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Fluorous Cylindrical Micelles of Controlled Length by Crystallization-Driven Self-Assembly of Block Copolymers in Fluorinated Media

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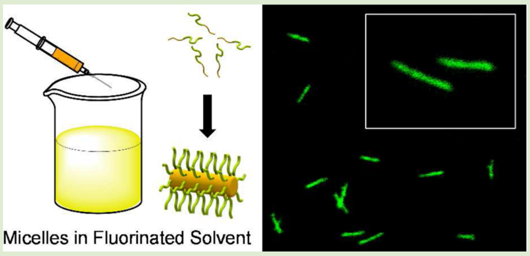
S Supporting Information

ABSTRACT: Fluorous solvents have recently found broad applications in medical treatments as well as catalytic transformations, yet the controlled self-assembly of nanomaterials in fluorinated media has remained a challenge. Herein, we report the synthesis of block copolymers containing a crystalline polyferrocenylsilane metalloblock and a highly fluorinated coil block and their controlled self-assembly in fluorinated media. Using the crystallization-driven self-assembly approach, cylindrical micelles have been prepared with controlled lengths and narrow length polydispersities by self-seeding. Finally, by partial functionalization of these block copolymers with fluorescent dye molecules, we show that well-defined, functional nanomaterials can be obtained in the fluorous phase.



Fluorous materials have recently attracted intense interest in materials science due to their resistance to oxidation, chemical and thermal stability, and extremely low surface energies.[1,2] Furthermore, they can often be purified using simple and low-cost procedures such as solid-phase or liquid–liquid extraction, which take advantage of the immiscibility between fluorous solvents and aqueous or organic phases. As a result of these properties, highly fluorinated materials have recently been used to fill unique roles as components of organic electronic devices,[3−5] metal–organic frameworks,[6−8] thin films,[9,10] and liquid crystals.[11,12] In addition, fluorinated surfaces have been successfully developed for use in superhydrophobic coatings,[13,14] nanocarriers,[15] and microarrays for biological analysis.[16]

More recently, block copolymers containing fluorinated blocks have appeared in a number of studies on the solution self-assembly of nanoscale materials from soft matter. The incompatibility between the fluorinated and nonfluorinated segments strongly promotes phase segregation in these systems, resulting in self-assembly to form micelles when the polymer is placed in a selective solvent for one of the blocks.[17,18] Making use of this feature, partially fluorinated block copolymer micelles with impressive morphological variety have been prepared, including cylinders,[19] toroids,[20] disks,[21] vesicles,[22] wormlike micelles,[23,24] and compartmentalized cylinders.[25] However, existing self-assembly studies predominantly make use of fluorinated polymers as the insoluble core block, using water or more common organic solvents as the self-assembly media.

Fluorous solvents, however, are of considerable current interest for both catalysis and biological applications. Since it was first reported by Horváth and Rábai in 1994,[26] the use of fluorinated solvents in fluorous biphasic catalysis has been used to greatly improve purification protocols and catalyst recycling in a number of chemical transformations.[27] Furthermore, fluorinated solvents have recently found use in medical applications due to the high solubility of molecular oxygen in fluorous media.[28] For example, perfluorodecalin (PFD) is the primary component of Fluosol-DA, a nontoxic artificial blood substitute approved by the U.S. FDA for use in human treatments.[29] Thus, the ability to access precise nanoscale morphologies in fluorous media represents an exciting challenge.

The crystallization-driven self-assembly (CDSA) method has recently emerged as a powerful tool for the construction of precise nanoscale architectures.[30] When crystalline-coil block copolymers are placed in a selective solvent for the coil block, self-assembly into micelles favors low-curvature structures such as cylinders (for core–corona block ratios of ∼1:6 to 1:20) and platelets (core:corona block ratios of ∼1:1), due to the favorable crystallization enthalpy of the core-forming block.[31−33] In several cases, this process has been shown to occur in a "living" manner analogous to a living covalent polymerization, such that the micelle termini remain active to further growth via epitaxy upon the addition of further unimer (molecularly dissolved block copolymer).[34−38] Using samples of presonicated micelle seeds as initiators, the formation of cylindrical or platelet micelle samples with very low polydispersities has become possible (L_w/L_n or A_w/A_n < 1.1, where L_w and A_w represent the weight-average length and area, and L_n and A_n represent the number-average length and area, respectively).[34,39] Using a series of block copolymers with a

