Polymer Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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First Amphiphilic Graft Copolymer Bearing Hydrophilic Poly(2-hydroxylethyl acrylate) Backbone Synthesized by Successive RAFT and ATRP

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ABSTRACT

A series of well-defined amphiphilic graft copolymers, consisting of a hydrophilic poly(2-hydroxyethyl acrylate) (PHEA) backbone and hydrophobic polystyrene side chains, was synthesized by the combination of reversible addition-fragmentation chain transfer (RAFT) polymerization, atom transfer radical polymerization (ATRP), and the grafting-from strategy. A new acrylate monomer containing ATRP initiating group, 2-hydroxyethyl 2-((2-chloropropanoyloxy)methyl)acrylate, was first prepared via a four-step procedure using 2-hydroxyethyl acrylate as starting material. This monomer was then RAFT homopolymerized to give a PHEA-based homopolymer bearing Cl-containing ATRP initiating group in every repeating unit with a narrow molecular weight distribution (M_w/M_n = 1.08). This homopolymer directly initiated ATRP of styrene to afford the desired well-defined poly(2-hydroxyethyl acrylate)-*graft*-polystyrene graft copolymers ($M_w/M_n \leq 1.30$) containing hydroxyl in every repeating unit of the backbone without polymeric functionality transformation. The self-assembly behavior of the obtained amphiphilic graft copolymers was investigated by dynamic light scattering (DLS) and transmission electron microscopy (TEM).

Keywords: graft copolymer; ATRP; RAFT; PHEA; self-assembly.

Introduction

Graft polymer is a special type of polymer in which multiple polymer chains are attached to a linear polymer. The main chain is commonly referred to as backbone and the branches as side chains. Due to their confined and compact structure, graft copolymers are endowed with fascinating properties including wormlike conformation, compact molecular dimension, and notable chain end effects in comparison with linear counterparts with similar molecular weight.[1-3] Progress in this field would deepen the understanding of the correlation between the architecture of copolymers and their micellization behaviors and improve the ability to tune the properties of polymers through chemical design.

The synthesis of well-defined graft copolymers is usually difficult due to their complicated and confined structure compared to the linear counterpart. Generally, three different strategies, defined as "grafting-through",[4-6] "grafting-onto",[7-9] and "grafting-from"[3,10-17] could be employed to synthesize graft copolymers. The "grafting-through" approach (polymerization of macromonomers with a polymerizable end group) seems to be not an easy task because graft copolymers attained via this way are often with broad molecular weight distributions from conventional radical polymerization or with well-defined structures but very low molecular weights while using living polymerization.[18] Graft polymers obtained via the "grafting-onto" method (addition of pre-synthesized side chains to a polymeric backbone) usually display an insufficient grafting efficiency and require further purification to remove the unreacted side chains.[8] Thanks to the advent of

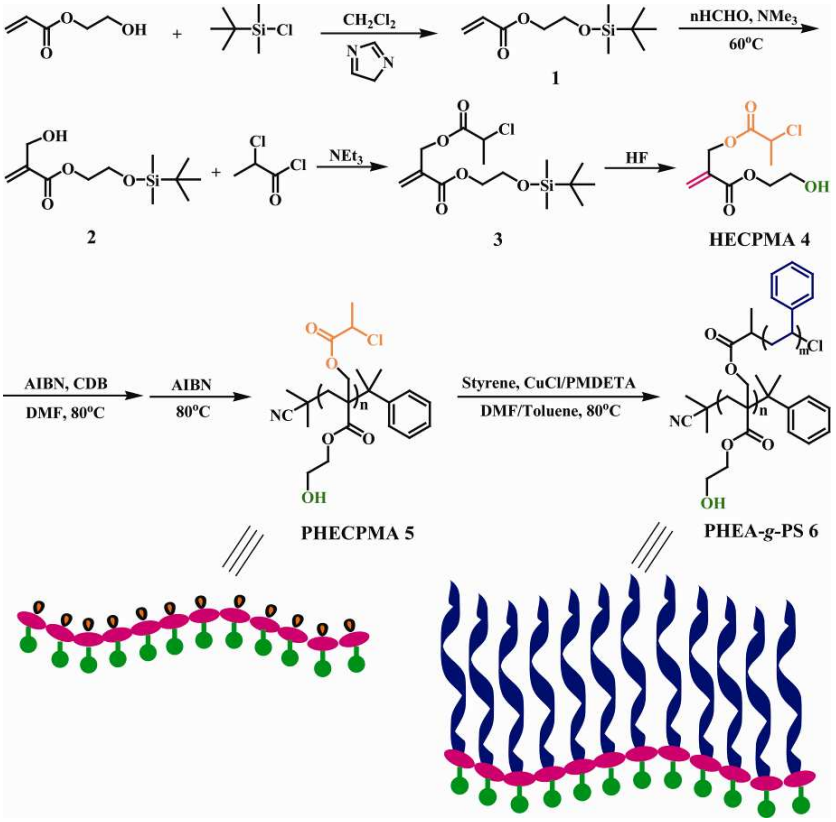
reversible-deactivation radical polymerization (RDRP), including atom transfer radical polymerization (ATRP),[19-23] reversible addition-fragmentation chain transfer (RAFT) polymerization,[24,25] and single-electron-transfer living radical polymerization (SET-LRP),[26,27] constructing graft polymers via the "grafting-from" strategy (polymerization of the second monomer for side chains initiated by pendant initiating sites on a polymeric backbone) is becoming more convenient, and simultaneously, of greater popularization in comparison with other two aforementioned methods. However, the backbone is usually needed to be chemically modified in order to introduce the active pendant initiating groups and the number of grafting sites is difficult to be regulated because of the complexity of macromolecular reaction. The characteristic example lay in polysaccharide backbone-based graft copolymers. Natural polysaccharides are renewable, non-toxic, biodegradable, and excellent biocompatible materials, and play a very important role in the design of biomaterials. Hydroxyls in polysaccharides were usually converted to ATRP initiating groups followed by ATRP of suitable monomers[28-33] or directly initiated ring opening polymerization (ROP) of lactones,[34-36] generating well-defined graft copolymers bearing polysaccharide backbone.

In this contribution, a unique approach is to design a new functional monomer tailored to graft polymers: a carbon-carbon double bond to form the backbone and an initiating site to graft the side chains. Besides, this new monomer should also contain a hydrophilic or at least potential hydrophilic group if we aim at synthesizing graft copolymers with hydrophilic backbone and hydrophobic side chains. This kind of

monomer can be homopolymerized or copolymerized with another suitable monomer without initiating site to give a well-defined backbone containing a certain amount of initiating groups. Then, the backbone can directly initiate the polymerization of a second monomer to afford well-defined graft copolymers without polymeric functional group transformation.

For 2-hydroxyethyl acrylate (HEA)- and 2-hydroxyethyl methylacrylate (HEMA)-based graft copolymer systems,[12,17,37-48] hydroxyls in PHEA/PHEMA polymer chain are usually utilized for preparing biodegradable polyester side chains via ROP,[49,50] or transformed into Cl- or Br-containing ATRP initiating groups followed by initiating ATRP/SET-LRP of suitable monomers,[12,37-44] or converted to alkyne followed by click reaction with azide-containing polymer.[8] The existence of protection process before the polymerization of HEA/HEMA and the deprotection process after the polymerization of HEA/HEMA obviously make the preparation of macroinitiator seem even complicated and inconvenient. Furthermore, the pendant hydroxyl of HEA/HEMA is employed for connecting the side chains in all previous related studies so that until now, none has reported on the graft copolymer containing a hydrophilic PHEA/PHEMA backbone with hydroxyl in every repeating unit of the backbone. To construct new HEA/HEMA-based graft copolymer with a hydrophilic PHEA/PHEMA backbone by preserving the hydrophilicity of hydroxyl, we designed and synthesized a novel trifunctional monomer, 2-hydroxyethyl 2-((2-chloro-propanoyloxy)methyl)acrylate (HECPMA), which possesses a polymerizable double bond, an ATRP initiating group (-OCOCH(CH_3)Cl), and a hydrophilic hydroxyl

simultaneously. The preparation of HECPMA was accomplished by a four-step process as shown in Scheme 1: protection of hydroxyl of HEA, insertion of hydroxymethyl via Baylis-Hillman reaction, corporation of ATRP initiating group, and deprotection of hydroxyl. HECPMA monomer was then RAFT homopolymerized to form a well-defined PHEA-based macroinitiator with an ATRP initiation group in every repeating unit followed by initiating ATRP of styrene to obtain the target poly(2-hydroxyethyl acrylate)-*g*-polystyrene (PHEA-*g*-PS) well-defined amphiphilic graft copolymers. The self-assembly behavior of PHEA-*g*-PS amphiphilic copolymer in aqueous media was then investigated in detail.



Scheme 1. Synthesis of 2-hydroxyethyl 2-((2-chloropropanoyloxy)methyl)acrylate (HECPMA) monomer and its application in constructing PHEA-*g*-PS well-defined amphiphilic graft copolymer.

