ORIGINAL ARTICLE

Small-angle X-ray scattering from the concentrated bulk phase separated from an amphiphilic block-copolymer solution

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Aqueous solutions of the doubly thermosensitive block copolymer poly(2-isopropyl-2-oxazoline)-b-poly(2-ethyl-2-oxazoline) heated to 50 °C underwent a macroscopic liquid/liquid phase separation. The small-angle X-ray scattering intensity recorded from the concentrated phase settled on the bottom of a sample indicated that this phase was in the disordered state without any microphase separation, although the block copolymer was amphiphilic in water at 50 °C. It was also confirmed that the contribution to the scattering intensities of individual copolymer chains and their aggregates existing in the coexisting concentrated phase was very small, compared with the total scattering intensity of the phase-separated solution, when the concentrated phase was suspended in the form of colloidal droplets in the lean phase.
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INTRODUCTION

Block copolymers that consist of either a hydrophilic and a thermosensitive block or two thermosensitive blocks form self-assemblies in water upon heating. Extensive studies have been performed recently on the temperature-induced self-assembly of such block copolymers, in view of their potential applications in drug delivery systems.[1–17] The block copolymer consisting of poly(N-isopropylacrylamide) (PNIPAM) and poly(ethylene glycol) has been studied most extensively.[1–7] With the advent of controlled polymerization techniques, it has become possible to prepare hydrophilic/thermosensitive block copolymers consisting of various kinds of blocks, for example, PNIPAM-b-poly(acrylic acid),[9] PNIPAM-b-poly(glycidol),[10] PNIPAM-b-poly(N-vinyl-2-pyrrolidone)[11] and doubly thermosensitive block copolymers consisting of two thermosensitive blocks, for example, block copolymers of vinyl ethers with different pendant groups,[12] block copolymers of polystyrenes and polyacrylates with pendant oxyethylene moieties,[13] and block copolymers of poly(acrylamide)s bearing different alkyl side chains.[15,16]

These hydrophilic/thermosensitive and doubly thermosensitive block copolymers often form self-assembled particles whose radii exceed 100 nm, being much larger than the contour length of the constituent block-copolymer chains. These self-assemblies are not simple spherical micelles.

Recently, we[18] investigated by small-angle X-ray scattering (SAXS) the self-assembled structure formed by the doubly thermosensitive block copolymer poly(2-isopropyl-2- oxazoline)-b-poly(2-ethyl-2-oxazoline) (PIPOZ-b-PEOZ) at 50 °C, a temperature at which the copolymer is amphiphilic. In aqueous solutions kept at 50 °C, the copolymer forms star-like micelles that further aggregate to form homogeneous concentrated-phase droplets. Eventually, the droplets coalesce into a liquid bulk phase. In Figure 1, we present SAXS results obtained in a previous study of an aqueous solution of PIPOZ-b-PEOZ heated at 50 °C for 3 min (open circles) and 19 min (full circles). Immediately after heating, the concentrated-phase droplets coexist with star-like micelles in the dilute phase, and after 19 min, the scattering signal of the droplets disappears, which indicates that the droplets have settled to the bottom of the sample outside the volume probed by the X-Ray beam. The dashed and solid curves in the figure are theoretical curves for star-like micelles with an aggregation number of 11 and for a mixture of star-like micelles and polydisperse spherical particles with a copolymer concentration as high as $0.8\,\mathrm{g\,cm^{-3}}$.[18] Because the SAXS profile with open circles has no sharp diffraction peak, it would seem that the concentrated-phase droplets do not undergo microphase separation.

