Title
Solvent Selectivity Governs the Emergence of Temperature Responsiveness in Block Copolymer Self-Assembly.

Permalink
https://escholarship.org/uc/item/8jz1n44d

Journal
Macromolecules, 54(6)

ISSN
0024-9297

Authors
Ianiro, Alessandro
Hendrix, Marco MRM
Hurst, Paul Joshua
et al.

Publication Date
2021-03-04

DOI
10.1021/acs.macromol.0c02759

Peer reviewed
Solvent Selectivity Governs the Emergence of Temperature Responsiveness in Block Copolymer Self-Assembly

Alessandro Ianiro,* Marco M.R.M. Hendrix, Paul Joshua Hurst, Joseph P. Patterson, Mark Vis, Michael Sztucki, A. Catarina C. Esteves, and Remco Tuinier*

Cite This: Macromolecules 2021, 54, 2912−2920

ABSTRACT: In highly selective solvents, block copolymers (BCPs) form association colloids, while in solvents with poor selectivity, they exhibit a temperature-controlled (de)mixing behavior. Herein, it is shown that a temperature-responsive self-assembly behavior emerges in solvent mixtures of intermediate selectivity. A biocompatible poly-ethylene(oxide)-block-poly-ε-caprolactone (PEO-PCL) BCP is used as a model system. The polymer is dissolved in solvent mixtures containing water (a strongly selective solvent for PEO) and ethanol (a poorly selective solvent for PEO) to tune the solvency conditions. Using synchrotron X-ray scattering, cryogenic transmission electron microscopy, and scanning probe microscopy, it is shown that a rich temperature-responsive behavior can be achieved in certain solvent mixtures. Crystallization of the PCL block enriches the phase behavior of the BCP by promoting sphere-to-cylinder morphology transitions at low temperatures. Increasing the water fraction in the solvent causes a suppression of the sphere-to-cylinder morphology transition. These results open up the possibility to induce temperature-responsive properties on demand in a wide range of BCP systems.

INTRODUCTION

Amphiphilic block copolymers (BCPs) have been given ample attention due to their interfacial properties and their ability to form well-defined supramolecular architectures. In selective solvents, BCPs associate to minimize the unfavorable contact between the solvent and the lyophobic blocks.1,2 Depending on chemical composition, chain lengths of the blocks, solvent quality, and concentration, BCPs form supramolecular architectures with different sizes and morphologies.3−5 These structures are of scientific, biological, and industrial interest.5−10 The preparation of stimuli-responsive BCPs becomes increasingly important as it enables to design smart materials which modify their properties under an external stimulus, such as temperature11,12 and light.13,14 At present, this strategy requires a careful design of the molecular architecture of the blocks, which may be challenging to realize from a synthetic point of view. An interesting alternative would be to induce new stimuli-responsive properties in commonly used and widespread BCPs, for instance, by controlling the solvency conditions. If the lyophobic and lyophilic blocks have a low tendency to segregate, BCPs lose the ability to self-assemble in poorly selective solvents, where there is a small solubility difference between the blocks.15,16 In such solvents, the (de)mixing behavior can be typically controlled by varying the solvent quality by means of temperature.17 In this work, it is investigated whether tuning the solvent selectivity by mixing a weakly selective solvent and a strongly selective solvent induces the emergence of a thermoresponsive self-assembly behavior. Solvent selectivity is known to affect the mass, the preferred morphology, and the dynamics of BCP supramolecular assemblies.16,18−22 Most of these investigations were carried out in organic solvents and with non-crystalline polymers, where the absence of H-bonding interactions and crystallization (quasi-ideal conditions) allowed the observed phenomena to be rationalized in terms of mean-field theories.18−20 In contrast, this study focuses on less ideal systems consisting in crystallizable23,24 poly-ethylene(oxide)-block-poly-ε-caprolactone (PEO-PCL) BCPs dispersed in H-bonding water−ethanol mixtures. These biocompatible and widespread copolymers show a temperature-controlled phase behavior in the weakly selective solvent ethanol,25 where the interplay between crystallization, phase separation, and block segregation leads to the formation of hierarchical structures.23 In contrast, in water, a strongly selective solvent for the PEO...
block and thus a poor solvent for PCL, the copolymers form colloidal self-assembled structures via amphiphilic self-assembly.

The effect of solvent selectivity in such types of systems is poorly understood, especially when the degree of selectivity is varied between poor and intermediate. We hypothesize that in this selectivity range lies a rich thermoresponsive phase behavior. To show this, the associative properties of a PEO-PCL BCP with the composition Me-EO45-CL30 are studied in water-ethanol mixtures at different temperatures with small- and wide-angle synchrotron X-ray scattering (SAXS/WAXS), cryogenic transmission electron microscopy (cryo-TEM), and scanning probe microscopy (SPM). The results reported in this work can, in principle, be applied to design processing strategies enabling to control the self-assembly of many BCP systems with temperature.