Experimental Section

Materials

Styrene (St, Aldrich, 99%) was washed with 5% aqueous NaOH solution to remove the inhibitor and then with water, dried over $MgSO_4$, and distilled twice from CaH_2 under reduced pressure prior to use. 2,2'-Azobis(isobutyronitrile) (AIBN, Aldrich, 98%) was recrystallized from anhydrous ethanol two times. Copper (I) chloride (CuCl, Aldrich, 98%) was purified by stirring overnight over CH_3CO_2H at room temperature, followed by washing the solid with ethanol, diethyl ether, and acetone prior to drying at 40°C *in vacuo* for one day. Triethylamine (Et_3N, Aldrich, 99.5%) was dried over KOH and distilled from CaH_2 under N_2 prior to use. Cumyl dithiobenzoate (CDB) was synthesized according to previous literature.[51] Dichloromethane (Aldrich, 99.5%), acetonitrile (CH_3CN, Aldrich, 99.8%), and dimethyl formamide (DMF, Aldrich, 99.8%) were dried over KOH and distilled from CaH_2 under N_2 prior to use. Toluene (Aldrich, 99.8%) and tetrahydrofuran (THF, Aldrich, 99%) were dried over CaH_2 and distilled from sodium and benzophenone under N_2 prior to use. 2-Hydroxyethyl acrylate (HEA, Aldrich, 97%), *tert*- butyldimethylsilyl chloride (TBDMSCl, Aldrich, 95%), imidazole (Alfa Asear, 99%), paraformaldehyde (nHCHO, Aldrich, 95%), 2-chloropropionyl chloride (Aldrich, 97%), trimethylamine (NMe_3, Aldrich, 99.5%), hydrofluoric acid (HF, Aldrich, 48 wt. %), and *N,N,N',N',N'*-pentamethyldiethylenetriamine (PMDETA, Aldrich, 99%) were used as received.

Characterizations

FT-IR spectra were recorded on a Nicolet AVATAR-360 FT-IR spectrophotometer with a 4 cm^{-1} resolution. All ^{1}H (400 MHz) and ^{13}C (125 MHz) NMR analyses were performed on a Bruker Avance 500 spectrometer in $CDCl_3$ and DMSO-d_6, tetramethylsilicone (^{1}H NMR) and $CDCl_3$ (^{13}C NMR) were used as internal standards. Electrospray ionization mass spectrometry (ESI-MS) was measured by an Agilent LC/MSD SL system. Elemental analysis was carried out on a Carlo-Erba1106 system. Chlorine content was determined by the titration with $Hg(NO_3)_2$. Relative molecular weights and molecular weight distributions were measured by conventional gel permeation chromatography (GPC) system equipped with a Waters 1515 Isocratic HPLC pump, a Waters 2414 refractive index detector, and a set of Waters Styragel columns (HR3 (500-30,000), HR4 (5,000-600,000), and HR5 (50,000-4,000,000), 7.8×300 mm, particle size: 5 μm). GPC measurements were carried out at 35°C using THF as eluent (flow rate: 1.0 mL/min). The system was calibrated with linear poly(methyl methacrylate) standards (for PHECPMA macroinitiator) and polystyrene standards (for PHEA-*g*-PS graft copolymers). Absolute molecular weights of the macroinitiator and graft copolymers were determined by GPC equipped with a multiangle light scattering detector (GPC/MALS), THF was used as the eluent with a flow rate of 1.0 mL/min, detectors: Wyatt Optilab rEX refractive index detector and Wyatt DAWN HELEOS 18-angle light scattering detector with a 50 mW solid-state laser operating at 658 nm. TEM images were obtained by a JEOL JEM-1230 instrument operated at 80 kV. Hydrodynamic diameter (D_h) was measured by dynamic

light scattering (DLS) with a Malvern Nano-ZS90 Zetasizer; the samples were allowed to equilibrate for 2 min at 25°C prior to measurement.

Synthesis of *tert*-Butyldimethylsilyloxyethyl Acrylate 1

In a dry 1000 mL three-neck flask sealed with a rubber septum, TBDMSCl (60.2 g, 39.9 mmol), imidazole (56.7g, 83.2 mmol), and 300 mL of dry dichloromethane were added under N_2 followed by adding HEA (34 mL, 33.3 mmol) dropwise over 30 min. A white precipitate formed immediately and the mixture was stirred at 0°C overnight and filtered to remove solids. The filtrate was washed with dilute Na_2CO_3 (aq., 3×200 mL) to remove unreacted TBDMSCl, dried over anhydrous $MgSO_4$ overnight. The filtrate was concentrated and distilled under reduced pressure (1 mbar/58°C) to give 46.5 g of colorless liquid, *tert*-butyldimethylsilyloxyethyl acrylate (HEA-TBDMS) **1**, with a yield of 61%. ^{1}H NMR ($CDCl_3$ without TMS): δ (ppm): 0.06 (s, 6H, Si(CH_3)$_2$), 0.88 (s, 9H, C(CH_3)$_3$), 3.84 (t, 2H, $CO_2CH_2CH_2$OSi), 4.22 (t, 2H, $CO_2CH_2CH_2$OSi), 5.84, 6.39 (q, 2H, CH_2=CH), 6.14 (q, 1H, CH_2=CH). ^{13}C NMR ($CDCl_3$ without TMS): δ (ppm): -5.5 (Si(CH$_3$)$_2$), 18.1 (C(CH$_3$)$_3$), 25.6 (C(CH$_3$)$_3$), 61.2 ($CO_2CH_2CH_2$OSi), 65.6 ($CO_2CH_2CH_2$OSi), 128.3 (CH_2=CH), 130.7 (CH_2=CH), 166.1 ($CO_2CH_2CH_2$OSi).

Synthesis of *tert*-Butyldimethylsilyloxyethyl (2-Hydroxymethyl)acrylate 2

HEA-TBDMS **1** (44.8 g, 19.4 mmol), nHCHO 2.9 g (9.7 mmol), and NMe_3 (23.2 mL, 11.7 mmol) were added to a 100 mL single-neck flask. The solution was stirred at

room temperature for 3 h followed by stirring at 60°C for 3 days. The aqueous phase was extracted by ether and all organic layers were merged and washed by brine followed by drying over $MgSO_4$. A colorless liquid, *tert*-butyldimethylsilyloxyethyl (2-hydroxymethyl)acrylate **2** (11.5 g, 45.4%), was obtained by silica column chromatography (eluent: ethyl acetate/hexane (*v:v*) = 1:5). ^{1}H NMR ($CDCl_3$ without TMS): δ (ppm): 0.06 (s, 6H, Si(CH_3)$_2$), 0.88 (s, 9H, C(CH_3)$_3$), 2.39 (s, 1H, CH_2OH), 3.85 (t, 2H, $CO_2CH_2CH_2OSi$), 4.26 (t, 2H, $CO_2CH_2CH_2OSi$), 4.33 (s, 2H, CH_2OH), 5.84, 6.28 (s, 2H, CH_2=C). ^{13}C NMR ($CDCl_3$ without TMS): δ (ppm): -5.4 (Si(CH_3)$_2$), 18.3 ($C(CH_3)_3$), 25.8 (C(CH_3)$_3$), 61.2 ($CO_2CH_2CH_2OSi$), 62.6 (CH_2=CCH_2OH), 66.0 ($CO_2CH_2CH_2OSi$), 126.0 (CH_2=C), 139.4 (CH_2=C), 166.2 (CH_2=$CHCO_2$).

Synthesis of *tert*-Butyldimethylsilyloxyethyl 2-((2-Chloropropanoyloxy)methyl)-acrylate 3

In a dry 250 mL three-neck flask sealed with a rubber septum, *tert*-butyldimethyl-silyloxyethyl (2-hydroxymethyl)acrylate **2** (10.0 g, 38.4 mmol), anhydrous Et_3N (6.4 mL, 38.4 mmol), and 120 mL of CH_2Cl_2 were added under N_2. The solution was cooled to 0°C and 4.0 mL of 2-chloropropionyl chloride was added dropwise over 20 min. The system was stirred at 0°C for 1 h and raised to room temperature with stirring overnight followed by filtration. A colorless liquid, *tert*-butyldimethylsilyl-oxyethyl 2-((2-chloropropanoyloxy)methyl)acrylate **3** (9.7 g, 72%), was obtained by silica column chromatography (eluent: ethyl acetate/hexane (*v:v*) = 1:50). ^{1}H NMR ($CDCl_3$ without TMS): δ (ppm): 0.07 (s, 6H, Si(CH_3)$_2$), 0.89 (s, 9H, C(CH_3)$_3$), 1.70 (d,

3H, CHClCH_3), 3.85 (t, 2H, $CO_2CH_2CH_2OSi$), 4.26 (t, 2H, $CO_2CH_2CH_2OSi$), 4.43 (q, 1H, CHClCH$_3$), 4.91 (q, 2H, CH_2=CCH_2O), 5.92, 6.42 (s, 2H, CH_2=C). ^{13}C NMR ($CDCl_3$ without TMS): δ (ppm): -5.3 (Si(CH_3)$_2$), 18.4 (C(CH_3)$_3$), 21.6 (CH_3CHCl), 25.8 (C(CH_3)$_3$), 52.4 (CH_3CHCl), 61.2 ($CO_2CH_2CH_2OSi$), 63.7 (CH_2=CCH_2O), 66.4 ($CO_2CH_2CH_2OSi$), 128.1 (CH_2=CH), 134.9 (CH_2=CH), 165.0 (CH_2=CHCO_2), 169.6 (CO_2CHCl).

