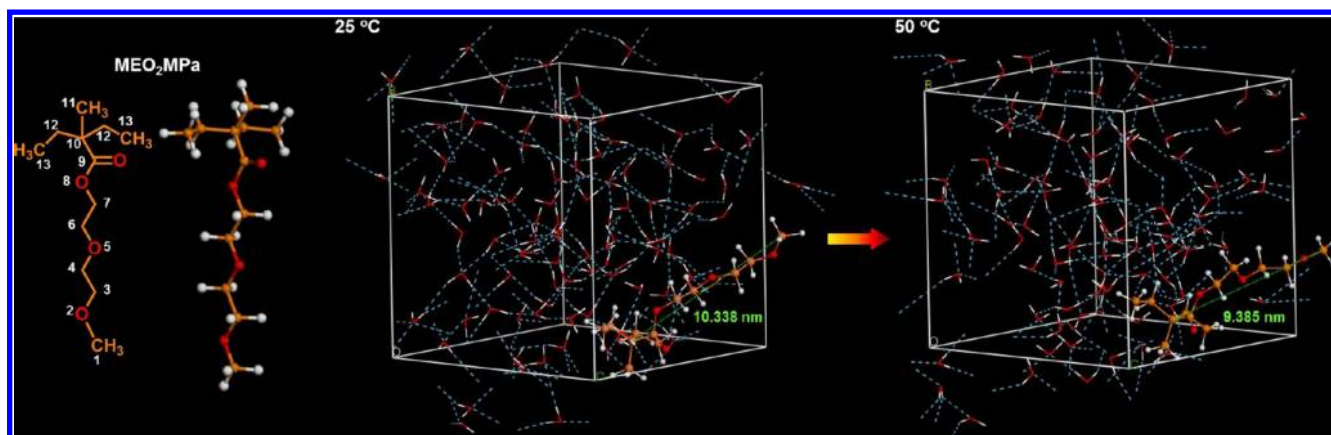
On the other hand, if we only consider C-H stretching modes of side chains, an interesting sequence can be found that the asymmetric stretching vibration has an earlier response than the symmetric stretching vibration, no matter for methyl or

methylene groups. As previously reported, the direction of asymmetric stretching vibration is parallel to the chain axis while that of symmetric stretching vibration is vertical to the chain axis.<sup>55</sup> Therefore, it is concluded that along with the dehydration process during heating oxyethylene side chains collapse first to get close to the hydrophobic backbones and then distort to expose hydrophilic ether oxygen groups to the “outer shell” of polymer chains as much as possible. Because of the disruption of the balance between hydrophobic and hydrophilic interactions, the individual dehydrated P-(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) chains tend to aggregate into more stable large micelles, corresponding to a sharp change below LCST. During this process the conformation of hydrophobic backbones with a slowest response does not change much, according to the absence of a precontraction process before phase transition as we observed in DLS measurements. Moreover, the cores in the just-formed micelles are only physically or loosely cross-linked by the “hydrogen bond bridges” between ether oxygen groups and water molecules. As temperature continuously increases above LCST, the length of “hydrogen bond bridges” is shortened, resulting in the continuous expelling of water or more densely aggregated micelles, which corresponds to a gradual change as shown in DLS, DSC, and frequency shift curves. For clarity, a schematic illustration was drawn to cover those dynamic changes of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) chains during heating, as depicted in Figure 10. In short, during the whole self-aggregation process, P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) chains successively experience “hydrated chains–dehydrated chains–loosely aggregated micelles–densely aggregated micelles” four consecutive conformation changes.

