Stimulus-Responsive Water-Soluble Polymers Based on 2-Hydroxyethyl Methacrylate

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ABSTRACT: The homopolymerization and block/statistical copolymerization of 2-hydroxyethyl methacrylate (HEMA) using atom transfer radical polymerization (ATRP) in methanol at 20 °C has been investigated. For the homopolymerizations, both high conversions and low polydispersities (M_w/M_n < 1.25) were obtained over a wide range of target degrees of polymerization. According to the literature, HEMA homopolymer is usually described as only water-swellable, but in this work low molecular weight HEMA oligomers (target degrees of polymerization, DP_n, less than 20) exhibited water solubility over a wide temperature range (no cloud point behavior). Furthermore, for actual DP_n's between 20 and 45, HEMA homopolymers exhibited inverse temperature solubility in dilute aqueous solution at pH 6.5, and their cloud points increased systematically as the DP_n was reduced. Gravimetric studies indicated that "water-insoluble" HEMA homopolymers with DP_n's higher than 50 were actually partially soluble: GPC studies confirmed that fractionation occurred due to preferential dissolution of the shorter chains. Furthermore, HEMA homopolymers with DP_n's up to 50 are water-soluble at pH 2.2 and do not exhibit cloud points. This is attributed to protonation of the terminal morpholine groups derived from the ATRP initiator. Thus, depending on the mean DP_n and the solution pH, water can be a good solvent, a marginal solvent or a nonsolvent for HEMA homopolymer. Chain extension (self-blocking) experiments conducted for the ATRP of HEMA in methanol at 20 °C using a Cu(I)Cl catalyst and bpy ligand indicated reasonable living character. Statistical copolymerizations of HEMA with other comonomers such as glycerol monomethacrylate (GMA) and 2-hydroxypropyl methacrylate (HPMA) allowed the cloud point behavior to be manipulated. Finally, a range of novel HEMA-based block copolymers were synthesized in which the HEMA block was either thermoresponsive or permanently hydrophilic, depending on its DP_n and the nature of the second block. Thus, diblock copolymer micelles with either hydroxylated cores or coronas could be prepared.

Introduction

2-Hydroxyethyl methacrylate (HEMA) is a commercially important monomer that is widely used in the manufacture of soft contact lenses and intraocular lenses.[1−3] HEMA copolymers exhibit excellent biocompatibility and good blood compatibility.[4,5] Other biomedical applications for HEMA-based materials include an embedding substrate for the examination of cells using light microscopy[6] and inert matrices for the slow release of drugs.[7,8] Although high molecular weight HEMA homopolymer is hydrophilic and has a relatively high degree of hydration (up to 42% water can be absorbed per unit mass of lightly cross-linked HEMA-based gel[9]), it is generally regarded as being only water-swellable, rather than water-soluble.[10−12] However, this observation may well be related to the presence of low levels of ethylene glycol dimethacrylate often found in HEMA monomer, which could lead to an extrinsic cross-linking reaction during its "homopolymerization". On the other hand, there has been at least one report of water-soluble polydisperse HEMA oligomers.[13]

The synthesis of controlled-structure HEMA-based block copolymers via anionic polymerization chemistry has been described by several research groups, but this approach requires protection of the alcohol functionality.[11,12,14−16] Such syntheses always involve at least three steps: synthesis of the protected monomer, its controlled polymerization, and subsequent removal of the protecting groups. Understandably, there have been few, if any, applications for controlled-structure HEMA-based (co)polymers.

Since its discovery[17a,b] in 1995, atom transfer radical polymerization (ATRP)[17c] has been shown to be a versatile technique for the controlled polymerization of many monomer classes, including acrylates,[18] methacrylates,[19] and styrenics.[20] Since ATRP involves polymer radicals, rather than ionic species, it is well suited to the polymerization of functional monomers such as HEMA. Generally ATRP syntheses are carried out at high temperatures either in the bulk or in nonaqueous media. However, we have recently reported that ATRP can be used to polymerize HEMA efficiently in protic media (methanol or methanol/water mixtures) at room temperature[21] to obtain near-monodisperse homopolymers (M_w/M_n = 1.20).

Herein we report the synthesis of a range of HEMA homopolymers and controlled-structure HEMA-based copolymers using methanolic ATRP at 20 °C. By systematically varying the target degree of polymerization (DP_n) and using high-purity HEMA monomer, we show that near-monodisperse low molecular weight HEMA

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homopolymers are water-soluble and, in some cases, exhibit inverse temperature solubility behavior. Moreover, depending on the nature of the ATRP initiator, HEMA homopolymers that exhibit significantly enhanced water solubility in acidic media can be obtained. Finally, several novel HEMA-based block copolymers were synthesized in which the HEMA block was either thermoresponsive or permanently hydrophilic, depending on its degree of polymerization, the solution pH, and the nature of the second block. Thus, diblock copolymer micelles with either HEMA-based cores or HEMA-based coronas could be prepared.

Experimental Section

Materials. HEMA monomer (distilled HEMA Ultra grade; <0.1% w/w ethylene glycol dimethacrylate content), HPMA (99%), monohydroxy-capped poly(propylene oxide) [PPO−OH; $DP_n = 33$; $M_n = 2100$; $M_w/M_n = 1.10$] (99%), and monohydroxy-capped poly(ethylene oxide) [PEO−OH; $DP_n = 45$; $M_n = 2000$; $M_w/M_n = 1.10$] (99%) were each provided by Cognis Performance Chemicals (Hythe, UK); each of these materials was used as supplied. GMA (95−99%) was kindly donated by Röhm (Germany). 4-(2-Hydroxyethyl)morpholine (99%), Cu(I)Br (98+%), 2,2′-bipyridine (bpy) (99+%), 2-bromoisobutyryl bromide (98%), triethylamine (99.5%), and methanol (99.9+%) were all purchased from Aldrich and were used as supplied. MMA (99%) was also obtained from Aldrich and passed through a basic alumina column to remove the inhibitor. Silica-60 gel was purchased from Merck (Germany) and was used as supplied for removal of the spent ATRP catalyst. The water used in all experiments was deionized and doubly distilled prior to use.

Initiator Synthesis. The ATRP initiator was synthesized by reacting 4-(2-hydroxyethyl)morpholine (10.000 g, 0.0763 mol) with stoichiometric quantities of 2-bromoisobutyryl bromide (17.549 g, 0.0763 mol) and triethylamine (7.706 g, 0.0763 mol) in dry toluene (200 mL) for 48 h at ambient temperature, as described previously.[21] The resulting reaction solution was filtered to remove the amine salt, stirred with activated carbon, dried with $MgSO_4$, and filtered, and the solvent was removed by vacuum distillation. ^{1}H NMR spectroscopy was used to calculate the degree of esterification, which proved to be greater than 99% in each case. The acronym given to this morpholine-based initiator was ME-Br. The syntheses of the PEO_{45}-Br and PPO_{33}-Br macroinitiators[22,23] have been reported previously. These syntheses are very similar to that of the ME-Br initiator, but 1.25 mol equiv of 2-bromoisobutyryl bromide and longer reaction times (5−7 days in dry toluene at 20 °C) were required. In both cases the reaction mixture was then filtered to remove the insoluble hydrobromide salt, stirred with activated carbon, dried with magnesium sulfate, and refiltered. The PPO_{33}-Br macroinitiator was dissolved in water at pH 9 and extracted several times with dichloromethane. The organic layer was dried using magnesium sulfate and filtered, and then the solvent was removed under reduced pressure. The PEO_{45}-Br macroinitiator was readily purified by successive precipitation into cold (<0 °C) diethyl ether, followed by drying under vacuum.

