A Novel Functional Polymer with Tunable LCST

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ABSTRACT: Poly(*N*-[(2,2-dimethyl-1,3-dioxolane)methyl]acrylamide) (PDMDOMA), a novel thermo-responsive polymer containing pendant dioxolane groups was synthesized via atom transfer radical polymerization (ATRP). Water soluble PDMDOMAs with controlled molecular weight and narrow molecular weight distribution were obtained. GPC−MALLS and MALDI−TOF−MS analysis verified the controlled nature of polymerization. It was found that an aqueous solution of PDMDOMA has a lower critical solution temperature (LCST) around 23 °C. The LCST of PDMDOMA was finely tuned over a wide temperature range by the partial hydrolysis of the acid labile dioxolane side group to form diol moieties (PDMDOMA diols). Unlike the traditional way of controlling LCST by copolymerization, the advantage of this method is that a series of thermo-responsive polymers with different LCST can be prepared from a single batch of polymer with comparable molecular weight profiles. The LCST of the resulting PDMDOMA diols increased almost linearly up to 28 mol % of diol in the copolymer and the LCST disappeared above 43 mol % diol content. The diol moiety generated during the hydrolysis was further oxidized to create aldehyde functionalities along the polymer backbone (PDMDOMA−aldehyde). The NMR analysis indicates that the aldehyde groups in the polymer exist in equilibrium with their covalent hydrates in water. The presence and reactivity of aldehyde groups on the PDMDOMA−aldehyde was verified by reaction with propylamine and aniline. The LCST of PDMDOMA−aldehyde did not change significantly compared to the precursor diol polymer. However, the propylamine or aniline derivatives showed a dramatic decrease in the LSCT possibly due to an increase in the hydrophobic character. The LCST of PDMDOMA−propylamine and PDMDOMA−aniline derivatives depends on the composition and nature of the attached groups. The structure of PDMDOMA and its derivatives were fully characterized by ^{1}H, ^{13}C, and 2D HMQC NMR, GPC−MALLS, and MALDI−TOF−MS.

1. Introduction

Thermo-responsive polymers represent an important class of stimuli-responsive materials which undergo phase transitions when the temperature is raised above the lower critical solution temperature (LCST). In aqueous solutions, the LCST is dependent on the hydrogen bonding capability of repeating units;[1,2] it is this special property that has made thermo-responsive polymers attractive and promising for many applications such as controlling bacterial aggregation,[3] protein adsorption and release,[4] cell adhesion, protein−ligand recognition, and drug delivery.[5,6] Polymers bearing amide groups form the largest group of thermo-sensitive polymers.[2] Among them, poly(*N*-isopropylacrylamide) (PNIPAM) and poly(*N*,*N*′-diethylacrylamide) (PDEAAM) are the most studied; they have similar LCSTs of 32−33 °C.[7,8] The LCST behavior of poly(propylene oxide) (PPO), poly(vinyl methyl ether) (PVME), and poly(2-alkyl-2oxazolines) have also been reported.[1,9] In addition, thermo-responsive behavior is ascribed to another class of biomacromolecules, elastin-like polypeptides (ELPs).[10]

Simply having thermo-responsive properties does not necessarily make these polymers useful materials. However, the addition of reactive functional groups can make them very attractive materials for the development of "smart" conjugates. For instance, it is known that when a thermo-responsive polymer is coupled with a biomacromolecule such as a protein, the polymer can confer this temperature sensitivity to the conjugate.[4,5,11] Unfortunately, conventional thermo-responsive polymers lack functionality, meaning facile modification and coupling is not possible. Therefore, additional functionality has to be introduced either to the polymer or protein.

Aldehyde groups are versatile functional groups and have been widely used to couple polymers with proteins and peptides.[12,15] Surprisingly, there has been little work done to develop an aldehyde-bearing thermo-responsive polymer. It is also preferable that the LCST of the polymer should be tunable within a wide temperature range in order for it to be useful for a variety of applications. One approach often used to control the LCST of a polymer is to make a copolymer with a second monomer of different hydrophilicity. This will lead to a copolymer with variable LCST depending on the compositions of different components. Preparation of thermo-responsive polymers or surfaces with variable LCST via this approach has been recently reported.[13] The precise control of composition, molecular weight, and distribution of the two monomers along the backbone of the polymer is critical in obtaining the desired LCST, which is somewhat difficult to achieve owing to differences in the reactivity of comonomers.

Here, we report an alternate approach toward the synthesis of functional stimuli responsive polymers. A novel polymer, poly(*N*-[(2, 2-dimethyl-1, 3-dioxolane)methyl]acrylamide) (PDMDOMA) has been synthesized via atom transfer radical polymerization (ATRP) at room temperature. The LCST of PDMDOMA was finely tuned between 23 and 49 °C by the controlled cleavage of the pendant dioxolane groups. Furthermore, the generated diol moiety can be oxidized to yield an aldehyde group, which acts as a coupling site for further functionalization while also retaining the thermo-responsive properties. The generation and reactivity of aldehyde groups was verified by reacting them with alkyl and aromatic amines.

2. Experimental Section

2.1. Materials and Methods. 2,2-Dimethyl-1,3-dioxolane-4-methanamine (Aldrich, 97%), methyl 2-chloropropionate (Aldrich,

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Scheme 1. Synthesis of PDMDOMA, PDMDOMA−Diol, and PDMDOMA−Aldehyde

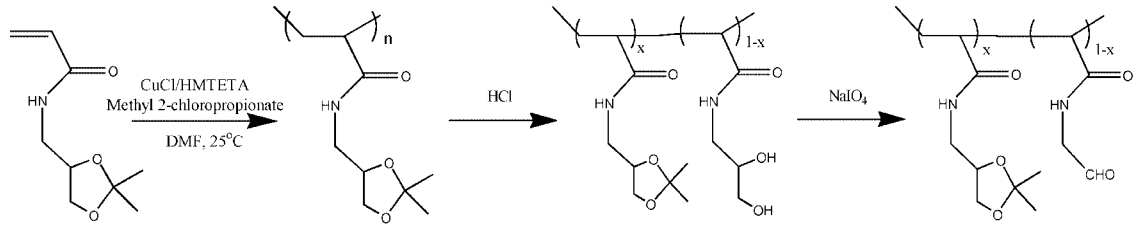


Table 1. Polymerization of DMDOMA with a MCP/Cu^{I}Cl/HMTETA^{f}-Based Catalytic System^{a}

sample	solvent	time (h)	convn (%)	$M_{n,th}$	$M_{n,SEC}$^{d}	$M_w/M_{n,\ SEC}$	$M_{n,SEC}$^{e}	$M_w/M_{n,\ SEC}$	$M_{n,\ MALDI-TOF}$	$M_w/M_{n,\ MALDI-TOF}$
	MeOH	24	3							
P1	toluene^{a}	24	65.2	4020	4400	1.09	4200	1.14	4425	1.09
P2	DMF^{a}	2	71.2	4391	4500	1.11	5200	1.12	4553	1.06
P3	DMF^{a}	4	95.5	5858	5800	1.07	6300	1.14	5126	1.07
P4	DMF^{b}	6	90.1	8325	9200	1.13	9800	1.18		
P5	DMF^{c}	6	82.3	15225			14500	1.19		

^{a} Experimental conditions: solvent:monomer = 3:1 (v/w), [DMDOMA]:[MCP] = 33:1 [MCP]:[CuCl]:[HMTETA]= 1:1:2; reaction temperature = 25 °C. ^{b} Experimental conditions: solvent:monomer = 3:1 (v/w), [DMDOMA]:[MCP] = 50:1 [MCP]:[CuCl]:[HMTETA]= 1:1:2; reaction temperature = 25 °C. ^{c} Experimental conditions: solvent:monomer = 3:1 (v/w), [DMDOMA]:[MCP] = 100:1 [MCP]:[CuCl]:[HMTETA]= 1:1:2; reaction temperature = 25 °C. ^{d} GPC was obtained in 0.05 M LiBr/DMF solution. ^{e} GPC was obtained by running PDMDOMA−diol (100%) in 0.1 M $NaNO_3$/aqueous solution. ^{f} MCP: methyl 2-chloropropionate. HMTETA: 1,1,4,7,10,10-hexamethyl triethylene tetramine.

99%), 1,1,4,7,10,10-hexamethyl triethylene tetramine (HMTETA, Aldrich, 97%), CuCl (Aldrich, 99+%), and $CuCl_2$ (Aldrich, 99.99%) were used as supplied. All other commercial reagents were purchased from Aldrich and were of the highest purity and used without further purification. Water was purified using a Mili-Q Plus water purification system (Milipore Corp., Bedford, MA) and was used in all experiments. ^{1}H NMR spectroscopy was performed on a Bruker AV400 MHz NMR spectrometer. ^{13}C NMR spectroscopy was performed on a Bruker AV600 MHz NMR spectrometer. Two-dimensional heteronuclear one bond proton carbon correlation experiments were registered in ^{1}H detected mode via multiquantum coherence (HMQC) on a Bruker AV600 MHz NMR spectrometer.

