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Synthesis of poly(2-hydroxyethyl methacrylate) end-capped with asymmetric functional groups *via* atom transfer radical polymerization†

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Poly(2-hydroxyethyl methacrylate) (PHEMA) end-capped with living chloride and alkyne groups was synthesized *via* ATRP of HEMA using CuCl/$CuCl_2$/2,2′-bipyridine as a catalyst in a solvent mixture of methanol and 2-butanone. The effects of parameters including the initiator, solvent, temperature and initial monomer to initiator ratios on polymerization were studied in terms of polymerization kinetics, the degree of polymerization (DP) and molar mass dispersity ($Đ$) of the resulting PHEMA polymer. ATRP of HEMA using propargyl 2-bromoisobutyrate (PBiB) as an initiator was poorly controlled, but those using 3-(trimethylsilyl)propargyl 2-bromoisobutyrate (TMSPBiB) and 3-(triisopropysilyl)propargyl 2-bromoisobutyrate (TiPSPBiB) as initiators were well-controlled. Moreover, the apparent propagation rate constant for ATRP of HEMA using the TMSPBiB initiator was higher than that using the TiPSPBiB initiator. The solvent mixture of methanol–2-butanone at different compositions greatly affected the polymerization controllability. A high molecular weight PHEMA sample with a DP of 1000 and a $Đ$ of 1.34 was obtained under appropriate conditions. The poly(2-hydroxyethyl methacrylate)-*block*-poly(butyl acrylate) (PHEMA-*b*-PBA) diblock copolymer was prepared through ATRP of BA using $(CH_3)_3Si–C\equiv C–PHEMA–Cl$ as a macroinitiator. The methoxyl polyethylene glycol-*block*-poly(2-hydroxyethyl methacrylate) (MPEG-*b*-PHEMA) diblock copolymer was prepared by click reaction between MPEG-N_3 and $HC\equiv C–PHEMA–Cl$. These two reactions demonstrated the reactivity of the asymmetric functional groups end-capping the PHEMA, and further provided modular examples for the synthesis of a novel well-defined (co)polymer with complex architectures.

Introduction

2-Hydroxyethyl methacrylate (HEMA) is one of the most important functional methacrylate commercial monomers because of its hydrophilic nature and hydroxyl groups with the capability of undergoing a wide variety of reactions.[1] Since Wichterle and Lim reported the use of the PHEMA hydrogel for biological applications in 1960,[2] several types of novel and important PHEMA-based polymeric materials have been developed, such as contact lenses, dental fillings, surgical implants, tissue engineering scaffolds, biosensors, catheters, hemodialysis membranes, wound dressings, drug delivery agents and so on.[3]

Recently, the development of polymer synthesis techniques enabled the synthesis of well-defined PHEMA-based (co)polymers with complex architectures and significantly broadened the application scope of PHEMA-based (co)polymers in novel nanomaterials.[3b]

Usually, conventional free radical polymerization (CFRP) techniques are employed to prepare HEMA-based (co)polymers due to their applicability for a broad range of monomers and tolerance to a variety of impurities often encountered in most industrial processes.[4] However, the major drawbacks of this technique include: (1) the difficulty in controlling the molecular weight (M_n) and molar mass dispersity ($Đ$) of the resulting (co)polymers and (2) the difficulty in preparing well-defined polymers with complex structures due to rapid transfer and termination reactions.[5]

It is well known that well-defined (co)polymers with controlled M_n, low $Đ$, as well as predesigned architecture are very important for fundamental research and commercial applications, including the disclosure of the relationship between the properties and the polymer structure, and some specific applications such as the overall design of the scaffold and

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nanomaterials with tailored structure.[6] Therefore, the controlled (co)polymerization of HEMA *via* living polymerization techniques has drawn many researchers' attention over the years.[3b] Given the labile protons in hydroxyl groups,[7] synthesis of well-defined PHEMA by anionic polymerization required multiple processes in which the HEMA monomers were firstly protected with a trimethylsilyl group and finally de-protected by removing the protecting groups.[7]

However, the emergence and development of living radical polymerization (LRP) techniques over the past two decades have allowed for the synthesis of well-defined polymers from a wide variety of functional monomers including HEMA. Currently, the three most effective LRP techniques including nitroxide mediated polymerization (NMP), atom transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer (RAFT) polymerization have been widely employed.[8] In comparison with the few successful preparation methods available for PHEMA-based (co)polymers *via* NMP[9] and RAFT,[10] ATRP is also one of the most promising methods for preparing well-defined (co)polymers based on PHEMA.[3b]

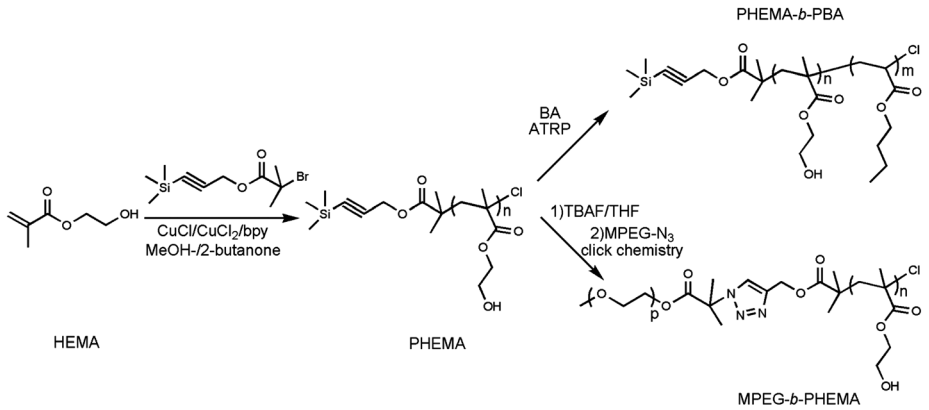
The ATRP of HEMA was first reported in 1999 by the Matyjaszewski group using the alkyl bromide initiator and the CuCl/2,2′-bipyridine (bpy) catalytic system in a mixed solvent of 2-butanone and 1-propanol at a volume ratio of 7/3.[1] In this mixed solvent, well-controlled polymerization of HEMA was demonstrated at 50 °C at $[M]_0/[I]_0$ = 100/1 in terms of the kinetic study, and PHEMA with M_n less than 40 000 g mol^{-1} and $Đ$ lower than 1.5 was achieved at 80% conversion after 20 h. In 2001, Armes's group reported ATRP of HEMA in methanol or binary mixtures of methanol and water (1/1, v/v) using the Br-capped oligo(ethylene glycol) initiator and the CuBr/bpy catalytic system at 20 °C.[11] The same group further prepared PHEMA homopolymers and the PHEMA based block or random copolymers using the CuCl/bpy catalyst and the 2-(*N*-morpholino)ethyl 2-bromo-2-methylpropionate (Me-Br) initiator in MeOH at 20 °C in 2004.[12] In these two polymerization systems, both high monomer conversions (more than 90% within a few hours) and narrow $Đ$ (1.2–1.3) were obtained with desired DP less than 100. By virtue of the controllable ATRP, they demonstrated that PHEMA homopolymers with the DP less than 20 are water soluble, and those with the DP in the range of 20–45 are partially water soluble, whereas those with the DP more than 45 are water insoluble.[12] Hocker *et al.* also reported the controlled ATRP of HEMA by using MPEO-Br or Br-PEO-Br as a macroinitiator and the CuCl/bpy catalytic system in ethylene glycol at 80 °C.[13] They found that HEMA conversion reached a very high value within a very short time, *i.e.*, 98% monomer conversion over 7 min, and the polydispersity of the resulting copolymers was in the range of 1.2–1.47. By a similar approach as mentioned above, ATRP of HEMA using different initiators and CuX/ligand catalytic systems in protic and polar aprotic solvents or even toluene has been utilized to synthesize PHEMA based copolymers with complex architectures, such as random copolymers,[14] block copolymers,[15] grafting copolymers,[16] polymer brushes,[17] multi-arm star copolymers,[18] macrocycles,[19] and other nano-structured polymeric materials/hybrids.[3b]

