

Feature Article

HYDRATION AND PHASE SEPARATION OF TEMPERATURE-SENSITIVE WATER-SOLUBLE POLYMERS*

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Abstract Collapse of a poly(*N*-isopropylacrylamide) (PNIPAM) chain upon heating and phase diagrams of aqueous PNIPAM solutions with very flat LCST phase separation line are theoretically studied on the basis of cooperative dehydration (simultaneous dissociation of bound water molecules in a group of correlated sequence), and compared with the experimental observation of temperature-induced coil-globule transition by light scattering methods. The transition becomes sharper with the cooperativity parameter σ of hydration. Reentrant coil-globule-coil transition in mixed solvent of water and methanol is also studied from the viewpoint of competitive hydrogen bonds between polymer-water and polymer-methanol. The downward shift of the cloud-point curves (LCST cononsolvency) with the mole fraction of methanol due to the competition is calculated and compared with the experimental data. Aqueous solutions of hydrophobically-modified PNIPAM carrying short alkyl chains at both chain ends (telechelic PNIPAM) are theoretically and experimentally studied. The LCST of these solutions is found to shift downward along the sol-gel transition curve as a result of end-chain association (association-induced phase separation), and separate from the coil-globule transition line. Associated structures in the solution, such as flower micelles, mesoglobules and higher fractal assembly, are studied by USANS with theoretical modeling of the scattering function.

Keywords: Cooperative dehydration; LCST phase separation; Poly(*N*-isopropylacrylamide); Cononsolvency; Coil-globule transition; Flower micelle.

INTRODUCTION

Aqueous solutions of temperature-sensitive poly(*N*-isopropylacrylamide) (PNIPAM) exhibit flat LCST cloud-point curves at around 32°C, which are almost independent both of the concentration up to 20 wt% and of the polymer molecular weight^[1–5]. The transmittance of light sharply diminishes in a very narrow temperature region where coil-globule transition (CG transition) of the polymer chain takes place^[6]. Sudden change in polymer conformation results in the temperature sensitivity. Although the origin of temperature-sensitivity had long been a mystery, we recently pointed out that it is caused by the cooperative dehydration of the bound water molecules upon heating^[7].

It was experimentally reported that the spinodal curves are also flat in a similar way to the cloud-point curve except in a very dilute regime^[3]. The solution does not phase separate even if it is brought to the unstable

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region above the spinodal, but instead particles of hundred nanometer scales consisting of the aggregates of PNIPAM chains are formed^[8, 9]. They are called mesoglobules. The inside of mesoglobules is highly concentrated, as high as 80 wt%, and vitreous. They persist for a long time.

On the basis of cooperative hydration, we study (1) sharp CG transition upon heating, (2) LCST with flat cloud point curves, (3) cononsolvency and reentrant CG transition in mixed solvents, (4) shift of LCST by the end-association of hydrophobically modified telechelic PNIPAM, (5) structure of flower micelles and transient gels.

TEMPERATURE-INDUCED COIL-GLOBULE TRANSITION OF PNIPAM CHAINS AND THEIR PHASE SEPARATION IN PURE WATER

The cooperativity in hydration is caused by the positive correlation between neighboring bound water molecules. If a water molecule succeeds in forming a hydrogen bond with an amide group on a chain, a second water molecule can form a bond more easily than the first one because the first molecule causes some displacement of the isopropyl group, which creates more access space for the next molecule. As a result, consecutive sequences of bound water appear along the chain, which leads to a pearl-necklace type chain conformation (Fig. 1^[7, 10]). When the chain is heated, each sequence is dehydrated in a group, resulting in the sharp collapse of the chain.

