# **Macromolecules**

## Tuning Biocompatible Block Copolymer Micelles by Varying Solvent Composition: Core/Corona Structure and Solvent Uptake

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#### **Supporting Information**

**ABSTRACT:** Block copolymer micelles enable the formation of widely tunable self-assembled structures in liquid phases, with applications ranging from drug delivery to personal care products to nanoreactors. In order to understand fundamental aspects of micelle assembly and dynamics, the structural properties and solvent uptake of biocompatible poly(ethylene oxide-*b*-*ɛ*-caprolactone) (PEO–PCL) diblock copolymers in deuterated water (D<sub>2</sub>O)/tetrahydrofuran (THF-*d*<sub>8</sub>) mixtures



were investigated with a combination of small-angle neutron scattering, nuclear magnetic resonance, and transmission electron microscopy. PEO–PCL block copolymers, of varying molecular weight yet constant block ratio, formed spherical micelles through a wide range of solvent compositions. Varying the solvent composition from 10 to 60 vol % THF- $d_8$  in D<sub>2</sub>O/THF- $d_8$  mixtures was a convenient means of varying the core–corona interfacial tension in the micelle system. An increase in THF- $d_8$  content in the bulk solvent increased the solvent uptake within the micelle core, which was comparable for the two series, irrespective of the polymer molecular weight. Whereas the smaller molecular weight micelle series exhibited a decrease in aggregation number with increasing THF- $d_8$  content in the bulk solvent, as anticipated due to changes in the core–corona interfacial tension. Differences in the dependencies of the micelle size parameters (core radius and overall micelle radius) on the solvent composition originated from the differing trends in aggregation number for the two micelle series. Incorporation of the known unimer content determined from NMR (described in the companion paper), and directly accounting for impacts of solvent swelling of the micelle core on the neutron scattering length density of the core, allowed refinement of and increased confidence in extracted micelle parameters. In summary, the two micelle series showed similar solvent uptake that was independent of the polymer molecular weight yet significantly different dependencies of their aggregation number and size parameters on the solvent composition.

#### INTRODUCTION

Amphiphilic block copolymers, like their small-molecule surfactant and lipid analogues, form diverse nanoscale assemblies when dissolved in a selective solvent for which the blocks have varying degrees of solubility.<sup>1,2</sup> The aggregates vary in morphology from spherical and cylindrical micelles to vesicles, and often coexisting structures are present.<sup>2–5</sup> Such self-assembled structures potentially have wide-ranging applications as drug delivery vehicles, nanoreactors, and encapsulants.<sup>5–7</sup> A diverse array of polymer constituents have been explored in block copolymer micelles. Micelle systems have been developed containing core-forming blocks of various

glassy,<sup>8,9</sup> semicrystalline,<sup>10</sup> and amorphous/rubbery polymers.<sup>11</sup> In aqueous systems, the corona is typically composed of poly(ethylene oxide),<sup>12,13</sup> though other polymers such as polyacids have also been examined.<sup>14–16</sup> The free energy of a block copolymer micelle solution is governed by three main contributions:<sup>17,23</sup> (1) core chain stretching, (2) corona chain repulsion, and (3) the core/corona interfacial tension. In block copolymer micelles, the micelle free energy and resulting

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Scheme 1. PEO-PCL Diblock Copolymer Synthesis



structure and size can be readily tuned. For example, the block copolymer molecular weight, block ratio, and concentration in the micelle solution govern the three contributions to the free energy, thus impacting the micelle morphology, critical micelle concentration and temperature, and micelle size and aggregation number.<sup>18–21</sup>

A powerful method to manipulate the micelle free energy and resulting structure is to vary the choice of solvent in the micelle solution.<sup>19</sup> Traditionally micelle solutions have been prepared in aqueous solvents; however, micelle solutions composed of organic solvents and their mixtures have also been explored.<sup>8,22</sup> A number of literature studies have explored the use of solvent mixtures as a method of tuning the micelle structure. Typically two solvents are employed: one which is a selective solvent, that is, a good solvent for the corona-forming block and a poor solvent for the core-forming block, and a second solvent which is a good solvent for both blocks. Varying the composition of the solvent mixture thus greatly influences the interfacial tension at the core-corona interface.<sup>9,23</sup> At low concentrations of the selective solvent, only unimers may be formed, which have been reported to transition to spherical micelles when the concentration of the selective solvent is increased (and therefore the interfacial tension is increased); upon further addition of the selective solvent, the micelle morphology transitions to cylinders and then vesicles.<sup>8,9,14,15,22,24</sup> The micelle size and aggregation number are also impacted by the composition of the solvent mixture. An increase in the concentration of the selective solvent, and associated increase in interfacial tension, generally increases the aggregation number (and reduces the number of micelles),  $^{9,11,24-28}$  which in turn minimizes the total core–corona interfacial area of the overall micellar system.<sup>15,19</sup> The increase in aggregation number is often accompanied by an increase in the micelle core radius;<sup>11,25-27,29</sup> however, this may be accompanied by changes in the partitioning of the solvents within the micelle core which is also influenced by the solvent composition.<sup>11,26,28</sup> In thermoresponsive systems, the solution temperature is another method of varying the solvent quality.<sup>30,31</sup> In Pluronic-based aqueous micelle systems, increasing the temperature decreases the solvent selectivity, which results in a decrease in aggregation number and core radius, a slight decrease in corona thickness, and increased swelling of the micelle core with solvent.<sup>32,33</sup>

In order to probe the effect of core–corona interfacial tension (through varying solvent composition) on micelle dimensions and solvent uptake, we have investigated the structure of block copolymer micelles composed of poly-(ethylene oxide-*b*- $\varepsilon$ -caprolactone) (PEO–PCL) diblock copolymers in deuterated water (D<sub>2</sub>O)/tetrahydrofuran (THF- $d_8$ ) mixtures, with a systematic range of solvent compositions. PEO–PCL diblock copolymers are biocompatible block copolymers, appropriate for physiological applications such as drug delivery.<sup>34</sup> PEO is a known hydrophilic polymer, often employed as the corona-forming block in aqueous block copolymer systems.<sup>12</sup> PCL is a hydrophobic, biodegradable,

and semicrystalline polymer, and in some studies the impact of crystallinity on the micelle structure has been examined, particularly in the case of larger aggregates such as worm-like micelles.<sup>10,35-37</sup> In our study, the influence of the THF- $d_8$ content in  $D_2O/THF$ - $d_8$  solvent mixtures has been investigated on two series of PEO-PCL block copolymer micelles, in which the block ratio was constant yet the overall block copolymer molecular weight varied. THF- $d_8$  is a good solvent and D<sub>2</sub>O is a poor solvent for the core-forming block, PCL, while both solvents are good solvents for the corona-forming block, PEO. The PEO-PCL block copolymers formed spherical micelles across a wide range of solvent compositions, ranging from 10 to 60 vol % THF- $d_8$  in the bulk solvent. At higher THF- $d_8$  content the block copolymers were fully soluble. Along with the companion paper by Kidd et al.,<sup>38</sup> we have employed a combination of small-angle neutron scattering (SANS), nuclear magnetic resonance (NMR), and transmission electron microscopy (TEM) analyses to explore the micelle structure and dynamics. Analysis of SANS data with the micelle form factor model developed by Pedersen et al., 39-42 combined with the hard sphere structure factor, has elucidated the following key structural parameters: core and corona radii, aggregation number, and uptake of solvent within the micelle core. Along with the measurements of micelle and free unimer diffusion coefficients, the free unimer content as a function of solvent composition was determined through NMR analysis<sup>38</sup> and incorporated to enhance the accuracy of the SANS analysis. Further, solvent swelling-induced changes in the neutron scattering length density of the micelle core were quantified as a means of determining the solvent content in the core. The core radius quantified through SANS was directly compared to that identified through TEM analysis. The influences of the solvent composition, through which the core-corona interfacial tension was varied, and the overall block copolymer molecular weight (at constant block ratio) on the micelle size, aggregation number, and solvent uptake were examined.

#### EXPERIMENTAL DETAILS

Materials. All chemicals were purchased from Sigma-Aldrich unless otherwise specified.

