

# Energetics and Mechanisms of poly(*N*-isopropylacrylamide) Phase Transitions in Water–Methanol Solutions

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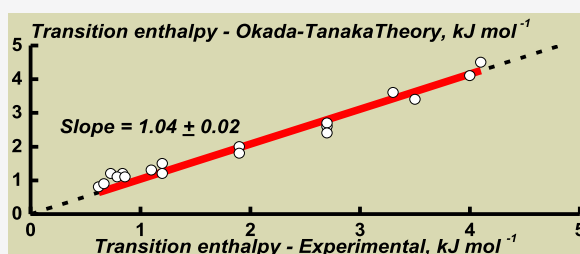
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**ABSTRACT:** The phase transitions of poly(*N*-isopropylacrylamide) (PNIPAM) in water–methanol mixed solutions were studied in detail by high-sensitivity differential scanning calorimetry. From this study, the dependences of the transition temperature, enthalpy, heat capacity increment, and width on the methanol molar fraction ( $x_{\text{MeOH}}$ ) were obtained. The transition temperature passed through a minimum at the methanol molar fraction  $x_{\text{MeOH}}^* \sim 0.35$ . At  $x_{\text{MeOH}} < x_{\text{MeOH}}^*$ , the transition enthalpy decreased quickly with the methanol content and became so small that it could not be measured, even with an increase in the polymer concentration by a hundred times (up to 150 mg mL<sup>-1</sup>).

Furthermore, over this  $x_{\text{MeOH}}$  range, the transition heat capacity increment being negative remained practically constant, but the transition width sharply increased. The transition thermograms were quantitatively described by the Okada–Tanaka theory, which takes into account the role of the polymer–solvent interaction cooperativity in the polymer thermoresponsivity. In terms of this approach, it is assumed that over the defined range of methanol content, PNIPAM possesses the cooperative hydro-solvation structure in the form of water–methanol complexes. The energetics of this structure smoothly decreases with the increase in the methanol content up to a complete disappearance of the structure at  $x_{\text{MeOH}} > x_{\text{MeOH}}^*$ . In this range of the methanol content, the phase behavior of PNIPAM seems to be dictated by regularities typical of polymer solutions in organic solvents, that is, how the Flory–Huggins parameter depends on temperature.



## INTRODUCTION

Solutions of poly(*N*-isopropylacrylamide) (PNIPAM) in the water–methanol mixed solvents revealed a paradoxical phase behavior. Individually, both water and methanol are good solvents for PNIPAM at definite temperatures, for example, below 30 °C. However, this mixture behaves as a poor solvent for PNIPAM under these conditions. The key aspects of this non-ordinary phenomenon known as co-nonsolvency were thoroughly reviewed by Scherzinger et al.<sup>1</sup> In particular, the dependence of the PNIPAM phase transition temperature on the methanol mole fraction ascertained by consistent data of different experimental techniques can be recognized as a reliable fact in this field. In contrast, the energetics of this transition was considered rather superficially. Despite numerous theoretical approaches that have been developed to date for the description of the co-nonsolvency phenomenon,<sup>2–13</sup> nobody has analyzed the energetics of the phase transition of PNIPAM in the water–methanol mixed solutions.

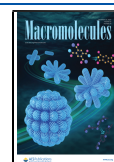
The cooperative nature of polymer–solvent interactions in the water–methanol solutions of PNIPAM was taken into account in the work by Tanaka et al.<sup>14</sup> Based on the conception of cooperative polymer–solvent interactions, which was earlier developed by Okada and Tanaka<sup>15,16</sup> for the description of the phase behavior of the PNIPAM aqueous

solution, Tanaka et al.<sup>14</sup> considered the competitive cooperative binding of water and methanol to identical sites of the polymer matrix. As a result of such reactions, there is a coexistence of independent sequences of bound molecules consisting of water and methanol. Such a combination of independent fragments of the hydration and solvation structures, the relative size of which depends on the mixed solvent composition, is considered as the decisive motif of the unusual phase behavior of PNIPAM in the water–methanol mixed solvent. This theoretical approach allows one to reproduce quantitatively a non-trivial trend of the cloud-point temperature of the system. The cloud-point temperature goes through a minimum upon the increase in the methanol concentration. The theory enables one to calculate the dependences of hydration and solvation degrees on temperature and the methanol concentrations. Therefore, it is of great interest to acknowledge this information for simulations of the

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differential scanning calorimetry (DSC) data<sup>17,18</sup> for this specific system.

It should be recognized that almost all known conceptions on the nature of the PNIPAM co-nonsolvency in water–methanol mixed solvents were mainly based on the experimental dependences of the phase separation temperature of PNIPAM solutions in these solvents on the methanol content. It seemed to us that these conceptions could not be considered as convincing enough without precise data on the energetics of the PNIPAM phase transitions in water–methanol mixed solvents. Here, it would be reasonable to underline that the first study of the PNIPAM phase transition in water–methanol mixed solutions by DSC was undertaken in 1991 by Schild et al.<sup>19</sup> However, because of the insufficient sensitivity of the scanning calorimeter used, it was possible to determine only the transition temperatures from the PNIPAM transition thermograms at the different methanol concentrations but not the transition enthalpy. Using extensive molecular dynamics simulations, Dalgicdir et al.<sup>20</sup> have calculated the coil-to-globule transition enthalpy of PNIPAM in the water–methanol mixed solutions as a function of the methanol molar fraction. They found that it goes through a minimum at the methanol molar fraction of about 0.2 but exceeds several times the transition enthalpy of PNIPAM in neat water at a methanol molar fraction of about 0.6. As we will show below, this last result is in obvious contradiction with the calorimetric data.