**RESULTS AND DISCUSSION**

The formation of dispersed Me-EO45-CL30 (50 mg·mL⁻¹) structures in water-ethanol mixtures containing water volume fractions in the range 0.1 < ϕw < 0.5 was studied by means of SAXS/WAXS. In addition, cryo-TEM and SPM were performed on selected samples to confirm the models used to fit the scattering data. Scattering measurements provide an ensemble-averaged representation of the system, while cryo-TEM and SPM provide detailed structural and morphological information at the single-particle level. The SAXS and WAXS measurements were combined into contour maps, where variations of the scattered intensities as a function of the scattering vector $q$ (see the Materials and Methods section for details) and temperature $T$ are displayed as color variations (Figure 1). Such a representation facilitates the comparison between data from different samples. The data are also represented as 3D plots, which help visualizing the features of the scattering curves (Figure 2). Selected scattering curves are individually analyzed to assess the morphology and size of the scattering particles. The analysis comprises both comparison of the measured data with theoretical models and analysis of the low $q$ scaling behavior of the scattered intensity $I \sim q^{-m}$. For non-interacting particles, the scaling exponent $m$ is related to the fractal dimension of the scattering objects, thereby providing information on their shape.

The SAXS data (Figures 1a and 2a,b) reveal that Me-EO45-CL30 is molecularly dissolved for $T > 20$ °C in mixtures with the composition in the range 0.1 < ϕw < 0.2. In this regime, the copolymer mean radius of gyration, obtained by fitting of the scattering data with a form factor for polymers with the excluded volume27 (Figure S1 in the Supporting Information), is $R_g \approx 2.7$ nm and is rather constant with temperature. This value is in good agreement with theoretical estimations (see the Supporting Information). Typically, the size of a polymer coil in solution increases with increasing temperature because the polymer and the solvent get more compatible. The solvation mechanism of the PEO-PCL BCP in water-ethanol mixtures, however, is complex and involves H-bonding interactions. With increasing temperature, the number of solvent molecules hydrogen-bonded to the polymer chains decreases, which counteracts the increase in polymer-solvent compatibility. Probably, $R_g$ does not significantly vary in the investigated temperature range due to this mechanism.

---

**Figure 1.** Contour maps of (a) small-angle (SAXS) and (b) wide-angle (WAXS) data from 50 mg·mL⁻¹ Me-EO45-CL30 in water-ethanol mixtures. The mixture composition is indicated inside each plot as the water volume fraction $\phi_w$. In the WAXS plots, PCL diffraction peaks can be recognized as horizontal lines.
An increase in the scattered intensity at low $q$ (structure factor contribution) can be recognized in the small-angle data for $0.1 < \phi_W < 0.2$ at $T > 20^\circ C$ (Figure S1 in the Supporting Information), indicating that attractive interactions between dissolved BCP molecules are operational. This leads to phase instabilities upon further decreasing the temperature: a sudden change in the scattering profiles occurs at $T \approx 20^\circ C$ (Figures 1a and 2a,b,f). The low-$q$ scaling of the scattered intensity $I \sim q^{-1}$ (Figure 3a) suggests the formation of cylindrical self-assembled structures. Comparison with a theoretical scattering model for core–shell cylinders$^{28}$ (Figure 3a) provides an estimation of the cross-sectional diameter of the PCL core. 

Figure 2. 3D representations of the SAXS data from 50 mg·mL$^{-1}$ Me-EO$_{45}$-CL$_{30}$ in ethanol–water mixtures with water volume fractions (a) $\phi_W = 0.1$, (b) $\phi_W = 0.2$, (c) $\phi_W = 0.3$, (d) $\phi_W = 0.4$, and (e) $\phi_W = 0.5$. The variable $\bar{q} = q \cdot 1$ nm is an adimensional scattering vector. (f) State diagram reporting the different morphologies obtained as a function of temperature and solvent composition according to the SAXS data.
These structural features are probably induced by crystalization and are likely responsible for the wide scattering peak at $q \approx 0.2$ nm$^{-1}$. Small-angle scattering experiments (approximately 160 nm). If the cylinders were shorter than 160 nm, a plateau would be observed in the low-$q$ regime. At $q \approx 0.2$ nm$^{-1}$, a rather wide and shallow diffraction peak is observed (Figure 3a), which may be caused by the presence of a $\sim 30$ nm structural periodicity inside the cylinders with rather polydisperse spacing, the presence of aggregates $\sim 30$ nm in diameter, or correlations in the spatial distribution of different cylinders. This aspect is further discussed later in the text. The formation of cylinders is associated with the simultaneous appearance of PCL diffraction peaks at wide scattering angles (Figure 1b). Hence, it can be concluded that the cylinders form via a crystallization-induced self-assembly process.

