Quantifying cosolvent-mediated interactions in the aggregation of thermoresponsive polymers

K. Kyriakos,1 M. Philipp,1 C.-H. Lin,1 M. Dyakonova,1
N. Vishnevetskaya,1 I. Grillo,2 A. Zaccone,3 A. Miasnikova,4
A. Laschewsky,4,5 P. Müller-Buschbaum,1 and C.M. Papadakis1,∗

1Fachgebiet Physik weicher Materie/Lehrstuhl für Funktionelle Materialien,
Physik-Department, Technische Universität München,
James-Franck-Str. 1, 85748 Garching, Germany
2Large Scale Structures Group, Institut Laue-Langevin,
6, rue Jules Horowitz, 38042 Grenoble, France
3Theorie weicher Materie, Physik-Department, Technische Universität München,
James-Franck-Str. 1, 85748 Garching, Germany
4Institut für Chemie, Universität Potsdam,
Karl-Liebknecht-Str. 24-25, 14476 Potsdam-Golm, Germany
5Fraunhofer Institut für Angewandte Polymerforschung,
Geiselbergstr. 69, 14476 Potsdam-Golm, Germany

(Dated: January 29, 2015)
Abstract

The aggregation kinetics of thermoresponsive core-shell micelles with a poly(N-isopropyl acrylamide) shell in pure water or in mixtures of water with the cosolvents methanol or ethanol at mole fractions of 5-% is investigated during a temperature jump across the respective cloud point. At the cloud point, aggregates are formed, and their growth is followed with time-resolved small-angle neutron scattering. Using the reversible association model, we determine the interaction potential between the aggregates from their growth rate in dependence on the cosolvent. We attribute the effect of the cosolvent on the interaction potential to the fact that the structured layer of hydration water around the aggregates is perturbed by the cosolvent, which reduces the repulsive hydration force between the aggregates. The effect is the more pronounced, the larger the molar volume of the cosolvent.

PACS numbers: 82.35.Jk Copolymers, phase transitions, structure. 61.25.he Polymer solutions. 61.05.fg Neutron scattering (including small-angle scattering)

*Electronic address: papadakis@tum.de
Colloidal dispersions of soft matter particles in aqueous media are ubiquitous, e.g. in paints or as drug delivery systems. Regarding their aggregation in solution, a number of mechanisms have been identified. A special kind of colloidal dispersions is formed by thermoresponsive polymers. In aqueous solutions, these polymers collapse and become water-insoluble above their cloud point $T_{cp}$ which results in the formation of mesoglobules in the colloidal size range [1]. However, the pathway from molecularly dissolved polymers to mesoglobules is under debate [2–4]. Because the chain collapse and the mesoglobule formation are reversible, a number of smart materials have been created on the basis of thermoresponsive polymers, for applications such as ultrafiltration [5] and drug delivery [6].

Poly(N-isopropyl acrylamide) (PNIPAM) is a widely studied thermoresponsive polymer because $T_{cp}$ is with $\sim 32 \degree C$ in a convenient range. Moreover, a large variety of mesostructures have been created, such as microgels [7], core-shell nanoparticles [8] and micelles [9].

The addition of a cononsolvent, e.g. a short chain alcohol, to aqueous solutions of PNIPAM homopolymers [10, 11] results in a considerable decrease of $T_{cp}$, in spite of the fact that these alcohols are good solvents for PNIPAM [12, 13]. The same effect has also been found for dispersions of PNIPAM microgels [14, 15] and for micellar solutions of block copolymers of PNIPAM with hydrophobic blocks [16]. Despite the vivid discussion regarding the origin of this phenomenon on the molecular level [10, 17–20], no agreement has been reached. Both, the arrangement of water and the cononsolvent along the PNIPAM chain in sequences as well as the change of the water structure by the kosmotropic alcohol have been put forward as possible mechanisms.

In the present work, we focus on the influence of two cononsolvents—methanol and ethanol—on the colloidal growth process of an aqueous PNIPAM-based micellar solution. We follow the growth of the aggregates formed by micelles with collapsed shells during heating of the solutions through $T_{cp}$, in pure water as well as in the presence of methanol or ethanol. This way, we vary the potential between the aggregates. Compared to the often studied PNIPAM homopolymer solutions, the micellar solutions have the advantage that the aggregation proceeds more slowly [16] and thus can be followed by time-resolved small-angle neutron scattering (TR-SANS) in detail.