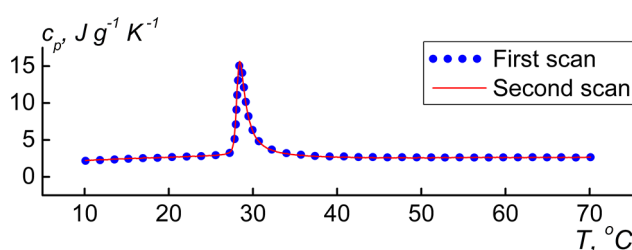
Therefore, we carried out a detailed study of these transitions in water–methanol mixed solvents of variable compositions at different polymer concentrations using high-sensitivity differential scanning calorimetry.<sup>21</sup> The dependences of the transition temperature, enthalpy, heat capacity increment, and width on the methanol concentration were obtained. The experimental data were considered in terms of the recent co-nonsolvency theory by Tanaka et al.<sup>14</sup> and the Okada–Tanaka model<sup>15</sup> developed originally to analyze cooperative effects in the hydration of macromolecules.

## EXPERIMENTAL SECTION

PNIPAM ( $M_n = 126,000$ ,  $M_v = 151,000$ , PDI 4.2) was obtained from Polymer source Inc., (sample #P6670-NIPAM). Methanol for HPLC and UHPLC and spectrophotometry (Baker), and water purified by reverse osmosis (Elix 3 Milli-Q Synthesis Water Purification Systems, Millipore) with a resistivity of  $18.2 \text{ M}\Omega \text{ cm}^{-1}$  were used.

The water–methanol mixed solvents of different methanol content were prepared by weight. The polymer was dissolved in a mixed solvent of the defined composition also by weight at room temperature. The obtained polymer solution was kept at  $-10 \text{ }^\circ\text{C}$  overnight and then placed into a water bath with a temperature between  $36$  and  $40 \text{ }^\circ\text{C}$  for  $5 \text{ min}$ . An aliquot of this solution was transferred into the sample cell of the calorimeter DASM-4 or DASM-4A (NPO “BioPribor”, Russian Federation) at the same temperature. The calorimeter was precooled down to  $-6 \text{ }^\circ\text{C}$  for  $\sim 1 \text{ h}$ , and then, the scanning experiment was performed over the temperature range from  $-3$  to  $70 \text{ }^\circ\text{C}$ . The preliminary calorimetric experiments were carried out with the heating rates  $1$ ,  $2$ , and  $4 \text{ K min}^{-1}$ . They showed that the results of the experiments did not depend on the heating rate. Therefore, the main part of the calorimetric experiments was done at a heating rate of  $1 \text{ K min}^{-1}$ . As a rule, two repeated scans were used in each experiment. Their results were not distinguished within the experimental limits. As an example, the apparent partial heat capacity functions ( $c_p(T)$ ) of PNIPAM at  $x_{\text{MeOH}} = 0.059$  calculated from the first and second scan data are compared in Figure 1.

The primary DSC data processing and conversion of the apparent partial heat capacity function of PNIPAM  $c_p(T)$  into the excess heat



**Figure 1.** Apparent partial heat capacity of PNIPAM in the water–methanol mixed solvent at  $x_{\text{MeOH}} = 0.059$ .

capacity function of the phase transition  $c_p^E(T)$  was performed by the Nairta 2.0 software (A.N. Nesmeyanov Institute of Organoelement Compounds). The transition baseline was produced by the spline interpolation between the pre- and post-transition linear segments of the  $c_p(T)$  function. The  $c_p^E(T)$  function was obtained by subtraction of the baseline from the  $c_p(T)$  function. The temperature of the maximum of the excess heat capacity function was taken as the transition temperature,  $T_t$ . The transition enthalpy,  $\Delta_t h$ , was determined by the integration of the excess heat capacity function. The transition heat capacity increment,  $\Delta_t c_p$ , at the transition temperature was calculated as a difference in the apparent partial heat capacities of PNIPAM in the post- and pre-transition states extrapolated to the transition temperature. The transition width,  $\Delta_t T$ , was determined as a ratio of the transition enthalpy to the maximal height of the excess heat capacity function,  $c_p^E(T_t)$ .

The cloud point temperatures of the PNIPAM solutions in the mixed water–methanol solvents were determined by light scattering using a Malvern Zetasizer Nano-ZS (Malvern Instruments Ltd, UK) or by visual observation of the solutions upon heating with a constant rate of  $1 \text{ K min}^{-1}$ .