For $\phi_W = 0.3$, three different states can be observed in the scattering profiles (Figures 1a and 2c). For $T \lesssim 40$ °C, the copolymers, characterized by a radius of gyration of $R_g = 2.7$ nm (Figure 3b), are molecularly dissolved. Spherical micelles with radius $R \approx 5.5$ nm form instead below $T \approx 40$ °C. The scattering pattern, in fact, contains a clear contribution from spherical scatterers at intermediate and low $q$, which reflects the insoluble core of the micelles (compared in Figure 3b with the form factor of a solid sphere). At high $q$, the scattering pattern is similar to the one of molecularly dissolved BCPs (Figure 3b) and is probably given by the sum of free polymer scattering and scattering from the well-solvated micelle corona.

The micellar state is stable over the temperature range $20 \lesssim T \lesssim 40$ °C. Below $T \approx 20$ °C, crystallization again induces the formation of cylindrical micelles. The cylindrical morphology is confirmed by SPM measurements (Figure 4a–c), which further suggest that the cylinders have a segmented or helical structure, with a pitch between 30 and 40 nm (Figure 4c). These structural features are probably induced by crystallization and are likely responsible for the wide scattering peak observed at $q \approx 0.2$ nm$^{-1}$ in the SAXS profiles. Further analysis is required to clarify the structure of the cylindrical micelles. A cross-sectional diameter of $D_{\text{core}} \approx 7$ nm (polydispersity 0.2, see the Materials and Methods section) and a shell thickness of $H_{\text{corona}} = 4$ nm. The arrow indicates the wide peak at $q \approx 0.2$ nm$^{-1}$. (b) Small-angle scattering profiles for Me-EO45-CL30 at $\phi_W = 0.3$ at $T = 30$ °C. Continuous curves are the theoretical form factors for polymer coils with the excluded volume (POL) with a radius of gyration of $R_g = 2.7$ nm, while the dashed curve is the theoretical form factor of uniform spheres (SPH) with radius $R = 5.5$ nm, used as a fitting model for the micelles.
This concentration dependence is quantified by the so-called structure factor $S(q,\phi)$. The predicted scattering curves of interacting hard spheres (HSs) at a volume fraction of $\phi_{HS} = 0.2$ are plotted in Figure 5a (details of the model are reported in the figure’s caption). Comparison of the modeled curves with the experimental SAXS data suggests that the PEO-PCL micelle concentration is high (close to 20% in volume), and correlation in their spatial distribution causes the decrease of the scattered intensities at low $q$ (Figure 5a).

Differential scanning calorimetry (DSC) analysis (see the Supporting Information) performed on a PCL homopolymer shows that the addition of water has a negligible effect on PCL crystallization. Hence, the suppression of the sphere-to-cylinder transition at $\phi_W = 0.5$ must be related to the...
amphiphilic nature of the BCP. The increase in solvent selectivity drives and increases in the block segregation. As a result, for $\phi_W > 0.4$, the micelle phase becomes more stable than the cylindrical crystalline phase. Due to confinement in the spherical core of the micelles, crystallization of PCL chains becomes more difficult, as testified by the lower crystallization temperature ($T \approx 0 \, ^\circ C$, see WAXS data in Figures 1b and S3 in the Supporting Information).

Interestingly, crystallization in the spherical core causes the appearance of attractive interactions between the micelles. Attractive interactions lead to the formation of micelle clusters which cause an uprisning of the scattered intensity at low $q$, as illustrated in Figure 5a.

The water-induced suppression of PCL crystallization is probably responsible for the progressive reduction of the wide peak observed at $q \approx 0.2 \, \text{nm}^{-1}$ in the low-angle scattering for $0.1 < \phi_W < 0.4$ ($T < 20 \, ^\circ C$, see Figure 3a). Such a reduction indicates that the helicity (Figure 4b,c) is progressively lost upon addition of water.

It is noted that the average cross-sectional diameter of the cylindrical micelles is consistently smaller than the diameter of the spherical micelles according to both SAXS and cryo-TEM. A sphere-to-cylinder transition allows a relaxation of the stretching degree of lyophobic chains and a concomitant increase in the stretching of the lyophilic chains. 33 This implies that the size of the insoluble domain of the self-assembled structure decreases, while the thickness of the lyophilic domains increases on passing from spheres to cylinders. The electron density difference between the solvent and the lyophilic domains of the assemblies is small because these are highly solvated. Therefore, SAXS and cryo-TEM mostly provide a characterization of the dense, desolvated lyophilic domains, which explains why the cross-sectional diameter of the cylinders results smaller than the diameter of the micelles.