Along with the progress of the ATRP technique, electron transfer ATRP (AGET-ATRP) and single-electron transfer living radical polymerization (SET-LRP) were also developed for the preparation of well-defined PHEMA. For example, in 2006, Matyjaszewski *et al.* reported well-defined PHEMA prepared by AGET-ATRP of HEMA in a solvent mixture of 2-butanone and MeOH (3/2, v/v) using ethyl 2-bromoisobutyrate as an initiator and CuX_2/bpy (tris(2-pyridylmethyl)-amine) (TPMA) and tin(II) 2-ethylhexanoate ($Sn(EH)_2$) used as reducing agents as the catalytic system at 50–70 °C,[20] the monomer conversion reached 53% after ~21 h with a targeted maximum DP of 250. Recently, Baker *et al.* also reported well-defined PHEMA with a target DP of less than 100 prepared from AGET-ATRP in MeOH using Me-Br as an initiator and CuX_2/TPMA/ascorbic acid or hydrazine at 25 °C.[21] In these cases, it was proposed that the active catalyst CuX was generated from CuX_2 reduced *in situ* with a reducing agent such as $Sn(EH)_2$,[20] ascorbic acid and hydrazine.[21] Very recently, Percec *et al.* reported SET-LRP of HEMA using the methyl α-bromophenylacetate initiator and the Cu(0)/Me_6TREN catalytic system in DMSO at 25 °C.[22] PHEMA samples with M_n in the range of 333 500–1 017 900 g mol^{-1} and $Đ$ less than 1.50 were synthesized by this approach.

The most important factors for the preparation of PHEMA *via* controlled ATRP are the initiator system, temperature, and solvent. The studies on the polymerization kinetics of HEMA reported so far mainly focused on a $[M]_0/[I]_0$ of ~100, and the polymerizations were controlled to a narrow targeting DP in some regions.

Herein, we revisit the current report on ATRP of HEMA using a new kind of initiator bearing the alkynyl group and a solvent mixture of 2-butanone and MeOH with the aim of exploring appropriate polymerization conditions to prepare PHEMA with a wide range of targeting DPs (80 to 1000) in a controlled manner. Some factors including initiators (unprotected or protected propargyl 2-bromoisobutyrate), solvents (MeOH or MeOH–2-butanone mixture in different compositions), temperature (30, 50 and 60 °C) and $[M]_0/[I]_0$ (80 : 1, 200 : 1, 500 : 1 and 1000 : 1) that affected the polymerization of HEMA were studied, and the ATRP's controllability of HEMA was investigated in the terms of kinetic study, M_n and $Đ$ of the resulting PHEMA sample. We also report the preparation of two diblock copolymers from PHEMA end-capped with asymmetric functional groups to demonstrate the successful preparation of PHEMA in a controlled/living fashion and provide model examples of the design and preparation of copolymers (Scheme 1).

While the current MeOH and solvent mixture of MeOH/2-butanone was employed for ATRP and AGET-ATRP of HEMA with a targeting DP of less than 250 using different initiating systems reported by Armes[12] and Matyjaszewski,[20] respectively, the initiator containing the alkynyl group for ATRP of HEMA was rarely reported. Only one paper was found reporting the preparation of PHEMA with a DP of ~112 and a narrow polydispersity of 1.24 using the 3-(trimethylsilyl)propargyl 2-bromoisobutyrate initiator in MeOH at 50 °C. However, relevant kinetic data were absent.[19] As shown in this paper, well-defined PHEMA samples with targeting DPs from 80 to 1000 were prepared successfully. More importantly, due to the hydroxyl groups end-capped with asymmetric functional groups,



Scheme 1 Schematic illustration for synthesis of $(CH_3)_3Si–C\equiv C–PHEMA–Cl$, PBA-*b*-PHEMA, and MPEG-*b*-PHEMA.

the resulting PHEMA provided various reaction sites for the design and synthesis of other novel well-defined copolymers and (co)polymers with complex architectures. Examples of these reactions included click chemistry based on the alkynyl group after the removal of a protecting group, chain-extension reactions from the halogen-terminated end,[23] ring-opening polymerization (ROP) of cyclic esters from the hydroxyl groups, and many others.[3b]

Results and discussion

1. Synthesis of different alkyne-containing initiators

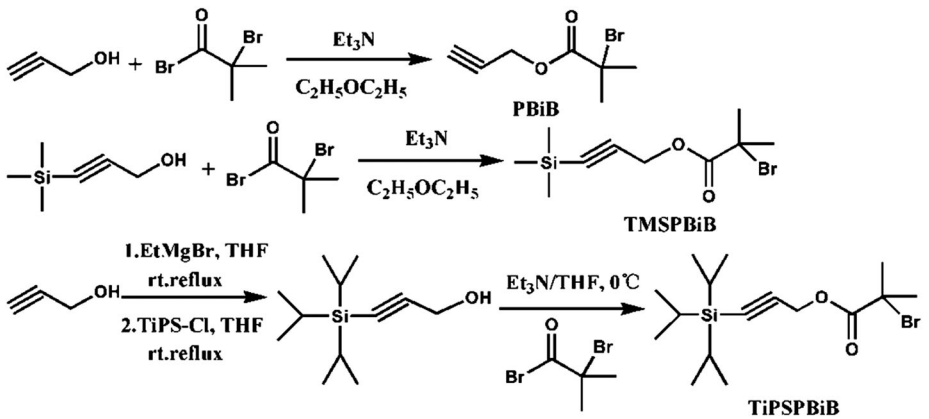
Three different initiators bearing alkyne groups (Scheme 2) were used for ATRP of HEMA to facilitate the introduction of a PHEMA homopolymer with terminal alkyne groups (R–C≡C–PHEMA–Cl). The initiators were successfully prepared as observed from the corresponding ^{1}H NMR spectra (Fig. S1 in ESI†).[24] The peak centrally located at 4.67 ppm from the proton of methylene adjacent to the alkyne group (–C≡C–CH_2–O–) could be used for evaluating the DP of the obtained PHEMA polymer.

