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In-situ IR Monitoring the Synthesis of Amphiphilic Copolymery P(HEMA-*co*-*t*BMA) *via* ARGET ATRP☆

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ABSTRACT

The amphiphilic copolymer poly(hydroxyethyl methacrylate-*co*-*tert*-butyl methacrylate) [P(HEMA-*co*-*t*BMA)] was synthesized by activators regenerated by electron transfer atom transfer radical polymerization (ARGET ATRP), with the synthesis process monitored by *in-situ* infrared spectroscopy (IR). The molecular weight, chemical structure and characteristics of the copolymer were determined by ^{1}H NMR, gas chromatography and gel permeation chromatography. The influences of various parameters on the living polymerization were explored. The molecular weight of the copolymer with narrow molecular weight distribution ($M_w/M_n < 1.50$) increases approximately linearly with the monomer conversion, indicating a good control of polymerization. In the reaction temperature range from 50 °C to 90 °C, the monomer conversion is higher at 60 °C. The *t*BMA conversion rate decreases gradually with the increase of *t*BMA content, while the HEMA conversion is hardly affected by HEMA content. Weak polar solvent is more favorable to the polymerization compared to polar solvent. The molar ratio of reducing agent to catalyst has significant effect on the polymerization and increasing the amount of reducing agent will accelerate the reaction rate but causes wider molecular weight distribution. It is indicated that *in-situ* IR monitoring contributes to a more in-depth understanding of the mechanism of methacrylate monomer copolymerization.

1. Introduction

Amphiphilic copolymers have unique structures with hydrophilic and hydrophobic chains, and can self-assemble to form core/shell polymeric micelles due to solubility difference of chain segments in selective solvent [1,2]. The outer hydrophilic shell of micelles provides a stable interface between the hydrophobic core and aqueous medium, and the inner hydrophobic core of micelles enhances the loading efficiency of hydrophobic drugs [3]. The polymeric micelles are excellent candidate for the administration of hydrophobic drugs and provide a controlled and targeted way to deliver the encapsulated hydrophobic drugs [4].

Activators regenerated by electron transfer atom transfer radical polymerization (ARGET ATRP), which is a preferential technique from both industrial and environmental viewpoints, can lower the concentration of catalyst by using an excess amount of reducing agent to regenerate Cu^I from Cu^{II} and maintaining appropriate Cu^I/Cu^{II} balance [5–8]. A variety of monomers, such as methyl methacrylate [9], styrene [10,11], butyl acrylate [12], and poly(hydroxyethyl methacrylate) [P(HEMA)] [13], have been polymerized by ARGET ATRP.

P(HEMA) contains pendant hydroxyl functionalities that render it hydrophilic, and has wide applications in areas of hydrogels [14], contact lenses [15], and drug delivery systems [16]. Poly(*tert*-butyl methacrylate) [P(*t*BMA)] can be converted to poly(methacrylic acid) (PMAA) by selective hydrolysis of the *tert*-butyl groups [17]. PMAA is a pH-responsive biomaterial, which contains carboxyls that are easily ionized above its p*K*a of 4.5 and affords the polymer pH-tunability for the controlled-release applications. Therefore, P(HEMA-*co*-MAA) derived from P(HEMA-*co*-*t*BMA) may serve as a pH-responsive amphiphilic carrier for drug delivery. Traditional copolymerization methods for creating hydrophilic HEMA and hydrophobic *t*BMA micelle networks offer little control over co-monomer distribution, molecular weight, or molecular weight distribution, which in turn restricts the design and synthesis of hydrophilic/hydrophobic micelle systems. In the present work, a linear P(HEMA-*co*-*t*BMA) random copolymer is synthesized by ARGET ATRP. The proposed mechanism is shown in Fig. 1, using $CuBr_2$/PMDETA as the catalyst and ethyl 2-bromoisobutyrate (EBriB) as the initiator with $Sn(Oct)_2$ as reducing agent. Temperature, monomer ratio, as well as the catalyst system will affect the structure of P(HEMA-*co*-*t*BMA), thus

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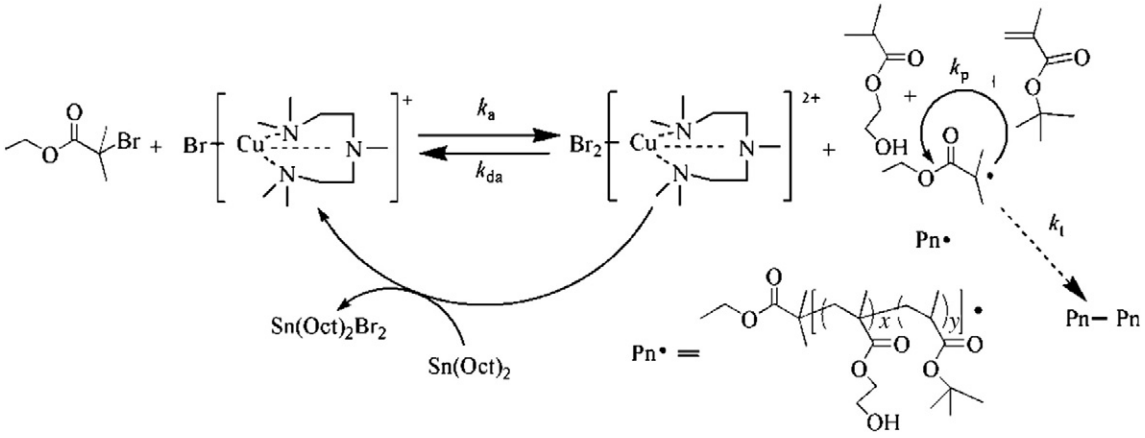

Fig. 1. The ARGET ATRP mechanism for P(HEMA-*co*-*t*BMA).

affecting its further applications. In our current work, we will explore how those factors affect the polymerization monitored by *in-situ* IR.

