Role of Bound Water and Hydrophobic Interaction in Phase Transition of Poly(*N*-isopropylacrylamide) Aqueous Solution

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ABSTRACT: It has been suggested that the phase transition of the poly(*N*-isopropylacrylamide) (PNiPAM) aqueous solution consists of at least two different processes: (1) a rearrangement of bound water around either hydrophobic or hydrophobic and hydrophilic group of PNiPAM and (2) a hydrophobic association of the hydrophobic groups in the PNiPAM chains or a residual interaction between the PNiPAM side chain residues. However, a single endothermic peak does not provide direct evidence for this suggestion. This study shows that the phase transition in PNiPAM aqueous solution comprises at least two processes by using temperature modulated differential scanning calorimetry. The single endothermic peak is separated into an endothermic and exothermic peak, and the heats from these peaks depend on the applied frequency. Curve fitting to experimental data interprets the transition mechanism of the PNiPAM aqueous solution in more detail, and the results and the limitation of the curve fitting are discussed.

Introduction

Hydrophobic effects in water medium play an important role in stabilizing the cell membrane and protein structure. The hydrophobic interaction drives the association of micelles and stabilizes the globular structure of proteins.[1] Unlike the van der Waals forces of nonpolar molecules, the hydrophobic interaction has been considered a complex result of the tendency of hydrophobic molecules to minimize the interface with water molecules and the corresponding entropy change of water molecules around the hydrophobic group.[2,3] At low temperatures, some protein structures are completely denatured because of the hydration of their hydrophobic groups,[4,5] and the water molecules around the hydrophobic group are referred to as water cages or as a clathrate-like water.[5−7]

This hydrophobic effect is also very important in the lower critical solution temperature (LCST) behavior of polymer aqueous solutions. A typical example showing the LCST behavior is a poly(*N*-isopropylacrylamide) (PNiPAM) aqueous solution, and it is well-known that the phase transition of the PNiPAM aqueous solution takes place at about 30 °C.[8−14] Since the concept of "water cage" around the isopropyl group in the PNiPAM side chain was introduced by Saito et al.[8,9] and Kim et al.,[10] PNiPAM has been suggested to have two types of bound water.[8−13] One is the water cage around the hydrophobic moiety, and the other is the bound water around the amide group (Figure 1).

Although the role of water cages in the PNiPAM aqueous solution has been controversial, many researchers seem to believe that the water cages are involved in the phase transition of the PNiPAM aqueous solution.[8−11,13,14] Otake et al.[8] interpreted their calorimetric data by using the illustration by Nemethy and Sheraga[15] and explained that the phase transition of the PNiPAM aqueous solution is a complex result of the change of water structure around the hydrophobic group and the changes in the state of the hydrophobic side

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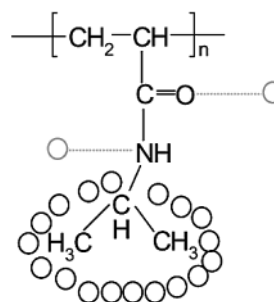
Figure 1. Chemical structure of PNiPAM and water structures around the PNiPAM chain below LCST, as suggested by other literature.[8−14] The waters around the isopropyl group of the PNiPAM residue are known to have well-ordered structures, and these kinds of water are called "water cages" or "water clathrates".[5−11,13−15]

chains. Shibayama et al.[11] and Ebara et al.[14] explained that the phase transition is the result of dissociation of water molecules around the hydrophobic groups of the PNiPAM chain. Recently, Grinberg et al.[13] suggested that the phase transition of the PNiPAM hydrogel consists of three different heats: the heat from apolar dehydration, polar dehydration, and the residual heat caused by the strong interactions (van der Waals or H-bonding interactions) of the residues of the PNiPAM chain.

Despite the suggested mechanisms that the phase transition of the PNiPAM aqueous solution consists of at least two different processes, there is a lack of experimental data that prove these mechanisms. Calorimetric methods have mostly been used to explain the phase transition phenomenon of the PNiPAM aqueous solution, but a single endothermic peak during the phase transition makes it difficult to provide a direct evidence for the above mechanisms.