ATRP Syntheses. *Homopolymerizations.* In a typical experiment, the ME-Br initiator (334 mg, 1.19 mmol) and HEMA monomer (4.664 g, 35.6 mmol) were degassed using dry nitrogen with stirring for approximately 30 min. Methanol (HPLC grade) was simultaneously degassed using dry nitrogen and then added via a double-tipped needle using standard Schlenk techniques. The bpy ligand (463 mg, 2.97 mmol) and the Cu(I)Cl catalyst (118 mg, 1.19 mmol) were added to this degassed solution. Polymerization occurred immediately, leading to an increase in viscosity and an exotherm of around 10 °C over 30 min. On exposure to air, the dark-brown reaction solution turned blue, indicating aerial oxidation of Cu(I) to Cu(II). Purification was achieved by passing the methanolic reaction solution through a silica column to remove the Cu(II) catalyst. The blue catalyst adsorbed onto the silica to yield a colorless aqueous solution. The methanol was removed by vacuum distillation to produce white polymer. Finally, precipitation into cold THF (approximately 3 °C) removed traces of residual HEMA monomer and/or unreacted initiator. Conversions of greater than 99% were routinely obtained, as judged by ^{1}H NMR. Analysis using DMF GPC (against PMMA standards) indicated an M_n of 10 900 g mol^{-1} and an $M_w/M_n = 1.24$.

Chain Extension Experiments. These were conducted under identical conditions to the homopolymerizations, with a second monomer charge being added at high conversion (as judged by ^{1}H NMR). In the case of self-blocking experiments the second monomer was HEMA, while either GMA or MMA comonomers were employed for the synthesis of genuine diblock copolymers. In the case of the chain-extended $HEMA_{30}$−$HEMA_{50}$ homopolymer, the ME-Br initiator (334 mg, 1.19 mmol) and HEMA monomer (4.664 g, 35.6 mmol) were degassed using dry nitrogen with continuous stirring for approximately 30 min. Methanol was simultaneously degassed using dry nitrogen and then added via double-tipped needle using standard Schlenk techniques. The bpy ligand (463 mg, 2.97 mmol) and the Cu(I)Cl catalyst (118 mg, 1.19 mmol) were added to this degassed solution. Approximately 30 min before the desired addition of the second HEMA monomer charge (7.795 g, 59.5 mmol), the preweighed monomer and methanol were degassed separately using dry nitrogen. Methanol (7.8 mL) was added to the monomer using standard Schlenk techniques to form a homogeneous solution. Immediately prior to the addition of the second monomer charge, the polymerizing solution was sampled under a positive nitrogen flow using a syringe. ^{1}H NMR and DMF GPC were used to determine the conversion and molecular weight for this aliquot. The second monomer charge was added via a double-tipped needle, and a second exotherm was recorded, indicating that a second-stage polymerization occurred. Purification was achieved using the same protocol as that used for the homopolymerizations. However, for the synthesis of the GMA_{50}−$HEMA_{30}$ diblock copolymer, the GMA monomer was polymerized first as a 50% w/v methanol solution using the ME-Br initiator to 98% conversion, and then a methanolic solution of HEMA monomer was added. For the preparation of the HEMA−MMA diblock copolymer the HEMA was polymerized first using ME-Br. A conversion of 92% was obtained after 3 h at 20 °C, and then the MMA was added and allowed to polymerize for 24 h at the same temperature. The original target block composition was ME−$HEMA_{50}$−MMA_{20}, but after purification the isolated diblock copolymer had a composition of ME−$HEMA_{60}$−MMA_{28}, as judged by end-group analysis using ^{1}H NMR spectroscopy. The difference was attributed to partial fractionation of this copolymer during its isolation and purification.

Diblock Copolymers via the Macroinitiator Approach. HEMA-based diblock copolymers were also prepared using a PPO_{33}-Br macroinitiator. Both the PPO_{33}-Br macroinitiator (5.000 g, 2.4 mmol) and the HEMA monomer (4.679 g, 35.7 mmol) were degassed in a round-bottomed flask equipped with a sidearm using a continuous nitrogen purge for around 30 min. Excess methanol was degassed separately. After approximately 30 min the methanol (9.7 mL) was added to the initiator/monomer solution to give a clear, homogeneous solution. The Cu(I)Cl (238 mg, 24 mmol) and bpy (0.936 g, 60 mmol) were introduced to the reaction vessel to start the polymerization. Aliquots were removed by syringe needle under a positive nitrogen flow and assessed by ^{1}H NMR. After the required reaction time, the dark-brown solution was exposed to air and diluted with excess methanol; termination occurred fairly rapidly (approximately 15 min) on exposure to air as indicated by the color change from brown to blue due to aerial oxidation of Cu(I) to Cu(II). The catalyst was removed from the PPO−HEMA diblock copolymer using a silica column with methanol as the mobile phase.

Statistical Copolymerizations. In a typical synthesis of $HEMA_{25}$-*stat*-GMA_{20}, ME-Br initiator (334 mg, 1.19 mmol), HEMA monomer (3.904 g, 29.8 mmol), and GMA monomer (3.808 g, 23.8 mL) were degassed using dry nitrogen with

stirring for approximately 30 min. Methanol (8.0 mL) was simultaneously degassed using dry nitrogen and then added to the initiator/monomer solution using standard Schlenk techniques. The bpy ligand (463 mg, 2.97 mmol) and the Cu(I)Cl catalyst (118 mg, 1.19 mmol) were added to this degassed solution. On exposure to air, the dark-brown reaction solution turned blue, indicating aerial oxidation of Cu(I) to Cu(II). Purification was achieved by passing the methanolic reaction solution through a silica column to remove the Cu(II) catalyst. The blue catalyst adsorbed onto the silica to yield a colorless aqueous solution. The methanol was removed by vacuum distillation to produce white polymer. ^{1}H NMR indicated very high conversions (>99%) in all cases. DMF GPC (against PMMA standards) indicated an M_n of 18 800 g mol^{-1} and an $M_w/M_n = 1.25$.

Characterization. Molecular weight distributions were assessed for untreated aliquots extracted from reaction solutions using a GPC setup comprised of three Polymer Laboratories PL gel 5 mm Mixed "B" columns, DMF eluent containing 10 μM lithium bromide, and a refractive index detector. A flow rate of 1.0 mL min^{-1} was used, and the column temperature was set at 70 °C. A series of near-monodisperse poly(methyl methacrylates) were used as calibration standards.

^{1}H NMR spectra were recorded in d_4-methanol using a 300 MHz Bruker AC-P spectrometer. The peak integral assigned to the six azamethylene protons of the morpholine-based initiator fragment at 2.5−2.7 ppm was compared to those due to the four oxyethylene protons of the HEMA residues at 3.7−4.2 ppm in order to calculate the mean DP_n.