In the present study, we carried out SAXS measurements on the coexisting concentrated bulk phase of aqueous PIPOZ-b-PEOZ after macroscopic liquid/liquid phase separation. The aim of this study is twofold: (1) to characterize more precisely the coexisting concentrated phase that is macroscopically separated from the heated aqueous block-copolymer solution; and (2) to assess whether microphase
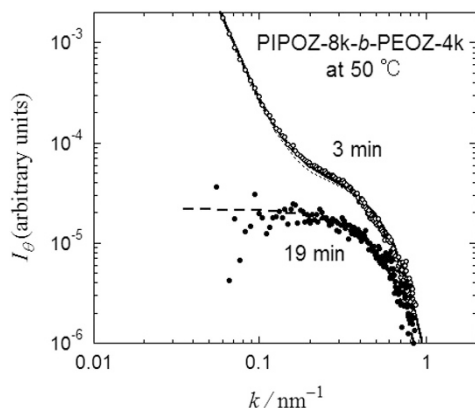
Figure 1 SAXS profiles of an aqueous solution of the sample PIPOZ-8k-*b*-PEOZ-4k (the original concentration: 0.0246 g cm^{-3}) heated to 50 °C for 3 min (open circles) and 19 min (full circles), and the previously obtained fitting results (solid and dashed curves).[18] See Equation (8) and the text following the equation for the thin dotted curve near the open circles.

separation occurs in the concentrated phase of aqueous PIPOZ-*b*-PEOZ after prolonged heating at 50 °C. If microphase separation occurs in the highly concentrated phase only after a long time, the few minutes of observations reported previously[18] were not sufficient to conclude that microphase separation does not occur in this system. Very recently, Sato and Takahashi[19] theoretically predicted the coexistence of star-like micelles and a homogeneous concentrated phase in a weakly amphiphilic block-copolymer solution. The experimental evaluation of the microphase separation status in the concentrated phase is important to confirm this theoretical prediction.

EXPERIMENTAL PROCEDURE

The PIPOZ-5k-*b*-PEOZ-4k sample used for SAXS measurements was synthesized as described previously.[18] The number average molar mass M_1 and the molar mass dispersity of the sample determined by SEC-MALS were 9100 g mol^{-1} and 1.04, respectively. The mole fraction of IPOZ monomer in the copolymer, as estimated by ^{1}H NMR, was 0.53. SAXS measurements were performed at the BL40B2 beamline in SPring-8 with an incident light of 0.1 nm wavelength and a camera length of 4164 mm. The scattered X-ray intensity was detected using a RIGAKU R-AXIS VII imaging plate detector. The sample was dissolved in water to prepare the test solution of mass concentration, $c=0.2$ g cm^{-3}. The solution was placed in a capillary cell with a 1.9 mm inside diameter. It was separated into two macroscopic phases after being kept at 50 °C for 240 min. Then, the incident X-ray beam was illuminated to the separated concentrated phase for 180 s to obtain the excess scattering intensity, I_θ, of the coexisting concentrated phase over the solvent intensity. As a reference, the SAXS measurement was also performed on the aqueous solution of PIPOZ-5k-*b*-PEOZ-4k before phase separation at 25 °C.

RESULTS AND DISCUSSION

Figure 2 shows a photograph of a phase-separated sample of PIPOZ-5k-*b*-PEOZ-4k within the capillary cell used for the SAXS measurements. Macroscopic phase separation was attained after the solution was kept at 50 °C for 240 min. The bottom concentrated phase was slightly turbid. The incident X-ray beam was focused at the height indicated by the red arrow in Figure 2. The excess SAXS intensity, I_θ, was measured under these conditions.

Figure 3 presents the angular dependence of I_θ (circles) for the concentrated phase at 50 °C in the configuration shown in Figure 2 and for the same solution at 25 °C, where it exists as a single phase. The abscissa is the magnitude of the scattering vector k. Let us first consider the result obtained at 25 °C. At $k > 0.1$ nm^{-1}, the data points
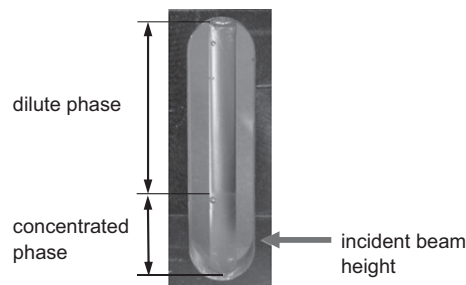