2. ATRP of HEMA using different alkyne-containing initiators

At the initial stage of the study, the controllability of ATRP of HEMA by using these three different initiators was preliminarily evaluated in terms of the kinetic study and the SEC profile of the resulting polymer. Three polymerization reactions of HEMA were carried out in methanol at 50 °C using CuCl/$CuCl_2$/bpy as a catalyst system in the presence of different initiators by setting $[HEMA]_0:[CuCl]_0:[CuCl_2]_0:[initiator]_0:[bpy]_0 = 80:1:0.05:1:2$. The kinetic data were collected with ^{1}H NMR spectra of the samples taken out from the reaction mixture at different reaction time intervals (Fig. S2 in ESI†), and the SEC profiles of the resulting polymers at the same monomer conversion of 50% were obtained in THF using PS as standard.

Fig. 1a shows that the semilogarithmic plot was apparently curved when PBiB was employed as the initiator, indicating that the ATRP of HEMA using PBiB as an initiator was not well controlled. This was also evidenced by a high $Đ$ of 1.9 for the resulting PHEMA sample with a monomer conversion of 50% and a SEC profile with a small shoulder as shown in Fig. 1b. The ill-controlled polymerization of HEMA by using PBiB as an initiator was believed to be caused by irreversible termination reaction among radical species or Glaser coupling reaction between terminal alkynes.[25]

In contrast, both kinetic plots were almost linear when TMSPBiB and TiPSPBiB were utilized as initiators. The linear correlation coefficients of the guided line were 0.984 and 0.955 for TMSPBiB and TiPSPBiB, respectively (Fig. 1a). The $Đ$ was 1.26 and 1.29 for PHEMA at 50% monomer conversion by using



Scheme 2 The synthesis routes towards the initiators of (a) propargyl 2-bromoisobutyrate (PBiB), (b) 3-(trimethylsilyl)propargyl 2-bromoisobutyrate (TMSPBiB), and (c) 3-(triisopropylsilyl)propargyl 2-bromoisobutyrate (TiPSPBiB).

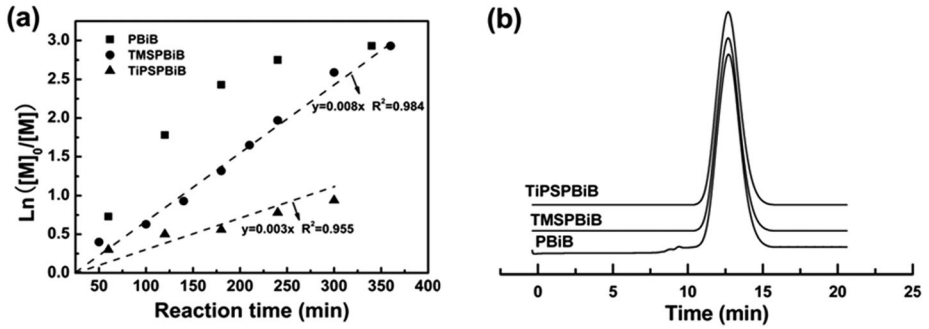


Fig. 1 ATRP of HEMA using different alkynyl-containing initiators in methanol at 50 °C by setting $[HEMA]_0 : [CuCl]_0 : [CuCl_2]_0 : [initiator]_0 : [bpy]_0$ = 80 : 1 : 0.05 : 1 : 2. (a) First-order kinetic data; (b) SEC curves of PHEMA with monomer conversion of 50%. The dashed lines are guides to the eye. The molar mass (M_n) from SEC was ~12 kg mol^{-1}.

TMSPBiB and TiPSPBiB, respectively. Moreover, both SEC curves were symmetric as shown in Fig. 1b. These results indicated that the ATRP of HEMA using either TMSPBiB or TiPSPBiB was better controlled compared to that using PBiB as an initiator. This was also consistent with the previous reports that acetylene-protection constrained the side reactions of Glaser coupling, leading to better control over the ATRP of styrene, methyl acrylate and *tert*-butyl acrylate.[24b,26]

Fig. 1a further shows that the polymerization rate was higher using TMSPBiB as an initiator compared to that using TiPSPBiB as an initiator for ATRP of HEMA under identical conditions. For example, the monomer conversion was up to 93% at 300 min when TMSPBiB was used as an initiator, while it was only 63% at identical reaction times when TiPSPBiB was used as an initiator. The apparent propagation constants (K_p^{app}) derived from the kinetic plots were 1.3 × 10^{-4} s^{-1} and 5.0 × 10^{-5} s^{-1} using TMSPBiB and TiPSPBiB as initiators, respectively. Therefore, TMSPBiB was chosen to initiate the polymerization of HEMA in the following studies.

3. Effect of solvent on ATRP of HEMA

The increase in the reaction rate as well as the reactivity of free radical accelerated either termination or chain transfer reaction for ATRP in polar solvents, constituting the main disadvantage of poor controllability.[21] ATRP in polar solvent generally resulted in polymers with higher $Đ$ than that in nonpolar media or in bulk.[5a,27] The polar solvents applied for synthesis of PHEMA by ATRP included water,[28] DMSO,[22] ethylene glycol,[13] methanol,[12,21] 2-butanone/1-propanol,[1] 2-butanone/methanol[20] and methanol/water.[11] It has been disclosed that the solvent polarity had a significant effect on the controllability of the ATRP of HEMA. Speaking in detail, the controllability of ATRP of HEMA increased with the decrease of solvent polarity.[1] Considering the solubility and polarity of the solvent, the polymerizations were performed in methanol and in the methanol–2-butanone mixture in the presented studies.

Fig. 2a shows kinetic plots for the ATRP carried out in different solvents. The kinetic plots for ATRPs of HEMA were almost linear for the solvents of methanol and methanol/2-butanone at 3/2 and 2/3 (m/m), suggesting that the polymerizations were well controlled. The apparent rate constants (K_p^{app}) for different solvent systems were different as calculated from linear kinetic plots (Fig. 2a). For example, K_p^{app} was 1.3 × 10^{-4} s^{-1} in methanol, 1.0 × 10^{-4} s^{-1} and 8.33 × 10^{-5} s^{-1} in methanol/2-butanone at 3/2, and 2/3 (m/m), respectively. This indicated that the methanol–2-butanone mixture, rather than methanol, resulted in a decrease of the apparent rate constant. Moreover, the apparent rate constant decreased with the increase of 2-butanone content in the solvent mixture. A similar trend was also observed in the previously reported AGET-ATRP of HEMA in methanol/2-butanone.[20]

The samples in small volumes were taken out from the reaction mixture at predesigned intervals. The monomer conversions and the molecular weights ($M_{n,NMR}$) of purified samples were calculated from ^{1}H NMR spectra (Fig. S3 in ESI†). The dependence of $M_{n,NMR}$ on monomer conversion is shown in Fig. 2b. The $M_{n,NMR}$ of PHEMA linearly increased with the increase of monomer conversion in methanol when the monomer conversion was below 83%. However, when the monomer conversion was above 83%, the molecular weights ($M_{n,NMR}$) of PHEMA were non-linearly increased with the increase of monomer conversion in methanol. This deviation may attribute to irreversible termination which increased with the increase of monomer conversion. These results were commonly observed in the ATRP of HEMA performed by Beers,[1] Armes[11,12] and other researchers.[21] For ATRPs of HEMA in methanol/2-butanone at 2/3 and 3/2 (m/m), the $M_{n,NMR}$ of PHEMA was linearly increased with the increase of monomer conversion. It should be noted that the $M_{n,NMR}$ was higher than the theoretical value at corresponding monomer conversion due to an initiator efficiency of ~75% as calculated from Fig. 2b.