Dynamic light scattering (DLS) studies were performed at 20 °C using a Brookhaven Instruments Corp. BI-200SM goniometer equipped with a BI-9000AT digital correlator using a solid-state laser (125 mW, $\lambda = 532$ nm) at a fixed scattering angle of 90°. The intensity-average hydrodynamic diameters, $\langle D_h \rangle$, and polydispersities of the micelles were obtained by cumulants analysis of the experimental correlation function using the Stokes−Einstein equation.[24]

Cloud Point Determination. PC-controlled Perkin-Elmer Lambda 2S or Lambda 25 UV/vis spectrophotometers were used to assess the cloud points of aqueous solutions of HEMA homopolymers and statistical copolymers. A cold aqueous solution of the (co)polymer (2.5 mL, 0.50% w/v) was transferred to a 10 mm path length quartz cuvette containing a stirrer bar. A temperature probe was immersed in the upper portion of the cuvette, and the solution temperature was increased slowly from 8 °C to around 70 °C using either a water bath or a PTP-1 Peltier system in conjunction with a PCP 150 Peltier system. The absorbance was monitored as a function of temperature at a fixed wavelength of 500 nm. Each cloud point was calculated by double extrapolation. The pH of the aqueous solution was adjusted using HCl or NaOH, as required.

Determination of Water Solubility of HEMA Homopolymers by Gravimetry. Selected HEMA homopolymers were assessed by attempted dissolution in aqueous solution at pH 6.5. In each case 10−20 mg of polyHEMA was dissolved in 2−4 mL of water: assuming 100% solubility, 0.50% aqueous solutions were expected. These solutions were stirred at 0−5 °C for approximately 48 h to ensure maximum aqueous solubility. A fixed volume (1.0 mL) of each solution was then filtered through a 0.2 μm nylon filter at 5 °C in order to remove any insoluble material. The resulting aqueous polymer solution was dried in a vacuum oven at 55 °C for 18 h to remove all traces of water. The fraction of dissolved polymer was determined gravimetrically. For HEMA homopolymers of higher DP_n only partial solubility was observed; in some cases the molecular weight distribution of the soluble fraction was assessed by DMF GPC.

Results and Discussion

Recently we reported[25] the use of an oligo(ethylene glycol)-based ATRP initiator to prepare a series of HEMA "homopolymers". However, this initiator is both highly hydrophilic and oligomeric in nature. In the present work we elected to use ME-Br (see Figure 1).

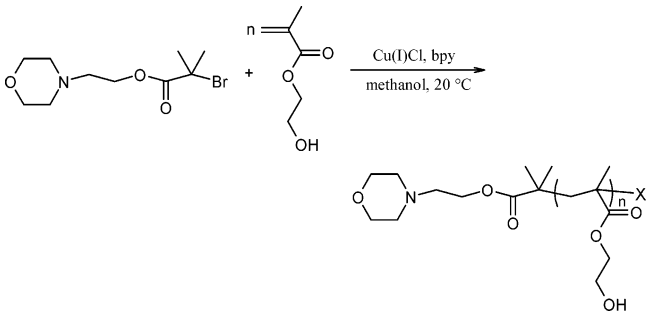

Figure 1. Reaction scheme for the controlled homopolymerization of 2-hydroxyethyl methacrylate (HEMA) via methanolic ATRP at 20 °C using the ME-Br initiator.

This initiator was considered less likely to produce a significant "end-group" effect when assessing the water solubility of the HEMA homopolymers (see below). Moreover, the morpholine protons also provide a useful ^{1}H NMR label for end-group analysis. In earlier work[25,26] substantial differences (up to an order of magnitude) between target molecular weights and GPC molecular weights (expressed as polystyrene equivalents) were reported for HEMA homopolymers prepared via ATRP. These discrepancies were due to large systematic errors incurred in the GPC analyses: not only are polystyrene calibration standards unlikely to be reliable for the analysis of methacrylic polymers, but DMF is only a marginal solvent for polystyrene, which leads to a significant over-estimation of the true molecular weight of the well-solvated HEMA homopolymers. This latter problem was not recognized in our earlier paper.[25] Thus, in the present work we elected to use poly(methyl methacrylate) standards for GPC calibration. DMF is a good solvent for poly(methyl methacrylate); hence, these standards are much more likely to have comparable hydrodynamic volumes to HEMA homopolymers in solution. The synthesis details and characterization data for various HEMA homopolymers are summarized in Table 1. By comparing the GPC data obtained using this new protocol with the DP_n's calculated from end-group analysis using ^{1}H NMR spectroscopy, it is clear that, with the exception of the lowest target DP_n, the GPC calibration error is reduced to only around 200−250%. For lower molecular weights there is very good agreement between the target DP_n's and those determined experimentally from ^{1}H NMR studies by end-group analysis of the ATRP initiator fragment. This indicates that very high initiator efficiencies are achieved using ME-Br in these syntheses. This interpretation is consistent with the approximately linear correlation obtained between the GPC M_n values and the target M_n's calculated from the HEMA/initiator molar ratios (see Figure 2). A gradual increase in polydispersity was observed as higher DP_n's were targeted (see Table 1), suggesting that progressively poorer control over the polymerization is obtained. Similar observations have been reported for other hydrophilic methacrylates such as 2-methacryloyloxyethyl phosphorylcholine.[27] Nevertheless, the homopolymerization of HEMA via ATRP in methanol at 20 °C afforded polymers with predetermined molecular weights and reasonably narrow molar mass distributions, at least for target DP_n values up to 75. To access higher DP_n's without loss of living character, a commercially available bifunctional ATRP initiator was evaluated, but judging by the final polydispersity, little or no improvement in control was achieved for an overall DP_n of 100 (see entry 13 in Table

Table 1. Summary of the Synthesis Parameters, Molecular Weight Data, and Cloud Points for HEMA Homopolymers Prepared via ATRP in Methanol at 20 °C

entry no.	target degree of polymerization	solvent	M_n (theory)	M_n (^{1}H NMR)	M_n (GPC)	M_w/M_n	solubility (and cloud point) in H_2O at pH 6.5
1	ME−HEMA$_{10}$	MeOH	1500	1600	5500	1.20	soluble
2	ME−HEMA$_{15}$	MeOH	2200	2300	7100	1.17	soluble
3	ME−HEMA$_{20}$	MeOH	2800	2800	8400	1.18	soluble
4	ME−HEMA$_{30}$	MeOH	4100	3600	10900	1.24	soluble (39 °C)
5	ME−HEMA$_{35}$	MeOH	4800	4100	12100	1.16	soluble (36 °C)
6	ME−HEMA$_{40}$	MeOH	5400	5200	13400	1.21	soluble (32 °C)
7	ME−HEMA$_{45}$	MeOH	6100	5700	14300	1.20	soluble (28 °C)
8	ME−HEMA$_{50}$	MeOH	6800	7100	14900	1.16	insoluble
9	ME−HEMA$_{60}$	MeOH	8100	8200	18600	1.22	insoluble
10	ME−HEMA$_{75}$	MeOH	10000	10000	21400	1.20	insoluble
11	ME−HEMA$_{85}$	MeOH	11400	11600	24000	1.26	insoluble
12	ME−HEMA$_{100}$	MeOH	13300	13600	31400	1.28	insoluble
13	HEMA$_{50}$−DEDB−HEMA$_{50}$	MeOH	13300		28500	1.48	insoluble
14	ME−HEMA$_{50}$	1:1 MeOH:H_2O	6800	6900	18 400	1.39	insoluble
15	ME−HEMA$_{50}$	H_2O	6800	6900	17700	1.52	insoluble

