



# Studies on the phase transition of hydrogels and aqueous solutions of thermosensitive polymers

Hiroyuki Kojima<sup>1</sup>

Received: 30 December 2017 / Revised: 3 February 2018 / Accepted: 5 February 2018 / Published online: 26 March 2018  
© The Society of Polymer Science, Japan 2018

## Abstract

In this review, our recent studies on the phase transition of hydrogels and aqueous solutions of thermosensitive homopolymers and copolymers are briefly summarized. On the basis of the concept of cooperative hydration, which is defined as the association-dissociation of water molecules bound to a polymer chain with a positive correlation between adjacent bound water molecules, we theoretically examine the following phenomena: (i) the high-temperature collapse of poly(*N*-isopropylacrylamide) (PNIPAM) gels in water; (ii) the reentrant volume phase transition of PNIPAM gels in mixed solvents of water/methanol; (iii) the temperature dependence of the swelling behavior of PNIPAM microgels in mixed solvents of water/methanol, the selective solvent adsorption of the gels and the selective solvent binding to the polymer chains; and (iv) the nonlinear depression of the lower critical solution temperature of thermosensitive copolymers in water as the monomer composition is varied. Our theoretical results are compared with the experimental data, and the molecular mechanisms are discussed.

## Introduction

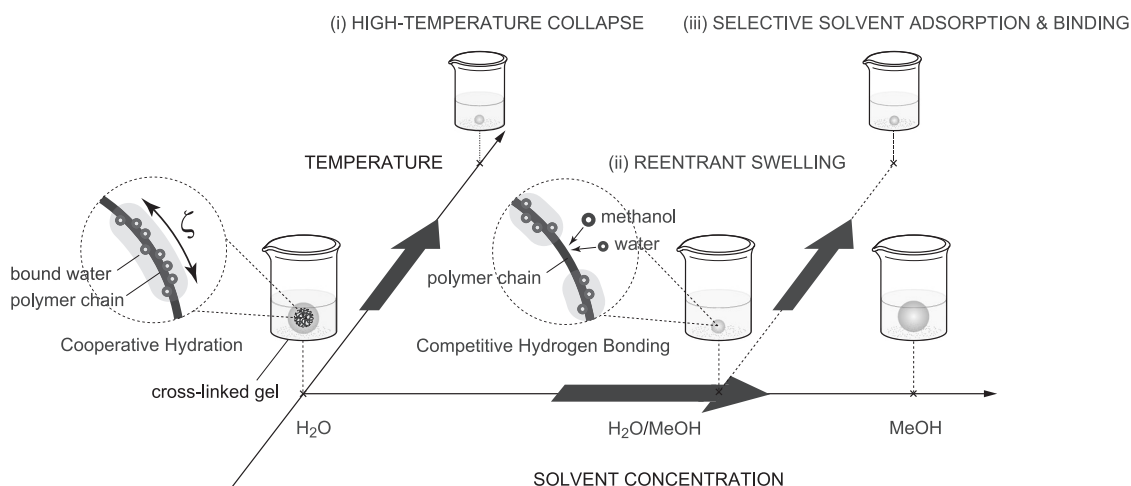
Poly(*N*-isopropylacrylamide) (PNIPAM) is a typical thermosensitive water-soluble polymer. Aqueous solutions of PNIPAM have a lower critical solution temperature (LCST) of approximately 32 °C [1]. In dilute aqueous solution, the PNIPAM chain shows a drastic conformation transition from a random coil to a globule when it is heated near the LCST [2]. Cross-linked PNIPAM gels also exhibit discontinuous volume changes around the LCST [3]. This phenomenon is called the volume phase transition. Because of their thermosensitivity, aqueous solutions and hydrogels of PNIPAM have been studied extensively for application in various fields [4]. The LCST of aqueous PNIPAM solutions and the volume phase transition temperature (VPTT) of PNIPAM hydrogels can be controlled by changing the conditions surrounding the polymer chains, such as the solvent concentration [5] and amount of salt added [6]. In mixed solvents of water/methanol, PNIPAM exhibits a peculiar phenomenon called cononsolvency [7], where each solvent is a good solvent for PNIPAM at room temperature

but becomes a poor solvent when the two are mixed. In addition, copolymerization with comonomers that constitute polymers with different water solubilities can also be used to change the LCST, which may depend on not only the monomer composition [8–15] but also the monomer arrangement along the chain [16].

It is important to understand the molecular mechanism of the phase transition phenomena to control the properties of the polymer at the molecular level. In terms of theoretical research, statistical thermodynamic theories of polymer solutions and gels have been developed [17–20]. These theories have enabled us to understand the phase behavior of polymer solutions and the swelling behavior of gels composed of non-polar polymers in non-polar solvents in terms of Flory's interaction parameter  $\chi$ . However, the phase behavior of aqueous polymer solutions and the swelling behavior of hydrogels can be quite different from those of non-polar systems. In these cases, the conventional Flory's interaction parameter  $\chi$  based on van der Waals interactions is insufficient for a comprehensive understanding of their behavior.