Figure 2 Picture of the phase-separated aqueous solution of PIPOZ-5k-*b*-PEOZ-4k ($c=0.2$ g cm^{-3}) in the capillary cell used for the SAXS measurement. A full color version of this figure is available at *Polymer Journal* online.
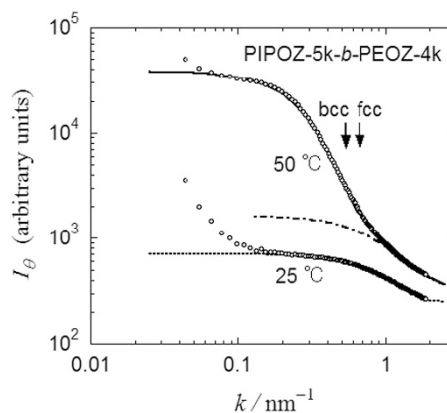

Figure 3 SAXS profiles of an aqueous solution of PIPOZ-5k-*b*-PEOZ-4k in the one-phase state at 25 °C ($c=0.2$ g cm^{-3}) and of the coexisting concentrated phase in the same test solution phase separated at 50 °C. The solid curve indicates theoretical values calculated by Equations (3)–(6) by using $c=0.39$ g cm^{-3}, $M_1=9100$ g mol^{-1} and the parameters are listed in Table 1. The dotted curve indicates the theoretical values for the single-chain component, calculated by Equations (1) and (2) with $c=0.20$ g cm^{-3} and $M_1=9100$ g mol^{-1}. See the text for the dot–dash curve.

can be fitted to the scattering function for a homogeneous concentrated polymer solution given by ref. 20

$$I_\theta = \frac{FM_1P_1(k)c}{1 + 2\gamma_{11}M_1P_1(k)c} \tag{1}$$

where F is an instrumental constant and M_1, $P_1(k)$ and γ_{11} are the molar mass, particle scattering function and effective second virial coefficient of the copolymer chain, respectively. Assuming a Gaussian chain for the copolymer chain and ignoring the difference in the excess electron density between the PIPOZ and PEOZ blocks (ca. 10% difference), we write $P_1(k)$ as[21,22]

$$P_1(k) = \frac{2\left[\exp(-k^2\langle S^2\rangle_1) - 1 + k^2\langle S^2\rangle_1\right]}{(k^2\langle S^2\rangle_1)^2 \exp\left(\frac{1}{16}k^2d_1^2\right)} \tag{2}$$

where $\langle S^2\rangle_1$ and d_1 are the mean square radius of gyration and the thickness of the Gaussian chain, respectively. Although water is a good solvent for PIPOZ-*b*-PEOZ at 25 °C, the molar mass M_1 ($=9100$ g mol^{-1}) is so low that the excluded volume effect may be neglected.

Sung and Lee[23] reported the unperturbed dimension of PEOZ in THF. We assumed that the unperturbed dimension of PIPOZ-5k-*b*-PEOZ-4k in 25 °C water is approximately the same as that of PEOZ

Table 1 Characteristics of the scattering components in the coexisting concentrated phase at 50 °C

i	Component	w_i	$m_{w,i}$	$m_{w,i}/m_{n,i}$	$\langle S^2 \rangle_i^{1/2}$ (nm)	d_i^2 (nm²)	γ_{ii} (cm³g⁻²mol)[a]
1	Single chain	0.9	1	1	2.3 (2.3)[b]	−2.0 (−2.8)[b]	1.5×10^{-4} (4.3×10^{-4})[b]
2	Aggregate	0.1	112	2	6.6[c]		1×10^{-6}

[a]$\gamma_{12} = 0$ cm³g⁻²mol.
[b]Value at 25 °C.
[c]Calculated from $c_{in,2} = 1.1$ g cm⁻³.