The variation of $Đ$ of PHEMA with monomer conversion in methanol, methanol/2-butanone at 2/3 and 2/3 (m/m) is shown in Fig. 2c. The $Đ$ of the PHEMA sample prepared in methanol/2-butanone at m/m = 2/3 was less than 1.3 when the monomer conversion was more than 90%, meanwhile the $Đ$ of the PHEMA sample as prepared in methanol or methanol/2-butanone 3/2 (m/m) was below 1.3 when the monomer conversion was less than 80%. The $Đ$ increased to more than 1.7 in methanol and 1.4 in methanol/2-butanone 3/2 (m/m) when the monomer conversion further increased to more than 90%. Moreover, the

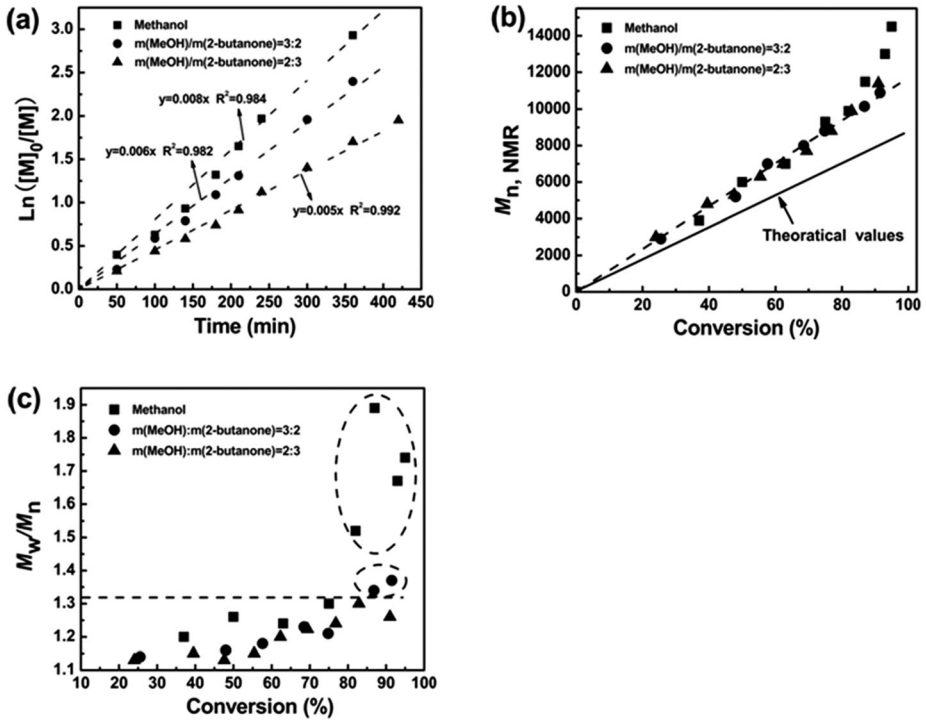


Fig. 2 ATRP of HEMA at 50 °C in different solvents by setting $[HEMA]_0 : [CuCl]_0 : [CuCl_2]_0 : [TMSPBiB]_0 : [bpy]_0 = 80 : 1 : 0.05 : 1 : 2$. (a) First-order kinetic plots; (b) $M_{n,NMR}$ variation of PHEMA with monomer conversion (the solid line represents the theoretical M_n), and (c) dependence of $Đ$ on conversion. The dashed lines are guides to the eye.

$Đ$ of PHEMA prepared in methanol/2-butanone at m/m = 2/3 was lower than that prepared in methanol, or methanol/2-butanone at m/m = 3/2 at identical monomer conversion. These results indicated that the controllability of ATRP (Ca) of HEMA exhibited a trend of solvent dependence which was expressed as follows: Ca (methanol/2-butanone 2/3) > Ca (methanol/2-butanone 3/2) > Ca (methanol).

The controllability variation of ATRP of HEMA with solvents was hypothesized to derive from homogeneity of the reaction mixture.[29] To confirm this hypothesis, controlled experiments were designed and carried out to evaluate the solubility of the catalyst complex and PHEMA in reaction media. The solubility of $CuCl_2$/bpy catalyst complexes in methanol, methanol/2-butanone (3 : 2, 2 : 3, or 1 : 4) and 2-butanone was measured using UV/vis spectroscopy by comparing ultraviolet absorption intensity of the dissolved sample (see experimental details and Fig. S4 in ESI†). The results showed that the solubility (S) of $CuCl_2$/bpy catalyst–ligand complexes exhibits the following trend: S($CuCl_2$/bpy/methanol/2-butanone at 2 : 3) > S($CuCl_2$/bpy/methanol/2-butanone at 3 : 2) > S($CuCl_2$/bpy/methanol) > S($CuCl_2$/bpy/methanol/2-butanone at 1 : 4) > S($CuCl_2$/bpy/2-butanone). The solubility of PHEMA in solvent was directly evaluated by dissolving the polymer sample in solvent (see experimental details and Fig. S4 in ESI†). The results clearly showed that the solvent mixture of MeOH/butanone at 2/3 was the best solvent for PHEMA with a DP of ~800. This could be further verified by the closest solubility parameter of MeOH/butanone at 2/3 to that of PHEMA as calculated from the Hansen model[30] (see Table S1, ESI†). Since the reaction mixture in MeOH/butanone at 2/3 (m/m) was the most homogenous, the controllability of ATRP of HEMA in MeOH/butanone at 2/3 (m/m) was better than those in methanol and MeOH/butanone (m/m = 3/2).

4. Effect of temperature on the ATRP of HEMA

In order to reveal the effect of temperature on the ATRP of HEMA, the polymerizations were carried out in the methanol/2-butanone mixture at 2/3 (m/m) at 30 °C, 50 °C and 60 °C, respectively, by setting the same reaction recipe of $[HEMA]_0 : [CuCl]_0 : [CuCl_2]_0 : [initiator]_0 : [bpy]_0 = 80 : 1 : 0.05 : 1 : 2$ (Fig. 3).

