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ARTICLE *in* MACROMOLECULES · AUGUST 2013

Impact Factor: 5.8 · DOI: 10.1021/ma401096r

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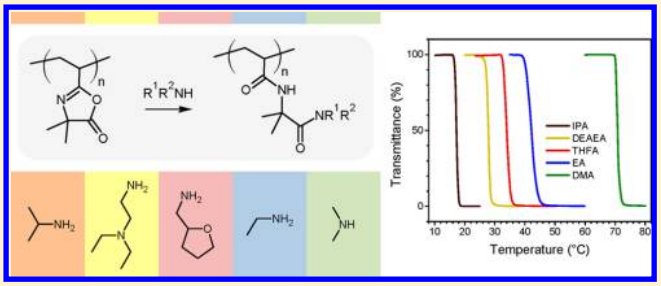
Thermoresponsive (Co)polymers through Postpolymerization Modification of Poly(2-vinyl-4,4-dimethylazlactone)

Yicheng Zhu, Jing Yang Quek, Andrew B. Lowe, and Peter J. Roth*

Centre for Advanced Macromolecular Design (CAMD), School of Chemical Engineering, University of New South Wales, UNSW Sydney NSW 2052, Australia

Supporting Information

ABSTRACT: Poly(2-vinyl-4,4-dimethylazlactone), pVDMA, is emerging as a versatile reactive platform in polymer chemistry. Herein, postpolymerization modification of pVDMA leading to thermoresponsive homo- and copolymers is investigated. VDMA was polymerized by reversible addition−fragmentation chain transfer (RAFT) polymerization. The resulting reactive scaffolds with molecular weights ranging from 3.0 to 12.5 kg/mol were converted with a selection of alcohols and amines of varying polarity into functional poly(2-acrylamido isobutyrate)s and poly(2-acrylamido isobutyramide)s with molecular weights ranging from M_n = 4.2−65.1 kg/mol and low polydispersity indices M_w/M_n < 1.37. Spectra obtained by ^{1}H NMR and infrared spectroscopic measurements conformed to the expected structures. While alcohols and amines producing water-soluble or water insoluble VDMA-derived homopolymers were identified, seven homopolymers were found to show a lower critical solution temperature in aqueous solution; those formed by reacting pVDMA with *N*-ethylamine, *N*-isopropylamine, *N*,*N*-dimethylamine, *N*,*N*-diethylamine, *N*,*N*-diethylaminoethylamine, Jeffamine M-600, and tetrahydrofurfurylamine (THF amine). Cloud points increased with decreasing molecular weight. With a cloud point of 31 °C, the phase separation of poly(tetrahydrofurfuryl 2-acrylamido isobutyramide) (pTAI) occurred close to body temperature, was highly reproducible, and, above a concentration of 0.5 wt %, was largely concentration independent. The transition temperature of pTAI-based copolymers could easily be tuned by reacting pVDMA with a mixture of THF amine and varying amounts of pentylamine or di(ethylene glycol) methyl ether amine.



INTRODUCTION

Postpolymerization modification—the chemical transformation of a reactive polymeric precursor into a new functional species—is a very versatile synthetic approach toward functional materials.[1−3] This concept allows the introduction of a wide variety of functional groups (including such that may not be compatible with polymerization conditions) into polymers and enables the production of large libraries of functional products with essentially identical degrees of polymerization from a single precursor. By exposing a reactive precursor to a mixture of modifying reagents copolymers with, ideally, a random distribution of functionality along the backbone is obtained that may be difficult to access through other routes. The history of this approach traces back to the early days of polymer chemistry—vulcanization[4] and hydrogenation[5] of rubber are prime examples that involve chemical transformation of a preformed polymer.[3] In recent years, postpolymerization modification has become a very attractive strategy within the paradigm of click-type chemistry, i.e., in combination with very robust and efficient chemical reactions that allow fast and quantitative modification of polymers. Cycloadditions (azide−alkyne, diene−dienophile), additions of thiols to unsaturated bonds (thiol−ene, thiol−yne), and substitution reactions on activated esters are some of the main cornerstones of this rapidly growing research field.[6−14]

Thermoresponsive polymers, materials that respond with a drastic change of solubility to subtle temperature changes, are an exciting class of materials that find application in a variety of fields.[15−19] A strong focus lies on polymers exhibiting a lower critical solution temperature (LCST) in aqueous solution. Such polymers undergo a reversible coil-to-globule transition when heated above the LCST. Depending on concentration, globular polymers aggregate above the LCST typically leading to a clouding of the mixture (when the aggregates reach a size sufficient to scatter light) and eventual precipitation of a polymer-rich phase.[20−24] Such smart synthetic polymers are rapidly spreading into other realms of science, including the entire biomedical arena.[25−29] There is therefore an increasing interest in exploiting the advantages of postpolymerization modification to produce well-defined, tailor-made stimulus-responsive materials.[30−38] For example, acrylate-based activated esters, such as poly(pentafluorophenyl acrylate) (pPFPA)[32] or poly(acetone oxime acrylate),[35] can very easily be converted

Received: May 25, 2013
Revised: July 24, 2013
Published: August 5, 2013

into thermoresponsive polyacrylamido species such as poly(*N*-cyclopropylacrylamide)[33] or the well-documented poly(*N*-isopropylacrylamide) (pNIPAM), which both have an LCST in water, by reaction with the corresponding amines (cyclopropylamine and isopropylamine), thus providing a versatile platform for the introduction of further functionality. Recently, Schattling et al.[38] took advantage of this tactic for the development of a thermo, redox, and light responsive copolymer and suggested its use for molecular information processing. The copolymer was prepared by incorporating three different functional groups into a pPFPA precursor: a diazobenzene functionality (which provided a reversible polarity change through photoisomerisation) and a 2,2,6,6-tetramethyl-1-oxyl-piperidine (TEMPO) functionality (enabling reversible reduction to the *N*-hydroxypiperidine derivative), while the majority of activated ester units was converted into pNIPAM, endowing the product copolymer with a thermal response that depended on the state of the two switchable groups.