1). It is also noteworthy that ATRP syntheses conducted in either a 1:1 methanol/water mixture or pure water produced significantly broader molecular weight distributions (see entries 14 and 15 in Table 1), albeit much faster polymerizations. Recently, Matyjaszewski and coworkers[28] reported the homopolymerization of HEMA in aqueous solution in the presence of up to 80% added Cu(II)Br_2. This protocol was adopted because the authors were concerned that the Cu(II)−Br bond was susceptible to hydrolysis in the presence of water, leading to less efficient deactivation of the polymer radicals, faster rates of polymerization, and higher polydispersities. Despite obtaining linear semilogarithmic kinetic plots and linear evolution of molecular weight with conversion, the polydispersities of these HEMA homopolymers prepared in aqueous solution were around 1.46, which is appreciably higher than those prepared in methanolic solution reported in the present study. It was also shown by the same group that addition of excess *n*-tetrabutylammonium chloride salt to a HEMA polymerization conducted in a 1:1 methanol: water mixture at 35 °C produced polydispersities as low as 1.17, but only 27% conversion was obtained. On the basis of our own experience, the ATRP of HEMA monomer is best conducted in methanol at 20 °C. This protocol leads to very high conversions within 4−5 h, linear semilogarithmic kinetic plots are obtained, and polydispersities are typically below 1.25.

HEMA homopolymer is usually considered to be only water-swellable, rather than a genuinely water-soluble polymer.[10−12] Indeed, above a target DP_n of 40, water-insoluble fractions were observed at pH 6.5, as expected. However, if lower DP_n's were targeted, HEMA homopolymers proved to be completely water-soluble at 20 °C and pH 6.5. This is not really surprising given that HEMA monomer is completely water-miscible in all proportions. However, as far as we are aware, this is the first systematic study of HEMA homopolymers that reveals how water solubility varies systematically according to the mean DP_n. Moreover, turbidimetric studies reveal that water-soluble HEMA homopolymers with mean DP_n's between 30 and 45 exhibited inverse temperature solubility (cloud point) behavior in dilute aqueous solution at pH 6.5 (see Figure 3). Cloud points ranged from 28 to 39 °C, with shorter polymer chains being more water-soluble. In fact, there is a linear relationship between the molecular weights of these HEMA homopolymers and their cloud points, as shown in the Supporting Information, Figure 1. It is also noteworthy that a target DP_n of approximately 35 at pH 6.5 leads to a cloud point of around 37 °C. Thus, within an admittedly narrow range of target DP_n, HEMA homopolymers are water-soluble and biocompatible and can exhibit thermoresponsive behavior at temperatures close to physiological conditions. This suggests that new biomedical applications may be feasible for this cheap, highly biocompatible material.

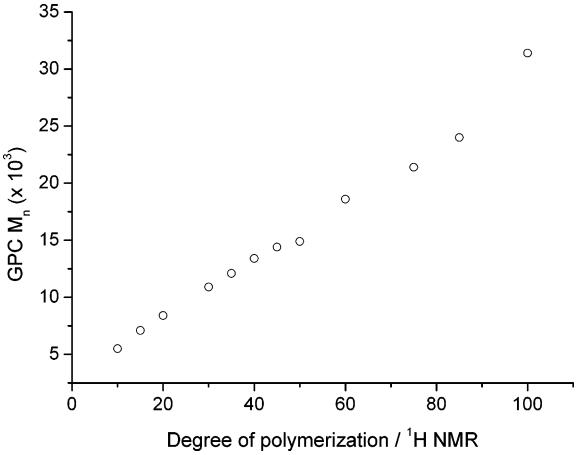

Figure 2. Evolution of M_n calculated from DMF GPC [vs poly(methyl methacrylate) calibration standards] as a function of actual degree of polymerization (determined by ^{1}H NMR) for the homopolymerization of HEMA using methanolic ATRP at 20 °C.

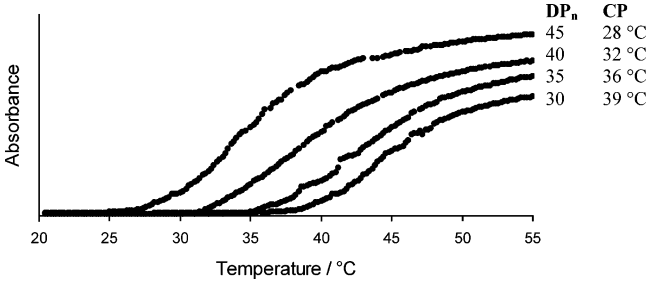

Figure 3. Turbidimetry data obtained for HEMA homopolymers of varying degrees of polymerization as a 0.5% w/v solution and pH 6.5 at 500 nm. Note: the abbreviation CP refers to cloud point.

Closer inspection of the apparently water-insoluble higher molecular weight HEMA homopolymers ($DP_n \geq 40$) revealed that a significant proportion of these samples dissolved at 20 °C, as indicated by the observation of surface activity (foaming). Although their polydispersities were relatively low, preferential dissolution

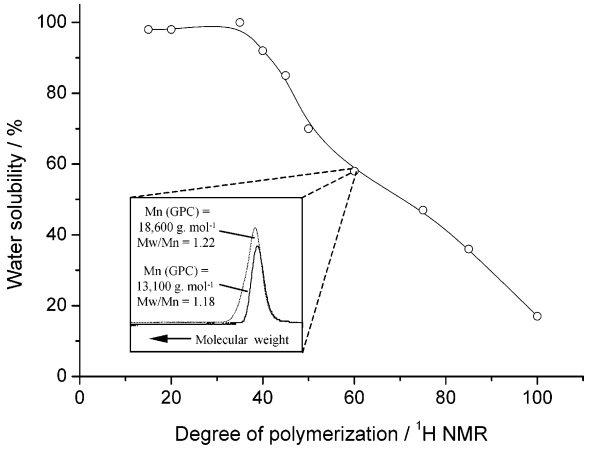

Figure 4. Effect of varying the actual degree of polymerization on the water solubility of the HEMA homopolymers at 5 °C, as judged by gravimetric analyses. The inset shows DMF GPC chromatograms obtained for the original (M_n = 18,600) and fractionated (M_n = 13,100) $HEMA_{60}$ homopolymer.

of the shorter chains was suspected. Gravimetry was used to assess the extent of aqueous solubility of some of these homopolymers at 5 °C and pH 6.5, and it was found that the water-soluble fraction decreased monotonically with increasing DP_n (see Figure 4). This suggested that fractionation was occurring; i.e., only the lower molecular weight fraction of each sample was water-soluble. This hypothesis was confirmed by DMF GPC analysis (see inset in Figure 4): the water-soluble fraction extracted from the HEMA homopolymer of DP_n = 60 had an M_n of 13 100 (M_w/M_n = 1.18). This particular HEMA homopolymer had an original M_n of 18 600 (M_w/M_n = 1.22), which indicates that water is a marginal solvent that preferentially dissolves the lower molecular weight chains.