with the same degree of polymerization in THF, that is, $\langle S^2 \rangle_1^{1/2} = 2.3$ nm, and we fitted Equations (1) and (2) to the experimental SAXS profile at 25 °C at $k > 0.15$ nm⁻¹. The dotted curve in Figure 3 shows the fitting result. Based on this fitting, we determined $\gamma_{11} = 4.3 \times 10^{-4}$ cm³ g⁻² mol and $d_1^2 = -2.8$ nm² and the instrumental constant F almost uniquely. The value of the effective second virial coefficient γ_{11} indicates that water is a good solvent for PIPOZ-5k-b-PEOZ-4k at 25 °C. The negative d_1^2 chosen is physically unreasonable, but it has been reported in several previous SAXS studies on polymers in dilute solutions.[24–26] This negative value may be due to the heterogeneous electron density distribution in the thickness direction of the polymer chain.[26,27]

The scattering function at 25 °C shows a sharp upswing at $k < 0.15$ nm⁻¹, which indicates the existence of a very small amount of a large scattering component in the solution. Polymer solutions occasionally contain minute amounts of 'irreversible aggregates' that can be detected only by the scattering technique, even if the solution is thermodynamically in one-phase region in the phase diagram. Because PIPOZ is known to be a crystalline polymer,[28–30] a small amount of PIPOZ-b-PEOZ may form semi-crystalline aggregates in the semi-concentrated aqueous solution ($c = 0.2$ g cm⁻³) used here.

The scattering function for the coexisting concentrated phase at 50 °C in Figure 3 shows a k dependence similar to that of the single chain before phase separation at 25 °C at $k \gtrsim 1$ nm⁻¹. It has a strong contribution that decays at a lower k, indicating the existence of a larger aggregated component present in the concentrated phase along with the single-chain component, contributing to I_θ at high k. Thus, we tried to fit I_θ at 50 °C by ref. 31

$$I_\theta = \frac{FM_1 c \left[w_1 P_1(k) + w_2 m_{w,2} P_2(k) + 2 w_1 w_2 m_{w,2} P_1(k) P_2(k)(\gamma_{11} + \gamma_{22} - 2\gamma_{12})M_1 c \right]}{\left[1 + 2 w_1 P_1(k) \gamma_{11} M_1 c \right]\left[1 + 2 w_2 m_{w,2} P_2(k) \gamma_{22} M_1 c \right] - 4 w_1 w_2 m_{w,2} P_1(k) P_2(k)(\gamma_{12} M_1 c)^2}$$

(3)

where w_i, M_i and $P_i(k)$ are the weight fraction, the molar mass and the particle scattering function of the component i ($i = 1$ for the single chain and $i = 2$ for the large aggregated component), respectively, $m_{w,2}$ is the weight-average aggregation number of component 2, and γ_{ij} is the effective second virial coefficient between the components i and j ($i, j = 1$ and 2). Component 2 may be responsible for the slight turbidity of the concentrated phase shown in Figure 2. We approximate $P_2(k)$ of component 2 by the scattering function for polydisperse spherical particles given by

$$m_{w,2} P_2(k) = \int_0^\infty \left[3 \times \frac{\sin(kR) - kR\cos(kR)}{(kR)^3} \right]^2 m_2 w(m_2) dm_2$$

(4)

where m_2 is the aggregation number of each spherical particle component, R is the radius of the sphere with m_2 and $w(m_2)$ is the weight fraction of the sphere with m_2 in the total component 2. The former is calculated from m_2 by

$$R = \left(\frac{3 m_2 M_1}{4\pi N_A c_{in,2}} \right)^{1/3}$$

(5)

with the Avogadro constant N_A and the internal copolymer mass concentration $c_{in,2}$ of the sphere, and the latter is assumed to be expressed by the log-normal distribution given by

$$w(m_2) = \frac{1}{\sqrt{2\pi} \ln(m_{w,2}/m_{n,2}) m_2} \exp\left[-\frac{\ln^2(m_2/\sqrt{m_{w,2} m_{n,2}})}{2\ln(m_{w,2}/m_{n,2})} \right]$$

(6)

with the number average aggregation number $m_{n,2}$ of component 2.