**Diblock Copolymer Synthesis and Characterization.** Monomethoxy-poly(ethylene oxide) (PEO) was purchased from Polymer Source and used as received.  $\varepsilon$ -Caprolactone ( $\varepsilon$ -CL, 97%) and benzene (ACS grade,  $\geq$ 99%) were purified through distillation (twice) over calcium hydride (CaH<sub>2</sub>, ACS reagent,  $\geq$ 95%). The catalyst 1,5,7triazabicyclo[4.4.0]dec-5-ene (TBD, 98%), was used as received and stored in an inert environment to prevent deactivation.

Poly(ethylene oxide-*b*- $\varepsilon$ -caprolatione) (PEO–PCL) diblock copolymers were synthesized using monomethoxy-PEO as a macroinitiator for the ring-opening polymerization of  $\varepsilon$ -CL (Scheme 1), following literature procedures.<sup>43,44</sup>  $\varepsilon$ -CL was added to a solution of PEO in benzene ( $\varepsilon$ -CL concentration was 0.24 g/mL, and PEO concentration was determined by the targeted copolymer block ratio assuming a monomer conversion of 0.80). A stock solution of TBD in benzene was added to the  $\varepsilon$ -CL/PEO solution (0.007 229 5 g of catalyst per g of  $\varepsilon$ -CL) to initiate the reaction. After sufficient time to achieve around 80% conversion (typically 1.5–2 h), the reaction was quenched with benzoic acid ( $\geq$ 99.5%). The resultant polymer was then dissolved in tetrahydrofuran (THF, chromatography grade,  $\geq$ 99.5%, inhibitor free) and precipitated in hexanes (ACS grade, >99%) 5 times. The polymer was dried under vacuum at room temperature overnight and then dried under vacuum at 60 °C for 8 h.

Proton nuclear magnetic resonance (<sup>1</sup>H NMR) experiments were performed on JEOL ECA-500 and ECX-400P instruments using deuterated chloroform (99.8 atom % D) as the solvent for the determination of weight fractions of the PEO and PCL blocks as well as the number-average molecular weight  $(M_n)$ . The molecular weight distribution (including the dispersity, D) was characterized using a Viscotek gel permeation chromatography (GPC) GPCmax instrument containing Agilent ResiPore columns using THF (OmniSolv, HPLC grade) as the mobile phase at 30 °C. The flow rate was 1 mL/min, and the injection volume was 100  $\mu$ L. Universal analysis, using the refractometer and viscometer, was employed for the characterization of D (the low light scattering signal precluded light scattering analysis). The PEO precursors purchased from Polymer Source had the following characteristics: (1)  $M_{\rm n} = 1.9$  kg/mol and D = 1.05 and (2)  $M_{\rm p} = 5.0$  kg/mol and  $\tilde{D} = 1.06$ . The PEO-PCL block copolymer characteristics are listed in Table 1.

#### Table 1. Characteristics of the PEO-PCL Block Copolymers

name	${M_{ m n,PEO}}^a$ (kg/mol)	${{M_{{ m n,PCL}}}^b}\ ({ m kg/mol})$	$D^{a}$	PCL <sup>b</sup> (mass %)	
PEO <sub>2k</sub> -PCL <sub>3k</sub>	1.9	2.9	1.13	60	
$PEO_{5k}-PCL_{8k}$	5.0	7.5	1.18	60	
<sup>a</sup> Determined	with GPC us	ing universal	analysis	(Figure S1).	
<sup>b</sup> Determined with <sup>1</sup> H NMR (Figure S2).					

Micelle Sample Preparation. Deuterium oxide (D<sub>2</sub>O, 99.9 atom % D) and fully deuterated tetrahydrofuran-d<sub>8</sub> (THF-d<sub>8</sub>, 99.5 atom % D) were used as received. THF- $d_8$  was added dropwise to a known mass of diblock copolymer in a vial, and the resulting solution was left overnight to ensure dissolution in solvent. The amount of  $THF-d_{s}$ used varied depending upon the desired  $D_2O/THF-d_8$  solvent ratio. D<sub>2</sub>O was added to the vial dropwise via syringe pump (Fisher Scientific 78-01001) using a 5 or 10 mL glass syringe at a rate of 8 mL of water/h and under vigorous stirring. The final solution contained 1 mass % polymer and 4 mL of solution ( $D_2O/THF-d_8$  mixture). After removing the stir bar, the vial was capped and sealed with Parafilm. The micelle solutions were sonicated (VWR Symphony, 35 kHz) at room temperature for 1 h and then filtered through a 0.45  $\mu$ m Nylon syringe filter (purchased from VWR). All micelle samples were sonicated again for 1 h at room temperature directly before data collection (SANS, DLS, NMR).

We note that we do not observe any nonequilibrium behavior in multiple measurements over 24 h postsonication, such as breaking apart and re-equilibration of micelles. We cannot conclusively show that we are perfectly at equilibrium, but we have highly reproducible results, including multiple measurements of NMR and SANS data on separate samples with the same composition and preparation procedure.

**Nomenclature.** "PEO<sub>Xk</sub>–PCL<sub>Yk</sub>" refers to a PEO–PCL block copolymer containing a PEO block of X kg/mol and PCL block of Y kg/mol. The "2k series" and "5k series" refer to micelle solutions containing  $PEO_{2k}$ –PCL<sub>3k</sub> and  $PEO_{5k}$ –PCL<sub>8k</sub>, respectively. As a further means of shorthand, "2k-X%" refers to a micelle solution containing  $PEO_{2k}$ –PCL<sub>3k</sub> in a D<sub>2</sub>O/THF-d<sub>8</sub> mixture of X vol % THF-d<sub>8</sub>. "5k-X%" refers to a micelle solution containing  $PEO_{5k}$ –PCL<sub>8k</sub> in a D<sub>2</sub>O/THF-d<sub>8</sub>.

**Dynamic Light Scattering (DLS).** DLS experiments were carried out using a Brookhaven Instruments BI-200SM Research goniometer system with a 637 nm, 30 mW laser, and a 400  $\mu$ m aperture. The intensity autocorrelation function was recorded at 25 °C using a 90° laser-detector angle. Six separate measurements of the correlation function were taken at each delay time, and the average was used in analysis of the data. At long delay times, the data fluctuated around

zero intensity, at which point the data were no longer used in the analysis. Refractive indices of the water/THF mixtures were obtained from the literature.<sup>45</sup> The autocorrelation function was analyzed using the method of cumulants to determine the average diffusion coefficient.<sup>46</sup> The hydrodynamic radius of the diffusing particles was calculated using the Stokes–Einstein relation

$$R_{\rm h} = \frac{k_{\rm B}T}{6\pi\eta D} \tag{1}$$

where D,  $k_{\rm B}$ , T, and  $\eta$  are the diffusion coefficient of the micelles, Boltzmann's constant, temperature, and viscosity of the solution, respectively. Additional details on the methods of cumulants analysis are provided in the Supporting Information. DLS data and fit to the method of cumulants are shown in Figure S3. Tables S1 and S2 summarize the DLS fitting results.

**Small-Angle Neutron Scattering (SANS).** SANS experiments were conducted at the High Flux Isotope Reactor (HFIR) at Oak Ridge National Laboratory on the CG-2 beamline. Data were collected using an incident beam wavelength of 4.72 Å, sample-to-detector distances of 2.5 and 19.3 m, and a scattering vector (q) range of 0.0028–0.533 Å<sup>-1</sup>. The scattering vector q is defined as  $q = 4\pi \sin(\theta/2)/\lambda$ , where  $\theta$  is the scattering angle and  $\lambda$  is the wavelength. The SANS data were reduced using Spice IGOR Pro (WaveMetrics) routines (developed by HFIR CG-2) to account for sample transmission, empty Hellma cell scattering, blocked beam (background) scattering, and the detector efficiency. The absolute intensity was calculated by calibrating with the open beam (without using standards) or, in some select cases, with an aluminum standard (when both methods were applied to the same data set, the obtained values of absolute intensity differed by less than 2%).