The effect of solution pH on the aqueous solution properties of the HEMA homopolymers was also investigated. It was found that there was essentially no difference in water solubility (i.e., no change in the cloud points) for HEMA homopolymers between pH 6.5 and pH 10.5. However, there was a dramatic increase in the water solubility of HEMA homopolymers at pH 2.2. HEMA homopolymers with DP_n up to 50 were completely water-soluble at this pH at temperatures up to 85 °C. Comparing these results to those obtained for the HEMA homopolymers at pH 6.5, the minimum DP_n required to ensure complete water solubility has been increased from 20 to 50 merely by adjusting the solution pH. Moreover, HEMA homopolymers with DP_n = 60 and 75 were fully water-soluble at 5 °C and exhibited cloud points of 31 and 20 °C, respectively, while HEMA homopolymers of DP_n = 85 and above remained only partially water-soluble at pH 2.2. One possible explanation for the enhanced solubility of the HEMA homopolymers could be increased hydrogen bonding between the polymer chains and the water molecules in acidic solution. Alternatively, the terminal morpholine units originating from the ME-Br initiator must become protonated at low pH: the resulting cationic charge would be expected to enhance the water solubility of the HEMA chains. Further evidence to support this "end-group" effect will be presented later.

Statistical Copolymerization of HEMA with Other Hydroxy-Based Methacrylates. Once it was established that HEMA homopolymers of sufficiently low molecular weight were both water-soluble and thermoresponsive, we sought to control their cloud point behavior at pH 6.5. In principle, statistical copolymerization of HEMA with a more hydrophilic (or more hydrophobic) monomer should lead to an increase (or decrease) in the cloud point. Similar systematic variations in water solubility have been previously reported for statistical copolymers of *N*-isopropylacrylamide with acrylamide.[29]

Table 2. Summary of the Near-Monodisperse HEMA-Based Statistical Copolymers Prepared by Methanolic ATRP at 20 °C

copolymer composition	HEMA (mol %)	M_n (theory)	M_n (GPC)	M_w/M_n	cloud point[a]
$HEMA_{40}$-*stat*-GMA_5	89	6000	14500	1.19	33
$HEMA_{35}$-*stat*-GMA_{10}	78	6300	17000	1.19	none
$HEMA_{30}$-*stat*-GMA_{15}	67	6500	17100	1.24	none
$HEMA_{25}$-*stat*-GMA_{20}	56	6600	18800	1.25	none
$HEMA_{50}$-*stat*-GMA_{10}	83	8300	17900	1.20	42
$HEMA_{10}$-*stat*-$HPMA_5$	67	2200	7400	1.22	27
$HEMA_{12}$-*stat*-$HPMA_3$	80	2200	7900	1.23	33

[a] In °C at pH 6.5.

In view of their obvious structural similarities to HEMA, glycerol monomethacrylate (GMA) and 2-hydroxypropyl methacrylate (HPMA) were chosen as suitable hydrophilic and hydrophobic comonomers, respectively. Save et al. have previously examined their homopolymerization via ATRP in detail; good living character was obtained for both monomers in methanol at 20 °C.[30] GMA monomer and the corresponding GMA homopolymer are highly hydrophilic and water-soluble in all proportions. In contrast, HPMA monomer is only soluble in water up to 13% at 25 °C,[30] and HPMA homopolymer is completely water-insoluble regardless of its target DP_n.

In an initial set of experiments, GMA was statistically copolymerized with HEMA at varying molar ratios, with an overall DP_n of 45 being targeted in all cases (see Table 2). This DP_n was chosen since HEMA homopolymer of this molecular weight is not fully water-soluble (at 5 °C approximately 15% remains insoluble) so the effect of incorporating the more hydrophilic GMA comonomer should be readily discernible. Addition of 11 mol % GMA led to a completely water-soluble HEMA−GMA statistical copolymer with a cloud point of 33 °C, which is 5 °C higher than the corresponding HEMA homopolymer. Statistical copolymers synthesized with as little as 22 mol % GMA were also water-soluble and exhibited no cloud point behavior at temperatures up to 95 °C. In a second experiment, 16 mol % GMA was copolymerized with HEMA at an overall target DP_n of 60. Only 58% of a HEMA homopolymer of this DP_n was water-soluble at 5 °C (see Table 1 and Figure 4), whereas the resulting HEMA−GMA statistical copolymer was fully water-soluble and had a cloud point of 42 °C (see Table 2).

The effect of copolymerizing the more hydrophobic HPMA monomer with HEMA was also assessed. In these syntheses an overall DP_n of only 15 was chosen since such HEMA homopolymers are completely water-soluble even above 85 °C. It was anticipated that the HEMA−HPMA statistical copolymers would become either completely water-insoluble or exhibit cloud point behavior, depending on their HPMA content. The incorporation of as little as 20 mol % HPMA produced a copolymer with a cloud point of 31 °C, while a copolymer containing 33 mol % HPMA phase-separated from water at 26 °C (see Table 2). It should be noted that the polydispersities of all of these HEMA-based copolymers

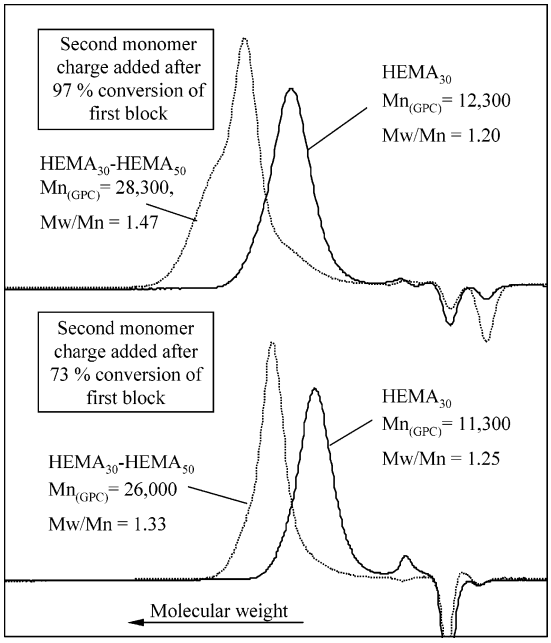

Figure 5. Self-blocking or chain extension experiments conducted for the homopolymerization of HEMA using methanolic ATRP at 20 °C. The effect of monomer conversion of the first HEMA block in chain extension experiments. Note the tailing to high and low molecular weights for the final polymer when the second monomer charge was added at higher conversion.

remained low at each of the comonomer ratios explored, and the overall conversions exceeded 99% in all cases.

In view of the above results it is clear that the judicious choice of comonomer and careful control over both the copolymer composition and target DP_n enables the water solubility and cloud point behavior of HEMA-based copolymers to be manipulated quite readily.