Synthesis of HECPMA 4

tert-Butyldimethylsilyloxyethyl 2-((2-chloropropanoyloxy)methyl)acrylate **3** (8.5 g, 24.3 mmol), HF (aq., 24.3 g, 485 mmol), and anhydrous CH_3CN were added to a 1000 mL plastic jar. The mixture was stirred for 2 h at room temperature followed by the addition of *conc.* NaOH aqueous solution for adjusting the pH of solution to 7.0. The aqueous phase was extracted by ether and all organic layers were merged followed by drying over $MgSO_4$ overnight. A colorless liquid, 2-hydroxyethyl 2-((2-chloropropanoyloxy)methyl)acrylate (HECPMA) **4** (2.68 g, 47%), was obtained by silica column chromatography (eluent: ethyl acetate/hexane (*v:v*) = 1:1). ESI-MS (*m/z*) found $(M + Na)^+$: 259. Anal. Calcd. for $C_9H_{13}O_5Cl$: C, 45.68%; H, 5.54%; Cl, 14.98%. Found: C, 45.49%; H, 5.59%; Cl, 14.66%. FT-IR: ν (cm^{-1}): 3447 (ν_{O-H}), 2955 (ν_{C-H}), 2884 (ν_{C-H}), 1718 ($\nu_{C=O}$), 1636 ($\nu_{C=C}$), 1449, 1379, 1309, 1273, 1164, 1076, 1024, 955, 816. ^{1}H NMR ($CDCl_3$): δ (ppm):1.70 (d, 3H, CHClCH_3), 1.91 (s, 1H, CH_2OH), 3.87 (t, 2H, $CO_2CH_2CH_2OH$), 4.33 (t, 2H, $CO_2CH_2CH_2OH$), 4.43 (q, 2H, CO_2CHCl), 4.93 (q, 2H, CH_2=CCH_2O), 5.95, 6.46 (s, 2H, CH_2=C). ^{13}C NMR ($CDCl_3$):

δ (ppm): 21.2 (CH$_3$CHCl), 52.3 (CH$_3$$C$HCl), 60.6 (CO$_2CH_2$$CH_2$OH), 63.6 (CH$_2$=C$CH_2$O), 66.6 (CO$_2$$CH_2CH_2$OH), 129.0 ($CH_2$=C), 134.4 (CH$_2$=$C$), 165.2 (CH$_2$=C$CO_2$), 169.6 ($CO_2$CHCl).

RAFT Homopolymerization of HECPMA

AIBN (18.6 mg, 0.11 mmol) and CDB (92.5 mg, 0.34 mmol) were first added into a 10 mL Schlenk flask (flame-dried under vacuum prior to use) sealed with a rubber septum for degassing and kept under N_2. Next, HECPMA **4** (2.00 g, 8.5 mmol) and 0.43 mL of anhydrous DMF were added via a gastight syringe. The flask was degassed by three cycles of freezing-pumping-thawing followed by immersing the flask into an oil bath set at 70^{o}C. The polymerization was terminated by immersing the flask into liquid N_2 after 10.5 h. THF was added to dilute the solution and the solution was precipitated into ether. The crude product was purified by repeated dissolution and precipitation followed by drying *in vacuo* overnight to give 1.41 g of pink powder.

To remove the dithiobenzoate end moiety, AIBN (1.23 g, 7.5 mmol) and 1.2 g of pink powder (0.375 mmol of dithiobenzoate group) were first added to a 100 mL Schlenk flask (flame-dried under vacuum prior to use) sealed with a rubber septum for degassing and kept under N_2. Next, 50 mL of anhydrous THF was added via a gastight syringe. The flask was immersed into an oil bath set at 60^{o}C and the reaction was quenched by liquid N_2 after 60 h. The solution turned colorless and was precipitated into ether after concentration. After repeated purification via dissolution

and precipitation, 0.72 g of white powder, poly(2-hydroxyethyl 2-((2-chloro-propanoyloxy)methyl)acrylate) (PHECPMA) **5**, was obtained by drying *in vacuo* overnight. GPC: M_n = 5,300 g/mol, M_w/M_n = 1.17. GPC/MALS: M_n = 13,460 g/mol, M_w/M_n = 1.08. FT-IR: ν (cm^{-1}): 3435 (ν_{O-H}), 2953 (ν_{C-H}), 2876 (ν_{C-H}), 1735 ($\nu_{C=O}$), 1450, 1380, 1253, 1175, 1075, 1008, 971, 912, 845, 748. ^{1}H NMR (DMSO-d_6): δ (ppm): 1.18 (12H, terminal C(CH_3)$_2$), 1.67 (3H, CHClCH_3), 1.97 (2H, CH_2CCO$_2$), 3.56 (2H, CO$_2$CH$_2$CH_2OH), 3.83 (2H, CO$_2$CH_2CH$_2$OH), 4.07 (2H, CO$_2$CCH_2O), 4.62 (1H, C*H*ClCH$_3$), 4.87 (1H, CH$_2$O*H*), 7.12-7.29 (5H, terminal C$_6H_5$). ^{13}C NMR (DMSO-d_6): δ (ppm): 21.7 (CHCl*C*H$_3$), 44.4 (*C*H$_2$CCO$_2$), 47.6 (*C*HClCH$_3$), 53.3 (CO$_2$CH$_2$*C*H$_2$OH), 58.6 (CO$_2$*C*CH$_2$O), 64.7 (CH$_2$*C*CO$_2$), 67.2 (CO$_2$*C*H$_2$CH$_2$OH), 126.1, 128.3 (*C*$_6$H$_5$), 169.3 (CH$_2$C*C*O$_2$), 172.5 (*C*O$_2$CHCl).

ATRP Graft Copolymerization of Styrene

In a typical procedure, PHECPMA **5** (6.0 mg, M_n = 13,460 g/mol, M_w/M_n = 1.08, 0.025 mmol ATRP initiating group) and CuCl (2.5 mg, 0.025 mmol) were first added to a 10 mL Schlenk flask (flame-dried under vacuum prior to use) sealed with a rubber septum for degassing and kept under N_2. Next, styrene (2.3 mL, 20 mmol), PMDETA (5 μL, 0.025 mmol), anhydrous DMF (2.0 mL), and anhydrous toluene (2.0 mL) were added via a gastight syringe. The flask was degassed by three cycles of freezing-pumping-thawing followed by immersing the flask into an oil bath set at 80^{o}C. The polymerization was terminated by immersing the flask into liquid N_2 after 2.5 h. The reaction mixture was diluted by THF and passed through an alumina

column to remove the residual copper catalyst. The solution was concentrated and precipitated into methanol. After repeated purification by dissolving in THF and precipitating in methanol, 18.8 mg of white powder, PHEA-*g*-PS **6c**, was obtained after drying *in vacuo* overnight. GPC: M_n = 84,000 g/mol, M_w/M_n = 1.24. GPC/MALS: M_n = 333,400 g/mol, M_w/M_n = 1.30. FT-IR: ν (cm^{-1}): 3497 (ν_{O-H}), 3082 (ν_{Ar-H}), 3060 (ν_{Ar-H}), 3025 (ν_{Ar-H}), 2924 (ν_{C-H}), 2851 (ν_{C-H}), 1735 ($\nu_{C=O}$), 1601, 1492, 1452, 1376, 1260, 1179, 1069, 1028, 757, 698. ^{1}H NMR ($CDCl_3$): δ (ppm): 1.57 (2H, $CH_2CHC_6H_5$), 1.83 (1H, $CH_2CHC_6H_5$ and 2H, CH_2CCO_2), 3.71(4H, $CO_2CH_2CH_2OH$), 4.30 (2H, CO_2CCH_2), 6.58, 7.08 (5H, C_6H_5).

Micellar Morphology

THF solution of PHEA-*g*-PS **6** (2 mg/mL) was added dropwise to water under vigorous stirring until the concentration of copolymer reached 0.01 or 0.03 mg/mL. THF was evaporated by stirring moderately overnight at room temperature. For TEM studies, 10 mL of micelle solution was deposited on an electron microscopy copper grid coated with carbon film and the water was evaporated at room temperature.

Results and discussion

Design and Synthesis of HECPMA Trifunctional Acrylate Monomer

Our desired monomer for constructing new graft copolymer based on a hydrophilic PHEA backbone is designed to comprise a polymerizable double bond, an ATRP initiating group, and a hydroxyl. Generally, hydroxyl is easy to be converted to ATRP

initiating group via common esterification reaction.[52] So in the current work, Baylis-Hillman reaction was utilized to introduce a hydroxymethyl to α-position of carbonyl in the starting material (HEA) followed by esterification with 2-chloropropionyl chloride to incorporate -COCH(CH_3)Cl ATRP initiating group. To exclude the side reaction of pendant hydroxyl in HEA with 2-chloropropionyl chloride during the esterification process, the pendant hydroxyl in HEA should be protected before Baylis-Hillman reaction.

Thus, the target HECPMA monomer was synthesized via a four-step procedure: protection of pendant hydroxyl in HEA, Baylis-Hillman reaction catalyzed by NMe_3, corporation of ATRP initiating group, and deprotection of hydroxyl by HF. The attainment of all intermediates was confirmed by ^{1}H NMR (Figure 1) and ^{13}C NMR (Figure 2). In the beginning protection step, we first tried to protect the hydroxyl with the commonly-used reagent, trimethylsilyl chloride, but it turned out that trimethylsilyl would be destroyed by the strong basic NMe_3 in the next Baylis-Hillman reaction. Therefore, *tert*-butyldimethylsilyl chloride was selected to take the place of trimethylsilyl chloride for reacting with the pendant hydroxyl in HEA.[53-55] After the reaction, new resonance peaks attributed to TBDMS group were found in NMR spectra, including the peaks located at 0.06 ("f", Si(C*H*$_3$)$_2$), 0.88 ("g", C(C*H*$_3$)$_3$) ppm in ^{1}H NMR spectrum (Figure 1A) and -5.5 ("6", Si(*C*H$_3$)$_2$), 18.1 ("7", *C*(CH$_3$)$_3$), 25.6 ("8", C(*C*H$_3$)$_3$) ppm in ^{13}C NMR spectrum (Figure 2A), which illustrated that we did attain *tert*-butyldimethylsilyloxyethyl acrylate (HEA-TBDMS) **1** intermediate after the reaction between HEA and TBDMSCl. The key step of the whole synthesis

process was the preparation of *tert*-butyldimethylsilyloxyethyl (2-hydroxymethyl)-acrylate **2** through Baylis-Hillman reaction of HEA-TBDMS. According to previous literature on Baylis-Hillman reaction of *n*-butyl acrylate,[56] we carried out the reaction using nHCHO as hydroxymethylation agent and NMe_3 as catalyst and solvent. The introduction of hydroxymethyl was confirmed by the appearance of characteristic peaks at 2.39 ("h", CH_2OH), 4.33 ("g", CH_2OH) ppm in ^1H NMR spectrum (Figure