Several studies [16, 21, 22] have shown that the aggregation of colloidal dispersions of soft matter often deviates from the diffusion limited (DLCA) [23] and the reaction limited colloidal aggregation (RLCA) models [24] used to describe the aggregation of hard matter
colloidal particles. Possible reasons are that the interaction between soft particles is often weak and that association and dissociation may occur simultaneously [8, 16, 25–27].

In the present work, we probe the aggregation of thermoresponsive micelles of P(S-d₈)-b-PNIPAM (P(S-d₈) stands for fully deuterated polystyrene) in the presence of cosolvents upon a rapid temperature increase (temperature jump) through \( T_{cp} \). TR-SANS enables us to characterize the micellar structure below \( T_{cp} \) and the growth of the aggregates above \( T_{cp} \) with a high time resolution (0.2 s). The findings are quantitatively analyzed using a modified reversible association model [8, 25]. The growth rate is related to the interaction potential between the aggregates, which reflects the properties of their hydration shell in the presence of a cosolvent.

We investigate a P(S-d₈)₁₁-b-PNIPAM₄₃₁ diblock copolymer [28], which was dissolved in pure D₂O, in mixtures of D₂O:d-MeOD and of D₂O:d-EtOD, each with 5 mole-% of the alcohol (d-MeOD and d-EtOD are fully deuterated methanol and ethanol, respectively). It has previously been observed that the reduction of \( T_{cp} \) is the stronger, the larger the molar volume of the cosolvent [13]. In all solutions, the polymer concentration was 30 mg/ml, i.e. far above the critical micelle concentration in D₂O [29]. \( T_{cp} \) is 30.0 ± 0.2 °C, 28.0 ± 0.2 °C and 27.0 ± 0.2 °C in D₂O, in D₂O:d-MeOD and in D₂O:d-EtOD, respectively.

TR-SANS measurements were performed at the high-flux instrument D22, ILL in Grenoble, France. Temperature jumps were realized using a modified Biologic SFM-300 stopped-flow instrument [22, 30]. The solutions were equilibrated at \( T_{cp} - 3 \) K and were transferred remotely into the sample cell which had been preheated to \( T_{cp} + 2 \) K. \( T_{cp} \) was crossed after 40.0 s, 9.0 s and 0.5 s for D₂O, D₂O:d-MeOD and D₂O:d-EtOD, respectively. The \( q \)-range was 0.03-2.0 nm⁻¹. The measuring times were between 0.2 s and 15 s, and the entire measurement lasted 1500 s. Detailed information about the sample preparation and the set-up is given in the Supplemental Material (SM).

SANS curves of P(S-d₈)₁₁-b-PNIPAM₄₃₁ in D₂O:d-MeOD are shown as an example in Fig. 1. Three different regimes are distinguished: (I) below \( T_{cp} \), scattering from micelles with swollen shells is observed (see below); (II) as soon as \( T_{cp} \) is crossed, their shells collapse, the micelles become hydrophobic and form aggregates which grow with time; (III) after a certain time, the aggregate size exceeds the instrumental resolution, but the surface structure of the aggregates can still be characterized. To quantify these observations, structural models are fitted to the curves (see the SM).
FIG. 1: SANS curves of P(S-d8)_{11}-b-PNIPAM_{431} in D_2O:d-MeOD during a temperature jump from 25 °C to 30 °C. Regimes I-III are indicated. The inset shows the temperature profile.

