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ARTICLE

Synthesis via RAFT of Amphiphilic Block Copolymers with Liquid-Crystalline Hydrophobic Block and Their Self-Assembly in Water

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ABSTRACT: Two families of amphiphilic diblock copolymers, in which the hydrophobic block was a cholesteryl-based smectic liquid-crystalline polymer and the hydrophilic block was either a neutral polymer with a lower critical solution temperature (LCST), poly(*N*,*N*-diethylacrylamide), or a copolymer containing acrylic acid moieties and poly(ethylene oxide) side chains, were successfully synthesized by reversible addition−fragmentation chain transfer (RAFT) polymerization. Nanoassemblies of these amphiphilic species in water or in buffer solution were prepared using the cosolvent method. The morphology of the nanoassemblies clearly depended on the weight fraction and the nature of the hydrophobic block. The amphiphilic liquid-crystal (LC) block copolymers with a hydrophobic/hydrophilic weight ratio of 74/26 or 65/35 formed long nanofibers, whereas the non-LC copolymers based on polystyrene of similar ratio formed vesicles or short cylindrical micelles. Such morphologies were assigned to the presence of a smectic order in the hydrophobic domain of the assemblies, as revealed by small-angle X-ray scattering (SAXS) and cryogenic transmission electron microscopy.

Introduction

Recent progress in the chemical design of block copolymers opens up the exciting possibility of creating a wide variety of polymeric nanomaterials.[1] In the past years, the synthesis of block copolymers with well-defined architectures became easily accessible thanks to the development of the controlled/living free-radical polymerization techniques.[2] In particular, a variety of amphiphilic block copolymers[1,3] can now be synthesized in a simple manner, using direct polymerization of functional monomers without the tedious protection−deprotection chemistries that are often needed in ionic polymerization. Those amphiphilic block copolymers have the ability to self-assemble[1,4] in selective solvents forming nano- or micrometric aggregates, such as spherical or elongated micelles, rods, vesicles (also called polymersomes), or other morphologies with various well-organized supramolecular architectures.[5,6] The morphology is hereby intimately related to the selective solvent used, the nature of the polymers, and the length and architecture of the segments.[7] Such nano-objects may find applications in various domains including drug delivery, biotechnology, material chemistry, etc.[8−10] With the purpose of forming polymer self-assemblies, coil−coil amphiphilic block copolymers have mostly been studied.[1] A few number of rod−coil or rod−rod amphiphilic block copolymers have also been reported, including synthetic copolymers containing crystalline[11] or liquid-crystalline (LC)[12−17] block(s) and copolymers containing polypeptide block(s).[18,19] Since several years, one of the authors' group (at the Institut Curie) has focused on the study of self-assemblies in water of amphiphilic block copolymers with a LC hydrophobic block. Thanks to the LC unit, they may be sensitive to physical stimuli (such as light, temperature, and magnetic field) allowing the design of stimuli-responsive nano-objects.[6] For example, photoresponsive polymersomes, which burst under UV illumination, have been recently obtained using azobenzene-containing LC block copolymers.[20] On the other hand, block copolymers with a LC hydrophobic block are good candidates to study the influence of additional orders in the rodlike block on the formation of macromolecular assemblies. We previously reported on spherical polymersomes formed in water from amphiphilic LC block copolymers, in which the hydrophobic block was a side-on nematic polymer and the hydrophilic block a poly(ethylene glycol) (PEG).[15] We also described ellipsoidal smectic polymersomes formed from another LC block copolymer, in which the LC block was a cholesteryl-based end-on smectic polymer.[16] For the same smectic block copolymer but with different block lengths and block ratios, polymer nanofibers with smectic fine structures were obtained.[17] These results indicate that the organization of the LC block, in addition to the proper hydrophobic/hydrophilic balance, influence significantly the morphologies of the nano- or micro-objects self-assembled in water.

In our systematic investigation on the self-assembly of amphiphilic LC block copolymers, we attempt to understand the chemical and physicochemical factors that govern and affect the formation of the nano- and micro-objects. In this paper we extend our previous study to new amphiphilic LC block copolymers in which different hydrophilic blocks other than linear PEG were used while the LC block was again a cholesteryl-based end-on smectic polymer (see Scheme 1). By changing the chemical nature and chemical functionality of the hydrophilic block, we

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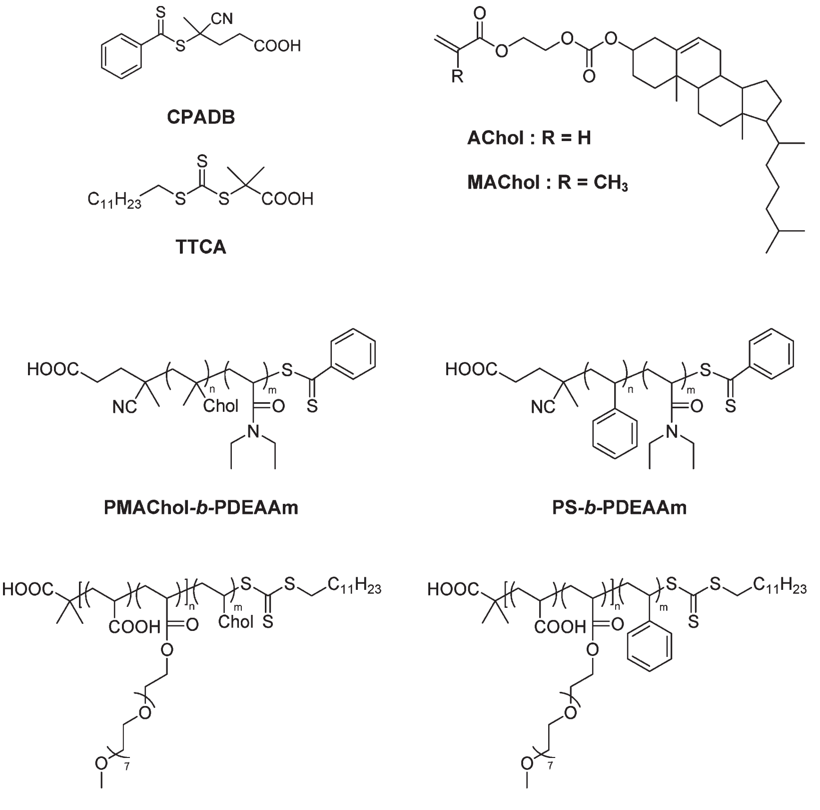
Scheme 1. Reversible Addition−fragmentation Transfer (RAFT) Agents, 4-(4-Cyanopentanoic acid) Dithiobenzoate (CPADB) and 2-(Dodecylthiocarbonothioylthio)-2-methylpropanoic Acid) (TTCA), and Cholesteryl Monomers, Cholesteryl Acryloyloxyethyl Carbonate (AChol) and Cholesteryl Methacryloyloxyethyl Carbonate (MAChol), Used in This Study[a]



[a] Structure of the different copolymers composed of AA (acrylic acid), PEGA (poly(ethylene glycol) methyl ether acrylate), S (styrene), DEAAm (*N*,*N*-diethylacrylamide).

aim to adjust the surface properties of the formed nano-objects. In this spirit, we designed new amphiphilic LC diblock copolymers with various hydrophilic blocks: poly(*N*,*N*-diethylacrylamide) (PDEAAm) and poly(acrylic acid-*co*-PEG acrylate) (P(AA-*co*-PEGA)). The RAFT (reversible addition−fragmentation transfer)[21,22] polymerization technique was chosen for its tolerance to a wide range of monomers and functional groups. Hitherto, only a few LC polymers or block copolymers have been synthesized by RAFT-mediated polymerization.[23−25] The hydrophobic LC block was a polymethacrylate or a polyacrylate containing a cholesteryl-based mesogen side group (PMAChol or PAChol, respectively). PMAChol and PAChol were selected for their ability to form smectic LC structure, which allowed us to study more deeply the influence of this mesophase on the morphology of the block copolymer self-assemblies. PDEAAm is a good model for neutral hydrophilic polymers, and it moreover exhibits a lower critical solution temperature (LCST) at 32 °C,[26] which may be of interest to tune the surface properties and the thermal stability of the formed objects. In this study, the PMAChol block length was kept constant whereas the PDEAAm block length was varied to cover a broad composition range (hydrophobic/hydrophilic ratio ranging from 92/8 to 45/55). P(AA-*co*-PEGA) is a pH-sensitive copolymer providing electrosteric stabilization at alkaline pH. It may also be of interest for postgrafting molecules onto the surface via reaction with the carboxylic acid groups. We present here the block copolymer synthesis and characterization and discuss their self-assembly in water as a function of the PDEAAm block length (i.e., overall composition) and of the nature of the hydrophilic block.