2.2. GPC and MALDI−TOF−MS. Absolute molecular weights of the polymers were determined by gel permeation chromatography (GPC) on a Waters 2690 separation module fitted with a DAWN EOS multiangle laser light scattering (MALLS) detector from Wyatt Technology Corp. with 18 detectors placed at different angles (laser wavelength λ = 690 nm) and a refractive index detector from Viscotek Corp. operated at λ = 620 nm. For PDMDOMA, 0.05 M LiBr/DMF solution was used as the mobile phase at a flow rate of 0.8 mL/min. Aliquots of 200 μL of the polymer solution were injected through Styragel columns (Waters) at 22 °C (guard column, Styragel HR1, elution range 100−5000 Da, and HR 5E mixed bed column, elution range 2000 to 4 × 10^6 Da). The d*n*/d*c* value for PDMDOMA in the mobile phase was determined at λ = 620 nm as 0.05 mL/g (determined online using the RI detector response from a number of different concentrations of pure polymer), which was used for calculating the molecular weights. For partial or 100% cleaved PDMDOMA, 0.1 M $NaNO_3$ aqueous solution was used as the mobile phase at a flow rate of 0.8 mL/min. Aliquots of 200 μL of the polymer solution were injected through the Ultrahydrogel columns at 22 °C (guard column, Ultrahydrogel linear with bead size 6−13 um, elution range 10^3 to 7 × 10^6 Da and Ultrahydrogel 120 with bead size 6 um, elution range 150 to 5 × 10^3 Da connected in series; from Waters). The d*n*/d*c* value for 100% cleaved PDMDOMA in 0.1 M $NaNO_3$ was determined at λ = 620 nm as 0.162 mL/g and was used for molecular weight calculations.

MALDI−TOF−MS was performed on a Bruker Biflex IV time-of-flight spectrometer using a 337nm nitrogen laser. All experiments were conducted at an accelerating potential of 19 kV. In general, mass spectra from 200 shots were accumulated to produce a final spectrum. THF, 2-(4-hydroxyphenylzao)benzoic acid (HABA) and sodium trifluoroacetate were used for the solvent, matrix, and cationizing agent respectively.

2.3. Synthesis of [(2,2-Dimethyl-1,3-dioxolane)methyl]acrylamide (DMDOMA) Monomer. Acryloyl chloride (3.2 mL, 39.0 mmol) was added dropwise to a stirred solution of 2,2-dimethyl-1,3-dioxolane-4-methanamine (5 mL, 38.5 mmol) and triethylamine (8.5 mL, 40 mmol) in dichloromethane (30 mL) at 0 °C by syringe. The reaction was allowed to reach room temperature and stirred for 4 h. The reaction mixture was filtered and washed with saturated sodium bicarbonate solution (5 mL) and water (5 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was removed by rotary evaporation. The crude product (~95% yield) was subsequently purified by flash column chromatography using hexane and ethyl acetate as eluent. The resulting purified product was colorless and the yield was ~67%.

^{1}H NMR (400 MHz, $CDCl_3$): C(C**H**$_3$)$_2$ δ 1.16, 1.24 (s, 6H), −O−C**H**−C δ 4.08 (m, 1H), −O−C**H**$_2$−C δ 3.88 (m, 1H), 3.36 (t, 1H), N−C**H**$_2$ δ 3.63 (m, 2H), −C**H**= δ 5.46 (t, 1H), =C**H**$_2$ δ 6.15 (t, 1H), 6.26 (t, 1H), -N**H** δ 6.04 (s, 1H).

2.4. Synthesis of PDMDOMA via Atom Transfer Radical Polymerization (ATRP). All ATRP polymerizations were carried out in a glovebox filled with argon. For a typical reaction (**P2**), a glass vial was loaded with CuCl (15 mg, 0.15 mM), HMTETA (80 mg, 0.30 mM) and DMDOMA (0.93 g, 5 mM) with 3 mL of DMF as the solvent, sealed with a rubber septum and cycled three times between argon and vacuum to remove oxygen. Methyl 2-chloropropionate (18.4 mg, 0.15 mM) was added into the vial and the reaction allowed to proceed at room temperature with magnetic stirring. After 2 h of reaction, 2.5 mL of the reaction mixture was removed using a syringe and the polymerization was terminated by exposure to air. The degree of monomer conversion was estimated by ^{1}H NMR. The reaction mixture was then dialyzed (MWCO 1 kDa) against water for 3 days with three times daily changes in water, filtered and lyophilized. The resulting PDMDOMA (**P2**) was a white, fluffy solid. PDMDOMAs with different molecular weights were produced by changing the monomer to initiator ratio. In the case of polymerizations in toluene, the polymer was precipitated in diethyl ether first and later dialyzed against water. All the polymers were characterized by GPC−MALLS, MALDI−TOF, and NMR spectroscopy.

^{1}H NMR (400 MHz, D_2O): C(C**H**$_3$)$_2$ δ 1.33, 1.42 (6H), −C**H**$_2$−C**H**− δ 1.5 to 1.7, 1.9−2.1 (broad peak), −O−C**H**−C δ 4.24 (1H), −O−C**H**$_2$−C δ 4.04 (1H), 3.66 (1H), NH−C**H**$_2$ δ 3.3 2H).

^{13}C NMR (150.9 MHz, D_2O): δ 24, 25.55 (C(**C**H$_3$)$_2$), 32−36 (broad peak, **C**H$_2$−**C**H), 41.4 (NH−**C**H$_2$), 66.1 (O−**C**H), 77.8 (O−**C**H$_2$), 109.5 (O$_2$−**C**(CH$_3$)$_2$), 175.9 (HN−**C**=O).

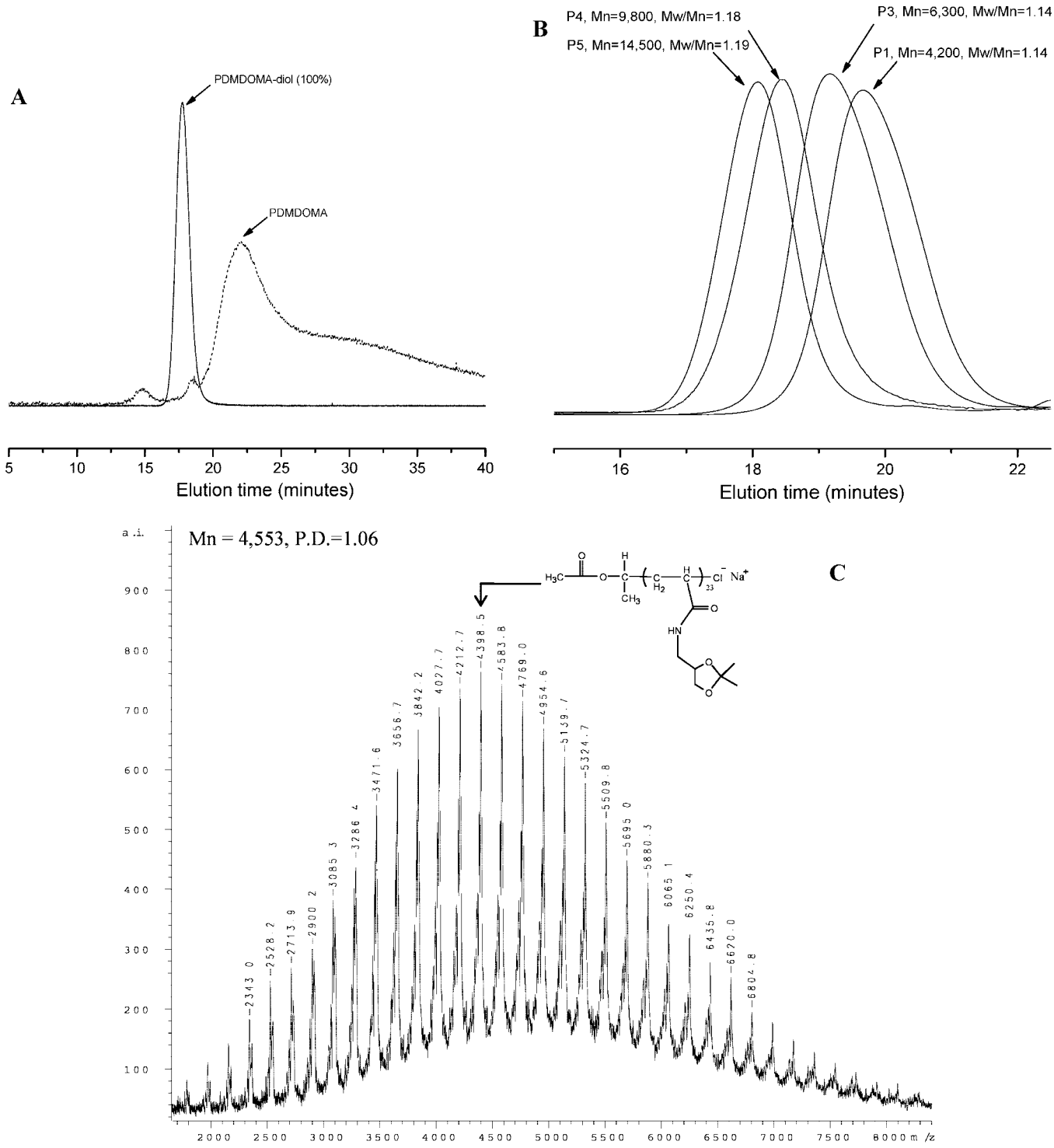


Figure 1. (A) Comparison of GPC−MALLS profiles of PDMDOMA and PDMDOMA−diol (100%) run in 0.1 M $NaNO_3$ aqueous solution. (B) GPC−RI profiles of PDMDOMA−diol (100%) with different molecular weights run in 0.1 M $NaNO_3$ aqueous solution. (C) MALDI−TOF−MS of PDMDOMA (**P2**).

2.5. Synthesis of PDMDOMA−Diol. PDMDOMA−diol was prepared by the cleavage of dioxolane groups of PDMDOMA with 1 M HCl. For a typical reaction, to obtain 6 mol % diol content in the polymer 20 mg of **P2** was dissolved into 2 mL of H_2O, followed by addition of 10 μL of 1 M HCl solution with stirring. The reaction was carried out at ambient temperature for 30 min and stopped by adjusting the pH to 7 using 1 M NaOH solution. The resulting solution was dialyzed against water (MWCO 1 kDa) for 3 days with three times daily changes in water and lyophilized. The degree of dioxolane cleavage was estimated by ^{1}H NMR in D_2O. The diol content in the polymer was varied by changing the time of hydrolysis and amount of HCl used.