2-Vinyl-4,4-dimethylazlactone (VDMA) has been receiving increasing attention in the polymer chemistry arena as a reactive monomer suited for postpolymerization modification.[39−42] The azlactone heterocycle exhibits high reactivity toward various nucleophiles including amines, alcohols, and thiols (the two latter typically with base catalysis),[43,44] and, incorporated into water-soluble materials, hydrolyses readily.[45] Compared to activated ester chemistry, a main advantage of the azlactone functionality is that the ring-opening reaction with nucleophiles is an addition reaction, which provides a significantly better atom economy and eliminates the need for separation of a leaving group. As a flexible reactive platform poly(VDMA) (pVDMA) has been used in various applications, for example, for surface functionalization by an alternating layer-by-layer deposition together with polyethylenimine,[46,47] including on the surface of hair, and for the fabrication of robust free-standing amine-reactive membranes.[48] Fournier et al. documented the use of pVDMA on a solid support as a nucleophile scavenger,[49] and as a catalyst support.[50] pVDMA has further been used for enzyme immobilization[51] and has been converted into biologically relevant species including glycopolymers[52] and polycations for DNA complexation.[53] The azlactone functionality has been explored as a very versatile building block in polymer chemistry. Laquièvre et al.[54] utilized a styrene-based azlactone monomer to prepare highly reactive homo- and copolymer platforms and incorporated fluorescent, electrochemical, biological, and perfluorinated moieties. Ho et al. recently introduced the azlactone functionality into the end groups of RAFT-made polymers by either employing a novel azlactone-functional chain transfer agent,[55] or by reacting the vinyl group of VDMA in a thiol-Michael addition reaction with a thiol-terminated (RAFT-derived) polymer.[56]

While VDMA has been incorporated as a reactive handle into thermoresponsive materials, allowing for a tuning of the response of inherently thermoresponsive polymers,[56,57] there has, to the best of our knowledge, been no study on transforming pVDMA directly into thermoresponsive (co)-polymers. With a growing interest in VDMA as a versatile tool in polymer chemistry, an understanding of how to endow a pVDMA scaffold with thermal responsiveness is of significant interest not only since potential applications of "smart" VDMA-derived polymers exist but also because this understanding inevitably provides information on the design of polymers exhibiting temperature independent solubility or insolubility in water—often a limiting, or desired, factor in the application of polymers. Whereas some types of stimulus-responsive behavior rely on the presence of a certain functional group (e.g., a photoisomerisable azobenzene group), thermoresponsiveness is typically not imparted by specific functional groups but relies on an appropriate hydrophilic−hydrophobic balance of the entire structure.[58] The 2-methylalanyl segment resulting from the ring-opening of the azlactone heterocycle must therefore be taken into account when considering the solubility of VDMA-derived polymers.

Herein, we present a systematic study on the aqueous solution behavior of a family of (co)polymers derived from pVDMA with a variety of amines and alcohols, and we identify several homopolymers exhibiting sharp and reproducible LCST behavior. For one species, poly(tetrahydrofurfuryl 2-acrylamido isobutyramide), obtained from the reaction of pVDMA with tetrahydrofurfurylamine, which is shown to have an LCST close to body temperature, a phase diagram and tuning of the transition temperature with coamines are presented.

EXPERIMENTAL SECTION

Materials. The monomer 2-vinyl-4,4-dimethylazlactone (VDMA),[57] the RAFT agent benzylpropyltrithiocarbonate (BPTC),[36] di(ethylene glycol) methyl ether amine,[31] and tri(ethylene glycol) methyl ether amine[31] were synthesized according to literature procedures. Ethylamine **5** and dimethylamine **13** were used as 2 M solutions in THF. Poly(propylene glycol) reagent **22** was *O*-(2-aminopropyl)-*O*′-(2-methoxyethyl)polypropylene glycol 500, referred to as Jeffamine 600. Azobis(isobutyronitrile) (AIBN) was recrystallized from methanol. Glycinamine hydrochloride, alaninamide hydrochloride and 2-aminobutyramide hydrochloride were purchased from Chem-Impex and used as received. All other chemicals were purchased from Sigma-Aldrich and used as received.

Instrumentation. NMR spectroscopic measurements were performed on a Bruker DPX 300 instrument. The internal solvent signal of was used as reference ($\delta(CDCl_3)$ = 7.26 ppm, $\delta(D_2O)$ = 4.79 ppm). Molar compositions of copolymers containing THF amine (**23**) and di(ethylene glycol) methyl ether amine (**20**) were determined by comparison of the integrals of the three broad singlets at 3.96, 3.85, 3.73 ppm (1 H each of THF group: C*H*−O−C*HH*) and the broad singlet at 3.19 ppm (CONH−C*H*H−THF) with the multiplet between 3.62−3.38 ppm (11 H from ethylene glycol side chain overlapping with the other exocyclic methylene group proton from THF amide: CONH−CH*H*−THF). Molar compositions of copolymers containing THF amine (**23**) and *n*-pentyl amine (**8**) were determined by comparison of the THF amide signals at 3.96, 3.85, 3.73, and 3.44 ppm (1 H each) with the broad singlet at 3.18 ppm (overlap of 1 H of THF amide: CONH−C*H*H−THF with 2 protons from *n*-pentyl side chain: −CONH−CH_2−C_4H_9); see spectra in the Supporting Information.

Size exclusion chromatography (SEC) was performed on a Shimadzu system with four phenogel columns in dimethylacetamide operating at a flow rate of 1 mL/min. Chromatograms were analyzed by Cirrus SEC software version 3.0. The system was calibrated with a series of narrow molecular weight distribution polystyrene standards with molecular weights ranging from 0.58−1820 kg/mol.

Fourier transform infrared spectroscopy (FTIR) was performed on a Bruker IFS 66/S instrument under attenuated total reflectance (ATR) and was analyzed on OPUS software version 4.0.

Turbidity measurements were performed on a Varian Cary 300 Scan spectrophotometer equipped with a Cary temperature controller and a Peltier heating element in quartz cuvettes of 10 mm path length at a wavelength of 520 nm with heating/cooling rates of 1 °C/min. Unless otherwise noted, polymer concentrations were 5 g/L. For clear solutions the baseline was corrected to zero absorbance, *A*. Transmittance, $T = 10^{-A}$, was plotted against temperature and cloud points were determined at 50% transmittance or at the average of

Table 1. Details of VDMA Homopolymers Used in This Study

code	equiv[a]	time[b] (h)	conversion[c] (%)	$M_{n,target}$ (kg/mol)	$M_{n,th.}$[e] (kg/mol)	$M_{n,NMR}$[f] (kg/mol)	$M_{n,SEC}$[g] (kg/mol)	PDI[g]
v1	105	10	97	14.9	14.5	12.5	64.4	1.14
v2	100	6	n.d.[d]	14.2	n.d.	12.0	53.6	1.16
v3	100	6	n.d.	14.2	n.d.	11.2	45.6	1.21
v4	50	6	96	7.2	6.9	7.1	20.5	1.27
v5	20	6	98	3.0	2.9	3.0	14.7	1.27

[a]Ratio of [VDMA] to [chain transfer agent] during polymerization. [b]Polymerization time. [c]Conversion determined by ^{1}H NMR of reaction sample with added $CDCl_3$ by comparing the monomer vinyl signals at 6.21 ppm (2 H) and 5.92 ppm (1 H) with the backbone methine signal (2.65 ppm, 1 H per monomer unit) . [d]Not determined. [e]Theoretical molecular weight calculated from conversion, feed ratio, and molecular weights of monomer and end groups. [f]NMR molecular weight calculated by comparison of the signal of the methyl group of the propyl trithiocarbonate ω terminus (1.017 ppm, 3 H) with the backbone methine signal (2.70, 1 H per monomer unit). [g]Polystyrene equivalent molecular weight and polydispersity index determined by SEC.

maximal and minimal transmittance for samples of which the transmittance did not decrease to ~0%.