**SANS Data Analysis.** The micelle form factor model was fit to the SANS data using three different methods: (1) SasView routines were implemented that were modified from those developed by the DANSE project, which included both the micelle form factor and hard sphere structure factor; (2) the same SasView routines were employed with form factor fitting only; and (3) Matlab code was developed in-house which employed form factor fitting only. In the SasView data fitting, the model was smeared to account for the instrumental wavelength spread,<sup>47,63</sup> and the data fitting was conducted with and without the presence of unimers, which were quantified using diffusion NMR analysis.<sup>38</sup> In the Matlab data fitting, model smearing was not implemented and unimer presence was not included.

The micelle form factor model was developed by Pedersen et al.<sup>40</sup> for the form factor of diblock copolymer micelles with a homogeneous core and a corona of noninteracting Gaussian chains. The form factor  $P_{\text{micelle}}(q)$  has four main contributions: self-correlation of the spherical core, self-correlation of the corona chains, correlation between the core and the corona, and self-correlation of the corona:

$$P_{\text{micelle}}(q) = N_{\text{agg}}^{2} \beta_{\text{core}}^{2} A_{\text{core}}^{2}(q) + N_{\text{agg}} \beta_{\text{corona}}^{2} P_{\text{chain}}(q) + 2N_{\text{agg}}^{2} \beta_{\text{coro}} \beta_{\text{corona}} A_{\text{core}}(q) A_{\text{corona}}(q) + N_{\text{agg}} (N_{\text{Agg}} - 1) \beta_{\text{corona}}^{2} A_{\text{corona}}^{2}(q)$$
(2)

$$\beta_{\rm core} = v_{\rm core} (\rho_{\rm core} - \rho_{\rm solvent}) \tag{3}$$

$$\beta_{\rm corona} = \nu_{\rm corona} (\rho_{\rm corona} - \rho_{\rm solvent}) \tag{4}$$

where  $N_{\rm agg}$  is the micelle aggregation number and represents the average number of diblock copolymer chains that form a micelle.  $\beta_{\rm core}$  and  $\beta_{\rm corona}$  represent the total excess scattering lengths of the core and corona, respectively. Specifically,  $\beta_{\rm corona}$  was calculated as the excess scattering length of the PEO block, where  $\rho_{\rm corona}$  is the scattering length density of the PEO block,  $v_{\rm corona}$  is the volume of the PEO block, and  $\rho_{\rm solvent}$  is the scattering length density of the bulk solvent. In the case of  $\beta_{\rm core}$ , we accounted for the effect of the presence of solvent (THF- $d_8$  and/or D\_2O) in the core on the excess scattering length. Therefore, an additional parameter was defined, the volume fraction of solvent (THF- $d_8$  and/or D\_2O) present in the core ( $f_{\rm solvent}$ ). The core

was assumed to contain PCL and solvent; therefore,  $f_{\rm solvent} + f_{\rm PCL} = 1$ , where  $f_{\rm PCL}$  is the volume fraction of PCL in the core. We note that the scattering length densities of THF- $d_8$  (6.35 × 10<sup>-6</sup> Å<sup>-2</sup>) and D<sub>2</sub>O (6.37 × 10<sup>-6</sup> Å<sup>-2</sup>) are quite similar, preventing us from distinguishing the type of solvent that was swelling the core. We then calculated  $\beta_{\rm core}$  as a function of  $f_{\rm solvent}$  using the following relationships:

$$\rho_{\rm core} = f_{\rm solvent} \rho_{\rm solvent} + f_{\rm PCL} \rho_{\rm PCL} \tag{5}$$

$$v_{\rm core} = \frac{v_{\rm PCL}}{f_{\rm PCL}} \tag{6}$$

where  $\rho_{\rm core}$  is the scattering length density of the core (including solvent and PCL) and  $\nu_{\rm core}$  is the core volume per PCL chain. Additionally,  $\nu_{\rm PCL}$  is the volume of the PCL block and  $\rho_{\rm PCL}$  is the scattering length density of the PCL block. The product  $N_{\rm agg}\nu_{\rm core}$  in eqs 2 and 3 yields the total volume of the core, which accounts for not only PCL chains but also the solvent present in the core, using eqs 5 and 6.

For the core self-correlation term, the amplitude (for a spherical homogeneous core with radius  $R_{core}$  and a smoothly decaying surface scattering length density) is found as

$$A_{\text{core}}(q) = \phi(qR_{\text{core}}) \exp\left(-\frac{q^2 \sigma_{\text{int}}^2}{2}\right)$$
(7)

$$\phi(qR_{\rm core}) = \frac{3[\sin(qR_{\rm core}) - qR_{\rm core} \cos(qR_{\rm core})]}{(qR_{\rm core})^3}$$
(8)

$$R_{\rm core} = \left(\frac{3}{4\pi} N_{\rm agg} v_{\rm core}\right)^{1/3} \tag{9}$$

 $\phi(qR_{\rm core})$  is the form factor amplitude of a sphere, and the exponential term in eq 7 accounts for a smoothly decaying scattering length density at the core–corona interface.  $\sigma_{\rm int}$  is the width of the core–corona interface.  $R_{\rm core}$  is calculated in eq 9 assuming that the total core volume,  $N_{\rm agg} \nu_{\rm core}$ , is spherical, where  $R_{\rm core}$  is the radius of the sphere. We note that  $R_{\rm core}$  is written as a function of  $\nu_{\rm core}$  in eq 9 (which is a function of  $f_{\rm PCL}$  and defined in eq 6, where  $f_{\rm PCL} = 1 - f_{\rm solvent}$  in the core). We chose to use  $f_{\rm solvent}$  as a fitting parameter (rather than fitting  $R_{\rm core}$  directly). In this way, we accounted for the effect of swelling of the core with solvent on  $\beta_{\rm core}$  and  $R_{\rm core}$  without increasing the total number of fitting parameters (i.e.,  $f_{\rm solvent}$  was a fitting parameter in place of  $R_{\rm core}$ ).

The self-correlation of the PEO chains in the corona (approximated as Gaussian chains with radius of gyration  $R_g$ ) was calculated using the Debye function:

$$P_{\text{chain}}(q) = \frac{2[\exp(-q^2 R_g^2) - 1 + q^2 R_g^2]}{(q^2 R_g^2)^2}$$
(10)

The scattering amplitude for the corona self-correlation term was calculated assuming the PEO corona chains had a radial density distribution,  $\rho_{\rm chain}(r)$ , following Pedersen et al.<sup>40</sup>

$$A_{\rm corona}(q) = \frac{4\pi \int \rho_{\rm chain}(r) \left[\frac{\sin(qr)}{qr}\right] r^2 dr}{4\pi \int \rho_{\rm chain}(r) r^2 dr} \exp\left(\frac{-q^2 \sigma_{\rm int}^2}{2}\right)$$
(11)

where  $\rho_{\text{chain}}(r)$  can be represented as a linear combination of two cubic b splines.

$$\rho_{\text{chain}}(r) = \frac{\rho_1(r) + a_1 \rho_2(r)}{1 + a_1} \tag{12}$$

For  $R_{\text{core}} \leq r < R_{\text{core}} + s$ 

$$\rho_1(r) = \frac{4(r - R_{\rm core} - s)^3 - (r - R_{\rm core} - 2s)^3}{4s^3}$$
(13)

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$$\rho_2(r) = \frac{-(r - R_{\rm core} - s)^3}{4s^3} \tag{14}$$

For  $R_{core} + s \leq r < R_{core} + 2s$ ,

$$\rho_1(r) = \frac{-(r - R_{\rm core} - 2s)^3}{4s^3}$$
(15)

Elsewhere

$$\rho_1(r) = 0 \tag{16}$$

$$\rho_2(r) = 0 \tag{17}$$

The parameter *s* describes the width of radial profile  $\rho_{\text{chain}}(r)$ , and  $a_1$  is the weighting factor for the linear combination of the two splines that make up that radial profile.  $A_{\text{corona}}$  can be rewritten as a function of the Fourier transforms of the two contributions to  $\rho_{\text{chain}}(r)$  (analytical forms of  $A_1(q)$  and  $A_2(q)$  are provided in eqs S6–S9 in the Supporting Information and were taken from Pedersen et al.<sup>40</sup>).