Chain Extension Experiments for HEMA Homopolymerizations. From the viewpoint of synthetic utility, the most desirable feature of a "living" polymerization is the ability to prepare well-defined diblock copolymers via sequential monomer addition. As a precursor to such syntheses, we investigated the living character of the chain extension of HEMA homopolymer with HEMA. Thus, HEMA was polymerized to high conversions (>95%), prior to the addition of a second batch of HEMA monomer to this polymerizing solution. Assuming that all chain ends remained reactive, a predetermined increase in molecular weight is expected, and the final polydispersity should remain low. Although the expected increase in molecular weight was achieved, a high molecular weight shoulder was observed in the GPC chromatogram (shown in Figure 5), suggesting that some termination by combination had occurred at high conversions. Moreover, there was also a small low molecular weight shoulder that corresponded to the original HEMA homopolymer precursor. These features contribute to a relatively high polydispersity of 1.47 for this chain-extended HEMA homopolymer, whereas the homopolymer precursor had a polydispersity of only 1.20. In view of these observations, another "self-blocking" experiment was performed in which the second monomer charge was added at only 73% conversion. In this case, the expected increase in molecular weight was also observed, but this time the GPC chromatogram remained symmetrical and the final polydispersity of the chain-extended HEMA homopolymer was only 1.33 (see Figure 5). This indicated that side reactions appear to be problematic for the polymerization of HEMA under monomer-starved conditions, as generally expected for ATRP syntheses.[31] However, efficient chain extension of HEMA homopolymers using other comonomers such as methyl methacrylate and 2-(diethylamino)ethyl methacrylate can be achieved even after relatively high HEMA conversions (see below).

Synthesis of HEMA-Based Block Copolymers. Living radical polymerization techniques such as ATRP are often exploited for the synthesis of well-defined block copolymers.[17c,32] A summary of several HEMA-based block copolymers prepared via one-pot syntheses using methanolic ATRP at 20 °C is presented in Table 3.

A well-defined $HEMA_{15}-PPO_{33}$ diblock copolymer with a GPC M_n of 10 000 and an M_w/M_n of 1.21 was prepared by homopolymerizing HEMA using a PPO-based macroinitiator (see entry 1 in Table 3). We have recently reported that the ATRP of GMA in methanolic solution is well-controlled.[30] Thus, GMA was selected for the preparation of a highly hydrophilic first block. HEMA monomer was added after 98% conversion of the GMA to give a well-defined diblock copolymer with an M_n of 21 700 and an M_w/M_n of 1.26 (see entry 2 in Table 3). Despite the relatively poor self-blocking behavior observed for HEMA, a HEMA−MMA diblock copolymer of relatively low polydispersity was obtained by the addition of MMA to a polymerizing HEMA solution after 92% conversion of the first monomer (see entry 3 in Table 3).

The aqueous solution properties of each diblock copolymer were assessed in turn by DLS. In each case appropriate conditions were employed to promote micellar self-assembly. The $HEMA_{20}-PPO_{33}$ diblock copolymer was initially molecularly dissolved at 5 °C and pH 2.5. The formation of PPO-core micelles was expected at elevated temperature, but only macroscopic precipitation occurred. This suggests that the HEMA block is not sufficiently hydrophilic to allow micelle formation, even at pH 2.5. In contrast, although water-insoluble at pH 6.5, the $HEMA_{60}-MMA_{28}$ diblock copolymer dissolved slowly over several hours when added directly to dilute HCl (pH 2.5) and formed near-monodisperse HEMA-corona micelles of 17 nm diameter. Figure 6 shows the ^1H NMR spectrum of the $HEMA_{60}-MMA_{28}$ diblock copolymer molecularly dissolved in d_4-methanol. Signals due to both the HEMA and MMA blocks are clearly visible at δ 3.7−4.2 and δ 3.6, respectively. If this solution is then diluted with DCl/D_2O, the latter signal disappears (see Figure 6b). This is expected since the hydrophobic MMA block forms dehydrated micelle cores under these conditions. On the other hand, the HEMA signals remain visible, since this block forms the solvated corona layer.

Zeta potentials of around +16 mV are obtained at low pH for micelles prepared from this $ME-HEMA_{60}-MMA_{28}$ diblock copolymer and are shown in the Supporting Information. These micelles precipitate from dilute aqueous solution at around pH 4.5, which is approximately the same pH at which the ME-Br initiator is deprotonated and becomes water-insoluble. It is also noteworthy that the $HEMA_{15}-PPO_{33}$ diblock does not contain terminal morpholine groups, and this copolymer cannot form stable micelles at low pH. Thus, the enhanced water solubility of the $ME-HEMA_{60}-MMA_{28}$ diblock copolymer and the various ME−HEMA

Table 3. Summary of the Various HEMA-Based Diblock Copolymers Prepared via One-Pot Syntheses in Methanolic ATRP at 20 °C

entry no.	target copolymer composition	first block			overall block copolymer		
		conv (%)[a]	M_n/GPC	M_w/M_n	conv (%)[a]	M_n/GPC	M_w/M_n
1	$PPO_{33}-HEMA_{15}$		10000[e]	1.21[e]	>99	10000	1.21
2	$GMA_{50}-HEMA_{30}$	98	15700[b]	1.29[b]	>99	21700[b]	1.26[b]
3	$HEMA_{50}-MMA_{20}$	92	11300[b]	1.22[b]	95	15200[b]	1.25[b]
4	$PEO_{45}-HEMA_{30}-DEA_{50}$	98	2000[c]	1.10[c,d]	>99	15700[c]	1.17[c]

[a] As determined by ^{1}H NMR. [b] As determined by DMF GPC against PMMA standards. [c] Determined by THF GPC against PMMA standards. [d] GPC data for the PEO_{45}-Br macroinitiator alone, since the $PEO_{45}-HEMA_{30}$ diblock is not soluble in THF. [e] GPC data for the PPO_{33}-Br macroinitiator alone.

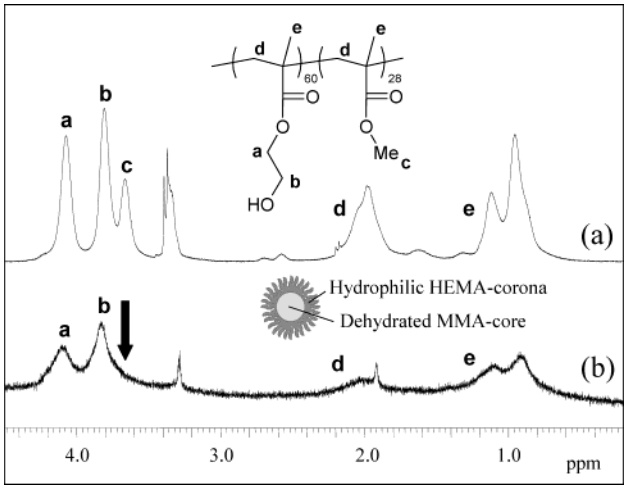

Figure 6. ^{1}H NMR spectra recorded for the $HEMA_{60}-MMA_{28}$ diblock copolymer: (a) molecularly dissolved in d_4-methanol as a 0.50% w/v solution and (b) dispersed as a 2.0% w/v aqueous micellar solution [d_4-methanol was used as a cosolvent to predissolve the copolymer, prior to its dilution with 0.01 M DCl/D_2O]. Note the disappearance of the proton resonance at δ 3.6 due to the MMA residues, indicating that this block forms the micelle cores.