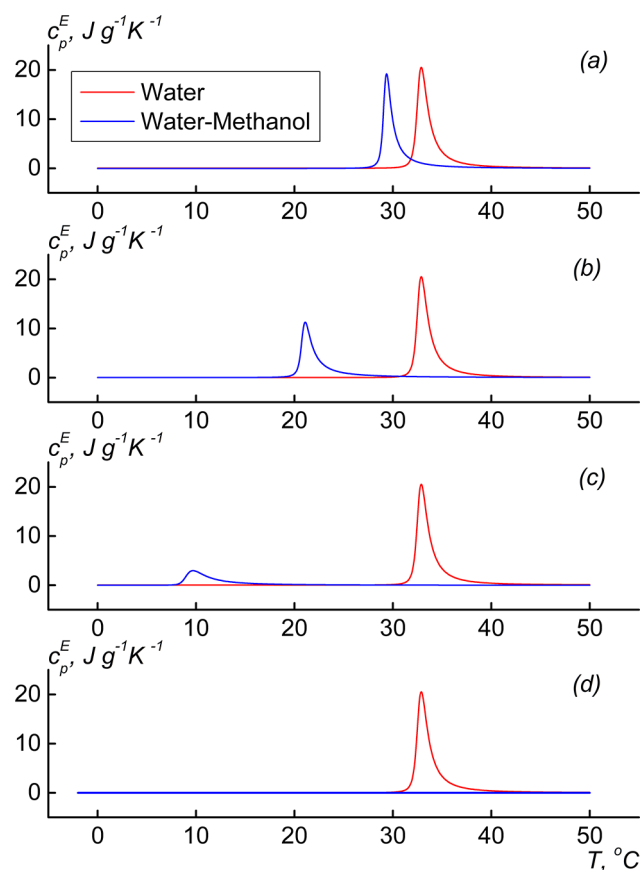
## RESULTS AND DISCUSSION

The reproducible transition thermograms of PNIPAM were obtained for a methanol content range  $x_{\text{MeOH}} = 0-0.25$ . Figure 2 provides an insight into the evolution of the transition thermograms of PNIPAM upon an increase in the methanol content. We see that the thermograms shift to lower temperatures, decrease in height, and significantly broaden, yet still conserve the main features of the PNIPAM heat capacity peak profile in neat water.

The dependences of the calorimetric transition parameters ( $T_t$ ,  $\Delta_t h$ ,  $\Delta_t c_p$ , and  $\Delta_t T$ ) upon the methanol content are given in Figure 3.

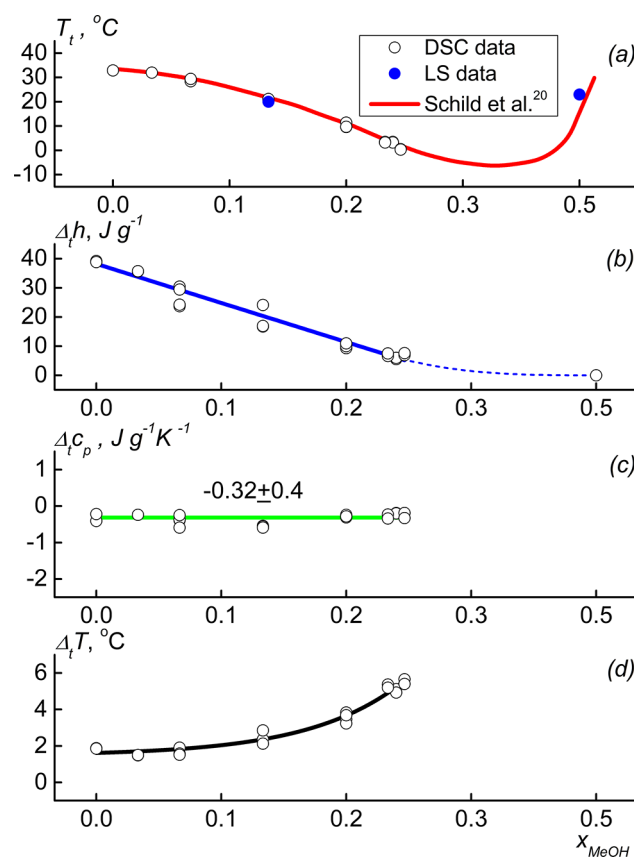
As a result of the increase in the methanol content, the transition temperature and the enthalpy decreased, the transition width increased, and the transition heat capacity increment being negative practically did not change. Our calorimetric and light-scattering data on the transition temperature as a function of the methanol content practically coincided with the DSC and turbidimetric data, as reported by Schild et al.,<sup>19</sup> for PNIPAM with nearly the same molecular weight reproduced in Figure 3a as a red smoothing spline line.