Synthesis of Poly(2-vinyl-4,4-dimethylazlactone) (pVDMA). VDMA homopolymers of different molecular weights were prepared according to the following example for **v1**: VDMA (2.1 g, 15.1 mmol, 105 equiv), BPTC (34.9 mg, 0.144 mmol, 1 equiv), AIBN (2.4 mg, 0.014 mmol, 0.1 equiv) and acetonitrile (3 mL) were combined in a flask, which was equipped with a stir bar and sealed with a rubber septum. After purging with nitrogen for 20 min, the mixture was stirred in a preheated oil bath at 70 °C for 10 h. The reaction was quenched with liquid nitrogen and the product was isolated by two precipitations in diethyl ether yielding 1.83 g of pVDMA. Further homopolymers with varying molecular weights were prepared with varying ratios of monomer to chain transfer agent and reaction time; see Table 1.

Postpolymerization Modification of pVDMA with Alcohols—Exemplary Procedure. pVDMA (69.6 mg, 0.5 mmol of monomer units) was dissolved in anhydrous dimethylformamide (DMF, 2 mL) and acrylamide (4 mg, 0.056 mmol) was added. In a separate vial, anhydrous DMF (1 mL), anhydrous methanol (0.5 mL, 12.3 mmol), and 1,8-diazabicycloundec-7-ene (DBU, 0.0748 mL, 0.5 mmol) were mixed and added into the polymer solution. The mixture was stirred at 50 °C overnight.

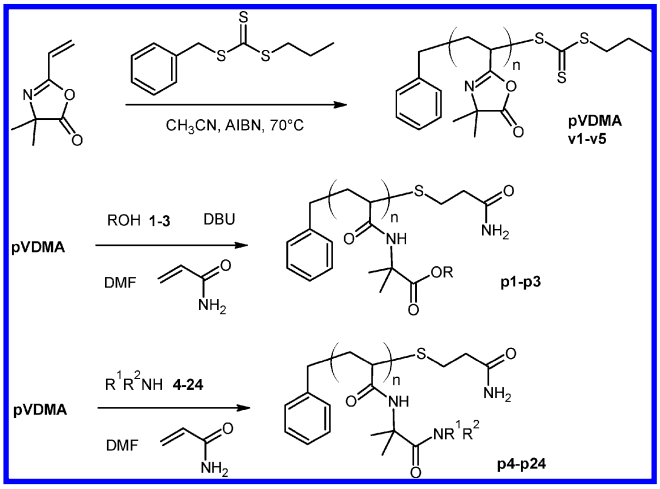
Postpolymerization Modification of pVDMA with Amines—General Procedure. pVDMA (69.6 mg, 0.5 mmol of monomer units) was dissolved in DMF (2 mL) and acrylamide (4 mg, 0.056 mmol) was added. In a separate vial, DMF (1 mL) and amine (1.5 mmol, 3 equiv) were mixed and then added into the polymer solution. The mixture was stirred at room temperature overnight. Copolymers were prepared by an analogous protocol using a total of 1.5 eq. of amine. For example, for a reaction containing a feed of 20% of *n*-pentylamine and 80% of THF amine, 0.3 equiv of *n*-pentylamine and 1.2 equiv of THF amine were mixed, then introduced into a solution containing 1 equiv of VDMA groups.

Purification of Modified VDMA Polymers. Product polymers were purified either by dialysis in methanol or water in regenerated cellulose membranes with a molecular weight cutoff of 3500 g/mol for 3 days with solvent changes twice a day, or by two precipitations into diethyl ether. Polymers were subsequently dried in vacuum. Yields ranged between 75 and 82%.

RESULTS AND DISCUSSION

Synthesis of pVDMA and Postpolymerization Modification. VDMA monomer was synthesized following a literature procedure.[57] Subsequent RAFT polymerization[59] was carried out using acetonitrile, AIBN, and BPTC as solvent, initiator, and chain transfer agent, respectively (see Scheme 1), yielding well-defined VDMA polymers **v1**–**v5**. Theoretical molecular weights, $M_{n,th}$, calculated from conversions, molecular weights determined by end groups analysis by ^{1}H NMR spectroscopy, $M_{n,NMR}$, polystyrene equivalent molecular weights, $M_{n,SEC}$, and polydispersity indices $M_{w,SEC}/M_{n,SEC}$,

Scheme 1. Synthesis of Reactive Poly(2-vinyl-4,4-dimethylazlactone) Precursors by RAFT Polymerization (Top), Post-Polymerization Modification with Alcohols Giving Poly(alkyl 2-acrylamido isobutyrate)s, p1–p3 (Middle), and Post-Polymerization Modification with Various Amines Giving Poly(*N*-alkyl 2-acrylamido isobutyramide)s and Poly(*N*,*N*-dialkyl 2-acrylamido isobutyramide)s p4–p24 (Bottom)[a]

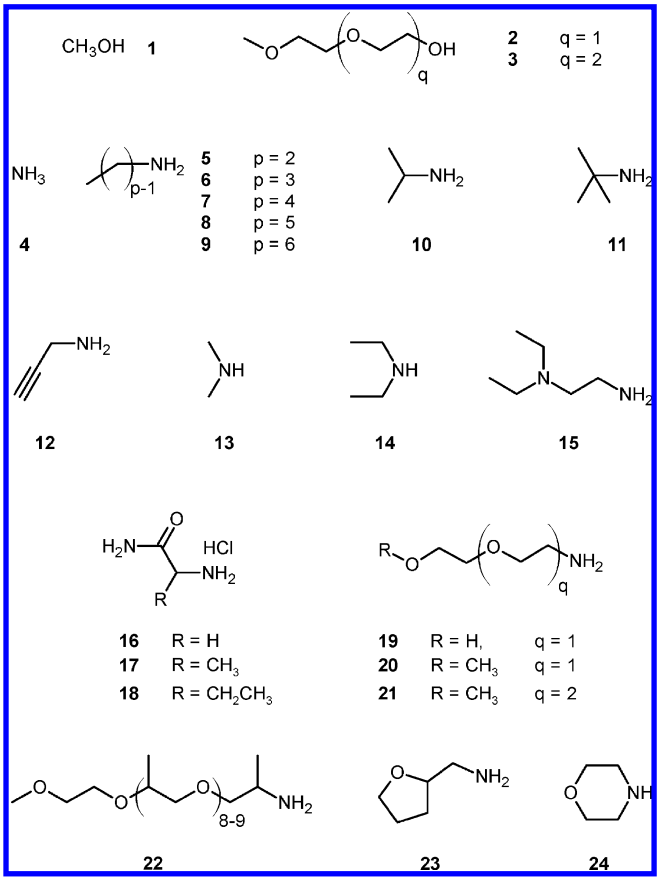


[a]Acrylamide was used to scavenge thiol end groups formed by aminolysis of RAFT thiocarbonylthio end groups.