Fig. 2 compiles representative resulting parameters for all solutions. The remaining parameters are given in the SM. In regime I, spherical core-shell micelles with a P(S-d8) core having a radius $r_{core} = 2.7$ nm and a PNIPAM shell of a thickness of $\sim 10$ nm are identified. The micellar radius, $r_{mic}$—and thus the shell thickness—are found to increase slightly as $T_{cp}$ is approached, especially for D_2O:d-MeOD, which already hints at the influence of the cononsolvent on the molecular conformation of PNIPAM close to $T_{cp}$. For D_2O:d-EtOD, $T_{cp}$ was reached very early, hampering the detection of a possible increase of $r_{mic}$. Still, the presence of swollen micelles in the very early stages is revealed. In regime II, aggregates of radius $r_{agg}^{cp} = 5.7 \pm 0.6$ nm, $15.6 \pm 1.1$ nm and $18.1 \pm 1.6$ nm are formed in D_2O, in D_2O:d-MeOD and in D_2O:d-EtOD, respectively, within less than $\sim 2$ s, which grow with time (Fig. 2). In D_2O, the aggregates are initially as small as one single collapsed micelle [29]. In contrast, for D_2O:d-MeOD and D_2O:d-EtOD, the aggregates consist initially of $\sim 15$ and $\sim 30$ collapsed micelles, which shows that the formation and growth of aggregates are the faster, the larger the molar volume of the cononsolvent. Thus, the aggregation is significantly accelerated by the cononsolvent. This is also reflected in the rate of the subsequent growth in regime II.
In regime III, the forward intensity $I(q \to 0)$ decreases with time (Fig. 1), reflecting the decrease of the specific surface of the aggregates, i.e. their continued growth. In this regime, $r_{agg}$ cannot be determined, but information on the surface properties of the aggregates is obtained. The Porod exponent $\alpha$ is initially $4.5 \pm 0.12$, $5.0 \pm 0.18$ and $5.1 \pm 0.17$ for D$_2$O, D$_2$O:d-MeOD and D$_2$O:d-EtOD (Fig. 2), thus larger than 4. This indicates that a gradient of polymer concentration normal to the aggregate surface is formed very rapidly, after $T_{cp}$ is crossed. With time, $\alpha$ increases to values of 5.5-5.8, suggesting the formation of a dense outer layer of collapsed polymers [22]. To conclude, we have several indications that the growth of aggregates is accelerated by cononsolvents, the aggregates are compact (and not fractal) and feature a dense polymer layer near their surface.

The growth rate of the aggregates above $T_{cp}$ is related to their interaction potential. To quantify this relationship, the aggregate radii, $r_{agg}(t)$, found in regime II are replotted in Fig. 3a after normalization by their initial values, $r_{agg}^{cp}$ (see above), and using a time reduced by the time $t_{cp}$ at which $T_{cp}$ is crossed. A linear dependence is observed in all three cases with the slope increasing with the molar volume of the cononsolvent molecule (see the SM), which confirms the anticipated acceleration of aggregate growth. To derive the interaction potential between the colloidal aggregates consisting of collapsed micelles, we adapt the reversible association model proposed for suspensions of thermoresponsive nanoparticles [8, 25], to the aggregates formed by self-assembled micelles. In this model, collapsed hydrophobic nanoparticles associate at a rate $k_+$ and dissociate with a rate $k_-;$ thus, the overall growth rate of the aggregates is related to the extent of dissociation. Since association is diffusion-limited, $k_+$ is given by [31]

$$k_+ = \frac{4 \pi D_{mut}}{\left( (2r_{agg}^{cp})^{-1} - (2r_{agg}^{cp} + \delta)^{-1}\right) e^{-V/k_BT} + (2r_{agg}^{cp} + \delta)^{-1}}$$

(1)

where $k_B$ is Boltzmann’s constant, $D_{mut} = k_B T/3 \pi \eta r_{agg}^{cp}$ the mutual diffusion coefficient of the aggregates, $T$ the target temperature, $\eta$ the viscosity of the solvent mixture [32] and $V$ the depth of the interaction potential. $\delta$ is the cut-off length of the potential and has been chosen at 10 nm, which is in the usual range of the hydrophobic interaction for particles in aqueous media [33]. $k_-$ is given by $k_- = (D/\delta^2) \exp(-V/k_BT)$, where $D = D_{mut}/2$ is the diffusion coefficient of the aggregates. This results in the following expression

$$\frac{dr_{agg}(t)}{dt} = ANK_{eff} r_{agg}^{cp}$$

(2)
FIG. 2: Fit parameters as a function of time after injection for the solutions in (a) D$_2$O, (b) D$_2$O:d-MeOD and (c) D$_2$O:d-EtOD. Left axis: Black squares: radii of the micellar cores, $r_{\text{core}}$; red circles: micellar radii, $r_{\text{mic}}$; blue diamonds: radii of gyration of the aggregates, $r_{\text{agg}}$. Right axis: Porod exponent $\alpha$ from the Guinier-Porod form factor (filled green triangles) and from the Porod law (open green triangles). The dashed and dotted lines mark the transition times between regimes I and II, $t_{cp}$, and between regimes II and III, respectively (see text).