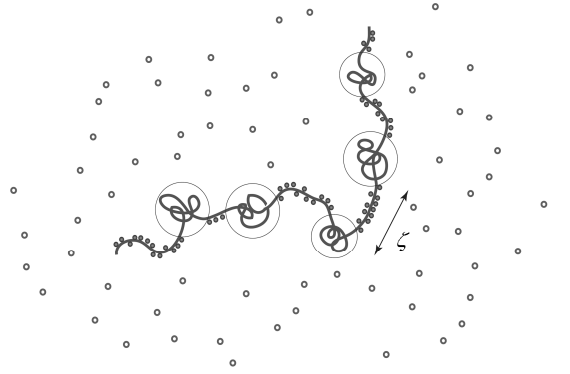


Fig. 1 Sequential hydrogen bonds formed along the polymer chain due to the cooperative interaction between the nearest neighboring bound water molecules (Printed with permission from the literature [7])
The type of polymer-water associated complex is specified by the index $j \equiv \{j_1, j_2, \dots\}$, where j_ζ is the number of sequences that consist of a run of hydrogen-bonded ζ consecutive water molecules.

Let us first specify the polymer conformation by the index $j \equiv \{j_1, j_2, \dots\}$, which indicates that the chain with total number n of repeat units carries the number j_ζ of the hydrated sequences of length ζ (in terms of the number of repeat units). The statistical properties of the chain is described by the canonical partition function

$$Z(T) \equiv \sum_j \exp[-\beta \Delta A(j)] = \sum_j \omega(j) \prod_\zeta (\eta_\zeta)^{j_\zeta}, \quad (1)$$

where $\omega(j) \equiv (n - \sum \zeta j_\zeta)! / \prod j_\zeta! [n - \sum (\zeta + 1) j_\zeta]!$ is the number of different ways to place the hydrated coils and collapsed globules alternatively along the chain. It is related to the entropy of hydration^[7, 11]. The weight η_ζ gives the statistical weight for the appearance of the sequence of length ζ . To describe cooperativity, let $-\varepsilon$ be the binding free energy of a water molecule, and let $-\Delta\varepsilon$ be the interaction energy between the nearest neighboring bound water molecules. Then, it is given by the Zimm-Bragg form^[12] $\eta_\zeta = \sigma \eta(T)^\zeta$, where $\sigma \equiv \exp(-\beta \Delta\varepsilon)$ is the cooperativity parameter, $\eta(T) \equiv \exp[(\varepsilon + \Delta\varepsilon)/k_B T]$ is the association constant of the hydrogen bonding. For random hydration, as seen in aqueous solutions of poly(ethylene oxide)s, cooperativity parameter

is $\sigma = 1$. Smaller σ gives stronger cooperativity.

Instead of summing up all possible types j , we find the most probable distribution j^* by minimizing the free energy, by which we calculate the average degree of hydration $\theta(j^*) \equiv \sum_{\zeta=1}^n \zeta j_{\zeta}^* / n$ and the mean end-to-end distance $\langle R^2 \rangle$. The latter is normalized by the reference value at 20°C, and is plotted in terms of the expansion factor $\alpha_R \equiv [\langle R^2 \rangle / \langle R^2 \rangle_{(T=20)}]^{1/2}$. Figure 2 compares our calculation with the experimental data^[6] of the mean radius of gyration measured by light scattering method. With stronger cooperativity, the transition becomes sharper. Calculation assumes $\sigma = 10^{-4}$ to fit the data. Other fitting parameters are: $n = 7.0 \times 10^4$, $\lambda_{w0} = 0.001$, $\gamma_w = 3.788$, $\Theta = 555$, $\sigma_w = 2 \times 10^{-5}$, $\kappa_w = 0.31$. (See Ref. [11] for detailed definition.)