determined by SEC, are given in Table 1. Molecular weights $M_{n,NMR}$ ranged from 3.0 to 12.5 kg/mol, and polydispersity indices were below 1.27. Precursors **v1**–**v3** had comparable molecular weights between $M_{n,NMR}$ = 11.2 kg/mol and $M_{n,NMR}$ 12.5 kg/mol and were reacted with a wide range of amines and alcohols, while polymers **v4** and **v5** with lower molecular weights of $M_{n,NMR}$ = 7.1 kg/mol and $M_{n,NMR}$ = 3.0 kg/mol were prepared to investigate the influence of molecular weight on the solubility of selected species. VDMA polymers were subjected to postpolymerization modification with a variety of alcohols and amines (Scheme 2) in DMF as solvent. Amines were used in 3-fold excess and reactions were carried out at room temperature with stirring overnight. For amines available as hydrochlorides, a stoichiometric amount of DBU was added to deprotonate the primary amines. DBU was also added to the reaction of pVDMA with alcohols. Since in all cases aminolysis/alcoholysis of the trithiocarbonate RAFT end group is a possible side reaction producing sulfhydryl-terminated polymers potentially leading to undesired disulfide byproducts of double molecular weight, acrylamide was added as a "soft"

dx.doi.org/10.1021/ma401096r | Macromolecules 2013, 46, 6475–6484

Scheme 2. Structures of Reagents Used To Modify pVDMA



electrophile to scavenge the sulfhydryl groups and to provide a benign end group (see Scheme 1).[60] Modified polymers, designated **p1**−**p24** according to numbers in Scheme 2, were obtained in high yield and high purity after purification by either precipitation into diethyl ether or by dialysis.

Polymers **p1**−**p24** were characterized by SEC, ^{1}H NMR, and FTIR spectroscopy. Polystyrene equivalent molecular weights, $M_{n,SEC}$, and polydispersity indices of all polymers are given in Table 2. While polymers derived from scaffolds **v3**−**v5** showed similar polydispersity indices as their parent polymers (as to be expected from a side group manipulation), polymers derived from the higher molecular weight precursors **v1** and **v2** showed slightly increased polydispersity indices than their parents, with the Jeffamine 600 modified polymer exhibiting the largest value of 1.37, suggesting, possibly, the occurrence of side reactions or unspecific interactions of the higher molecular weight bisamide derivatives with the SEC column material. For reference, expected molecular weights, $M_{n,exp}$, are included in Table 2. These values were calculated from the degrees of polymerization of the precursors (from ^{1}H NMR data, Table 1) and the molecular weights of the respective monomer units after an assumed full conversion, and range between 4.2 kg/mol (sample **p6c**, derived from **v5** and *n*-propylamine) and 65.1 kg/mol (sample **p22** obtained from reacting **v1** with Jeffamine 600).

Representative SEC traces of the pVDMA precursor **v1** and three polymers derived from this precursor, **p13**, **p14**, **p23a**, are shown in Figure 1. The apparent molecular weight of modified polymers depended on the nature of the modifying agent. All SEC traces of modified polymers were unimodal, suggesting that unwanted side-reactions of the RAFT end group leading to double molecular weight species had not occurred, presumably due to addition of the acrylamide scavenger.

Representative ^{1}H NMR spectra of modified polymers are shown in Figures S1−S3 in the Supporting Information. All spectra conformed to the expected structures of the product polymers. Integration of signals and comparison of the resonances of the backbone (methine at 2.22 ppm and methylene at 1.76 ppm) and the two methyl groups of the 2-methylalanyl spacer (1.54 ppm) with the signals assigned to the introduced side groups suggested, within the accuracy of this method, a quantitative conversion of the reactive VDMA moieties.

FTIR spectroscopy served as a very useful tool in determining the completeness of postpolymerization modifications. Representative spectra are shown in Figure 2. The absorbance spectrum of pVDMA, top plot in Figure 2, showed weak absorbance bands at 2978, 2933, and 2869 cm^{-1}, originating from the 4,4-dimethyl groups on the azlactone ring, and the methylene and methine backbone signals, respectively. In the carbonyl region (1900−1600 cm^{-1}), the precursor polymer showed two strong bands, at 1815 cm^{-1} (lactone C═O stretch) and 1668 cm^{-1} (C═N stretch) characteristic of the reactive azlactone heterocycle. The product of the reaction of **v1** with tetrahydrofurfurylamine (THF amine), **p23a**, gave rise to the middle plot in Figure 2. Absent from the spectrum of the precursor, **p23a** had a broad band of medium intensity around 3300 cm^{-1}, characteristic of N−H stretching of amides. Within the C−H stretch region from 3000−2800 cm^{-1}, the methylene absorbance at 2940 cm^{-1} had increased compared to the starting material suggesting the presence of further −CH_2− groups. Most noticeably, the carbonyl region differed between pVDMA and **p23a**. The strong lactone band (1815 cm^{-1}) had entirely disappeared, suggesting complete conversion of the azlactone cycles. Instead, the IR spectrum of **p23a** showed strong bands at 1645 and 1533 cm^{-1}, characteristic of amide C═O stretching and N−H bending, respectively. The spectrum of methanol-modified pVDMA, **p1**, bottom plot in Figure 2, showed bands similar to those of **p23a** in the N−H and C−H stretch region from 3500−2800 cm^{-1}. Likewise, the azlactone C═O absorbance at 1815 cm^{-1} had entirely vanished from the spectrum of **p1**, suggesting complete conversion of the azlactone cycle also for the reaction with methanol. In addition to two characteristic amide bands at 1645 and 1527 cm^{-1}, **p1** showed a strong absorbance at 1725 cm^{-1}, which was assigned to the stretching vibration of the methyl ester C═O group. In summary, FTIR spectroscopy conformed to the expected product structures and suggested complete reaction of the VDMA groups. Furthermore, the spectrum of the bis-amide polymer **p23a** did not show any distinguishable bands indicative of carboxylate functionality (expected around 1560 cm^{-1}), indicating that all VDMA groups of the precursor had reacted, as intended, with THF amine and that no hydrolysis of remaining azlactones had occurred during work-up by dialysis in water.