It was impossible to carry out any DSC experiments at  $x_{\text{MeOH}} = 0.3-0.4$ , where the  $T_t(x_{\text{MeOH}})$  dependence passed through a minimum, which could not be accurately defined because the low-temperature limits of the DASM-4 and DASM-4A microcalorimeters are equal to  $-10 \text{ }^\circ\text{C}$ . Therefore, a series of DSC experiments was performed for the PNIPAM solutions with  $x_{\text{MeOH}} \sim 0.5$ . According to light scattering, the phase separation of PNIPAM at  $x_{\text{MeOH}} \sim 0.5$  was observed with a cloud point temperature of  $23 \text{ }^\circ\text{C}$ . In the DSC series, the polymer concentration was varied from  $2$  to  $150 \text{ mg mL}^{-1}$ . However, the polymer thermogram did not reveal any heat



**Figure 2.** Excess heat capacity functions of PNIPAM in a reference aqueous solution ( $1 \text{ mg mL}^{-1}$ ) and in water–methanol solutions of different methanol molar fractions: 0.059 (a), 0.123 (b), 0.194 (c), and 0.458 (d). The PNIPAM concentration is 1 (a,b), 2 (c), and 150 (d)  $\text{mg mL}^{-1}$ .

capacity peaks and practically reproduced the calorimeter baseline in the temperature range  $0\text{--}130 \text{ }^\circ\text{C}$ , even at the highest polymer concentration ( $150 \text{ mg mL}^{-1}$ ). Based on this fact, we assumed that the transition enthalpy is about zero in these conditions. Some possible reasons behind this paradoxical behavior—the athermic phase transition upon heating—could be a superposition of factors such as a substantial decrease in the transition enthalpy with a strong transition broadening or a change in the phase transition mechanism: the transition initiated by the melting of the highly ordered cooperative hydro-solvation structure of the polymer is transformed to a transition triggered by a simple worsening of the solvent quality typical of polymer solutions in organic solvents. In the first case, a small temperature change causes very fast drastic changes in the conformational, and, therefore, energetic states of macromolecules. The cooperative melting transition is easily registered by DSC as a relatively narrow heat capacity peak.<sup>21</sup> In the second case, the system state changes radically upon heating only at the crossing point of the binodal because of the incipience of the new concentrated phase and then changes very slowly because further changes in the coexisting phase compositions are evolved slowly in the diffusion regime.<sup>22,23</sup> The low re-equilibration rate of the phase separation in the water–methanol PNIPAM solution at  $x_{\text{MeOH}} \sim 0.5$  upon heating in the course of the calorimetric experiment seems to be a rather probable reason in explaining



**Figure 3.** Transition temperature (a), enthalpy (b), heat capacity increment (c), and width (d) of PNIPAM in water–methanol solutions at different methanol molar fractions according to DSC and LS data. The red curve in panel (a) reproduces the DSC and turbidimetric data of Schild et al.<sup>19</sup>

why there is no heat capacity peak in the high-sensitivity DSC thermogram of this solution.

It is of importance to note that the transition heat capacity increment of PNIPAM in the water–methanol mixed solvents is negative. This is typical for many thermoresponsive polymer systems, aqueous solutions, and hydrogels.<sup>17,18,24–33</sup> The negative heat capacity increment implies that the transition under investigation is associated with a significant decrease in the solvent-accessible surface area of macromolecules or gel subchains because of the melting of their hydration structure and subsequent aggregation. It seems that this concept could be applied to the PNIPAM solutions in the water–methanol mixed solvents at the relatively low methanol content ( $x_{\text{MeOH}} < 0.25$ ). Therefore, there is apparently some analogy between solvation structures in the aqueous thermoresponsive polymer systems and the PNIPAM solutions in the diluted water–methanol mixed solvents.

The theory of the co-nonsolvency phenomenon of PNIPAM in the water–methanol mixed solvents which takes the cooperative nature of polymer–solvent interactions into account was elaborated by Tanaka et al.<sup>14</sup> In this theory, the temperature dependences of the hydration and solvation degrees of the polymer  $\theta_A(T, w_B)$  and  $\theta_B(T, w_B)$  at the different weight fractions of methanol ( $w_B$ ) allow one to determine the current enthalpy of the system as follows

$$H(T, w_B) = H_A^\circ \times \theta_A(T, w_B) + H_B^\circ \times \theta_B(T, w_B) \quad (1)$$

**Table 1.** Parameters<sup>a</sup> of the Okada–Tanaka Model Fitted to Excess Heat Capacity Functions of PNIPAM Transitions in Aqueous Methanol Solutions at Different Methanol Molar Fractions

$x_{\text{MeOH}}$	$\Delta_t H^\circ$ , kJ mol <sup>-1</sup>	$\Delta_t H^{\text{th}}$ , kJ mol <sup>-1</sup>	$T^*$ , K	$10^6 \sigma$	$r$
0.029	3.6 ± 0.1	4.3 ± 0.2	305.8 ± 0.1		
0.059	2.7 ± 0.2	3.1 ± 0.2	302.8 ± 0.2		
0.123	1.9 ± 0.2	2.1 ± 0.3	295.0 ± 0.1		
0.194	1.1 ± 0.1	1.3 ± 0.1	284.6 ± 0.4	4.5 ± 0.1 <sup>b</sup>	0.991 ± 0.004 <sup>b</sup>
0.232	0.75 ± 0.05	1.2 ± 0.1	279.2 ± 0.2		
0.240	0.64 ± 0.02	0.85 ± 0.05	278.4 ± 0.2		
0.248	0.76 ± 0.03	1.1 ± 0.1	276.6 ± 0.2		

<sup>a</sup> $\Delta_t H^\circ$  is the calorimetric transition enthalpy per PNIPAM monomer unit.  $\Delta_t H^{\text{th}}$  is the van't-Hoff transition enthalpy.  $T^*$  is the reference temperature at which the hydro-solvation equilibrium constant  $\lambda = 1$ . <sup>b</sup>Average values of the cooperativity parameter and Pearson's correlation coefficient over the array of all experimental data at different methanol concentrations.

where  $H_A^\circ$  and  $H_B^\circ$  are the standard enthalpies of hydration and solvation, respectively.