In this article, we tried to show that the phase transition of the PNiPAM aqueous solution consists of at least two different processes by using temperature modulated differential scanning calorimetry (TMDSC). It has been reported that TMDSC is used to resolve the heat which is related to complex processes, i.e., separat-

ing the melting and crystallization peak of the semi-cryastalline polymers.[16,17] Using this technique, it is expected that the single endothermic peak could be separated if there are at least two different thermal relaxation processes, as suggested by many investigators.[8,9,13] We used curve fitting to the experimental data in order to obtain detailed information about the phase transition of the PNiPAM aqueous solution. We discussed our experimental data, commented on the limitation of the curve-fitting results, and compared our curve-fitting results with literature data.

Experimental Section

PNiPAM Synthesis. PNiPAM was synthesized by conventional free radical polymerization. The monomer was purified twice by recrystallization in hexane. It was then polymerized using 2,2′-azobis(isobutyronitrile) initiator in tetrahydrofuran (THF) at 70 °C for 12 h under the flow of excess nitrogen. This polymer solution was purified by transferring it to an excess of diethyl ether, and the procedure was repeated twice for further purification. Gel permeation chromatography result (THF at 40 °C) shows that the synthesized Pnipaam has M_n = 64 800 with a polydispersity index of 2.67.

TMDSC Experiment. The principle of TMDSC is basically the same as the conventional DSC except that the temperature is increased in a sinusoidal fashion, as shown in the following equations:

$$T(t) = T_0 + \beta_0 t + A \sin \omega t$$

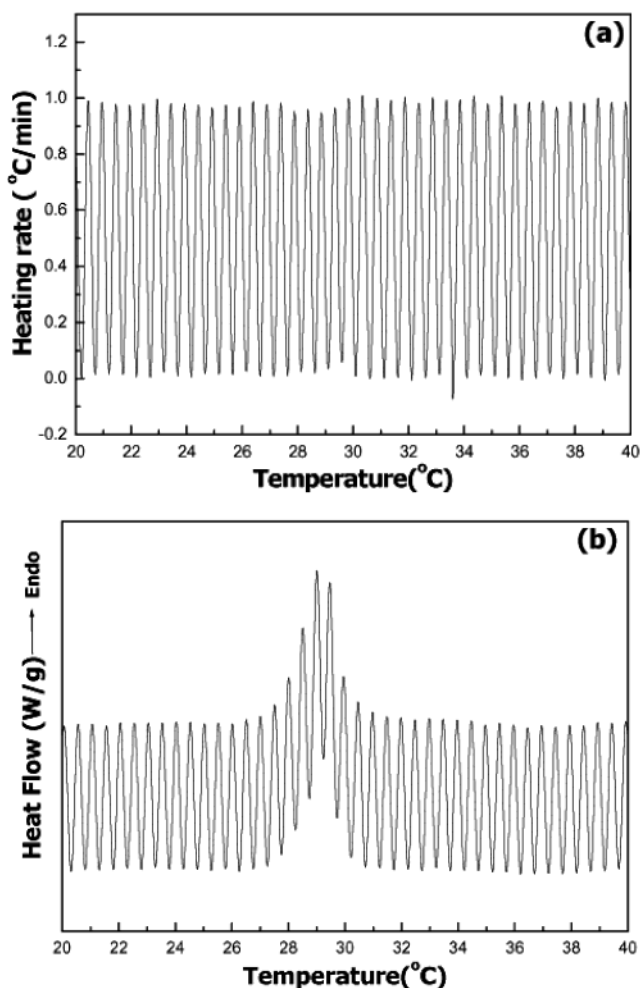$$\frac{dT(t)}{dt} = \beta_0 + A\omega \cos \omega t \qquad (1)$$

where ω is the angular frequency ($=2\pi f$) and A is the temperature amplitude. The measured heat flow (Φ) is an underlying component (Φ_u) related to the conventional DSC signal, which is superimposed by a periodic component (Φ_p).