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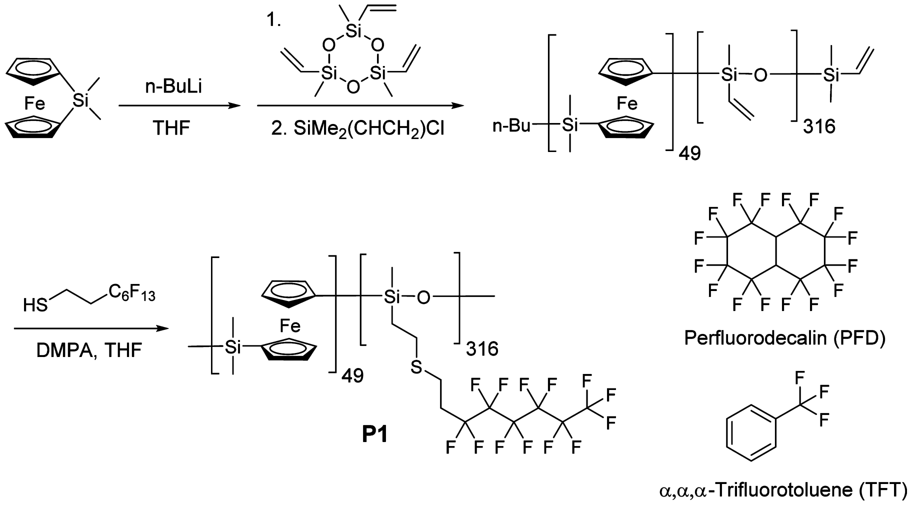
Scheme 1. Synthesis of Polymer P1 by Postpolymerization Modification of a PFS-*b*-PMVS Block Copolymer[a]



[a]Structures of the fluorinated solvents used in this study are also shown. DMPA = 2,2-dimethoxy-2-phenylacetophenone.

crystallizable poly(ferrocenyldimethylsilane) (PFS) metalloblock, we herein report the first example of living CDSA in fluorinated media. We further demonstrate that cylindrical micelles of controlled length may be prepared in fluorinated solvents by self-seeding and extend these findings to the preparation of functional micelles in the fluorous phase.

Diblock copolymers containing a crystalline PFS block and a fluorinated coil block can be conveniently accessed by postpolymerization modification of PFS-*b*-PMVS (PMVS = poly(methylvinylsiloxane)) diblock copolymers. Reaction of PFS_{49}-*b*-PMVS_{316} (where the subscripts refer to the number-average degrees of polymerization) with 1*H*,1*H*,2*H*,2*H*-perfluorooctanethiol by photoinitiated hydrothiolation[40,41] gave quantitative conversion to polymer **P1**, in which the coil block contains 53% fluorine by weight (Scheme 1 and Figures S1 and S2, Supporting Information).

To investigate the self-assembly of this block copolymer, we examined the use of three solvents: THF, a known good solvent for PFS; PFD, a heavily fluorinated solvent, and *α*,*α*,*α*-trifluorotoluene (TFT), a lightly fluorinated solvent miscible with both THF and PFD, in which both the crystalline and coil blocks would be expected to have some mobility. After dissolving **P1** in TFT (60 mg/mL), only unimer film was observed by TEM after 24 h, suggesting that TFT may act as a good solvent for both blocks. After allowing the solution to stand for 1 week, however, the exclusive formation of cylindrical micelles was observed, indicating that TFT is indeed a poor solvent for PFS (Figure 1). Dissolution of **P1** in 1:1 THF:TFT (30 mg/mL), however, was found to allow this polymer to remain molecularly dissolved indefinitely.

Next, we investigated if using a poorer solvent for PFS as the selective solvent could accelerate the self-assembly process, by adding small amounts of PFD to TFT solutions of **P1**. While only unimer was observed in the form of thin films by TEM from solutions containing 1% PFD after 24 h, 5% PFD solutions were found to contain primarily cylindrical micelles, and in the case of 10% PFD solutions, only cylindrical micelles were observed. Self-assembly in pure PFD however was not successful, leading only to ill-defined aggregates even after slow cooling of the solution from 100 °C. We suspect that the solubility of PFS in PFD is so low that the PFS chains have essentially no mobility in this medium, precluding self-assembly to an ordered micelle structure. Once formed, however, cylindrical micelles of **P1** were found to be colloidally stable in solutions containing 95% PFD, which is promising for future studies on the potential applications of these structures.