From a thermodynamic perspective, in the absence of crystallization, the sphere-to-cylinder morphology transition is driven by a favorable increase in the overall conformational entropy of the BCP chains. 33 However, in the present case, spherical micelle are the preferred morphology under conditions where crystallization is suppressed (high $T$, high $\phi_W$). Hence, different from classic BCP self-assembly, there is a marked enthalpic driving force for the sphere-to-cylinder crystallization-induced morphology transition.

Finally, it is noted that the transition from the molecularly dissolved state to the micelle state is observed only for $\phi_W = 0.3$. Intuitively, one can imagine that this transition takes place when the energy difference per BCP molecule between the micelle and the solvated state ($\Delta g_{SA}$) is comparable to the thermal energy ($\Delta g_{SA} \approx k_BT$, where $k_B$ is Boltzmann’s constant and $T$ is the temperature). Given the complex and non-ideal nature of the system, it is difficult to quantify how $\Delta g_{SA}$ depends on $\phi_W$ and $T$. However, considering that PCL is highly hydrophobic and that PEO in water becomes less soluble at high temperatures, 34 one can safely assume that $\Delta g_{SA}$ increases quite steeply with increasing $\phi_W$. As a result, the soluble state becomes quickly unfavorable ($\Delta g_{SA} > k_BT$) in the investigated $T$ range for $\phi_W > 0.3$. Conversely, for $\phi_W < 0.3$, $\Delta g_{SA} < k_BT$ at high temperature, while at low ($T < 20 \, ^\circ C$) temperatures, crystallization-induced self-assembly is energetically favored over micellization.

**CONCLUSIONS**

PEO-PCL BCPs exhibit a temperature-responsive self-assembly behavior, which emerges when the BCPs are dispersed in solvent mixtures of intermediate selectivity (mixtures of a weakly selective solvent and a strongly selective solvent). The solvent mixture composition enables to tailor the morphology transitions. For the PEO-PCL copolymer studied here, crystallization of the lyophobic PCL blocks triggers an additional morphology transition from spherical micelles to semicrystalline cylindrical micelles. Upon drying, dispersions of these semicrystalline cylindrical micelles might aggregate forming planar hierarchical structures resembling those of certain biomaterials like, for instance, chitin. Gaining control over this process appears a promising perspective to design and prepare biomimetic hierarchical materials and deserves further investigations.

The strategy proposed in this study can be applied to BCPs with different molar masses in order to access a wide range of morphologies and can in principle be applied to many kinds of BCPs. Predictive models need to be developed to design a priori systems with predefined responsivity. Elucidating the
effect of sequential variations in temperature and solvent composition could further expand the potential of this strategy toward the creation of nanomaterials with complex architectures.

**MATERIALS AND METHODS**

**Materials.** The Me-EO₄₅-CL₃₀ BCPs used in this study were prepared via bulk ring opening polymerization catalyzed by fumaric acid, as described in a previous work.² The PEO (MeEO₄₅, Mₙ = 2 kDa) initiator used for the preparation of the copolymers was from Sigma-Aldrich. Absolute (dehydrated) ethanol was from BioSolve. Deionized water was prepared by means of a Milli-Q apparatus.

The copolymer was characterized via ¹H nuclear magnetic resonance (¹H NMR) and size exclusion chromatography (SEC) to determine the composition and the molar mass dispersity Dₑ, respectively. The ¹H NMR measurements (Figure S6a in the Supporting Information) were carried out on a Varian 400 (400 MHz) spectrometer at 25 °C in deuterated chloroform.

Size-exclusion chromatography–multiple-angle laser light scattering (SEC-MALS) was performed with a water-Wyatt advanced polymer chromatography (APC)-MALDI-R1 system with a an ACQUITY APC system containing a dual-column system with ACQUITY APC XT 900 Å 2.5 μm and 200 Å 2.5 μm and two detectors (Wyatt uDAWN MALS and Wyatt OptiLab T-REx) measuring the light scattering and refractive index, respectively. The solvent was acetonitrile with a flow rate of 0.5 mL/min. The results are plotted in Figure S6 in the Supporting Information.

In all experiments, the samples were prepared by dissolving the BCP directly in the various solvent mixtures. The initial sample preparation is not expected to affect the observed morphology transitions as the thermal history of the samples is erased by heating to T = 70 °C prior to each thermal cycle. Without thermal reset, pathway dependence should be expected.