Experimental Section

Materials. 4,4′-Azobis(4-cyanopentanoic acid) (ACPA, >98%, Fluka), 2,2′-azobis(isobutyronitrile) (AIBN, >98%, Fluka), anhydrous acrylic acid (AA, >99%, Fluka, Scheme 1), poly(ethylene glycol) methyl ether acrylate (PEGA, M_n = 454 g mol^{-1}, >99% Aldrich, Scheme 1), 1,3,5-trioxane (>99%, Fluka), and the solvents 1,4-dioxane (from SDS, synthesis grade), *N*,*N*-dimethylformamide (DMF, for analysis from VWR), and tetrahydrofuran (THF, for analysis from VWR Normapur) were used as received. Styrene (S, 99%, Aldrich) was distilled under reduced pressure before use. The liquid-crystalline monomers cholesteryl acryloyloxyethyl carbonate (AChol, Scheme 1) and cholesteryl methacryloyloxyethyl carbonate (MAChol, Scheme 1) were synthesized as described elsewhere.[27] *N*,*N*-Diethylacrylamide (DEAAm, Scheme 1) was synthesized at a temperature below 10 °C in dry THF by reaction of acryloyl chloride (96%, Alfa Aesar) with a 2-fold excess of diethylamine (>99%, Acros) following an already published protocol.[28] Monomer characterization results by ^{1}H and ^{13}C NMR are given in the Supporting Information. The RAFT agents 4-(4-cyanopentanoic acid) dithiobenzoate (CPADB) and 2-(dodecylthiocarbonothioylthio)-2-methylpropanoic acid) (TTCA) were synthesized as described elsewhere.[29,30] The molecular structures of the monomers and RAFT agents can be found in Scheme 1.

Synthesis of the Macromolecular RAFT Agents. *Poly(cholesteryl methacryloyloxyethyl carbonate) MacroRAFT Agent (PMAChol−DTB).* In a typical experiment, the polymerization of MAChol (4.35 g, 8.0 × 10^{-3} mol) was carried out in 20 mL of 1,4-dioxane with ACPA (14.0 mg, 5.6 × 10^{-5} mol) as an initiator and CPADB (75.6 mg, 2.7 × 10^{-4} mol) as a

Table 1. Macromolecular Characteristics for the Amphiphilic Diblock Copolymers PMAChol-*b*-PDEAAm, PS-*b*-PDEAAm, P(AA-*co*-PEGA)-*b*-PAChol, and P(AA-*co*-PEGA)-*b*-PS Prepared via Reversible Addition–Fragmentation Chain Transfer (RAFT) Polymerization in the Presence of PMAChol–DTB, PS–DTB, or P(AA-*co*-PEGA)–TTC MacroRAFT Agents (See Scheme 1)[a]

						DP$_n$		
sample	hydrophobic block	hydrophilic block	M_n (g/mol) of the hydrophobic block	M_n (g/mol) of the hydrophilic block	hydrophobic/hydrophilic weight ratio	hydrophobic block	hydrophilic block	M_w/M_n
P1	PMAChol	PDEAAm	10700[b]	13100[d]	45/55[d]	19	103	1.20[b]
P2	PMAChol	PDEAAm	10700[b]	3800[d]	74/26[d]	19	30	1.16[b]
P3	PMAChol	PDEAAm	10700[b]	2700[d]	80/20[d]	19	21	1.20[b]
P4	PMAChol	PDEAAm	10700[b]	900[d]	92/8[d]	19	7	1.14[b]
P5	PS	PDEAAm	11000[b]	4100[d]	73/27[d]	106	32	1.13[b]
P6	PAChol	P(AA-*co*-PEGA)	15500[c]	8300[c]	65/35[c]	29	30	1.30[b]
P7	PS	P(AA-*co*-PEGA)	14150[c]	8300[c]	63/37[c]	136	30	1.25[b]

[a] PMAChol, PAChol, PDEAAm, AA, and PEGA correspond to poly(cholesteryl methacryloyloxyethyl carbonate), poly(cholesteryl acryloyloxyethyl carbonate), poly(*N*,*N*-diethylacrylamide), acrylic acid, and poly(ethylene glycol) methyl ether acrylate, respectively. [b] The number-average molar masses, M_n, and the polydispersity indexes (M_w/M_n) were determined by size exclusion chromatography (SEC) in tetrahydrofuran (THF) with a calibration curve based on poly(methyl methacrylate) (PMMA) standards for PMAChol and on polystyrene (PS) standards for PS samples. [c] M_n was determined by SEC in THF equipped with a light scattering (LS) detector. [d] M_n and the number-average degree of polymerization, DP$_n$, and the hydrophobic/hydrophilic block weight ratios were determined by ^{1}H NMR.

RAFT agent. The solution was poured in a septum-sealed flask, purged for 45 min with nitrogen, and heated to 80 °C in a thermostated oil bath under stirring. For kinetic studies (see Supporting Information, Figure SI-1), sampling was performed at regular time intervals, and the polymerization was finally quenched after 7 h (91% conversion) by immersion of the flask in iced water. The monomer conversion was determined by ^{1}H NMR spectroscopy in CDCl$_3$ by the relative integration of the protons of MAChol at 5.3 ppm, as an internal reference (C=C*H* proton on the cholesterol side chain), and its vinylic protons at 5.5 and 6.0 ppm. For the synthesis of the living PMAChol–DTB used as a macroRAFT agent, the polymerization was stopped after 4 h at 75% of monomer conversion. The polymer was recovered by precipitation in methanol and dried under reduced pressure. It was analyzed by size exclusion chromatography (SEC) in THF solution and calculation of the number-average molar mass (M_n) and of the polydispersity index (M_w/M_n with M_w the weight-average molar mass) was made with a calibration curve based on poly(methyl methacrylate) standards (PMMA) (M_n = 10 700 g mol^{-1}, M_w/M_n = 1.12). The high purity of the macroRAFT agent was checked by ^{1}H NMR in CDCl$_3$ (no detectable vinylic protons), and its number-average degree of polymerization, DP$_n$, was calculated (C=C*H* proton on the cholesterol side chain at 5.3 ppm and the aromatic protons of the RAFT agent at the chain end at 8 ppm) (DP$_n$ = 23, i.e., M_n = 12 900 g mol^{-1}, which is in agreement with the molar mass determined by SEC). The chain-end functionality was determined by UV–vis spectrophotometry analysis (using a Cary 219 from Varian) of known weight concentration of the polymer in THF. The molar concentration of dithiobenzoate chain ends was derived from the absorbance at 520 nm (assuming the polymer has the same molar extinction coefficient as CPADB, i.e., ε = 105 L mol^{-1} cm^{-1}), and a high chain-end functionality of ~100% was calculated using M_n = 10 700 g mol^{-1} derived from SEC in THF.