According to definition<sup>14</sup>

$$H_A^\circ = -R\Theta_{0A} \times \gamma_A \quad (2)$$

$$H_B^\circ = -R\Theta_{0B} \times \gamma_B \quad (3)$$

where  $R$  is the gas constant;  $\Theta_{0A}$  and  $\gamma_A$  are the apparent theta-temperature and the energetic parameter of water–polymer interaction, respectively;  $\Theta_{0B}$  and  $\gamma_B$  are the apparent theta-temperature and the energetic parameter of methanol–polymer interaction. Note that the theta temperatures  $\Theta_{0A}$  and  $\Theta_{0B}$  relate to the hypothetical Flory–Huggins solutions of PNIPAM in water and methanol without polymer–solvent hydrogen-bonding. The fitting of the Okada–Tanaka model of cooperative hydration to the PNIPAM–water phase diagram has shown that  $\Theta_{0A} = 565$  K.<sup>15</sup>

In the first approximation, the excess enthalpy of the system related to the transition could be expressed in the form

$$\Delta H^E(T, w_B) = H(T, w_B) - H(T_0, w_B) \quad (4)$$

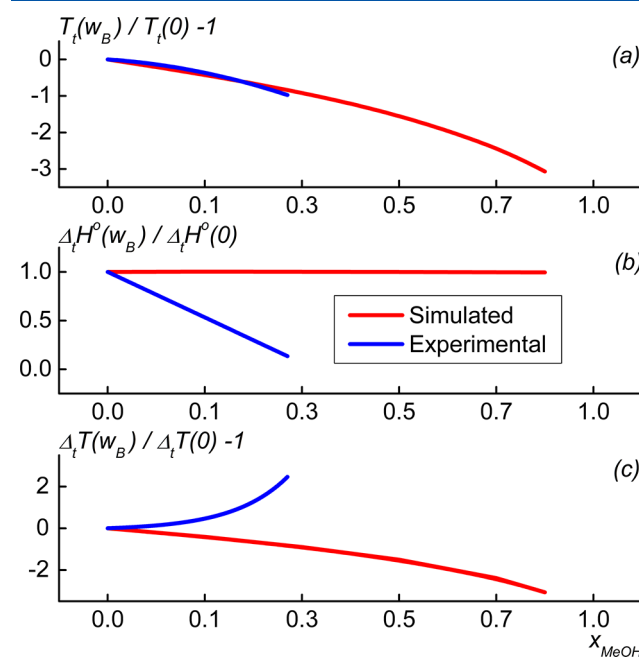
where  $T_0$  is the apparent initial temperature of a DSC experiment. Then, the excess heat capacity of the transition, that is, the transition thermogram, can be calculated by the numeric differentiation of the  $\Delta H^E(T, w_B)$  function

$$C_p^E(T, w_B) = \frac{d}{dT}(\Delta H^E(T, w_B)) \quad (5)$$

We used this approach for simulations of the transition thermograms and determination of their calorimetric parameters,  $T_0$ ,  $\Delta_t H^\circ$ , and  $\Delta_t T$ , as a function of the methanol molar fraction using the model parameters for PNIPAM, as presented in Table 1 of the work.<sup>34</sup> These are the equilibrium constant of hydration at the temperature  $\Theta_{0A}$ ,  $\lambda_{A0} = 0.002$ ; the reduced water–polymer interaction energy,  $\gamma_A = 3.5$ ; the hydration cooperativity parameter,  $\sigma_A = 0.27$ ; the hypothetical temperature at which the polymer hydration vanished,  $\Theta_{0A} = 565$  K; the ratio of water volume to the volume of polymer monomer unit,  $n_A = 1$  for water–PNIPAM interaction, and the equilibrium constant of methanol solvation at the temperature  $\Theta_{0B}$ ,  $\lambda_{B0} = 0.0042$ ; the reduced methanol–polymer interaction energy,  $\gamma_B = 3.0$ ; the methanol solvation cooperativity parameter,  $\sigma_B = 0.4$ ; the hypothetical temperature at which the polymer solvation vanished,  $\Theta_{0B}$ ; and the ratio of methanol volume to the volume of polymer monomer unit,  $n_B = 2$  for methanol–PNIPAM interaction at the arbitrary suggestion that  $\Theta_{0B} = \Theta_{0A}$ . The algorithm of calculations of the  $\theta_A(T, w_B)$  and  $\theta_B(T, w_B)$  functions is discussed in the Supporting

Information. To exclude possible effects of scaling factors at the comparison of the simulated and experimental data, we used the reduced forms of the transition parameters:  $T_t(w_B)/T_t(0) - 1$ ,  $\Delta_t H^\circ(w_B)/\Delta_t H^\circ(0)$ , and  $\Delta_t T(w_B)/\Delta_t T(0) - 1$ .