In recent years, the application of *in-situ* IR in monitoring reaction process has attracted extensive attention. For the polymerization, *in-situ* IR can monitor the change of monomer concentration, analyze the monomer conversion and product composition, determine the reaction end point timely and avoid blind operation, and explore the reaction mechanism [18,19]. It is used for studying the formation of carbon–carbon and carbon–heteroatom bonds catalyzed by transition metals and exploring new synthesis technology [20]. By detecting the starting and end points of reaction precisely and tracking the material accumulation, the *in-situ* IR can improve the safety of the operating process [21]. It is also used to monitor the emulsion homopolymerization and copolymerization of butyl acetate, methyl methacrylate and vinyl acetate [22], and the emulsion crosslinking copolymerization kinetics of methyl acrylate and isobutyric acid [23]. In the synthesis of phenol formaldehyde prepolymer, the online infrared can track the change of polymer structure and prevent the formation of byproducts [24].

Herein, for the synthesis of P(HEMA-*co*-*t*BMA) with low molecular weight distribution using ARGET ATRP, the effects of temperature, monomer ratio, solvent, and molar ratio of reducing agent to the catalyst on the monomer conversion are monitored by *in-situ* IR. The reaction kinetics and mechanism of the copolymerization of hydrophilic HEMA/hydrophobic *t*BMA monomers are systematically investigated, which will provide the guidance for copolymerization of P(HEMA-*co*-*t*BMA) and this kind of hydrophilic/hydrophobic monomers.

2. Experimental

2.1. Materials

Tert-butyl methacrylate (*t*BMA, TCI-EP) was washed with sodium hydroxide solution (10%), distilled from calcium hydride, and stored under argon at −20 °C. 2-Hydroxyethyl methacrylate (HEMA, 99%, Aldrich) was purified by passing through a neutral alumina column followed by distillation and stored under argon at −20 °C. Toluene was distilled from calcium hydride. Ethyl 2-bromoisobutyrate (99%, Aldrich), N,N,N′,N″,N″-pentamethyldiethylenetriamine (PMDETA, 99%, Aldrich), anisole, $CuBr_2$, *n*-hexane, dichloromethane, stannous octoate ($Sn(Oct)_2$), methanol, tetrahydrofuran (THF), acetone, and all other reagents were used as received.

2.2. Measurements

The number average molecular weight (M_n) and polydispersity index (M_w/M_n) were determined by gel permeation chromatography (GPC) adopting an Agilent 1200 series GPC system equipped with a LC quant pump, three columns including PL gel 5 mm 50 nm, 1000 nm and 10000 nm columns in series and a RI detector. The column system was calibrated with a set of monodisperse polystyrene standards using HPLC grade THF as the mobile phase with a flow rate of 1.0 ml·min^{-1} at 30 °C.

^{1}H NMR spectral measurements were executed on a Bruker AVANCE III 400 NMR spectrometer (Switzerland) operated at 400 MHz, using deuterated chloroform ($CDCl_3$) as solvent and tetramethylsilane as the internal standard. The temperature was 25 °C.

Gas chromatography (GC) was carried out on an Agilent Technologies 6820 series II Network GC system equipped with a poly(dimethylsiloxane) capillary column (12 m × 200 μm × 0.25 μm) using H_2 as eluent at a flow rate of 1.5 ml·min^{-1} and a temperature ramp rate of 10 °C·min^{-1}. The temperature of the injector and detector was kept constant at 250 °C with a H_2 flow rate of 40 ml·min^{-1}. Anisole (1/1 by volume to HEMA) was added to the polymerization medium as an internal GC standard. GC samples were diluted with acetone prior to characterization.

2.3. In-situ IR

A ReactIR iC10 reaction analysis system (Mettler-Toledo AutoChem, Switzerland) equipped with a light conduit and DiComp (diamond composite) insertion probe was used to collect mid-FTIR spectra of the condensation components. FTIR spectra were collected every minute in the wave number range between 4000 cm^{-1} and 650 cm^{-1} at a resolution of 8 cm^{-1}. The reaction information was provided by *in-situ* IR detecting the disappearance of the C═C vibration peak (1638 cm^{-1}) of the comonomers [25]. The total conversion (α) of monomers HEMA and *t*BMA during the polymerization was calculated according to Eq. (1). The conversion of monomer HEMA or *t*BMA was obtained by ConcIRT™ software (spectral region: 800–1200 cm^{-1}, time region: 0–60 min) [17]. ConcIRT™, using a type of mathematical algorithm known as curve-resolution, is a powerful tool for analyzing a broad range of reactions because the characteristic peaks of HEMA and *t*BMA around 800–1200 cm^{-1} are completely different, which can be used to calculate the conversion of HEMA and *t*BMA using the ConcIRT™ software. When adding the first monomer *t*BMA, ConcIRT™ will calculate the associated component spectrum and relative concentration profile. And ConcIRT™ will re-analyze the former reaction spectra of *t*BMA and update the individual component spectra and profiles when adding the second monomer HEMA. Therefore, we can calculate the conversion of HEMA and *t*BMA through their concentration profiles:

$$\alpha = \frac{A_0 - A_t}{A_0} \times 100\% \quad (1)$$

where A_0 and A_t are the peak heights at reaction times $t = 0$ and 1638 cm^{-1}, respectively.