

Synthesis of zwitterionic block copolymers via RAFT polymerization

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Abstract

A series of poly [2-(dimethylamino)ethyl methacrylate (DMA)–sodium acrylate (SA)] diblock copolymers were synthesized using reversible addition-fragmentation chain transfer (RAFT) polymerization. The polymerization exhibits controlled characters: well-controlled molecular weight, narrow molecular weight distribution, molecular weight increasing with polymerization time. The zwitterionic diblock copolymers show rich solution behaviors. Dynamic light scattering (DLS) indicated the formation of micelles and reverse micelles of copolymers is affected by net charge density of copolymers. Microcalorimetry studies showed that the lower critical solution temperature (LCST) increases with incorporation of hydrophilic segments in buffer.

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1. Introduction

Zwitterionic block copolymers has received interests because they are not only considered as synthetic analogues of biological macromolecules such as proteins and nucleotides, but also have the potential applications such as drag reduction [1], sewage treatment, protein isolation and purification [2], emulsion formulations [3]. Since Stille's group first reported the synthesis of zwitterionic block copolymers using anionic polymerization in the early 1970s [4,5], much effort has focused on the synthesis and aqueous solution behaviors of zwitter-

ionic block copolymers [6–11]. In 1994, Patrickios et al. [12,13] reported the synthesis of diblock, triblock and statistical methacrylic block copolymers utilizing group transfer polymerization (GTP) [14]. Armes et al. [15,16] synthesized diblock copolymers of 2-(dimethylamino)ethyl methacrylate (DMA) with methacrylic acid (MAA) using GTP. Because the monomers suitable for anionic polymerization and GTP are limited, it is obvious that the usable monomers are greatly increased by introduction of radical polymerization into the preparation of zwitterionic block copolymers. The recent developments in controlled free radical polymerization techniques allow for synthesis of zwitterionic block copolymers. The first synthesis of zwitterionic block copolymers via controlled radical polymerization was reported by Gabaston et al., who described the TEMPO-mediated polymerization [17] to prepare block

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copolymers comprising of sodium 4-styrenesulfonate and DMA [18]. Donovan et al. [19–21] prepared a series of zwitterionic block copolymers via reversible addition-fragmentation chain transfer (RAFT) polymerization [22–25]. Armes et al. have reported the synthesis of new class of zwitterionic block copolymers [26–28] using atom transfer radical polymerization (ATRP) [29,30]. However, a facile synthesis of well-defined zwitterionic block copolymers is a challenge utilizing controlled free radical polymerization techniques without protecting group chemistry [31].

In this work, we synthesized a series of diblock zwitterionic copolymers which comprise of weakly basic PDMA block and weakly acidic acrylic acid block (acidified sodium acrylate) using RAFT polymerization without using protecting group chemistry. The self-assembly configuration of these kinds diblock copolymers were studied in extra-stimuli such as pH and temperature through dynamic light scattering (DLS) and microcalorimetry.

2. Experimental section

2.1. Materials

2-(dimethylamino) ethyl methacrylate (DMA, 98%) was purchased from Aldrich, α -methylstyrene (98%) and acrylic acid (98%) were purchased from Shanghai Chemical reagents Co., each of these monomers was distilled under reduced pressure prior to use. Sodium acrylate (SA) was prepared according to the procedure described by Annenkov et al. [32]. *N,N*-azobis (isobutyronitrile) (AIBN, 98%) was recrystallized from ethanol and dried at room temperature in vacuum oven. Tetrahydrofuran (THF) was distilled from a purple sodium solution prior to use. Absolute diethyl ether was treated with 98% concentrated sulfuric acid and distilled. Other materials were used as received.