The comparison of the simulated and experimental transition parameters in the reduced forms is presented in Figure 4.



**Figure 4.** Simulated and experimental transition parameters of PNIPAM in water–methanol solutions as a function of the molar fraction of methanol. The experimental data are presented as fitted polynomial functions. The transition temperatures are given in degree Celsius.

Based on the considerations given above, we were only able to observe a decent agreement for the reduced transition temperature. However, there are principal disagreements for the transition enthalpy and width. According to the experiments, the transition enthalpy diminishes rapidly with an increasing methanol concentration while, in contrast, the simulated transition enthalpy does not depend on the methanol concentration. The experimental and simulated dependences of the transition width display a much more significant difference. The theory predicts that the transition peak will narrow upon an increase in the methanol concentration. The calorimetric experiment shows that the

increase in the methanol concentration produces a significant broadening of the transition peak.

We assume the following reason for these disagreements: the theory suggests the coexistence of the independent sequences of bound water and alcohol molecules. In other words, the hydro-solvation structure of the macromolecule is considered as the alternation of the independent hydration and solvation regions. This conception seems to be oversimplified when taking into account the very high affinity of methanol to water.

Indeed, it is well-known that methanol and water form complexes of variable compositions in solutions.<sup>35</sup> Moreover, the water–methanol complexes are found in clathrates.<sup>36</sup> The latter is of particular importance in our discussion because the clathrates provide a basic model for the development of the modern concepts on hydrophobic hydration.<sup>37</sup> These features allow us to consider the hydro-solvation shell of a polymer, PNIPAM in particular, in water–methanol solutions as a single integrated structure, similar to that proposed first by Zhang and Wu.<sup>38</sup>

The energetics of this structure is smoothly changed with the methanol concentration. In that case, the transition thermograms of PNIPAM in the water–methanol solutions can be analyzed in terms of the Okada–Tanaka theory.<sup>15,16</sup>

This theory is a generalization of the Flory–Huggins theory for aqueous solutions of polymers, in which the solvent–polymer interaction is considered as the cooperative adsorption of solvent molecules on a linear polymer matrix. In that case, a sense of the cooperativity conception means that there is a significant interaction between the adsorbed water molecules as a result of which the adsorbed water molecules are distributed on the polymer matrix not randomly, but form extended enough sequences. The complex array of these sequences defines the hydration structure of the polymer. By the physical meaning, such a definition of the hydration of macromolecule is adopted from the theory of coil–helix transitions in polypeptides.<sup>39</sup> There is a deep formal analogy between the dehydration of the macromolecule upon heating and the melting of the polypeptide helix. In both cases, a probability of interruption of the linear ordered array of the bound water molecules or polypeptide monomer units in the helix state is defined by a value of the cooperativity parameter  $\sigma < 1$ . Based on these principles, the Okada–Tanaka theory enables one to calculate strictly the temperature dependence of the polymer hydration needed for the analysis of scanning calorimetry data.

Initially, the Okada–Tanaka theory was developed to describe the cooperative hydration of PNIPAM in aqueous solutions. Using the aqueous solutions of poly(ethylaminophosphazene)<sup>17</sup> and chitosan,<sup>18</sup> as well as some polymer hydrogels<sup>40</sup> as examples, we were able to demonstrate that the Okada–Tanaka theory could be successfully used to analyze the DSC data on the polymer thermoresponsivity. We applied this approach for the description of the phase-transition thermograms of PNIPAM in the water–methanol solutions of different compositions suggesting that the main theory parameters discussed below depend on the methanol concentration.

According to the Okada–Tanaka concept,<sup>15</sup> the phase separation heat of aqueous solutions of PNIPAM is equal to the dehydration heat of the polymer upon heating. In this case, the excess transition heat capacity per a monomer unit of the polymer can be defined as follows:

$$C_p^E(T) = \Delta_t H^\circ \left( 1 - \frac{d\theta(T)}{dT} \right) \quad (6)$$

where  $\Delta_t H^\circ$  and  $\theta(T)$  are the calorimetric transition enthalpy per a monomer unit and the temperature dependence of the polymer hydration degree, respectively. The dependence  $\theta(T)$  can be calculated in terms of the Okada–Tanaka theory of the cooperative hydration of macromolecules.<sup>15</sup>

According to the Okada–Tanaka theory, the polymer hydration degree is a function of a generic parameter  $q$  and the hydration cooperativity parameter  $\sigma$

$$\theta(q, \sigma) = \frac{\sigma \times q \times w_1(q)}{1 + \sigma \times [w_0(q) + w_1(q)]} \quad (7)$$

where

$$w_0(q) = \sum_{\xi=1}^n q^{\xi-1} = \begin{cases} n & (q = 1) \\ \frac{q^n - 1}{q - 1} & (q \neq 1) \end{cases} \quad (8)$$

$$w_1(q) = \sum_{\xi=1}^n \xi \times q^{\xi-1} = \begin{cases} \frac{n \times (n + 1)}{2} & (q = 1) \\ \frac{q^n \times [1 + n \times (q - 1)] + 1}{(q - 1)^2} & (q \neq 1) \end{cases} \quad (9)$$

and  $n$  is the apparent polymerization degree of the polymer.