$$\Phi = \Phi_u + \Phi_p \qquad (2)$$

Figure 2 shows the temperature oscillation to the PNiPAM aqueous solution and corresponding heat flow response of this system. The periodic component of the heat flow could be written as complex form if a system shows a dynamic thermal response:[18]

$$\Phi_p = A\omega \left(C_{p,x} + \frac{1}{1 + \omega^2\tau^2}\Delta H\left(\frac{dX}{dT}\right)_{T=T_0} \right) \cos \omega t +$$
$$A\omega \left(\frac{\omega\tau}{1 + \omega^2\tau^2}\Delta H\left(\frac{dX}{dT}\right)_{T=T_0} \right) \sin \omega t \quad (3)$$

where $C_{p,x}$ is the static heat capacity, which is time independent because this results from the fast molecular motion of the system. X is the degree of transformation if the thermal event occurs in a system, i.e., phase transition in this system. τ is the relaxation time of transformation of a process or the time required for a process to thermally equilibrate. The expression in the first parentheses in eq 3 is a real part of heat capacity (C'), and the expression in the second parentheses is an imaginary part of heat capacity (C''). C' defines the heat capacity which responds to the thermal stimulus, and C'' is defined as the heat capacity which is shown in a long time later but not shown within the time scale of thermal change. The definition and concept of dynamic heat capacity (C' and C'') are well illustrated by Schawe[19] and Jeong[20] in their reviews. From above equations, the reversing (Φ_{rev}) and nonreversing (Φ_{non}) heat flows can be obtained by using the following equations:

Figure 2. Temperature oscillation to the PNiPAM aqueous solution and corresponding heat flow response of this system. (a) The sinusoidal heating rate is applied to the PNiPAM solution (15 wt %) with amplitude A and angular frequency ω ($=2\pi f$): $dT(t)/dt = \beta_0 + A\omega \cos \omega t$. (b) Then the thermal response of the PNiPAM solution is superimposed by two components: underlying heat flow and periodic part of heat flow, $\Phi = \Phi_u + \Phi_p$. From (b) and eq 4, the reversing and nonreversing heat flows can be obtained.

$$\Phi_{rev} = \beta_0 C^*, \quad C^* = \frac{Q_{amp}}{A} = \sqrt{C'^2 + C''^2} \qquad (4a)$$

$$\Phi_{non} = \Phi_u - \Phi_{rev} \qquad (4b)$$

where C^* is the complex heat capacity and Q_{amp} is the heat flow amplitude.

The terms "reversing" and "nonreversing" are written here following the notation of Gill et al.[16] The reversing heat represents the heat that is responsive to the applied frequency, and the nonreversing heat is the residual heat that is not responsive to the frequency. Therefore, these terms should not be confused with the real and imaginary part of the heat capacity and with the concepts of reversibility and irreversibility.

In the TMDSC experiments for the PNiPAM aqueous solution, 3, 5, and 15 wt % PNiPAM aqueous solutions were prepared. The temperature amplitude was ±0.08 °C, and the frequency (f) was in the range 0.1−0.01 Hz. The PNiPAM solution stored at 4 °C was filled in a sample pan and scanned from 0 to 60 °C with a heating rate of 0.5 °C/min. The instrument used in this experiment was a DSC 2910 (TA Instrument).
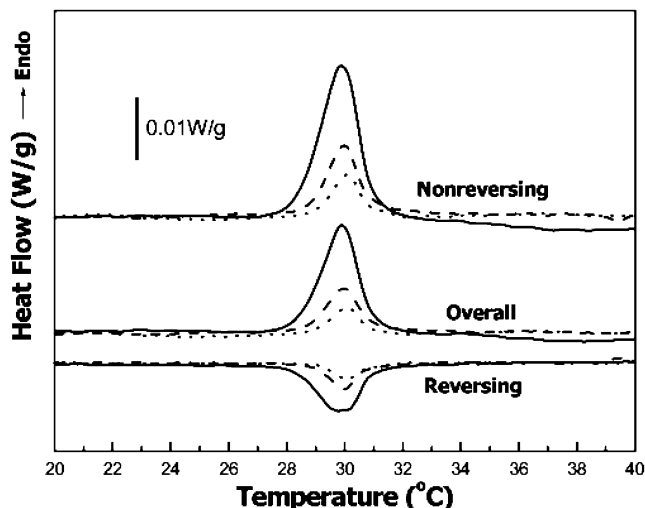
Figure 3. TMDSC thermogram for 3 (· · ·), 5 (- - -), and 15 wt % (—) PNiPAM solution. Heating rate is 0.5 °C/min, heat amplitude is ±0.08 °C, and frequency = 0.017 Hz.