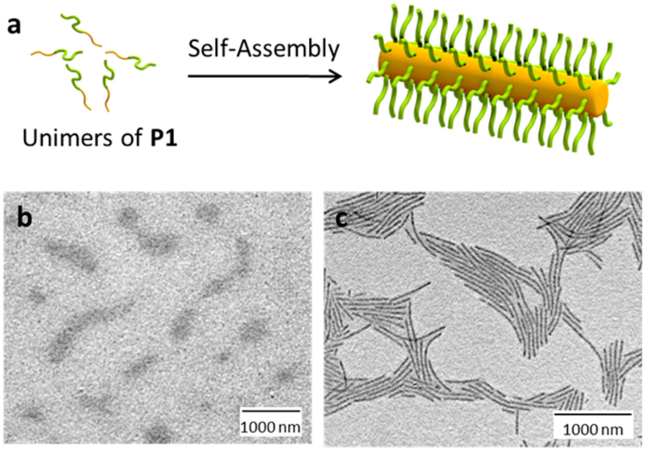


Figure 1. (a) Schematic representation of the self-assembly of **P1** to form cylindrical micelles. PFS = yellow, PMVS functionalized with perfluoroalkane = light green. (b,c) TEM micrographs of a drop-cast sample of **P1** in TFT (60 mg/mL) after 24 h (b) and 1 week (c).

While the above experiments provide a quantitative route to cylindrical micelles that are polydisperse in length, many emerging applications in nanoscience require objects with precisely controlled dimensions. Self-seeding has recently been shown to be an effective technique for forming near-monodisperse micelles with crystalline cores,[38,42,43] by selective dissolution of micelle regions with lower crystallinity. In contrast to small molecules, polymer crystals generally exhibit broad melting point ranges as a result of the varying degrees of crystallinity present in the sample. By heating micelles with a crystalline core to a point within this melting point range in a given solvent, segments with lower crystallinity dissolve to form unimer, while more highly crystalline regions survive. Upon cooling, these remaining crystallites may act as nucleation sites for epitaxial growth, resulting in elongated micelles of low polydispersity. Taking advantage of the interplay between temperature and solvent quality for the core block,[43] we found

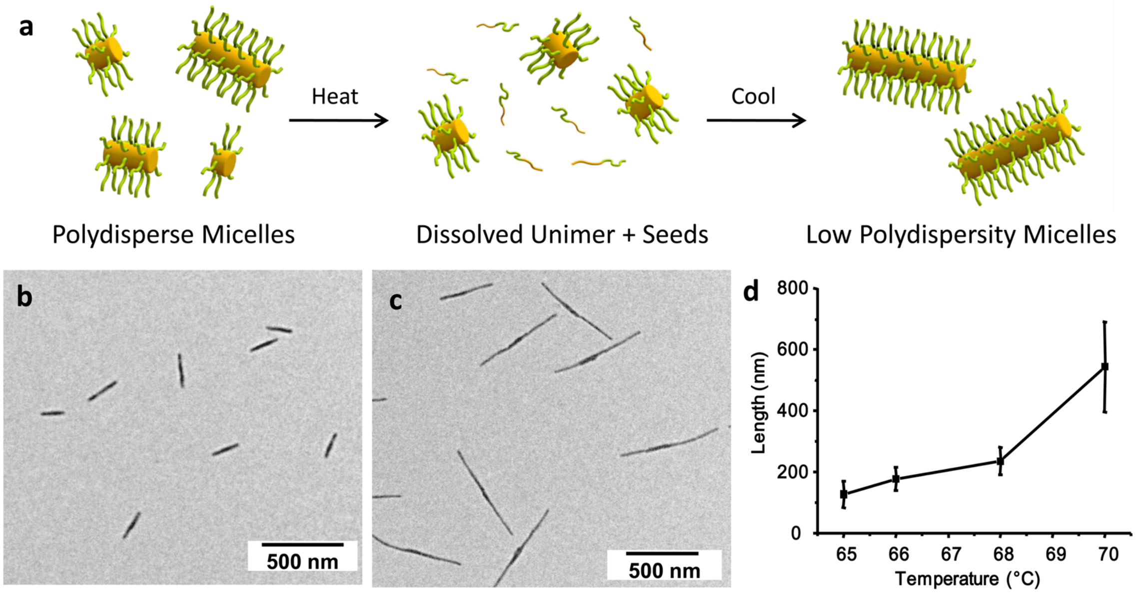
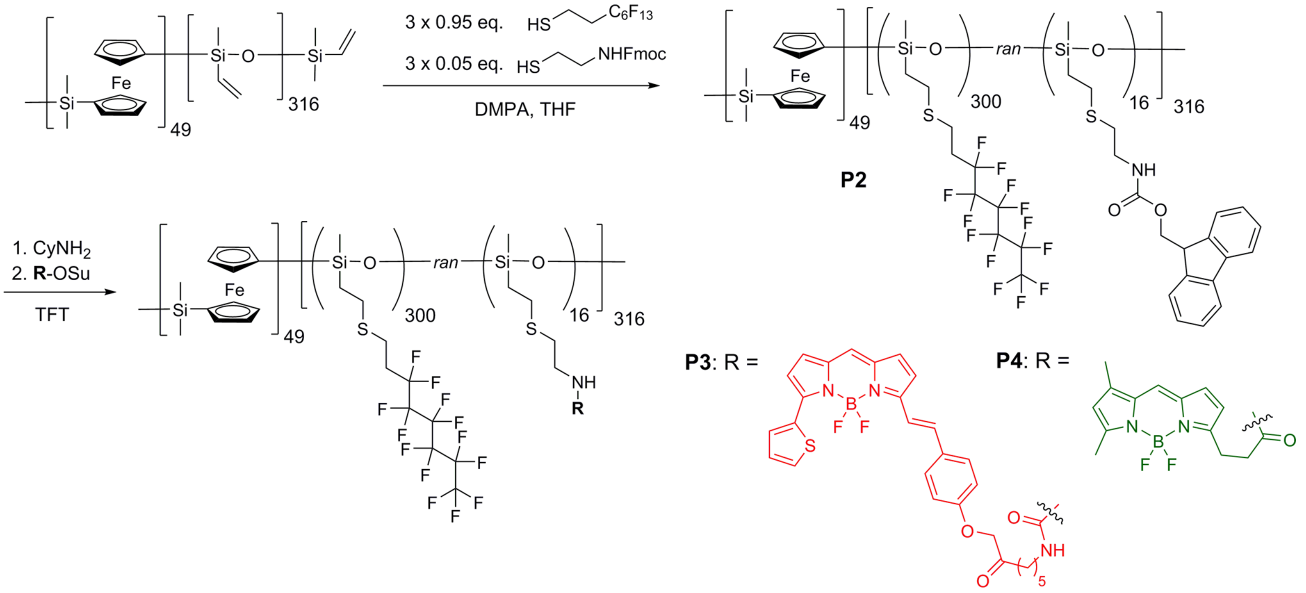