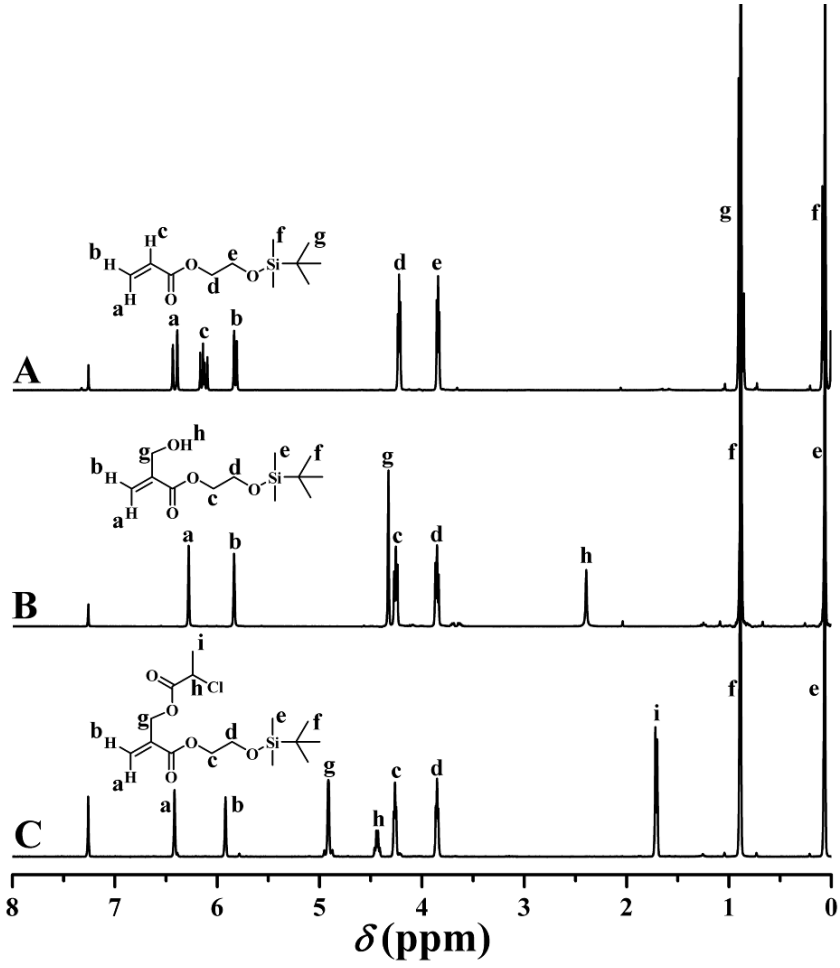


Figure 1. ^1H NMR spectra of *tert*-butyldimethylsilyloxyethyl acrylate **1** (A), *tert*-butyldimethylsilyloxyethyl (2-hydroxymethyl)acrylate **2** (B), and *tert*-butyldimethyl-silyloxyethyl 2-((2-chloropropanoyloxy)methyl)acrylate **3** (C) in $CDCl_3$ (without TMS).

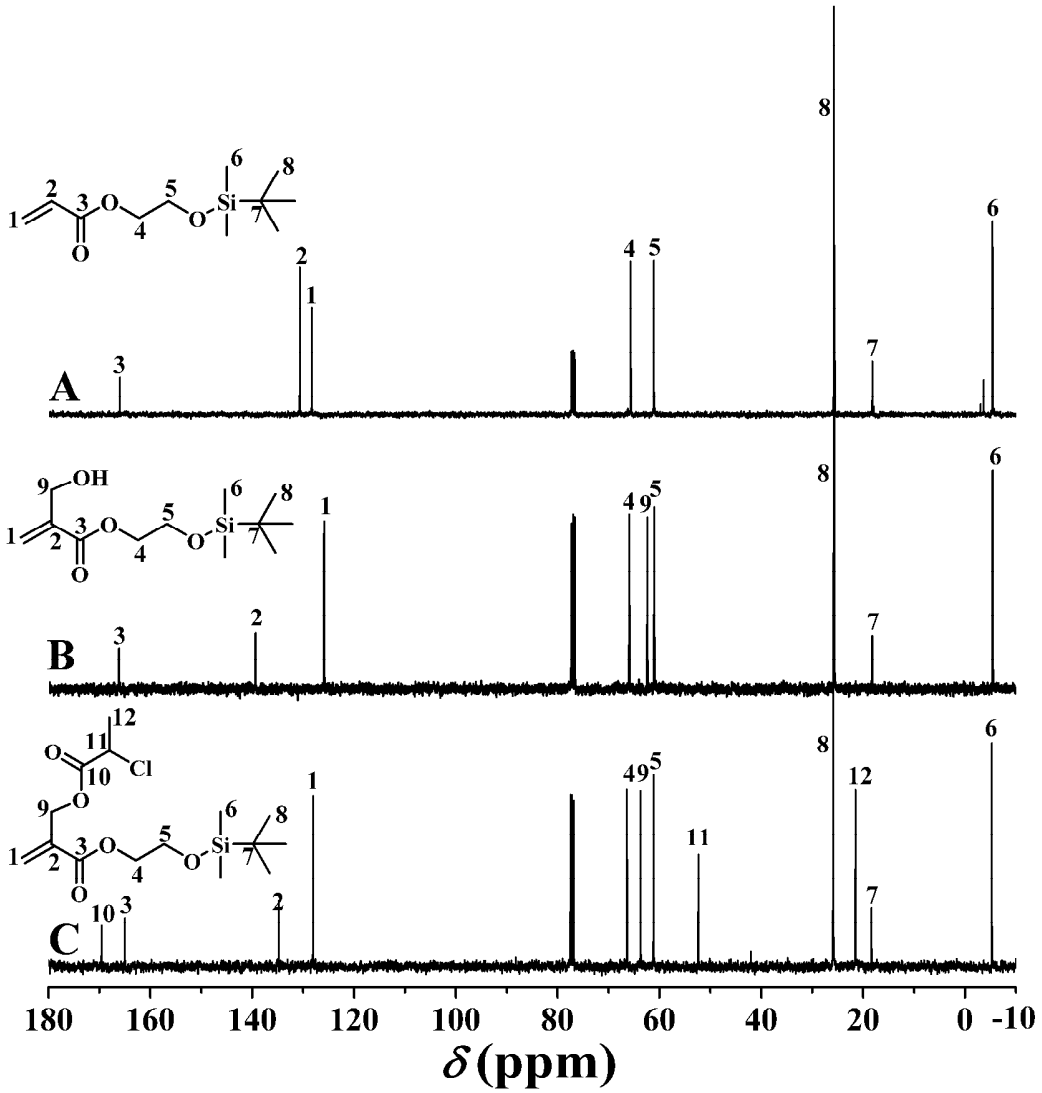


Figure 2. ^{13}C NMR spectra of *tert*-butyldimethylsilyloxyethyl acrylate **1** (A), *tert*-butyldimethylsilyloxyethyl (2-hydroxymethyl)acrylate **2** (B), and *tert*-butyldimethylsilyloxyethyl 2-((2-chloropropanoyloxy)methyl)acrylate **3** (C) in $CDCl_3$ (without TMS).

1B), and 62.6 ("9", *C*H_2OH) ppm in ^{13}C NMR (Figure 2B). The following step was the transformation of newly attached hydroxymethyl in intermediate **2** into 2-chloropropanoyloxyl for inserting ATRP initiating group. New peaks at 1.70 ("i") and 4.43 ("h") ppm in ^{1}H NMR spectrum (Figure 1C) corresponded to 4 protons of

-OCOC*H*($C*H_3$)Cl ATRP initiating group; whereas the peaks located at 21.6 ("13"), 52.4 ("11"), and 169.6 ("10") ppm in ^{13}C NMR spectrum (Figure 2C) belonged to the carbons in -O*C*O*C*H(*C*H_3)Cl group. Furthermore, the signal attributed to hydroxyl at 2.39 ppm disappeared after reaction as shown in Figure 1C. All these evidences demonstrated that -OCOCH(CH_3)Cl ATRP initiating group was successfully introduced to intermediate **3**.

Deprotection of TBDMS group in intermediate **3** will generate the targeted monomer, 2-hydroxyethyl 2-((2-chloropropanoyloxy)methyl)acrylate (HECPMA) **4**. The removal of TBDMS protecting group is usually conducted under acidic[57,58] and basic[59,60] conditions. We first tried to remove TBDMS group in THF solution of tetrabutylammonium fluoride (TBAF), but the destruction of -OCOCH(CH_3)Cl initiating group occurred due to its sensitivity to basic environment. Alternatively, we conducted the reaction using HF (in CH_3CN) in a plastic jar instead of glass container due to the existence of F^-. After 2 hours, TBDMS protecting group was completely removed.