^{1}H NMR (400 MHz, D_2O) of PDMDOMA−diol (400 MHz, D_2O, 100%): −C**H**$_2$−C**H**− δ 1.5 to 1.7, 1.9−2.1 (broad peak), −O−C**H**−C δ 3.64 (1H), −O−C**H**$_2$−C δ 3.52, 3.41 (2H), NH−C**H**$_2$ δ 3.0 to 3.3 (2H).

^{13}C NMR (150.9 MHz, D_2O) of PDMDOMA−diol (150.9 MHz, D_2O, 100%): 32−36 (broad peak, **C**H$_2$−**C**H), 42.9 (NH−**C**H$_2$), 64.48 (**C**H−OH), 71.2 (**C**H$_2$−OH), 175.8 (HN−**C**=O).

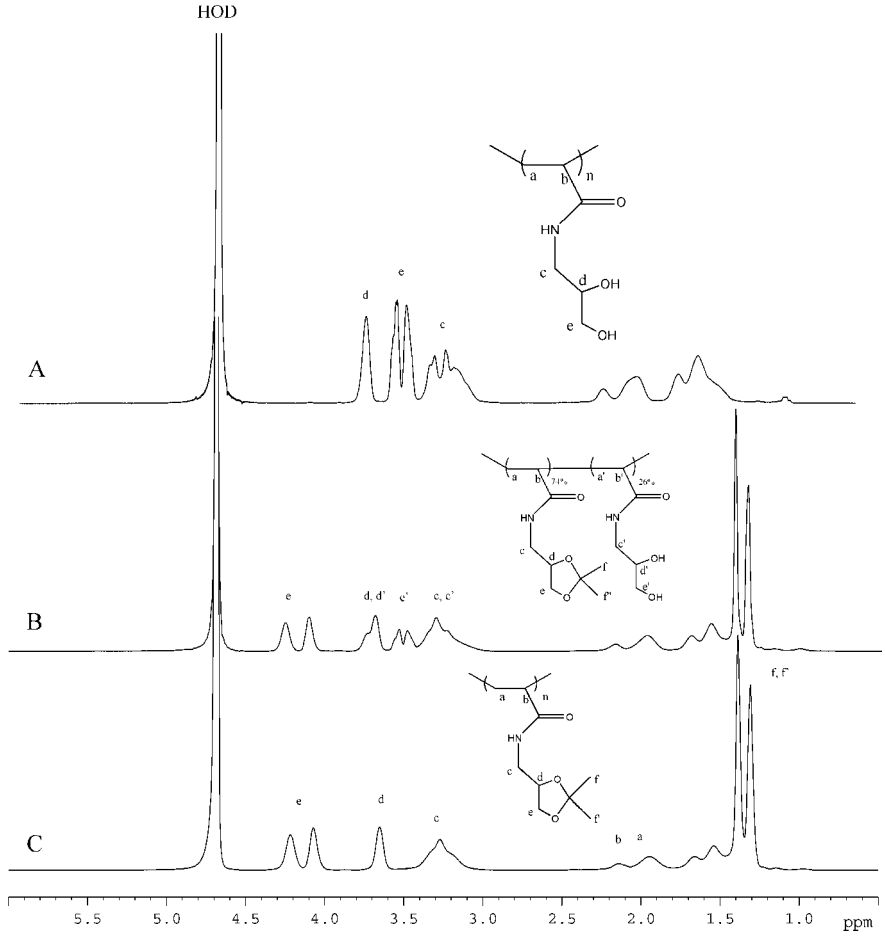


Figure 2. Evolution of ^{1}H NMR spectra from (C) PDMDOMA to (B) PDMDOMA−diol (26%); to (A) PDMDOMA−diol (100%).

2.6. Synthesis of PDMDOMA−Aldehydes. PDMDOMA−aldehydes are synthesized from PDMDOMA−diol by a periodate oxidization. For a typical reaction, 10 mg of the obtained PDMDOMA−diol (6%) derivative was dissolved into 1 mL of H_2O and sodium periodate was added to give a concentration of 100 mM. The reaction proceeded at ambient temperature for 4 h, followed by dialysis (MWCO 1 kDa) against water for 24 h (three times changes in water) and lyophilized. The obtained white, fluffy solid was stored at −80 °C until use. The aldehyde content in the polymer was varied by changing the diol polymer precursors.

^{1}H NMR of PDMDOMA−aldehyde (400 MHz, D_2O, 100%): –C**H**$_2$−C**H**− δ 1.5 to 1.7, 1.9−2.1 (broad peak), NH−C**H**$_2$− δ 3.0 to 3.3, −C**H**(OH)$_2$ δ 5.1 (hydrate), −C**H**O δ 9.5.

^{13}C NMR of PDMDOMA−aldehyde (150.9 MHz, D_2O, 100%): 32−36 (broad peak, **C**H$_2$−**C**H), 42.6 (NH−**C**H$_2$, aldehyde), 44.4 (NH−**C**H$_2$, hydrate), 87.6. (−**C**H(OH)$_2$), 176.5 (HN−**C**=O).

2.7. Reactivity of PDMDOMA−Aldehydes. The PDMDOMA−aldehyde was reacted with aniline or propylamine and the adduct was later reduced to obtain the amine coupled polymer. For a typical reaction, PDMDOMA−aldehyde (**P2**, 6%, 20 mg) was dissolved in 2 mL of 1:1 H_2O/MeOH (v/v) solution and aniline (100 μL) was added. After overnight reaction at ambient temperature, 100 mg of $NaCNBH_3$ was added and the solution was stirred for another 2 h. The obtained solution was dialyzed (MWCO 1 kDa) against water for 3 days and lyophilized. The resulting solid was white and fluffy. Derivatives with different degrees of substitution of aniline were obtained by varying the PDMDOMA−aldehydes. A similar procedure was employed for the synthesis of PDMDMOA−propylamine derivatives.

2.8. Determination of the Lower Critical Solution Temperature (LCST). The thermo-responsive properties of PDMDOMA, PDMDOMA−diol, PDMDOMA−aldehyde, and PDMDOMA−amine derivatives were investigated with a Varian 4000 UV−vis spectrometer equipped with multicell, thermoelectric temperature controller (±0.1 °C). Transmittance through aqueous solutions of polymer (5 mg/mL) at λ = 500 nm was recorded at every 0.5 °C interval. For each temperature, the solution was equilibrated for 10 min. The LCST was defined as the midpoint of the temperature-transmission curve.

3. Results and Discussion

3.1. Synthesis of PDMDOMA. The [(2,2-dimethyl-1,3-dioxolane)methyl]acrylamide (DMDOMA) monomer was synthesized from 2,2-dimethyl-1,3-dioxolane-4-methanamine by reacting with acryloyl chloride. The synthesis of PDMDOMA was accomplished by ATRP (Scheme 1). Different ATRP initiating systems were explored (Table 1). Initially methyl bromoisobutyrate (MBriB) and CuBr/HMTETA catalyst system was tested. The ratio of DMDOMA to MBriB was 50:1 while MBriB/CuBr/HMTETA = 1:1:2. After 48 h, only 12.2% and 20.1% conversions were obtained in toluene and DMF respectively. Elevated temperature also failed to produce higher monomer conversions. We attribute the low monomer conversion in these polymerizations to the side reactions caused by acrylamide-based DMDOMA monomer. It is reported that ATRP of acrylamides can be complicated by nucleophilic displacement of C−Br bond at the chain end by an amide monomer.[16]

To overcome this difficulty, methyl 2-chloropropionate (MCP) was chosen as the initiator in the next set of experiments. The enhanced stability of the C−Cl bond compared to the C−Br bond was anticipated to produce better results in this case. Also the polymerizations were carried out at room temperature to decrease the relative rates of nucleophilic side reactions

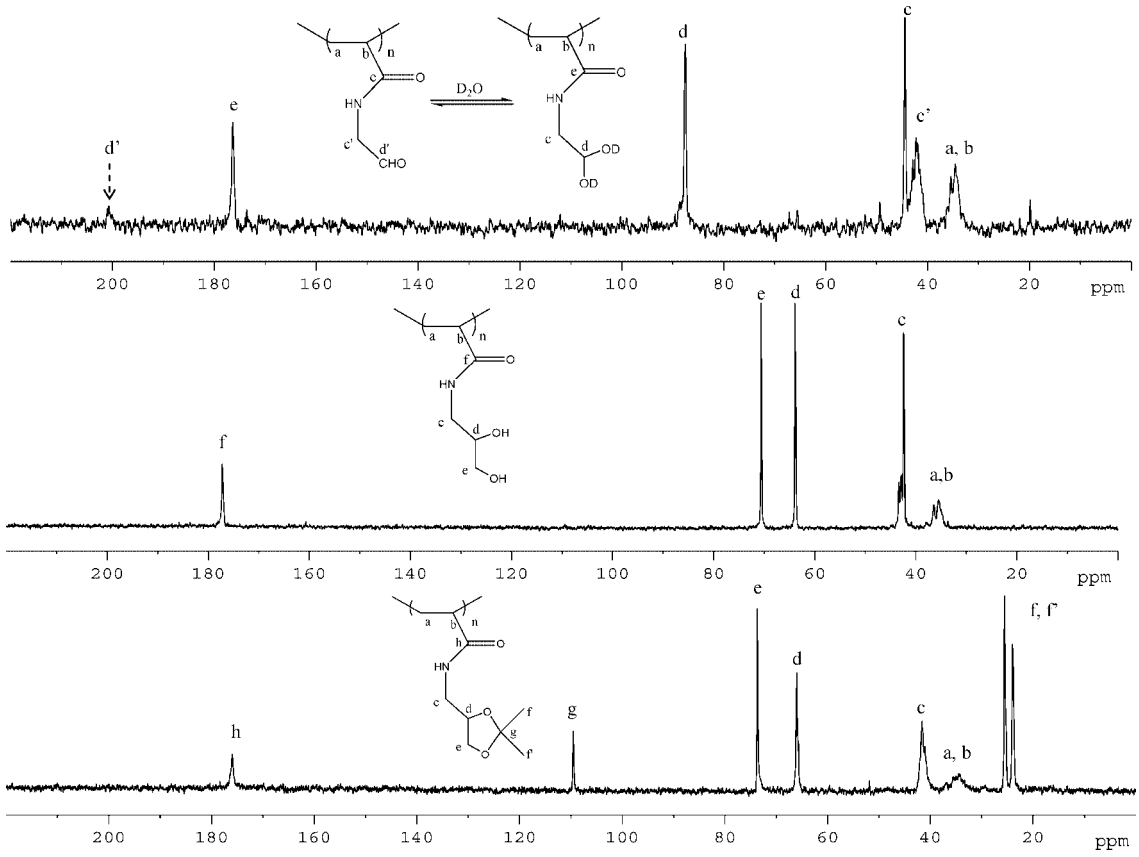


Figure 3. ^{13}C NMR: (A) PDMDOMA (100%); (B) PDMDOMA−diol (100%); (C) PDMDOMA−aldehyde (100%) in D_2O.