Among many parameters and functions in Equations (3)–(6), we chose the same M_1, $\langle S^2 \rangle_1^{1/2}$, and F as those used at 25 °C. Because the excluded volume effect can be neglected due to the low M_1 value, the single copolymer chain may keep the unperturbed state even in the poor solvent. The total copolymer mass concentration, c, of the concentrated phase was determined gravimetrically[18] to be 0.39 g cm⁻³. Then, we first fitted I_θ at high k by Equation (1) to determine γ_{11} and d_1^2. Next, we changed w_1 ($= 1 - w_2$) and $m_{w,2}$ to fit the plateau of I_θ at a low k by Equation (3) and then fitted I_θ for intermediate k by Equation (3), adjusting $m_{w,2}$, $c_{in,2}$ and $m_{w,2}/m_{n,2}$. According to the change in w_1, we re-adjusted γ_{11} to fit I_θ at high k again. Because water is a poor solvent for the copolymer at 50 °C, the effective second virial coefficients γ_{22} and γ_{12} were assumed to be zero at the first fitting, and γ_{22} was then slightly adjusted to obtain the best fitting in the low and intermediate k regions; γ_{12} was kept at zero throughout the fitting because of its insensitivity to I_θ.

The fitting result is indicated by the solid curve in Figure 3, and the parameter values chosen are listed in Table 1. The dash–dot curve in Figure 3 indicates the scattering component for the single chain (component 1) calculated by Equations (1) and (2), with c replaced by $c w_1$ and the same w_1, M_1, $\langle S^2 \rangle_1$, γ_{11} and d_1^2 as in the case of the solid curve (the value of d_1^2 was slightly different from that at 25 °C, which may arise from the dehydration of the PIPOZ block chain at 50 °C).

As seen from the solid and dash–dot curves, the scattering from component 2 is predominant in the low k region, but the weight fraction w_2 is only 10%, and the single-chain component 1 is predominant in the concentrated phase. Component 2 consists of ca. 100 copolymer chains and has a z-average root-mean-square radius of gyration $\langle S^2 \rangle_2^{1/2}$ of 6.6 nm. It has a very high density $c_{in,2} = 1.1$ g cm⁻³, which is identical to the inverse of the partial specific volume of the copolymer. These results imply that component 2 is the micro-crystallite of the copolymer. Although we do not have evidence for the crystallite formation in our solution, some researchers[28–30] have reported the formation of micro-crystallites in phase-separated aqueous PIPOZ samples.

One may expect microphase separation in concentrated solutions of amphiphilic block copolymers.[32] If microphase separation occurred in the concentrated phase of aqueous PIPOZ-b-PEOZ, it should be possible to observe some diffraction peaks in the SAXS profile. If spherical micelles of aggregation number m form body-centered cubic

(bcc) or face-centered cubic (fcc) lattices in the concentrated phase, a first-order diffraction peak should appear at $k = k_d$, indicated by the arrows in Figure 3. This was calculated by

$$k_d = 2\pi \left(\frac{N_A c}{m M_1 N} \right)^{1/3} \quad (7)$$

with the number of micelles per unit cell $N = 2$ for bcc and 4 for fcc, as well as $M_1 = 9100 \text{ g mol}^{-1}$, $m = 11$,[18] and $c = 0.39 \text{ g cm}^{-3}$. There are no peaks in the SAXS profile for the concentrated phase at 50 °C around this k region. Hence, we conclude that the concentrated phase of the phase-separated solution of PIPOZ-b-PEOZ is disordered and that microphase separation does not occur, even after the concentrated phase stays at 50 °C for 240 min. Although differential scanning calorimetry demonstrated that dehydration occurs only for the PIPOZ block chain in PIPOZ-b-PEOZ in 50 °C water and that star-like micelles form in the dilute phase (cf. Figure 1),[18] the amphiphilicity of PIPOZ-b-PEOZ may not be sufficiently strong for microphase separation to take place in the concentrated phase. A similar conclusion was reached in a theoretical study by Sato and Takahashi[19] on the coexistence of star-like micelles and a homogeneous concentrated phase in dilute solutions of weakly amphiphilic block copolymers.

