End Group Polarity and Block Symmetry Effects on Cloud Point and Hydrodynamic Diameter of Thermoresponsive Block Copolymers

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ABSTRACT: Thermoresponsive block copolymers are of interest for delivery vehicles in the body. Often an interior domain is designed for the active agent and the exterior domain provides stability in the bloodstream, and may carry a targeting ligand. There is still much to learn about how block sequence and chain end identity affect micelle structure, size, and cloud points. Here, hydrophilic oligo(ethylene glycol) methyl ether acrylate and more hydrophobic di(ethylene glycol) methyl ether methacrylate monomers were polymerized to give amphiphilic block copolymers with amphiphilic chain ends. The block sequence and chain end identity were both controlled by appropriate choice of RAFT chain transfer agents to study the effect of 'matched' and 'mismatched' chain end polarity with amphiphilic block sequence. The affect of matching or mismatching chain end polarity and block sequence was studied on the hydrodynamic diameter, cloud point, and temperature range of the chain collapse on linear di- and triblock copolymers and star diblock polymers. The affects of matching or mismatching chain end polarity were significant with linear diblock copolymers but more complex with triblock and star copolymers. Explanations of these results may help guide others in designing thermoresponsive block copolymers. © 2015 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2015**, *53*, 2838–2848

KEYWORDS: block copolymers; end group polarity; hydrodynamic diameter; light scattering; star polymers; stimuli-sensitive polymers

INTRODUCTION Stimuli-responsive (co)polymers are "smart" materials that undergo significant conformational changes when environmental conditions are changed appropriately.[1] Typical stimuli include change in temperature,[2–4] pH,[5] intensity of light,[6] and humidity.[7] They have been extensively investigated for biomedical uses, especially for drug (or other active ingredient) delivery.[8,9] Thermoresponsive materials that possess a "Lower Critical Solution Temperature" (LCST) are of interest as drug delivery vehicles.[2] The LCST is usually approximated as the cloud point (CP) of a solution, and is measured by a change in light transmission resulting from phase separation of the polymer from the solvent.

The CP of a polymer depends on the balance between changes in enthalpy arising from hydrogen bonding between water and polymer and entropy when this bonding is broken and the water molecules are no longer ordered around the polymer.[10–12] Specifically this means the the CP is not only controlled by polymer composition but to a greater or lesser degree on degree of polymerization, polydispersity, end groups, and architecture.[13–18] For a given composition it can also vary with the concentration of the solution being tested. However, the magnitude of each of these effects depends on the specific polymer being studied.[18,19] For example poly(*N*-isopropylacrylamide) (PNIPAM),[19] which is probably the most studied stimuli–response polymer, has a CP that is relatively independent of molecular weight and end group. For example, the CP of PNIPAM with *tert*-butyl and methyl end groups and a 30-fold difference in molecular weight, 1.78×10^4 g/mol versus 4.75×10^5 g/mol, had less than 1 °C difference, that is, 30.83 °C to 30.18 °C. In fact, the influence of various chain end groups (*tert*-butyl, methyl, trityl and amide) on the CP of PNIPAM was similarly negligible, ranging from only 29.74 °C to 30.83 °C. PNIPAM backbones may be relatively unaffected by these changes because the repeat unit contains amide groups, so the effects of two end groups that both interact with the same homopolymer domain, are relatively insignificant. This may also explain why more flexible thermoresponsive polymers show more significant effects from changes in end group identity.[20]

Studies of linear and branched PNIPAM copolymers with an imidazole comonomer showed significant effects of architecture on CP.[21] Depending on the monomer composition, the

Additional Supporting Information may be found in the online version of this article.

CP of the linear PNIPAM copolymers ranged from 32 to 20 °C, while the CP of the different branched PNIPAM copolymers ranged from 29 to 11 °C. The CP declined as the imidazole comonomer content rose in both linear and branched copolymers. These copolymers were made using reversible addition−fragmentation chain transfer (RAFT) polymerization, giving polymers asymmetric end groups, but the reduction in CP is primarily attributed to the imidazole groups forming stronger hydrogen bonds with each other. However, the branched PNIPAM copolymers also had a lower CP than linear PNIPAM copolymers at the same monomer ratio. This suggests that the linear copolymers yielded more stable micelles than did the branched ones.

The LCST of triblock copolymers[18] (ABC type) and their aggregation behavior have been studied.[3] One of the thermoresponsive blocks was hydrophilic and nonionic [(ethylene glycol) methyl methacrylate, EGMA], the second block (*N,N*-dimethylaminoethyl methacrylate, DMAEMA) was both hydrophilic and ionizable, and the third block (n-butyl methacrylate, BuMA) was hydrophobic and nonthermoresponsive. The researchers found that by altering the position of the hydrophobic block, but maintaining the overall composition, the CP ranged from 54 to 72 °C. They attributed the effect to the position of the hydrophobic block altering the micelle structure. Another study of triblock copolymers with one hydrophilic block and two thermoresponsive blocks[3] reported that changes in micellar shape and size were controlled by temperature.

Polymers from di(ethylene glycol) methyl ether methacrylate (DEGMA $M_n = 188$ g/mol) and oligo(ethylene glycol) methyl ether acrylate (OEGA $M_\mathrm{n} = 480$ g/mol) are a newer class of thermoresponsive materials, with excellent potential as smart biocompatible materials.[3,10,11] These EG-based monomers can be polymerized to give polymers with well-defined structure, composition, and tunable LCST using controlled radical polymerization methods. They can also produce thermoresponsive nanoparticles (NPs) with EG moieties already at the aqueous interface. That allows them to be used as drug delivery vehicles and administered into the bloodstream without additional surface modification to resist nonspecific protein absorption, extending survival time in the blood. A diblock copolymer using these monomers was thought to have value for "surfactant on demand" applications[3] since the CP of these blocks can be tuned over a broad temperature range compared with PNIPAM.[22]

Overall the evidence of end group effects on CP is still somewhat conflicting, largely because the studies involve different polymers and copolymers, molecular weights, architectures, etc. However, the overall weight of the evidence suggests that micelles form below the CP and that hydrophobic chain ends promote this formation, while hydrophilic chain ends effect the hydration and organization of the (co)polymer below the CP.[3] Nevertheless, additional research is needed, especially in the area of amphiphilic diblock copolymers, where there is little prior research.

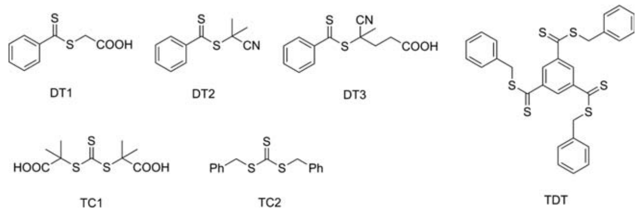


FIGURE 1 CTAs to be studied.