$$A_{\text{corona}}(q) = \frac{[A_1(q) + a_1 A_2(q)]}{(1+a_1)} \exp \frac{(-q^2 \sigma_{\text{int}}^2)}{2}$$
(18)

Polydispersity in micelle size was accounted for using a Schulz distribution for the core radius.  $^{11}\,$ 

$$G(R_{\rm c}) = \frac{R_{\rm core}^Z}{\Gamma(Z+1)} \left(\frac{Z+1}{\langle R_{\rm core} \rangle}\right)^{Z+1} \exp\left[-\frac{(Z+1)R_{\rm core}}{\langle R_{\rm core} \rangle}\right]$$
(19)

$$Z = \frac{1}{\sigma_{Rc}^2} - 1 \tag{20}$$

where  $\langle R_{\rm core} \rangle$  is the average core radius and  $\sigma_{Rc}$  is the core radius polydispersity. Combining this polydispersity term with the micelle form factor obtains the coherent scattered intensity, which can then be added to the incoherent scattering intensity to calculate the total scattering intensity (*c* is the micelle concentration and *M* is the micelle mass):

$$I_{\text{coherent}}(q) = \frac{c}{M} \int P_{\text{micelle}}(q) G(R_{\text{core}}) \, \mathrm{d}R_{\text{core}}$$
(21)

$$I(q) = I_{\text{coherent}}(q) + I_{\text{incoherent}}(q)$$
(22)

Equation 21 accounts for the form factor contribution to the scattering only, which is valid at low micelle volume fraction. At higher micelle contents, the contribution from interactions between micelles is included as a structure factor:<sup>40</sup>

$$I_{\text{coherent}}(q) = \frac{c}{M} \int (P_{\text{micelle}}(q) + A_{\text{micelle}}(q)^2 (S_{\text{micelle}}(q) - 1)) \times G(R_{\text{core}}) \, dR_{\text{core}}$$
(23)

where  $A_{\text{micelle}}$  is the micelle scattering amplitude

$$A_{\text{micelle}} = N_{\text{agg}}\beta_{\text{core}}A_{\text{core}} + N_{\text{agg}}\beta_{\text{corona}}A_{\text{corona}}$$
(24)

and  $S_{\rm micelle}$  is the hard sphere structure factor based on the Percus–Yevick closure (a description of our calculations is provided in the Supporting Information, including eqs S10–S24).<sup>40,48–50</sup>

To simplify calculations, 20-point Gaussian quadrature was used in place of integration. The equations were written as a Python code and implemented in SasView using the advanced custom model editor. The following fitting parameters were used:  $N_{agg}$ ,  $f_{solvent}$ ,  $\sigma_{Rc}$ ,  $\sigma_{int}$ ,  $I_{incoherent}$ , s, and  $a_1$ . Additionally, inclusion of the structure factor eq 23 required one additional fitting parameter:  $\Delta R_{hs}$ , where  $R_{interaction} = R_{core} + \Delta R_{hs}$  and  $R_{interaction}$  is the interaction radius. Input parameters to the model, determined through independent measurements, included the polymer weight concentration, the molecular weights and mass densities of the core and corona blocks of PEO–PCL, the radius of gyration ( $R_g$ ) of PEO (calculated using the statistical segment length of PEO reported in the literature<sup>11</sup>), and the known scattering length densities of the PEO block, PCL block, and bulk solvent (mixture of

THF- $d_8$  and  $D_2O$ ). The differential evolution fitting method was employed, providing a balance of computation speed and robustness, and was allowed to run until no further changes were observed in the reported  $\chi^2$  value (i.e., goodness-of-fit). Smearing of the model was accounted for using the resolution function provided in Kline et al.<sup>47</sup>

In cases where the structure factor was not included in the fitting, the total micelle radius,  $R_{\text{micelle}}$ , and the width of the corona, H, were calculated from the corona density profile,  $\rho_{\text{chain}}(r)$  (eq 12). The calculated corona density profile  $\rho_{\text{chain}}(r)$  was rescaled to  $\hat{\rho}_{\text{chain}}(r)$  by relating the total volume of the corona to the integral of the radial profile:

$$N_{\rm agg}\nu_{\rm corona} = 4\pi \int \hat{\rho}_{\rm chain}(r)r^2 \,\mathrm{d}r \tag{25}$$

The value of  $R_{\rm micelle}$  was calculated as the value of r at which  $\hat{\rho}_{\rm chain}(r)$  was equal to 0.02 (following the literature  $^{11,31,42,51}$ ). The corona thickness was then calculated as  $H = R_{\rm micelle} - R_{\rm core}$ . In cases where the structure factor was included in the fitting, the total micelle radius was taken to be  $R_{\rm interaction} = R_{\rm core} + \Delta R_{\rm hs}$  and the corona thickness  $H = \Delta R_{\rm hs}$  where  $\Delta R_{\rm hs}$  is a fitting parameter.

**Transmission Electron Microscopy.** Solutions for cryo-TEM experiments were vitrified on carbon-coated grids using an FEI Vitrobot. Cryo-TEM imaging was conducted on a FEI Tecnai G2 Spirit BioTwin at the Microscopy and Cytometry Facility of the Huck Institutes of the Life Sciences, Pennsylvania State University. Brightfield images were acquired at a 120 kV accelerating voltage. Image analysis was carried out using ImageJ.

Contact Angle Measurement and Calculation of Interfacial Tension. Polycaprolactone (PCL) ( $M_n = 1.9 \text{ kg/mol}$ , D = 1.09) was dissolved in THF (at a loading of 0.02 g/mL) and added dropwise on to a 1 cm by 1 cm, single sided polished  $\langle 100 \rangle$  silicon wafer (Mechanical grade, University Wafers). The wafer was loaded into a Brewer Science Cee 200CB spin-coater and spun at 3000 rpm for 1 min. The wafer was subsequently dried at room temperature overnight. A drop of the D<sub>2</sub>O/THF- $d_8$  mixture with desired THF- $d_8$  content (of approximate volume 1  $\mu$ L) was placed on the coated wafer, and the contact angle-measuring instrument (DataPhysics, Germany) at ambient temperature using SCA 20 software. The contact angle was averaged over four measurements on the same surface. Young's equation was employed to calculate the interfacial tension of the D<sub>2</sub>O/THF- $d_8$  solvent drop on PCL ( $\gamma_{PCL-solvent}$ ):

$$\gamma_{\rm PCL-solvent} = \gamma_{\rm PCL} - \gamma_{\rm solvent} \cos \theta \tag{26}$$

where  $\gamma_{PCL}$  is the air–PCL interfacial energy (taken from Biresaw et al., <sup>52</sup> but also consistent with that compiled in Biresaw et al. <sup>53</sup>),  $\gamma_{solvent}$  is the surface tension of the D<sub>2</sub>O/THF-d<sub>8</sub> mixture, and  $\theta$  is the measured contact angle. It has been reported that deuteration has little impact on interfacial energies; <sup>54</sup> therefore, literature values for  $\gamma_{solvent}$  using hydrogenous H<sub>2</sub>O/THF were used in the calculations. <sup>55</sup>

#### RESULTS AND DISCUSSION

Micelle Preparation and Characterization with Dynamic Light Scattering. PEO<sub>2k</sub>-PCL<sub>3k</sub> and PEO<sub>5k</sub>-PCL<sub>8k</sub> block copolymers were synthesized through the ring-opening of  $\varepsilon$ -caprolactone with a monomethoxy-PEO macroinitiator, and the polymer characteristics are presented in Table 1. <sup>1</sup>H NMR and GPC data obtained from PEO<sub>2k</sub>-PCL<sub>3k</sub> and PEO<sub>5k</sub>-PCL<sub>8k</sub> are shown in Figures S1 and S2. The 2k series (containing  $PEO_{2k}-PCL_{3k}$ ) and 5k series (containing  $PEO_{5k}-PCL_{8k}$ ) micelle solutions were prepared by dissolution of each polymer in THF- $d_8$  overnight, followed by the dropwise addition of D2O, and subsequent filtering prior to analysis. DLS data (shown in Figure 1 and Figure S3) were obtained on the micelle solutions, and  $R_{\rm h}$  and D were extracted through fitting the correlation function with the method of cumulants (Tables S1 and S2). The DLS data were consistent with narrow, unimodal distributions of micelles, with no evidence of micelle