Aqueous Solution Properties of VDMA-Derived Polymers. With a large variety of novel, well-defined VDMA-derived homopolymers in hand, solubility in aqueous solution was assessed next. Temperature dependent solubility between 0 and 90 °C was determined for all polymers **p1**−**p24** in deionized water at a concentration of 5 g/L. Results are summarized in Table 2. Modification of pVDMA with the shortest alcohol, methanol, produced an insoluble polymer, **p1**; see Table 2. Homologues derived from longer chain alcohols

dx.doi.org/10.1021/ma401096r | *Macromolecules* 2013, 46, 6475−6484

Table 2. List of Polymers Derived from pVDMA through Post-Polymerization Modification, SEC Data, and Solubility in Water

code	alcohol/amine	parent pVDMA	$M_{n,exp.}$[a] (kg/mol)	$M_{n,SEC}$[b] (kg/mol)	PDI[b]	cloud point[c] (°C)
p1	methanol (**1**)	**v3**	13.7	76.7	1.22	I
p2	di(ethylene glycol) methyl ether (**2**)	**v3**	20.6	86.4	1.21	S
p3	tri(ethylene glycol) methyl ether (**3**)	**v3**	24.1	88.1	1.21	S
p4	ammonia (**4**)	**v1**	13.9	50.8	1.22	S
p5	ethylamine (**5**)	**v1**	16.4	63.9	1.20	42.2
p6a	*n*-propylamine (**6**)	**v1**	17.6	62.2	1.15	I
p6b	*n*-propylamine (**6**)	**v4**	10.1	28.0	1.27	I
p6c	*n*-propylamine (**6**)	**v5**	4.2	19.0	1.26	7.9
p7a	*n*-butylamine (**7**)	**v1**	18.8	63.4	1.16	I
p7b	*n*-butylamine (**7**)	**v4**	10.8	28.3	1.26	I
p7c	*n*-butylamine (**7**)	**v5**	4.4	19.4	1.26	I
p8a	*n*-pentylamine (**8**)	**v1**	20.1	61.5	1.17	I
p8b	*n*-pentylamine (**8**)	**v4**	11.5	28.4	1.26	I
p8c	*n*-pentylamine (**8**)	**v5**	4.7	20.3	1.24	I
p9	*n*-hexylamine (**9**)	**v1**	21.3	64.4	1.28	I
p10a	isopropylamine (**10**)	**v3**	15.8	59.4	1.21	17.3
p10b	isopropylamine (**10**)	**v4**	10.1	28.3	1.27	20.9
p10c	isopropylamine (**10**)	**v5**	4.2	19.6	1.27	22.1
p11	*tert*-butylamine (**11**)	**v1**	18.8	63.3	1.18	I
p12	propargylamine (**12**)	**v1**	17.2	67.6	1.29	I
p13	dimethylamine (**13**)	**v1**	16.4	74.5	1.27	70.8
p14	diethylamine (**14**)	**v1**	18.8	85.1	1.25	24.4
p15	diethylaminoethylamine (**15**)	**v2**	21.8	n.d.[d]	n.d.	27.9
p16	glycinamine hydrochloride (**16**)	**v1**	18.9	73.2	1.26	S
p17	alaninamide hydrochloride (**17**)	**v1**	20.1	84.7	1.30	S
p18	2-aminobutyramide hydrochloride (**18**)	**v1**	21.4	87.0	1.35	S
p19	2-(2-aminoethoxy) ethanol (**19**)	**v1**	21.6	86.0	1.28	S
p20	di(ethylene glycol) methyl ether amine (**20**)	**v1**	22.9	58.4	1.27	S
p21	tri(ethylene glycol) methyl ether amine (**21**)	**v1**	26.7	61.0	1.29	S
p22	Jeffamine 600 (**22**)	**v1**	65.1	95.6	1.37	24.8
p23a	tetrahydrofurfurylamine (**23**)	**v2**	20.5	60.0	1.26	30.9
p23b	tetrahydrofurfurylamine (**23**)	**v5**	5.0	18.2	1.27	31.3
p24	morpholine (**24**)	**v2**	19.3	90.3	1.20	S

[a]Expected molecular weight calculated from molecular weight of precursor (determined by ^{1}H NMR spectroscopy) and weight of modified monomer units assuming full conversion. [b]Polystyrene equivalent molecular weight and polydispersity index determined by SEC. [c]Solubility in water, at a concentration of 5 g/L; S = soluble between 0 and 90 °C, I = insoluble between 0 and 90 °C; value = lower critical solution temperature type cloud point measured at a concentration of 5 g/L by turbidity (soluble below this temperature). [d]Not determined.

can be expected to be more hydrophobic than the methyl ester variant **p1** and likewise to be insoluble in water. We therefore prepared the di- and tri(ethylene glycol) methyl ether modified polymers **p2** and **p3**. Both the corresponding acrylate[61] and methacrylate[62] analogues show LCST behavior in water which was therefore also expected for the 2-acrylamido isobutyrate analogues derived from pVDMA. Both polymers, **p2** and **p3**, were, however, found to be soluble in water up to a temperature of 90 °C. Potentially, traces of water in the ethylene glycol reagents could have hydrolyzed pVDMA units producing hydrophilic acid groups increasing solubility of the copolymers. In the search for thermoresponsive homopolymers derived from pVDMA, we therefore next considered amines. Amines exhibit higher reactivity toward pVDMA than alcohols and water, thus reducing potential unwanted hydrolysis reactions. Poly(2-acrylamido isobutyramide), **p4**, derived from pVDMA **v1** and ammonia, showed temperature-independent solubility in water, indicating the strong ability of the amide functional groups to H-bond with water, compared to the methyl ester function of water insoluble polymer **p1**. In the series of *N*-*n*-alkyl-modified pVDMA products derived from **v1**, namely, **p5**, **p6a**, **p7a**, **p8a**, and **p9**, polymers were insoluble in water with a side chain length of or above three carbons. For the shortest tested *N*-*n*-alkylamine, ethylamine, the resulting polymer **p5** was found to show LCST behavior in water with a cloud point of 42 °C; see Figure 3. The 2-acrylamido isobutyramide analogue of pNIPAM, poly(isopropyl 2-acrylamido isobutyramide), **p10a**, with an $M_{n,exp.}$ of 15.8 kg/mol, also showed LCST behavior in water. With a cloud point of 17 °C **p10a** displayed a decreased solubility in water compared to pNIPAM with an LCST of 32 °C.[63] The difference in solubility between the *n*-propyl derivative, **p6a** (insoluble), and the isopropyl derivative, **p10a** (soluble below 17 °C), both with comparable $M_{n,exp.}$, was striking. Presumably, with a higher number of conformational isomers, the *n*-alkyl chain poses a greater entropic challenge for hydration by water molecules. Since LCST-type phase separation is driven by the gain of (temperature weighed) entropy when hydrating water molecules abandon the polymer chain, polymer molecules requiring an entropically less favorable (more structured) hydration sphere will have lower cloud points than less challenging molecules. In the case of **p6a** and **p10a**, we assume that the insoluble *n*-propyl species **p6a** has a theoretical cloud point below 0 °C making it insoluble in the observed temperature