Polystyrene MacroRAFT Agent (*PS–DTB*). The polymerization of styrene (25.2 g, 0.24 mol) was carried out with AIBN (16.4 mg, 9.9 × 10^{-5} mol) as an initiator and CPADB (103 mg, 3.7 × 10^{-4} mol) as a RAFT agent. The solution was poured in a septum-sealed flask, purged for 30 min with nitrogen, and heated to 70 °C in a thermostated oil bath under stirring. For kinetic studies, sampling was performed at regular time intervals, and the polymerization was finally quenched after 6 h and 30 min by immersion of the flask in iced water. The monomer conversion was 18% as determined by gravimetry. The polymer was recovered by precipitation in ethanol and dried under reduced pressure. It was analyzed by SEC in THF solution using a calibration curve based on polystyrene (PS) standards: M_n = 11 000 g mol^{-1}, M_w/M_n = 1.11.

Poly(*acrylic acid-co-PEG acrylate*) *MacroRAFT Agent* (*P*(*AA-co-PEGA*)*-TTC*). In a typical experiment, the copolymerization of AA (1.45 g, 2.0 × 10^{-2} mol) and PEGA (9.16 g, 2.0 × 10^{-2} mol) was carried out with ACPA as an initiator (29.9 mg, 1.1 × 10^{-4} mol) and TTCA as a RAFT agent (574 mg, 1.58 × 10^{-3} mol) in 9.85 g of DMF. 1,3,5-Trioxane (266 mg, 3.0 × 10^{-3} mol) was added as an internal reference for NMR analysis. The solution was poured in a septum-sealed flask, purged for 30 min with nitrogen, and heated to 80 °C in a thermostated oil bath under stirring. For kinetic studies, sampling was performed at regular time intervals, and the polymerization was finally quenched after 2 h (93% conversion) by immersion of the flask in iced water. The overall monomer conversion was determined by ^{1}H NMR spectroscopy in CDCl$_3$ by the relative integration of the internal reference peak and the vinylic proton peaks of AA and PEGA at 5.5 and 6.0 ppm. For the synthesis of the living P(AA-*co*-PEGA)-TTC that was later used as a macroRAFT agent, polymerization was stopped after 35 min at 77% of monomer conversion. The polymer was recovered by precipitation in diethyl ether and then dried under reduced pressure. The relative number-average molar mass and polydispersity index were determined by SEC in THF using a PS calibration curve derived from the refractive index detector (M_n = 5500 g mol^{-1}, M_w/M_n = 1.16). Combination of the signals of the refractive index detector and the light scattering (LS) detector allowed us to determine an absolute value of M_n = 8300 g mol^{-1}. The average refractive index increment, d*n*/d*c*, was determined in-line by injecting the copolymer at four different concentrations. The d*n*/d*c* for P(AA-*co*-PEGA)-TTC in THF at 40 °C was 0.059. Composition of the copolymer was determined using quantitative ^{13}C NMR analysis via the relative integration of the signals at 176 ppm (C=O of AA) and at 174 ppm (C=O of the ester group in PEGA). In addition, an acid–base titration was performed on an aqueous copolymer solution (7.4 × 10^{-3} mol L^{-1}) with a 0.04 N NaOH aqueous solution in order to determine the number of AA units per chain.

Synthesis of the Diblock Copolymers. *PMAChol-b-PDEAAm Diblock Copolymers by PMAChol–DTB-Mediated RAFT Polymerization of DEAAm.* Various polymerizations of DEAAm were performed with different monomer/macroRAFT agent ratios to target different lengths of the hydrophilic block. The polymerizations were carried out in 1,4-dioxane at 80 °C with ACPA as an initiator and PMAChol–DTB (M_n = 10 700 g mol^{-1}, M_w/M_n = 1.12) as a reversible chain transfer agent. In a typical experiment (Table 1, sample **P1**), the polymerization of

DEAAm (352 mg, 2.8×10^{-3} mol) was carried out with PMAChol−DTB (244 mg, 2.4×10^{-5} mol) and ACPA (1.33 mg, 4.8×10^{-6} mol) in 1.13 mL of 1,4-dioxane. The solution was placed in a septum-sealed flask, purged for 30 min with nitrogen in an ice bath, and heated at 80 °C in a thermostated oil bath under stirring. The polymerization was finally quenched after 6 h (70% conversion) by immersion of the flask in iced water. The monomer conversion was determined by ^{1}H NMR spectroscopy in $CDCl_3$ by the relative integration of the protons of the macroRAFT agent at 5.3 ppm (C=C*H* proton on the cholesterol side chain) and the vinylic protons of DEAAm at 5.7, 6.1, and 6.7 ppm. The copolymer was purified by precipitation in hot water and recovered by lyophilization. It was analyzed by SEC in THF solution and calculation of M_n and of M_w/M_n was made with a calibration curve based on PMMA standards. The number-average degree of polymerization, DP_n (and consequently M_n), of the second block was calculated using ^{1}H NMR of the copolymer (in $CDCl_3$) comparing the relative integration of the C=C*H* proton on the cholesterol side chain (5.3 ppm, PMAChol block) and the protons of the PDEAAm block (CH_2 of the ethyl group at 3.3 ppm). Detailed characteristics of the block copolymers are summarized in Table 1 and in the Supporting Information (Table SI-1).

PS-b-PDEAAm Diblock Copolymer by PS−DTB-Mediated RAFT Polymerization of DEAAm. The polymerization of DEAAm was performed in 1,4-dioxane at 80 °C with ACPA as an initiator and PS-DTB as a reversible chain transfer agent (see Table 1, experiment **P5**). The monomer DEAAm (423 mg, 3.3×10^{-3} mol) was mixed with PS-DTB (M_n = 11 000 g mol^{-1}; 670 mg, 6.1×10^{-5} mol) and ACPA (3.4 mg, 1.2×10^{-5} mol) in 1.37 mL of 1,4-dioxane. The solution was placed in a septum-sealed flask, purged for 30 min with nitrogen in an ice bath, and heated at 80 °C in a thermostated oil bath under stirring. The polymerization was finally quenched after 3 h and 10 min by immersion of the flask in iced water. The monomer conversion (62%) was determined by ^{1}H NMR spectroscopy in $CDCl_3$ by the relative integration of the protons of the internal reference (1,3,5-trioxane) at 5.3 ppm and the vinylic protons of DEAAm at 5.7, 6.1, and 6.7 ppm. The copolymer was purified by precipitation in water and recovered by lyophilization. It was analyzed by SEC in THF solution, and calculation of M_n and of M_w/M_n was made with a calibration curve based on PS standards. The number-average degree of polymerization, DP_n (and consequently M_n), of the second block was calculated using ^{1}H NMR analysis of the copolymer (in $CDCl_3$) comparing the relative integration of the aromatic protons on the PS block (∼6 ppm) and the protons of the PDEAAm (CH_2 on the ethyl group at 3.3 ppm). Detailed characteristics of the block copolymer **P5** are summarized in Table 1 and in the Supporting Information (Table SI-1).