**Small- and Wide-Angle Synchrotron X-ray Scattering.** SAXS/WAXS measurements were performed at the ID02 beamline of ESRF in Grenoble. The high brilliance of the synchrotron source enabled extremely short measurement times (10 ms), allowing to perform kinetic measurements. Measurements were performed in 1 mm quartz capillaries which were cooled down from T = 70 °C to T = −20 °C by means of a Linkam heating stage. Before filling the capillaries, the BCP solutions were preheated at 70 °C on a heating plate. A cooling rate of χₛ = 10 °C min⁻¹ was applied. The scattered X-rays were simultaneously detected using two CCD detectors, Rayonix LX-170HS collecting the atomic diffraction from the system at wide angles and Rayonix MX-170HS collecting the small-angle scattering. The small-angle detector was placed at a 1 m distance from the sample to access a scattering vector (q) range of 0.06 < q < 6 nm⁻¹. Automatic data reduction and calibration were performed at the beamline.

Multiple analysis cycles were performed for some selected samples (data not shown). The data obtained in the different cycles did not show significant differences, demonstrating the reproducibility of the observed processes.

**Analysis of the Scattering Data.** The scattered signal of an empty capillary, used as a background, was recorded at different temperatures, −20 °C < T < 70 °C. Background subtraction was automatized by means of a custom-made script. Ethanol was not included in the background for two reasons: first, different capillaries have different diameters, and therefore, subtraction of the ethanol signal could have resulted in negative scattering data at high q; second, the scattering of ethanol is expected to be q-independent at small angles, and hence, its contribution is a constant. The script for the background subtraction operates as follows: the scattering patterns of the empty capillaries and the samples are indexed based on the acquisition temperature. For each sample, the script subtracts the background recorded at the closest temperature. The temperature differences between the sample and background were always smaller than 1 °C.

Comparison or fitting of the scattering data with theoretical form factors and structure factors was performed with SasView⁶ 4.2. To provide details about the scattering models used here, the original papers are cited during the discussion. For details about the implementation of these models, the reader is referred to SasView documentation. Some parameters of the scattering models are accompanied by polydispersity indices. These represent the ratio between the average parameter value and the width (i.e., standard deviation) of the simulated Gaussian distribution. If polydispersity is not indicated, the parameter is assumed to be uniform.

**Scanning Probe Microscopy.** Height and phase characterizations were performed with an NT-MDT Solver Next SPM in the semicontact (tapping) mode using the Bruker silicon tips, RTESP-150 as well as PEAKFORCE-HIRS-F-A. The RTESP-150 were in general used for revealing the larger scale and have a typical spring constant of 6 N/m, a resonance frequency of 150 kHz, and a tip radius size of 8 nm. The PEAKFORCE-HIRS-F-A were applied for higher resolution and have a typical spring constant of 0.35 N/m, a resonance frequency of 165 kHz, and a tip radius size of 1 nm.

The sample was prepared as follows: 50 mg·mL⁻¹ copolymer dispersions in a water–ethanol mixture containing a water volume fraction of ϕ_w = 0.3 were first heated to T = 70 °C and then cooled to room temperature overnight. The solution was then diluted 100 times with a ϕ_w = 0.3 water–ethanol mixture, deposited on a silicon wafer, and dried with a nitrogen flow.

The cross-sectional diameter of the cylinders was determined by averaging the cross-sectional height (see Figure 4a for an example) of three different cylinders. For each cylinder, the cross-section was measured at four different locations.

**Cryogenic Transmission Electron Microscopy.** Cryo-TEM samples were prepared on QUANTIFOIL R2/2 (Electron Microscopy Sciences) grids. Grids were glow-discharged for 70 s to increase hydrophilicity prior to sample loading. Vitrification was carried out using an Automatic Plunge Freezer ME GP2 (Leica Microsystems) with 5 μL of the sample. Grid preparation was performed at 95% humidity, and the grids were blotted for 3 s prior to plunging into liquid propane. Cryo-TEM samples were then placed on a Gatan cryo-TEM holder and imaged on a JEOl 2100F TEM using a Schottky-type field emission gun operating at 200 keV. Images were recorded using SerialEM software in the low-dose mode with a Gatan OneView CMOS camera at a 4k × 4k resolution. Prior to vitrification, samples of PCL₆₅-b-PEG₃₅ (50 mg/mL) were heated up to 70 °C and cooled with an average cooling rate of 20 °C/min. Following cooling, samples were immediately diluted to 10 mg/mL and vitrified. Dilution was necessary in order to image the sample using cryo-TEM. Selected images have been analyzed to determine the size of the spherical micelles and the cross-sectional diameter of the cylindrical micelles. The analysis (see Figure 5d,e) was performed on 100 particles per sample; the data in the main text are presented as the average ± standard deviation.