✉ Hiroyuki Kojima  
kojima@phys.polym.kyoto-u.ac.jp

<sup>1</sup> Department of Polymer Chemistry, Graduate School of Engineering, Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8510, Japan



**Fig. 1** Schematic depiction of our studies: (i) high-temperature collapse of poly(*N*-isopropylacrylamide) (PNIPAM) gels in water, (ii) reentrant volume phase transition of PNIPAM gels in mixed solvents of water/methanol, and (iii) temperature dependence of the swelling behavior of PNIPAM gels in mixed solvents of water/methanol. Model

gel consisting of cooperatively hydrogen-bonded polymer chains with solvent molecules. In cases (ii) and (iii), both solvent molecules are assumed to be capable of forming hydrogen-bonds with the polymer chains, so that they compete in forming hydrogen-bonds with the polymer chains

Okada and Tanaka applied the theory of associating polymer solutions [21], which enables us to explicitly describe the molecular association in a thermal equilibrium system, to aqueous PNIPAM solutions based on the concept of cooperative hydration. Cooperative hydration is defined as the association-dissociation of water molecules bound to a polymer chain with a positive correlation between adjacent bound water molecules [22]. These authors succeeded in deriving the characteristic features of the phase behavior of aqueous PNIPAM solutions.

In this short review, our recent theoretical studies on the following phenomena of thermosensitive hydrogels (Fig. 1) and aqueous copolymer solutions on the basis of the concept of cooperative hydration are briefly summarized:

- (i) High-temperature collapse of PNIPAM gels in water [23]
- (ii) Reentrant volume phase transition of PNIPAM gels in mixed solvents of water/methanol [24]
- (iii) Temperature dependence of the swelling behavior of PNIPAM microgels in mixed solvents of water/methanol [25]
- (iv) Nonlinear depression of the LCST of thermosensitive copolymers in water as the monomer composition is varied [26]

## (i) High-temperature collapse of PNIPAM gels in water

Cross-linked PNIPAM gels, though nonionic, undergo a discontinuous volume phase transition from a low-

temperature swollen state to a high-temperature collapsed state in water approximately 32 °C as the temperature is varied [3]. The molecular origin of this phenomenon remains to be fully understood.

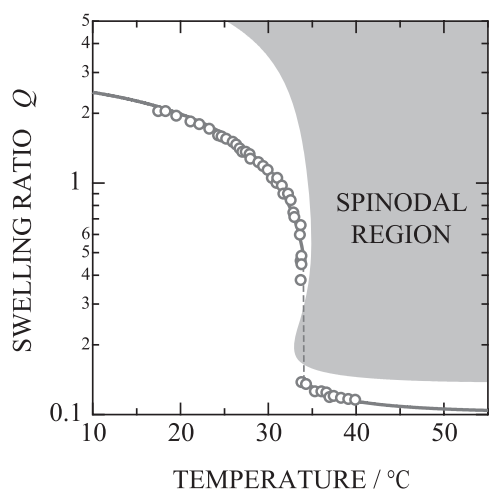
A phenomenological study of the high-temperature collapse of PNIPAM gels in water on the basis of the Flory-Rehner model of gels [20] was conducted by Hirotsu [27]. Assuming that Flory's interaction parameter  $\chi$  between the polymer and water is a function of the temperature and polymer concentration  $\chi = \chi_0 + \chi_1\phi + \dots$ , he noted out that the volume phase transition occurs when  $\chi_1$  exceeds a threshold value.

In this study, to elucidate the molecular origin of such discontinuity, we explicitly consider the cooperative hydration of polymers [23]. The free energy of the hydrogel is assumed to be the sum of three parts.

$$\Delta F = \Delta_{\text{el}}F + \Delta_{\text{mix}}F + \Delta_{\text{hyd}}F \quad (1)$$

The first term,  $\Delta_{\text{el}}F$ , is the elastic free energy, based on the assumption of a Gaussian network model with affine deformation. The second term,  $\Delta_{\text{mix}}F$ , is the mixing free energy, based on Flory-Huggins theory [17–20], where we consider that the network is a gigantic molecule and bound water molecules on the polymer chains lose their translational freedom.

The interaction parameter  $\chi$  in the mixing free energy is assumed to be a decreasing function of temperature,  $\chi = A + B/T$ , with  $B > 0$ , due to the cohesive energy, in contrast to Hirotsu's phenomenological parameter,  $\chi(T) = A + B/T$ , with  $B < 0$ . (Please note that  $\chi_0$  and  $\chi_1$  in this review are written as  $\chi_1$  and  $\chi_2$ , respectively, in ref. [27]). The third term,  $\Delta_{\text{hyd}}F$ , is the hydration free energy, which expresses the contribution from the associative interactions



**Fig. 2** Comparison between the experimental data [27] of the swelling ratio (symbols) and the theoretical calculation results (solid line) on the basis of cooperative hydration. The shaded area shows the calculated unstable (spinodal) region. (Adapted with permission from ref. [23]. © 2010 American Chemical Society).