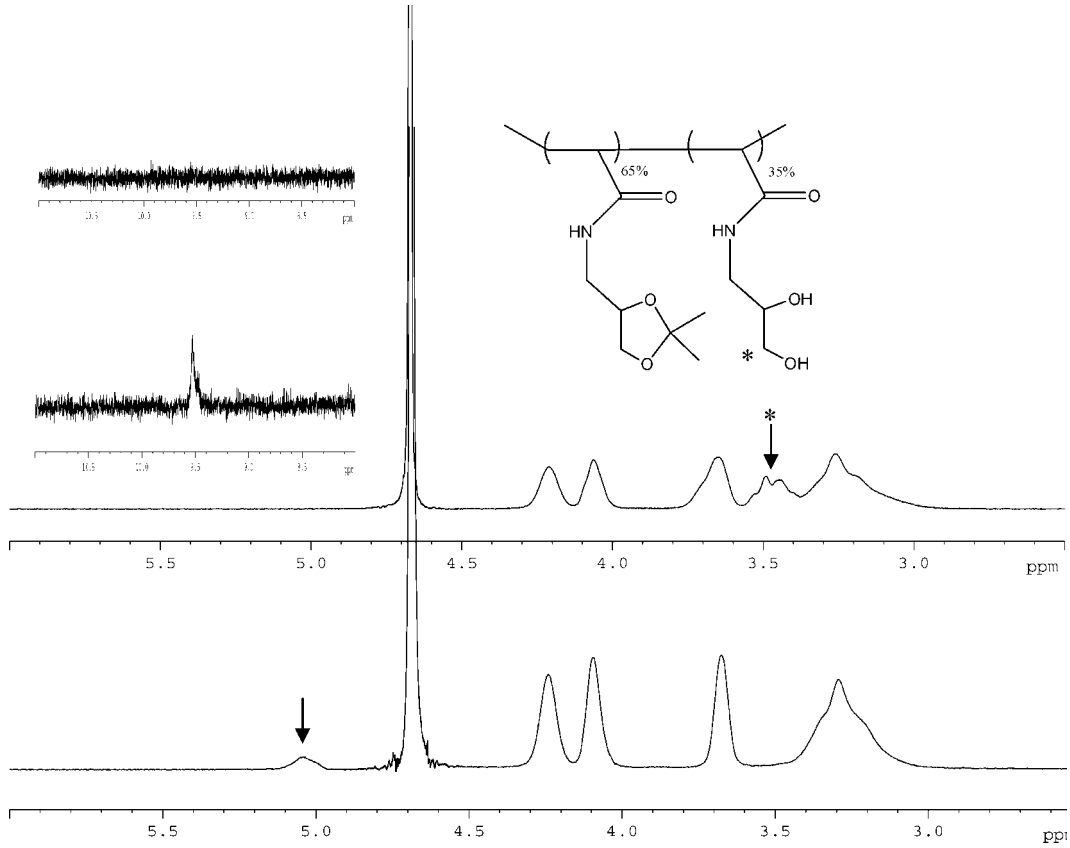


Figure 4. ^{1}H NMR of PDMDOMA−diol (35%, top) and PDMDOMA−aldehyde (35%, bottom) in D_2O. The spectra were collected on a Bruker AV400 (400 MHz) NMR spectrometer.

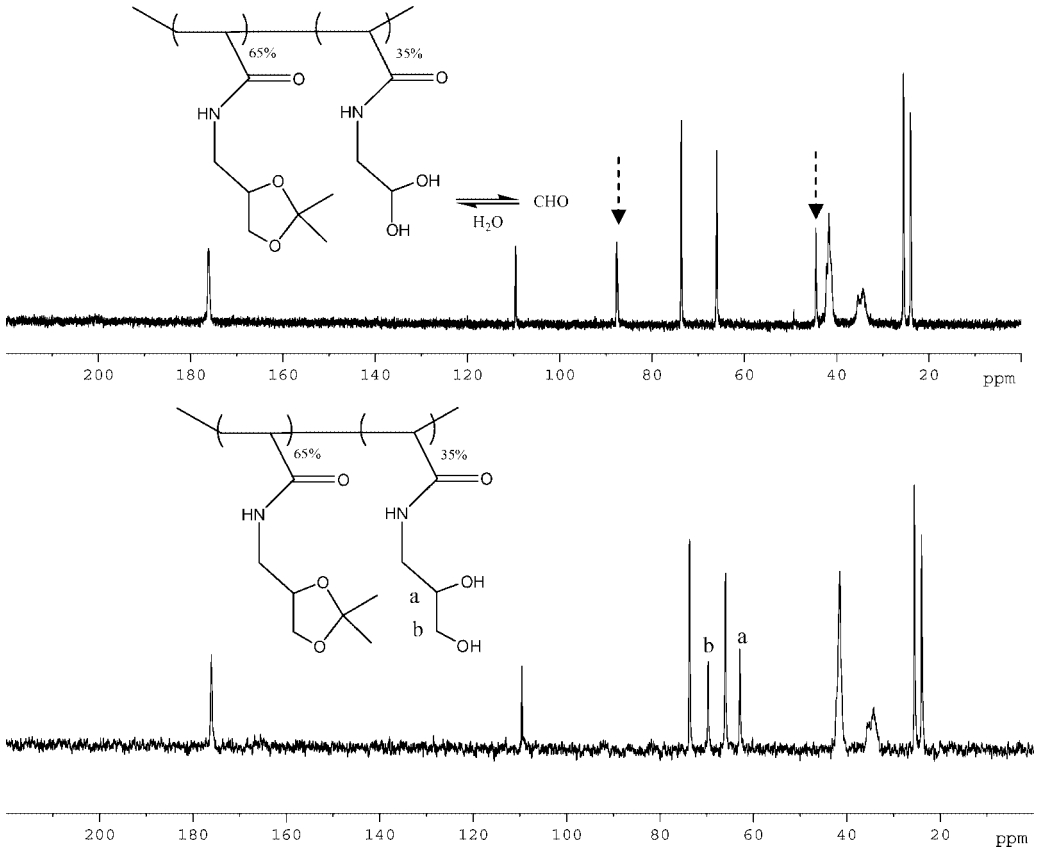
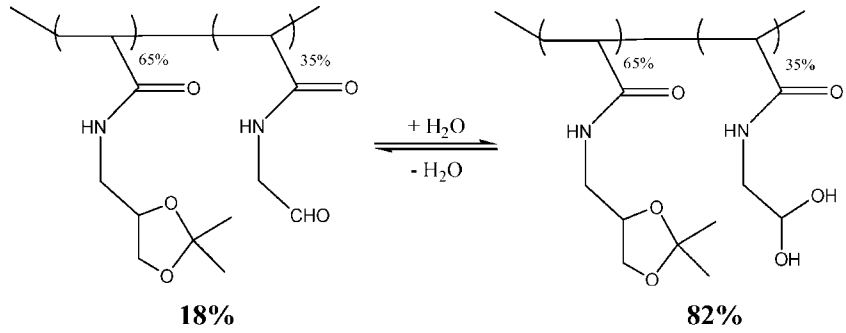


Figure 5. ^{13}C NMR of PDMDOMA−diol (35%, bottom) and PDMDOMA−aldehyde (35%, top) in D_2O.

Scheme 2. Equilibrium of PDMDOMA−Aldehyde with PDMDOMA−Aldehyde (Hydrate) in Water



18% PDMDOMA-aldehyde (35%)

82% PDMDOMA-aldehyde (hydrate, 35%)

compared to polymerization. Different polymerization conditions were investigated and the results are given in Table 1. The polymerization in methanol was not successful; only 3% monomer conversion was obtained after 24 h of reaction. In contrast, ATRP of DMDOMA in toluene (monomer:MCP = 33:1) yielded 65.2% and 68.7% conversion after 24 and 48 h respectively. Although the experimental molecular weight was closer to theoretical molecular weight with low polydispersity (Table 1; **P1**), the incomplete conversion indicates the possibility of termination reactions that limit the monomer conversion.

The polymerizations in DMF afforded a faster reaction and higher conversions (Table 1; **P2**−**P5**). For instance, with a DMDOMA to MCP ratio of 33:1, we obtained 71.2% and 95.5% monomer conversion after 2 and 4 h, respectively. A good agreement with the theoretical molecular weight coupled with a narrow molecular weight distribution and an almost quantitative conversion (Table 1; **P2** and **P3**) suggests a well-controlled polymerization process under the conditions studied. Higher monomer to initiator ratios produced a higher molecular weight PDMDOMA (Table 1; **P4** and **P5**), also supporting the notion of a controlled polymerization.