Figure 2. (a) Schematic representation of the self-seeding of micelles of **P1** to form micelles with low polydispersity. (b,c) TEM micrographs of short (b) (L_n = 127 nm, L_w/L_n = 1.12) and long (c) (L_n = 544 nm, L_w/L_n = 1.07) fluorinated micelles. (d) Plot of number-average micelle length vs annealing temperature in 4:1 TFT:PFD. Error bars indicate the standard deviation, σ, for the length distribution.

Scheme 2. Synthesis of Functional Polymers P3 and P4[a]



[a] Su = *N*-hydroxysuccinimidyl, *ran* indicates a random copolymer.

that micelles of controlled length with low polydispersity ($L_w/L_n < 1.1$) could be formed by self-seeding in mixtures of TFT/PFD by varying either the self-seeding temperature or the solvent composition. Using these methods, micelles with number-average lengths ranging from ca. 120 to 540 nm were successfully prepared (Figure 2 and Figure S3 and Tables S1 and S2, Supporting Information).

Led by advances in self-assembly methods, the preparation of block copolymer micelles with intrinsic functionality has recently generated considerable research interest.[44−46] Given the broad applications of fluorous-phase materials, we sought to determine if well-defined, functional micelles could be prepared by CDSA in the fluorous phase. In a recent study by Patton and co-workers,[47] it was shown that concurrent reaction of multiple thiols having similar S−H bond energies could be used to introduce multiple functionalities to alkyne-terminated surfaces. In this work, the authors further showed that the relative ratios of surface functionalization with each thiol could be controlled by the molar ratio of the thiols present in the reaction.

Adopting a similar approach, we synthesized a second block copolymer by reaction of PFS_{49}-*b*-$PMVS_{316}$ with an excess of both 1*H*,1*H*,2*H*,2*H*-perfluorooctanethiol and *N*-Fmoc-2-aminoethanethiol (Fmoc = fluorenylmethyloxycarbonyl) in a 95:5 ratio (Scheme 2). Thiol−ene click reaction of this mixture gave polymer **P2**, which showed ∼3% incorporation of Fmoc-functionalized thiols into the corona block by ^{1}H NMR, with the remainder of the vinyl groups bearing fluorous chains. We suspect the small difference in functionalization ratio between