(hydration) between the polymer and water, which is not included in the interaction parameter  $\chi$  in the mixing free energy.

We employ the simplest form of the statistical weight  $\eta_\zeta$  for a sequence of bound water molecules with length  $\zeta$ ,

$$\eta_\zeta = \sigma \lambda(T)^\zeta \quad (2)$$

as proposed by Zimm and Bragg for the study of the coil-to-helix transition of polypeptide chains [28]. The front factor  $\sigma$ , which is called the cooperativity parameter, gives the free energy penalty for a sequence of bound water molecules, and  $\lambda(T)$  is the association constant of the hydrogen bond. This model includes the case of random hydration which is given by  $\sigma = 1$ . The smaller value of  $\sigma$  represents stronger cooperativity.

We obtain the chemical potentials from the total free energy  $\Delta F$  and then calculate the equilibrium swelling ratio and hydration degree of the polymer network chains, under the association equilibrium conditions for hydrated polymer chains and the osmotic swelling equilibrium condition of the gel. A spinodal curve is obtained from the bulk modulus  $K = 0$ .

From systematic investigation of the cooperative effect, we found that the transition becomes sharper as the cooperativity becomes stronger, and the discontinuous transition can occur if the hydration is sufficiently cooperative, while the volume change is continuous in the case of random hydration (not shown here, see ref. [23]). Figure 2 compares the theoretical calculations with the experimental data [27] on the swelling ratio of PNIPAM gels. We found good agreement between our theoretical results and the experimental data.

By investigating the renormalization of the  $\chi$ -parameter for cooperative hydration, we showed the interpretation that the threshold value of Hirotsu's  $\chi_1$  [27], which is required for the discontinuous volume change, is due to the strong cooperativity in hydration.

## (ii) Reentrant swelling of PNIPAM gels in mixed solvents of water/methanol

The behavior of cross-linked PNIPAM gels is sensitive not only to temperature but also to the nature of solvents, as they are in aqueous solutions. PNIPAM gels exhibit reentrant swelling in mixed solvents of water/methanol with an increasing methanol concentration of the solution outside the gel [5, 29].

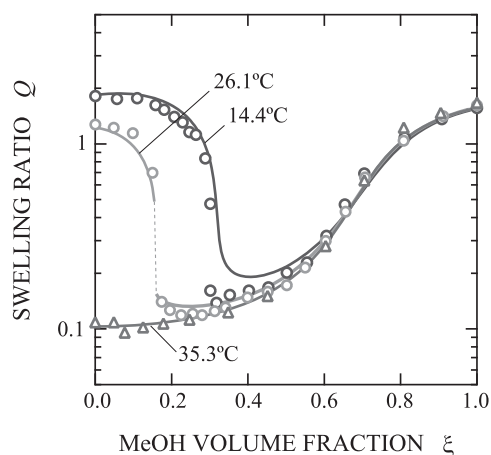
Schild et al. [30]. noted that the phase behavior of PNIPAM in mixed solvents of water/methanol is insensitive to the polymer concentration and suggested that the cononsolvency is caused by the local interactions between the solvents and polymer rather than by the modification of interactions between water and methanol due to the existence of the polymer.

Although many studies have been conducted to understand the molecular origin of cononsolvency from theoretical and experimental viewpoints, there is room for further study. The molecular mechanisms proposed thus far are classified into the following three types:

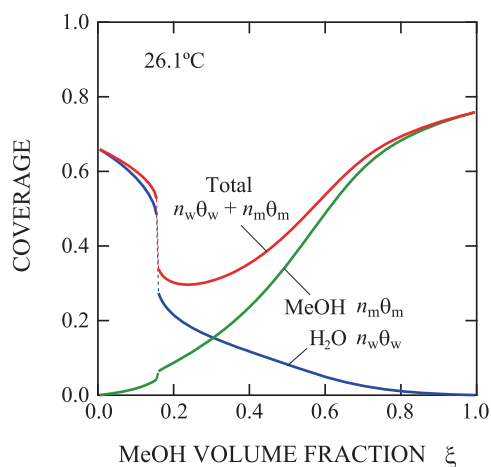
- Cluster formation of water and methanol molecules by hydrogen bonds [31]
- Concentration fluctuation in the close vicinity of the critical regime [32]
- Selective solvent adsorption as a result of the competition between polymer-water and polymer-methanol hydrogen bonds [33–35]

In case (a), stoichiometric structures of water and methanol molecules are formed through hydrogen bonds, and they act as a poor solvent for PNIPAM. In case (b), the concentration fluctuation near the polymer chains induces attractive interactions between polymer chain segments. This hypothesis may be important for partially miscible mixtures, such as water/tetrahydrofuran mixtures, but may be not crucial for completely miscible mixtures of water/methanol. In case (c), Tanaka et al. [33–35]. theoretically showed that the competitive hydrogen bonding of both solvent molecules to the polymer chains results in cononsolvency, and obtained good agreement between the theoretical results and the experimental data for a single chain and in solutions of PNIPAM in mixed solvents of water/methanol.