The aqueous GPC characterization was not successful due to the aggregation of PDMDOMA in water and its adsorption to the GPC columns. This is likely due to the amphiphilic nature of PDMDOMA. A representative GPC−MALLS profile of PDMDOMA (Figure 1A) shows a broad tailing in 0.1 M $NaNO_3$ solution indicative of column adsorption. Similar observations have been made for other amphiphilic polymers.[14] Therefore, GPC analysis was carried out in 0.05 M LiBr/DMF, producing unimodal peaks. Although PDMDOMA showed no aggregation and adsorption in DMF, the reproducibility of GPC data was poor. Figure 1S (Supporting Information) shows a typical GPC−MALLS profile of PDMDOMA in 0.05 M LiBr/DMF. The asymmetrical nature of the GPC profile was due to a baseline drift caused by the absorption of moisture by the DMF eluent from the atmosphere, which could lead to the inaccurate

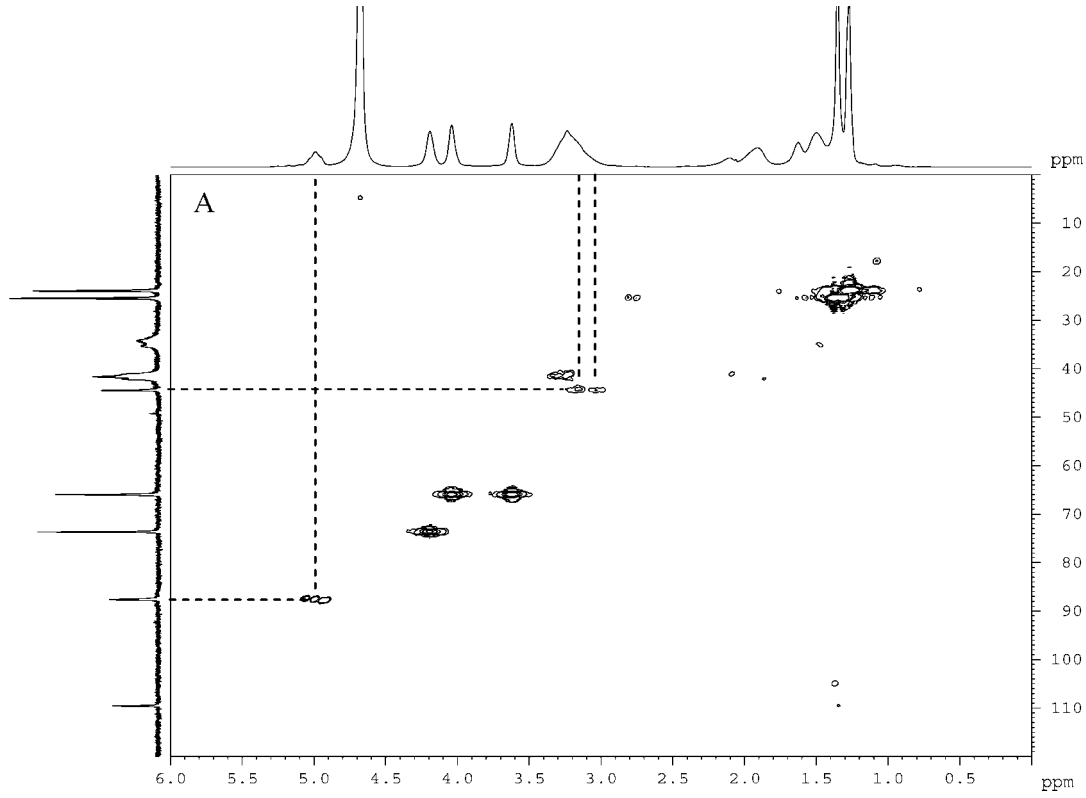


Figure 6. 2D HMQC NMR spectrum of PDMDOMA−aldehyde (35%) in D_2O.

estimation of molecular weight. Also, DMF was more difficult to handle compared to the aqueous system with respect to hazard and cost. Thus, the dioxolane groups of PDMDOMA were completely cleaved by HCl to yield the PDMDOMA−diol derivative (100%), which produced a unimodal GPC profile in aqueous 0.1 N $NaNO_3$ (Figure 1, parts A and B), indicating a lack of column adsorption or aggregation. Also, a very stable baseline and symmetric peak profile allowed unambiguous estimation of molecular weight in this case. A comparison of molecular weight and polydispersity obtained for PDMDOMA in different GPC solvent systems is given in Table 1.

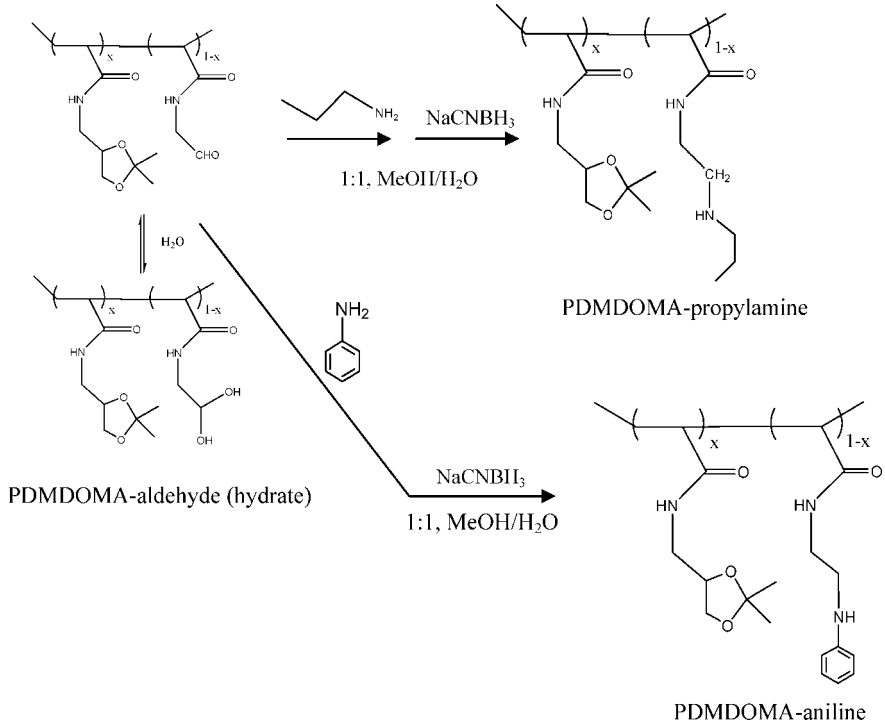
The structure of PDMDOMA was further characterized by ^1H and ^{13}C NMR (Figure 2C and 3A) and MALDI−TOF analysis (Figure 1C). The proton and carbon signals from NMR matched the theoretical expectation. The molecular weight obtained from MALDI−TOF−MS also supports the GPC results. In addition, MALDI−TOF−MS of PDMDOMA (**P2**, Figure 1C) indicates a repeat mass of 185 Da, which matches the molar mass of the repeating unit of PDMDOMA. Further analysis of the end group from a single mass at 4398.5 Da revealed that it was composed of ^{23}Na, 23 PDMDOMA repeat units and methyl 2-chloropropionate (ATRP initiator). The measured molecular mass is 2 Da lower than the calculated mass which is within the instrumental error.

3.2. Synthesis of PDMDOMA−Diols. PDMDOMA−diols with different molar composition of the diol moiety in the polymers were obtained by the partial cleavage of PDMDOMA with diluted HCl. It is known that ketal groups can be easily removed by acid hydrolysis. By adjusting the reaction conditions and concentration of acid used in these experiments, we were able to control the composition of diol moiety in the PDMDOMA polymer from 2.5% to 100%. As discussed previously, 100% hydrolyzed PDMDOMA (PDMDOMA−diol, 100%) is highly soluble in water and yielded a symmetrical GPC profile in aqueous solution. In contrast, column absorption and aggregation was observed for partially cleaved PDMDOMA−diols reflected by aqueous GPC−MALLS profiles (Figure 2S, Supporting Information) indicating a gradual increase in hydrophilicity of polymer chains with increasing amounts of diol moiety. The higher the content of diol moiety, the lower the column absorption; consequently less tailing was observed in the chromatogram. The gradual increase in hydrophilicity also led to variations in the LCST, which will be discussed in the following section.

The change in the chemical structure from PDMDOMA to PDMDOMA−diols (100%) was verified by ^1H NMR. Figure 2 shows that the intensity of ketal groups decreased with increasing degree of cleavage while the 100% cleaved sample showed no evidence of ketal groups in the polymer. The result was also verified by ^{13}C NMR (Figure 3C) as evidenced by the disappearance of the carbon signals representing the ketal groups. Although a different matrix (DHB, IAA, HABA) was used to obtain MALDI−TOF−MS of PDMDOMA−diol (100%), the result was not satisfactory due to the low intensity of the signals. Although the reason remains unclear, it is possible that PDMDOMA−diol (100%) is only soluble in water, in which the matrix has limited solubility (DHB, IAA, HABA). This might lead to insufficient mixing of the polymer and matrix causing difficulty in the ionization of the polymer. A MALDI−TOF−MS of PDMDOMA−diol (23%) was readily obtained in THF using DHB as the matrix supporting our speculation (Figure 7S, Supporting Information).

3.3. Synthesis of PDMDOMA−Aldehydes and PDMDOMA−Amines. The PDMDOMA−diol derivative was further oxidized using sodium periodate to generate PDMDOMA−aldehydes. The aldehyde polymer was characterized by ^1H and ^{13}C NMR in D_2O. A representative ^1H NMR of PDMODMA−aldehyde along with the parent PDMDOMA−diol (35%) is given in Figure 4. After a 4 h reaction, protons representing the diol moiety at 3.5 ppm completely disappeared while a new peak appeared at 5.1 ppm. Also a peak at 9.5 ppm was observed after the oxidation which was attributed to the aldehyde proton.