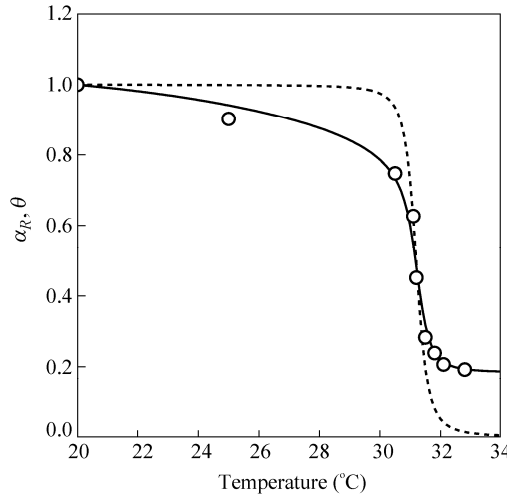


Fig. 2 The expansion factor α_R (solid line) and the degree of hydration θ (dotted line) plotted against temperature (Printed with permission from the literature [11])
The expansion factor is compared with the experimental data obtained by Fujishige *et al*^[6].

We next consider a model solution in which the number N_1 of polymer chains with n repeat units are mixed with the number N_0 of water molecules. We are based on the lattice-theoretical picture of polymer solutions, and divide the system volume V into cells of size a , each of which can accommodate either a water molecule or a statistical repeat unit of the polymer. We assume incompressibility of the solution, so that we have $\Omega = N_0 + nN_1$, where $\Omega \equiv V/a^3$ is the total number of cells.

To describe adsorption of water, let $N(j)$ be the number of polymer-water (p-w) complexes whose type is specified by the index j (see Fig. 1). The total DP of a complex is given by $n(j) \equiv n[1 + \theta(j)]$.

Then, the free energy of mixing is given by

$$\beta \Delta F = N_{fw} \ln \phi_{fw} + \sum_j N(j) \ln \phi(j) + \beta \sum_j \Delta A(j) N(j) + \chi(T) \phi(1 - \phi) \Omega, \quad (2)$$

where $\phi(j) \equiv n(j)N(j)/\Omega$ is the volume fraction of the complex j , N_{fw} the number of free water molecules in the solution, and $\phi_{fw} \equiv N_{fw}/\Omega$ their volume fraction. $\chi(T)$ is the Flory's interaction parameter for the van der Waals interaction in the background. $\Delta A(j)$ defined in Eq. (1) is the conformational free energy to form a complex of the type j measured relative to the reference conformation $j_0 \equiv \{0, 0, \dots\}$ where no water molecule is adsorbed.

By finding the chemical potentials for the hydrated polymer and water from this free energy, and imposing the hydration equilibrium condition $\Delta\mu(j) = \Delta\mu(j_0) + n\theta(j)\Delta\mu_{fw}$, we can study the solution properties such as hydration, phase separation and spinodals. Figure 3 draws the spinodal curves for different cooperative parameters σ with fixed other parameters. It theoretically demonstrates how the bottom part of the miscibility

loops becomes flatter with decrease in σ . In the calculation, usual miscibility domes with UCST appear at low temperature, but these are not observable in the experiments because of the freezing of water.

Figure 4 compares theoretical calculation with experimental data^[3] on the spinodal points. In the experiments, the upper part of the miscibility square is impossible to observe because temperature is too high. Theoretical parameters used are $\Theta_0 = 555$ and $\lambda_0 = 0.002$ for $n = 100$, and $\Theta_0 = 565$ and $\lambda_0 = 0.003$ for $n = 1000$. Other parameters are fixed at $\gamma = 3.5$, $\sigma = 0.3$. The polymer molecular weight used in the experiment is $M_w = 615500$, so that the nominal number of monomers is roughly given by $n = 5400$. Since the statistical unit used in the lattice theory must be regarded as a group of monomers, we have tried to fit the data by $n = 100$ and 1000 . (Theoretical calculation does not depend so much upon the number n if it is larger than 500.) We have seen a good agreement by fixing the cooperative parameter at $\sigma = 0.3$.