**ASSOCIATED CONTENT**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.0c02759.

Prediction of gyration radius for Me-EO₄₅-CL₃₀ crystalization of PCL in water–ethanol mixtures; DSC data for PEO 2 kDa and PCL 2 kDa in different water–ethanol mixtures; SAXS profiles for 50 mg·mL⁻¹ Me-EO₄₅-CL₃₀ dispersions in water–ethanol mixtures with ϕ_w=0.1 and ϕ_w=0.2 at a temperature of T = 60 °C; topography and phase composite images showing hierarchical leaf-shaped planar particles which appear upon drying by the assembly of cylindrical micelles; WAXS profiles for 50 mg·mL⁻¹ Me-EO₄₅-CL₃₀ dispersed in water–ethanol mixtures with ϕ_w=0.3 and ϕ_w=0.5 at a temperature T = −20 °C; cryo-TEM micrographs of
Me-EO_{45}-CL_{30} samples dispersed in water–ethanol mixtures; cryo-TEM image of a leaf-shaped planar particle which appears to be formed by assembled cylindrical micelles, similar to the particles observed via SPM; $^1$H NMR and SEC-MALS trace for PEO_{45}-b-PCL_{30} and DSC data for PEO 2 kDa and PCL 2 kDa in different water–ethanol mixtures analyzed upon cooling and heating (PDF)

**AUTHOR INFORMATION**

**Corresponding Authors**

Alessandro Ianiro — Laboratory of Physical Chemistry, Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands; Institute for Complex Molecular Systems (ICMS), Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands; Adolphe Merkle Institute, University of Fribourg, 1700 Fribourg, Switzerland; orcid.org/0000-0003-4709-4350; Email: Alessandro.ianiro@unifr.ch

Remco Tuinier — Laboratory of Physical Chemistry, Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands; Institute for Complex Molecular Systems (ICMS), Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands; orcid.org/0000-0002-4096-7107; Email: r.tuinier@tue.nl

**Authors**

Marco M.R.M. Hendrix — Institute for Complex Molecular Systems (ICMS) and Laboratory of Self-Organizing Soft Matter, Laboratory of Macromolecular and Organic Chemistry, Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands

Paul Joshua Hurst — Department of Chemistry, University of California, Irvine, Irvine, California 92697-2023, United States; orcid.org/0000-0002-1826-2549

Joseph P. Patterson — Department of Chemistry, University of California, Irvine, Irvine, California 92697-2023, United States; orcid.org/0000-0002-1975-1854

Mark Vis — Laboratory of Physical Chemistry, Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands; Institute for Complex Molecular Systems (ICMS), Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands; orcid.org/0000-0002-2992-1175

Michael Szтucki — ESRF, The European Synchrotron Radiation Facility, 38000 Grenoble, France

A. Catarina C. Esteves — Laboratory of Physical Chemistry, Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands; Institute for Complex Molecular Systems (ICMS), Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.macromol.0c02759

**Author Contributions**

A.I. and R.T. conceived the study; A.I. and A.C.C.E synthesized the polymer; A.I., R.T., M.V., and M.M.R.M.H. performed the scattering measurements; M.M.R.M.H. performed the SPM measurements; M.S. provided beamline support; J.P.P. and P.J.H. performed the cryo-TEM and SEC analyses. All authors contributed to the data interpretation and to the manuscript writing.

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

The authors thank the European Synchrotron Radiation Facility (Grenoble, France) for the provision of synchrotron radiation facilities and the ID02 beamline staff for the excellent support. Furthermore, the authors thank Lisa Timmers for help with the SAXS measurements. Cryo-TEM images were obtained using the instrumentation at the IMRI (ps.uci.edu/imri/) facilities at UC Irvine. M.V. acknowledges the Netherlands Organisation for Scientific Research (NWO) for a Veni grant (no. 722.017.005). The authors thank M. Chi for kindly performing the DSC characterization of PEO and PCL homopolymers.

**ABBREVIATIONS**

BCPs, block copolymers; SAXS, small-angle synchrotron X-ray scattering; WAXS, wide-angle synchrotron X-ray scattering; SPM, scanning probe microscopy; PEO, poly-ethylene(oxide); PCL, poly-$\epsilon$-caprolactone; cryo-TEM, cryogenic transmission electron microscopy; $^1$H NMR, $^1$H nuclear magnetic resonance; SEC, size exclusion chromatography

**REFERENCES**

(1) Blanazs, A.; Armes, S. P.; Ryan, A. J.; Armes, S. P.; Ryan, A. J. Self-Assembled Block Copolymer Aggregates: From Micelles to Vesicles and Their Biological Applications Self-Assembled Block Copolymer Aggregates: From Micelles to Vesicles and Their Biological Applications. Macromol. Rapid Commun. 2009, 30, 267–277.