2.2. Synthesis of RAFT agents

2.2.1. Synthesis of dithiobenzoic acid (DTBA)

Dithiobenzoic acid was prepared according to the method described by Bai et al. [33]. The Grignard reagent reacted with carbon disulfide in dry THF (30 ml) at -5°C for 1 h. The mixture was decomposed with ice-cold dilute hydrochloric acid (100 ml). The organic layer was separated and extracted with ice-cold 10% sodium hydroxide solution (50 ml \times 3). The alkaline solution was washed with diethyl ether three times and acidified with ice-cold 10% hydrochloric acid solution, finally extracted with diethyl ether. The ether solution was washed with distilled water three times. After evaporation of the solvent, pure DTBA was obtained in

40.2% yield. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 6.5 (s, 1H, $-\text{C}(\text{C}=\text{S})\text{SH}$), 7.0–7.9 (m, 5H, aromatic H).

2.2.2. Synthesis of cumyl dithiobenzoate (CDB) [34]

A mixture of DTBA (5.059 g, 0.036 mol), α -methylstyrene (4.017 g, 0.040 mol) and carbon tetrachloride (40 ml) was heated at 70°C for 5 h. The resultant mixture was reduced to crude oil that was purified by silica-gel column chromatography using *n*-hexane as eluent. The pure CDB was 47.3% yield as dark purple oil. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 2.00 (s, 6H), 7.20–7.60 (m, 8H), and 7.84 (m, 2H).

2.3. Polymerization

A mixture of DMA, RAFT agent, AIBN and anisole (DMA:anisole = 1:2 (v/v)) was added to 5 ml ampoule with a magnetic stirring bar. The mixture was degassed by freeze–vacuum–thaw cycle three times. Then, the ampoule was sealed under vacuum, and immersed in oil bath thermostated at 80°C for a predetermined time. Then, the ampoule was opened; the reaction mixture was added into excess of *n*-hexane. The polymer PDMA was precipitated, filtered and dried in a vacuum oven at 40°C for 24 h.

The block copolymers of PDMA-*b*-SPA were synthesized by the solution of SA:PDMA:AIBN = 500:5:1 (molar ratio), methanol:distilled water (v/v) = 2:1.5 as solvent. The mixture was degassed by three freeze–pump–thaw cycles. The ampoule was sealed under vacuum, immersed in an oil bath thermostated at 80°C for a predetermined time. Then, the ampoule was opened; the reaction mixture was added into excess of THF, the copolymer was filtered and dried at 40°C in a vacuum oven for 12 h. Then, the copolymer was firstly dialyzed in dilute sodium chloride solution, and then in methanol with dialyzer (3500 molar mass). After evaporation of methanol, the copolymer was dried at 40°C in a vacuum oven for 24 h.

2.4. Characterization

2.4.1. Nuclear magnetic resonance spectroscopy

^1H NMR spectra were performed in a Bruker AVANCE300 NMR spectrometer, using CDCl_3 as solvent for PDMA, tetramethylsilane (TMS) as internal reference, and D_2O as solvent for block copolymers.

2.4.2. Gel permeation chromatograph (GPC)

Molecular weight ($M_{n,\text{GPC}}$) and molecular weight distribution (M_w/M_n) of PDMA homopolymers were obtained on a Waters 150C Gel Permeation Chromatograph (GPC) equipped with 10^3 , 10^4 , and 10^5 Å Waters Ultrastaygel columns, using THF as the eluent at a flow rate of 1.0 ml/min. The calibration was carried out with polystyrene standards.

2.4.3. Aqueous GPC

Aqueous GPC of copolymers was performed on a Waters 2690 apparatus with two columns in series (Waters Ultrahydrogel 250, 200) and a Waters 410 refractive index detector using 0.5 M acetic acid/0.5 M sodium acetate as the eluent and poly (ethylene oxide) as the standards. The flow rate was 0.50 ml/min.

2.4.4. Other analytical techniques

FT-IR spectra were recorded on Bruker Co. EQUINOX55 spectrometer. Elemental analysis experiments were performed on Elementar Co. Vario EL III elemental analyzer.

2.4.5. Dynamic light scattering (DLS)

DLS were performed on a commercial laser light scattering spectrometer (ALV/SP-125) equipped with an ALV-5000 multi-tau digital time correlator and a He–Ne laser (Uniphase, 22 mW at $\lambda = 632.8$ nm) at 25 °C. The scattering angle was 90°. The average hydrodynamic radius (R_h) of the micelles was obtained by cumulants analysis of the correlation function. The polymer solutions in phosphate buffers with a concentration of 1.0 mg/ml were filtered by a 0.8 μ m filter before being analyzed.

