

Stimuli-Responsive Hybrid Macromolecules: Novel Amphiphilic Star Copolymers With Dendritic Groups at the Periphery

Ivan Gitsov and Jean M. J. Fréchet*

Baker Laboratory, Department of Chemistry
Cornell University Ithaca, New York 14853-1301

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In this study we explore the possibility of building an amphiphilic hybrid macromolecule that responds to changes in its environment through changes in the types of micelles it forms. These “stimuli-responsive” materials¹ contain multiple dendritic blocks attached to the ends of a star polymer which can micellize differently in response to changes in the surrounding medium. In this approach the central hydrophilic poly(ethylene glycol) star has arms that are long and flexible enough to serve either as spacers or as encapsulating “wrappers” for the hydrophobic dendritic blocks that are attached to their extremities. It should be mentioned that, in spite of theoretical predictions for micellar stars² and advances in the synthetic techniques that are available, there are essentially no prior studies of amphiphilic stars and end-functionalized star polymers as stimuli-responsive macromolecules. This is because the groups that had been selected for placement at the periphery were either too small or too large to enable the loop formation that is required as a response to the external stimulus.^{2,3} However, because of the large disparity in the polarity and solubility of the dendritic and PEG components and because of the dense and compact structure of the dendritic groups placed at the periphery of the stars, the systems described in the present study can be expected to adopt vastly different conformations in solution as the solvent polarity is varied. Therefore, these unusual dendritic stars would constitute the first instance of polymers capable of forming totally different types of monomolecular micelles in response to changes in the surrounding medium.

The synthesis of hybrid starlike macromolecules containing dendrimers has now been reported by several research groups.^{4–6} In all cases the dendritic moiety is used as the core for the star to form structures with a predictable number of arms. In spite of its advantages, this approach ultimately produces traditional stars with dense, compact nuclei that have fixed chemical composition and properties. The unique reactivity of convergent dendrimers^{7,8} that possess a single reactive group at their focal points enables the formation of hybrid stars with an entirely different architecture, namely, with the dense and semirigid dendritic groups at the periphery.

In this study we use the well-known Williamson ether synthesis to form the link between the dendritic block and the PEG star.^{9,10} The coupling reaction proceeds smoothly at room

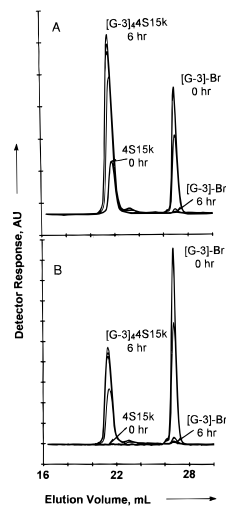


Figure 1. Reaction of a four-arm PEG star (4S15k) with a third-generation dendritic bromide, [G-3]-Br, monitored by SEC with double detection.¹³ (A) dRI detector traces; (B) UV detector traces.

temperature and, depending on the dendrimer generation, requires different reaction times to go to completion.¹¹ These times vary from 3 and 6 h for the second-generation and third-generation dendrimers to 22 h for the fourth-generation dendrimer. The reaction is easily monitored by size-exclusion chromatography (SEC) with double detection (Figure 1). The yields are 90% for the second-generation hybrid, 85% for the third-generation, and 80% for the fourth-generation. The polymers obtained are white solids that are both able to crystallize and to form spherulites despite their high amorphous dendrimer content. The DSC analyses show that with the increase of the dendrimer generation the melting transition of the hybrids is shifted to lower temperatures ($T_m = 57, 42.2^\circ\text{C}, 40.7, \text{ and } 32.9^\circ\text{C}$ for 4S15k, 4S15k[G-2]₄, 4S15k[G-3]₄, and 4S15k[G-4]₄, respectively).¹²

Preliminary investigations of the materials both by SEC with coupled viscometry (SEC/VISC) and by ¹H-NMR¹³ show that, in solution, the molecules respond to changes in the polarity of the solvents used to dissolve them by adjusting both their size and their molecular geometry. The process is presented

(10) Materials: The dendritic bromides used throughout this study were synthesized according to a method already described.⁷ The four-arm star poly(ethylene glycol) with nominal molecular weight 15 000, 4S15k, having pentaerithritol core, was obtained from Shearwater Polymers, Inc. Tetrahydrofuran (THF, Aldrich) was dried over sodium wire and distilled prior to use. NaH (95%, Aldrich) was used without purification.