As shown in Fig. 3a, the kinetic plots for ATRP of HEMA carried out at 30 °C, 50 °C and 60 °C were almost linear, suggesting that the polymerizations were well controlled. The apparent rate constants of the polymerizations at different temperatures were calculated from linear kinetic plots, *i.e.*, 1.5×10^{-4} s^{-1} at 60 °C, 8.33×10^{-5} s^{-1} at 50 °C and 7.33×10^{-5} s^{-1} at 30 °C. It is found that the lower reaction temperature resulted in a decrease of the apparent rate constant. Additionally, a linear relationship of $Ln(K_p^{app})$ and $1/T$ was obtained (see Fig. S5 in ESI†), and the reaction activation energy (E_a) extrapolated from the linear plot was 16.05 kJ mol^{-1} based on the Arrhenius equation.[31] This value was comparable to that of 13.6 kJ mol^{-1} reported in the literature.[21]

In Fig. 3b, the $M_{n,NMR}$ of PHEMA increased linearly with monomer conversion at three different temperatures. The $M_{n,NMR}$ of PHEMA was higher than its theoretical values, and the initiator efficiency approached to 75% regardless of temperature. All the $Đ$ of PHEMAs were below 1.30. Furthermore, the $Đ$ values obtained at 30 °C were higher than those obtained

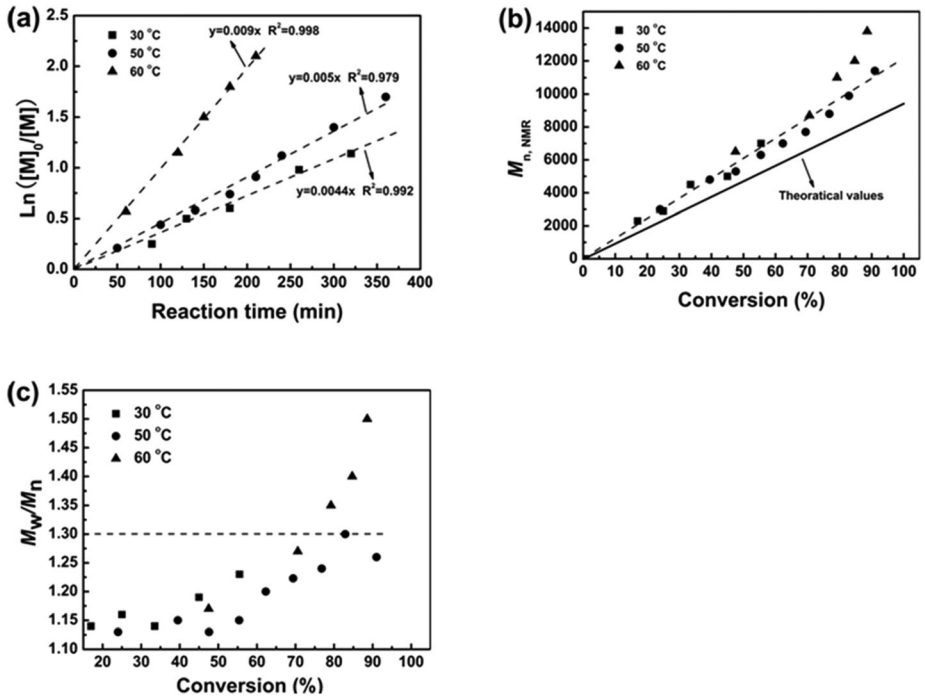


Fig. 3 ATRP of HEMA carried out in a methanol/2-butanone mixture (m/m = 2/3) at various temperatures by setting $[HEMA]_0 : [CuCl]_0 : [CuCl_2]_0 : [initiator]_0 : [bpy]_0 = 80 : 1 : 0.05 : 1 : 2$. (a) First-order kinetic plots; (b) $M_{n,NMR}$ variation of PHEMA with monomer conversion (the solid line represents the theoretical M_n) and (c) dependence of $Đ$ from SEC on conversion. The dashed lines are guides to the eye.

at 50 °C at identical monomer conversion (Fig. 3c). The $Đ$ of PHEMAs obtained at 60 °C was below 1.30 when the monomer conversion was below 75%, but increased to 1.53 when the monomer conversion increased to 90%. The results indicated that the ATRP of HEMA using the current system could be well controlled at moderate temperatures, *i.e*, 50 °C.

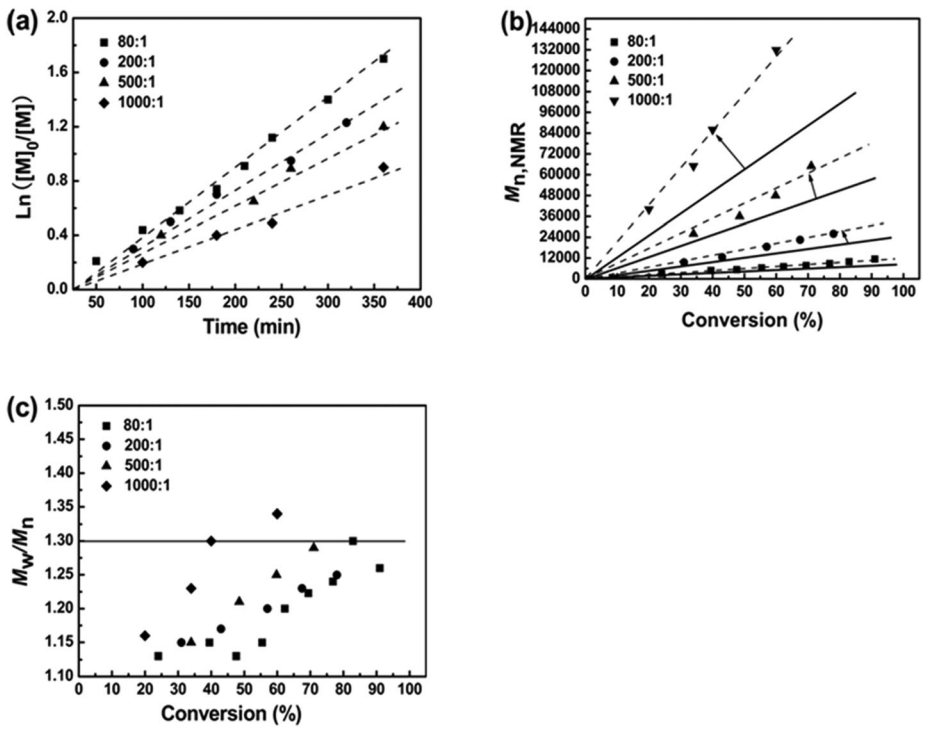


Fig. 4 ATRP of HEMA in methanol/2-butanone (m/m = 3/2) at 50 °C by varying $[M]_0/[I]_0$. (a) First-order kinetic plots; (b) $M_{n,NMR}$ variation of PHEMA with monomer conversion (the solid lines represent the theoretical M_n) and (c) dependence of $Đ$ on conversion. The dashed lines are guides to the eye.