Scheme 3. Stepwise Reductive Amination of PDMDOMA−Aldehyde with Propylamine and Aniline



The unusual low intensity of the aldehyde peak and the appearance of a new peak at 5.1 ppm in the ^{1}H NMR spectra suggest that the structural identity of the PDMODMA−aldehyde may not be straightforward. Therefore, ^{13}C and 2D HMQC NMR experiments were conducted to elucidate the correct structure. ^{13}C NMR spectra (Figure 5) shows that the signals from two carbons (64.5 ppm, 71.2 ppm) (labeled as a and b) in PDMDOMA−diol (35%) representing the diol moiety disappeared after the oxidation while two new carbon signals were observed at 43 and 87 ppm; the later is the typical for the carbon of covalent hydrate (1,1-diol).[17] Thus we believe that PDMDOMA−aldehyde in aqueous conditions exists in equilibrium with its covalent hydrate (Scheme 2). The ratio of the hydrate to the aldehyde form was estimated to be ca. 82:18 from ^{1}H NMR (Figure 4).

To further substantiate these results, a 2D HMQC NMR spectrum of PDMDOMA−aldehyde (35%) was acquired (Figure 6). The proton signal at 5.1 ppm shows good correlation with the carbon signal at 87 ppm, which further verifies the hydrate structure for the aldehyde. This result also suggests the presence

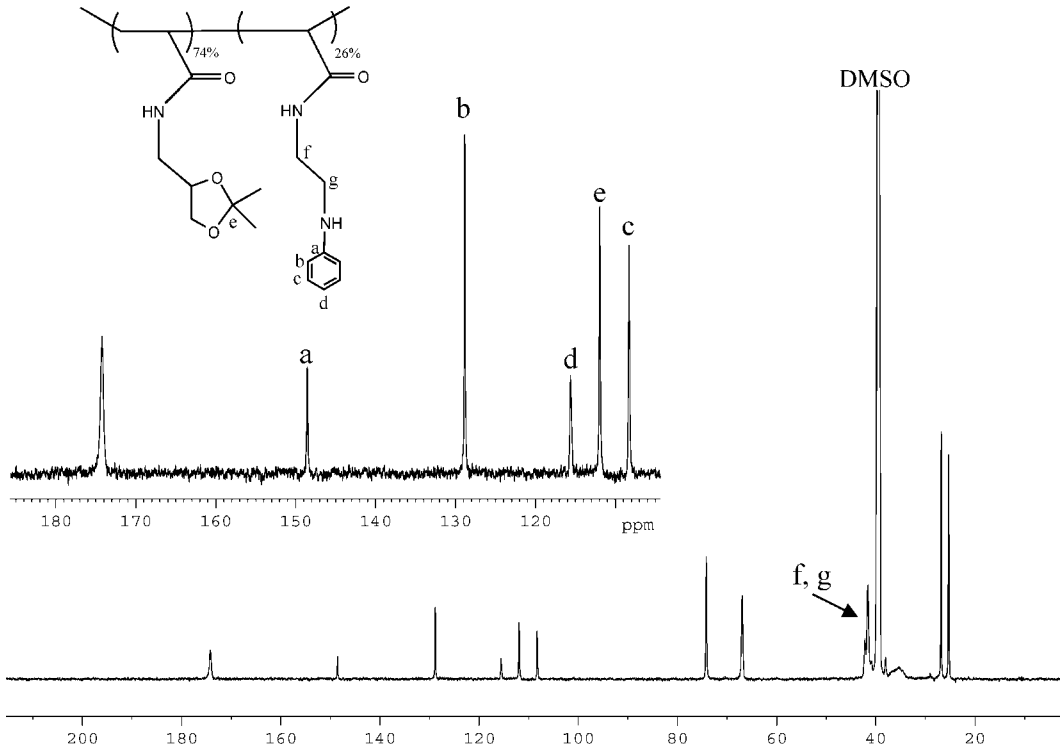


Figure 7. ^{13}C NMR spectrum of PDMDOMA−aniline (26%) in DMSO-d_6.

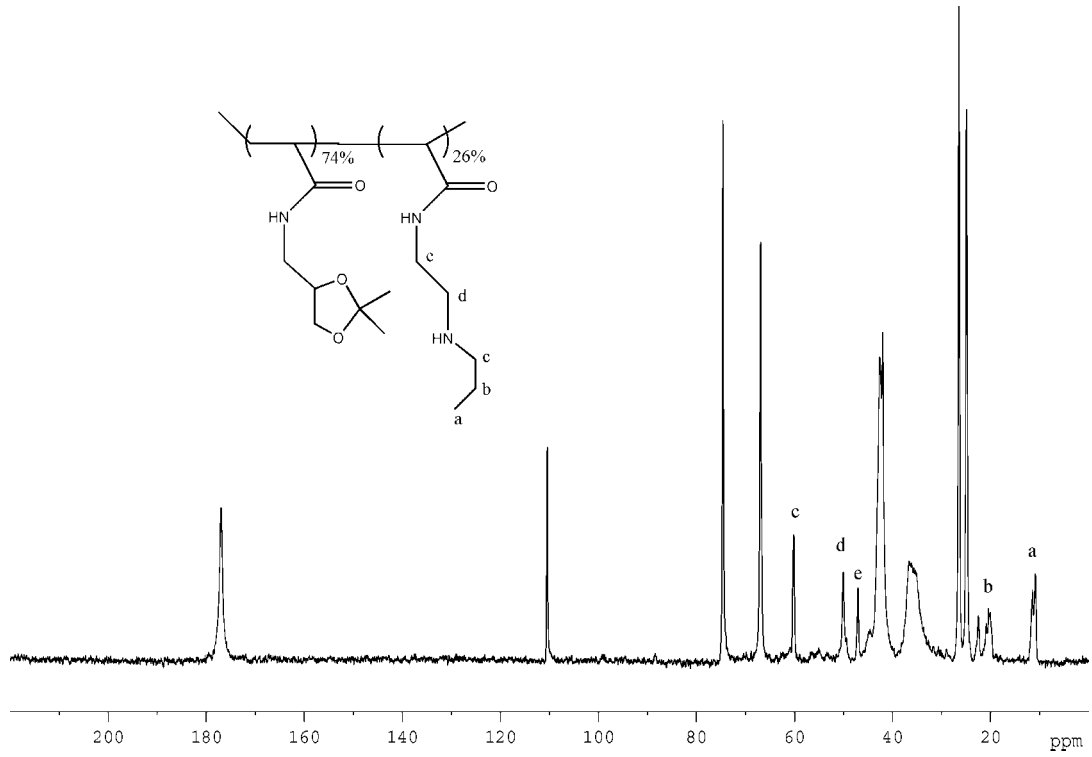


Figure 8. ^{13}C NMR spectrum of PDMDOMA−propylamine (26%) in D_2O.

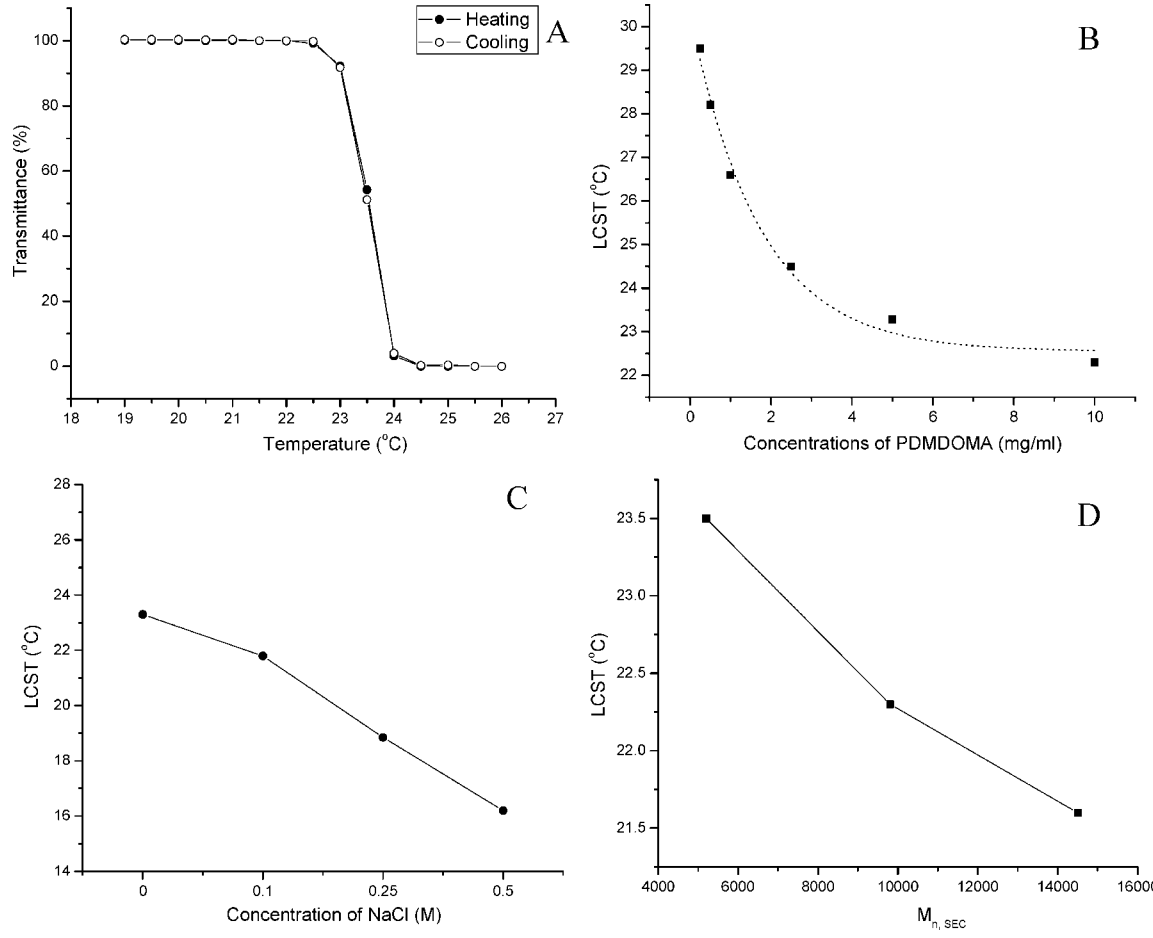


Figure 9. (A) Transmittance changes during a heating (solid dots) and cooling cycle (hollow dots) of 5 mg/mL of PDMDOMA (**P2**) in water. (B) Effect of polymer concentrations on LCST of PDMDOMA (**P2**). (C) Effect of concentrations of NaCl on LCST of PDMDOMA (**P2**). (D) Effect of molecular weight of PDMDOMA on LCST.