In this work, we extend our previous theoretical model of thermosensitive gels in pure solvent to that of gels in



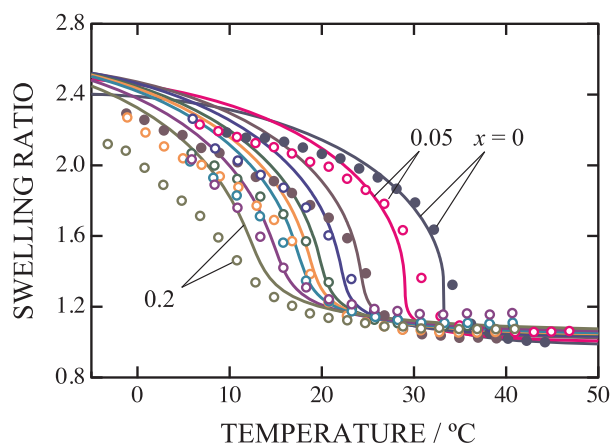
**Fig. 3** Comparison between the experimental data [27] (symbols) and the theoretical calculation results (solid line) for the swelling ratio plotted against the volume fraction of methanol outside the gel. (Reproduced from ref. [24] with permission from the Royal Society of Chemistry)



**Fig. 4** Coverage by each type of solvent molecule at 26.1 °C plotted against volume the fraction of methanol outside the gel. (Reproduced from ref. [24] with permission from the Royal Society of Chemistry)

mixed binary solvents, where both solvent molecules are capable of forming hydrogen bonds with the polymer chains.

Figure 3 shows a comparison between the theoretical calculations [24] of swelling curves and the experimental data [27]. The theoretical result reproduces the reentrant swelling behavior of PNIPAM gels including the discontinuous transition at 26.1 °C. Figure 4 shows the coverage on polymer chains by bound solvent molecules at 26.1 °C at different methanol concentrations, where  $n_\alpha$  ( $\alpha = w, m$ ) is the volume of solvent  $\alpha$  molecules in the units of the cell volume,  $\theta_\alpha$  ( $\alpha = w, m$ ) is the degree of hydrogen bonds between the polymer and solvent  $\alpha$  and  $n_w$  and  $n_m$  are set to be 1 and 2, respectively. We found that in the collapsed region, where the methanol volume fraction  $\xi$  outside the gel is  $0.2 < \xi < 0.4$ , the total



**Fig. 5** Comparison between the experimental data (symbols) and the theoretical calculation results (solid lines) for the swelling ratio plotted against temperature. The mole fraction  $x$  of methanol outside the gel varies from curve to curve. (Adapted with permission from ref. [25]. The labels of Fig. 11 in ref. [25] were changed)

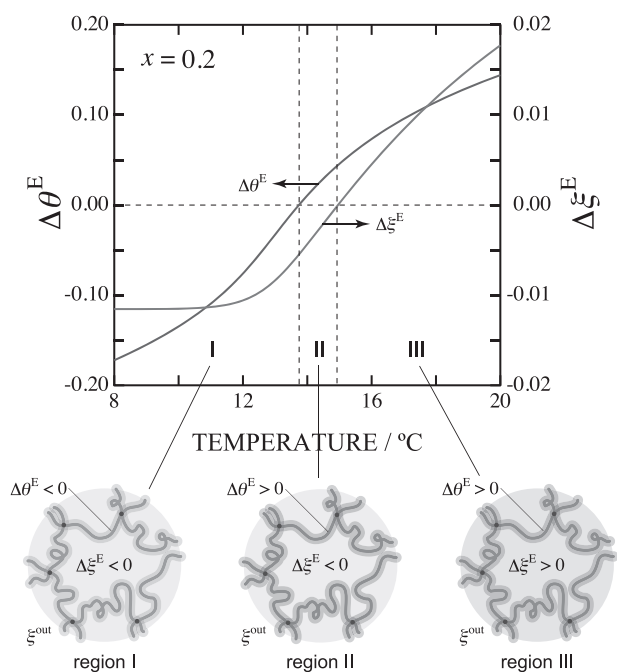
coverage by both solvents (red line) reaches the minimum at  $\xi \approx 0.2$ .

### (iii) Temperature dependence of the swelling of PNIPAM microgels in mixed solvents of water/methanol

We studied the temperature dependence of the swelling behavior of PNIPAM microgels in mixed solvents of water/methanol. Using the dynamic light scattering technique, we examined the temperature dependence of the particle size, and we measured the VPTT in various concentrations of methanol. The experimental details, which are only summarized in the following, can be found in ref. [25].