Similarly, the sequence order for the cooling process of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in D<sub>2</sub>O can be deduced as follows ( $\rightarrow$  means prior to or earlier than): 2862 cm<sup>-1</sup>  $\rightarrow$  1080 cm<sup>-1</sup>  $\rightarrow$  2821 cm<sup>-1</sup>  $\rightarrow$  2837 cm<sup>-1</sup>  $\rightarrow$  3000 cm<sup>-1</sup>  $\rightarrow$  2922 cm<sup>-1</sup>  $\rightarrow$  1103 cm<sup>-1</sup>  $\rightarrow$  2947 cm<sup>-1</sup>  $\rightarrow$  1716 cm<sup>-1</sup>  $\rightarrow$  2889 cm<sup>-1</sup>  $\rightarrow$  2978 cm<sup>-1</sup>  $\rightarrow$  1732 cm<sup>-1</sup>, or  $\nu_{\text{s}}(\text{CH}_3)(-\text{OCH}_3)(\text{hydrated}) \rightarrow \nu(\text{C-O-C})(\text{hydrated}) \rightarrow \nu_{\text{s}}(\text{CH}_2)(-\text{OCH}_2\text{CH}_2\text{O}-)(\text{hydrated}) \rightarrow \nu_{\text{s}}(\text{CH}_2)(-\text{OCH}_2\text{CH}_2\text{O}-)(\text{dehydrated}) \rightarrow \nu_{\text{as}}(\text{CH}_3)(-\text{OCH}_3)(\text{dehydrated}) \rightarrow \nu_{\text{as}}(\text{CH}_2)(\text{backbone}) \rightarrow \nu(\text{C-O-C})(\text{dehydrated}) \rightarrow \nu_{\text{as}}(\text{CH}_2)(-\text{OCH}_2\text{CH}_2\text{O}-)(\text{hydrated}) \rightarrow \nu(\text{C=O})(\text{hydrated}) \rightarrow \nu_{\text{s}}(\text{CH}_3)(-\text{OCH}_3)(\text{dehydrated}) \rightarrow \nu_{\text{as}}(\text{CH}_3)(\text{backbone}) \rightarrow \nu(\text{C=O})(\text{dehydrated})$ . Although PCMW results show that during cooling all the groups of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) have a relatively cooperative

**Figure 10.** Schematic illustration of the dynamic self-aggregation and self-disaggregation mechanism of P(MEO<sub>2</sub>MA-*co*-OEGMA<sub>475</sub>) in water during heating and cooling.





**Figure 11.** Left: chemical structure of MEO<sub>2</sub>MPa. Right: the initial and final structures of the MEO<sub>2</sub>MPa/water amorphous cell at 25 and 50 °C, respectively, after molecular dynamics run (100 K steps) at NVT conditions. Red represents O atoms; white, H atoms; and orange, C atoms. Blue dotted lines represent the hydrogen bonds.

response, 2DCOS can still discern the subtle sequence order taking place. Without considering the differences in stretching modes, the sequence can be described as  $-\text{OCH}_3 \rightarrow \text{C}-\text{O}-\text{C} \rightarrow -\text{OCH}_2\text{CH}_2\text{O}- \rightarrow \text{CH}_2$  (backbone)  $\rightarrow \text{C}=\text{O} \rightarrow \text{CH}_3$  (backbone). Obviously, the conformation changes of oxyethylene side chains along with the hydration process still have an earlier response than hydrophobic backbones, indicating a dominating role of side chains during the whole self-aggregation and self-disaggregation process. In contrary to the heating process, during cooling the revival of collapsed side chains is driven by the group motions of free terminal  $-\text{OCH}_3$  groups and the elongation of the “hydrogen bond bridges” until a complete abrupton below LCST. On the other hand, merely considering the C–H stretching modes of side chains, we can find that the symmetric stretching vibration has an earlier response than the asymmetric stretching vibration, no matter for methyl or methylene groups. It suggests that during cooling the conformation changes of oxyethylene side chains are just opposite to the heating process; in other words, along with the hydration process during cooling collapsed oxyethylene side chains first distort to get in contact with more water molecules leading to more hydrophilic chains and then extend to get away from the hydrophobic backbones. Therefore, as shown in Figure 9, the self-disaggregation process of P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) during cooling can be roughly considered to be the inverse process of the self-aggregation process during heating, which may explain the good thermal reversibility of POEGMA chains.

**3.6. Molecular Dynamics Simulation.** To further confirm the proposed mechanism in Figure 10, especially the dominating role of oxyethylene side chains, we performed molecular dynamics simulation. Similar to previous DFT calculations,<sup>37,38</sup> we also chose 2-(2-methoxyethoxy)ethyl 3-methyl-3-pentanoate (MEO<sub>2</sub>MPa, chemical structure as shown in Figure 11) to be a model compound to represent P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) chains. An amorphous cell consisting of one MEO<sub>2</sub>MPa and 94 water molecules was constructed at 25 °C. Hydrogen bonding was defined using a set of geometric criteria:  $r_{\text{O}\cdots\text{H}} < 2.6 \text{ \AA}$ ,  $\angle \text{O}-\text{H}\cdots\text{O} > 150^\circ$ .<sup>56</sup> Then molecular dynamics run at NVT (constant particle number, volume, and temperature) conditions at 50 °C was carried out for 100 K steps (1 fs each). The initial and final optimized structures of the MEO<sub>2</sub>MPa/water amorphous cell are presented in Figure 11.