**Figure 1.** DLS data obtained from the 2k-10% micelle solution, containing  $PEO_{2k}-PCL_{3k}$  in a 10/90 THF- $d_8/D_2O$  solvent mixture. Solid curve represents the fit using the method of cumulants. Additional DLS data and fitting results are shown in Figure S3 and Tables S1–S2.

aggregation. The polymer concentration in the micelle solutions (1 mass % polymer) was well above the previously reported critical micelle concentration of a PEO-PCL diblock copolymer (0.002 mass %).<sup>36</sup> Previous work by Du et al.<sup>35</sup> reported spherical micelles in water when the PEO-PCL block copolymer contained 59-70 mass % PCL. Here, both the 2k and 5k series contained 60 mass % PCL in the PEO-PCL block copolymer, within the range of compositions reported for spherical micelles in water. Though PCL is a semicrystalline polymer, we do not anticipate that the PEO-PCL micelle solutions in  $D_2O/THF-d_8$  mixtures studied here contain semicrystalline cores for the following reasons: (1) A cosolvent additive like THF- $d_8$  generally swells the micelle core,<sup>11</sup> which is anticipated to disrupt crystallization. (2) Even when a cosolvent is not added, there is often sufficient water swelling of the PEO-PCL micelle core to disrupt crystallization (in a prior study, crystallization was only observed at low temperatures or with higher molecular weight PCL blocks than used in our study<sup>10</sup>). (3) Crystallization promotes formation of morphologies other than spherical micelles.<sup>10,56</sup> (4) NMR spectroscopy measurements (notably, narrow line widths for PCL core signals) reported in our companion paper also strongly support the absence of crystallization.<sup>3</sup>

Interfacial Tension of the Polycaprolactone–Solvent Interface. The core–corona interfacial tension has a great impact on the micelle free energy<sup>17</sup> and resulting micelle structure.<sup>8,9,14,15,22–24</sup> In our study, the core–corona interfacial tension is readily varied through modification of the D<sub>2</sub>O/ THF- $d_8$  ratio in the bulk solvent. We measured the contact angles of D<sub>2</sub>O/THF- $d_8$  mixtures on a spin-cast PCL surface and calculated the interfacial tensions of D<sub>2</sub>O/THF- $d_8$  mixtures on PCL employing Young's equation (assuming a negligible impact of deuteration on interfacial tension<sup>54</sup>) (Table S3 and Figure S4). The contact angle decreased as the THF- $d_8$  content in the D<sub>2</sub>O/THF- $d_8$  mixture increased. As the THF- $d_8$  content was increased from 0% to 10%, a slight increase in interfacial tension was calculated (a large error was associated with measurements using the pure D<sub>2</sub>O droplet). However, as the THF- $d_8$  content varied from 10 to 60%, the concentration range relevant to our micelle study, the interfacial tension steadily decreased as the THF- $d_8$  content increased.

Characterization of Micelle Structural Parameters through Small-Angle Neutron Scattering. The structural characteristics of two series of micelles were examined with SANS: 2k series (containing  $PEO_{2k}-PCL_{3k}$ ) and 5k series (containing  $PEO_{5k}-PCL_{8k}$ ). In each series, the vol % THF- $d_8$ in the bulk solvent was varied from 10% to 60%. Fully hydrogenous polymers were employed in deuterated solvents in order to enhance the scattering contrast; scattering length densities of the micelle components are shown in Table 2. The

 Table 2. Scattering Length Densities of Micelle

 Components<sup>a</sup>

component	scattering length density $(Å^{-2})$
THF-d <sub>8</sub>	$6.35 \times 10^{-6}$
$D_2O$	$6.37 \times 10^{-6}$
PEO	$6.36 \times 10^{-7}$
PCL	$8.47 \times 10^{-7}$

<sup>*a*</sup>Calculated using the known scattering lengths of C, H, D, and O atoms<sup>57</sup> and the chemical structure and mass density of each molecule.

scattering intensity as a function of scattering vector q for all micelle solutions is shown in Figure 2. The data were fit using the micelle form factor model (described in Experimental Details), which includes six structural parameters extracted from the model fitting to the data ( $N_{\rm agg'} f_{
m solvent}$ ,  $\sigma_{
m Rc'}$ ,  $\sigma_{
m int'}$ , s, and  $a_1$ ). One other fitting parameter was also extracted,  $I_{incoherent}$ , to describe the incoherent scattering resulting from the bulk solvent. From these seven fitting parameters, the micelle size parameters, core radius  $(R_{core})$ , corona thickness (H), and overall micelle radius  $(R_{\text{micelle}})$  were calculated. Additionally, when the contribution of the structure factor was included, there was an additional fitting parameter,  $\Delta R_{\rm hs}$ , where  $R_{\rm interaction}$ =  $R_{\rm core}$  +  $\Delta R_{\rm hs}$  and  $R_{\rm interaction}$  is the interaction radius. The corona thickness *H* was then taken to be the value of  $\Delta R_{hst}$  and the overall micelle size was  $R_{\text{interaction}}$ . The fit of the micelle form factor model, with the inclusion of the structure factor, to two representative data sets is shown in Figure 2; additional model fitting is shown in Figures S5-S15. All extracted model parameters are summarized in Tables S4-S15. The micelle form factor model captures key features of the data, including the low-q plateau, drop-off in intensity at intermediate q, and



**Figure 2.** SANS data obtained from (a) 2k series and (b) 5k series. The micelle form factor model (fit to the data using SasView, solid black curve, including contribution of the structure factor, incorporation of unimer analysis from Table 3, and model smearing) is shown for (c) 2k-10% ( $PEO_{2k}-PCL_{3k}$  in 10% THF- $d_8/90\%$  D<sub>2</sub>O) and (d) 5k-10% ( $PEO_{5k}-PCL_{8k}$  in 10% THF- $d_8/90\%$  D<sub>2</sub>O) micelle solutions. Error in measured I is smaller than the data points.

features at intermediate q due to the presence of the corona. The micelle volume fraction was relatively small in the 2k series (in the range of 4–8 vol %; Table S5) and slightly larger in the 5k series (in the range of 5–10 vol %; Table S7); nonetheless, inclusion of the structure factor improved the goodness-of-fit across all micelle compositions (Tables S16 and S17). Furthermore, fitting the form factor alone did not correctly capture the features at low and intermediate q in the data (a direct comparison of fitting the data with and without the structure factor is shown in Figures S5-S15). For this reason, the figures that we have included in the main text show parameters quantified when the structure factor was included in the analysis. In the following sections, trends in key parameters obtained from fitting this model to the data are discussed. We note that SANS data obtained from sample 2k-60% were not analyzed due to the presence of micelle aggregation (evidenced by a low-q upturn).

Probing the Effect of a Small Molecule Additive on Aggregation Number and Solvent Uptake. The low-q region in the SANS data is most highly influenced by variations in the aggregation number  $(N_{\rm agg})$  and solvent volume fraction in the micelle core  $(f_{solvent})$ . In the 2k series, the low-q plateau intensity decreased with increasing THF- $d_8$  content, whereas in the 5k series the low-q plateau intensity was nearly constant (Figure 2).  $N_{\rm agg}$  and  $f_{\rm solvent}$  were extracted from the model and are shown in Figure 3. We note that the presence of solvent in the micelle core greatly impacts the excess scattering length of the core ( $\beta_{core}$ ). In our study,  $f_{solvent}$  was employed as a fitting parameter, from which  $\beta_{\rm core}$  was calculated. As THF- $d_8$  and  $D_2O$  have nearly identical scattering length densities (6.35 ×  $10^{-6}$  and 6.37 ×  $10^{-6}$  Å<sup>-2</sup>, respectively, Table 2), we are not able to distinguish whether it is THF-d<sub>8</sub> or D<sub>2</sub>O which is present within the micelle core, due to their similar scattering length densities (Table 2). It is well-known that even a solvent that is a poor solvent for the core-forming polymer (such as water in aqueous systems with a hydrophobic core) can still be present in the core at significant concentrations.<sup>33,40</sup> For this reason, we assume that both solvents are present in the core, and  $f_{\text{solvent}}$  represents the total solvent content.