(11) A typical synthesis of a hybrid dendritic star is performed as follows. 4S15k (0.453 g, 3.02×10^{-5} mol) and second-generation dendritic bromide, [G-2]-Br (0.1 g, 1.238×10^{-4} mol), were placed in two-neck reaction flask equipped with reflux condenser and dissolved in 10 mL of dry THF. NaH (0.01 g, 4×10^{-4} mol) was added under vigorous stirring, and the reaction mixture was kept under positive nitrogen pressure at room temperature. The formation of the hybrid star was followed by SEC with double detection. The stirring was stopped after 3 h, and the clear liquid over the excess of NaH was decanted and precipitated in hexanes. The hybrid star 4S15k[G-2]₄ was obtained as white powder, yield 0.492 g (90.6%). ¹H-NMR (CDCl₃, δ): 3.63 (s, CH₂CH₂O), 4.47 (s, PhCH₂OCH₂), 4.94 + 5.00 (s, PhCH₂O), 6.51–6.66 (m, PhH), 7.28–7.40 (m, PhH). ¹³C-NMR (CDCl₃, δ): 65.35 (PhCH₂OCH₂CH₂), 69.90, 69.95 (PhCH₂O), 70.5 (CH₂CH₂O), 101.31, 101.57, 105.76, 106.33 (ArC), 127.51, 128.00, 128.63 (PhCH), 136.74, 137.29, 143.41, 160.09, 160.17 (PhC + ArC).

(12) Thermal analyses were performed on a Seiko SSC 5200 differential scanning calorimeter at a heating rate of $10^\circ\text{C}/\text{min}$.

(13) The SEC line consisted of a M510 pump, an U6K universal injector, an UV 486 detector (all Waters), differential refractive index detector—dRI (Milton Roy), and differential viscometer Model 110 (Viscotek). The separation was achieved across a set of four 5 μm PL Gel columns (Polymer Laboratories) with porosities of 100 Å, 500 Å, 1000 Å, and Mixed C. The mobile phase was THF (45 $^\circ\text{C}$) eluting at 1 mL/min. ¹H-NMR studies were performed on a Bruker WM 300 (300 MHz) in deuterated chloroform, methanol, and THF at room temperature. The proton signals of the solvents were used as internal standards.