After a long enough time of molecular dynamics run at a much higher temperature, the conformation of MEO<sub>2</sub>MPa and hydrogen bonds in the system changed. We calculated the hydrogen bonding interaction energy between MEO<sub>2</sub>MPa and water molecules at 25 and 50 °C, respectively, as shown in Table 2. After molecular dynamics run at 50 °C, the hydrogen

**Table 2. Simulated Hydrogen Bonding Interaction Energy between MEO<sub>2</sub>MPa and Water and Valence Energy of MEO<sub>2</sub>MPa at 25 and 50 °C**

		energy (kcal/mol)	
		25 °C	50 °C
hydrogen bonding energy	MEO <sub>2</sub> MPa + water	−361.9	−363.2
	water	−334.5	−356.3
	MEO <sub>2</sub> MPa	0	0
	interaction	−27.4	−6.9
valence energy	MEO <sub>2</sub> MPa	53.3	66.7

bonding interaction energy between MEO<sub>2</sub>MPa and water molecules is nearly 4 times reduced, indicating a strong dehydration process of MEO<sub>2</sub>MPa. The conformation of MEO<sub>2</sub>MPa becomes collapsed or distorted, which can be judged from either the distance between C1 and C10 (from 10.338 to 9.385 nm as shown in Figure 11) or by the valence energy of MEO<sub>2</sub>MPa (from 53.3 to 66.7 kcal/mol). The molecular dynamics simulation results primarily support our proposed mechanism by 2DCOS that upon heating the dehydration of oxyethylene side chains would collapse first to get close to the hydrophobic backbones.

#### 4. CONCLUSION

In this paper, we attempt to explore the dynamic self-aggregation and self-disaggregation mechanism of thermoresponsive POEGMA chains in water during heating and cooling by a combination method of DLS, DSC, <sup>1</sup>H NMR, IR spectroscopy, and molecular dynamics simulation. The mostly investigated P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) was chosen as the studied object with a predicted LCST value of 31.1 °C. As stated by DLS and DSC, P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) exhibits a phase transition with a sharp change below LCST and a gradual change above LCST, which is largely different from PNIPAM but very similar to PVCL. P(MEO<sub>2</sub>MA-co-OEGMA<sub>475</sub>) chains would continuously expel water molecules

or dehydrate even after the phase transition, and the apparent phase transition is found to be mainly arising from the multiple chain aggregation without a precontraction process of individual polymer chains. According to temperature-variable  $^1\text{H}$  NMR analysis, the phase separation degree of  $\text{P}(\text{MEO}_2\text{MA-co-OEGMA}_{475})$  is rather lower than that of PNIPAM. FT-IR analysis further confirmed our results and find that the self-aggregation process of  $\text{P}(\text{MEO}_2\text{MA-co-OEGMA}_{475})$  is dominated by the conformation changes of side chains. PCMW additionally determined the phase transition temperature to be ca.  $32.5^\circ\text{C}$  during heating and ca.  $31^\circ\text{C}$  during cooling, as well as the transition temperature ranges to be  $30.5\text{--}37^\circ\text{C}$  during heating and  $28.5\text{--}33^\circ\text{C}$  during cooling. Finally, 2DCOS was employed to elucidate the thermally reversible dynamic hydration mechanism of  $\text{P}(\text{MEO}_2\text{MA-co-OEGMA}_{475})$  chains, which successively experience "hydrated chains—dehydrated chains—loosely aggregated micelles—densely aggregated micelles" four consecutive conformation changes during the self-aggregation process. The driving force of the self-aggregation process should be the dehydration of side chains, which collapse first to get close to the hydrophobic backbones and then distort to expose hydrophilic ether oxygen groups to the "outer shell" of polymer chains as much as possible. The collapse and dehydration of oxyethylene side chains to get close to the hydrophobic backbones during heating have also been supported by molecular dynamics simulation. During cooling all the groups of  $\text{P}(\text{MEO}_2\text{MA-co-OEGMA}_{475})$  have a relatively cooperative response but can still be roughly considered to be the inverse process of the self-aggregation process during heating, which may explain the good thermal reversibility of POEGMA chains.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

Temperature variable  $^1\text{H}$  NMR spectra of PNIPAM in  $\text{D}_2\text{O}$  as well as the operation details of the sequence order determination during heating and cooling. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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