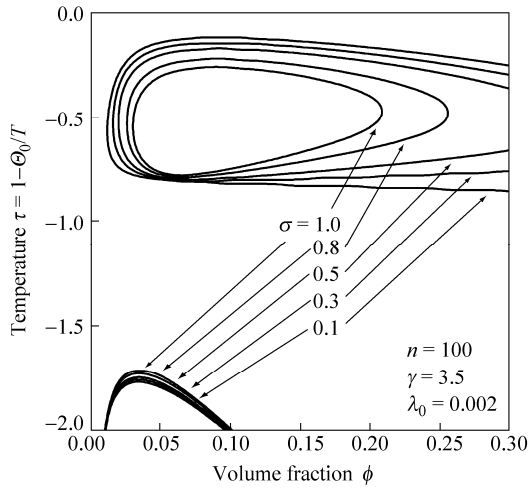


Fig. 3 Spinodal lines drawn on the (reduced) temperature and concentration plane for different cooperative parameter σ (Printed with permission from the literature [7])
The bottom part of the miscibility square becomes flatter with decrease in the cooperative factor σ .

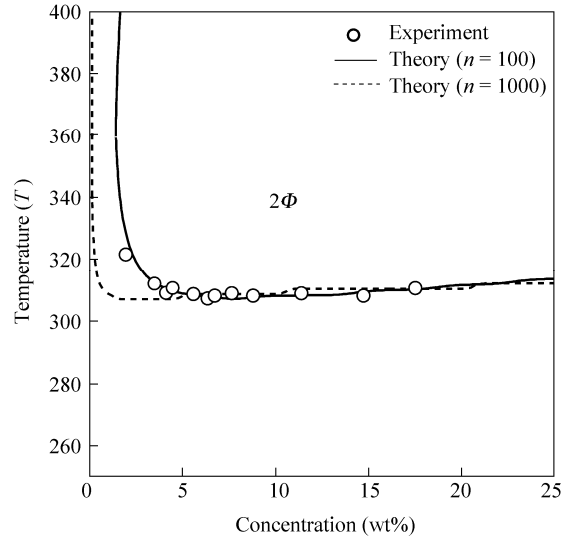


Fig. 4 Phase diagrams of aqueous PNIPAM solution (Printed with permission from the literature [7])
Experimental data (o) of the spinodal curve is compared with theoretical calculation; The DP of the polymer is $n = 100$ (solid line) and $n = 1000$ (broken line).

REENTRANT COIL-GLOBULE-COIL TRANSITION IN MIXED SOLVENT OF WATER/METHANOL

If methanol is mixed to such aqueous PNIPAM solutions, polymer chain collapses^[13], cross-linked gels undergo volume phase transition^[14, 15], and polymer solutions phase separate^[16–18], although methanol is a good solvent for PNIPAM. If two good solvents become poor when mixed, they are called cononsolvents. In water/methanol mixture, cononsolvency is most evident at around 0.35 mole fraction of methanol. The mixture recovers good solvency at high concentration of methanol. We show here that such a peculiar reentrant behavior of the solutions is caused by the competitive hydrogen bonding of water and methanol onto the polymer chain^[11]. The effect becomes strongest where the competition is highest. The total number of bound molecules shows a minimum at this point.

Figure 5 shows the expansion factor for the end-to-end distance $\alpha_R \equiv [\langle R^2 \rangle / \langle R^2 \rangle_0]^{1/2}$ (solid lines) and the total coverage $\theta \equiv \theta^{(w)} + \theta^{(m)}$ (broken lines) plotted against the molar fraction x_m of methanol, $\langle R^2 \rangle_0$ is the value in pure water. The calculation was done by assuming that all parameters are symmetric and with the methanol/water volume ratio $p = 1$ as a test case. The cooperativity parameter σ varies from curve to curve. We can clearly see that the total coverage takes a minimum value at $x_m = 0.5$ (stoichiometric concentration) as a

result of the competition, so that the end-to-end distance also takes minimum at $x_m = 0.5$. A slight deviation from stoichiometry is nonlinearly magnified on the chain by cooperativity (nonlinear amplification). As cooperativity becomes stronger, the depression of the end-to-end distance becomes narrower and deeper. A slightest bias in the bulk composition x_m from the symmetry results in a sharp recovery (majority rule). In a real mixture, the association constant and cooperativity parameter are different for water and methanol, so that we expect asymmetric behavior with respect to the molar fraction.