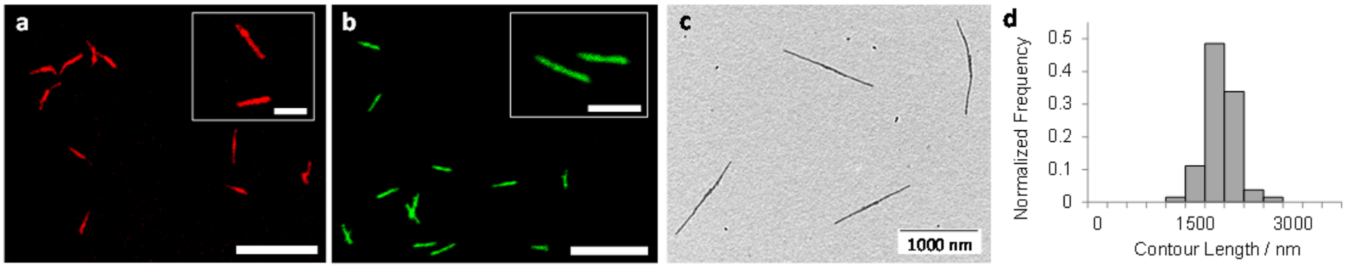


Figure 3. LSCM images of micelles of **P3** (a) and **P4** (b) in 4:1 TFT:PFD. Scale bars = 6 μm, inset scale bars = 2 μm. (c) TEM micrograph of low-polydispersity **P3** micelles formed by seeded growth. (d) Histogram showing the number-average length distribution of the sample shown in (c) (N = 136).

the reaction mixture and the final polymer to be attributable to small differences in the reactivities of the respective thiols.

The use of Fmoc-protected amine as the second thiol was designed to satisfy three criteria: (i) deprotection of the Fmoc group is mild and does not require strong acids or bases, which could cause the PFS or PMVS chains, respectively, to degrade; (ii) the products of deprotection can be easily removed by reprecipitation of the polymer; and (iii) deprotection affords reactive groups which may be used to install additional functionality in a modular fashion. We also note that direct installation of amine groups via reaction with unprotected cysteamine hydrochloride[39,44] was not possible due to solubility differences between this reagent and the polymer.

Thus, stirring **P2** with cyclohexylamine at room temperature followed by reprecipitation in hexanes afforded a partially fluorinated block copolymer with ~3% free amine groups in the coil block. As a proof of concept, we then prepared polymers **P3** and **P4** by subsequent reaction with the succinimidyl esters of fluorescent green BODIPY-FL and red BODIPY 630/650 dyes, which may be conveniently carried out at room temperature. This gave fluorinated polymers which exhibited bright green and red fluorescence, respectively (Figure S4, Supporting Information). As the preparation of well-defined fluorescent nanoscale rods and cylinders has recently generated interest for electronic and diagnostic applications,[48−51] the ability to prepare well-defined fluorescent micelles in the fluorous phase represents an attractive goal.

Interestingly, self-assembly of these polymers in TFT in the same manner as **P1** gave only ill-defined aggregates. Despite their low loading, we presume that the highly polar dye molecules exhibit very poor solubility in TFT, interfering with the self-assembly process. We reasoned, however, that more well-behaved assembly might be possible from preformed initiation sites at higher temperatures and thus investigated the seeded growth of **P3** and **P4** from pre-existing micelles of **P1**.

Addition of unimer solutions of **P3** and **P4** (10 mg/mL in 1:1 THF:TFT) at room temperature to a 0.1 mg/mL sample of micelles of **P1** in 4:1 TFT/PFD again gave only ill-defined aggregates. However, when the sample was first heated to 64 °C (just below the onset of self-seeding at 66 °C in this solvent mixture), elongated micelles were formed with $L_w/L_n < 1.1$ (Figure 3). Examination of these micelles by laser scanning confocal microscopy (LSCM) revealed that the fluorescent block copolymers had indeed been incorporated into the elongated micelles (Figure 3a and b). As with micelle solutions of **P1**, these structures remain colloidally stable upon dilution to 95% PFD, representing a route to well-defined, functional nanomaterials in the fluorous phase.

In summary, we have demonstrated a facile synthesis of fluorinated block copolymers and their self-assembly into micelles in fluorinated solvents by CDSA. Furthermore, micelles of controlled length may be accessed by self-seeding protocols, giving structures with low length polydispersities. Finally, we have shown that CDSA can be used to access well-defined functional nanomaterials in fluorinated solvents, which may have applications in fluorous phase catalysis and for sensing and diagnostics in biologically relevant fluorous media.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, as well as synthetic and characterization details for all polymers and micelle samples. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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