5. Preparation of PHEMA with controlled molecular weight

In order to investigate the feasibility of the PHEMA with well-controlled molecular weight, polymerizations of PHEMA were carried out under identical conditions except the variation of $[M]_0/[I]_0$. Fig. 4a shows that the kinetic plots were all linear for $[M]_0/[I]_0$ at 80/1, 200/1, 500/1, and 1000/1. However, the apparent polymerization rate decreased with the increase of $[M]_0/[I]_0$. This was not surprising since a higher $[M]_0/[I]_0$ resulted in a lower concentration of active species in the reaction system. The $M_{n,NMR}$ increased linearly with the increase of monomer conversion regardless of $[M]_0/[I]_0$, indicative of the feasibility for preparation of PHEMA with controlling molecular weight using the current reaction system. The initiator efficiency, as calculated from the ratio between the $M_{n,NMR}$ and the corresponding theoretical values, decreased with the increase of $[M]_0/[I]_0$. The initiator efficiency was 75%, 73%, 68%, and 59% for [$[M]_0/[I]_0$ = 80, 200, 500, and 1000, respectively]. This could be explained by the fact that a portion of the initiator could be easily oxidized and inactivated in a deoxidization process at higher $[M]_0/[I]_0$.[32] Although the $Đ$ of PHEMA increased with $[M]_0/[I]_0$ at identical monomer conversion, all the prepared PHEMA samples had a $Đ$ of less than 1.34, indicating that all the polymerizations occurred under control (Fig. 4c).

6. Synthesis of a diblock copolymer

To evaluate the reactivity characteristics of the asymmetric end-groups of the $(CH_3)_3Si–C\equiv C$PHEMA–Cl homopolymers, two chain growth experiments were carried out, namely ATRP of *n*-butyl acrylate (*n*BA) using $(CH_3)_3Si–C\equiv C$PHEMA–Cl as a macroinitiator and click reaction between $HC\equiv C$–PHEMA–Cl and MPEG-N_3. Firstly, block copolymer PHEMA-*b*-PBA was obtained in high yield of ~68.4% within 10 h. $(CH_3)_3Si–C\equiv C$–PHEMA–Cl as a macroinitiator initiated the ATRP of butyl acrylate (BA) in 50% m/m DMF solution at 90 °C by setting $[BA]_0:[PHEMA\text{-}Br]_0:[CuCl]_0:[PMDETA]_0 = 100:1:1:1$. Secondly, diblock copolymer MPEG-*b*-PHEMA was successfully synthesized by click reaction between alkynyl-terminated PHEMA and azide-terminated MPEG. The alkyne terminated PHEMA was obtained by the removal of the trimethylsilyl group *via* hydrolysis catalyzed by tetrabutyl ammonium fluoride using a similar procedure.[33] Azide-terminated MPEG was obtained through the reaction of MPEG with 2-bromoisobutyryl bromide followed by the reaction of MPEG-Br with sodium azide. Azide terminated MPEG (1.2 equivalent) was coupled to the alkynyl end of PHEMA by ''click reaction'' using CuBr/PMDETA as a catalyst in DMF at 30 °C for 24 h (see Scheme 2) in a yield of 82.6%. The successful preparation of these diblock copolymers was verified by ^{1}H NMR spectroscopy. The peaks were well analyzed and assigned (see Fig. S6 in ESI†). In the SEC curves (Fig. 5), the obtained PHEMA-*b*-PBA and MPEG-*b*-PHEMA diblock copolymers showed obvious shift to left owing to the increase of molecular weight compared to the precursor PHEMA and MPEG. The $Đ$ of the obtained PHEMA-*b*-PBA and MPEG-*b*-PHEMA diblock copolymers were 1.34 and 1.37, respectively.

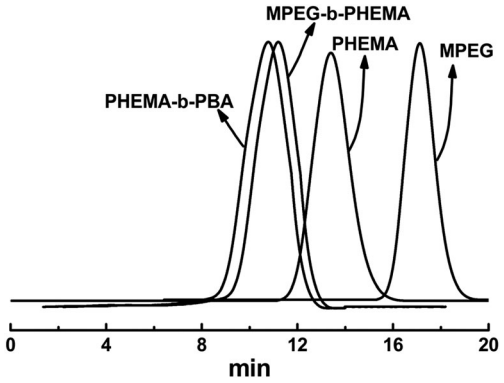


Fig. 5 SEC curves of PHEMA, MPEG, and the obtained PHEMA-*b*-PBA and MPEG-*b*-PHEMA diblock copolymers, respectively.

Conclusions

The controllable ATRP of HEMA was achieved by tuning the reaction parameters, including temperature, solvents, initiators and recipes. Well-defined PHEMA polymers end-capped with living chloride and alkyne terminal groups were achieved by using TMSPBiB as an initiator and CuCl/$CuCl_2$/bpy as a catalyst in methanol/2-butanone. The solvent mixture of methanol/2-butanone at a mass ratio of 3/2 led to better polymerization controllability. PHEMA samples with a wide range of DPs (the degree of polymerization) from 80 to 1000 and $Đ$ below 1.34 were obtained under appropriate conditions. The activity of chloride and alkyne terminal groups was confirmed by the successful preparation of diblock copolymers PHEMA-*b*-PBA and MPEG-*b*-PHEMA, which were obtained by ATRP of BA using $(CH_3)_3Si–C\equiv C$–PHEMA–Cl as a macroinitiator and click reaction between azide-terminated MPEG and $HC\equiv C$–PHEMA–Cl, respectively. The studies provided a facile synthetic modular route for the design and synthesis of novel copolymers.

Experimental section

Materials and reagents

2-Hydroxyethyl methacrylate (HEMA, 98%, Sigma Aldrich) was purified according to procedure described in our previous papers.[1,34] HEMA solution (25% v/v) in water was washed with hexane for 5 times to remove ethylene glycol diacrylate. Then, HEMA was salted out from the aqueous phase by addition of NaCl and separated by extraction with diethyl ether for 4 times. The organic layer was collected and dried over anhydrous $MgSO_4$ before filtration and evaporation in a rotary evaporator at 35 °C. HEMA was obtained *via* distillation at 80 °C under reduced pressure. *n*-Butyl acylate (BA, 98%, Sigma Aldrich) was washed thrice with an equal volume of 5 wt% NaOH aqueous solution, and then washed with water until the acidity–alkalinity of the water was tested to be neutral. It was dried over anhydrous $MgSO_4$ before being distilled under reduced pressure. The purified HEMA and BA were kept at 4 °C prior to use. Cuprous chloride (Cu^ICl, 95%, Sigma Aldrich) was purified by stirring with acetic acid overnight, filtration, repeatedly washing in

sequence with ethanol and diethyl ether, and drying under vacuum conditions.[35] 2-Bromoisobutyryl bromide (98%), copper chloride ($CuCl_2$), 2,2′-bipyridine (bpy, 99%), 3-(trimethylsilyl)-propargyl alcohol (TMS-OH, 98%), triisopropylchlorosilane (TiPS-Cl, 97%), ethyl magnesium bromide (3.0 M solution in diethyl ether), ethylene diamine tetraacetic acid disodium salt (EDTA), tetrabutyl ammonium fluoride (TBAF, 1 M solution in THF), sodium azide (NaN_3) (99%), and propargyl alcohol (PA, 98%) were all from Aldrich and used as received. Triethylamine (Et_3N, 98%), 2-butanone (98%) and diethyl ether (99%) were purified by refluxing with sodium for 12 h before distillation. Methanol (99%) was purified by magnesium and iodine to remove water. Water employed in all experiments was double-distilled. All other reagents and solvents were of analytical grade and used without further purification, if not specified.