P(AA-co-PEGA)-b-PAChol Diblock Copolymer via P(AA-co-PEGA)−TTC-Mediated Polymerization of AChol. The polymerization of AChol was performed in 1,4-dioxane at 80 °C with ACPA as an initiator and P(AA-*co*-PEGA)-TTC as a reversible chain transfer agent (Table 1, sample **P6**). The polymerization of AChol (1.56 g, 2.96×10^{-3} mol) was carried out with P(AA-*co*-PEGA)-TTC (M_n = 8300 g mol^{-1}; 405 mg, 7.4×10^{-5} mol) and ACPA (4.6 mg, 1.64×10^{-5} mol) in 2 mL of 1,4-dioxane. The solution was placed in a septum-sealed flask, purged for 30 min with nitrogen in an ice bath, and heated at 80 °C in a thermostated oil bath under stirring. The polymerization was finally quenched after 6 h (95% conversion) by immersion of the flask in iced water. The monomer conversion was determined by ^{1}H NMR spectroscopy in $CDCl_3$ by the relative integration of the protons of the AChol monomer at 5.3 ppm (C=C*H* proton on the cholesterol side chain) and the vinylic protons at 5.7, 6.1, and 6.7 ppm. The copolymer was purified by precipitation in water and recovered by lyophilization. It was analyzed by SEC in THF solution, and M_n was derived from the light scattering (LS) response (d*n*/dc = 0.117) while M_w/M_n was calculated with a calibration curve based on PS standards. Detailed characteristics of the block copolymers are summarized in Table 1 and in the Supporting Information (Table SI-2).

P(AA-co-PEGA)-b-PS Diblock Copolymer via P(AA-co-PEGA)−TTC-Mediated Polymerization of S. The polymerization of styrene was performed in 1,4-dioxane at 80 °C with ACPA as an initiator and P(AA-*co*-PEGA)-TTC as a reversible chain transfer agent (Table 1, sample **P7**). The polymerization of S (3.96 g, 3.8×10^{-2} mol) was carried out with P(AA-*co*-PEGA)-TTC (M_n = 8300 g mol^{-1}; 319 mg, 5.86×10^{-5} mol) and ACPA (3.34 mg, 1.19×10^{-5} mol) in 3.7 mL of 1,4-dioxane. The solution was placed in a septum-sealed flask, purged for 30 min with nitrogen in an ice bath, and heated at 80 °C in a thermostated oil bath under stirring. The polymerization was finally quenched after 22 h and 35 min (33% conversion) by immersion of the flask in iced water. The monomer conversion was determined by gravimetry. The copolymer was purified by precipitation in water and recovered by lyophilization. It was analyzed by SEC in THF solution, and Mn was derived from the light scattering (LS) response (d*n*/dc = 0.185) while M_w/M_n was calculated with a calibration curve based on PS standards. Detailed characteristics of the block copolymers are summarized in Table 1 and in the Supporting Information (Table SI-2).

Self-Assembly of the Amphiphilic Block Copolymers in Water. The self-assembly process and turbidity measurements were performed according to published procedures.[31] In detail, the diblock copolymers were first dissolved in 1,4-dioxane, which is a good solvent for all polymer blocks, at a concentration of 1.0 wt %. After an equilibration period of 15 h, deionized water or a buffered aqueous solution was added very slowly to 1.5 mL of the solution under gentle shaking. After every addition of water droplet (or buffer solution), the solution was left to equilibrate for 10 min or more until the optical density was stable. The optical density (turbidity) was measured at a wavelength of 650 nm using a quartz cell (path length = 2 cm) with a Unicam UV−vis spectrophotometer. The cycle of water addition, equilibration, and turbidity measurement was continued until the increase in turbidity upon water addition remained very small. The turbid solution was then dialyzed against water (or buffer solution) for 3 days to remove 1,4-dioxane using a Spectra/Por regenerated cellulose membrane with a molar mass cutoff of 3500 Da.

Characterization Techniques. ^{1}H NMR spectra for determination of the monomer conversion were recorded at room temperature using a 250 MHz Bruker spectrometer in 5 mm diameter tubes. The purity of the PMAChol−DTB macroRAFT agent was determined in $CDCl_3$ solution with a 500 MHz Bruker spectrometer. ^{13}C NMR (125 MHz) was performed at room temperature with a Bruker spectrometer in 10 mm diameter tubes.

The number-average molar mass (M_n), the weight-average molar mass (M_w), and the molar mass distribution (polydispersity index: PDI = M_w/M_n) were determined by size exclusion chromatography (SEC) using THF as an eluent at a flow rate of 1 mL min^{-1}. Two types of SEC apparatus were used in this study: (a) a routine device equipped with a Viscotek VE 5200 automatic injector and two columns thermostated at 40 °C (PSS SDV, linear M, 8 mm × 300 mm, bead diameter: 5 μm, separation range: 400−10^6 Da). Detection was made with a differential refractive index detector (LDC analytical Refracto Monitor IV). The Viscotek OmniSEC software was used for data analysis; calculation was made with a calibration curve based on poly(methyl methacrylate) (PMMA) and polystyrene (PS) standards (from Polymer Laboratories). (b) A more sophisticated apparatus with a triple detector array (TDA, model 302 from Viscotek) equipped with a two angle light scattering (LS) detector (LALS, $\theta = 7°$, RALS, $\theta = 90°$, laser λ = 670 nm), a refractive index detector (λ = 670 nm), and three Polymer Laboratories Mixed C columns (5 μm) thermostated at 40 °C (the inline viscometer was not used in this work). The average molar masses were calculated from the LS signal with the OmniSec software, using the average refractive index

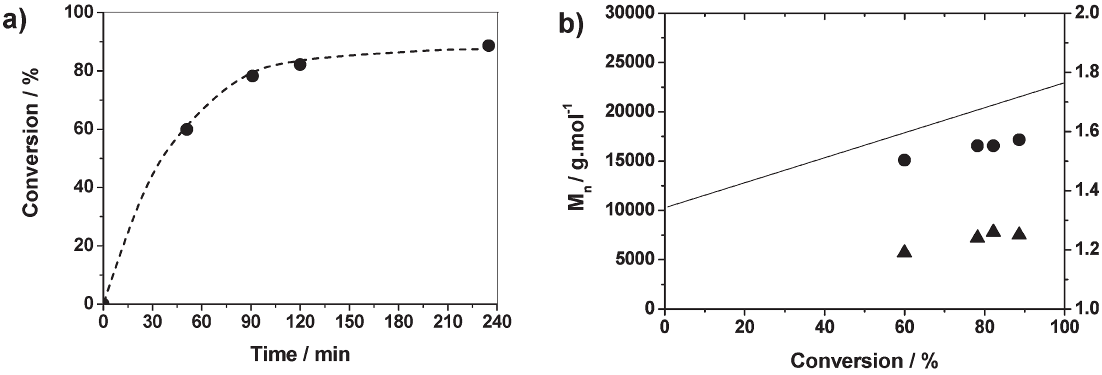


Figure 1. Polymerization of *N,N*-diethylacrylamide (DEAAm) in the presence of the poly(cholesteryl methacryloyloxyethyl carbonate) macromolecular RAFT agent, PMAChol−DTB, in 1,4-dioxane at 80 °C: (a) evolution of the monomer conversion in % with time and (b) evolution of the number-average molar mass (M_n) (●) and M_w/M_n (▲) with conversion (size exclusion chromatography in THF using a poly(methyl methacrylate) calibration) (experiment **P2**, Table 1). The straight line corresponds to the theoretical M_n values.

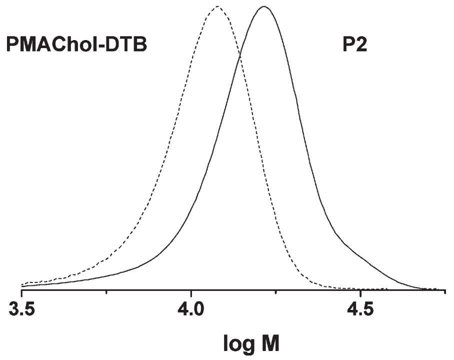


Figure 2. Size exclusion chromatograms in THF of the poly(cholesteryl methacryloyloxyethyl carbonate) macromolecular RAFT agent, PMAChol−DTB, and of the PMAChol-*b*-PDEAAm diblock copolymer **P2** obtained after chain extension with *N,N*-diethylacrylamide (DEAAm) (see Table 1 for the characteristics).

increment (d*n*/d*c*) measured for each sample with the inline refractometer. All polymers were first analyzed using the routine SEC, and only the P(AA-*co*-PEGA)−TTC (macroRAFT agent) and the amphiphilic diblock copolymers containing this type of block were injected in the other system.