We previously[22] studied the effect of diblock sequence on the CPs of linear diblock copolymers of DEGMA and OEGA with amphiphilic chain ends (dithioester and carboxylic acid). The CP of a series of copolymers, with the same block sequence, rose linearly as the hydrophilic block length rose, as expected. Less expected though was that the difference in CP of diblock copolymers with similar composition but different block sequence could be as little as 1.0 °C or as much as 28.0 °C. While molecular weight was previously shown to not significantly affect the CP[23] designing amphiphilic block copolymers with amphiphilic end groups has a significant impact on the CP. This likely arises from the effects on chain conformation and how the different chain end groups interact with the different polymer domains.

Here we continue our study of asymmetric end group effects on the CP of DEGMA and OEGA block copolymers to include additional end groups, and architecture. Our overall objective is to better understand these effects on amphiphilic block copolymers from EG-containing monomers, because their CPs can be tuned over a broad range and their biocompatibility and resistance to protein absorption make them increasingly important copolymers for drug delivery vehicles.

Figure 1 shows the structure of and abbreviations used for the six CTAs that are studied in this paper. Illustrations of the block structures and abbreviations for the diblock copolymers in this work are given in Figure 2.

EXPERIMENTAL

Materials

Di (ethylene glycol) methyl ether methacrylate (DEGMA $M_\mathrm{n} = 188.2$ g/mol) and oligo (ethylene glycol) methyl ether acrylate (OEGA $M_\mathrm{n} = 480$ g/mol) were purified by passing over a neutral aluminum oxide column to remove residual inhibitor. 2, 2′-Azoisobutyronitrile (AIBN) was recrystallized from ethanol. The following reagents were used as received: carbon disulfide, chloroform, acetone, sodium hydroxide, ligroin, hydrochloric acid, benzene tricarboxylic acid, benzyl mercaptan, phosphorus pentasulfide, 1,4-dioxane, tetrabutylammonium hydrogen sulfate, hexane, *S*-(thiobenzoyl)thioglycolic acid (DT1) 2-cyano-2-propyl benzodithioate (DT2), and 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (DT3). The remaining CTAs were synthesized using procedures given below.

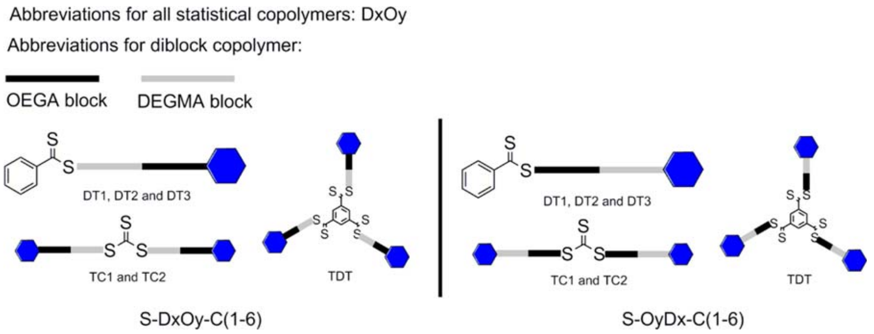


FIGURE 2 This graphical illustration (blue hexagons represent the "C" end) is used to give a simplified image of polymer structure, and show their abbreviated designations. "S" as a chain end refers to a dithioester or trithiocarbonate group from the CTA, while "C" refers to the other chain end resulting from an asymmetric CTA. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

CTA Synthesis

Synthesis of S, S′-bis(α,α′-dimethylacetic acid) trithiocarbonate (BDAT/TC1)

TC1 was synthesized according to a published method (Scheme 1).[24] Carbon disulfide (2.74 g, 0.036 mol), chloroform (10.75 g, 0.09 mol), acetone (5.23 g, 0.09 mol), and tetrabutylammonium hydrogen sulfate (0.241 g, 0.071 mol) were mixed with 12 mL of ligroin in a 250 mL round bottom. Then NaOH solution (50%, 20.16 g) was added dropwise into the mixture over 1.5 h while maintaining the temperature below 25 °C. After the addition was complete the reaction was maintained at 22–25 °C for 12 h while being stirred with a magnetic stirrer. Once the reaction was completed, 90 mL H_2O was added to dissolve the yellow solids, followed by adding 12 mL of HCl_{conc} to acidify the aqueous solution and yield crystalline solids. After filtration and washing several times by H_2O, the crude compound (3.26 g, 32.11%) was purified by recrystallization in toluene and acetone (3:1 v/v). ^{1}H NMR ($CDCl_3$): 1.68 (s, —$C\underline{H}_3$, 12H), Supporting Information Figure S1.

Synthesis of Dibenzyl trithiocarbonate (TC2)

TC2 was synthesized following the method given in a published paper[25] (Scheme 2): Carbon disulfide (800 mg, 10.5 mmol) and benzyl chloride (1.27 g, 10.0 mmol) were added into 10 mL DMF. The reactor was placed in an ice bath and then potassium carbonate (1.38 g, 10.0 mmol) was added into the DMF solution. The reaction mixture was stirred and maintained at 40 °C for 24 h before being quenched by pouring into ice water. The mixture was extracted by ethyl acetate and dried with anhydrous sodium sulfate. After filtering and removing the solvent, a yellow oil product was obtained (2.60 g, 89.66%). ^{1}H NMR ($CDCl_3$): 4.60 (s, Ar—$C\underline{H}_2$— 4H), 7.21–7.35 (m, Ar—$\underline{H}$, 10H), Supporting Information Figure S2.

Synthesis of 1,3,5-Benzenetricarbodithioic acid (TDT)

TDT was prepared using a known procedure[26] (Scheme 3): Benzene tricarboxylic acid (2.00 g, 0.0095 mol), benzyl mercaptan (3.50 g, 0.029 mol), P_4S_{10} (3.18 g, 0.0072 mol), and dioxane (150 mL) were introduced into a three-necked flask. The mixture was heated and maintained at reflux (100 °C) for 24 h. The solution was concentrated down to about 20% of the original volume, and the solid waste product was removed by filtration. Then CH_2Cl_2 was added to the filtrate, and the mixture was filtered a second time. The solution was then passed through a short silica gel column using hexane:CH_2Cl_2 (5:1) as eluent. The crude compound was then purified through a second column of silica gel using hexane:EtOAc (9:0.5) as eluent (yield = 12.1%). ^{1}H NMR ($CDCl_3$): 4.58 (s, —S—$C\underline{H}_2$—, 6H), 7.23–7.58 (m, CH_2—Ar$\underline{H}$, 15H), 8.68 (s, Ar$\underline{H}$, 3H), Supporting Information Figure S3.