Our experimental data of the VPTT are in good agreement with the cloud point of linear PNIPAM reported by Winnik et al. [7]. This supports the assumption that the existence of cross-links has no major influence on the cononsolvency of PNIPAM in mixed solvents of water/methanol. Using small-angle neutron scattering measurements, we also studied the particle structure of PNIPAM microgels and obtained inhomogeneous density profiles of PNIPAM particles in various  $D_2O/MeOD$  mixtures. Our results are similar to the data reported by Walter et al. [36]. This suggests that the cononsolvency behavior is not sensitive to the network structure.

Based on the above findings, to analyze the experimental data on the microgels, we employ here the previous theory on macrogels with uniform density by assuming that the effect of the inhomogeneity is localized in the limited surface layer. This treatment can lead to a slight deviation from the experimental data of the swelling curves at low temperatures, but we regard the deviation as not serious.



**Fig. 6** The excess methanol adsorption  $\Delta\xi^E$  and the excess methanol binding  $\Delta\theta^E$  in the vicinity of the transition point at a mole fraction of  $x = 0.2$  of methanol. An illustration of the network corresponding to regions I, II, and III is shown at the bottom. (Adapted with permission from ref. [25]. Fig. 20(a) and Fig. 21 in ref. [25] were combined)

Figure 5 shows a comparison between the theoretical swelling curves and the experimental data of the swelling ratio of PNIPAM microgels plotted against temperature. The agreement is good except for the low-temperature swollen state as mentioned above, where the discrepancies may be due to the inhomogeneous polymer density profile near the surface.

It has been reported that PNIPAM gels excessively adsorb alcohol in mixed solvents of water/alcohol, such as ethanol and 1-propanol, in the collapsed states [37]. We now examine the difference between the methanol compositions inside and outside the gel and investigate the local methanol composition in the vicinity of network chains by analyzing the degree of hydrogen bonds between polymer and water and between polymer and methanol. Here, we introduce the excess (selective) adsorption  $\Delta\xi^E$  of methanol and the excess (selective) binding  $\Delta\theta^E$  of methanol defined as

$$\Delta\xi^E \equiv \xi^{\text{in}} - \xi^{\text{out}} \quad (3)$$

$$\Delta\theta^E \equiv \frac{n_m\theta_m}{n_w\theta_w + n_m\theta_m} - \xi^{\text{out}} \quad (4)$$

where  $\xi^{\text{in}} \equiv \phi_m^{\text{in}}/(\phi_w^{\text{in}} + \phi_m^{\text{in}})$  is the composition of methanol inside the gel; and  $\xi^{\text{out}}$  is that outside the gel, which was written as  $\xi$  in the previous section (ii) of this review; and  $\phi_w^{\text{in}}$  and  $\phi_m^{\text{in}}$  are the volume fractions of water and methanol,

respectively, inside the gel. In the case of  $\Delta\xi^E > 0$ , the gel retains a higher methanol concentration than the outside solution. The gel selectively adsorbs methanol. On the other hand,  $\Delta\theta^E$  is defined as the ratio of the coverage by each solvent  $n_\alpha\theta_\alpha$  ( $\alpha = w, m$ ) to the total coverage  $n_w\theta_w + n_m\theta_m$  by both solvents.

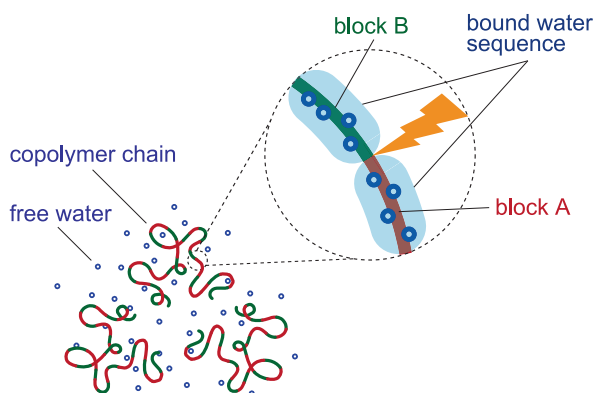
Figure 6 shows the temperature dependence of  $\Delta\xi^E$  and  $\Delta\theta^E$  at a mole fraction  $x = 0.2$  (volume fraction  $\xi \approx 0.33$ ) of methanol. The sign inversion of the excess adsorption and excess binding of methanol occurs near the VPTT. In region I, the gel excessively adsorbs water, and the water composition in the vicinity of the chains is higher than that of the outside solution. The opposite situation occurs in region III. We found an interesting situation in region II:  $\Delta\xi^E < 0$  and  $\Delta\theta^E > 0$ . This means that the chains retain a higher methanol composition in the vicinity of themselves than in the outside solution, and at the same time, the gel retains a higher water composition than does the outside solution.