Synthesis of initiators

The initiators, propargyl 2-bromoisobutyrate (PBiB), 3-(trimethylsilyl)propargyl 2-bromoisobutyrate (TMSPBiB), and 3-(triisopropylsilyl)propargyl 2-bromoisobutyrate (TiPSPBiB), were synthesized by the esterification reaction between the hydroxyl groups of unmodified or modified propargyl alcohol and 2-bromoisobutyryl bromide, as shown in Scheme 2.

PBiB was synthesized following the literature procedure.[24a] In brief, propargyl alcohol (3.0 g, 0.054 mol), triethylamine (6.0 g, 0.059 mol) and anhydrous diethyl ether (150 mL) were added into a 250 mL flask which was pre-cooled with ice bath. 2-Bromoisobutyryl bromide (13.8 g, 0.059 mol) was added dropwise *via* a syringe over 30 min. After stirring at room temperature for 12 h, the reaction mixture was filtered, washed in sequence with 5 mL of 1 mol L^{-1} HCl, 50 mL of 3% $NaHCO_3$ solution and water for several times until the pH value of the aqueous phase was around 7. The organic layer was collected, dried over anhydrous $MgSO_4$, rotary evaporated and distilled under reduced pressure to obtain a colorless liquid (6.17 g) at a yield of 61%. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.96 (6H, –OCO–C(CH_3)$_2$Br), 2.38–2.42 (1H, $CH\equiv$C–CH_2–OCO–), 4.76–4.78 (2H, HCC–CH_2–OCO–).

TMSPBiB was synthesized with the same synthesis and purification procedure as PBiB except that 3-(trimethylsilyl)-propargyl alcohol (7.0 g, 0.054 mol) were added. The finally colorless liquid was weighted to be 10.93 g and the yield was 73%. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.14–0.19 (9H, protons of trimethylsilyl groups), 1.91 (6H, –OCO–C(CH_3)$_2$Br), 4.76 (2H, –C$\equiv$C–CH_2–OCO–).

TiPSPBiB was synthesized in two steps according to the literature.[36] Firstly, the alkynyl group of propargyl alcohol was protected with the triisopropylsilyl group. Secondly, the hydroxyl group of 3-(triisopropylsilyl)propargyl alcohol was reacted with 2-bromoisobutyryl bromide.

Propargyl alcohol solution (0.57 g, 10.2 mmol) in THF (10 mL) was added dropwise into 10 mL of ethylmagnesium bromide (30 mmol) solution in THF and refluxed for 18 h. And then, triisopropylchlorosilane (2.79 g, 14.5 mmol) in THF (10 mL) was added dropwise and refluxed for 5 h. After pouring into 15 mL of 10% (m/m) HCl solution, the solution was extracted with diethyl ether (100 × 4 mL) four times. The organic layers were washed with 15 mL of 10 wt% NaCl solution, dried with anhydrous $MgSO_4$ and rotary evaporated to generate 1.70 g of 3-(triisopropylsilyl)propargyl alcohol at 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.60 (s, 2H, –C$\equiv$C–CH_2–OH), 1.06–1.05 (m, 18H, ((CH_3)$_2$CH)$_3$Si–), 0.14–0.19 (m, 3H, ((CH_3)$_2$CH)$_3$Si–).

2-Bromoisobutyryl bromide (1.88 mL, 15.2 mmol) was added dropwise to a solution of obtained 3-(triisopropylsilyl)propargyl alcohol (1.7 g, 8.0 mmol) and triethylamine (2.12 mL, 15.2 mmol) in THF (50 mL) at 0 °C, and stirred for 2 h at room temperature. The mixture was filtered, rotary evaporated and purified using column chromatography (hexane/ethyl acetate = 95 : 5). The final colorless oil was 1.88 g and the yield was 65%. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.67 (s, 2H, –C$\equiv$C–CH_2–O_2C), 1.95 (s, 6H, –O_2C–C(CH_3)$_2$Br), 1.07 (m, 18H, ((CH_3)$_2$CH)$_3$Si–), 0.14–0.19 (m, 3H, ((CH_3)$_2$CH)$_3$Si–).

ATRP of HEMA

ATRP is strongly solvent-dependent. Protic solvents lead to quick and poorly controllable reaction possibly due to competitive coordination of solvent to the Cu(II) center, therefore, the controlled polymerization of HEMA in protic solvents by employing a catalyst system initially containing a sufficient Cu(II)–halide complex.[20] Thus, in our system, $CuCl_2$ ([CuCl]/[$CuCl_2$] = 20/1) was employed in all the reaction recipes.

The ATRP of HEMA was performed in a home-made dual-flask apparatus in which two 25 mL flasks were connected *via* a glass pipe with a diameter of 0.8 cm and a length of 5 cm. In a typical experiment, 2,2′-bipyridine (91 mg, 0.58 mmol), TMSPBiB (80 mg, 0.29 mmol), HEMA (3.00 g, 23.1 mmol) and methanol (1.2 mL) were added into one flask, while CuCl (29 mg, 0.29 mmol), $CuCl_2$ (2 mg, 0.015 mmol), 2-butanone (1.8 mL) and a magnetic stir bar were loaded into the other flask. The liquid mixture in the two dual-flasks were bubbled with argon for half an hour and then subjected to three freeze–pump–thaw cycles under an argon atmosphere, and then thoroughly transferred into one of the flasks *via* a vacuum line system. The dual-flask apparatus was immediately placed in thermostatic oil baths at 50 °C (defining t = 0). The reaction mixture was initially dark brown and transparent and the polymerization occurred immediately, leading to an increase in viscosity over 30 min. Samples for the kinetics study were taken out *via* argon purged syringe at predesigned time intervals and quickly transformed to vials which were pre-cooled with liquid nitrogen for DMF, SEC and ^{1}H NMR analysis, respectively. The reaction was stopped after 5 h by freezing the flask with liquid nitrogen before exposure to air. Once switched with air, the dark brown reaction solution turned blue, indicative of aerial oxidation of Cu(I) to Cu(II). Subsequently, the dark bluish reaction mixture was diluted with 15 mL of methanol and passed through a silica column to remove copper–ligand complexes and the resulting colorless aqueous solution was concentrated to about 5 mL *via* rotary evaporation and precipitated out over diethyl ether (200 mL) to remove the HEMA monomer and other impurities. The crude

product was further purified by re-dissolving in 5 mL of methanol and precipitated out over 100 mL of diethyl ether. This procedure was repeated thrice. The precipitates were collected and dried under vacuum for 72 h to generate white PHEMA polymers. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.14–0.19 (9H, protons of trimethylsilyl groups), 0.86–1.22 (–CH_2–C(CH_3)–), 1.97 (–CH_2–C(CH_3)–), 3.86–4.23 (–OCH_2CH_2O–), 4.67 (–C≡C–CH_2–O_2C). M_n and $Đ$ from SEC were 14 000 g mol^{-1} and 1.26, respectively.