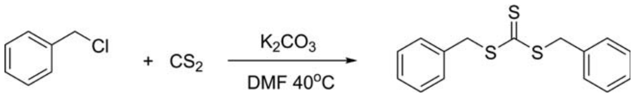
Synthesis of Statistical P(DEGMA-co-OEGA) (D_xO_y) Copolymer

A typical RAFT synthesis procedure is illustrated in Scheme 4. An example procedure, using DT3 as CTA, is as follows: DEGMA (1.88 g, 0.01 mol), OEGA (4.80 g, 0.01 mol), DT3 (0.056 g, 2×10^{-4} mol) and AIBN (0.0033 g, 2×10^{-5} mol) were dissolved in 1,4-dioxane (30 mL) and the mixture was degassed with N_2 for 30 min. The RAFT polymerization was performed at 85 °C with continuous stirring while under the protection of N_2 gas. After 48 h, the mixture was concentrated using a rotary evaporator and precipitated three times in cold hexane (0 °C, ice bath). The product was dried in vacuo at 80 °C for 3 h to obtain a viscous copolymer (5.84 g) with a yield of 86.6%.

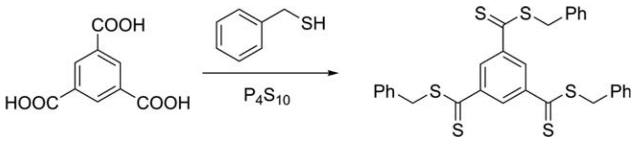
Synthesis of Diblock P(DEGMA-b-OEGA) Copolymers (S-D_xO_y-C(1–6) and S-O_yD_x-C(1–6)) by Two-Step RAFT Polymerization

All the diblock copolymers were synthesized in a similar way, exemplified here by the synthesis of S-$D_{50}O_{50}$-C with DT3 (Scheme 5). OEGA (4.8 g, 0.01 mol), DT3 (0.056 g, 2×10^{-4} mol), AIBN (0.0016 g, 1×10^{-5} mol) and 1, 4-dioxane (30 mL) were mixed and degassed for 30 min. The mixture

SCHEME 1 TC1 synthesis.



SCHEME 2 TC2 synthesis.



SCHEME 3 TDT synthesis.

was heated at 85 °C under the protection of N_2 (g) for 48 h. The resulting macro-CTA (S-O_{50}-C) was isolated by concentration using a rotary evaporator. The crude product was precipitated three times in cold hexane (0 °C, ice bath). After drying at 80 °C for 3 h *in vacuo*, the purified macro-CTA was obtained (4.40 g, 90.6%).

In the second step, the macro-CTA (S-O_{50}-C), DEGMA (1.88 g, 0.01 mol), AIBN (0.0016 g, 1×10^{-5} mol) and 1,4-dioxane (30 mL) were mixed and degassed for 30 min, and then heated and stirred for 48 h at 85 °C under N_2 gas protection. The reaction mixture was concentrated and precipitated in cold hexane (0 °C, ice bath) and dried *in vacuo* at 80 °C for 3 h. The overall yield of S-$D_{50}O_{50}$-C is 82.1% (5.53 g). They were then dialyzed for 3 days using dialysis tubes with a 3500 cut off.

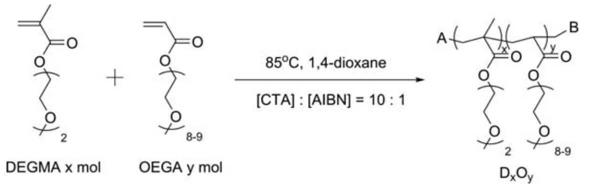
Characterization

^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Unity Inova400 at 400 MHz. F_o is the ratio of OEGA in the diblock copolymer which was calculated using the integration values from ^{1}H NMR spectra. The full details of the calculation and methods are given elsewhere.[22] The NMR spectrum in Figure 3 identifies key hydrogen bands, whose populations were calculated by eq 1 for F_o:

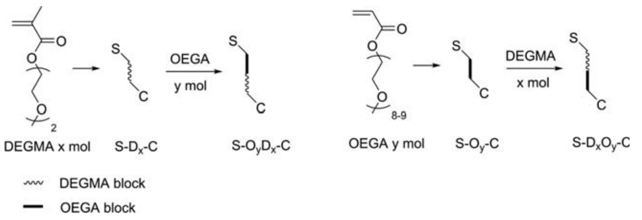
Fo calculation:

$$\frac{3\times(1-F_0)+3\times F_0}{6\times(1-F_0)+32\times F_0}=\frac{\text{Integration of } H_\text{d}}{\text{Integrations of } \left(H_\text{f}+H_\text{g}+H_\text{h}+H_\text{i}\right)} \tag{1}$$

UV–vis spectra were recorded using a Perkin Elmer UV/vis spectrometer (Lambda 35) equipped with a Peltier based temperature controller. All the CPs of the aqueous copolymer solutions were determined at a wavelength of $\lambda = 500$ nm. The aqueous solutions were loaded into quartz cuvettes at a concentration 7.5 ± 2.5 mg/mL so that the initial transmittance (T%) was 90%. The transmittance (T%) was recorded at each 1 °C interval, using a heating/cooling rate of 1 °C/min. When the temperature approached the CP ($\Delta T\% > 2\%$), the heating/cooling rate was lowered to 0.1 °C/min. At each temperature where T% was to be measured the solution was maintained for 2 min at that temperature before the T% was recorded to ensure the transmittance was stable. The test was concluded when the T% decreased to a minimum of 2% of the maximum T%. Then, all the transmittance values were normalized on to a 0–100% scale. The CP curves were then plotted with normalized transmittance values versus temperature. The temperature value of the normalized $T\% = 50\%$ was defined as the CP. The transition range (ΔT) of the copolymer was defined as the change of the temperature values from $T\% = 90\%$ to $T\% = 10\%$.



SCHEME 4 Statistical copolymer synthesis.



SCHEME 5 Diblock copolymer synthesis.

A dynamic light scattering (DLS) instrument (Coulter NP4 plus, Beckman Coulter, Fullerton, CA) was used to test the hydrodynamic diameter (D_h) of the copolymer in aqueous solutions.

Molecular weights were determined by gel permeation chromatography (GPC, Viscoteck GPCmax VE2001, Malvern Instruments Ltd, UK), equipped with Viscotek 270 dual detector and VE 3580 RI detector. One SDV GPC Analytical column of 1000 Angstrom, 5 μm and dimension of 8 × 300 mm (Polymer Standard Service, USA) and THF were used as stationary and mobile phases, respectively. 1.0 mg/mL of each polymer sample in THF solution was prepared and filtered through 0.2 μm syringe filter before injection with 100 μL for test. Poly(ethylene glycol) (Polymer Standard Service, USA) was used as standards for molecular weight calibration with a concentration of 1.0 mg/mL. The calibration data are in Supporting Information Table S1 and Supporting Information Figure S4, and a representative spectrum is given in Supporting Information Figure S5.