(2) Mai, Y.; Eisenberg, A. Self-Assembly of Block Copolymers. Chem. Soc. Rev. 2012, 41, 5969–5985.

(3) Holder, S. J.; Sommerdijk, N. A. J. M. New Micellar Morphologies from Amphiphilic Block Copolymers: Disks, Toroids and Bicontinuous Micelles. Polym. Chem. 2011, 2, 1018–1028.

(4) Mckenzie, B. E.; Friedrich, H.; Wirix, M. J. M.; de Visser, J. F.; Monaghan, O. R.; Bomans, P. H. H.; Nudelman, F.; Holder, S. J.; Sommerdijk, N. A. J. M. Controlling Internal Pore Sizes in Bicontinuous Polymeric Nanospheres. Angew. Chem. 2015, 127, 2487–2491.

(5) Karayianni, M.; Pispas, S. Self-Assembly of Amphiphilic Block Copolymers in Selective Solvents. Fluorescence Studies of Polymer Containing Systems; Springer International Publishing: Switzerland, 2016; pp 27–64.

(6) Haag, R. Supramolecular Drug-Delivery Systems Based on Polymeric Core – Shell Architectures. Angew. Chem., Int. Ed. 2004, 43, 278–282.

(7) Alexandridis, P. Amphiphilic Copolymers and Their Applications.Curr. Opin. Colloid Interface Sci. 1996, 1, 490–501.

(8) Chen, J.; Wang, F.; Liu, Q.; Du, J. Antibacterial Polymeric Nanostructures for Biomedical Applications. Chem. Commun. 2014, 50, 14482–14493.

(9) Wang, T.; Jiang, J.; Xiao, Y.; Zou, Y.; Gao, J.; Du, J. Preparation of Polymersomes in Pure Water for Facile Antibacterial Applications. RSC Adv. 2015, 5, 55602–55607.

(10) Otsuka, H.; Nagasaki, Y.; Kataoka, K. Self-Assembly of Poly(Ethylene Glycol) -Based Block Copolymers for Biomedical Applications. Curr. Opin. Colloid Interface Sci. 2001, 6, 3–10.