The chemical structure of HECPMA **4** monomer was confirmed by FT-IR, ESI-MS, ^{1}H NMR, and ^{13}C NMR. The typical proton resonance peaks of double bond were located at 5.95 ("b") and 6.46 ("a") ppm in ^{1}H NMR spectrum (Figure 3A). The signals at 1.91 ("e") and 4.43 ("g") ppm originated from 1 proton of CH_2O*H* and 1 proton of -OCOC*H*(CH_3)Cl, respectively, demonstrating the existence of hydroxyl and ATRP initiating group. The integration areas of the corresponding peaks (Figure S1) also supported the target chemical structure. Besides, the double bond and two

carbonyls can be also verified by the peaks appeared at 129.0 ("1"), 134.4 ("2"), 165.2 ("3"), and 169.6 ("7") ppm in ^{13}C NMR spectrum (Figure 3B). Characteristic peaks at 3447 (ν_{O-H}), 1718 ($\nu_{C=O}$), and 1636 ($\nu_{C=C}$) cm^{-1} in FT-IR spectrum corresponded to hydroxyl, carbonyl, and C=C double bonds, respectively. ESI-MS result showed the addition of Na^+ to the molecular iron peak of HECPMA to generate the product ion peak at *m/z* 259. Moreover, C, H, and Cl contents were determined to be 45.49%, 5.59%, and 14.66% by element analysis, which were very close to the calculated contents of 45.68%, 5.54%, and 14.98%. In a word, all these points evidenced the successful synthesis of ATRP-initiating-group-containing monomer **4**.

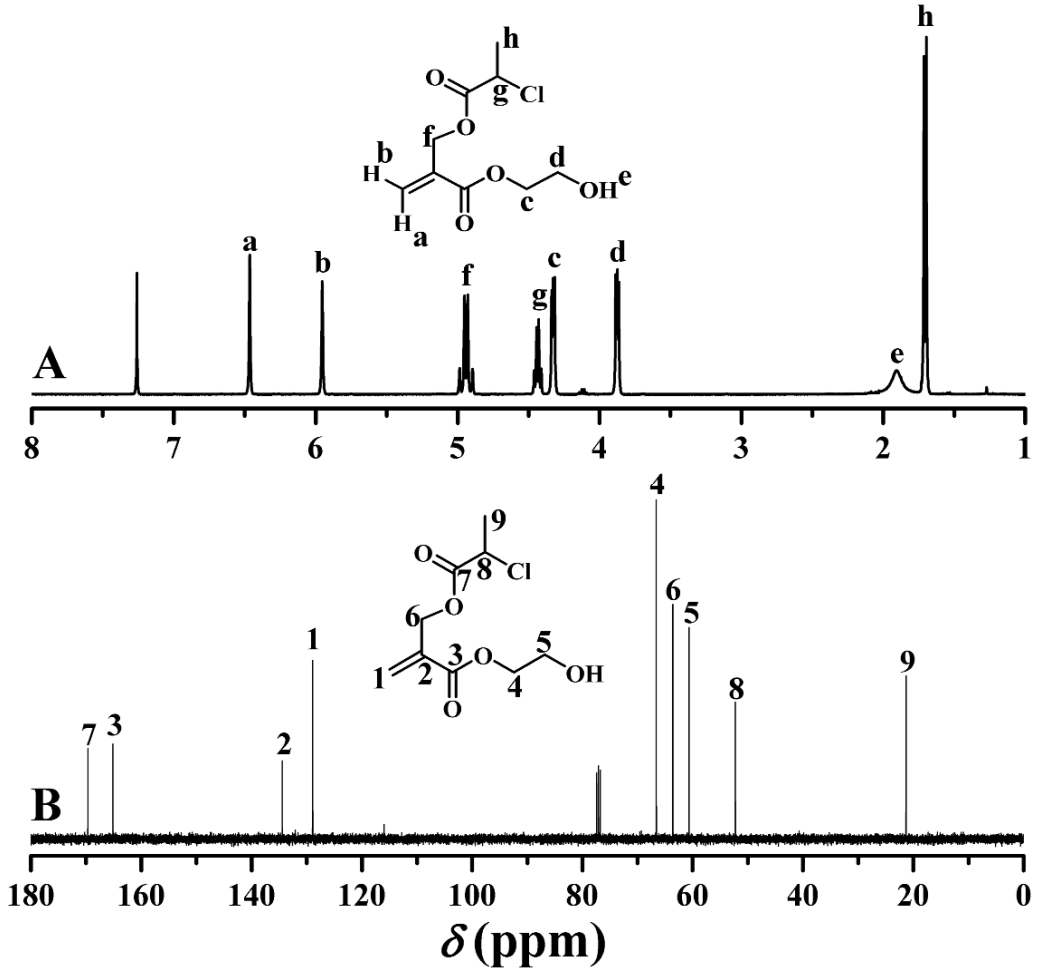


Figure 3. ^1H (A) and ^{13}C (B) NMR spectra of HECPMA **4** monomer in $CDCl_3$.

Preparation of ATRP Macroinitiator

ATRP of functional monomers containing ATRP initiation group has been reported to give hyperbranched polymer rather than linear polymer.[61,62] Thus, a proper way to polymerize this ATRP-initiating-group-containing functional monomer, HECPMA, turns out to be RAFT polymerization. Among these years, RAFT polymerization appears to be the most versatile process among different RDRP techniques due to its mild reactions conditions, variety of monomers for which polymerization can be controlled, tolerance of monomer functionalities, and utilization for the preparation of copolymers with different architectures.[63-71] In particular, RAFT polymerizations of acrylate monomers have been extensively investigated[72-74] and CDB was frequently selected as the chain transfer agent (CTA) during the past decades.[75,76] In the current case, HECPMA **4** monomer was RAFT homopolymerized in DMF at 80^{o}C using AIBN as initiator and CDB as CTA, generating a well-defined PHECPMA **5** homopolymer, i.e. macroinitiator containing -OCOCH(CH_3)Cl initiating group in every repeating unit, with a low polydispersity of 1.17. Note that the conversion of the monomer should be controlled to be not too high to avoid any possible crosslinking and intermolecular coupling reactions.

The as-prepared PHECPMA **5** homopolymer possessed a terminal dithiobenzoate group. Although its content was quite low, it may affect the following ATRP graft polymerization and its pink color may interfere the observation during the polymerization. Therefore, AIBN (20 eq.) was used to remove the dithiobenzoate moiety without influencing the polymeric architecture.[10,77] A white powder was

obtained after the reaction, indicating the absence of dithiobenzoate residue.

The successful attainment of PHECPMA **5** macroinitiator was assured by FT-IR, ^{1}H NMR, and ^{13}C NMR. Typical stretching vibration absorption signal of double bond at 1636 cm^{-1} disappeared in FT-IR spectrum (Figure 4A), so did the peaks of double bond at 5.95, 6.46 ppm in ^{1}H NMR spectrum (Figure 5A) and 129.0, 134.4 ppm in ^{13}C NMR spectrum (Figure 5B). In addition, the proton resonance signals of polyacrylate chain was found to be located at 1.97 (C*H*$_2$CCO$_2$) ppm in ^{1}H NMR spectrum and 44.4 (*C*H$_2$CCO$_2$), 64.7 (CH$_2$*C*CO$_2$) ppm in ^{13}C NMR spectrum. All these results witnessed the performance of RAFT homopolymerization of HECPMA **4** monomer. These characterization techniques can also gave us some other information. In FT-IR spectrum, the peak at 1735 cm^{-1} corresponded to the stretching vibration absorption of carbonyl and the broad peak at 3435 cm^{-1} belonged to the stretching

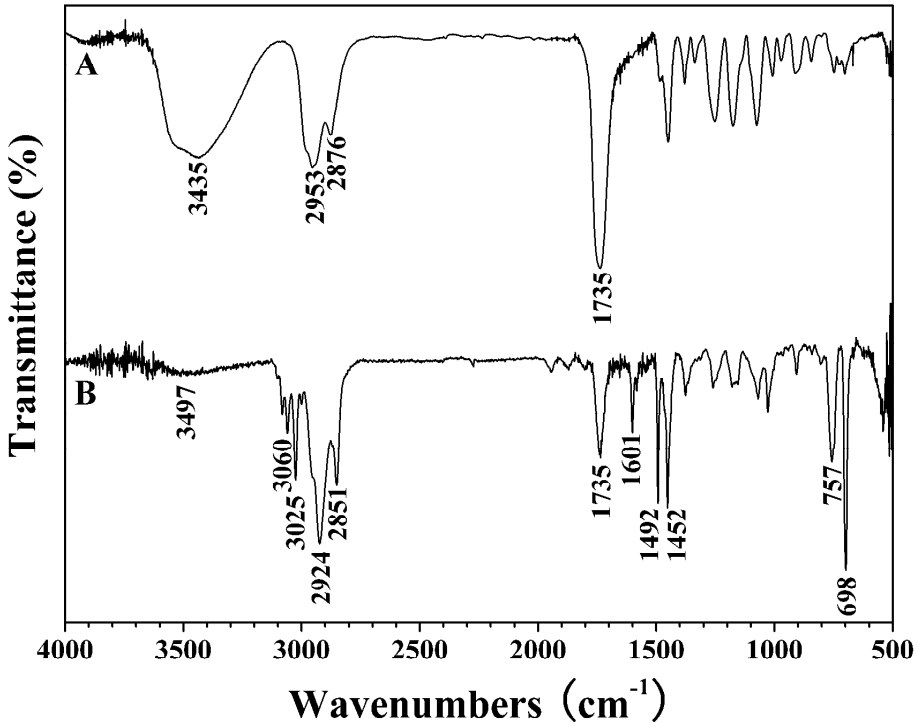


Figure 4. FT-IR spectra of PHECPMA **5** (A) and PHEA-*g*-PS **6** (B).

vibration absorption of hydroxyl. In ^{1}H NMR spectrum, the resonance signal of 1 proton of CH_3CHCl appeared at 4.62 ppm, verifying the preservation of ATRP initiating group; the proton signal of CH_2CCH_2O was shifted from 4.93 ppm to 4.07 ppm after polymerization because of the consumption of double bond; the presence of hydroxyl was affirmed by the resonance signal of CH_2CH_2OH at 4.87 ppm. Moreover, the weak proton resonance signals between 7.12-7.29 ppm and weak peaks at 126.1 and 128.3 ppm in ^{13}C NMR spectrum were attributed to the phenyl end group, which confirmed the RAFT mechanism of the polymerization.