RESULTS AND DISCUSSION

The statistical (control) and block copolymers of OEGA and DEGMA were prepared using three different categories of CTAs, with the theoretical ratio of OEGA to DEGMA at 50:50. After the composition was confirmed to be similar to the theoretical composition the effects of end group and architecture were studied on nanoparticle size, CP, and the temperature range of the coil–globule transition. The copolymer composition, D_h, CP, and ΔT are all given in Table 1. The theoretical number-average molecular weight is defined as shown in eq 2:

The theoretical number-average molecular weight calculation:

$$M_\text{n}(\text{th})=\frac{[DEGMA]_\text{o}\times M(DEGMA)+[\text{OEGA}]_\text{o}\times M(\text{OEGA})}{[CTA]_\text{o}}+M(\text{CTA}) \tag{2}$$

In eq 2, [DEGMA]o, [OEGA]o, and [CTA]o are the initial concentrations of the monomers and CTA, while M(DEGMA),

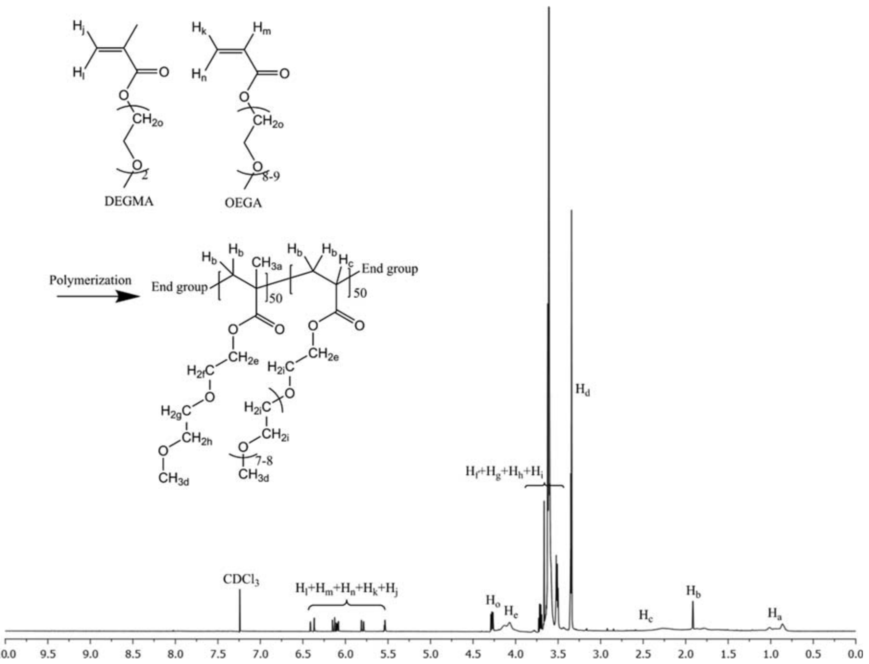


FIGURE 3 NMR spectrum of copolymer with the responsible hydrogen atoms identified.

M(OEGA), and *M*(CTA) are their molecular weight. The molecular weight of S-$D_{50}O_{50}$-C1 and S-$O_{50}D_{50}$-C1 were measured by matrix-assisted laser desorption/ionization—time of flight (MALDI-TOF). All the specimens were tested by GPC and showed a molecular weight similar to theoretical but often a broad PDI attributed to a high molecular weight fraction not separated by the dialysis tube. Most of the PDIs were between 2.46 and 3.72, but two were above 4 and 2 were above 5 (Supporting Information Table S2). However, several other researchers have indicated the CPs of these polymers are not significantly altered by molecular weight differences.[19,23,27] That seems to be the case here also, as the specimens with the broadest PDI (the star polymers at 5.69 and 5.86, and S-$D_{50}O_{50}$-C3 at 4.71) had CPs that occurred over a narrow temperature range (Table 1). For example the star polymers collapsed over a 2.0 and 1.2 °C range. Also, S-$D_{50}O_{50}$-C3 with its 4.71 PDI collapsed over a 3.5 °C range while S-$O_{50}D_{50}$-C3 had a PDI of 2.47 and collapsed over a 7.5 °C range.

Measured Copolymer Composition

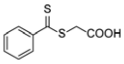
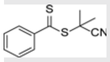
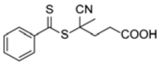
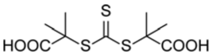
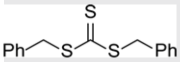
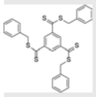
The copolymer composition was measured using ^{1}H NMR, and is reported as F_o. The F_o of the statistical copolymer is close to the theoretical 50% (47–55%) for all the copolymers regardless of the CTA used. Therefore, these CTAs did not significantly affect the reaction of the two monomers. However, the order of monomer addition used to synthesize the diblocks does effect the composition of the diblock copolymers.

Specifically, the F_o in S-Dx**Oy**-C (O block formed first), ranged from 46 to 57% which is similar to the range found for the statistical copolymers, but when we reversed the order of monomer addition, to produce S-Oy**Dx**-C and the D block first, F_o was even higher, ranging from 60 to 72%. The effect on overall copolymer composition arises because of the effect of the pendent EG chain (oligoethylene oxide with 8–9 pendent EG groups versus diethylene glycol with only 2 pendant EG groups) on the solvation and mobility of the growing chain end. That is, by reacting the OEGA first, the longer EG side chain of the OEGA allows the polymer to retain greater solvation and mobility, which increases the yield of OEGA. The compositional differences shown in Table 1 show that OEGA consistently yields higher reaction efficiency than DEGMA. Conversely, when the DEGMA is reacted first, the resulting polymer is less soluble and this slows the reaction with respect to DEGMA. We propose this as the major reason for the differences in composition, although it cannot be ignored that some reactivity difference in the monomers can be attributed to the methyl group on the radical-bearing carbon of DEGMA lowering the reactivity compared to OEGA. This is because the methyl groups add electron density to the propagating radical chain end and perhaps some additional steric hindrance, but those effects are inherent to the monomer and independent of block sequence.

CP of Statistical Copolymers

Earlier studies have reported the effects of composition and end groups on the CP of OEGA/DEGA acrylates and OEGMA/DEGMA methacrylate copolymers.[3,11,12,28] In our prior work, we looked at OEGA/DEGMA diblock copolymers, where we used OEGA instead of OEGMA to enhance the hydrophobicity difference of the two monomers.[22] The relationship between the copolymer composition and CP of the statistical from these two monomers followed a similar relationship of F_o/CP described by our prior work, $\mathrm{CP} = 0.907F_o + 20.4$ (using only DT1), and first shown by Lutz et al.[11]. From the linear