Results and Discussion

TMDSC Thermograms for PNiPAM Aqueous Solution. Figure 3 shows the TMDSC thermograms for 3, 5, and 15 wt % PNiPAM aqueous solutions (f = 0.017 Hz). The overall heat flow is the same as the heat measured by the conventional DSC. However, it can be seen that the single endotherminc peak by the overall heat flow is separated into an endothermic peak (nonreversing heat flow) and an exothermic peak (reversing heat flow). These thermograms show the same pattern for all concentrations we tested. In Figure 3, it is clearly demonstrated that at least two different thermal relaxation processes are involved in the phase transition of the PNiPAM aqueous solution.

To clarify the origin of the peaks, it is necessary to characterize the processes involved in the phase transition. As suggested by Otake et al.,[8] the phase transition is induced by the change of water structure around the hydrophobic group and the association of the hydrophobic groups. Grinberg et al.[13] suggested that three different processes are involved in the phase transition: (1) polar dehydration, (2) apolar dehydration, and (3) strong interaction between the PNiPAM residues. The hydrogen bonds of water cages, water−polar group, and the waters around the polar group are known to be stronger than the bulk water.[4,12,21−24] Therefore, the heat required for the water to rearrange to bulk water is endothermic. The exothermic heat seems to be required for the intermolecular interaction between isopropyl groups or amide groups of the PNiPAM chain, as supported by the literature.[12,25,26]

One might think from this description that the nonreversing heat arises solely from the rearrangement of bound water to bulk water and that the reversing heat results solely from the hydrophobic association or the intermolecular interaction between the PNiPAM residues. However, it may be that one process contributes to both the reversing and the nonreversing heat unless at least two processes have a relaxation time much higher or lower than the frequency range we tested (0.1−0.01 Hz). Then it is expected that these heats change with the applied frequency, as shown in eq 3.

The above explanation is illustrated in Figure 4. We observed the variation of the reversing and the nonre-
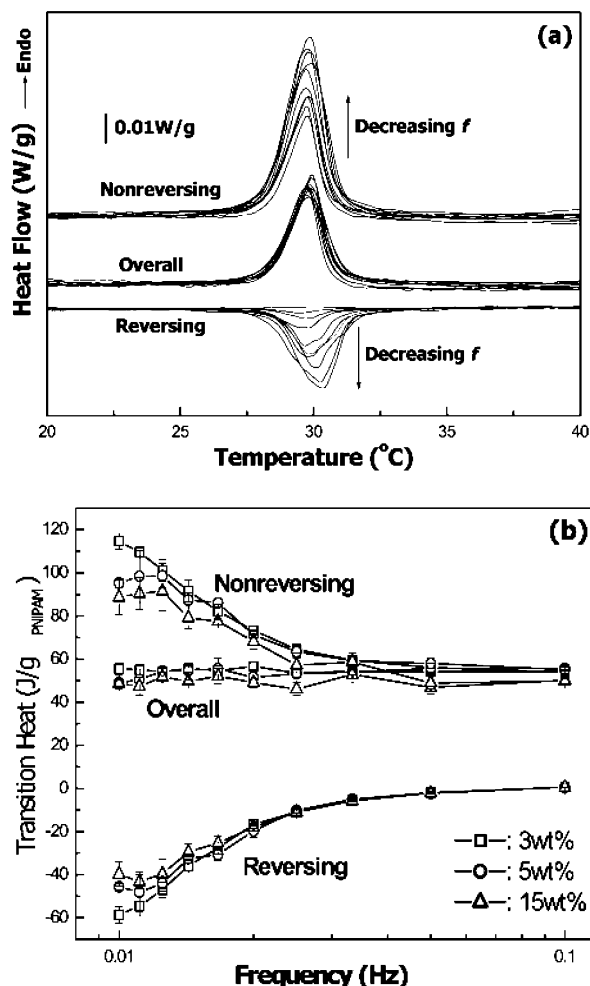