#### (iv) Nonlinear depression of the lower critical solution temperature in aqueous solutions of thermosensitive random copolymers

Tuning the transition temperature is important for tailoring the thermal properties of thermosensitive polymer systems for specific applications. This tuning can be achieved by copolymerization with different monomers that constitute polymers with different solubilities in water.

The phase transitions of aqueous solutions and hydrogels of random copolymers, such as *N*-isopropylacrylamide (NIPAM) polymerized with acrylamide [8], with sodium acrylate [9], with butyl methacrylate [10], with acrylic acid, with dimethylacrylamide [11], with ethylene oxide [12], and with *N*-methacrylamide [13], have been studied so far. Their transition temperatures shift monotonically to either lower or higher temperatures with increasing comonomer composition.

In the case of statistically random copolymers of NIPAM and *N,N*-diethylacrylamide (DEAAM), the VPTT of the hydrogels and the LCST of the aqueous solutions change nonlinearly with the monomer composition and reach the minimum at the intermediate composition of DEAAM [14, 15]. According to Plamper et al. [16], the transition temperature also depends on the monomer arrangement along the chain. This dependency is considered to be due to the formation of intramolecular hydrogen bonding between neighboring amide groups of NIPAM and DEAAM from the analysis using infrared spectroscopy. However, the mechanism is still open for discussion because consensus has not yet been reached regarding the band assignments of PNIPAM, even in the amide I and II regions [38, 39].



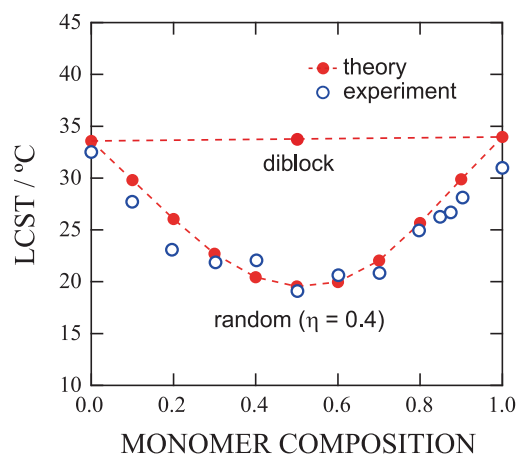
**Fig. 7** Model solution consisting of hydrogen-bonded copolymer chains in water. Both the A and B segments are capable of forming hydrogen bonds with water molecules. Contiguous trains of bound water molecules form hydrogen bonds cooperatively along the polymer chain. The cooperativity is blocked at the A-B boundary.

In this study, our group applies the concept of cooperative hydration [22] to the study of the nonlinear depression of the LCST in aqueous NIPAM-DEAAM copolymer solutions. The mechanism of hydration of each type of monomer is probably different because of their structure. We assume that cooperative sequences of bound water molecules along the chain cannot extend over different types of monomers. We do not consider the intramolecular hydrogen bonds between amide groups.

To investigate the relationship between the phase behavior and the monomer arrangement, we introduce a parameter  $\eta$  to specify the randomness of the monomer arrangement along the chain, which varies from 0 to 2. At  $\eta = 1$ , the copolymer chain has a completely random structure. The chain has a block-like arrangement of the comonomers when  $\eta < 1$  and has an alternating tendency when  $\eta > 1$ .

By systematic analysis of the effect of the monomer arrangement on the LCST, we found that the LCST of aqueous random copolymer solutions shifts to lower than that of each homopolymer solution. The hydration behavior becomes less sharp when the monomer sequence of the chains has a more alternating tendency. In contrast, for block copolymers such as diblock copolymers, the LCST changes linearly with the monomer composition. It is also found that a nonlinear depression of LCST does not occur in the case of random hydration. The nonlinear effect appears when the average block length of the comonomers is shorter than the average sequence length of the cooperative hydration.

Figure 7 shows a comparison between the theoretical results and the previously reported experimental data of the LCST of aqueous solutions of random copolymers [15]. We found that  $\eta = 0.4$  by fitting our calculation to



Comparison between the theoretical calculation results (closed circles) and the experimental data [15] (open circles) for the LCST at a volume fraction of polymer of  $\phi = 0.1$  plotted against the monomer composition. By fitting,  $\eta$  was determined to be 0.4. (Adapted with permission from ref. [26]. Fig. 1 and Fig. 12 in ref. [26] were combined)

the experimental data. The copolymer chains have a more block-like arrangement than that predicted by the random statistics. In the case of diblock copolymers, the theoretical LCST lies on the line that connects the LCSTs of each homopolymer solution, as reported in the literature [16], and the nonlinear depression of LCST does not occur.

## Conclusions

I have summarized our recent theoretical studies on the phase transition of hydrogels and aqueous solutions of thermosensitive homopolymers and copolymers on the basis of the concept of cooperative hydration.