dx.doi.org/10.1021/ma401096r | Macromolecules 2013, 46, 6475−6484

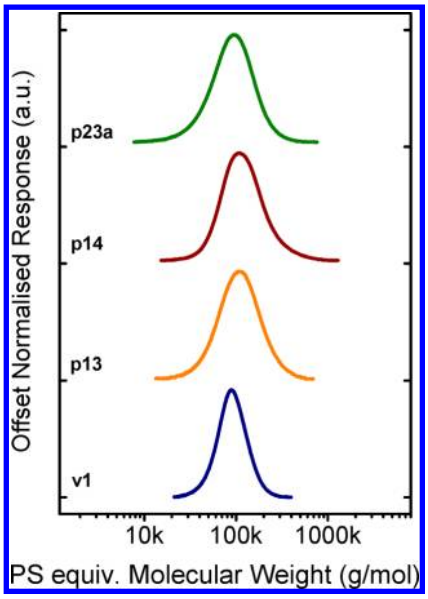


Figure 1. Representative SEC traces of pVDMA precursor **v1** (bottom) and polymers derived from **v1** by reaction with dimethylamine (**p13**), diethylamine (**p14**), and tetrahydrofurfurylamine (**p23a**) showing monomodal, nearly symmetrical molecular weight distributions.

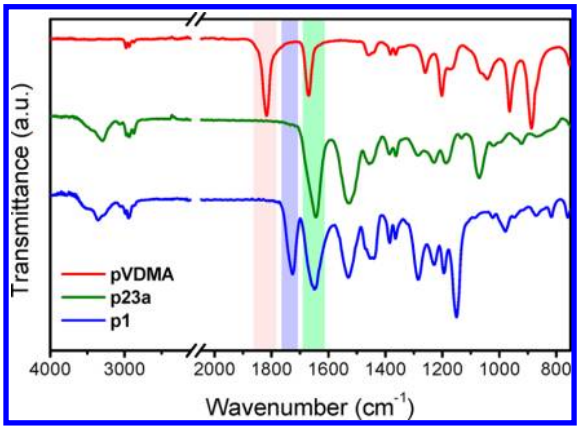


Figure 2. Representative FT-IR spectra of pVDMA **v1** (top), THF amine-modified pVDMA, **p23a** (middle), and methanol-modified pVDMA, **p1** (bottom), indicating complete conversions. The characteristic carbonyl C═O stretching bands of lactone (red), ester (blue), and amide (green, including azlactone C═N stretching in top spectrum) are emphasized by colored bars.

range. A similar trend exists for the acrylamide derivatives, with poly(*n*-propylacrylamide) showing a somewhat lower cloud point of 25 °C than the isopropyl isomer pNIPAM.[64] Poly(2-acrylamido isobutyramide)s with *tert*-butyl (**p11**) and propargyl (**p12**) side chains were found to be insoluble in water.

For a selection of amines, the influence of molecular weight on water solubility of the derived species was assessed. *n*-Propylamine (**6**), *n*-butylamine (**7**), *n*-pentylamine (**8**), and isopropylamine (**10**) were also reacted with precursors **v4** and **v5**, respectively. For the *n*-propyl derivatives, **p6a−c**, only the sample with the lowest $M_{n,exp.}$ of 4.2 kg/mol was soluble in cold water with a cloud point of 8 °C, suggesting again that the higher molecular weight sister polymers **p6a** and **p6b** ($M_{n,exp.}$ = 17.1 kg/mol and 10.1 kg/mol, respectively) had theoretical LCSTs below 0 °C and indicating an increased solubility with a

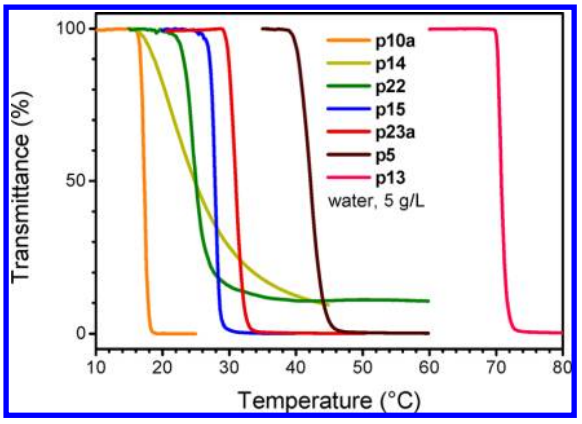


Figure 3. Temperature dependent transmittance of aqueous solutions of homopolymers found to exhibit LCST behavior. See Scheme 3 for corresponding structures.

decreasing molecular weight. For the homologues with *n*-butyl (**p7a−c**) and *n*-pentyl (**p8a−c**) side chains, however, even the lowest molecular weight species **p7c** ($M_{n,exp.}$ = 4.4 kg/mol) and **p8c** ($M_{n,exp.}$ = 4.7 kg/mol) were found to be insoluble in water. A molecular weight dependent LCST-type behavior was observed for the isopropyl derivatives, **p10a−c**. Recall that **p10a** with an $M_{n,exp.}$ of 15.8 kg/mol had a cloud point of 17 °C. Consistent with an increased solubility with decreasing molecular weight as observed for the *n*-propyl isomers, **p10b** ($M_{n,exp.}$ = 10.1 kg/mol) and **p10c** ($M_{n,exp.}$ = 4.2 kg/mol) had cloud points of 21 and 22 °C, respectively.

In addition to primary monoalkylamines, the secondary dialkylamines dimethylamine and diethylamine were also studied. Poly(*N*,*N*-dimethyl 2-acrylamido isobutyramide), **p13**, showed a sharp LCST transition at 71 °C. Although the constitutional isomer **p5** (with *N*-ethyl side chains, cloud point 42 °C) possesses an NH group expected to act as H-bond donor in water (thereby assisting solubility), **p13** with its *N*,*N*-dimethyl function showed a higher solubility in water. Presumably, similar to the above comparison of **p6** and **p10**, rotation of the *N*-ethyl groups gives rise to a larger effective hydrophobic volume, thus making it entropically less favorable to hydrate one ethyl group vs two methyl groups. The sister polymer of **p13**, **p14** carrying *N*,*N*-diethyl functionality had a lower cloud point of 24 °C, as to be expected for a more hydrophobic species, showing decreased solubility compared to the monoethyl species **p5** and higher solubility than the constitutional *n*-alkyl isomer **p7** (*N*-*n*-butyl groups, insoluble), in agreement with the above discussion. The turbidity curve of **p14**, however, showed a rather broad transition compared to the other thermoresponsive polymers, Figure 3, suggesting that the latter is, perhaps, less ideal for applications requiring a sharp thermal response. Similar to **p10** when compared with pNIPAM, the two *N*,*N*-dialkyl poly(2-acrylamido isobutyramide) species **p13** and **p14** showed lower solubility in water than the corresponding acrylamido analogues poly(*N*,*N*-dimethyl acrylamide) (soluble) and poly(*N*,*N*-diethyl acrylamide) (LCST of 33 °C).[65] A sharp LCST transition was observed for **p15** carrying diethylaminoethyl side chains with a cloud point of 28 °C in neutral water. A study exploiting the dual temperature/pH responsiveness of this species will be published elsewhere.