2.4.6. Microcalorimetry

Thermal transitions of 1.0 mg/ml dilute phosphate buffers of both PDMA homopolymers and PDMA-*b*-SPA diblock copolymers were measured with a VP-DSC from Microcal Co. The heating rate is 1.0 °C/min.

3. Results and discussion

3.1. Synthesis and characterization of homo and block polymers

CDB was selected for the RAFT agents as they have been confirmed to be effective in polymerization of methacrylate monomers [34,25,35]. Simultaneously, one requirement for forming a narrow polydispersity

AB block copolymer in a batch polymerization is that the first-formed polymeric thiocarbonylthio compound should have a high transfer constant in the subsequent polymerization step to give B block [25]. Therefore, when we prepared a block copolymer, the methacrylate block was prepared first. Fig. 1 is a ^1H NMR spectrum of a PDMA homopolymer. The peak at 7.86 ppm is the characteristic signal of the two aromatic protons ortho to the dithio group, indicating that RAFT agent moiety remains at one end of the polymer. Results of the homopolymers are described in Table 1. The number average molar masses $M_{n,\text{NMR}}$ are calculated using the equation:

$$M_{n,\text{NMR}} = (I_{4.04}/I_{7.86})M_m + M_{\text{RAFT}} \quad (1)$$

where M_m , M_{RAFT} are the molar mass of monomer and RAFT agent, respectively. $I_{4.04}$, $I_{7.86}$ are the integral values of the peaks at $\delta = 4.04$ ppm and 7.86 ppm,

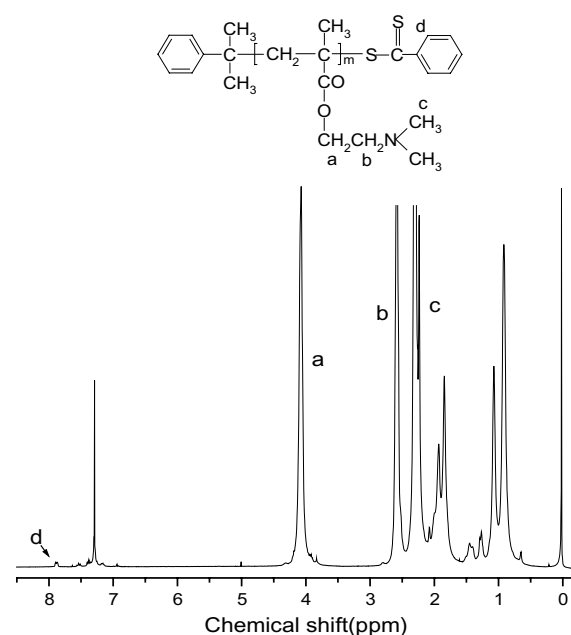


Fig. 1. ^1H NMR spectrum of PDMA homopolymer in CDCl_3 .

Table 1
Conditions and results of the polymerization of DMA

Sample ^a	RAFT agent	Molar ratio ^b	Conversion (%) ^c	$M_{n,\text{th}}$ ^d (g/mol)	$M_{n,\text{NMR}}$ ^e (g/mol)	$M_{n,\text{GPC}}$ ^f (g/mol)	M_w/M_n ^f
A ₁	CDB	160:1:0.1	86	21,875	21,153	10,570	1.14
A ₂	CDB	140:1:0.1	84	18,735	15,658	7934	1.19

^a A₁, A₂: Poly[2-(dimethylamino)ethyl methacrylate (PDMA)] homopolymers of different number average molecular weight.

^b The ratio DMA:RAFT agent:AIBN.

^c Conv(%) = $[I_{4.04}/(I_{4.04} + I_{4.24})] \times 100\%$, where $I_{4.04}$ and $I_{4.24}$ are the integral values of the peaks at $\delta = 4.04$ (polymer O—CH₂—) and 4.24 (monomer O—CH₂—), respectively.

^d Calculated according to Eq. (2).