First, we showed that cooperative hydration induces discontinuous volume changes in the gels in water with varying temperatures. The discontinuous volume phase transition can occur if the hydration is sufficiently cooperative. Second, by extending our theory to mixed binary solvent systems, where both solvent molecules are capable of forming hydrogen bonds with the polymer, we showed that competitive hydrogen bonding induces the reentrant swelling behavior. Our results reproduced the reentrant swelling behavior, including the discontinuous volume changes. Third, we investigated the excess solvent adsorption of the gel and the excess solvent binding to the polymer by analyzing our experimental data on microgels using our theory. We noted the possibility that selective water adsorption of the gels and selective methanol binding to the polymer chains occur near the transition temperature. Finally, we derived the phase diagram of aqueous solutions of thermosensitive copolymers, discussed the effect of the monomer composition and arrangement on the lower critical solution temperature, and compared our findings with

previously reported experimental data. We found that an alternating tendency in the monomer arrangement of copolymer chains inhibits cooperative hydration and makes the transition less sharp. This induces the nonlinear depression of the LCST as the monomer composition is varied.

**Acknowledgements** This work was partially supported by a Grant-in-Aid for Scientific Research (B) from the Japan Society for the Promotion of Science under Grant Number 19350057, a Grant-in-Aid for JSPS Fellows, and the Deutsche Forschungsgemeinschaft within the Collaborative Research Center SFB 985. The author wishes to thank all of his coworkers, especially Professor Fumihiko Tanaka, Professor Walter Richtering, and Dr. Christine Scherzinger for their active collaborations and for helpful discussions.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

### References

- Heskins M, Guillet JE. Solution properties of poly(*N*-isopropylacrylamide). *J Macromol Sci Chem*. 1968;2:1441–55.
- Fujishige S, Kubota K, Ando I. Phase transition of aqueous solutions of poly(*N*-isopropylacrylamide) and poly(*N*-isopropylmethacrylamide). *J Phys Chem*. 1989;93:3311–3.
- Hirokawa Y, Tanaka T. Volume phase transition in a nonionic gel. *J Chem Phys*. 1984;81:6379–80.
- Schild HG. Poly(*N*-isopropylacrylamide): experiment, theory and application. *Prog Polym Sci*. 1992;17:163–249.
- Hirotsu S. Phase transition of a polymer gel in pure and mixed solvent media. *J Phys Soc Jpn*. 1987;56:233–42.
- Zhang Y, Steven F, Bergbreiter ED, Cremer PS. Specific ion effects on the water solubility of macromolecules: PNIPAM and the hofmeister series. *J Am Chem Soc*. 2005;127:14505–10.
- Winnik F, Ringsdorf H, Venzmer J. Methanol-water as a con-solvent system for poly(*N*-isopropylacrylamide). *Macromolecules*. 1990;23:2415–6.
- Dong LC, Hoffman AS. Thermally reversible hydrogels: III. immobilization of enzymes for feedback reaction control. *J Cont Release*. 1986;4:223–7.
- Hirotsu S, Hirokawa Y, Tanaka T. Volume-phase transitions of ionized *N*-isopropylacrylamide gels. *J Chem Phys*. 1987;87:1392–5.
- Bae YH, Okano T, Kim SW. “On-off” thermocontrol of solute transport. I. temperature dependence of swelling of *N*-isopropylacrylamide networks modified with hydrophobic components in water. *Pharm Res*. 1991;8:531–7.
- Shibayama M, Mizutani S, Nomura S. Thermal properties of copolymer gels containing *N*-isopropylacrylamide. *Macromolecules*. 1996;29:2019–24.
- Bhalerao VS, Varghese S, Lele AK, Badiger MV. Thermo-reversible hydrogel based on radiation induced copolymerisation of poly(*N*-isopropylacrylamide) and poly(ethylene oxide). *Polymer*. 1998;39:2255–60.
- Djokpe E, Vogt W. *N*-isopropylacrylamide and *N*-isopropylmethacrylamide: cloud points of mixtures and copolymers. *Macromol Chem Phys*. 2001;202:750–7.
- Keerl M, Richtering W. Synergistic depression of volume phase transition temperature in copolymer microgels. *Colloid Polym Sci*. 2007;285:471–4.
- Maeda Y, Yamabe M. A unique phase behavior of random copolymer of *N*-isopropylacrylamide and *N,N*-diethylacrylamide in water. *Polymer*. 2009;50:519–23.
- Plamper FA, Steinschulte AA, Hofmann CH, Drude N, Mergel O, Herbert C, Erberich M, Schulte B, Winter R, Richtering W. Toward copolymers with ideal thermosensitivity: solution properties of linear, well-defined polymers of *N*-isopropyl acrylamide and *N,N*-diethyl acrylamide. *Macromolecules*. 2012;45:8021–6.
- Flory PJ. Thermodynamics of high polymer solutions. *J Chem Phys*. 1942;10:51–61.
- Huggins ML. Some properties of solutions of long-chain compounds. *J Phys Chem*. 1942;46:151–8.
- Flory PJ. Principles of polymer chemistry. Chapter 12, Cornell University Press, Ithaca, NY, 1953.
- Flory PJ. Statistical mechanics of swelling of network structures. *J Chem Phys*. 1950;18:108–11.
- Tanaka F. Polymer physics: Applications to molecular association and thermoreversible gelation. Cambridge: Cambridge University Press; 2011.
- Okada Y, Tanaka F. Cooperative hydration, chain collapse, and flat LCST behavior in aqueous poly(*N*-isopropylacrylamide) solutions. *Macromolecules*. 2005;38:4465–71.
- Kojima H, Tanaka F. Cooperative hydration induces discontinuous volume phase transition of cross-linked poly(*N*-isopropylacrylamide) gels in water. *Macromolecules*. 2010;43:5103–13.
- Kojima H, Tanaka F. Reentrant volume phase transition of cross-linked poly(*N*-isopropylacrylamide) gels in mixed solvents of water/methanol. *Soft Matter*. 2012;8:3010–20.
- Kojima H, Tanaka F, Scherzinger C, Richtering W. Temperature dependent phase behavior of PNIPAM microgels in mixed water/methanol solvents. *J Polym Sci Part B*. 2013;51:1100–11.
- Kojima H, Tanaka F. Nonlinear depression of the lower critical solution temperatures in aqueous solutions of thermo-sensitive random copolymers. *J Polym Sci Part B*. 2013;51:1112–23.
- Hirotsu S. Softening of bulk modulus and negative Poisson’s ratio near the volume phase transition of polymer gels. *J Chem Phys*. 1991;94:3949–57.
- Zimm BH, Bragg JK. Theory of the phase transition between helix and random coil in polypeptide chains. *J Chem Phys*. 1959;31:526–35.
- Amiya T, Hirokawa Y, Hirose Y, Li Y, Tanaka T. Reentrant phase transition of *N*-isopropylacrylamide gels in mixed solvents. *J Chem Phys*. 1987;86:2375–9.
- Schild HG, Muthukumar M, Tirrell DA. Cononsolvency in mixed aqueous solutions of poly(*N*-isopropylacrylamide). *Macromolecules*. 1991;24:948–52.
- Zhang G, Wu C. The water/methanol complexation induced reentrant coil-to-globule-to-coil transition of individual homopolymer chains in extremely dilute solution. *J Am Chem Soc*. 2001;123:1376–80.
- Hao J, Cheng H, Butler P, Zhang L, Han CC. Origin of con-solvency, based on the structure of tetrahydrofuran-water mixture. *J Chem Phys*. 2010;132:154902-1–154902-9.
- Tanaka F, Koga T, Winnik FM. Temperature-responsive polymers in mixed solvents: competitive hydrogen bonds cause con-solvency. *Phys Rev Lett*. 2008;101:028302.
- Tanaka F, Koga T, Kojima H, Winnik FM. Temperature- and tension-induced coil-globule transition of poly(*N*-isopropylacrylamide) chains in water and mixed solvent of water/methanol. *Macromolecules*. 2009;42:1321–30.
- Tanaka F, Koga T, Kojima H, Xue N, Winnik FM. Preferential adsorption and co-nonsolvency of thermoresponsive polymers in