Polymers displaying water solubility over the entire temperature range from 0−90 °C were prepared from pVDMA by

dx.doi.org/10.1021/ma401096r | *Macromolecules* 2013, 46, 6475−6484

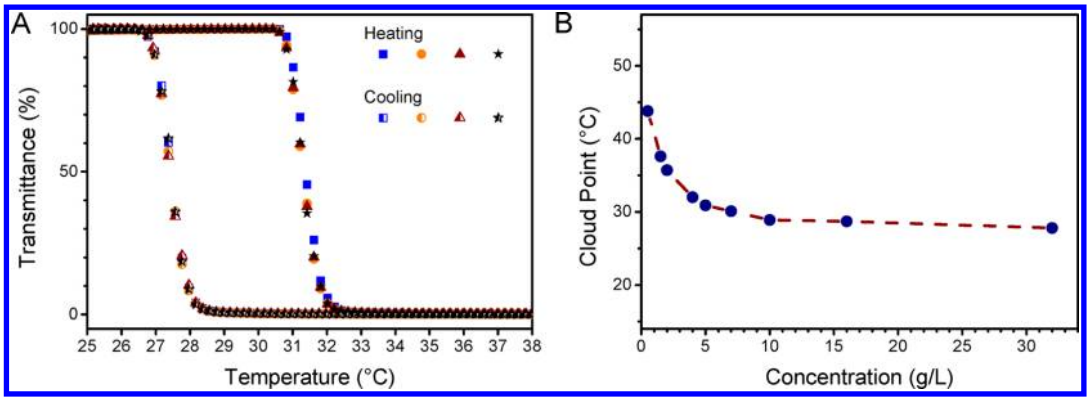


Figure 4. (A) Four heating/cooling cycles for THF amide functional polymer **p23a** in water showing sharp reproducible transitions with a hysteresis of ~4 °C. For clarity, individual data points are potted since curves overlap. (B) phase diagram of **p23a** in water showing a flat region above concentrations of ~5 g/L and the expected upward sloping for lower concentrations. Dashed line is added to guide the eye.

Table 3. Overview of Copolymers Prepared From reacting pVDMA v2 with a Mixture of THF Amine (23) and a Co-Amine

		% co-amine				
code	name	feed[a]	found[b]	M_n[c] (kg/mol)	PDI[c]	cloud point[d] (°C)
p(23/8$_{0.28}$)	*n*-pentylamine (**8**)	20	28	54.5	1.20	I
p(23/8$_{0.13}$)	*n*-pentylamine (**8**)	10	13	55.2	1.21	15.7
p(23/8$_{0.05}$)	*n*-pentylamine (**8**)	5	5	55.6	1.20	22.3
p(23/20$_{0.19}$)	di(ethylene glycol) methyl ether amine (**20**)	20	19	54.7	1.20	39.9
p(23/20$_{0.27}$)	di(ethylene glycol) methyl ether amine (**20**)	30	27	56.6	1.20	43.4
p(23/20$_{0.35}$)	di(ethylene glycol) methyl ether amine (**20**)	40	35	56.7	1.20	47.2

[a]Molar percentage of coamine in feed. [b]Molar percentage of *n*-pentyl or di(ethylene glycol) methyl ether side chains incorporated into copolymers determined by ^{1}H NMR. [c]Polystyrene equivalent molecular weight and polydispersity index determined by SEC. [d]cloud point at a concentration of 5 g/L in water determined by turbidity measurement; I = insoluble.

reaction with the three tested amide carrying amines glycinamide (**16**), alaninamide (**17**), and 2-aminobutyramide (**18**). Similar to the ethylene glycol ester species **p2** and **p3**, the corresponding amide versions **p20** and **p21** were fully water-soluble, reflecting the similar behavior found for the acrylamido species.[31] Formally substituting a methyl ether on **p20** for a hydroxyl end group gave 2-(2-hydroxyethoxy)ethylamine-functional polymer **p19**, which (with higher hydrophilicity than **p20**) was water-soluble at all tested temperatures. LCST behavior was, however, achieved by substituting the ethylene glycol side chains of **p20** and **p21** for a more hydrophobic poly(propylene glycol) chain using commercially available Jeffamine 600 (**22**). Polymer **p22** exhibited an LCST transition at 25 °C, with the transmittance not decreasing as far as other samples, however.

We next investigated two cyclic ethers, tetrahydrofurfuryl-amine (**23**) and morpholine (**24**). Poly(tetrahydrofurfuryl 2-acrylamido isobutyramide), **p23a**, derived from precursor **v2**, was found to show a sharp LCST transition at 31 °C. Although the morpholine-modified sister polymer **p24** exhibited a similar cyclic structure, it was fully water-soluble. This is less surprising when compared to the *N*,*N*-diethyl species **p14** (recall: LCST transition at 24 °C). Formally, the two ethyl "arms" of **p14**, which can be expected to rotate and make a hydrophobic contribution to the polymer's polarity, are "tied together" by the ether bond in **p24**. This undoubtedly reduces the hydrophobic nature of the side groups (in a way comparable to tetrahydrofuran, with its "arms tied", being water-soluble while diethyl ether with rotating "arms" is not) and introduces an H-bond acceptor, the ether oxygen, explaining an increased solubility of **p24** compared to that of **p14**.

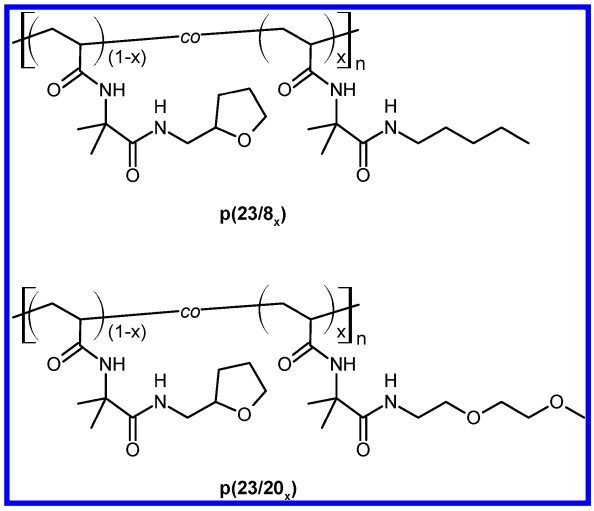
With a sharp LCST transition close to body temperature and simple derivation from pVDMA with a cheap commercially available amine, poly(tetrahydrofurfuryl 2-acrylamido isobutyramide), pTAI, **p23a**, was investigated in more detail. The transition was highly reproducible (see Figure 4a) and showed sharp transitions for both heating and cooling with a hysteresis of ~4 °C between the curves (at heating and cooling rates of 1 °C/min), very comparable to acrylamido-based thermoresponsive polymers.[31] Cloud points were determined for solutions with concentrations varying between 0.5 and 32 g/L and a phase diagram, Figure 4b, was plotted. The phase diagram showed the expected trend of cloud points increasing toward lower concentrations. For concentrations above 5 g/L (0.5 wt %), the phase boundary was rather flat making the macroscopic phase separation reliable and predictable in this region. The LCST, the minimum of this curve, appeared to lie at a concentration above 32 g/L. A sample with a lower molecular weight, **p23b**, derived from precursor **v5** and having an $M_{n,exp}$. of 5.0 kg/mol showed a very comparable cloud point only 0.4 °C higher than **p23a**.