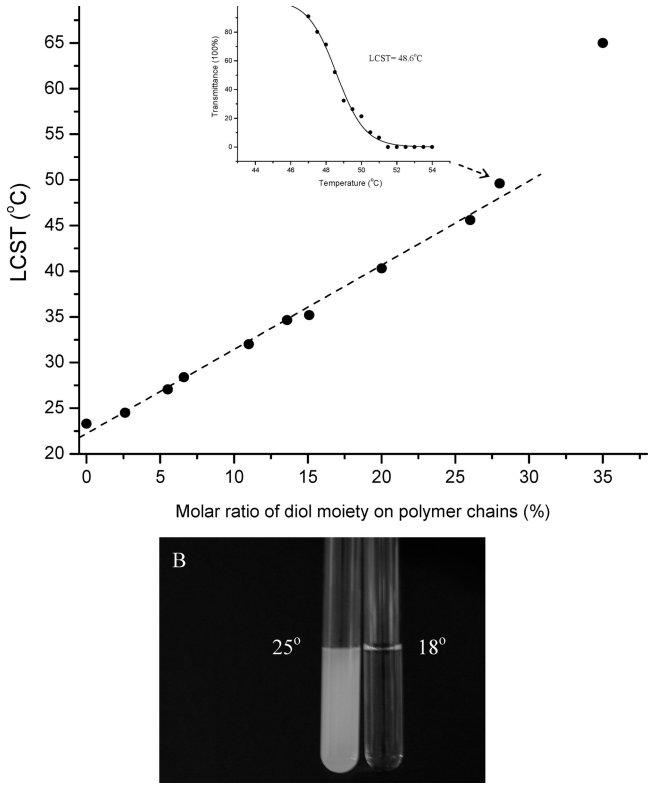


Figure 10. (A) relationship between LCST and molar ratio of the diol moiety on P2. When diol content of the polymer was increased to 43%, no LCST was observed even up to 85 °C. (B) Illustration of the phase transition of PDMDOMA. Two PDMDOMA solutions with the same concentration (5 mg/mL) were incubated in water bath at 25 and 18 °C respectively, removed, and photographs were taken immediately.

of more than one type of hydrate carbon in the polymer, as evidenced by the three cross peaks correlated with proton at 5.1 ppm. This could be due to the existence of different sequence of DMDOMA (ketal) and DMDOMA−aldehyde units along the polymer chain owing to the random distribution of these two units. Although the carbon signal representing the aldehyde was not observed in ^{13}C NMR due to its very low intensity ratio in equilibrium with the hydrate, HMQC NMR spectrum shows a correlation of the aldehyde proton at 9.5 ppm with the carbon signal at 200 ppm (Figure 3S, Supporting Information) suggesting the presence of aldehyde carbon.

The verification of a covalent hydrate structure for PDMDOMA−aldehyde should resolve concerns about formation of a hemiacetal in water or cross-linking reactions during oxidation of 1,2-diols. Also the PDMDOMA−aldehyde showed good stability in water; no side reaction was observed for a PDMDOMA−aldehyde aqueous solution even after storing it at room temperature for 3 days. ^{13}C NMR of PDMDOMA−aldehyde (100%) (Figure 3C) shows that even at higher aldehyde content there was no side reaction. Again, the hydrate in equilibrium with the aldehyde, was predominant in water. A weak peak at 200 ppm was observed in this case corresponding to the carbon signal of aldehyde. The aldehyde content in the polymer was varied using different PDMDOMA−diols (6% to 100%) as precursor.

As demonstrated previously by other researchers, the aldehyde group can be an important functional group with regard to the development of bioconjugate polymers.[12,15] To demonstrate the reactivity of PDMDOMA−aldehyde, PDMDOMA−aldehydes (6% and 26%) were reacted with aniline and propylamine via a reductive amination reaction (Scheme 3). To avoid dialkylation, which is common in the reaction of aldehyde and primary amines, a stepwise reaction was chosen instead of simultaneous addition of amine and reducing agent. Because of the poor solubility of PDMDOMA−imines in water (especially when the aldehyde content was high), the coupling and subsequent reduction reactions were carried out in a 1:1 water/methanol medium. The ^1H NMR of PDMDOMA−aniline (26%) in D_2O shows poor resolution at ambient temperature (Figure 4S) due to the increased hydrophobicity, leading to only partial dissolution of PDMDOMA−aniline (26%) in water.

Unambiguous ^1H and ^{13}C NMR were obtained in DMSO-d_6. Figure 7 shows a ^{13}C NMR spectrum of PDMDOMA−aniline (26%), where the carbon signals at 149, 129, 116 and 108 ppm were assigned to the carbons of the aromatic ring. Two carbons adjacent to NH (f and g) were not well resolved due to overlap with the DMSO peak. The structure of PDMDOMA−propylamine (26%) was also verified by ^{13}C NMR (Figure 8) and ^1H NMR spectra (Figure 5S). In general, the reductive amination reaction was complete as evidenced by the disappearance of aldehyde (or hydrate) peaks from the spectra. The complete conversion of aldehyde groups to amine groups in reductive amination also supports the conclusion that the covalent hydrate exists in equilibrium with the aldehyde group (Scheme 2) in water and also demonstrates the reactivity of the aldehyde groups in PDMDOMA−aldehyde.

3.4. The LCST Behavior of PDMDOMA and Its Derivatives. Typical LCST behavior was observed for aqueous solutions of PDMDOMA (Figure 9A); the polymer was precipitated above the phase transition temperature in water (Figure 10B). Figure 9A shows that PDMDOMA (**P2**, 5 mg/mL) underwent an abrupt phase transition between 23 and 24 °C, showing little hysteresis during cooling and heating cycles. The LCST of PDMDOMA was found to be 23.5 °C at 5 mg/mL concentration. The phase transition of the polymers was also verified by the light scattering (Figure 6S), which indicates similar LCST behavior to that measured in the turbidity study (Figure 9A). Further studies show that the LCST of PDMDOMA is affected by the polymer concentration, the addition of salt and the molecular weight. Similar observations were reported for PNIPAM, a well-known thermo-responsive polymer.[1] The effect of polymer concentration on the LCST is illustrated in Figure 9B; an increasing polymer concentration (0.25 to 10 mg/mL) results in a decrease of phase transition temperature from 29.5 to 22.3 °C. Figure 9C shows the dependence of salt concentration on the LCST of PDMDOMA. An increase in NaCl concentration from 0 to 0.5 M decreased the LCST from 23.5 to 16 °C. The phase transition temperature also decreased slightly from 23.5 to 21.6 °C when the molecular weight increased from 5200 to 14500 Da (Figure 9D).

Although the LCST of PDMDOMA showed some changes in response to various parameters, the magnitude of the change was limited: it varied only within a narrow range. Although the addition of salt had a relatively stronger impact on LCST, it only decreased it. Therefore, a series of partial cleavages of dioxolane side group in PDMDOMA−**P2** by HCl was carried out to provide a diol functionalized polymer (PDMDOMA−diols). In the current study, the reaction time was fixed to 30 min, while different volumes of 1 M HCl were added to the PDMDOMA solution to control the degree of cleavage. Due to the increased hydrophilicity of the diol moiety compared to the dioxolane group, the LCST of the partially cleaved PDMDOMA derivative gradually increased with increasing diol content in the polymer (Figure 10A). The LCST increased from 23.5 to 49 °C when the degree of cleavage was varied from 0 to 28%. Nearly a linear relationship between the LCST and the molar concentration of diol moiety was observed (up to 28 mol %).