- mixed solvents of water/methanol. *Macromolecules*. 2011;44:2978–89.
36. Walter J, Sehr J, Vrabec J, Hasse H. Molecular dynamics and experimental study of conformation change of poly(*N*-isopropylacrylamide) hydrogels in mixtures of water and methanol. *J Phys Chem B*. 2012;116:5251–9.
37. Mukae K, Sakurai M, Sawamura S, Makino K, Kim SW, Ueda I, Shirahama K. Swelling of poly(*N*-isopropylacrylamide) gels in water-alcohol (C<sub>1</sub>-C<sub>4</sub>) mixed solvents. *J Phys Chem*. 1993;97:737–41.
38. Katsumoto Y, Tanaka T, Ozaki Y. Relationship between the coil-globule transition of an aqueous poly(*N*-isopropylacrylamide) solution and structural changes in local conformations of the polymer. *Macromol Symp*. 2004;205:209–23.
39. Katsumoto Y, Tanaka T, Ihara K, Koyama M, Ozaki Y. Contribution of intramolecular C=O...H-N hydrogen bonding to the solvent-Induced reentrant phase separation of poly(*N*-isopropylacrylamide). *J Phys Chem B*. 2007;111:12730–7.



Hiroyuki Kojima was born in Hyogo, Japan (1983) and received his B.S. (2009), M.S. (2011), and ph.D. degree (2013) from Kyoto University under the supervision of Professor Fumihiko Tanaka. He received a Research Fellowship for Young Scientist of the Japan Society for the Promotion of Science (2012–2013). He joined the faculty of Department of Polymer Chemistry, Graduate School of Engineering, Kyoto University in 2013 as an assistant professor. He received Award for Encouragement of Research in Polymer Science (2017) from The Society of Polymer Science, Japan. His research field is physical chemistry of polymers.