^e Calculated according to Eq. (1).

^f Measured by GPC.

respectively. The theoretical values $M_{n,th}$ are calculated based on the polymer yields, assuming that the RAFT agents are reacted completely. The number average molar masses $M_{n,th}$ are calculated using the equation:

$$M_{n,th} = M_{RAFT} + (M_m[M]_0 \text{Conv} (\%) / [\text{RAFT}]_0) \quad (2)$$

where $[M]_0$, $[\text{RAFT}]_0$, Conv (%), M_m and M_{RAFT} are the initial concentration of the monomer and RAFT agent, fraction conversion, molar mass of the monomer and RAFT agent, respectively. It shows that the polymers have controlled molecular weight and narrow molecular weight distribution. $M_{n,th}$ is in a good agreement with $M_{n,NMR}$, which implies RAFT agent efficiency is very high and each macromolecule almost contains the dithiobenzoate group.

In the next stage, block copolymers were prepared by RAFT polymerization of SA at 80 °C using the PDMA homopolymers as the macro-RAFT agent. It has been confirmed to be excellent that the block copolymers were prepared utilizing the macro-RAFT agents [36,37]. The well-defined diblock copolymers of PDMA-*b*-PSA were successfully prepared. The processes are shown in Scheme 1, and the results are shown in Table 2. Fig. 2 is a ^1H NMR spectrum of diblock copolymer. The block composition was determined using signals at $\delta = 4.04$ ppm and 0.6–3.0 ppm, corresponding to ester methylenes of PDMA and other groups of copolymer, respectively. So the composition is determined using equation:

$$\frac{\text{PDMA}}{\text{SPA}} = \frac{I_{4.04}/2}{[I_{0.6-3.0} - \frac{13}{2}I_{4.04}]/3} \quad (3)$$

where I is the integral of the signal. Table 3 is the results of elemental analysis experiments. The contents of nitrogen element of the dried copolymers decreased with increase of polymerization time. These suggested that molar mass of SPA block increased with polymerization time. Fig. 3 is IR spectra of polymers. Compared with homopolymer, two strong absorption peaks at around

Table 2

A summary of results about the block copolymers

Sample ^a	Copolymer composition (A:B) ^b	$M_{n,NMR}$ ^c (g/mol)	M_w/M_n ^d
A ₁ B ₁	77:23	24,913	1.18
A ₁ B ₂	66:34	27,639	1.23
A ₂ B ₃	77:23	18,384	1.19
A ₂ B ₄	58:42	23,332	1.23

^a A₁, A₂: Poly[2-(dimethylamino)ethyl methacrylate (PDMA)] fragments of different number average molecular weight, B₁, B₂, B₃, B₄: Sodium polyacrylate (SPA) fragments of different number average molecular weight.

^b Calculated according to Eq. (3).

^c Determined with ^1H NMR spectroscopy.

^d Determined by aqueous GPC.

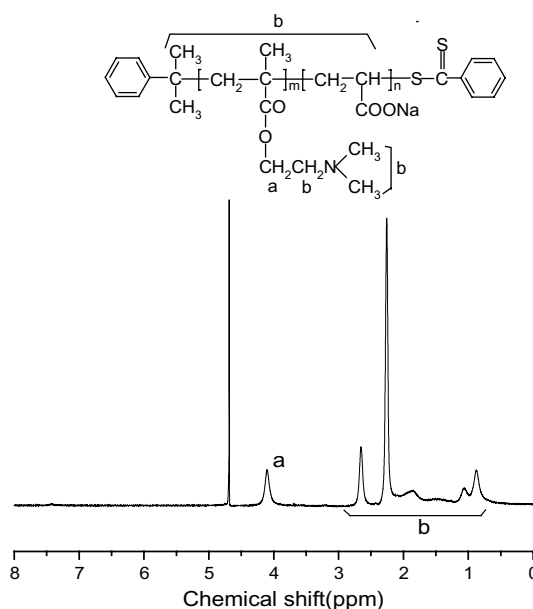
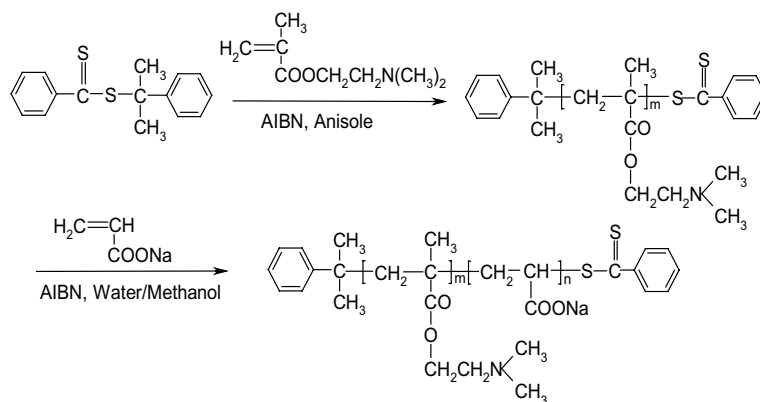