with $A$ being a numerical coefficient related to the scattering intensity, $I(q \rightarrow 0)$ and to $r_{agg}^{cp}$ (see the SM). $N$ is the initial concentration of aggregates at $t_{cp}$, estimated from the polymer concentration and assuming an aggregation number of 30 polymers/micelle [34]. For the solutions in D$_2$O:d-MeOD and D$_2$O:d-EtOD, the initial aggregates were as-
sumed to consist of ~ 15 and ~ 30 micelles [35] collapsed micelles, respectively. \( K_{\text{eff}} = 16k_3^3N^2/(2k_+ + 4k_+N - 2.62k_-) \) is the effective association constant. This approach offers the possibility to extract the depth of the potential \( V \) from the growth rate of the aggregates. The fits of Eq. 2 to the data are shown in Fig. 3a. The slopes amount to \((24.4 \pm 0.5) \times 10^{-3} \text{s}^{-1}\), \((29.9 \pm 0.6) \times 10^{-3} \text{s}^{-1}\) and \((55.4 \pm 0.5) \times 10^{-3} \text{s}^{-1}\), for \( \text{D}_2\text{O} \), \( \text{D}_2\text{O}:d\text{-MeOD} \) and \( \text{D}_2\text{O}:d\text{-EtOD} \), corresponding to \( K_{\text{eff}} \) values of \((0.947 \pm 0.008) \times 10^{-18} \text{s}^{-1}\), \((9.0 \pm 0.04) \times 10^{-18} \text{s}^{-1}\) and \((6.5 \pm 0.05) \times 10^{-18} \text{s}^{-1}\).

FIG. 3: (a) Normalized aggregate radii as a function of the reduced time. Solution in \( \text{D}_2\text{O} \) (black squares), in \( \text{D}_2\text{O}:d\text{-MeOD} \) (red triangles) and in \( \text{D}_2\text{O}:d\text{-EtOD} \) (blue diamonds). The solid lines are the fits of Eq. 2. (b) Total interaction potentials for the aggregation of collapsed micelles in pure \( \text{D}_2\text{O} \) (black line), in \( \text{D}_2\text{O}:d\text{-MeOD} \) (red line) and in \( \text{D}_2\text{O}:d\text{-EtOD} \) (blue line). Inset in (b) \( F_0 \) for the three ratios of molar volumes, \( V_{m,\text{alc}}/V_{m,\text{D}_2\text{O}} \), for values of \( \lambda \) ranging from 1 nm to 2.4 nm increasing by 0.2 nm, as indicated.
Using these $K_{eff}$ values allows us to calculate the interaction potential between two colloidal aggregates. We assume a truncated Lennard-Jones potential

$$U(h) = \begin{cases} 
U_{LJ}(h) - U_{LJ}(\delta) & \text{for } h \leq \delta \\
0 & \text{for } h > \delta 
\end{cases}$$

(3)

with $U_{LJ}$ the classic Lennard-Jones potential of depth $V$

$$U_{LJ}(h) = 4V \left[ \left( \frac{\sigma}{h} \right)^{12} - \left( \frac{\sigma}{h} \right)^{6} \right].$$

(4)

$\sigma = 2 \times r_{agg}^{cp}$ is the finite distance at which the inter-particle potential is zero. From the experimentally determined depths of the potentials, $U$, the interaction potentials for the three solutions are reconstructed (Fig. 3b). For D$_2$O:d-EtOD, the well is with $-8.2k_B T$ deeper than in D$_2$O:d-MeOD ($-7.6k_B T$), and in pure D$_2$O ($-5.7k_B T$). Hence, the observed alteration of the aggregation kinetics is indeed related to the influence of the cononsolvent on the interaction potential. These absolute values of the well depths are within the expected range [25].

The potential can be assumed to comprise an attractive part, due to the hydrophobic interaction between the aggregates, and a repulsive part. The repulsion at short distances (up to a few nm) is attributed to layers of structured water hydrating the surface of the colloidal aggregates. It has been previously shown that even above $T_{cp}$, the collapsed PNIPAM forms H-bonds with water [36, 37], which is requisite for a hydration layer. We propose that alcohol molecules are present in this layer of structured water near the aggregate surface and alter its structure [38]. Consequently, both the strength and the range of the resulting repulsive interaction potential are affected by the cononsolvent, leading to an acceleration of the aggregate growth.