Figure 6 shows a comparison between the experimental mean radii of gyration (circles) obtained by laser light scattering measurements^[13] and mean end-to-end distances obtained by theoretical calculations (solid line). Both are normalized by the reference value in pure water. The total coverage θ , including bound water and bound methanol, is also plotted (broken line). The molecular weight of the polymer used in the experiment is $M_w = 2.63 \times 10^7 \text{ g mol}^{-1}$, and hence we fixed $n = 10^5$. The volume ratio is set to be $p = 2$ from the molecular structure of methanol. For larger p , it turned out that the recovery of the expansion factor at high methanol composition was not sufficient. In order to have a sharp collapse at around $x_m \approx 0.17$ we had to fix the cooperativity as high as $\sigma_w = 10^{-4}$. Similarly, to produce the gradual recovery at around $x_m \approx 0.4$, we used $\sigma_m = 10^{-3}$. The existence of p-w and p-m competition may be detectable experimentally by techniques such as Fourier-transformed infrared spectroscopy.

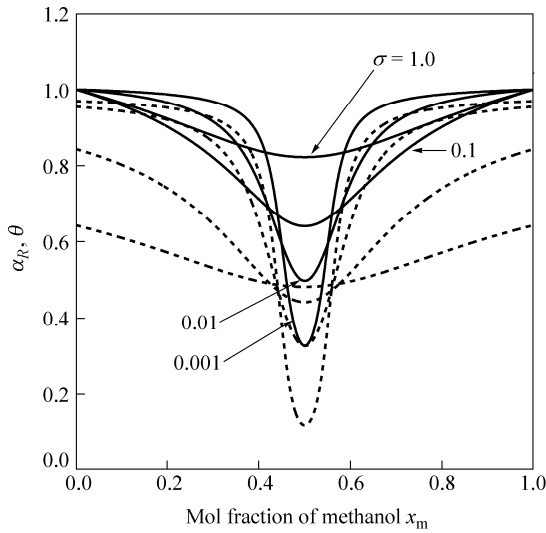


Fig. 5 The normalized end-to-end distance (solid lines) and the total coverage by bound molecules (broken lines) plotted against the molar fraction of methanol (Printed with permission from the literature [11])

The DP of the polymer chain is fixed at $n = 100$; The volume ratio of the solvents is fixed at $p = 1$; The cooperativity parameter $\sigma_w = \sigma_m$ is varied from curve to curve; The association constants are fixed at $\tilde{\lambda}_w = \tilde{\lambda}_m = 1.8$; The monomer expansion factors are fixed at $\kappa_w = \kappa_m = 2.0$.

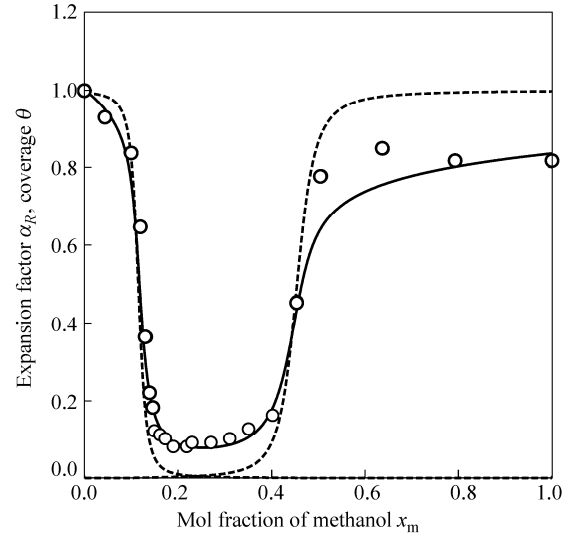


Fig. 6 Comparison between the present calculation (line) of the expansion factor for the mean square end-to-end distance for $n = 10^5$ and $p = 2$ and the experimental data of the radius of gyration by Zhang and Wu (circles)^[13] (Printed with permission from the literature [11])

The total coverage is also plotted (broken line).