Fig. 2. ^1H NMR spectrum of diblock copolymer in D_2O .



Scheme 1. Synthetic pathways for the preparation of diblock copolymers via RAFT polymerization.

Table 3

A summary of results about the polymers using element analysis

Sample ^a	Time (h) ^b	N (%)	C (%)	H (%)
A ₁		8.939	59.87	9.547
A ₁ B ₁	12	7.490	56.33	7.384
A ₁ B ₂	48	6.378	50.02	6.603
A ₂		8.950	60.75	9.688
A ₂ B ₃	12	7.362	55.89	7.576
A ₂ B ₄	48	6.491	50.99	6.814

^a A₁, A₂: Poly[2-(dimethylamino)ethyl methacrylate (PDMA)] fragments of different number average molecular weight, B₁, B₂, B₃, B₄: Sodium polyacrylate (SPA) fragments of different number average molecular weight.

^b Polymerization time of sodium acrylate.

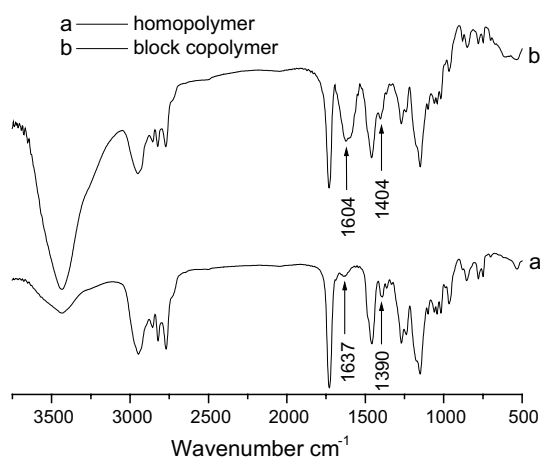


Fig. 3. FT-IR spectra of homopolymer PDMA and A₁B₂ diblock polymer.

1604 cm⁻¹ and 1404 cm⁻¹ appeared in the block copolymer spectroscopy. This implied that the SPA segments were formed in the block copolymer [38]. Simultaneously, good evidences for genuine block copolymer formation were obtained from our studies of the self-assembly of copolymers in solutions.

3.2. pH-dependent formation of micelles and reverse micelles

Fig. 4 shows the dependence of the hydrodynamic radius (R_h) of diblock copolymer on pH. It is agreement with solubility curve presented by Cohen et al. [39]. At pH values lower than 5.5, R_h is 100–130 nm, suggesting that core-shell micelles are formed. Simultaneously, an increase of pH toward the isoelectric point (IEP, pH = 6.0) of copolymer in solution results in an increase of R_h . It implies that the micelles swell or slightly aggregate with reducing interactions between