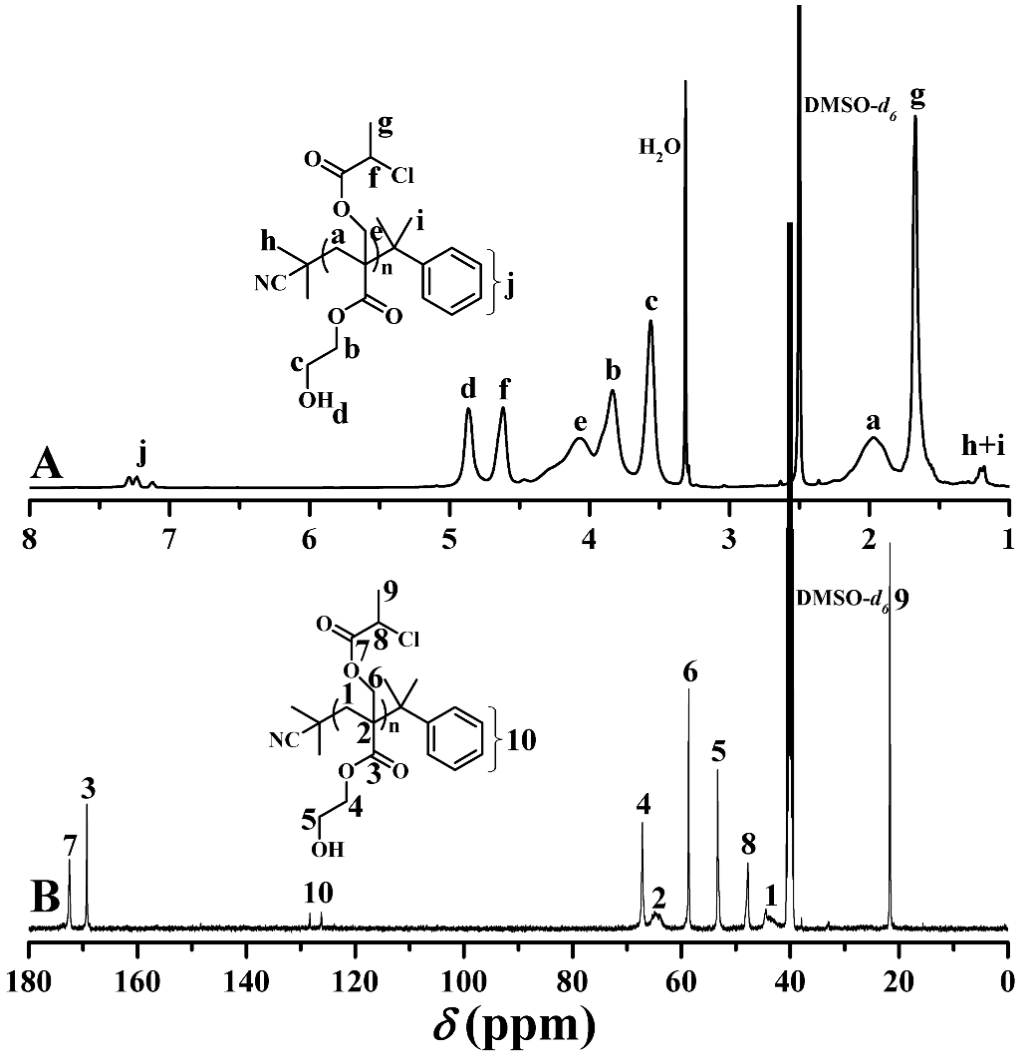


Figure 5. ^{1}H (A) and ^{13}C (B) NMR spectra of PHECPMA **5** in DMSO-d_6.

To calculate the number of HECPMA repeating unit in PHECPMA **5** homopolymer, absolute molecular weight of PHECPMA **5** was determined by GPC/MALS in THF. From the data of absolute molecular weight ($M_{n,GPC/MALS}$ = 13,460 g/mol), we can estimate that every PHECPMA **5** chain possesses 56.1 Cl-containing ATRP initiating groups according to eq 1.

$$n_{HECPMA} = (M_{n,GPC/MALS}-187)/236.5 \quad (1)$$

Synthesis of PHEA-*g*-PS Well-Defined Graft Copolymer

The pendant -OCOCH(CH_3)Cl groups along PHECPMA chain was designed to initiate ATRP of appropriate monomers. ATRP[19-23] is one of the most powerful and versatile RDRP processes which enables the precise control over molecular weight, molecular weight distribution, and functionality.[78] It can be carried out in a variety of different conditions and is tolerant of most functional groups. Overall, ATRP facilitates the preparation of various copolymers (i.e. random, block, and graft) via the control of initiators and monomers.[11,22,78-85] In the current work, styrene was chosen to elucidate our speculation. PHEA-*g*-PS graft copolymers were synthesized by ATRP graft copolymerization of St initiated by PHECPMA **5** macroinitiator using CuCl/PMDETA as catalytic system. In consideration of different solubility of PHECPMA and PS, a 1:1 mixture of DMF (good solvent for PHECPMA) and toluene (good solvent for PS) was employed as solvent for graft polymerization. Various PHEA-*g*-PS graft copolymers with different molecular weights were synthesized by varying the feeding ratio of styrene to Cl-containing ATRP initiating group (200:1,

400:1, or 800:1) and the polymerization time (1.75 h~3.75 h) as listed in Table 1. It is clear to see that the molecular weights of all graft copolymers (at least 169,000 g/mol) are much higher than that of PHECPMA **5** macroinitiator (13,460 g/mol), indicating that ATRP of styrene was indeed performed. Furthermore, GPC curves of all graft copolymers displayed relatively narrow molecular weight distributions ($M_w/M_n \leq 1.31$) as shown in Figure 6. To achieve this goal, high feeding ratios of styrene monomer to ATRP initiating group (200:1, 400:1, or 800:1) and low conversions of styrene (<10%) were employed in the present study to suppress the undesirable intermolecular coupling reactions.[52,86]

Table 1. Synthesis of PHEA-*g*-PS **6** Graft Copolymer[a]

Entry	[St]:[Cl group]	time (h)	M_n[b] (g/mol)	M_w/M_n[b]	$M_{n,GPC/MALS}$[c] (g/mol)	M_w/M_n[c]	n_{St}[d]
6a	200:1	1.75	45,600	1.28	169,000	1.17	26.7
6b	400:1	1.75	62,500	1.31	181,100	1.22	28.7
6c	800:1	2.50	84,000	1.24	333,400	1.30	54.8
6d	800:1	3.75	127,300	1.27	398,400	1.23	65.9

[a] Initiated by PHECPMA **5** macroinitiator ($M_{n,GPC/MALS}$ = 13,460 g/mol, M_w/M_n = 1.08) in a DMF/toluene mixture (*v*:*v* = 1:1), [Cl group]:[CuCl]:[PMDETA] = 1:1:1, polymerization temperature: 80°C. [b] Measured by GPC in THF at 35°C. [c] Obtained by GPC equipped with a multiangle light scattering detector(GPC/MALS) in THF with a flow rate of 1.0 mL/min. [d] The number of St repeating unit per side chain obtained from GPC/MALS.

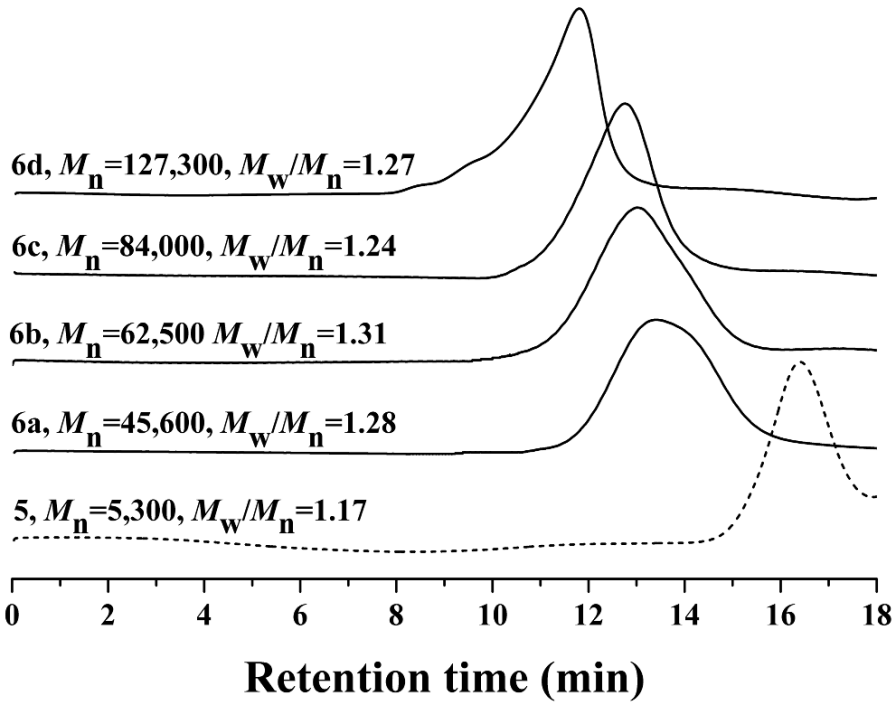


Figure 6. GPC traces of PHECPMA **5** and PHEA-*g*-PS **6** in THF.