The mesomorphic properties of the LC homopolymer PMAChol−DTB were studied in bulk by thermal optical polarizing microscopy using a Leitz Ortholux microscope equipped with a Mettler FP82 hot stage. Differential scanning calorimetry (DSC) was performed using a Perkin-Elmer DSC7. The instrument was calibrated with a Perkin-Elmer indium calibration kit (mp, 429.78 K (156.60 °C); Δ*H*, 6.80 cal g^{-1}) for temperature and enthalpy changes. The sample was scanned from −10 to 210 °C with heating and cooling rates of 10 °C/min. T_g was taken as the half C_p extrapolated point in the C_p jump, and liquid crystal transition temperature was taken as the peak temperatures in DSC thermograms.

The LC structures of the PMAChol−DTB homopolymer in bulk and in the nano-objects formed by the diblock copolymers in aqueous dispersion were studied at room temperature by X-ray scattering using Cu Kα radiation (λ = 1.54 Å) from a 1.5 kW rotating anode generator. The powder sample of PMAChol−DTB was introduced into a glass capillary (diameter = 1 mm) and heated in an oil bath at 200 °C (higher than the isotropic-to-smectic transition) in order to remove air bubbles. The capillary was then cooled at room temperature for X-ray scattering experiment. The aqueous dispersion of diblock copolymers nano-objects were introduced into a capillary (diameter = 2 mm). The diffraction patterns were recorded on photosensitive imaging plates.

The morphological analysis of the aqueous dispersions of diblock copolymer nano-objects was then performed by transmission electron microscopy (TEM) on samples stained by uranyl acetate or by cryogenic transmission electron microscopy (cryo-TEM) on samples fast frozen in liquid ethane. The TEM images were recorded using a Philips CM120 electron microscope equipped with a Gatan SSC 1K_1K CCD camera, and the cryo-TEM images were recorded using a Philips CM 120 kV Lab6. Image acquisition and image analysis were performed on the PICT IBISA Imaging Facility.

Results and Discussion

1. Synthesis and Characterization of the Amphiphilic Block Copolymers. *Synthesis of the PMAChol-b-PDEAAm and PS-b-PDEAAm Amphiphilic Diblock Copolymers by RAFT.* In order to study the influence of the length of the hydrophilic PDEAAm block on the block copolymer self-assembly, four copolymers (Table 1, **P1−P4**) exhibiting the same hydrophobic LC block (M_n = 10 700 g mol^{-1}; DP_n = 19) but varying in the length of the hydrophilic block (M_n = 900−13 100 g mol^{-1}; DP_n = 7−103) were prepared. In a first step, the poly(cholesteryl methacryloyloxyethyl carbonate) macromolecular RAFT agent with a dithiobenzoate reactive end group (PMAChol−DTB) was synthesized by RAFT-mediated polymerization in 1,4-dioxane solution at 80 °C using CPADB (Scheme 1) as a reversible chain transfer agent. The polymerization was well controlled with M_n = 10 700 g mol^{-1}, a low polydispersity index (M_w/M_n = 1.12), and very high chain-end functionality. PMAChol−DTB was then chain-extended with DEAAm in 1,4-dioxane solution (a good solvent for the monomer and the block copolymer) at 80 °C. The polymerizations were quite fast, reaching high conversion within 3−4 h as illustrated in Figure 1a. They exhibited the characteristics of a controlled system with the linear increase of M_n with monomer conversion, low polydispersity indexes (Figure 1b), and a complete shift of the SEC peaks toward higher molar masses (Figure 2), indicating high crossover efficiency, due to favorable polymerization order. The experimental M_n values were below the theoretical line due to weakly adapted SEC calibration based on PMMA. A similar procedure was used to synthesize a model amphiphilic block copolymer composed of a hydrophobic polystyrene block (see the Experimental Section). All copolymer characteristics are summarized in Table 1.

Synthesis of the P(AA-co-PEGA)-b-PAChol and P(AA-co-PEGA)-b-PS Amphiphilic Diblock Copolymers by RAFT. A second type of block copolymer was synthesized where AChol (Table 1, **P6**) was used as the hydrophobic monomer,

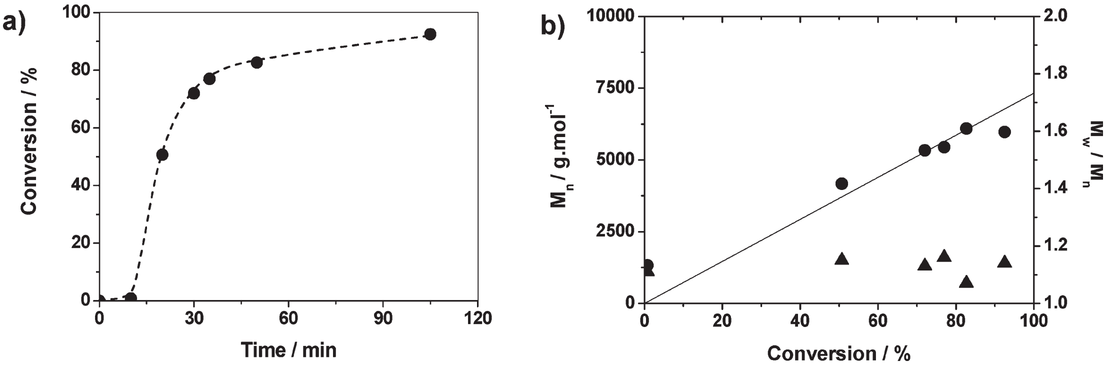


Figure 3. Copolymerization of acrylic acid (AA) and poly(ethylene glycol) methyl ether acrylate (PEGA) (initial molar ratio: 50/50) in the presence of TTCA in *N,N*-dimethylformamide at 80 °C: (a) evolution of the overall monomer conversion in % with time and (b) evolution of the number-average molar mass (M_n) (●) and M_w/M_n (▲) with conversion (M_n determined by size exclusion chromatography in THF using a polystyrene calibration). The straight line corresponds to the theoretical M_n values.

and the hydrophilic block was composed of a poly(acrylic acid-*co*-poly(ethylene glycol) methyl ether acrylate) random copolymer. A model amphiphilic block copolymer (Table 1, **P7**) exhibiting a hydrophobic polystyrene block (see the Experimental Section) was also synthesized. The choice of the hydrophilic segment was based on the previous results of self-assembly of PEG-*b*-PAChol diblock copolymers.[16,17] It was shown that PEG allowed polymersomes and fibers to be formed in aqueous dispersions, thanks to the steric stabilization imparted by this neutral hydrophilic block. Here we were interested in providing additional electrostatic stabilization via the use of the pH-sensitive acrylic acid units.