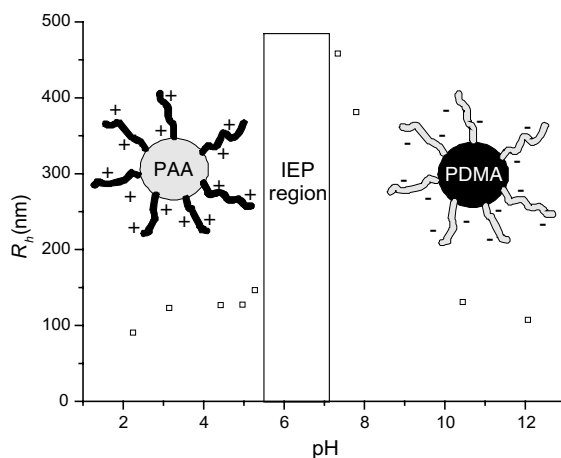


Fig. 4. Hydrodynamic radius of the A₁B₂ diblock copolymer as a function of pH for concentration 1.0 mg/ml solutions at 25 °C.

copolymers and solvent for gradually decreasing in net charge density of copolymers (increase pH). Large aggregates are formed at pHs around IEP of copolymer, reflecting the phase separation of diblock copolymer at a low interactions of copolymers with solvent (low net charge density). At pH values a little higher than the IEP region, R_h is 350–500 nm. These sizes of R_h are too large to represent simple core-shell micelles: it is possible that compound micelles are formed under these conditions [40]. R_h decreases with increase of pH above IEP, suggesting disaggregation of large compound micelles with increase of the interactions of copolymers with solvent (negative net charge density increase). At extreme pH values (pH = 12.0 or 3.0) consistency of micelles R_h values is observed, this can be attributed to the approximate net charge density (positive or negative).

These experiments showed that the micelles and reverse micelles of the block copolymer formed in solution and suggested that the self-assembly of the copolymers in solutions are greatly effected by the net charge density of the copolymers.

3.3. Temperature-induced phase separation of copolymers [41]

Fig. 5 shows the effect of the SPA segments and pH on the LCST of polymers in phosphate buffers. The temperatures at maxima of microcalorimetry are referred to as LCST of the polymers. Fig. 5 shows that the LCST shifts from 74.4 °C to 79.8 °C with incorporation of SPA at pH = 7.0. It describes that the LCST shifts to a higher temperature with the incorporation of the hydrophilic SPA. This is consistent with the phenomena report for block PDMA copolymer [42]. On the other

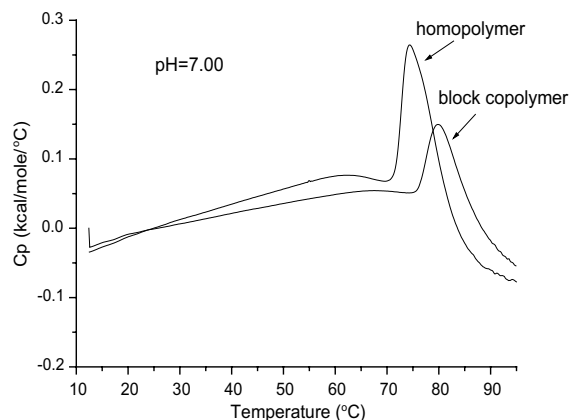


Fig. 5. Thermograms of solutions A₁ homopolymer and A₁B₂ diblock copolymer for concentration 1.0 mg/ml at 25 °C.

hand, it is well known that PDMA has a LCST at about 50 °C in water [43], but we observed it is about 75 °C in buffer. It has been implied that LCST behavior is affected by addition of phosphate in buffer. Coulombic interactions of copolymer and solvent lead to better solubility of the polymer in buffer, so LCST increased. With increasing temperature, the Coulombic interactions weaken. When the temperature is above the LCST, interactions between hydrophobic polymer groups become dominant, which leads to hydrophobic polymer collapse and phase separation.

4. Conclusions

Zwitterionic diblock copolymers with low polydispersities have readily been synthesized using RAFT polymerization without protecting group chemistry. Moreover, according to DLS and microcalorimetry experiments, self-assembly of copolymer is observed: micelles and reverse micelles are formed in buffer on adjusting the pH and phase separation of polymers take place in buffer on increasing temperature.

The zwitterionic triblock copolymers have been prepared and can be expected to exhibit the richer solution behaviors than the corresponding diblock copolymers and their aqueous properties are being studied. The detail reports will be submitted in the future.

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