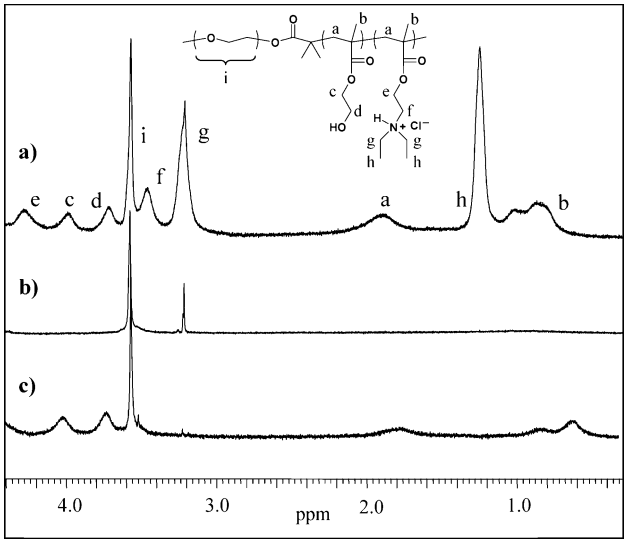

Figure 7. ^{1}H NMR spectra recorded for the $PEO_{45}-HEMA_{30}-DEA_{50}$ triblock copolymer at (a) pH 2 and 20 °C, (b) pH 12 and 20 °C, and (c) pH 12 and 3 °C. Note the oxyethylene proton resonances reappear at δ 3.6−4.2 ppm in (c).

homopolymers was considered most likely to be due to protonation of the terminal morpholine group derived from the ME-Br initiator. To verify this hypothesis, two HEMA homopolymers of $DP_n = 20$ and 50 were synthesized using the ethyl 2-bromoisobutyrate initiator previously reported by Matyjaszewski and co-workers.[33] At pH 6.5, these two homopolymers had essentially the same cloud points as the corresponding two ME−HEMA homopolymers. However, the two ethyl 2-bromoisobutyrate-initiated homopolymers did not exhibit increased water solubility at pH 2.5. This indicates that protonation of the morpholine end group is responsible for the enhanced hydrophilicity of ME−HEMA homopolymers observed at low pH.

The $GMA_{50}-HEMA_{30}$ diblock copolymer dissolved molecularly at pH 6.5 and 20 °C but formed polydisperse colloidal aggregates of around 140 nm diameter at elevated temperatures due to weak attractive interactions between the hydrophobic HEMA blocks. The cores of these micellar aggregates are presumably relatively hydrated, as the scattered light intensity was significantly lower than that normally found for compact, core−shell micelles. Moreover, variable temperature ^{1}H NMR studies (not shown) indicated that the HEMA signals were not attenuated relative to the GMA signals at elevated temperatures.

The polymerization of HEMA using a poly(ethylene oxide)-based macroinitiator with a DP_n of 45, followed by the in situ addition of 2-(diethylamino)ethyl methacrylate (DEA), leads to a well-defined $PEO_{45}-HEMA_{30}-DEA_{50}$ triblock copolymer (entry 4, Table 3) with a final M_w/M_n of 1.17, as reported previously.[34] However, in this earlier report we did not fully appreciate the thermoresponsive behavior of HEMA homopolymer. In view of the new water-solubility data reported in the present study, we decided to revisit the aqueous solution behavior of this triblock copolymer. A ^{1}H NMR spectrum recorded at 20 °C in DCl/D_2O (approximately pH 2) shows signals assigned to the PEO, HEMA, and the DEA residues, which are all completely water-soluble at low pH (see Figure 7a). On raising the solution pH, the triblock copolymer forms DEA-core micelles (DEA signals are suppressed) with a mixed corona of PEO and HEMA blocks at pH 8, providing that the temperature is kept below 5 °C.[30] At pH 12 and 20 °C, the ^{1}H NMR signals due to the HEMA block are also suppressed, suggesting that this central block becomes dehydrated at ambient temperature (see Figure 7b). This is despite the fact that a HEMA homopolymer of the same DP_n remains water-soluble under these conditions. Presumably this is because the hydrophobic DEA chains have a negative influence on the cloud point of the central HEMA block. To confirm that the HEMA block is thermoresponsive, a ^{1}H NMR spectrum was recorded at pH 12 and 3 °C (see Figure 7c). This spectrum clearly shows the reappearance of the HEMA signals at δ 3.6−4.2. Thus, the central HEMA block can become part of the micelle core or the micelle corona, depending on the precise solution conditions. Variable temperature DLS experiments were performed on the aqueous copolymer micelles at pH 11 (see Figure 8). A significant increase in micelle diameter was observed at around 7 °C, which

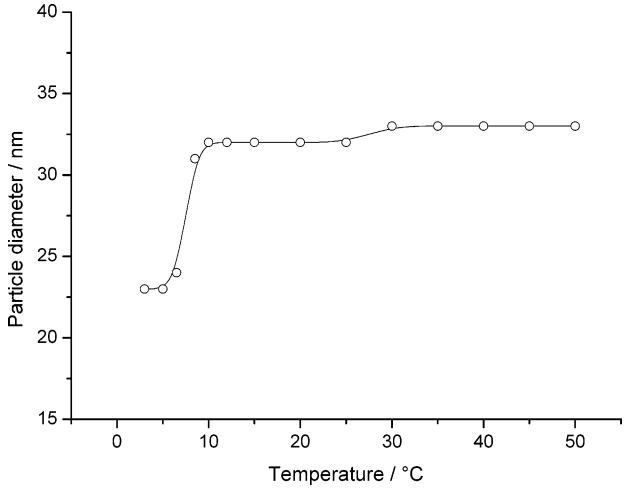

Figure 8. Variation of intensity-average micelle diameter with temperature for a 0.50% w/v solution of PEO_{45}−$HEMA_{30}$−DEA_{50} micelles at pH 11. Note the increase in micelle diameter at around 7 °C as the water-soluble HEMA block becomes progressively dehydrated and forms the micelle cores, along with the hydrophobic DEA block.

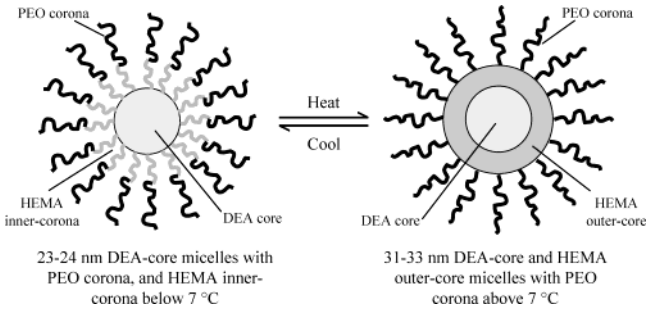

Figure 9. Schematic representation of the temperature-dependent self-assembly of a 0.50% w/v solution of a PEO_{45}−$HEMA_{30}$−DEA_{50} triblock copolymer at pH 11. Below 7 °C, the HEMA block forms the hydrophilic inner shell of the micelle corona. Above 7 °C, the HEMA block forms the hydrophobic outer layer of the micelle core.

is interpreted as the effective "cloud point" of the central HEMA block. Below 7 °C, the HEMA residues are hydrated, and at higher temperatures the HEMA residues are dehydrated; this subtle shift in the hydrophilic−hydrophobic balance of the copolymer chains leads to a change in the internal structure of the micelles (see Figure 9).