TABLE 1 Copolymer Composition, D_h, CP, and ΔT

CTA	Sample	Y_D (%)[a]	Y_O (%)[b]	$Y_{overall}$ (%)	F_o (%)[c]	D_h (nm)	M_n (th)[d]	M_w (GPC)[e]	CP (°C)	ΔT (°C)
				Dithioester CTAs						
 DT1	$D_{50}O_{50}$	–	–	70	55	–	–	–	66.3	5.0
	$S\text{-}D_{50}O_{50}\text{-}C1$	38	89	75	49	152	33,612[f]	44,000	48.9	1.6
	$S\text{-}O_{50}D_{50}\text{-}C1$	69	85	80	68	254	33,612[g]	27,900	27.6	4.0
 DT2	$D_{50}O_{50}$	–	–	91	55	–	–	–	71.0	2.5
	$S\text{-}D_{50}O_{50}\text{-}C2$	43	92	78	46	134	33,621	38,800	54.7	1.5
	$S\text{-}O_{50}D_{50}\text{-}C2$	39	85	72	75	252	33,621	29,200	35.3	10
 DT3	$D_{50}O_{50}$	–	–	87	54	–	–	–	69.4	2.5
	$S\text{-}D_{50}O_{50}\text{-}C3$	60	91	82	50	143	33,679	30,900	54.2	3.5
	$S\text{-}O_{50}D_{50}\text{-}C3$	40	96	80	72	305	33,679	21,300	30.2	7.5
				Trithiocarbonate CTAs						
 TC1	$D_{50}O_{50}$	–	–	94	54	–	–	–	74.7	2.5
	$C\text{-}O_{25}D_{50}O_{25}\text{-}C$	61	90	82	53	103	33,682	37,800	29.2	2.5
	$C\text{-}D_{25}O_{50}D_{25}\text{-}C$	73	83	80	60	266	33,682	22,700	31.8	5.7
 TC2	$D_{50}O_{50}$	–	–	90	47	–	–	–	67.5	3.0
	$Ph\text{-}O_{25}D_{50}O_{25}\text{-}Ph$	59	92	83	42	184	33,690	30,800	40.5	4.5
	$Ph\text{-}D_{25}O_{50}D_{25}\text{-}Ph$	84	89	88	60	115	33,690	33,800	25.2	2.0
	Star CTA									
 TDT	$(D_{50}O_{50})_3$	–	–	79	50	–	–	–	66.1	1.2
	$S\text{-}(D_{50}O_{50})_3\text{-}C6$	55	89	80	57	95	100,734	77,100	57.5	2.0
	$S\text{-}(O_{50}D_{50})_3\text{-}C6$	43	88	75	63	130	100,734	81,400	24.6	1.2

[a] Percent yield for the polymerization of the monomer DEGMA.

[b] Percent yield for the polymerization of the monomer OEGA.

[c] The ratio of OEGA in the diblock copolymer, calculated from eq 1.

[d] Theoretical number-average molecular weight, calculated from eq 2.

[e] Molecular weight tested by GPC. PDI are given in Supporting Information Table S2. For linear polymers, these ranged from 2.46 to 4.71, but for stars were 5.69–5.86.

[f] Molecular weight tested by MALDI-TOF: $M_w = 38{,}555$ PDI = 1.12.

[g] Molecular weight tested by MALDI-TOF: $M_w = 33{,}653$ PDI = 1.12.

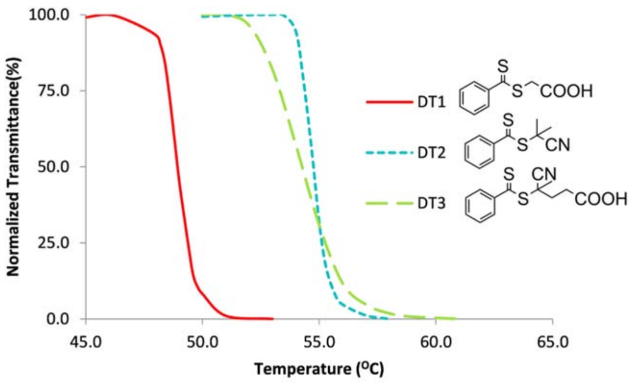
relationship generated from the statistical copolymers in that work,[22] the CP for a theoretical $F_o = 50$) should around 65.7 °C. The CTAs used here gave slightly different polar end groups, and different architectures, and yet the measured CPs of the statistical copolymers generated here ($D_{50}O_{50}$) were similar, regardless of end group or architecture, ranging from 66.3 to 74.7 °C. And, the measured CP is very close to the value predicted by the linear relationship, using the actual composition again regardless of the end group or the architecture: DT1/66.3 °C, DT2/71.0 °C, DT3/69.7 °C, TC1/74.7 °C, TC2/67.5 °C, and TDT/66.1 °C.

Therefore, although end group identity and placement significantly affect the CP of diblock copolymers, as shown in the following section, end group effects on statistical copolymers are generally small. However, if the reactivity ratios of the monomers are significantly different so they tend towards a blocky copolymer structure an end group effect should still be anticipated.

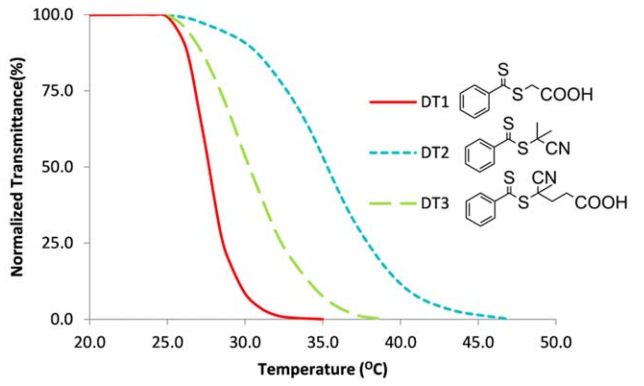
Effect of End Group on Diblock Copolymer Properties

The six DEGMA/OEGA (1:1) diblock copolymers prepared from DT1–3 gave an actual F_o ranging from 0.47 to 0.55. The copolymers possessed the same hydrophobic end group ($PhCS_2$) but slightly different hydrophilic chain ends. The effect of the changes in end group structure on the CPs was measurable but small, regardless of the hydrophilic chain end. The largest difference was 7.7 °C ($S\text{-}O_{50}D_{50}\text{-}C2$ compared to $SO_{50}D_{50}\text{-}C1$). The difference polarity was insignificant in comparison to the effects from chain end placement.