In the lower molecular weight 2k series,  $N_{\rm agg}$  decreased with increasing THF- $d_8$  content in the bulk solvent, whereas in the higher molecular weight Sk series  $N_{\rm agg}$  was relatively constant (Figure 3a), consistent with trends observed in the low-q scattering intensity upon varying THF- $d_8$  content. There are many reports in the literature that show  $N_{\rm agg}$  decreases as the interfacial tension of the core and bulk solvent decreases<sup>9,11,24–28</sup> (which also impacts the interfacial tension is high, the total interfacial area of the micelle system is decreased by increasing  $N_{\rm agg}$  which also decreases the total number of micelles. As the interfacial tension is reduced,  $N_{\rm agg}$  then decreases.

In our system, varying the THF- $d_8$  content in the bulk solvent tunes the PCL/solvent and core/corona interfacial tensions. THF- $d_8$  is a good solvent for PCL and D<sub>2</sub>O is a poor solvent for PCL; thus, as the THF- $d_8$  content in the solvent increases, the interfacial tension decreases. The behavior observed in the 2k series, in which  $N_{agg}$  decreased with increasing THF- $d_8$  content in the bulk solvent, is therefore consistent with prior studies.<sup>9,11,24–28</sup> However, the larger molecular weight 5k series exhibited a nearly constant  $N_{agg}$  (and plateau intensity) as the THF- $d_8$  content in the bulk solvent varied. We may also consider that variations in the solvent



**Figure 3.** (a) Aggregation number  $(N_{agg})$  and (b) % solvent in the micelle core  $(100\% \times f_{solvent})$  as functions of the amount of THF- $d_8$  in the bulk solvent for 2k (black  $\blacksquare$ ,  $\Box$ ) and 5k (green  $\blacklozenge$ ,  $\diamondsuit$ ) series. Closed (open) symbols indicate analysis excluding (and including) incorporation of the unimer content (Table 3). Error bars represent the effect of 10% loss in polymer content; error on model fitting is estimated to be smaller than the data point size. Parameters shown in this figure were obtained through SasView fitting of the micelle form factor model, including contributions of the structure factor and model smearing.

quality also impact the core chain stretching and corona chain repulsion terms of the micelle free energy,<sup>17,19</sup> which can promote a change in morphology as the interfacial tension is reduced.<sup>8,9,14,15,22,24</sup> In our system, spherical micelles are formed at all solvent compositions; however, the balance of these three factors (interfacial tension, core chain stretching, corona repulsion) may promote the constant  $N_{agg}$  observed in the 5k series over the range of solvent compositions. Alternatively, it is possible that the larger molecular weight of the 5k series prevents equilibration of the micelles, also evidenced by lack of unimers in the 5k series at all THF- $d_8$  contents probed, other than 60% (Table 3, Kidd et al.<sup>38</sup>).

We may also consider trends in  $N_{agg}$  with the core and corona block molecular weights (or number of repeat units in each block,  $N_{core}$  and  $N_{corona}$  for the core and corona blocks, respectively). In the 5k series, both  $N_{core}$  and  $N_{corona}$  are a factor of around 2.6 greater than that in the 2k series (the block ratio,  $N_{core}/N_{corona}$  is the same in both series). Whereas increasing  $N_{core}$  is generally known to increase  $N_{agg}^{17,21,58,59}$  increasing  $N_{corona}$  typically has the opposite effect and decreases  $N_{agg}^{58}$ 

Table 3. Unimer Content in Micelle Solutions Obtained from Kidd et al.<sup>38</sup>

micelle solution	unimer content <sup>a</sup> (%)
2k-10%	12
2k-30%	12
2k-40%	18
2k-50%	34
5k-60%	45

<sup>*a*</sup>Unimer content, determined from NMR in Kidd et al.,<sup>38</sup> was accounted for in the SANS data fitting. The mass of polymer in unimers was subtracted from the total mass to calculate the mass of polymer in micelles (parameter M in eqs 21 and 23). The unimer content of micelle solution 2k-20% was not directly measured in ref 38, and we assumed 12% unimer content through interpolation. The Sk series micelle solutions, other than Sk-60%, had a nonmeasurable unimer content (<10%).

Förster et al. have identified a scaling law to describe the aggregation number which is applicable to a large number of micelle systems:<sup>58</sup>  $N_{agg} \sim N_{core} \alpha N_{corona}^{-\beta}$  where  $\alpha = 2$  and  $\beta =$ 0.8, consistent with theoretical predictions.<sup>60</sup> If we examine the 2k-10% and 5k-10% micelle samples, both containing 10 vol % THF- $d_8$  in the bulk solvent, we find that  $N_{agg}$  is surprisingly larger for the 2k-10% micelle sample ( $N_{agg}$  is 275 and 149 for 2k-10% and 5k-10%, respectively), whereas the scaling law indicated above predicts the opposite trend. However, if the exponent  $\alpha$  in the scaling law is less than one (holding  $\beta$  at 0.8), as previously observed in a limited number of micelle systems,<sup>61</sup> then our data are consistent with the scaling law predictions. Our data at 10 vol % THF- $d_8$  (for which there are data points at two different molecular weights) imply  $\alpha = 0.17$ if  $\beta$  is fixed at 0.8. If we consider the data at other vol % THF, the extracted values of  $\alpha$  fluctuate but are all less than one (and approaching one at the highest THF content). The origin of this scaling behavior warrants further study.

Both the 2k and 5k series showed a systematic increase in the swelling of solvent within the micelle core ( $f_{\text{solvent}}$ ), in which  $f_{\text{solvent}}$  was similar for the two series (Figure 3b). The solvent uptake of the core was quite significant, with  $f_{\text{solvent}}$  varying from 0.20 to 0.70 when the THF- $d_8$  content in the bulk solvent varied from 10% to 60 vol %. A large degree of core swelling by solvent has been observed in other micelle systems containing various core-forming polymers.<sup>11,26,28</sup>

Probing the Effect of a Small Molecule Additive on Micelle Size. The scattering length density profile within the corona was modeled with two cubic b splines,  $\rho_1(r)$  and  $\rho_2(r)$ , whose relative importance was weighted with parameter  $a_1$ . The corona parameter s (shown schematically in Figure S16) details the range of r (distance from the center of the micelle) for which each of the two cubic b spline functions contribute. All of the model fits to the SANS data shown here resulted in a1 values greater than 10<sup>10</sup>, in which case the relative importance of  $\rho_1(r)$  was negligible. In this case,  $\rho_{\text{chain}}(r)$  simplifies to  $\rho_2(r)$ . Similarly, s was larger than the corona thickness (H) for both series at all solvent contents (Tables S4-S15 and Figure S17), reinforcing that there is only one spline used in calculating  $\rho_{\rm chain}(r)$ . This result is consistent with literature showing that micelles in which  $R_{\text{core}}$  is greater than H (i.e., crew-cut micelles) have a more homogeneous corona density profile, in contrast to the star-like micelles with  $H > R_{core}$ .<sup>62</sup> A representative plot of  $\hat{\rho}_{chain}(r)$  is shown in Figure 4, which has been rescaled according to the procedures in the Experimental Details.



**Figure 4.** Rescaled corona profile  $\hat{\rho}_{chain}(r)$  (green solid curve) as a function of *r* for 2k-10%. Corona thickness *H* is defined as  $R_{interaction} - R_{core}$ . The corona profile shown here was obtained through SasView fitting of the micelle form factor model, including contribution of the structure factor, incorporation of unimer analysis from Table 3, and model smearing.