Figure 4. (a) Reversing, nonreversing, and overall heat flow thermograms as a function of the applied frequency, f, for 15 wt % PNiPAM aqueous solution. (b) Reversing, nonreversing, and overall transition heats as a function of f for 3, 5, and 15 wt % PNiPAM aqueous solutions.

versing heat flow by changing the applied frequency within the instrumental frequency range (f = 0.1−0.01 Hz). Figure 4a shows the reversing, nonreversing, and overall heat flows for the 15 wt % PNiPAM aqueous solution. As can be seen, the reversing and the nonreversing heats change with the frequency, but the overall heat remains constant for all frequencies (∼50 J/g$_{PNiPAM}$). Figure 4b shows that the reversing, nonreversing, and overall transition heats change for 3, 5, and 15 wt % PNiPAM aqueous solutions as a function of the applied frequencies. Although the magnitude of heat and the trends are little different for each concentration, it is evident that the reversing and the noreversing heats change when maintaining the same overall heats as frequency changes. These findings suggest that the reversing or nonreversing heat is not the contribution of a single process. However, the fact that one process contributes to both the reversing and nonreversing heat makes it difficult to obtain a detailed information about the process and to describe the transition mechanism of the PNiPAM aqueous solution.

Curve Fitting of Experimental Data. To overcome these difficulties, a curve fitting to the experimental data (Figure 5) was carried out for a wide range of angular frequencies. For the curve fitting, we used the equation suggested by Claudy and Vignon, as shown in eq 3.[18] However, the equation they derived is valid only
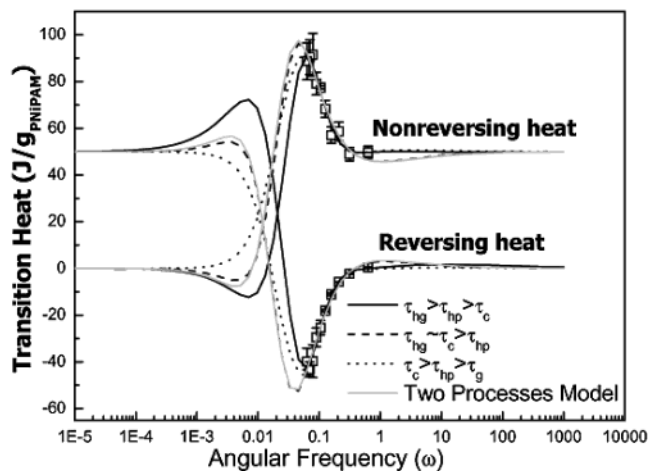
Figure 5. Example of curve fitting to experimental data (15 wt %) for $\Delta H_c = 400$ J/g$_{PNiPAM}$ and $\Delta H_{res} = -350$ J/g$_{PNiPAM}$ (two processes model) and $\Delta H_{hg} = 400$ J/g$_{PNiPAM}$, $\Delta H_{res} = -500$ J/g$_{PNiPAM}$, and $\Delta H_c = 150$ J/g$_{PNiPAM}$ (three processes model). The three processes model is grouped into three cases: $\tau_{hg} > \tau_{res} > \tau_c$, $\tau_{hg} \sim \tau_c > \tau_{res}$, and $\tau_c > \tau_{res} > \tau_{hg}$.