Preparation of PHEMA-*b*-PBA by chain extension *via* ATRP

PHEMA-*b*-PBA (Scheme 2) was prepared *via* ATRP of BA by using chloro-terminated PHEMA ($Đ$ = 1.16 from SEC, DP = 121 evaluated from ^{1}H NMR) as a macroinitiator. The polymerization was carried out at 90 °C for 10 h by using a recipe described as follows: macroinitiator (0.51 g, or 0.032 mmol of terminal chloride groups), DMF (9 g, 50% m/m), CuCl (3.17 g, 0.032 mmol), PMDETA (5.55 g, 0.032 mmol), and BA (0.82 g, 6.40 mmol). The isolation and purification procedure of this block copolymer $(CH_3)_3$Si–C≡C–PHEMA-*b*-PBA was the same as the procedure used for the $(CH_3)_3$Si–C≡C–PHEMA–Cl homopolymer. The yield was 68.4%. SEC: $Đ$ = 1.26, M_n = 37 200 g mol^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.14–0.19 (9H, protons of trimethylsilyl groups), 0.86–1.22 (–CH_2–C(CH_3)– of PHEMA), 1.97 (–CH_2–C(CH_3)– of PHEMA or –CH_2–CH– of PBA), 3.86–4.23 (–OCH_2-CH_2O– of PHEMA), 4.21 (–OCH_2– of PBA), 2.27 (–OCH_2–CH_2– of PBA), 1.27–1.67 (–OCH_2CH_2–CH_2CH_3 of PBA).

Preparation of MPEG-*b*-PHEMA by click reaction

1.5 g of $(CH_3)_3$Si–C≡C–PHEMA–Cl (DP = 121, $Đ$ = 1.16, 0.095 mmol of terminal trimethylsilyl groups) and 1 mL of TBAF (1.15 mmol, 10.0 eq.) were dissolved in 8.5 mL of THF and stirred at room temperature for overnight (Scheme 1). Then, the reaction mixture was rotary evaporated to eliminate THF, and the polymer was obtained by precipitation into diethyl ether, and dried under vacuum. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.86–1.22 (–CH_2–C(CH_3)–), 1.97 (–CH_2–C(CH_3)–), 3.86–4.23 (–OCH_2CH_2O–), 4.67 (–C≡C–CH_2–O_2C–). The disappearance of peak at δ = 0.14–0.19 ppm in ^{1}H NMR spectra confirmed the complete removal of the trimethylsilyl terminal group of the purified polymer HC≡C–PHEMA–Cl.

Monomethoxy polyethylene glycol (M_n = 5000 g mol^{-1}) with azido terminal functional group (MPEG-N_3) was obtained according to the literature method.[37] First, monomethoxy polyethylene glycol (5.0 g, or 1.0 mmol of hydroxyl group), and dry triethylamine (0.15 g, 1.5 mmol) were dissolved in THF (40 mL) and 2-bromoisobutyryl bromide (0.35 g, 1.5 mmol) was added dropwise. The mixture was stirred at room temperature for 24 h. After filtration, the solvent was rotary evaporated and the product was redissolved in CH_2Cl_2 and then precipitated into cold diethyl ether (100 mL) and dried under vacuum. The polymers were re-dissolved in CH_2Cl_2 (4 mL) and precipitated into diethyl ether (20 mL). MPEG-Br (4.69 g, the yield was 91%) was obtained by drying under vacuum for 24 h. Second, MPEG-Br (1.0 g, 0.2 mmol) and sodium azide (26.0 mg, 0.4 mmol) were dissolved in DMF (10 mL) and stirred at 120 °C for 6 h. After cooling to room temperature, 10 mL of water was added, and then extracted by CH_2Cl_2 three times. The combined CH_2Cl_2 solution was washed with cool water thrice condensed and dried with anhydrous $MgSO_4$ overnight, and then precipitated in cold diethyl ether. 0.92 g of MPEG-N_3 at a yield of 93% was obtained as white powder by drying at 30 °C for 24 h. ^{1}H NMR (400 MHz, DMF-d_6, δ, ppm): 3.38 (CH_3–O–), 3.75 (–CH_2–CH_2–), 3.92 (–OCH_2CH_2O–CO–), 1.96 (–CH_2–N_3).

The click reaction was performed as follows (Scheme 2): 6.4 mg of CuBr (0.063 mmol), 11.7 mg of PMDETA (0.063 mmol), 0.1 g of HC≡C–PHEMA–Cl (0.063 mmol of terminal alkynyl groups), MPEG-N_3 (0.333 g, 0.065 mmol) and 8 mL of DMF were added into the flask and degassed for 50 min by blowing with argon. The solution was stirred for 48 h at 80 °C. After reaction, the mixture was diluted with 15 mL of dichloromethane and passed through the silica column to remove the catalyst. Then, the mixture was rotary-evaporated to remove CH_2Cl_2 before dialyzed against water (molecular weight cut-off is 14 000 g mol^{-1}) by changing water every 4 h over 7 days. Finally, the solution in the dialysis bag was collected and freeze dried for 12 h to generate 0.35 g product as a white powder at a yield of 82.6%. SEC: $Đ$ = 1.19, M_n = 22 100 g mol^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.86–1.22 (–CH_2–C(CH_3)–), 1.97 (–CH_2–C(CH_3)–), 3.32 (–OCH_3), 3.86–4.31 (–OCH_2CH_2O–).

Characterization

^{1}H NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on a Bruker 400 spectrometer at 30 °C. The peak integral ratios of the two protons of the propargyl group (–C≡C–CH_2–O) introduced from the initiator at 4.67 ppm and the two oxyethyl or ethylene protons of the PHEMA at 4.34 ppm or 5.58 ppm were used to calculate the monomer conversion (conv. = $2(\delta_{4.34}/2 - \delta_{5.58})/\delta_{4.34} \times 100\%$), the degree of polymerization (DP = $2(\delta_{4.34}/2 - \delta_{5.58})/\delta_{4.67}$) and the theoretical molecular weight of PHEMA ($M_{n,theor}$ = 130.15 × ([M]$_0$/[I]$_0$) × conv. + $M_{initiator}$).

The molecular weight and molar mass dispersity of samples were measured at 25 °C using a size exclusion chromatography (SEC) system consisting of a Waters 1515 pump, a Styragel Packed Column, and a Waters Model 410 refractive index detector. Narrow disperse polystyrene with molecular weights in the range of 1.31 × 10^3 to 3.64 × 10^6 g mol^{-1} was used as a standard for calibration. Tetrahydrofuran (THF) was used as the eluent at a flow rate of 1 mL min^{-1}. The concentration of the sample was around 3 mg mL^{-1} and the sample solution was filtered through the 0.45 μm membrane before injection. To have the PHEMA well dissolved in THF which was used as an eluent in the SEC analysis, the PHEMA homopolymer and the diblock copolymer containing the PHEMA block were acetylated with acetic anhydride in dry pyridine before SEC measurements.

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