The chemical structure of PHEA-*g*-PS **6** graft copolymer was examined by FT-IR and ^{1}H NMR. In comparison with FT-IR spectrum of PHECPMA **5** macroinitiator (Figure 4A), new signals ascribed to polystyrene side chains could be found. The bands located at 3082, 3060, and 3025 cm^{-1} corresponded to characteristic stretching vibration absorption of C-H in benzene ring, while the bands at 1601, 1492, and 1452 cm^{-1} came from skeletal vibration of benzene ring. In particular, two sharp peaks at 757 and 698 cm^{-1} witnessed the existence of mono-substituted benzene ring in PS side chains. The peak at 1735 cm^{-1} (ester carbonyl) and 3497 cm^{-1} (hydroxyl) demonstrated the existence of PHEA backbone. Figure 7 shows ^{1}H NMR spectrum of PHEA-*g*-PS **6** graft copolymer. The resonance peaks at 6.58 ("g") and 7.08 ppm ("i+h") were attributed to 5 protons of benzene ring in PS side chains and the peak at 1.57 ("e") ppm was attributed to 2 protons of methylene in St repeating unit. In order

to visualize the existence of PHEA backbone, we chose graft copolymer **6a** with the shortest PS side chains (M_n = 169,000 g/mol, M_w/M_n = 1.17) to conduct ^{1}H NMR measurement. Though the peaks were very weak, we still found the trail of relevant signals assigned to PHEA backbone: the peak at 4.30 ppm ("d") belonged to 2 protons of $CH_2CC\mathit{H}_2O$; the broad peak at 3.71 ppm ("b+c") originated from 4 protons of $CO_2C\mathit{H}_2C\mathit{H}_2OH$. In summary, FT-IR and ^{1}H NMR tests proved the co-existence of PHEA backbone and PS side chains in PHEA-*g*-PS **6** graft copolymer.

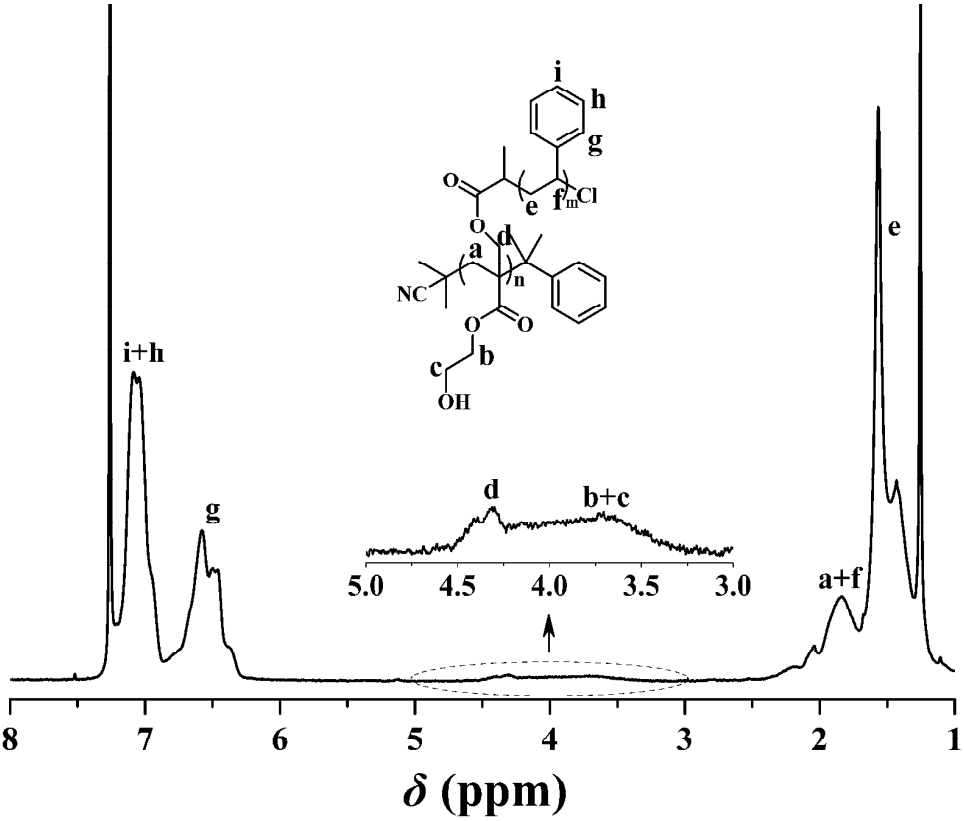


Figure 7. ^{1}H NMR spectrum of PHEA-*g*-PS **6** graft copolymer in $CDCl_3$.

The evaluation of initiation efficiency for graft polymerization would be usually calculated from ^{1}H NMR.[87] As ^{1}H NMR spectra of PHECPMA **5** macroinitiator and PHEA-*g*-PS **6** graft copolymer were recorded in different deuterated solvents (DMSO-d_6 for PHECPMA and $CDCl_3$ for PHEA-*g*-PS), ^{1}H NMR spectrum of

PHECPMA **5** in $CDCl_3$ was shown in Figure S2. Unfortunately, the signal of -OCOC*H*(CH_3)Cl at 4.48 ppm (peak "f" in Figure S2) should be overlapped with that of PHEA backbone (peaks "b" "c", and "d" in Figure 7), making it difficult to calculate the initiation efficiency of -OCOCH(CH_3)Cl initiating groups. However, in our previous report,[10] poly(*tert*-butyl 2-((2-bromo-propanoyloxy)methyl)acrylate) (P*t*BBPMA) was used as macroinitiator for the preparation of graft copolymers with poly(methyl acrylate) side chains. The initiation efficiency was as high as 100% which was measured by ^{1}H NMR. Given the similar structure of our macroinitiator PHECPMA **5** with P*t*BBPMA and living/controlled characteristic of ATRP, the initiation efficiency was assumed to be 100% in the current case.[88-90]

Since the molecular weight of graft copolymer measured by GPC is very different from the 'real' value, absolute molecular weights of PHEA-*g*-PS graft copolymers were measured by GPC/MALS in THF. From the data of absolute molecular weights of graft copolymers and macroinitiator (M_n = 13,460 g/mol), the number of St repeating unit per side chain (n_{St}) can be calculated according to eq 2 (56.1 is the number of -OCOCH(CH_3)Cl initiation site on the backbone; 13,460 and 104 are the molecular weights of PHECPMA **5** homopolymer and styrene, respectively) and the results are summarized in Table 1.

$$n_{St} = (M_n - 13{,}460)/(56.1 \times 104) \qquad (2)$$

The semilogarithmic plot of Ln($[M]_0$/[M]) versus time, as depicted in Figure S3, shows the conversion of styrene increased with a linear dependence on the time. The first order polymerization kinetics demonstrated a constant number of propagating

species during the polymerization, which is a typical character of ATRP.[19] Thus, all aforementioned results supported that PHEA-*g*-PS **6** graft copolymer possessed a well-defined structure: a poly(2-hydroxyethyl acrylate) backbone (56.1 repeating units) and 56.1 polystyrene side chains (26.7-65.9 repeating units per side chain).

Self-Assembly Behavior of PHEA-*g*-PS Amphiphilic Graft Copolymer

As it is well known, polystyrene is a kind of hydrophobic polymer and the hydroxyl in PHEA backbone bears hydrophilicity. Therefore, PHEA-*g*-PS **6** graft copolymers, consisting of a hydrophilic PHEA backbone and hydrophobic PS side chains, are endowed with an amphiphilic property. This provides an opportunity to investigate their self-assembly behavior in aqueous media. The micellar structures aggregated by PHEA-*g*-PS **6** amphiphilic graft polymers were visualized by TEM as shown in Figure 8. Graft polymers **6** all aggregated to form spherical micelles while their concentrations were all 1×10^{-5} g/mL (Figure 8). Especially, the core-corona structure, consisting of hydrophobic PS as core and hydrophilic PHEA as corona, can be observed distinctly in the micelles formed from PHEA-*g*-PS **6a** (Figure 8A) which bears the shortest PS side chains. DLS measurements provided the sizes of these aggregates of 87.3-110.5 nm with a concentration of 1×10^{-5} g/mL (Figure 9). When raising the concentration of PHEA-*g*-PS **6d** graft copolymer aqueous solution to 3×10^{-5} g/mL, the copolymer aggregated into unique bowl-shaped micelles (Figure 10), which have been previously reported on polystyrene-based amphiphilic diblock[91] and triblock[92] copolymers.