The core radius  $R_{\rm core}$  was calculated from the volume of the micelle core, which was determined using fitting parameters  $N_{\rm agg}$  and  $f_{\rm solvent}$  (refer to Experimental Details). The corona thickness, H, was determined as the fit value of  $\Delta R_{\rm hs}$ , with inclusion of the structure factor in the analysis. The overall micelle size, taken to be the interaction radius ( $R_{\rm interaction}$ ), was calculated as  $R_{\rm interaction} = R_{\rm core} + H$ . The micelle size parameters are summarized in Figure 5 for both the 2k and 5k micelle series.

For the lower molecular weight 2k series, the core radius  $R_{\rm core}$  was relatively constant, and exhibited a slight maximum at intermediate THF- $d_8$  concentrations in the bulk solvent, while the corona thickness H showed a minor decrease with decreasing THF- $d_8$  content in the bulk solvent. These trends in  $R_{\text{core}}$  and H resulted in the overall micelle radius  $R_{\text{interaction}}$ also exhibiting a slight maximum at intermediate THF- $d_8$ concentrations in the bulk solvent, mimicking the trend observed in  $R_{\rm core}$ . In the higher molecular weight 5k series, an increase in  $R_{core}$  with THF- $d_8$  content accompanied a relatively constant H, and R<sub>interaction</sub> increased with increasing THF-d<sub>8</sub> content. Hydrodynamic radii characterized from DLS (Tables S1 and S2) were in reasonable agreement with  $R_{\text{interaction}}$  values. Minor differences may possibly be attributed to uncertainties in measurement of the solution viscosities, required for calculation of the hydrodynamic radii from the measured DLS diffusion coefficients.

The trends in  $R_{\rm core}$  can be understood by considering trends in  $N_{\rm agg}$  and  $f_{\rm solvent}.$  For the 2k series,  $N_{\rm agg}$  decreased significantly above 30% THF- $d_8$  in the bulk solvent while  $f_{\rm solvent}$  linearly increased; the net effect was a relatively constant  $R_{\rm core}.$  The swelling of the core by solvent was therefore counteracted by the decreasing number of chains per micelle. In the Sk series, however,  $N_{\rm agg}$  was fairly insensitive to the THF- $d_8$  content in the bulk solvent, while the solvent content in the core increased, and therefore  $R_{\rm core}$  increased linearly with the THF- $d_8$  content in the bulk solvent. A decrease in the core–corona interfacial tension is expected to decrease  $N_{\rm agg}$  and  $R_{\rm core}^{17}$  which was observed in prior studies, even in the presence of increased solvent uptake by the core.  $^{11,24-26,29}$  In our system,



**Figure 5.** Effect of THF- $d_8$  content in the bulk solvent on size parameters of (a) 2k and (b) 5k series micelles:  $R_{\text{interaction}}$  (blue  $\blacklozenge$ ,  $\diamondsuit$ ),  $R_{\text{core}}$  (black  $\blacksquare$ ,  $\Box$ ), and H (red  $\blacklozenge$ ,  $\triangleright$ ). Errors due to polymer loss and model fitting are estimated to be smaller than the data point size. Closed (open) symbols indicate analysis excluding (and including) incorporation of the unimer content in the analysis (Table 3). Size parameters shown here were calculated from fitting parameters obtained through SasView fitting of the micelle form factor model, including contribution of the structure factor and model smearing.  $R_{\text{interaction}}$  is the hard-sphere radius quantified through incorporation of the overall micelle radius.

however, the core swelling greatly impacted the trends observed in  $R_{\text{core}}$ . *H* is also predicted to decrease with decreasing interfacial tension of the core–corona interface,<sup>17</sup> which has been previously reported,<sup>11,25</sup> and observed for the 2k series in our study.

The core–corona interfacial width ( $\sigma_{int}$ ) and core polydispersity ( $\sigma_{Rc}$ ), as well as *s* described previously, have the greatest impact on the intermediate *q* region in the scattering profile (between 0.05 and 0.2 Å<sup>-1</sup> in Figure 2). As  $\sigma_{int}$  increases, the once-sharp interface between the core and corona becomes wider and more diffuse. As the % THF-*d*<sub>8</sub> in the bulk solvent increased, we observed a general trend of increasing  $\sigma_{inv}$  with a few anomalous data sets that did not agree with this general trend (Figure S18). The core polydispersity ( $\sigma_{Rc}$ ) showed differing trends in the 2k and 5k series (Figure S19).  $\sigma_{Rc}$ increased with increasing THF-*d*<sub>8</sub> content in the bulk solvent in the 2k series and showed a maximum value at intermediate THF- $d_8$  content in the Sk series. Notably,  $\sigma_{\rm Rc}$  of the 2k series increased significantly at the THF- $d_8$  content at which  $N_{\rm agg}$  decreased rapidly.

Summary of Micelle Structural Parameters. A schematic is shown in Figure 6 which summarizes the observed



**Figure 6.** Schematic illustrating changes in micelle aggregation, size, solvent uptake, and unimer content as the THF- $d_8$  content was increased for the 2k and 5k series. Black and red chains represent PCL and PEO, respectively. Blue and green circles represent water and THF- $d_8$ , respectively.

trends in the 2k and 5k series micelle structural parameters (aggregation number, size, solvent uptake, unimer content) as the THF- $d_8$  content in the micelle solution was varied.

We compare the overall micelle size characterized from SANS with that reported in the companion paper employing diffusion NMR measurements on equivalent micelle samples of the same compositions.<sup>38</sup> In the 2k series,  $R_{\text{interaction}}$  (from SANS) varied from 12 to 14 nm over solvent compositions of 10–50 vol % THF- $d_8$ , exhibiting a local maximum at 30 vol % THF- $d_8$ . NMR measurements characterized the hydrodynamic radius as 12 to 17 nm over the same range of solvent compositions, also exhibiting a local maximum at 30 vol % THF- $d_8$ .<sup>38</sup> In the 5k series,  $R_{\text{interaction}}$  (from SANS) varied from 15 to 19 nm over solvent compositions of 10-50 vol % THF $d_{8}$ , whereas the NMR measurements indicated the hydrodynamic radius was slightly smaller, in the range of 12-16 nm over the same solvent compositions.<sup>38</sup> In both measurements for the 5k series, the overall micelle size increased with increasing THF- $d_8$  content. The NMR and SANS results were thus generally in good agreement with one another. We note that SANS and NMR diffusometry measure the overall micelle size in different ways. In the SANS measurements, the micelle size is taken to be the hard-sphere interaction radius characterized through fitting the structure factor to the SANS data (in combination with the block copolymer micelle form factor). In the NMR measurements, the hydrodynamic radius is extracted through the Stokes-Einstein equation, employing measurements on the hydrodynamically moderated translational motion of the particles through a viscous fluid. We therefore do not anticipate quantitative agreement between the techniques, but rather expect that they may identify similar trends in the data, as shown here.

At a bulk solvent composition of 60 vol % THF- $d_{s}$ , we observed greater discrepancies between the SANS and NMR measurements. In the 2k-60% sample, SANS analysis was not conducted as micelle aggregation was observed (identified as an increase in low-q scattering). This behavior was observed in two separately prepared samples for the SANS measurements, but in a third independently prepared sample, used for the NMR measurements, micelle aggregation was not observed, and thus those results are included in the companion paper.<sup>38</sup> In the 5k-60% sample, we observed strikingly different results for the overall micelle size from the two techniques, characterized as  $R_{\text{interaction}} = 20 \text{ nm}$  (SANS) and a hydrodynamic radius of 8 nm (NMR) for this solvent composition. As 60 vol % THF- $d_8$  is located at the phase boundary, above which pure unimers form, we hypothesize that the micelles prepared at this solvent composition are extremely sensitive to slight variations in the sample preparation process, and perhaps the sample-to-sample reproducibility is not as robust as at the other compositions (we note that at all other solvent compositions, for both the 2k and 5k series, we were able to reliably reproduce our results on independently prepared samples).