In a first step, the poly(acrylic acid-*co*-poly(ethylene glycol) methyl ether acrylate) macromolecular RAFT agent with a trithiocarbonate reactive end group (P(AA-*co*-PEGA)−TTC) (initial molar ratio AA/PEGA = 50/50) was prepared by RAFT-mediated polymerization in DMF solution at 80 °C using TTCA (Scheme 1) as a reversible chain transfer agent. The copolymerization of AA and PEGA was fast, reaching high conversion within 1−2 h as illustrated in Figure 3a. A short inhibition period of ca. 10 min was observed corresponding most probably to the RAFT pre-equilibrium stage. The number-average molar mass was $M_n = 8300$ g mol^{-1} at 77% conversion, and the polydispersity index ($M_w/M_n = 1.16$) was very low. The composition of the copolymer, 42 mol % of AA and 58 mol % of PEGA, was determined using ^{13}C NMR and was further confirmed with an acid−base titration. Those values indicate similar reactivities of the two comonomers, resulting in a rather low composition drift in the copolymer. P(AA-*co*-PEGA)−TTC was then chain-extended with AChol or S in 1,4-dioxane solution at 80 °C. Low polydispersity indexes (Table 1) and a complete shift of the SEC peaks toward higher molar masses (Figure 4) were observed in both cases.

From those results, it is clearly illustrated that RAFT is a very convenient method to synthesize the target amphiphilic diblock copolymers with very narrow molar mass distribution and well-defined composition and block lengths. The design of LC block copolymers with a tunable hydrophilic block (i.e., variable in nature, length, and composition) becomes thus easily feasible, hence pathing the way for the elaboration of a broad variety of new, self-assembled nano-objects.

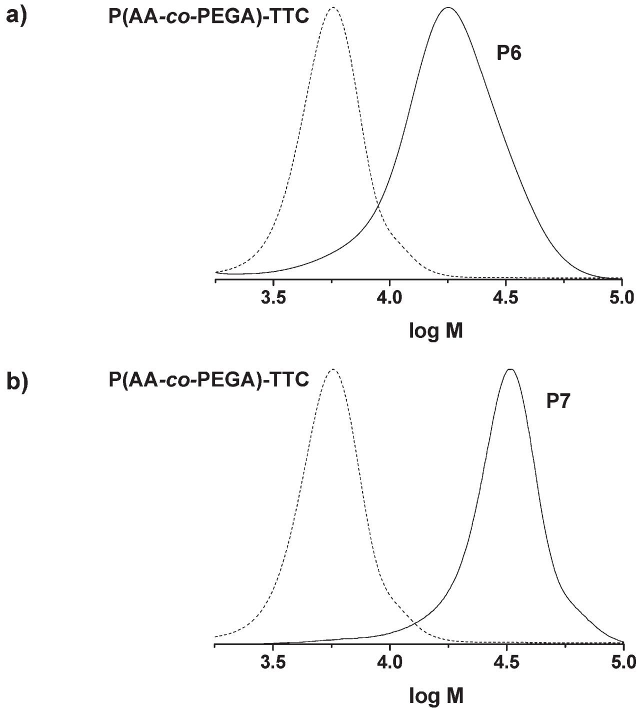
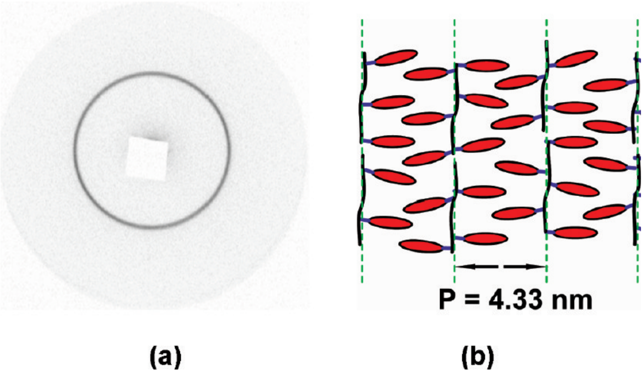


Figure 4. Size exclusion chromatograms of the poly(acrylic acid-*co*-poly(ethylene glycol) methyl ether acrylate), P(AA-*co*-PEGA)−TTC, macroRAFT agent, and of the diblock copolymers P(AA-*co*-PEGA)-*b*-PAChol, **P6** (a), and P(AA-*co*-PEGA)-*b*-PS, **P7** (b), obtained after chain extension in THF with cholesteryl acryloyloxyethyl carbonate and styrene, respectively (see Scheme 1 and Table 1).

2. Mesomorphic Properties of the Hydrophobic PMAChol Homopolymer. The hydrophobic blocks PMAChol and PAChol are composed of monomers containing a cholesteryl-based mesogenic group (see Scheme 1). The polymer PMAChol in its pure state, i.e., the PMAChol−DTB macroRAFT agent with $M_n = 10\,700$ g mol^{-1}, exhibits a thermotropic smectic A phase. This was indicated by the fan-shaped birefringent textures observed under polarizing microscope (see Supporting Information Figure SI-2) and confirmed by the small-angle X-ray scattering (SAXS) pattern with the Bragg reflection located at $q = 4\pi \sin(\alpha/\lambda) = 2\pi/P$ (q is the wave vector and 2α is the scattering angle) (see Figure 5a). It was deduced that the smectic layer spacing was $P = 4.33$ nm, which is between l and $2l$, $l = 2.78$ nm being the extended mesogen length estimated by Dreiding models (including the methyl group in the polymethacrylate backbone). Therefore, the mesophase was an interdigitated smectic A phase (SmA$_d$),[32] as shown in Figure 5b. The complete phase sequence of the homopolymer PMAChol−DTB is g−80 °C−SmA$_d$ 155 °C−I, as determined by differential scanning calorimetry at 10 °C min^{-1} (see Supporting Information



(a) (b)

Figure 5. (a) Small-angle X-ray scattering pattern of the poly(cholesteryl methacryloyloxyethyl carbonate) (PMAChol) homopolymer. (b) Molecular organization model, where the red ellipsoids represent the cholesteryl-based mesogens and the black lines the polymethacrylate backbones.

Figure SI-3). The polymer PAChol in its pure state exhibits also an interdigitated SmA_d phase as already discussed in a previous paper.[16,17] The phase sequence of the homopolymer PAChol with M_n = 5230 g mol^{-1} and M_w/M_n = 1.11 is g−68 °C−SmA_d 156 °C−I, and the smectic layer spacing is P = 4.29 nm.

We will next investigate the self-assembly of the amphiphilic diblock copolymers containing these smectic hydrophobic blocks in a selective solvent. The key questions are the role of the smectic order in the self-assembling and whether the smectic order persists in the self-assemblies.

3. Self-Assembly of the PMAChol-*b*-PDEAAm and PS-*b*-PDEAAm Diblock Copolymers in Water. Self-assemblies of the PMAChol-*b*-PDEAAm diblock copolymer series (**P1**−**P4** in Table 1) in dilute water solution were performed with the aid of the cosolvent 1,4-dioxane to favor the initial solubilization of the diblock copolymer and plasticize the hydrophobic block during the self-assembling process. As detailed in the Experimental Section, the block copolymers were first dissolved in 1,4-dioxane, and deionized water was added very slowly to the solution up to a water concentration of about 50 wt % (see Supporting Information, Figure SI-4 for turbidity curves as a function of the quantity of added water). The turbid suspensions were then dialyzed against deionized water to remove all dioxane. For comparison, self-assembly of a non-LC block copolymer, PS-*b*-PDEAAm (**P5**), which had the same molar mass and hydrophobic/hydrophilic ratio as **P2**, was also prepared in a similar way. The morphological analysis of the particles in the final water suspensions was then performed by TEM on samples stained by uranyl acetate or by cryo-TEM on sample fast frozen in liquid ethane.