Pairing the hydrophobic $PhCS_2$— chain end with the hydrophobic (compared to OEGA) DEGMA block drops the CP by 15–17 °C relative to the CP of the statistical copolymers



(a) S-$D_{50}O_{50}$-C(1-3)



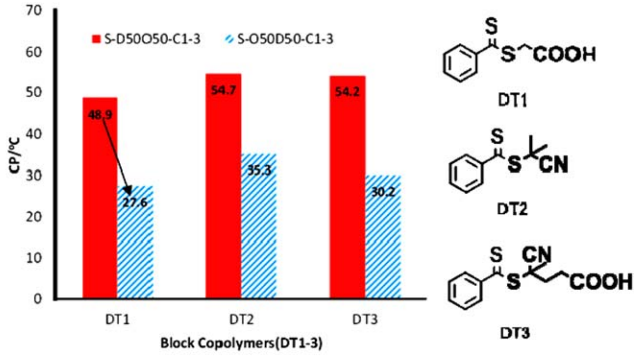
(b) S-$O_{50}D_{50}$-C(1-3)

FIGURE 4 CP curves of diblock copolymers from DT1–3, showing (a) S-DxOy-C(1–3) and (b) S-OyDx-C(1–3). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

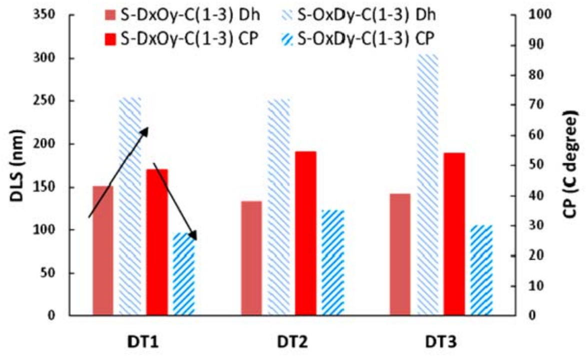
(Table 1) prepared using the same CTAs. However, pairing the hydrophobic $PhCS_2$— chain end with the hydrophilic OEGA block drops the CP by 36–39 °C. Furthermore, the CP curves show a relatively narrow transition (ΔT) for the coil collapse when the hydrophobic chain end is paired to the hydrophobic DEGMA block [Fig. 4(a)], but pairing the hydrophobic chain end to the hydrophilic OEGA block results in the coil collapse occurring over a much broader temperature range [Fig. 4(b)]. The relative effect of chain end placement on CP is more clearly seen in a bar chart format [Fig. 5(a)].

The relationship between the CP of linear OEGA/DEGMA diblock copolymers and amphiphilic end groups is clear: matching the polarity of block with end groups (i.e., pairing the hydrophilic OEGA block with the hydrophilic end group and the more hydrophobic DEGMA block with the hydrophobic end group) gives a higher CP and a more narrow transition than blocks paired to end groups of a different polarity.

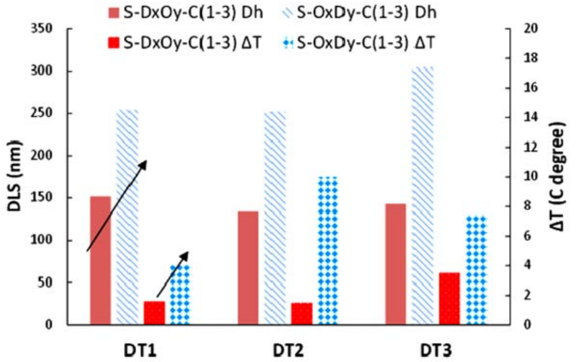
Figure 5(a–c) illustrates the significant differences in CP and D_h that result from that pairing the hydrophobicc end to the hydrophobic DEGMA block giving S-DxOy-C (DT1–3) compared to when the pairing is reversed. The “mixed pairing” of the hydrophobic chain end to the hydrophilic block (S-OyDx-CDT1–3) gives a significantly lower CP because it results in a less orderly and efficient hydration sphere, so less energy is required to collapse the coil [Fig. 6(a)]. This same effect causes a clear correlation between end group pairing and the D_h [Fig. 5(b)]. For example, for the three diblock copolymers where the hydrophobic chain end is paired to the hydrophobic DEGMA (S-DxOy-C) block the only CP detected is near ~55 °C and the D_h is ~150 nm. Conversely, for the three copolymers where the end group pairing is reversed, that is, S-OyDx-C copolymers, the CP is near ~30 °C and the D_h is ~250–300 nm. Compared to the effects of end group placement, the effect of identity of the hydrophilic end group on CP and D_h was quite small. Figure 5(c)



(a) CP of block copolymer (DT1-3)



(b) D_h and CP



(c) D_h and ΔT

FIGURE 5 Bar charts comparing (a) CPs based on end group and block sequence, (b) D_h and CP, and (c) D_h and ΔT. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

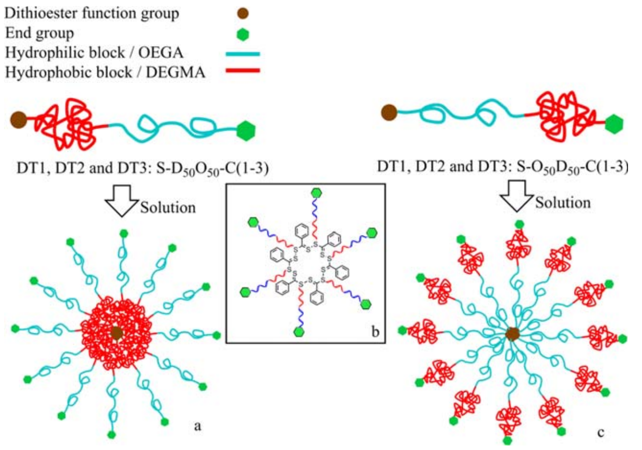


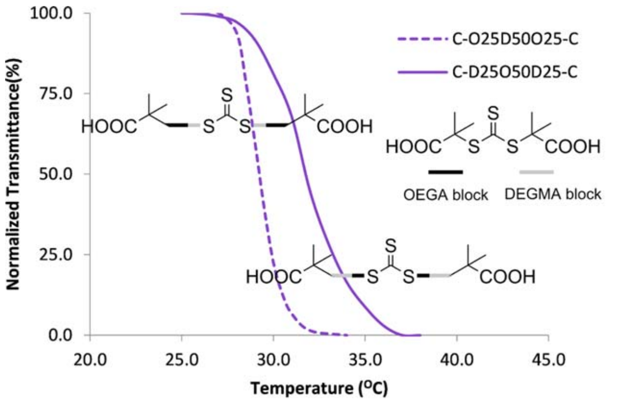
FIGURE 6 Affect of temperature on conformations of (a) S-DxOy-C, where chain end and block polarity are matched; (b) possible interactions between dithioester chain ends in the micellar core; and (c) S-OyDx-C, where chain end and block polarity are mismatched. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

shows the correlation also exists between chain end pairing and D_h and ΔT of the coil collapse. Pairing the hydrophobic chain end with the hydrophobic block results in a smaller D_h and a significantly smaller ΔT compared to the mixed pairing of the hydrophilic chain end to the hydrophobic block.