for the Debye-like relaxation. Since more than one type of molecular relaxations is possible for one process in a real system, we modified eq 3 by using a stretched exponent β[27] as follows:

$$\Phi_p = A\omega\left(C_{p,x} + \left(\frac{1}{1 + \omega^2\tau^2}\right)^\beta \Delta H\left(\frac{dX}{dT}\right)_{T=T_0}\right)\cos\omega t +$$
$$A\omega\left(\left(\frac{\omega\tau}{1 + \omega^2\tau^2}\right)^\beta \Delta H\left(\frac{dX}{dT}\right)_{T=T_0}\right)\sin\omega t \quad (5)$$

where β is a stretched exponent expressing the deviation from Debye relaxation with the value of $1-0$. When β reaches 1, the relaxation would assume a Debye-like form and eq 5 becomes eq 3. Since the change in $C_{p,x}$ is related to the baseline change before and after the transition (Figure 3), this change is negligible when a thermal event takes place. Therefore, when the transition is completed $((dX/dT)_{T=T_0 \gg T_{tr}} = 1)$ and the multi-processes are involved in the phase transition, the reversing and nonreversing heat can be expressed by using eqs 4 and 5:

$$\Delta H_{rev} \approx \sum_{i=hg,c,res} \Delta H_i\left[\left(\left(\frac{1}{1 + \omega^2\tau_i^2}\right)^{\beta_i}\right)^2 + \right.$$
$$\left.\left(\left(\frac{\omega\tau_i}{1 + \omega^2\tau_i^2}\right)^{\beta_i}\right)^2\right]^{1/2} \quad (6)$$

$$\Delta H_{non} \approx \sum_{i=hg,c,res} \Delta H_i\left(1 - \left[\left(\left(\frac{1}{1 + \omega^2\tau_i^2}\right)^{\beta_i}\right)^2 + \right.\right.$$
$$\left.\left.\left(\left(\frac{\omega\tau_i}{1 + \omega^2\tau_i^2}\right)^{\beta_i}\right)^2\right]^{1/2}\right) \quad (7)$$

Equations 6 and 7 assume that one relaxation process does not affect the other relaxation processes, and these types of expressions are similar to those described by Sato et al. in their dielectric study of an ethanol−water mixture.[28] Subscript $i = $ hg is defined as the process relating to the rearrangement of water molecules around

the amide group to bulk water, $i = $ c is the rearrangement of water cages to bulk water, and $i = $ res is the intermolecular interaction between the PNiPAM residues.

In this curve fitting, we assumed that the phase transition consists of "two" or "three" processes, based on the suggested mechanisms by Otake et al.[8] ("two" processes) and Grinberg et al.[13] ("three" processes) (the two processes model and the three processes model). In the two processes model, the phase transition consists of the rearrangement of cage waters around the isopropyl group to the bulk water ($i = $ c) and the hydrophobic association of the hydrophobic groups ($i = $ res). In the three processes model, the phase transition consists of the dehydration of the waters from the polar ($i = $ hg) and apolar ($i = $ c) group of the PNiPAM residue and the intermolecular interaction between the PNiPAM residues ($i = $ res).

Figure 5 exemplifies the results of curve fitting for the two and three processes model. From the dynamic point of view, these fitting curves seem to be reasonable. Since the system could not be thermally responsive to the applied frequency when $1/\tau \ll \omega$, the reversing heat approaches 0 and the nonreversing heat approaches the overall heat (~ 50 J/g$_{PNiPAM}$) as the frequency goes to the high frequency. The opposite situation is expected for $1/\tau \gg \omega$.

Limitation of Curve-Fitting Results. Before discussing the curve-fitting results of the TMDSC data, it is rational to comment on the limit of the curve-fitting results. As can be seen in Figure 5, both two and three processes model are well fitted to the experimental data. However, it is difficult to find the exact values of the parameter (β, τ, ΔH) for each process from this curve fitting. Instead, we can only obtain the broad value of β, τ, and ΔH (Table 1) because TMDSC in itself can cover the frequencies only 1 decade. The model fittings show a sinusoidal variation with frequency whereas the data are monotonic. Just where the fitting curve peaks the experimental data stop. Therefore, the data appear to cover too small a frequency range to be tested by the model, which covers 8 decades.

Despite the above difficulties, we found that each parameter has some ranges for good fitting. Therefore, the results of the curve fitting are expected to give a good chance to estimate the relaxation parameters and also to sketch a possible transition mechanism.