The generic parameter  $q$  as a function of temperature can be found from the equation

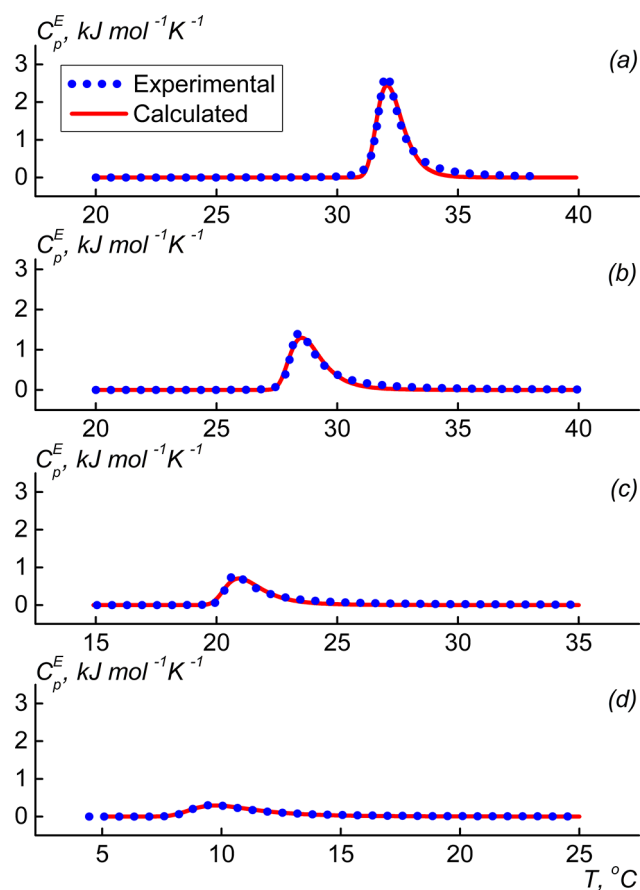
$$q = \lambda(T) \times \frac{[1 - \varphi - \varphi \times \theta(q, \sigma)] \times \exp\left(\frac{q \times \varphi}{1 - \varphi - \varphi \times q}\right)}{1 + \sigma \times q \times w_0(q)} \quad (10)$$

where  $\lambda(T)$  is the equilibrium hydration constant of the monomer unit of the polymer, and  $\varphi$  is the polymer volume fraction. The  $\lambda(T)$  function is given by the van't Hoff equation in the form

$$\lambda(T) = -\frac{\Delta_t H^{\text{vh}}}{R} \left( \frac{1}{T} - \frac{1}{T^*} \right) \quad (11)$$

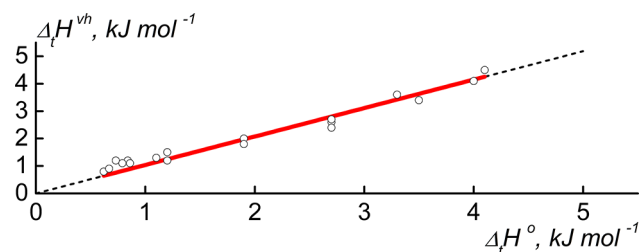
where  $\Delta_t H^{\text{vh}}$  is the van't Hoff transition enthalpy and  $T^*$  is the reference temperature at which  $\lambda = 1$ . A solution of eqs 7–11 together makes it possible to find the  $q(T, \Delta_t H^{\text{vh}}, T^*, \sigma)$  function at a given  $n$  value. Then, this function should be inserted into eqs 7–9, and the hydration degree as a function of temperature ( $\theta(T)$ ) can be calculated at the given values of  $\Delta_t H^{\text{vh}}$ ,  $T^*$ , and  $\sigma$ . Taking the  $\theta(T)$  dependence and  $\Delta_t H^\circ$  as an additional parameter, we fitted eq 6 to the experimental thermograms. It allowed us to find the optimal values of  $\Delta_t H^\circ$ ,  $\Delta_t H^{\text{vh}}$ ,  $T^*$ , and  $\sigma$  at  $n = 1000$  which is approximately consistent with the molecular weight of the PNIPAM sample under investigation. The fitting procedure was performed by the Mathcad 14 software using the Quasi-Newton algorithm. The fitting results are summarized in Figure 5 and Table 1.

The fitting results indicate that the Okada–Tanaka theory, in general, well describes the transition thermograms of PNIPAM in the water–methanol solutions of different



**Figure 5.** Excess heat capacity functions of PNIPAM per monomer unit at the different methanol concentrations, %: 5, (a), 10 (b), 20 (c), and 30 (d). Calculations were carried out by the Okada–Tanaka model. The model parameters are summarized in Table 1. A number of the experimental points are omitted for more clear presentation.