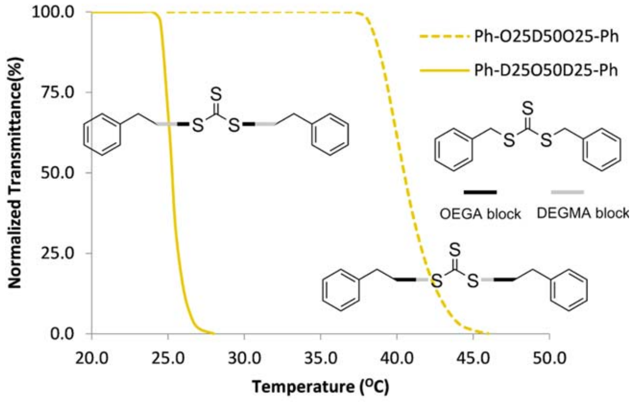
It is clear that pairing the hydrophobic chain end with the hydrophobic block the impact on the CP, D_h and ΔT are substantial. All of these effects arise from a small and well-ordered micellar structure, where the hydrophobic block is already collapsed, or nearly collapsed, and the hydrophilic block is well hydrated with the hydrophilic chain end facilitating that hydration. The chain end pairing may lead to structures something like that shown in Figure 6(a) for temperatures below the CP. A structure like this could also account for why a separate CP is not detected for the DEGMA block in the core, since it is either completely collapsed or nearly so, and the CP of pure PDEGMA with similar chain ends is ~25 °C.[22] Therefore, since it is so poorly hydrated we did not detect any additional change. The orderly structure within the hydrophobic core may also be assisted by interactions between the dithioester groups, such as those suggested in Figure 6(b).

Conversely when the chain end polarity and block polarity are mismatched, a structure more like that shown in Figure 6(c) may exist. This type of structure would be expected to have a lower CP and a greater D_h, compared to the structure shown in Figure 6(a), because of a less hydrated OEGA coil within the micellar core, along with a less orderly collapse from the expulsion of water from the hydrated OEGA block. Because this coil is less ordered, the ΔT is broader than the values measured for the S-DxOy-C copolymers.

As stated above the exact identity of the polar chain end does have some impact on the CP and D_h even for the same block sequence (but with difference CTAs), but this is far less than the effect from changing block sequence. For example, when the block sequence was the same the polar chain end identity resulted in no more than a 7.7 °C impact on CP (S-$O_{50}D_{50}$-C2 and S-$O_{50}D_{50}$-C1), and no more than a 53 nm impact on the D_h (S-$O_{50}D_{50}$-C2 and S-$O_{50}D_{50}$-C3. But when comparing the same CTA but with the block sequence reversed we found the CP have the of as much as 24 °C (S-$D_{50}O_{50}$-C3 and S-$O_{50}D_{50}$-C3) and the D_h difference increased to 163 nm (S-$D_{50}O_{50}$-C3 and S-$O_{50}D_{50}$-C3).



(a) CP of C-$O_{25}D_{50}O_{25}$-C and C-$D_{25}O_{50}D_{25}$-C



(b) CP of Ph-$O_{25}D_{50}O_{25}$-Ph and Ph-$D_{25}O_{50}D_{25}$-Ph

FIGURE 7 Graphs of transmittance versus temperature for symmetrical triblock copolymers that have symmetric chain ends that are both (a) hydrophilic or (b) hydrophobic. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 2 Effect of End Groups on Thermoresponse Properties of Symmetrical Triblock Copolymers

Polymers	CTA	CP (°C)	D_h (nm)	ΔT (°C)
C-$O_{25}D_{50}O_{25}$-C	TC1	29.2	103	2.5
Ph-$O_{25}D_{50}O_{25}$-Ph	TC2	40.5	184	4.5
C-$D_{25}O_{50}D_{25}$-C	TC1	31.8	266	5.7
Ph-$D_{25}O_{50}D_{25}$-Ph	TC2	25.2	115	2.0

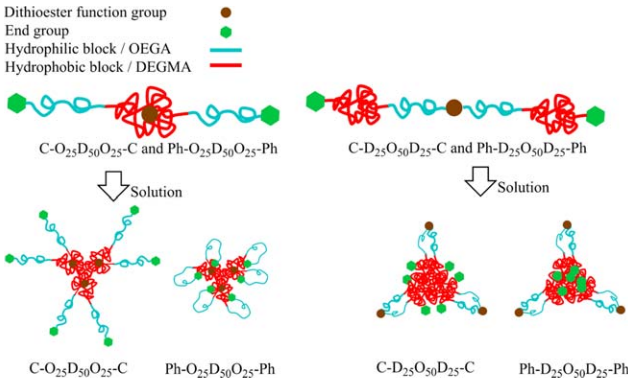


FIGURE 8 Proposed structures for symmetrical triblock copolymers from TC1 and TC2 in aqueous solution. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Trithiocarbonate CTAs (TC1 and TC2) and Their Symmetric Copolymers

Trithiocarbonate CTAs were used to produce symmetrical triblock ($O_{25}D_{50}O_{25}$ or $D_{25}O_{50}D_{25}$) copolymers. The trithiocarbonate CTAs, TC1, and TC2, also gave symmetric hydrophobic or hydrophilic chain ends respectively, where the hydrophilic chain ends are designated as "C", and the hydrophobic chain ends are designated as "Ph". The thermal data shown in Figure 7 are also summarized in Table 2**.** Model structures for these copolymers are proposed in Figure 8.

When the chain end and terminal block polarity are matched (i.e., hydrophobic end groups are paired with terminal hydrophobic blocks or hydrophilic chain ends are paired with terminal hydrophilic blocks) the CP, D_h, and ΔT are similar**.** Specifically, the CPs for C-$O_{25}D_{50}O_{25}$-C and Ph-$D_{25}O_{50}D_{25}$-Ph were 29.2 ad 25.2 °C, the D_h's were 103 and 115 nm, and ΔT's were 2.5 and 2.0 °C. Therefore, these copolymers produced similar micelle size and hydration and an orderly coil collapse.

When the chain end and block polarity of the triblock copolymers are mismatched the CP, D_h, and ΔT are higher than those of the triblocks with matched chain end and block polarity. Also, the properties of the "mismatched polarity" triblock pair differ significantly from each other, while the properties of the "matched polarity" triblock pair were very similar to each other. For example, C-$D_{25}O_{50}D_{25}$-C has DEGMA blocks with hydrophilic chain ends, and has a CP a little higher than the two matched triblocks, 31.8 °C compared to 29.2 and 25.2 °C for C-$O_{25}D_{50}O_{25}$-C, and Ph-$D_{25}O_{50}D_{25}$-Ph respectively, but the CP of Ph-$O_{25}D_{50}O_{25}$-Ph, with OEGA blocks bonded to hydrophobic chain ends, is 40.5 °C. The two "mismatched polarity" triblock copolymers also have significantly larger D_h's and broader ΔT's than the "matched polarity" triblock copolymers. The C-$D_{25}O_{50}D_{25}$-C has a D_h of 266 nm and a ΔT of 5.7 °C, more than twice as large as those of the "matched polarity" triblock copolymers, and Ph-$O_{25}D_{50}O_{25}$-Ph has D_h of 184 nm and a ΔT of 4.5 °C. Possible structures arising from these mismatched polarity triblock copolymers in water are also given in Figure 8. The larger D_h of 266 nm and ΔT of C-$D_{25}O_{50}D_{25}$-C suggests that the short DEGMA blocks are not effectively collapsed and the collapse above the CP is not efficient. But the results from Ph-$O_{25}D_{50}O_{25}$-Ph are difficult to explain. The CP of this triblock copolymer is almost 9 °C greater than that of the other triblock structures. However, it is also important to note that the composition of this triblock copolymer also differed more that the other copolymers from the theoretical value. The Ph-$O_{25}D_{50}O_{25}$-Ph copolymer had a Fo of only 42, while the Fo was 53–60 for the other triblock copolymers. Nevertheless these data do not seem consistent with the other findings.