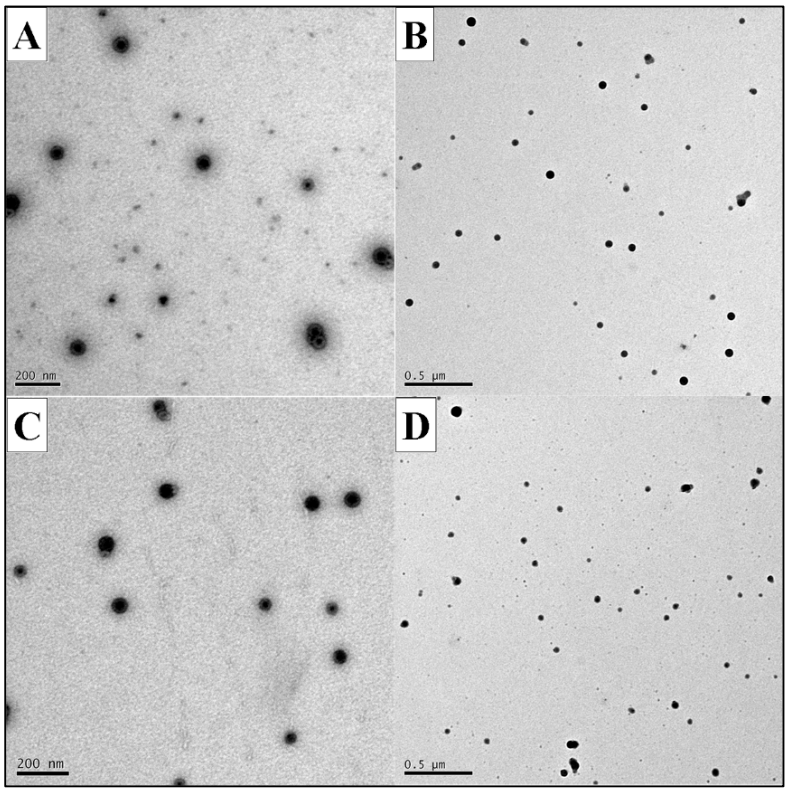


Figure 8. TEM images of aggregates formed by PHEA-*g*-PS **6a** (A), **6b** (B), **6c** (C), **6d** (D) with a concentration of 1×10^{-5} g/mL.

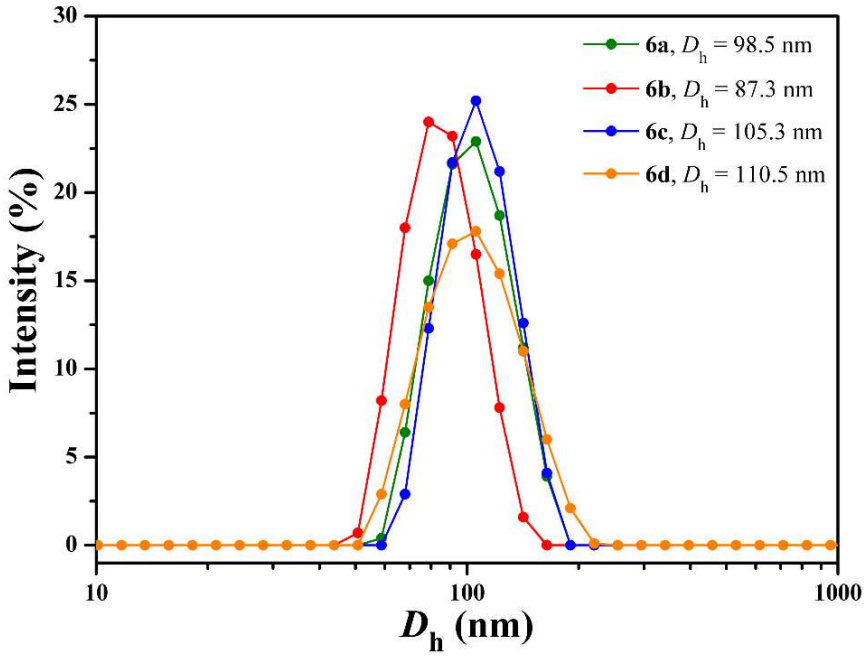


Figure 9. Hydrodynamic diameter distributions of micelles formed by PHEA-*g*-PS **6** with a concentration of 1×10^{-5} g/mL.

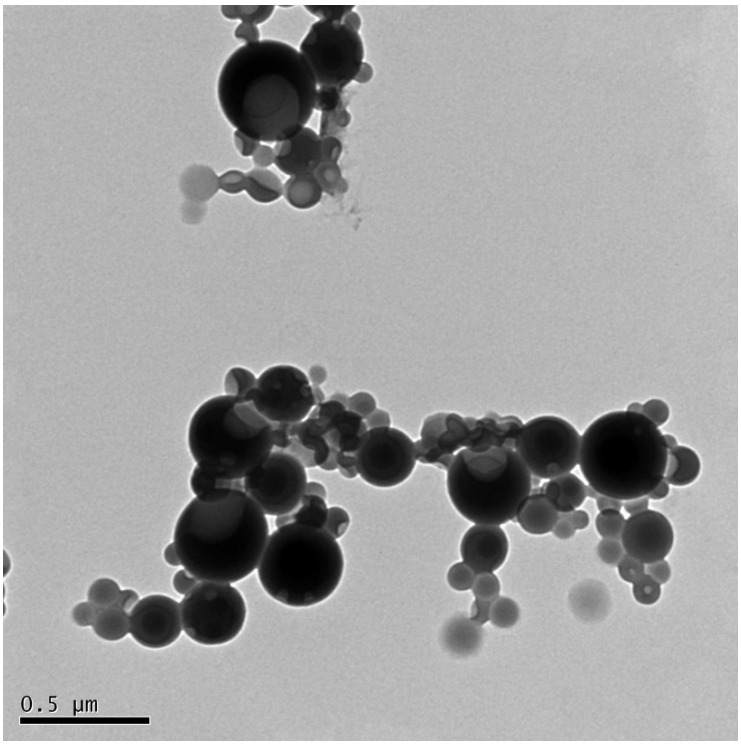


Figure 10. TEM image of PHEA-*g*-PS **6d** with a concentration of 3×10^{-5} g/mL.

Conclusions

We have reported the detailed synthesis of a novel trifunctional acrylate monomer containing a hydroxyl and an ATRP initiating group as well as its application in the convenient synthesis of PHEA-*g*-PS well-defined graft copolymers with narrow molecular weight distributions ($M_w/M_n \leq 1.30$) through sequential RAFT polymerization and ATRP. Both the syntheses of backbone and side chains are controllable. The graft copolymer possessed hydrophilic PHEA backbone and hydrophobic PS side chains, thus PHEA-*g*-PS bears amphiphilic nature, which was affirmed by TEM and DLS. To our best knowledge, this is the first example of amphiphilic graft copolymer bearing hydrophilic PHEA backbone. TEM tests showed that the copolymers aggregated to form common spherical micelles with

hydrodynamic diameters of 87.3-110.5 nm at lower concentration (1×10^{-5} g/mL) and form unique bowl-shaped micelles at higher concentration (3×10^{-5} g/mL). The formation of bowl-shaped micelles can be attributed to the existence of polystyrene side chains.[88,89] The development of this trifunctional acrylate monomer will make a great contribution to the controlled synthesis of well-defined graft copolymers not only because the synthesis process of graft copolymers needs no post-polymerization functionality transformation, but because this ATRP-initiating-group-containing monomer could be copolymerized with another suitable monomer without ATRP initiating group to synthesize well-defined backbones containing a certain amount of initiating sites and furthermore, to synthesize graft copolymers with tunable density of side chains, as well as because the hydrophobic polystyrene side chains in the current case can be easily extended to various hydrophobic or hydrophilic polymers to generate a great deal of amphiphilic or double hydrophilic graft copolymers.

Acknowledgments

The authors thank the financial supports from National Natural Science Foundation of China (21174158 and 21274162) and Shanghai Scientific and Technological Innovation Project (12JC1410500 and 13ZR1464800).

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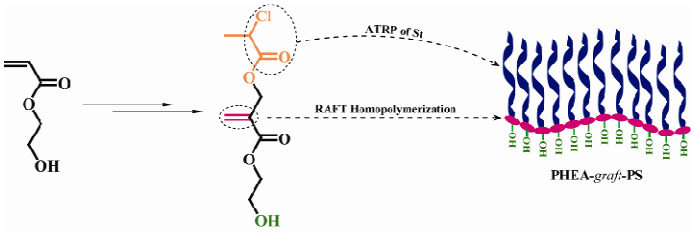
First Amphiphilic Graft Copolymer Bearing Hydrophilic Poly(2-hydroxylethyl acrylate) Backbone

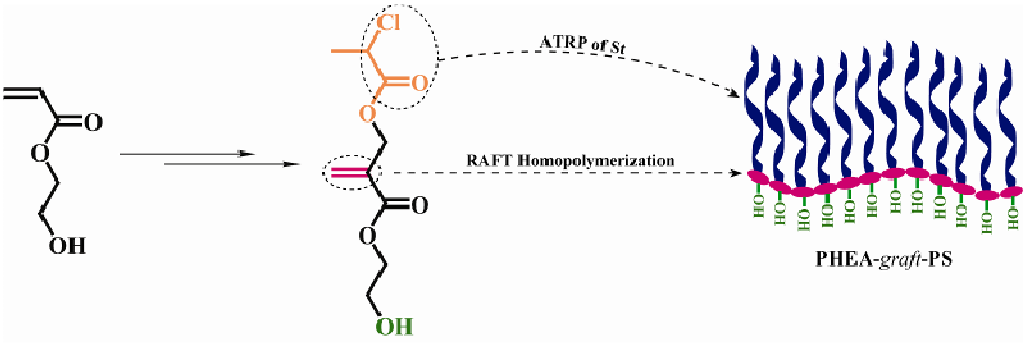
Xiuyu Jiang, Xue Jiang, Guolin Lu, Chun Feng, Xiaoyu Huang**



Graphical Abstract

First Amphiphilic Graft Copolymer Bearing Hydrophilic Poly(2-hydroxylethyl acrylate) Backbone Synthesized by Successive RAFT and ATRP

Xiuyu Jiang, Xue Jiang, Guolin Lu, Chun Feng, Xiaoyu Huang**



This article reports the first synthesis of well-defined amphiphilic graft copolymers, consisting of a hydrophilic poly(2-hydroxyethyl acrylate) (PHEA) backbone and hydrophobic polystyrene side chains, by the combination of reversible addition-fragmentation chain transfer (RAFT) polymerization, atom transfer radical polymerization (ATRP), and the grafting-from strategy.