Conclusions

We have exploited ATRP to demonstrate that HEMA-based homopolymers of sufficiently low DP_n are actually water-soluble, rather than merely water-swellable. Moreover, HEMA homopolymers with DP_n's of between 20 and 35 exhibit thermoresponsive behavior, with cloud points ranging from 28 to 39 °C at pH 6.5. At lower DP_n's no inverse temperature solubility behavior was observed. Higher molecular weight HEMA homopolymers ($DP_n > 40$) were only partially soluble in water at pH 6.5, and the soluble fraction decreased monotonically with increasing DP_n, as judged by gravimetry experiments. The hydrophilicity of the HEMA homopolymers was also found to be unexpectedly pH-dependent. At pH 2.2 all HEMA homopolymers up to a DP_n of 75 were soluble at 10 °C. Under the same conditions, homopolymers with DP_n's of 60 and 75 had cloud points of 31 and 20 °C, respectively. Control experiments with nonfunctional ATRP initiators indicate that the enhanced water solubility of these HEMA homopolymers in acidic solution is due to protonation of their tertiary amine end groups, rather than an intrinsic property of the HEMA homopolymers. The cloud point behavior observed at pH 6.5 could be tuned over a wide range by copolymerizing with either a more hydrophilic hydroxy-functional monomer such as glycerol monomethacrylate or a more hydrophobic monomer such as 2-hydroxypropyl methacrylate. Judicious choice of pH, temperature, and block composition enabled both HEMA-core and HEMA-corona micelles to be prepared from various HEMA-based diblock copolymers. Finally, it has been shown that the central HEMA block of a PEO−HEMA−DEA triblock copolymer can form either the micelle core or micelle corona depending on the solution pH and temperature.

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Supporting Information Available: Figures showing the relationship between the actual degree of polymerization and cloud point for water-soluble thermoresponsive HEMA homopolymers (Figure S1) and zeta potential data for ME−$HEMA_{60}$−MMA_{28} diblock copolymer micelles (Figure S2). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Wichterle, O.; Lim, D. *Nature (London)* **1960**, *185*, 118.
(2) Barrett, G. D.; Constable, I. J.; Steward, A. D. *J. Cataract Refract. Surg.* **1986**, *12*, 623.
(3) Menace, R.; Skorpik, C.; Juchem, M.; Scheidel, W.; Schranz, R. J. *J. Cataract Refract. Surg.* **1989**, *15*, 264.
(4) Seifert, L. M.; Green, R. T. *J. Biomed. Mater. Res.* **1985**, *19*, 1043.
(5) Okano, T.; Aoyagi, T.; Kataoka, K.; Abe, K.; Sakurai, Y.; Shimadada, M.; Shinohara, I. *J. Biomed. Mater. Res.* **1986**, *20*, 919.
(6) Bennet, H. S.; Wyricks, A. D.; Lee, S. W.; McNeil, H. J. *Stain Technol.* **1976**, *51*, 71.
(7) Canal, T.; Peppas, N. A. *J. Biomed. Mater. Res.* **1989**, *23*, 1183.
(8) Mijajima, M.; Okano, T.; Kim, S. W.; Higushi, W. I. *J. Controlled Release* **1987**, *5*, 179.
(9) Pinchuk, L.; Eckstein, E. C.; Van der Mark, M. R. *J. Biomed. Mater. Res.* **1984**, *18*, 671.
(10) Montheard, J. P.; Kahovec, J.; Chappard, D. In *Desk Reference of Functional Polymers Syntheses and Applications;* Arshady, R., Ed.; American Chemical Society: Washington, DC, 1997; Chapter 5.3.
(11) Ishizone, T.; Han, S.; Okuyama, S.; Nakahama, S. *Macromolecules* **1986**, *19*, 1294.
(12) Mori, H.; Wakisaka, O.; Hirao, A.; Nakahama, S. *Macromol. Chem. Phys.* **1994**, *195*, 3213.
(13) Haddleton, D. M.; Depaquis, E.; Kelly, E. J.; Kukulj, D.; Morsley, S. R.; Bon, S. A. F.; Eason, M. D.; Steward, A. G. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 2378.
(14) Gregoris, D. E.; Russel, G. A.; Andrade, J. D.; De Visser, A. C. *Polymer* **1978**, *19*, 1279.
(15) Sogah, D. Y.; Hertler, W. R.; Webster, O. W.; Cohen, G. M. *Macromolecules* **1987**, *20*, 1473.

(16) Nagasaki, Y.; Ito, H.; Kato, M.; Kataoka, K.; Tsuruta, T. *Polym. Bull. (Berlin)* **1995**, *35*, 137.
(17) (a) Kato, M.; Kamagaito, M.; Sawamoto, M.; Higashimura, T. *Macromolecules* **1995**, *28*, 1721. (b) Wang, J. S.; Matyjaszewski, K. *J. Am. Chem. Soc.* **1995**, *117*, 5614. (c) Patten, T. E.; Matyjaszewski, K. *Adv. Mater.* **1998**, *10*, 901.
(18) Xia, J. H.; Gaynor, S. G.; Matyjaszewski, K. *Macromolecules* **1998**, *31*, 5989.
(19) Haddleton, D. M.; Kukulj, D.; Duncalf, D. J.; Heming, A. J.; Shooter, A. J. *Macromolecules* **1998**, *31*, 5201.
(20) Patten, T. E.; Xia, J.; Abernathy, T.; Matyjaszewski, K. *Science* **1996**, *272*, 866.
(21) Robinson, K. L.; Weaver, J. V. M.; Armes, S. P.; Diaz Marti, E.; Meldrum, F. C. *J. Mater. Chem.* **2002**, *12*, 890.
(22) Robinson, K. L.; de Paz Banez, M. V.; Wang, X.-S.; Armes, S. P. *Macromolecules* **2001**, *34*, 5799.
(23) (a) Liu, S.; Armes, S. P. *J. Am. Chem. Soc.* **2001**, *123*, 9910. (b) Liu, S.; Weaver, J. V. M.; Tang, Y.; Billingham, N. C.; Armes, S. P.; Tribe, K. *Macromolecules* **2002**, *35*, 6121.
(24) (a) Chu, B. *Laser Light Scattering*; Academic Press: New York, 1974. (b) Berne, B. J.; Pecora, R. *Dynamic Light Scattering*; Plenum Press: New York, 1976.
(25) Robinson, K. L.; Khan, M. A.; de Paz Banez, M. V.; Wang, X.-S. *Macromolecules* **2001**, *34*, 3155.
(26) Beers, K. L.; Boo, S.; Gaynor, S. G.; Matyjaszewski, K. *Macromolecules* **1999**, *32*, 5772.
(27) Ma, Y.; Lobb, E. J.; Armes, S. P.; Billingham, N. C.; Lewis, A. L.; Lloyd, A. W.; Salvage, J. P. *Macromolecules* **2002**, *35*, 9306.
(28) Tsarevsky, N. V.; Pintauer, T.; Glogowski, E.; Matyjaszewski, K. *ACS Polym. Prepr.* **2002**, *43* (2), 201.
(29) Zhang, J.; Pelton, R. *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 2137.
(30) Save, M.; Weaver, J. V. M.; Armes, S. P.; McKenna, P. *Macromolecules* **2002**, *35*, 1152.
(31) Matyjaszewski, K.; Shipp, D. A.; McMurtry, G. P.; Pakula, T. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 2023.
(32) (a) Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001**, *101*, 3689. (b) Matyjaszewski, K.; Xia, J. H. *Chem. Rev.* **2001**, *101*, 2921.
(33) Matyjaszewski, K.; Wang, J. L.; Grimaud, T.; Shipp, D. A. *Macromolecules* **1998**, *31*, 1527.
(34) Liu, S.; Weaver, J. V. M.; Save, M.; Armes, S. P. *Langmuir* **2002**, *18*, 8350.

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