To quantify these effects, we model the attractive part of the potential by a truncated LJ potential where, for simplicity, the depth $V_{att}$ is fixed at $-10k_B T$ without loss of validity. A repulsive potential is added which we assume to be entirely due to the repulsive hydration force. (Electrostatic interactions are not considered, since the polymers are not charged.)

To quantify the repulsive part of the potential, an empirical expression for the hydration potential [33], modified to account for the curvature of the aggregate surface is used:

$$U_{rep}(h) = F_0 \pi r_{agg}^{cp} \lambda^2 \exp(-h/\lambda)$$

(5)
where $F_0$ is the force constant of hydration characterizing the strength of the interaction and $h$ the distance between the centers of the particles. $\lambda$ is a measure of the width of the layer of structured water near the surface of the aggregates. Since both $F_0$ and $\lambda$ are a priori unknown, we assume values of $\lambda$ covering the expected range for ordered water layers on hydrophobic surfaces (1 – 2.5 nm [33]) and calculate the corresponding $F_0$ values for $h = 2^{1/6} \times (2 \times r_{cp}^{agg})$; i.e at the distance where the depth of the potential reaches the experimental value found in the previous paragraph. We find that, for all values of $\lambda$, $F_0$ decreases as the molar volume of the cononsolvent increases (inset of Fig. 3b), as expected for a weakening of the repulsion between aggregates.

We have recently found that the isothermal addition of $d$-MeOD to micellar solutions of PS-$b$-PNIPAM diblock copolymers in $D_2O$, results in characteristic aggregate growth behavior [16], which was consistent with an energy barrier that keeps increasing with $r_{agg}$. In the present case of shallow temperature jumps, an earlier and qualitatively different stage of growth is addressed. We note that cononsolvent-mediated forces between (hydrophilic) silica surfaces in an aqueous medium have been reported as well, showing decreasing hydration forces upon the addition of methanol [39].

To summarize, we relate the aggregation kinetics of self-assembled thermoresponsive polymeric nanoparticles (core-shell micelles), occurring on the mesoscopic length scale, to the interaction potential and provide an explanation on a molecular level. To this end, we combine TR-SANS data from micelle-forming P(S-$d_8$)-$b$-PNIPAM diblock copolymer solutions during temperature jumps across $T_{cp}$ with a theoretical model describing reversible association. We focus on the influence of the kosmotropic cononsolvents—methanol and ethanol—and find that the repulsive interaction potential between the aggregates formed by the collapsed micelles is reduced by these cononsolvents. We propose that these alter the structure of the hydration layers around the aggregates, which cause the repulsive hydration force (Fig. 4). The larger the cononsolvent molecules, the stronger is the effect. On the one hand, our results contribute to an improved understanding of colloidal growth in thermoresponsive systems and demonstrate how the kinetics of the switching process may be tuned by a cononsolvent. Moreover, since the properties of the structured water layer affect not only the responsivity of synthetic polymers [20, 36], but also the functionality and aggregation of biological molecules [40, 41], the results presented here may contribute to an enhanced understanding also in this field.
FIG. 4: Schematic drawing of the proposed model (not to scale). (a) In pure D$_2$O, layers of structured water (blue circles) are present near the aggregate surface (grey) and are at the origin of the repulsive hydration force. (b) The alcohols (green ellipses) perturb the water structure within these layers and form complexes, reducing the repulsive force.

Acknowledgments

This work is based upon experiments performed at the D22 instrument at the Institut Laue-Langevin (ILL), Grenoble, France, providing excellent equipment. Financial support by DFG within the priority program SPP1259 "Intelligente Hydrogelse" (Pa771/4, Mu1487/8, La611/7) is gratefully acknowledged.

[34] The value was calculated using the mass density of PS (1.05 g/cm$^3$), the degree of polymerization, $N_{P(S-ds)} = 11$ and the volume of the spherical core having a radius $r_{core} = 2.7$ nm.
[35] The values were found by dividing the volume of the aggregates at $T_{cp}$ by the volume of a single, collapsed micelle of radius $r_{mic} = 5.7$ nm.