**SANS Model Fitting Uncertainty.** In a complex model such as the micelle form factor model, there are many fitting parameters that might be highly correlated (positively or negatively), to the point that they cannot be uniquely determined. Using a population-based fitting algorithm known as DREAM, the correlations between all fitting parameters were investigated for this model and are discussed in more detail in the Supporting Information. Briefly,  $N_{agg}$  was found to have little correlation with the other parameters with the exception of  $f_{solvent'}$  for which there was a slight negative correlation (as one increases, the other decreases). By contrast, the behaviors of  $f_{solvent'}$  s,  $\sigma_{int'}$  and  $\sigma_{Rc}$  were highly correlated (Figure S20).

We considered three main quantifiable sources of error in the SANS experiments and modeling: (1) instrumental error on the measured scattering intensity,  $^{63}(2)$  error in model fitting to the SANS data, and (3) error in measured polymer mass used in micelle preparation. The wavelength spread of the instrument was directly incorporated into the model smearing.<sup>63</sup> The error on the scattering intensity (I) was typically smaller than the data points. The effect of error in I on the model fitting parameters was insignificant for all micelle solutions. The error in model fitting was also considered. In order to study how much each parameter affected the goodness-of-fit in the minimization of  $\chi^2$ , a single parameter was varied from the best-fit results, and the resultant  $\chi^2$  recorded. Then, the difference in  $\chi^2$  was plotted against the difference in the parameter. Using this, an error threshold (in this case, 2%) was established providing the limits of the parameter within which a similar quality of fit could be obtained (Figure S21). Generally, the model fitting errors were also quite small. The final error considered was the uncertainty in the total polymer mass that composes the micelles. During micelle synthesis and preparation, there is a small amount of loss of sample, likely due to aggregation and subsequent filtering. We quantified this loss for select samples and found it to be typically <5% of the total mass. As such, we set a threshold as 10% sample loss in order to probe the impact of the mass loss on the SANS data fitting. The SANS data sets were fit using polymer concentrations of 1 mass

% (the targeted concentration, representing no loss during sample preparation) and 0.9 mass % (a 10% loss during sample preparation). Accounting for the loss of polymer resulted in a higher  $N_{agg}$  and lower  $f_{solvent}$  (error bars in Figure 3). However, the micelle size parameters were in most cases unaffected (error bars in Figure 5). In summary, the potential for polymer loss during the micelle preparation process was regarded as the most impactful source of error, though still fairly minimal (experimentally determined to be less than 5% loss in mass). The results of the error analysis are summarized in Tables S4–S15.

Incorporating Unimer Content in SANS Data Fitting. The unimer content in each micelle sample was characterized through NMR (reported in the companion paper<sup>38</sup>) and is summarized in Table 3. The existence of unimers reduces the total mass of polymer found in micelles. This reduced micelle mass was accounted for in fitting the micelle form factor model to the SANS data. The scattering from the unimers themselves was not modeled directly as it was overwhelmed by the micelle scattering. Including the presence of unimers reduced the value of  $N_{\text{agg}}$  and increased  $f_{\text{solvent}}$  obtained from the micelle fitting (Figure 3); however, the overall trends in  $N_{agg}$  and  $f_{solvent}$  with THF- $d_8$  content in the bulk solvent were largely unchanged. One notable exception is micelle solution 5k-60%, which contained a significantly large unimer content of 45% (Table 3), which had the impact of greatly increasing  $N_{agg}$  and reducing  $f_{solvent}$  (Figure 3). Including the presence of unimers in the analysis had little impact on the micelle size parameters  $(R_{core}, H, R_{interaction}, Figure 5)$  for both the 2k and 5k series.

Verifying Core Radius through Transmission Electron Microscopy. In order to verify the results of the SANS data analysis, R<sub>core</sub> was probed through TEM for selected samples: 2k-10%, 2k-30%, and 2k-50%. Samples were vitrified and imaged under cryogenic conditions to preserve the micelle structure. The resulting images are shown in Figure 7a and Figure S22. We expect only the PCL cores to be visible in TEM micrographs due to the low contrast between solvated corona chains and solvent. We compare the size of the micelle core radius we obtain from TEM to results from SANS in Figure 7b and find very good agreement between the two techniques. Although aggregation of the micelles due to sample preparation for TEM<sup>64</sup> is sometimes visible, in particular for the 2k-50% sample, the aggregation does not appear to change  $R_{core}$  (see Figure S23 and Table S18 of the Supporting Information for details). Altogether, SANS and TEM yield a quantitative estimate of  $R_{\rm core}$  and demonstrate that this parameter is insensitive to the THF- $d_8$  content in the bulk solvent for the 2k series.

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The effect of core—corona interfacial tension, modified through varying solvent composition, on the structural parameters and solvent uptake in PEO—PCL block copolymer micelles was explored. PEO—PCL block copolymers, of varying molecular weight yet constant block ratio, formed spherical micelles through a wide range of solvent compositions, varying from 10% to 60 vol % THF- $d_8$  in D<sub>2</sub>O/THF- $d_8$  mixtures. In both micelle series, an increase in THF- $d_8$  content in the bulk solvent increased the solvent uptake within the micelle core. In particular, the solvent content in the micelle core increased linearly with THF- $d_8$  content in the bulk solvent and was comparable for the two series, irrespective of the polymer molecular weight.



**Figure 7.** (a) TEM micrograph of the 2k-10% micelle solution. (b) Micelle core radius  $R_{core}$  determined from SANS (black  $\blacksquare$ ) and TEM (green  $\triangle$ ) for the 2k micelle series. Additional micrographs are shown in Figure S22.  $R_{core}$  values from SANS were calculated from fitting parameters obtained through SasView fitting of the micelle form factor model, including contribution of the structure factor, incorporation of unimer analysis from Table 3, and model smearing. Error in  $R_{core}$  values from SANS is smaller than the data points (described within the text).

In the lower molecular weight 2k micelle series, increasing the THF- $d_8$  content in the micelle solution resulted in a drastic decrease in aggregation number. The decrease in aggregation number was counteracted by increased swelling of the core by solvent, resulting in a core radius that was relatively insensitive to the solvent composition, and exhibited a slight maximum at intermediate THF- $d_8$  content. The corona thickness was also not strongly dependent on the THF- $d_8$  content, and the overall micelle radius mimicked the trends observed in the core radius, with a slight maximum exhibited at intermediate THF- $d_8$ content.

In the higher molecular weight Sk series, the aggregation number surprisingly showed little change with varying THF- $d_8$ content in the bulk solvent. The increase in solvent uptake of the core with increasing THF- $d_8$  content therefore increased the core radius, which was accompanied by a relatively constant corona thickness; thus, the overall micelle size showed a slight increase with increasing THF- $d_8$  content in the bulk solvent. Incorporation of the known unimer content determined from NMR into the SANS analysis had little impact on the characterized micelle size parameters; however, the aggregation number increased and the solvent uptake of the core decreased when the unimer content was included in the analysis.

In summary, the two micelle series showed similar solvent uptake that was independent of the polymer molecular weight, yet significantly different dependencies of their aggregation number on the solvent composition. Differences in the behaviors of the micelle size parameters (core radius and overall micelle radius) as the solvent composition varied originated from the differing trends in aggregation number for the two micelle series. These results on a model system highlight the significant impact of small molecule additives on the structural properties of block copolymer micelles, highly relevant to applications, such as drug delivery vehicles or nanoreactors, in which the encapsulated species may yield significant influence over the micelle self-assembly.

#### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macro-mol.6b02580.

GPC and NMR data obtained from the PEO-PCL block copolymers (Figures S1 and S2); DLS data obtained from micelle solutions (Figure S3) and parameters obtained from DLS data fitting (Tables S1 and S2); contact angle and interfacial tension measurements (Table S3 and Figure S4); SANS data obtained from micelle solutions and model fitting (Figures S5-S15); parameters extracted from the SANS model fitting (Tables S4-S15 and Figures S16-S19); correlations between SANS model fit parameters (Figure S20); effect of varying micelle parameters on the goodness-of-fit (Figure S21 and Tables S16 and S17); TEM micrographs obtained from select micelle solutions (Figure S22), and micelle core radii (Table S18) and core size distributions (Figure S23) characterized from TEM micrographs (PDF)

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#### Notes

The authors declare no competing financial interest.

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