Stretched Exponent (β) and Relaxation Time (τ). We summarized the curve-fitting results for the two models in Table 1. In the three processes model, three cases are well fitted to the experimental data, whereas only one case is well fitted to the experimental data in the two processes model. The parameters obtainable from this curve fitting are β, τ, and ΔH, and these values are very broad because of the limitation mentioned in the previous section. For the stretched exponent, β, we cannot tell exactly whether these values are reasonable because of a lack of data to be compared. Zhu and Napper [29] reported that the β for the transition from extended chain to loopy coil of the PNiPAM chain on the polymer particle is $0.74-0.79$. Compared with their data with β_{res} for our case, which is closely related to the molecular motion of the PNiPAM chains, the two cases in the three processes model ($\tau_{hg} > \tau_{res} > \tau_c$ and $\tau_{hg} \sim \tau_c > \tau_{res}$) have reasonable values. For the relaxation time of each process, τ, all the cases range from a few seconds to 10^3 s, which is roughly consistent with the

Table 1. Curve-Fitting Results for the Experimental Data[a]

	model	three processes			two processes
		$\tau_{hg} > \tau_{res} > \tau_c$	$\tau_{hg} \sim \tau_c > \tau_{res}$	$\tau_c > \tau_{res} > \tau_{hg}$	
R^2		0.96−0.99	≥0.94−0.98	≥0.96−0.98	0.94−0.97
ΔH (J/g_{PNiPAM})	ΔH_{hg}	≥150−200	≥150−200	≥150	
	ΔH_c	≥70	≥70	≥90	≥300
	ΔH_{res}	≤−220	≤−220	≤−200	≤−250
β	β_{hg}	0.6−0.9	0.5−0.86	0.52−0.84	
	β_c	0.7−0.9	0.5−0.88	1	0.5−0.86
	β_{res}	0.7−0.9	1	0.5−0.84	1
τ (s)	τ_{hg}	33−1000	33−1000	5−10	
	τ_c	5−10	50−1000	50−1000	200−1000
	τ_{res}	13−33	20−50	8−20	20−50

[a] These results were summarized for all concentrations (3, 5, and 15 wt %). R^2 = root-mean-square of the fitting coefficient to the experimental data. Subscripts: hg = process relating to the rearrangement of water molecules around the amide group to bulk water; c = process relating to the rearrangement of water cages to bulk water; res = process relating to the intermolecular interaction between the PNiPAM residues. β = stretched exponent (dimensionless) expressing the deviation from Debye relaxation with the value of 1−0. Refer to eqs 5−7 in the text. τ = relaxation time of each process.

value by Zhu and Napper[30] and by Matuso and Tanaka[31] for the coil-to-globule transition of the PNiPAM and swelling and shrinking process of the PNiPAM hydrogel, respectively.

Transition Heat (ΔH). Let us first consider the heat for the rearrangement of water cages to bulk water, ΔH_c. In the two processes model, our results show that the heat for the rearrangement of water cages to bulk water, ΔH_c, needs at least 300 J/g_{PNiPAM}, which is equivalent to ~33.9kJ/mol based on the PNiPAM monomer unit. Compared with reported data, this value is higher than the heat suggested by Grinberg et al. (79 J/$g_{polymer}$)[13] and the heat required for the rearrangement of water cages around propane (7.9−22.5 kJ/mol).[21−23,32,33] From a comparison of our data with the above references, it is suggested that the other types of water molecules (water around a hydrophilic group) can be involved in the phase transition.

In the three processes model, our results showed that ΔH_c requires at least 70 J/g_{PNiPAM} (~7.9 kJ/mol), which is very close to reported data.[13,21−23, 32,33] On the other hand, the heat for the rearrangement of bound water around the hydrophilic group to the bulk water, ΔH_{hg}, needs at least 150−200 J/g_{PNiPAM} (17−22.6 kJ/mol). It is reported that 9−12 kJ/mol is required to form hydrogen bonds between C=O, N−H, and water molecules.[12,26] Tamai et al. reported that there are two kinds of bound water around the hydrophilic group of the PNiPAM chain: water directly hydrogen bonded with the amide group and water just around the amide group with a different energy state from bulk water.[12] When considering these types of water, on the basis of the data in ref 12, it is calculated that ΔH_{hg} about 18.7 kJ/mol is required to totally rearrange the bound water around the hydrophilic group to bulk water.