A rapid analysis by TEM with negative staining revealed that all block copolymers formed nano-objects in water (see Figure 6), except the most hydrophobic block copolymer **P4** (hydrophobic/hydrophilic ratio = 92/8), which was unable to form well-defined nano-objects, but collapsed to form macroscopic aggregates. Most of the nano-objects formed by **P1** (hydrophobic/hydrophilic ratio = 45/55) were cylindrical and some of them spherical. The diameter of the cylinders and spheres was around 25−30 nm, while their length varied from 25 to 500 nm. More interestingly, the copolymer **P2** (hydrophobic/hydrophilic ratio = 74/26) formed very long nanofibers (50 nm to 1 μm in length and 25−30 nm in diameter). The copolymer **P3** (hydrophobic/hydrophilic ratio = 80/20) formed again nanospheres or cylinders, but the length of the cylinders was smaller than 200 nm. From the present data, we cannot explain the large difference of morphology between **P2** and **P3**, in which the molar composition was rather close. The PS-*b*-PDEAAm (**P5**) copolymer, a non-LC analogue of **P2**, formed only spherical vesicles with rather heterogeneous sizes, of 50−300 nm in diameter (Figure 6, **P5**).

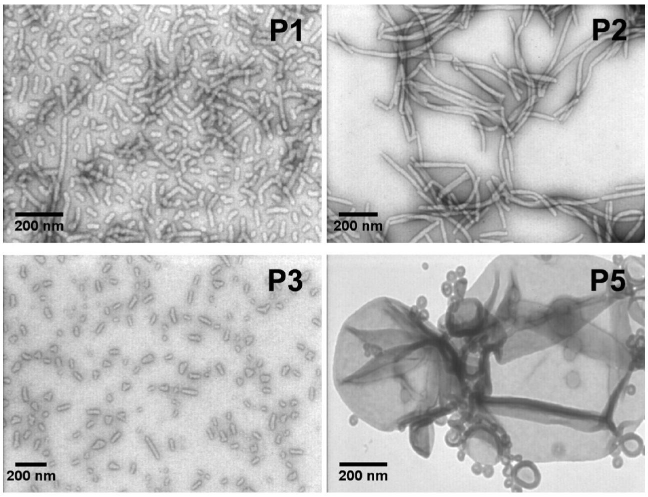


Figure 6. Transmission electron micrographs of self-assemblies of amphiphilic diblock copolymer in water: poly(cholesteryl methacryloyloxyethyl carbonate)-*b*-poly(*N*,*N*-diethylacrylamide), PMAChol-*b*-PDEAAm, **P1**, **P2**, **P3**, and polystyrene-*b*-poly(*N*,*N*-diethylacrylamide (PS-*b*-PDEAAm), **P5** (see Table 1 and Scheme 1). Scale bar = 200 nm.

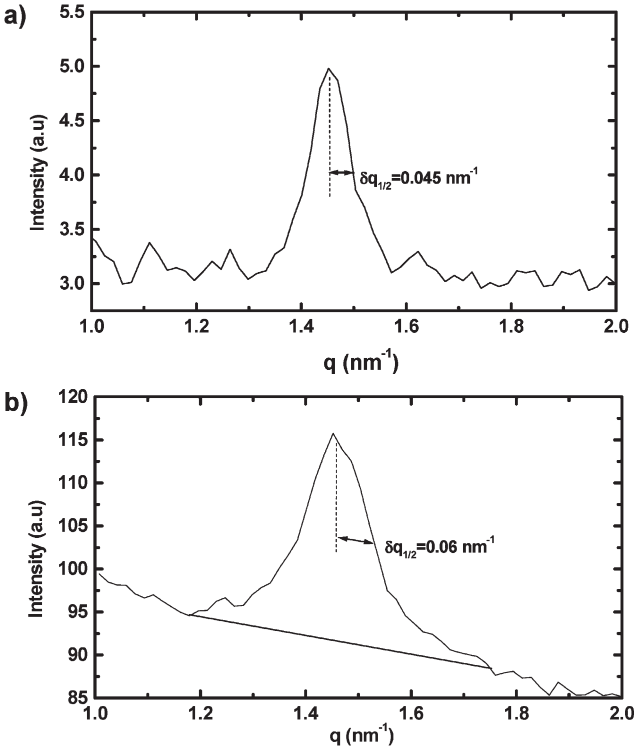


Figure 7. Small-angle X-ray scattering intensity as a function of the wave vector for the self-assemblies in water of the poly(cholesteryl methacryloyloxyethyl carbonate)-*b*-poly(*N*,*N*-diethylacrylamide), PMAChol-*b*-PDEAAm, diblock copolymers **P1** (a) and **P2** (b) (see Table 1). $\delta q_{1/2}$, i.e., half-width at half-maximum, of the scattering intensity peak are indicated. The experimental resolution $\delta q_{1/2(\mathrm{R})}$ was around 0.03 nm^{-1}.

In order to know whether the smectic order persisted in the nano-objects formed by the PMAChol-*b*-PDEAAm diblock copolymer series, aqueous dispersions of **P1** and **P2** were

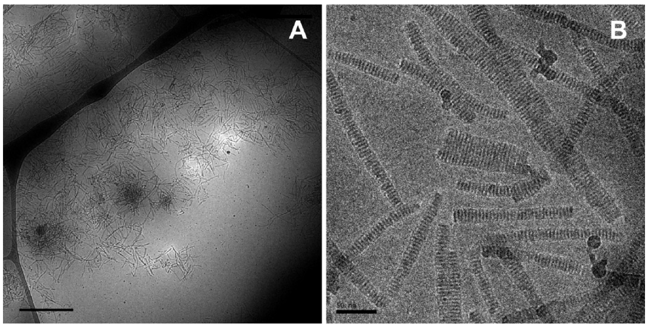


Figure 8. Cryo-TEM images of the water suspension of the poly(cholesteryl methacryloyloxyethyl carbonate)-*b*-poly(*N*,*N*-diethylacrylamide), PMAChol-*b*-PDEAAm, diblock copolymer **P2**. (A) Scale bar = 1 μm. (B) Scale bar = 50 nm.

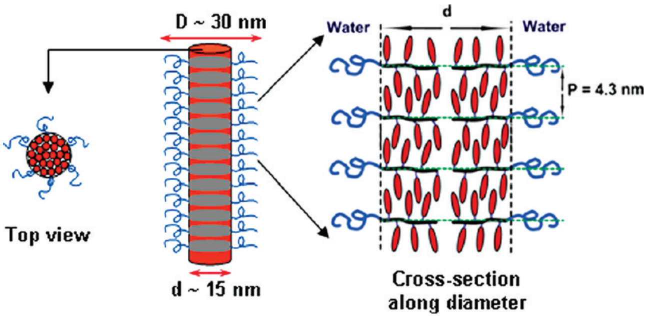


Figure 9. Schematic representation of the smectic nanofibers formed by self-assembly of the amphiphilic block copolymers containing an end-on liquid crystalline block via the cosolvent method.

analyzed by SAXS. Bragg reflection (see Figure 7) revealed a positional order of 4.33 nm, which was in good agreement with the layer spacing of $\mathrm{SmA_d}$ structure of the LC block. Note that the Bragg peaks were rather sharp with a narrow hwhm (half-width at half-maximum, $\Delta q_{1/2}$ in Figure 7). The correlation length of the smectic structure L was estimated by the Scherrer formula: $L = 0.9\pi/(\delta q_{1/2}{}^2 - \delta q_{1/2(\mathrm{R})}{}^2)^{1/2}$, where the experimental resolution $\delta q_{1/2(\mathrm{R})}$ was around 0.03 nm^{-1}. We found $L_{\mathbf{P1}} = 54$ nm for the copolymer **P1** and $L_{\mathbf{P2}} = 84$ nm for the copolymer **P2**. This means that the smectic layer normal should be along the long axis of the fibers, but not along their diameter, which was found to be only in the 25−30 nm range. It is also reasonable to find $L_{\mathbf{P2}}$ larger than $L_{\mathbf{P1}}$ because the fibers were in average longer for copolymer **P2** than for **P1** (see Figure 6).