Theoretical modelling of PNIPAM solutions in mixed solvent of water/methanol was attempted by using three interaction parameters of Flory type^[16], but analysis was incomplete; no definite conclusion was drawn due to the unbiguity of their temperature dependence. Similarly to Eq. (2), we start from the free energy with competitive hydrogen bonds

$$\begin{aligned} \beta \Delta F = & N_{fw} \ln \phi_{fw} + N_{fm} \ln \phi_{fm} + \sum_{j_w} N(j_w) \ln \phi(j_w) + \sum_{j_m} N(j_m) \ln \phi(j_m) \\ & + \beta \sum_{j_w, j_m} \Delta A(j_w, j_m) N(j_w, j_m) + [\chi_{pw} \phi_p \phi_w + \chi_{pm} \phi_p \phi_m + \chi_{wm} \phi_w \phi_m] \Omega. \end{aligned} \quad (3)$$

Because water and methanol are mixed well to each other, we have $\chi_{wm} = 0$. Also, methanol dissolves PNIPAM at all temperature, we assume $\chi_{pm} = 0$.

Let $\phi_p \equiv \phi$, $\phi_w \equiv (1 - \phi)(1 - \nu_m)$, $\phi_m \equiv (1 - \phi)\nu_m$ be the volume fraction of PNIPAM, water and methanol, and let $G_{\alpha, \beta} \equiv [\partial \mu_\alpha / \partial \phi_\beta]$ be the Gibbs determinant for the ternary mixture. Figure 7 shows the spinodal lines obtained from the condition for stability limit $|G| = 0$ plotted on the plane of reduced temperature $\tau \equiv 1 - \Theta/T$ and volume fraction of methanol ν_m . The volume fraction of the polymer is fixed at $\phi = 0.1$. We need experimental data in pure methanol to fix the parameters pertaining to methanol, but since they are not available, we fix cooperativity parameter at $\sigma_m = 0.3$, and change the amplitude λ_{m0} (entropy contribution) in the association constant $\lambda_m(T) = \lambda_{m0} \exp[\gamma_m(1 - \tau)]$. From the miscibility loop in pure water, we have two boundaries (UCST and LCST) which shift downwards with the mole fraction of methanol. The downward shift of the lower boundary from LCST is called LCST cononsolvency. Also we have other phase boundary starting from the miscibility dome in pure water (called UCST cononsolvency).

Figure 8 magnifies LCST cononsolvency and plot by the real temperature. The minimum of the cloud-point curve depends upon the strength of p-m hydrogen bond, but the initial slopes (proportional to the preferential adsorption coefficient) of the curves are independent of it. In the experiment^[16–18], the temperature drop is the largest, from 31.5°C down to −7°C, for specific molar fraction $x_m = 0.35$ of methanol. Hence, we can estimate λ_{m0} to be as small as 0.001.

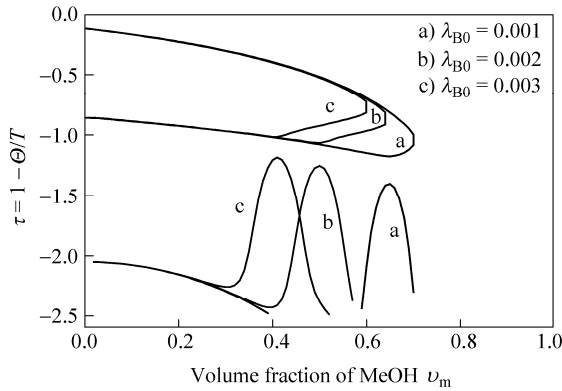


Fig. 7 The phase separation region plotted on the reduced temperature-solvent composition plane

The UCST miscibility dome expands sharply in a very narrow region of the volume fraction of methanol. The miscibility loop shifts downward with the methanol volume fraction.