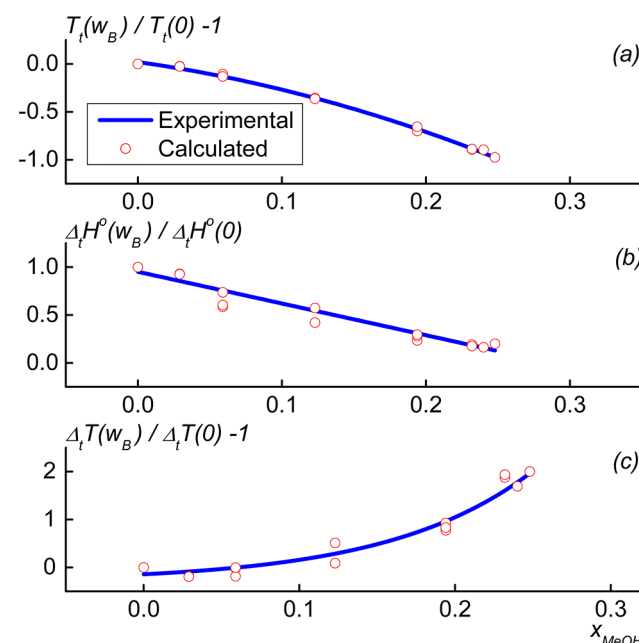
compositions. The mean value of Pearson's correlation coefficient between the experimental and calculated data is  $0.991 \pm 0.004$  within all the arrays of the methanol concentrations. The next support of the adequacy of the Okada–Tanaka approach to the DSC data interpretation for the PNIPAM water–methanol solutions is provided by a comparison of the calorimetric and van't Hoff transition enthalpies, as given in Figure 6.



**Figure 6.** Correlation between the van't Hoff and calorimetric transition enthalpies of PNIPAM in the aqueous methanol solutions with  $x_{\text{MeOH}} = 0.029\text{--}0.248$ :  $\Delta_t H^{\text{vh}}/\Delta_t H^{\circ} = 1.04 \pm 0.02$ ; the coefficient of determination is 0.999. Both enthalpies were calculated per PNIPAM monomer unit. Both enthalpies were determined by fitting of the Okada–Tanaka model (eqs 6–11) to the excess heat capacity functions of PNIPAM at the different methanol molar fractions.

It shows that despite the very large variations in both enthalpies depending on the methanol concentration, their ratio remains to be very close to unity ( $\Delta_t H^{\text{vh}}/\Delta_t H^{\circ} = 1.04 \pm 0.02$  at the coefficient of determination of 0.999). As it is well-known, the coincidence of the calorimetric and van't Hoff enthalpies is a powerful argument for the validation of the proposed transition mechanism.<sup>21</sup> Thus, the successful description of the transition thermograms of PNIPAM in the water–methanol mixed solutions in terms of the Okada–Tanaka theory seems to support the concept of the formation and evolution of the mixed hydro-solvation structure of the polymer.

An additional illustration of the efficiency of the thermogram description by the Okada–Tanaka model is given in Figure 7,



**Figure 7.** Experimental and calculated by the Okada–Tanaka model transition parameters of PNIPAM in water–methanol solutions as a function of the molar fraction of methanol: (a) reduced transition temperature increment; (b) reduced transition enthalpy; and (c) reduced transition width increment. The experimental data are presented as fitted polynomial functions. The transition temperatures are given in degree Celsius.

where the experimental and calculated reduced thermogram parameters in the same forms as in Figure 4 are compared. This comparison supports that the Okada–Tanaka model quite adequately describes the DSC data on the phase transition of PNIPAM in the mixed water–methanol solutions. Consequently, a possible role of methanol in the co-solvency phenomenon of PNIPAM is consistent with the hypothesis on the participation of this cosolvent in a common, united hydro-solvation shell of the polymer formed by water–methanol complexes.

## CONCLUSIONS

Based on the calorimetric data, we suggest that the minimum point of the  $T_t(x_{\text{MeOH}})$  function can be considered as an apparent boundary between two different mechanisms of phase separation in the water–methanol PNIPAM solutions. To the left to this point, the phase separation is triggered by the cooperative melting of the united hydro solvation structure of

the polymer, formed by ordered water–methanol complexes, with the measurable heat effect. Alternatively, to the right to the minimum point, the phase separation is caused by a smooth decrease in the solvent quality as this is typical of polymer solutions in organic solvents. In this range of the methanol content, the phase behavior of PNIPAM seems to be dictated by a manner in which the Flory–Huggins parameter depends on temperature. Studies of such systems by differential scanning calorimetry are rather problematic because of the low transition energetics,<sup>41,42</sup> and very slow kinetics of the temperature-induced re-equilibration of the coexisting phases in the course of the phase separation upon the temperature scanning.<sup>22,23</sup>

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.macromol.0c02253>.

Algorithm of analysis of the DSC data for the PNIPAM phase transition in water–methanol mixed solutions in terms of the theory by Tanaka, F.; Koga, T.; Kojima, H.; Xue, N., Winnik, F.M. *Macromolecules*, **2011**, *44* (8), 2978–2978 (PDF)

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### Notes

The authors declare no competing financial interest.

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