The water suspension of **P2** was then investigated by cryo-TEM in order to confirm the detailed structure of the nanofibers (see Figure 8). As shown in Figure 8A with a 3000× magnification, the nanofiber lengths were in average between 100 and 500 nm. The high-magnification cryo-TEM image (Figure 8B) clearly shows the smectic structure with a layer spacing of 4.3 ± 0.1 nm and the layer normal along the long axis of the nanofibers. The diameter of the hydrophobic domain was in average between 10 and 16 nm (cryo-TEM reveals only the hydrophobic LC part). Our smectic polymer nanofibers were then very similar to those observed in the PEG-*b*-PAChol series reported previously.[17] On this basis, a schematic representation of the molecular organization in the nanofibers is proposed in Figure 9, highlighting the role of the smectic order in the hydrophobic domain.

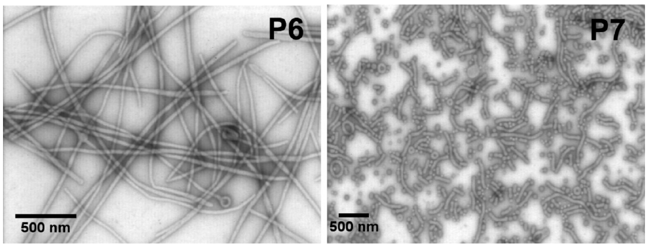


Figure 10. Transmission electron micrographs of the dried aqueous assemblies of poly(acrylic acid-*co*-poly(ethylene glycol) methyl ether acrylate)-*b*-poly(cholesteryl acryloyloxyethyl carbonate), P(AA-*co*-PEGA)-*b*-PAChol, **P6** (left), and poly(acrylic acid-*co*-poly(ethylene glycol) methyl ether acrylate)-*b*-polystyrene, P(AA-*co*-PEGA)-*b*-PS, **P7** (right), diblock copolymers at pH = 7.2. Scale bar = 500 nm (see Scheme 1 and Table 1).

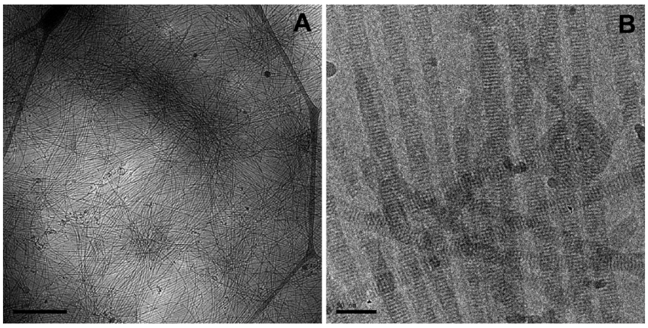


Figure 11. Cryo-transmission electron microscopy (TEM) images of the nanofibers formed with the liquid crystal poly(acrylic acid-*co*-poly(ethylene glycol) methyl ether acrylate)-*b*-poly(cholesteryl acryloyloxyethyl carbonate), P(AA-*co*-PEGA)-*b*-PAChol, diblock copolymer **P6**, self-assembled in water buffered at pH = 7.2. (A) Scale bar = 1 μm. (B) Scale bar = 50 nm (see Scheme 1 and Table 1).

In conclusion, the cholesteryl-based hydrophobic block in the amphiphilic block copolymer self-assemblies maintained its smectic LC order and influenced the morphology of the formed nano-objects. Indeed, with similar block ratio, the smectic block copolymer (**P2**) formed nanofibers, whereas the non-LC block copolymers (**P5**) formed vesicles with different sizes.

As the PDEAAm hydrophilic block is a temperature-sensitive polymer with a LCST around 32 °C, we studied also the response of the nano-objects to a temperature change. Self-assemblies were first prepared at 4 °C with **P1** and **P2** (dialysis also performed at 4 °C). TEM with negative staining showed that the nano-objects were long nanofibers for **P2** and short cylinders for **P1**. When heating to 60 °C was performed (i.e., above the LCST of PDEAAm, which then became hydrophobic), precipitation could be followed by eyes. After cooling to room temperature, the sample was re-analyzed by TEM with negative staining. Interestingly, we found the same nanofibers as before. This temperature sensitivity might be used to easily recover or concentrate the nano-objects without using high-speed centrifugation.

4. Self-Assembly of Diblock Copolymers P(AA-*co*-PEGA)-*b*-PAChol and P(AA-*co*-PEGA)-*b*-PS in Water. Self-assemblies of P(AA-*co*-PEGA)-*b*-PAChol (**P6**) and of its non-LC homologue P(AA-*co*-PEGA)-*b*-PS (**P7**) in dilute aqueous solution were performed in the same way as described above, except that aqueous buffer solutions at pH = 7.2 and at pH = 4.0 were used in place of deionized water (in the water addition step and in the dialysis process) (see Supporting Information, Figure SI-5, for turbidity curves as a function of the quantity of added buffer solution at pH = 7.2). For the block copolymer **P6** in the buffer solution at pH = 7.2, the TEM images in Figure 10 show the formation of very long nanofibers, which were of several micrometers in length and of 25−40 nm in diameter. At pH = 4.0, the nano-objects were very similar to those formed at pH = 7.2. In contrast, the non-LC homologue, P(AA-*co*-PEGA)-*b*-PS (**P7**), formed spherical or cylindrical (length < 500 nm) micelles. As shown by the cryo-TEM image of the nanofibers formed by **P6** at pH = 7.2 (Figure 11), a smectic order was also clearly observed. Again, we confirm the conclusion of the preceding section: a smectic hydrophobic block favors the formation of long nanofibers, in which the layer structures persist. The advantage of the P(AA-*co*-PEGA)-*b*-PAChol block copolymer is that it possesses functional groups (−COOH) in the hydrophilic shell of the nanofibers. This opens up the possibility to make functionalized nano-objects, which may find interesting applications in bioengineering.

Conclusion

Two families of amphiphilic diblock copolymers, in which the hydrophobic block was a cholesteryl-based smectic LC polymer and the hydrophilic block was either a neutral polymer with a LCST or a copolymer containing acrylic acid moieties and poly(ethylene oxide) side chains, were successfully synthesized by RAFT-mediated controlled radical polymerization. Nanoassemblies of these amphiphilic species in water or in buffer solution were prepared using the cosolvent method. The morphology of the nanoassemblies clearly depended on the weight fraction and the nature of the hydrophobic block in the diblock copolymer. Irrespective of the nature of the hydrophilic part, the amphiphilic LC block copolymers with a hydrophobic/hydrophilic weight ratio of 74/26 (PMAChol-*b*-PDEAAm) or 65/35 (P(AA-*co*-PEGA)-*b*-PAChol) formed very long nanofibers. In a different way, the non-LC copolymers based on polystyrene with similar ratio formed vesicles or short cylindrical micelles. Such morphologies were assigned to the presence of a smectic order in the hydrophobic domain of the assemblies, as revealed by SAXS. Cryo-TEM allowed the direct imaging of the smectic order with the layer normal parallel to the nanofiber long axis. These nanofibers with thermoresponsive or functionalizable hydrophilic surface may find applications in biotechnology.

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Supporting Information Available: NMR characterization of the monomers, kinetics of MAChol polymerization in the presence of CPADB, detailed experimental conditions for the synthesis of the amphiphilic diblock copolymers, birefringent textures of the PMAChol−DTB macroRAFT agent observed under polarizing microscope, differential scanning calorimetry of the PMAChol−DTB homopolymer, turbidity curves for the diblock copolymers self-assembling procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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