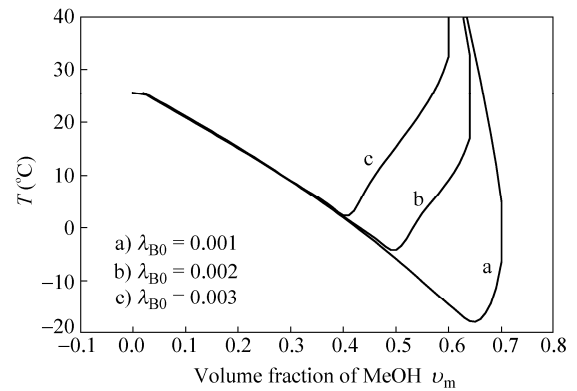


Fig. 8 The LCST cononsolvency region is magnified on the temperature-volume fraction plane

The initial slope of the LCST downward shift remains the same for 3 different strength of the methanol hydrogen bonds.

PHASE DIAGRAMS OF AQUEOUS SOLUTIONS OF HYDROPHOBICALLY MODIFIED TELECHELIC PNIPAMS

Let us move to the aqueous solutions of polymers carrying short hydrophobic chains at both chain ends (telechelic chelic associating polymers).

The solution properties drastically change when PNIPAM chains are hydrophobically modified. In particular, telechelic PNIPAMs carrying short alkyl chains at their chain ends exhibit a variety of associative structures, from flower micelles to gel networks. In the solutions of telechelic PNIPAM, hydration coexist with end-chain association. The LCST of these solutions is found to decrease along the sol-gel transition line as a

result of end-chain association (association-induced phase separation). The LCST deviates from the collapse transition line. We relate the magnitude of the LCST drop to the cooperativity parameter of hydration (Fig. 9)^[19]. The LCST decreases substantially (*ca.* 100 K) in the case of random hydration ($\sigma = 1$ for PEO), whereas only a small shift (*ca.* 5 K to 10 K) occurs in the case of cooperative hydration ($\sigma = 0.3$ for PNIPAM). The molecular weight dependence of the LCST curves is inverted; shorter chains show lower LCST (Fig. 9). Such an inverted molecular weight dependence is brought by the fact that the number density of the end-chain hydrophobes is larger for the shorter chains when compared at the same weight concentration, and hence tendency for association is stronger for the shorter chains. As a result, the average molecular weight of the aggregates becomes larger, so that the phase separation region expands. Results are compared with experimental observations of the cloud points of tel-PEO and tel-PNIPAM in water.

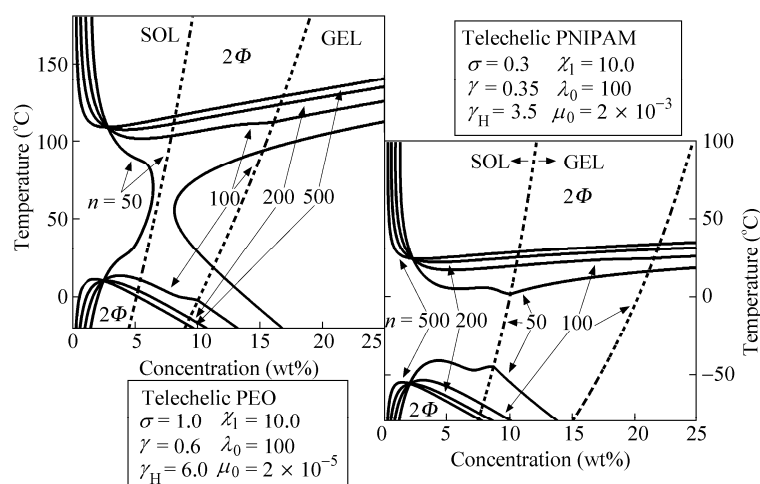


Fig. 9 Comparison of the phase diagrams of telechelic associating polymers with random hydration ($\sigma = 1.0$, left) and with cooperative hydration ($\sigma = 0.3$, right) (Printed with permission from the literature [19]) Spinodal lines (solid lines) and sol/gel transition lines (broken lines) are shown.