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Scheme 1

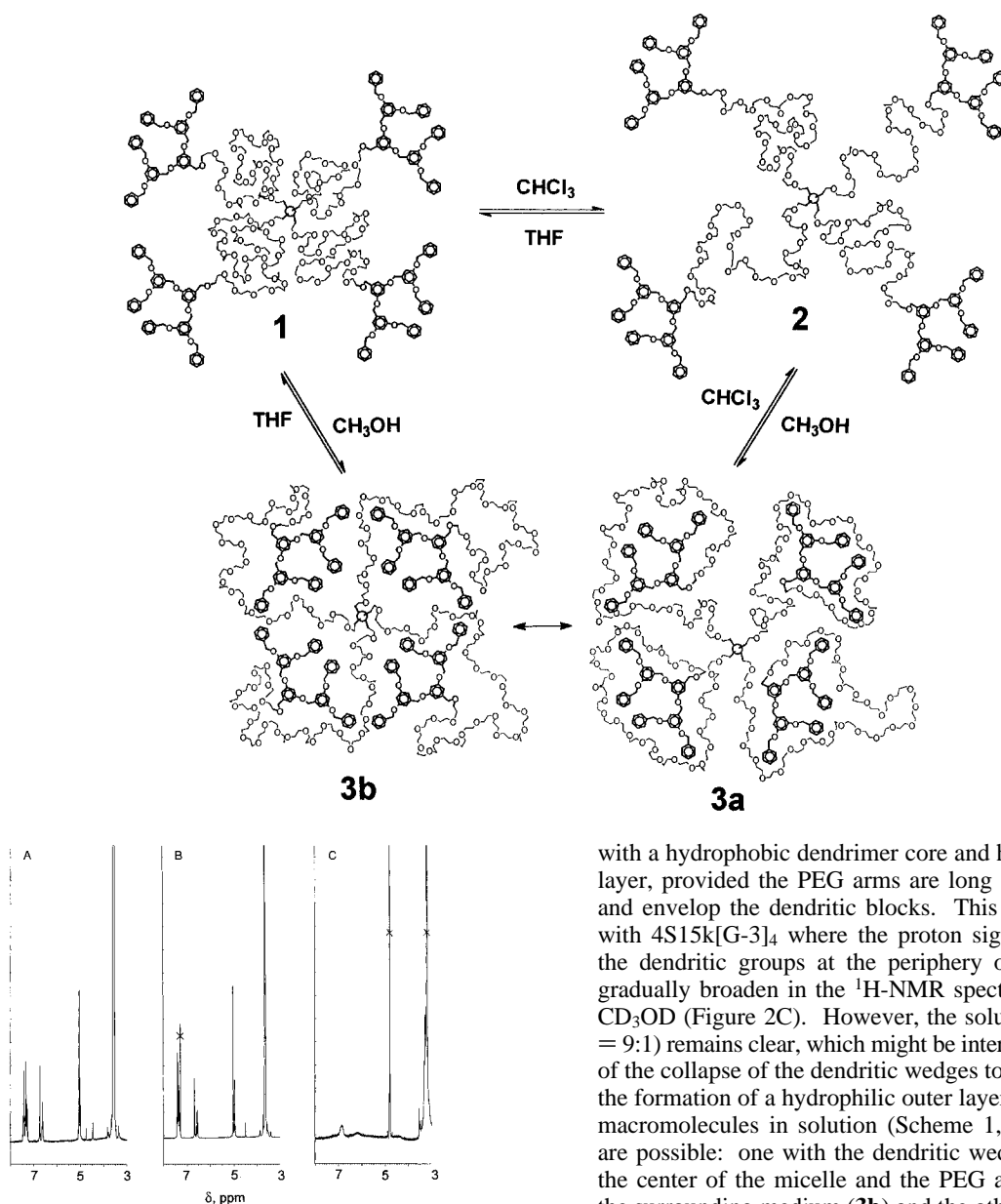


Figure 2. $^1\text{H-NMR}$ spectra of $4\text{S}15\text{k}[\text{G}-3]_4$ recorded in solvents with different polarities:¹³ (A) $\text{THF-}d_8$; (B) CDCl_3 ; (C) CD_3OD .

schematically in Scheme 1. In THF the hybrid stars form monomolecular micelles that have a hydrophilic core consisting of compactly packed PEG arms, surrounded by a loose hydrophobic shell of dendritic wedges extending outward (Scheme 1, **1**). A similar behavior was observed earlier for the ABA copolymers containing PEG as the linear B block and dendrimers as the A blocks.⁹ This assignment is supported both by the appearance of a single peak corresponding to these unimolecular micelles in the SEC traces (Figure 1) and the observation of a lower than calculated intensity for the PEG protons in the $^1\text{H-NMR}$ spectra recorded in $\text{THF-}d_8$ (Figure 2A). In chlorinated solvents— CHCl_3 or CH_2Cl_2 —in which both building blocks are readily soluble, the stars expand to adopt their fully extended conformation, but the core-shell structure is preserved by the covalent bonds linking the four arms (Scheme 1, **2**). The measured intensities of the proton signals in the $^1\text{H-NMR}$ spectra for both constituents are in agreement with the calculated values (Figure 2B). In polar or aqueous media (CH_3OH or $\text{H}_2\text{O}/\text{CH}_3\text{OH}$), the stars adopt another form

with a hydrophobic dendrimer core and hydrophilic outer PEG layer, provided the PEG arms are long enough to form loops and envelop the dendritic blocks. This is obviously the case with $4\text{S}15\text{k}[\text{G}-3]_4$ where the proton signals characteristic for the dendritic groups at the periphery of the star in $\text{THF-}d_8$ gradually broaden in the $^1\text{H-NMR}$ spectrum upon addition of CD_3OD (Figure 2C). However, the solution ($\text{CD}_3\text{OD}/\text{THF-}d_8 = 9:1$) remains clear, which might be interpreted as an indication of the collapse of the dendritic wedges to form a new core with the formation of a hydrophilic outer layer that keeps the hybrid macromolecules in solution (Scheme 1, **3**). Two forms of **3** are possible: one with the dendritic wedges tightly packed in the center of the micelle and the PEG arms forming loops in the surrounding medium (**3b**) and the other with each dendritic block “wrapped” individually in its PEG arm and somewhat extended in the aqueous medium (**3a**). The data available at this time is not sufficient to determine which form is preferred. The influence of the length and the number of arms of the PEG star on the size and shape of the resulting hybrids is currently under investigation.

Conclusion

The results obtained show that a new class of amphiphilic hybrid macromolecules is obtained by a simple synthetic procedure that utilizes easily accessible components. The materials formed have a constant chemical composition, but they are able to respond to changes in the surrounding medium by forming monomolecular micelles with different core-shell structures.

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