An accelerated increase in the LCST has been observed at higher diol content in the polymer. For instance, when the degree of cleavage was 35%, the LCST increased to 65 °C while no

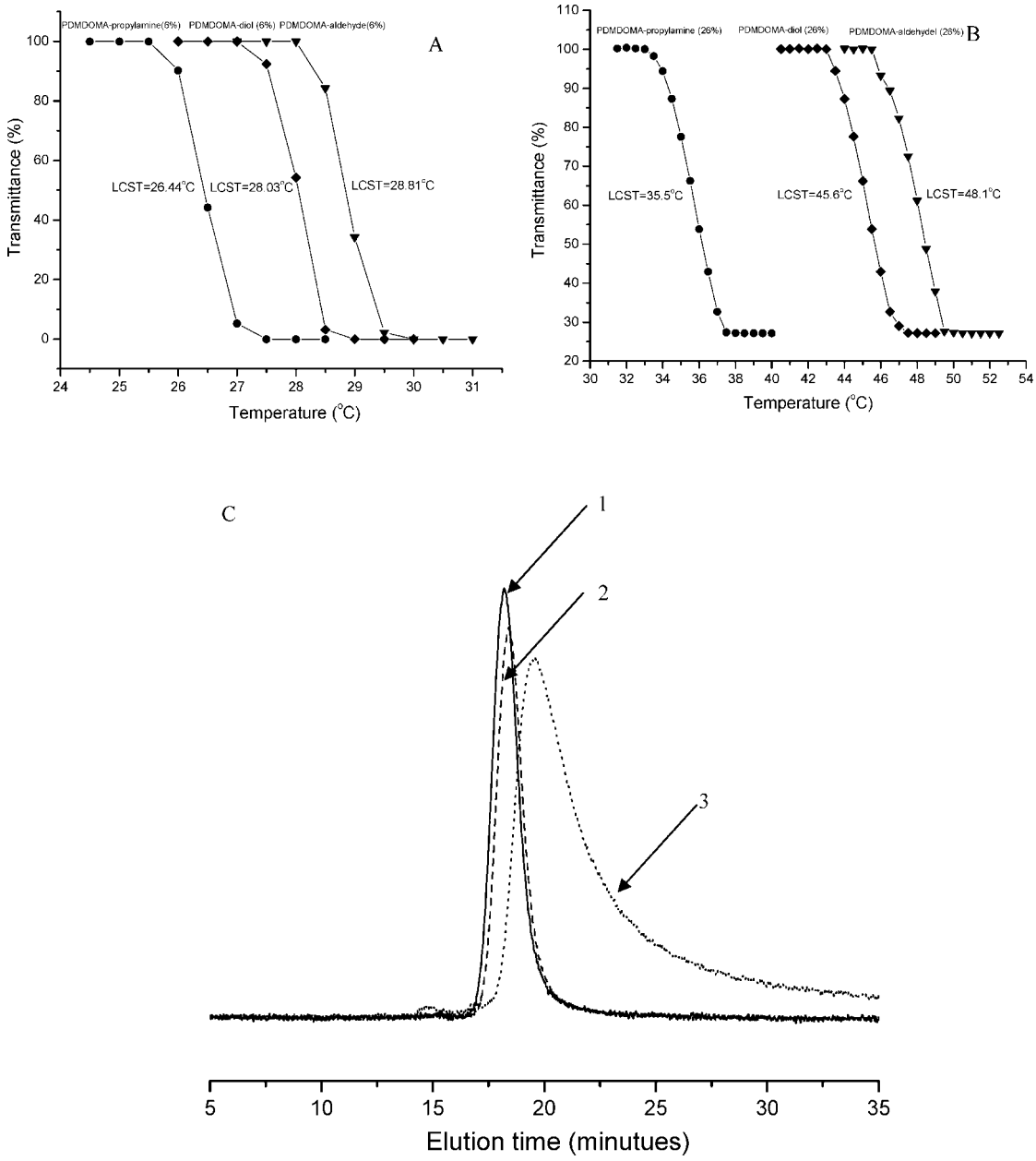


Figure 11. (A) Illustration of the LCST of PDMDOMA−diol (6%, diamond), PDMDOMA−aldehyde (6%, triangle) and PDMDOMA−propylamine (6%, dot). (B) LCST of PDMDOMA−diol (26%, diamond), PDMDOMA−aldehyde (26%, triangle) and PDMDOMA−propylamine (26%, dot). (C) GPC traces of PDMDOMA−diol (26%, 1), PDMDOMA−aldehyde (26%, 2) and PDMDOMA−propylamine (26%, 3).

LCST behavior was observed for polymers with a diol content of 43% even at 85 °C. This accelerated increase in LCST implies that when the molar ratio of the diol moiety in the polymer chain reaches a certain level, the inter and intra molecular hydrogen bonding of the polymer chains and the hydrogen bonding to water molecules undergo a sharp change, leading to a dramatic increase in LCST. The detailed study of the effects of salt, polymer concentration and molecular weight on the LCST of PDMDOMA−diol (as well as aldehyde and amine derivatives) is outside the scope of the current study and these dependences have not yet been investigated in detail although their effects on the LCST behavior of PDMDOMA derivatives can be anticipated based on the behavior of PDMDOMA and other stimuli sensitive polymers.[1]

In contrast to PDMDOMA, which showed an abrupt phase transition between 23 and 24 °C, 28% cleaved PDMDOMA−diol showed a gradual phase transition between 47 and 52 °C (inset in Figure 10A). A similar observation was observed for 35% cleaved polymer (PDMDOMA−diol, 35%) (data not shown). The slow phase transition could be due to the stronger hydrogen bonding capability and hydrophilicty of the diol moiety, which slowed down the transition from swollen coil to dense globule during heating. The random distribution of diol moieties on the polymer chains could also be involved.

Compared to the conventional methods of controlling the LCST of polymers via copolymerization or block copolymerization, the current approach provides a facile method via the quantitative hydrolysis of the pendant groups on the preformed polymer. More importantly, the PDMDOMA, PDMDOMA−diols, PDMDOMA−aldehydes, and PDMDOMA−amines with different LCSTs were prepared from a single batch of polymer, resulting in comparable molecular weights and polydispersities. It is known that the precise control of composition of the two components in a copolymerization is difficult owing to the different ratio of reactivity of comonomers. Thus the current approach to control LCST has a distinct advantage over conventional methods when considering system for model theoretical studies or for industrial purposes.

The LCST of the PDMDOMA−aldehyde was close to the parent PDMDOMA−diol (1,2-diol). For example, as shown in Figure 11A, the LCST of PDMDOMA−aldehyde (6%) was not significantly different from that of PDMDOMA−diol (6%). When the molar ratio of the aldehyde moiety increased to 26%, the LCST of PDMDOMA−aldehyde (26%) was slightly increased (Figure 11B) (2.3 °C). A similar LCST in this case is mainly attributed to the similar hydrophilicity of PDMDOMA−aldehyde (hydrate, 1,1-diol) and diol (1,2-diol). Figure 11C shows the PDMDOMA−aldehyde (26%) had almost the same elution time and GPC profile compared to its diol counterpart, indicating comparable molecular weights and polydispersity.

In contrast to the minor effect of aldehyde groups on the LCST of PDMDOMA, the coupling of aniline or propylamine showed much more pronounced impact. In the case of 6% propylamine derivatized polymer, the LCST was decreased almost 2 °C compared to the parent aldehyde polymer (Figure 11A). A larger difference was observed in the case of the 26% propylamine derivatized polymer (Figure 11B) (48−35 °C). The increase in hydrophobicity after the covalent attachement of propylamine to PDMDOMA−diol should account for this behavior. Such a change is also reflected in the GPC profile of PDMDOMA−propylamine (26%) (Figure 11C, line 3), which showed severe column adsorption and tailing in sharp contrast to PDMDOMA−diol or PDMDOMA−aldehyde (26%) (Figure 11C, lines 1 and 2). The presence of the aromatic ring in PDMDOMA−aniline (26%) had more impact on the LCST, as evidenced by the very low phase transition temperature (around 0 °C). The aniline derivative formed a turbid solution when the temperature was above 5 °C.

A comparison of the LCST of PDMDOMA−diol, aldehyde, aniline, and propylamine (6% and 26% substituted) reveals that the hydrophilicity/hydrophobicity of the pendant group plays an essential role in the phase transition of PDMDOMA derivatives with temperature. The presence of diol and aldehyde groups on the polymer led to the increase in LCST due to their higher hydrophilicity (presence of two hydroxyl groups) compared to the dioxolane group, whereas the coupling of propylamine led to a moderate decrease in LCST compared to the diol or aldehyde counterpart (Figure 11). This is due to the replacement of highly hydrophilic groups with a three-carbon aliphatic chain of higher hydrophobicity. A significant decrease in LCST was not observed may be due to the presence of a hydrophilic secondary amine along with alkyl chains. The addition of a more hydrophobic aromatic group in PDMDOMA−aniline at a similar concentration produced a much larger decrease of LCST compared to propylamine. The PDMDOMA−aniline (26%) was not soluble in water at ambient temperature. Furthermore, an increase in the derivatization of the aldehyde groups, i.e. increase in the hydrophobic content, produced a much larger decrease in the LCST. For example, the difference between the LCST of PDMDOMA−propylamine (6%) compared to its parent PDMDOMA−aldehyde (6%) is about 2 °C whereas when the derivatization was increased to 26%, the difference increased to 13 °C. Similar observations were noted for the PDMDOMA−aniline derivatives (data not shown). Our results suggest that by controlling the hydrophilicity/hydrophobicity of pendant groups, PDMDOMA derivatives with different LCSTs can be readily prepared.

4. Conclusions

ATRP of [(2,2-dimethyl-1,3-dioxolane) methyl]acrylamide produced polymers with controlled molecular weights and narrow molecular weight distributions under the conditions studied. It is possible to finely tune the LCST of this novel polymer over a wide temperature range without changing its backbone structure. Thermo-responsive aldehyde polymers were synthesized by cleaving the pendant dioxolane groups and subsequently oxidizing the 1,2-diols. The ^{1}H and ^{13}C NMR analysis demonstrates that the PDMDOMA−aldehyde exists predominantly as a covalent hydrate in water. The reactivity of PDMDOMA−aldehyde was verified by the reductive amination reactions with aniline and propylamine. The LCST of PDMDOMA derivatives depends on the hydrophilic or hydrophobic content in the polymer. An increase in the hydrophilicity (e.g., 1,2-diol or 1,1-diol) led to an increase in the phase transition temperature, while the addition of propylamine or aniline (hydrophobic components) caused a decrease in the phase transition temperature. The current study provides a novel approach to making polymers which combine two important properties: thermo-responsiveness and functionality via reactive aldehyde groups. Such polymers could prove to be a versatile template for the synthesis of novel "smart" polymer conjugates.

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Supporting Information Available: Figures showing GPC profiles, ^{1}H and HMQC NMR spectra, and light scattering results for PDMDOMA derivatives. This information is available free of charge via the Internet at http://pubs.acs.org.

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