Star Block Copolymers (TDT)

The CP curves of three-arm star copolymers with diblock arms having different block sequence are shown in Figure 9. Only hydrophobic chain ends were studied here because carboxylate groups were not successfully achieved on the terminal phenyl groups. The architecture of a star polymer was expected to facilitate a simple and orderly collapse of the

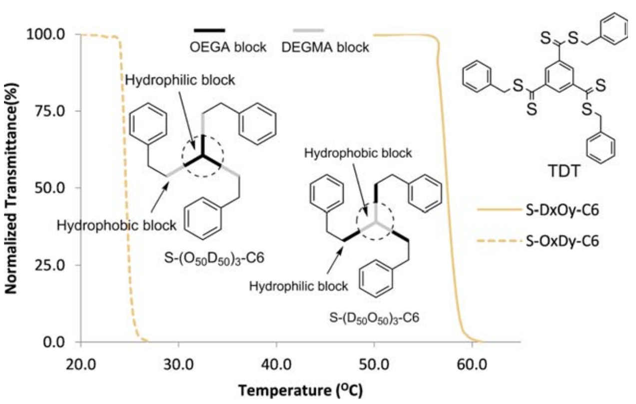


FIGURE 9 CP of star block copolymers. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

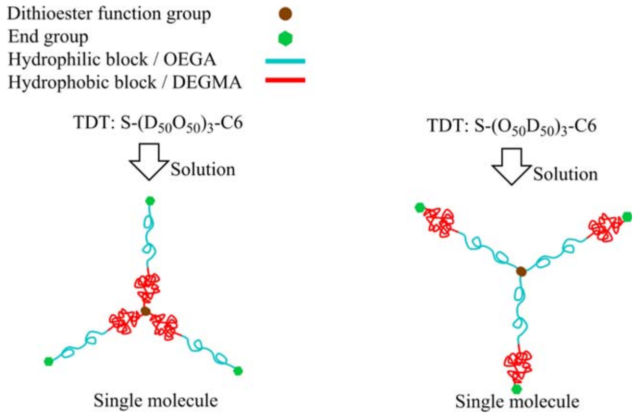


FIGURE 10 Proposed structure of star copolymers in aqueous solution. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

arms at the CP, so it was not surprising that both copolymers had a narrow ΔT (2.0 and 1.2 °C), despite the broad PDI of the polymers. The block sequence gave a somewhat greater effect on the D_h with S-$(O_{50}D_{50})_3$-C6 giving a larger micelle (130 nm) than S-$(D_{50}O_{50})_3$-C6 (95 nm) where the hydrophilic blocks formed the micelle's shell. When the hydrophobic DEGMA block is buried in the interior of the micelle it is more poorly hydrated than when it is the shell layer of the micelle, and so it is already collapsed or nearly collapsed, as illustrated in Figure 10. However, the OEGA block is well hydrated. Surprisingly though, the CPs of the two star copolymers are quite different, with S-$(D_{50}O_{50})_3$-C6 having a CP that at 57.5 °C is nearly 33 °C higher than the star copolymer with the inverse block sequence, S-$(O_{50}D_{50})_3$-C6 which had a CP of 24.6 °C. It is thought that neither the OEGA nor the DEGMA blocks of the S-$(O_{50}D_{50})_3$-C6 copolymers are well hydrated.

CONCLUSIONS

Di- and triblock copolymers were easily prepared by RAFT polymerization using the hydrophilic OEGA and comparatively hydrophobic DEGMA with a series of different CTAs to study amphiphilic copolymers with different architectures and end groups. Linear diblock copolymers with amphiphilic end groups allowed the thermoresponse properties of diblock copolymers where the polarity of the blocks and chain ends was matched, to be compared to those of diblock copolymers with similar compositions but with block and chain end polarity being mismatched. Other CTAs allowed the synthesis of symmetrical triblock copolymers and allowed the effect of block sequence to be studied in conjunction with end groups that were matched or mismatched with respect to block polarity, and star diblock copolymers allowed the effect of block sequence with hydrophobic end groups to be studied in an architecture that will facilitate an orderly collapse of the chains.

When comparing the diblock copolymers the effect of pairing end groups to blocks with different hydrophobicity is clear. Pairing the hydrophilic block with the hydrophobic chain end yields micelles with a lower CP and a higher D_h and ΔT. The D_h is almost twice as large as when the hydrophobicity of the block and chain end is better matched. When the blocks and chain ends are matched the hydrophilic block forms an efficient hydration sphere, giving the higher CP, while the hydrophobic block is effectively collapsed giving a smaller D_h and ΔT. However, mismatching disrupts the hydration giving a lower CP, and the hydrophobic block with hydrophilic chain end is also partially hydrated and perhaps aggregated leading to a larger D_h and ΔT. The star polymer shows a different trend because the architecture inhibits aggregation, so the difference in D_h and ΔT is less significant but placing the hydrophilic block on the outer shell clearly allows a more effective and orderly hydration sphere as proven by the much higher CP. The triblock copolymers showed slightly more complicated result. Matching chain ends to block hydrophobicity/philicity yielded the smallest D_h and ΔT supporting the concept of the hydrophobic block being precollapsed and the small ΔT collapse of the hydrated hydrophilic block. However, when the chain ends were mismatched to block polarity the results were contradictory. The larger D_h and ΔT supported a less orderly micelle structure with a less orderly collapse, but the CPs were not consistent. The mismatched triblock with hydrophilic chain ends yielded a CP nearly identical to those of the triblock copolymers with matched chain ends and blocks, while the triblock with hydrophobic chain ends paired to hydrophilic blocks gave a much higher CP, suggesting an efficient and orderly hydration sphere.

Overall, the results are consistent with hydrophobic chain ends controlling micelle formation and hydrophilic blocks controlling hydration, and the data show that mismatching the hydrophilicity of the block to that of the chain end leads to disruption of the hydration sphere with a lowering of the CP and a broadening of the temperature range for the chain collapse. The architecture of a three-arm start reduced the extent of these effects, but was still consistent overall. The one exception to this was found for a symmetrical triblock copolymer with hydrophobic chain ends paired to hydrophilic blocks. The reason for this is not clear. Other analytical methods such as Small Angle Neutron Scattering may be needed to fully understand how pairing blocks with end groups of different hydrophobicity affect the hydration, aggregation and collapse of amphiphilic copolymers, but given the likely growing importance of these EG-containing monomers and their thermoresponse properties in the biomedical area, these materials are worthy of more study.

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