SOLUTION STRUCTURE OF TELECHELIC PNIPAM AS STUDIED BY NEUTRON SCATTERING

On the basis of the results from a small-angle neutron scattering (SANS) study of aqueous solutions of a telechelic PNIPAM with octadecyl end groups, we developed a theoretical model of the self-assembly of this polymer in water as a function of temperature and concentration^[20].

This model leads to the following description (Fig. 10). In solutions of concentration 10 gL^{-1} kept between 10°C and 20°C , telechelic PNIPAMs ($M_n = 22200 \text{ g mol}^{-1}$) associate in the form of flower micelles, containing about 12 polymer chains, assembled in a 3-layered core-shell morphology with an inner core consisting of the octadecyl units, a dense inner shell consisting of partly collapsed PNIPAM chains and an outer shell of swollen hydrated chains. Drastic changes in the scattering profile of the solution heated above 31°C are attributed to the formation of mesoglobules (diameter of *ca.* 40 nm) consisting of about 1000 polymer chains. On further heating, the aggregation number of the mesoglobules increases. It reaches a value of *ca.* 9000 at 34°C and stays constant upon further heating.

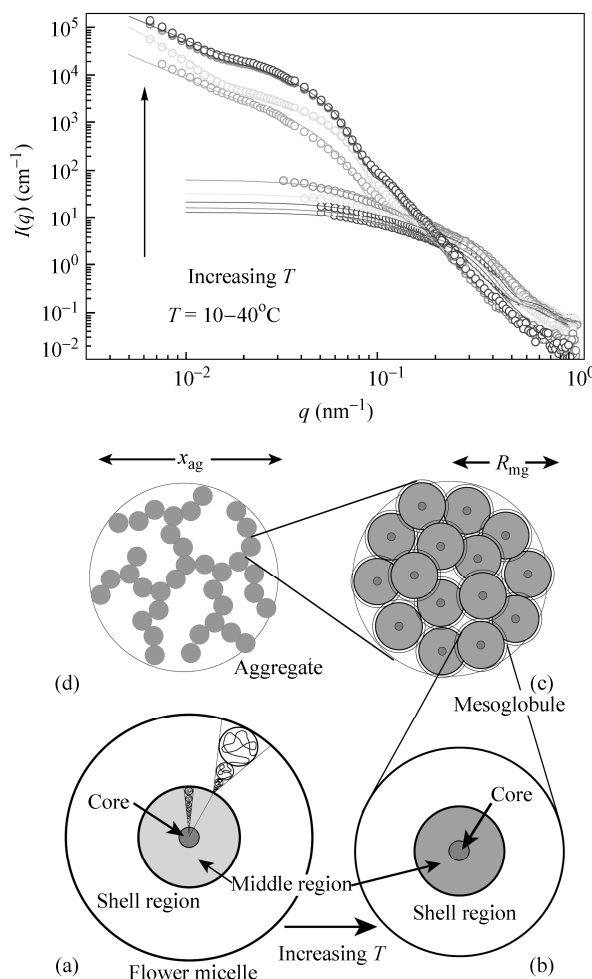


Fig. 10 (Top) Neutron scattering intensity of the $c = 10 \text{ gL}^{-1}$ solution of telechelic PNIPAMs ($T = 10\text{--}40^\circ\text{C}$): (a) (b) 3-layered flower micelles, (c) mesoglobules and (d) fractal aggregate of mesoglobules

In solutions of lower concentration (1 gL^{-1}), association of flower micelles and mesoglobules does not occur, however the structure of individual flower micelles and mesoglobules is not affected by the change in concentration. In solutions of 50 gL^{-1} in which flower micelles are expected to be partially connected by bridge chains, a peak attributed to correlation between flower micelles appears in the scattering profiles recorded at low temperature ($10\text{--}20^\circ\text{C}$). In spite of the intermicellar bridging connection, the overall temperature dependence of the scattering profile at 50 gL^{-1} remains similar to that at 10 gL^{-1} .

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