(11) Blanazs, A.; Verber, R.; Mykhaylyk, O. O.; Ryan, A. J.; Heath, J. Z.; Douglas, C. W.; Armes, S. P. Sterilizable Gels from
Thermoresponsive Block Copolymer Worms. J. Am. Chem. Soc. 2012, 134, 9741–9748.
(12) Derry, M. J.; Mykhaylyk, O. O.; Armes, S. P. A Vesicle-to-Worm Transition Provides a New High-Temperature Oil Thickening Mechanism. Angew. Chem., Int. Ed. 2017, 56, 1746–1750.
(13) Blasco, E.; Serrano, J. L.; Piñol, M.; Oriol, L. Light Responsive Vesicles Based on Linear-Dendritic Block Copolymers Using Azobenzene-Aliphatic Codendrons. Macromolecules 2013, 46, 5951–5960.
(14) Zhao, Y. Photocontrollable Block Copolymer Micelles: What Can We Control? J. Mater. Chem. 2009, 19, 4887–4898.
(15) Sato, T.; Takahashi, R. Competition between the Micellization and the Liquid-Liquid Phase Separation in Amphiphilic Block Copolymer Solutions. Polym. J. 2017, 49, 273–277.
(16) Ianiro, A.; Wu, H.; van Rijt, M. M. J.; Vena, M. P.; Keizer, A. D. A.; Esteses, A. C. C.; Tuinier, R.; Friedrich, H.; Sommerdijk, N. A. J. M.; Patterson, J. P. Liquid–Liquid Phase Separation during Amphiphilic Self-Assembly. Nat. Chem. 2019, 11, 320–328.
(17) Zhang, Q.; Hoogenboom, R. Polymers with Upper Critical Solution Temperature Behavior in Alcohol/Water Solvent Mixtures. Prog. Polym. Sci. 2015, 48, 122–142.
(18) Bang, J.; Jain, S.; Li, Z.; Lodge, T. P.; Pedersen, J. S.; Kesselman, E.; Talmon, Y. Sphere, Cylinder, and Vesicle Nano-aggregates in Poly(Styrene-b-Isoprene) Diblock Copolymer Solutions. Macromolecules 2006, 39, 1199–1208.
(19) Wang, E.; Zha, J.; Zhao, D.; Xie, S.; Bates, F. S.; Lodge, T. P. Effect of Solvent Selectivity on Chain Exchange Kinetics in Block Copolymer Micelles. Macromolecules 2020, 53, 417–426.
(20) Hanley, K. J.; Lodge, T. P.; Huang, C.-I. Phase Behavior of a Block Copolymer in Solvents of Varying Selectivity. Macromolecules 2000, 33, 5918–5931.
(21) Di Cola, E.; Lefebvre, C.; Beffieux, A.; Narayanan, T.; Borsali, R. Micellar Transformations of Poly(Styrene-b-Isoprene) Block Copolymers in Selective Solvents. Soft Matter 2009, 5, 1081–1090.
(22) Lodge, T. P.; Pudil, B.; Hanley, K. J. The Full Phase Behavior for Block Copolymers in Solvents of Varying Selectivity. Macromolecules 2002, 35, 4707–4717.
(23) Ianiro, A.; Chi, M.; Hendrix, M. M. R. M.; Koc, A. V.; Eren, E. D.; Sztucki, M.; Petukhov, A. V.; De With, G.; Esteses, A. C. C.; Tuinier, R. Block Copolymer Hierarchical Structures from the Interplay of Multiple Assembly Pathways. Polym. Chem. 2020, 11, 2305–2311.
(24) Brigham, N.; Carandang, A.; Allen, K.; Van Horn, R. M.; Nardi, C. Manipulation of Crystallization Sequence in PEO- b-PCL Films and the Liquid-Liquid Phase Separation in Amphiphilic Block Copolymer Solutions. Macromolecules 2017, 50, 8996–9007.
(25) Ianiro, A.; Jiménez-Pardo, I.; Esteses, A. C. C.; Tuinier, R. One-Pot, Solvent-Free, Metal-Free Synthesis and UCST-Based Purification of Poly(Ethylene Oxide)/Poly-ε-Caprolactone Block Copolymers. J. Polym. Sci., Part A: Polym. Chem. 2016, 54, 2992–2999.
(26) Qi, W.; Ghoroghchian, P. P.; Li, G.; Hammer, D. A.; Therien, M. J. Aqueous Self-Assembly of Poly(Ethylene Oxide)-Block-Poly(ε-Caprolactone) (PEO-b-PCL) Copolymers: Disparate Diblock Copolymer Compositions Give Rise to Nano- and Meso-Scale Bilayered Vesicles. Nanoscale 2013, 5, 10908–10915.
(27) Hammouda, B. SANS from Homogeneous Polymer Mixtures: A Unified Overview. In Polymer Characteristics; Springer Berlin Heidelberg: Berlin, Heidelberg, 1993; pp 87–133.
(28) Livesey, I. Neutron Scattering from Concentric Cylinders. Intraparticle Interference Function and Radius of Gyration. J. Chem. Soc. Faraday Trans. 1987, 83, 1445–1452.
(29) Fournet, A.; Guinier, G. Small-Angle Scattering of X-rays; John Wiley & Sons, Inc.: New York, 1955.
(30) Morawetz, H. Light Scattering from Polymer Solutions; Huglin, M., Ed.; Academic Press Inc.: London, 1973.
(31) Yang, F.-C.; Peters, R. D.; Dies, H.; Rheinstädter, M. C. Hierarchical, Self-Similar Structure in Native Squid Pen. Soft Matter 2014, 10, 5541–5549.
(32) Percus, J. K.; Yevick, G. J. Analysis of Classical Statistical Mechanics by Means of Collective Coordinates. Phys. Rev. 1958, 110, 1–13.
(33) Zhulina, E. B.; Borisov, O. V. Theory of Block Polymer Micelles: Recent Advances and Current Challenges. Macromolecules 2012, 45, 4429–4440.
(34) Shikata, T.; Okuzono, M.; Sugimoto, N. Temperature-Dependent Hydration/Dehydration Behavior of Poly(Ethylene Oxide) in Aqueous Solution. Macromolecules 2013, 46, 1956–1961.
(35) Narayanan, T.; Sztucki, M.; Van Vaerenbergh, P.; Léonardon, J.; Gorini, J.; Claustre, L.; Sever, F.; Morse, J.; Boesecke, P. A Multipurpose Instrument for Time-Resolved Ultra-Small-Angle and Coherent X-Ray Scattering. J. Appl. Crystallogr. 2018, 51, 1511–1524.
(36) Doucet, M.; Cho, J. H.; Alina, G.; Bakker, J.; Bouwman, W.; Butler, P.; Campbell, K.; Gonzales, M., Heenan, R.; Heenan, R.; Jackson, A.; Juhás, P.; King, S.; Kienzle, P.; Krzywon, J.; Markvardsen, A.; Nielsen, T.; O’Driscoll, L.; Potrzebowski, W.; Ferraz Leal, R.; Richter, T.; Rozyczko, P.; Snow, T.; Washington, A. SasView; Zenodo, 2018, https://doi.org/10.5281/zenodo.1412041.