In a previous study,[18] we fitted the SAXS profile for the phase-separated dilute solution of a PIPOZ-b-PEOZ sample, where the dilute phase contains micelles (component S) with a weight-average aggregation number $m_{w,S}$ and the concentrated phase exists as colloidal droplets (component L) consisting of $m_{w,L}$ copolymer chains, by the equation

$$I_\theta = F M_1 c \left[w_S m_{w,S} P_S(k) + w_L m_{w,L} P_L(k) \right] \quad (8)$$

In Figure 1, we reproduce the previous SAXS profile (open circles) for a dilute aqueous solution of PIPOZ-8k-b-PEOZ-4k with $c = 0.0246 \text{ g cm}^{-3}$ heated at 50 °C for 3 min. At higher and lower k, the contributions of the first and second terms of Equation (8), respectively, are predominant. Thus, we can almost uniquely determine w_i, $m_{w,i}$ and $P_i(k)$ ($i = S, L$) by fitting the SAXS profile as shown in Figure 1, which characterizes both the polymer species in the coexisting dilute phase and the colloidal particles of the coexisting concentrated phase in the phase-separated polymer solution.

In the previous study, we calculated $P_L(k)$ of the concentrated-phase droplets by Equations (4)–(6). Although Equations (4)–(6) give the scattering function for uniform density spheres, the concentrated phase is not perfectly uniform, and the individual single chains and aggregated components in the concentrated-phase scatter X-rays, as demonstrated in Figure 3. We examine here the contribution of the heterogeneity in the concentrated-phase droplet to $P_L(k)$. The scattering function for composite particles is known to consist of the form factor of the subparticle and the structure factor of the composite particle.[33] When the concentrated-phase droplet is viewed as a sphere consisting of single chains and their aggregates, $P_L(k)$ may be written as

$$P_L(k) = \frac{w_1 P_1(k) + w_2 m_{w,2} P_2(k)}{m_{w,L}} P_{UDS}(k) \quad (9)$$

where $P_1(k)$ and $P_2(k)$ are the form factors of the single chain and aggregates in the concentrated phase, respectively, and $P_{UDS}(k)$ is the structure factor of a uniform density sphere. The previous study[18] used $P_L(k)$ calculated by Equation (9) with $P_1(k) = P_2(k) = 1$, and the previous fitting result is shown by the solid curve in Figure 1.

Assuming that the concentrated-phase droplet in the aqueous solution of the previous sample, PIPOZ-8k-b-PEOZ-4k contained

the same aggregated component as the one present in the concentrated phase of the aqueous solution of the present sample, PIPOZ-5k-b-PEOZ-4k, we have calculated $P_L(k)$ by Equation (9) and then I_θ by Equation (8). As shown by the thin dotted curve in Figure 1, the result is very close to the solid curve, which demonstrates that the form factors of the individual single chains and their aggregates in the concentrated-phase droplet hardly affect the total scattering function. In other words, it is difficult to study the heterogeneity inside the concentrated phase in the colloidal droplet state by SAXS.

CONCLUSION

SAXS measurements were performed on the macroscopically phase-separated concentrated phase of an aqueous solution of the thermosensitive block copolymer poly(2-isopropyl-2-oxazoline)-b-poly(2-ethyl-2-oxazoline) at 50 °C. The scattering function obtained was fitted by the theoretical model of a mixture of single copolymer chains and very condensed aggregates of chains in the disordered state, which demonstrates that microphase separation does not occur in the concentrated phase of this amphiphilic block copolymer. This result is consistent with a theoretical prediction[19] that star-like micelles and a homogeneous concentrated phase can coexist in dilute solutions of weakly amphiphilic block copolymers.

Furthermore, the contribution to the total scattering intensity of individual copolymer chains and their aggregates in the coexisting concentrated-phase droplet is very small for phase-separated polymer solutions in which the concentrated phase exists in the form of colloidal droplets. This confirms the validity of the method for characterizing the coexisting concentrated phase dispersed as colloidal particles in a phase-separated solution by SAXS that was used previously.[18]

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