The ΔH_{hg} calculated by Grinberg et al. (polar dehydration)[13] requires 400 J/g_{PNiPAM} (45.3 kJ/mol of PNiPAM monomer unit). This value is higher than our lower limit (150−200 J/g_{PNiPAM}) and reported values (18.7 kJ/mol).[12] The different values of ΔH_{hg} in these references make it difficult to interpret our result. On the basis of the heat calculated from the data by Tamai et al. (18.7 kJ/mol),[12] our data (17−22.6 kJ/mol) might suggest that the water molecules around the hydrophilic group are totally restructuring to bulk water. In contrast, comparison of our result (150−200 J/g_{PNiPAM}) with the value suggested by Grinberg et al. (400 J/g_{PNiPAM}) gives a possibility that a part of water molecules around the hydrophilic group still remains after the phase transi-

tion. Suetoh and Shibayama[11] explained that a considerable amount of bound water still remains after the phase transition on the basis of their calculation. This suggestion supports the idea that the shape of PNiPAM after the phase transition is not a compact globular form, but a molten globular form, as suggested by Tiktopulo et al.[34,35]

ΔH_{res}, the heat for the hydrophobic association of the PNiPAM chains or the intermolecular interactions between the PNiPAM residues, has at least −250 J/g_{PNiPAM} (−28.4kJ/mol in the two processes model) and −200 J/g_{PNiPAM} (−22.6 kJ/mol in the three processes model) from curve fittings. Although our results cover the heat calculated by Grinberg et al. (−440 J/g_{PNiPAM}, −49.8 kJ/mol),[13] the lower limits are smaller than their value.

Grinberg et al. commented that the residual heat is related to the cooperative interactions of the residues in the collapsed state, and these interactions are most likely of van der Waals type although those caused by hydrogen bonding cannot be excluded. It is expected that an intermolecular hydrogen bond would form between the amide groups from which the water molecules are displaced. From our results, however, it is hard to tell which factor (van der Waals or intermolecular hydrogen bond between PNiPAM chains) is the major contributor to ΔH_{res} because it is not exactly known how many water molecules around an amide group are displaced. It is thought that the degree of contribution of the intermolecular hydrogen bond to ΔH_{res} depends on the number of water molecules displaced from amide group of the PNiPAM chain.

Summary and Conclusions

We showed by using TMDSC that the phase transition of the PNiPAM aqueous solution consists of at least two different thermal processes. This was achieved by resolving the single endothermic heat, which is shown in conventional calorimetry, into an endothermic and an exothermic peak, and these heats changed in response to the applied frequency to the PNiPAM aqueous solution. We tried curve fitting to the experimental data in order to predict a transition mechanism of the PNiPAM aqueous solution by using "two" and "three" processes models. However, we could not obtain an exact value of the transition heat (ΔH) for each process from this curve fitting because TMDSC can cover only 1 decade ($10^{-1}−10^{-2}$ Hz). Instead, we obtained the transi-

tion heats with broad values. Analyzing our data within this limitation, we summarized as follows:

Comparison of our data with reported values showed that the three processes model seems more realistic than the two processes model because the heat for the rearrangement of water cages to bulk water is higher than the reported value. This implies that the phase transition does not seem to occur only by restructuring the water molecules around the hydrophobic group in the PNiPAM chain. Instead, in the three processes model, the water molecules around the hydrophilic group also rearrange to bulk water, although it is not known how much portion of these water molecules participate in this process. It is also thought that the intermolecular interaction between the PNiPAM chains is not attributable only to hydrophobic association of the hydrophobic groups. Some of the intermolecular hydrogen bonds between the amide groups can also contribute to this heat, and the hydrogen bond would form between the sites where the water molecules are displaced from the amide groups. But it is still uncertain which factor is the dominant contributor to the heat of the intermolecular interaction between the PNiPAM chains, ΔH_{res}. To precisely describe the phase transition of the PNiPAM aqueous solution, our current results should be compared with the PNiPAM aqueous solution with different molecular weights (also with narrow molecular weight distribution), and more advanced relaxation techniques should be required.

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