pTAI-Based Copolymers. As mentioned above, an important advantage of the postpolymerization modification approach is that statistical copolymers can easily be prepared that have essentially identical degrees of polymerization to the parent polymer. This fact was exploited to demonstrate that the phase separation temperature of **p23a** can easily be tuned by reacting pVDMA with mixtures of tetrahydrofurfurylamine (THF amine, **23**) with *n*-pentylamine (**8**) or di(ethylene glycol) methyl ether (DEG) amine (**20**). Feed ratios of coamines, molar composition of resulting copolymers, and SEC results are summarized in Table 3. In all cases, FTIR

dx.doi.org/10.1021/ma401096r | *Macromolecules* 2013, 46, 6475−6484

spectroscopy and ^{1}H NMR spectroscopy indicated complete conversion of the azlactone cycles, with the latter method serving well to calculate the molar composition of copolymers. Reactions containing 1.5 eq. of total amines with 5%, 10%, and 20% of this amount being amine **8**, and with 20%, 30%, and 40% of total amine feed being amine **20** (remainder THF amine), were run. *n*-Pentylamine appeared to have a higher reactivity toward the azlactone groups compared to THF amine, with a higher relative amount of *n*-pentyl groups being incorporated into the copolymers. Contrary to that, DEG amine (**20**) was slightly less reactive than THF amine, with copolymers containing a lower percentage of DEG chains than the feed ratio. Apparent molecular weights determined by SEC increased with a decreasing content of *n*-pentyl side chains and increased with an increasing amount of DEG side chains, as expected for the real molecular weights of the copolymers. While polymer **p(23/8$_{0.28}$)** (containing 28 mol % of *n*-pentyl side chains; see Scheme 4) was insoluble in water, all other copolymers displayed LCST behavior; see Figure 5. As was to be expected for copolymers with higher hydrophobic content, solubility in water decreased with an increasing content of *n*-pentyl side chains with **p(23/8$_{0.05}$)** and **p(23/8$_{0.13}$)** having cloud points of 22 and 16 °C, respectively. The hydrophilic DEG side chains, on the other hand, increased solubility of the copolymers with cloud points increasing with an increasing DEG content. The phase separation temperature of the copolymer series appeared to be somewhat less sensitive to the introduction of DEG side chains, with an increase of DEG content of ∼8% only increasing the cloud point by 3−4 °C. Polymers **p(23/20$_{0.19}$)**, **p(23/20$_{0.27}$)**, and **p(23/20$_{0.35}$)** had cloud points of 40 °C, 43 °C, and 47 °C, respectively. A low variation of the cloud point with a controllable difference of composition is an important prerequisite for a precise tuning of the phase separation temperature of **p23**. Together with an easy room temperature synthesis from pVDMA, this makes pTAI a promising thermoresponsive platform for the development of novel smart materials from pVDMA.

Scheme 4. Structures of Copolymers Based on THF Amine-Modified pVDMA Found to Show LCST Behavior[a]



[a]For details, see Table 3.

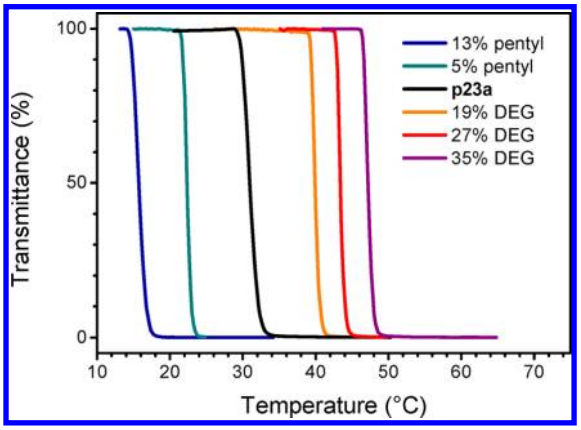
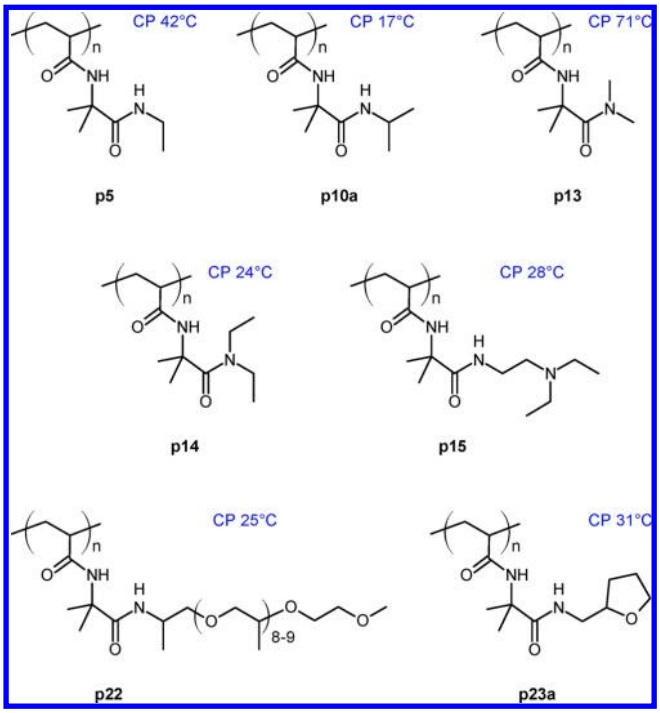


Figure 5. Transmittance plots for copolymers containing THF amide side chains and varying amounts of *n*-pentyl or di(ethylene glycol) methyl ether (DEG) side chains together with a **p23a** homopolymer.

Scheme 3. Structures of pVDMA-Derived Homopolymers Found to Show LCST Behavior with Cloud Points Measured on Aqueous Solutions at a Concentration of 5 g/L



CONCLUSION

Transforming reactive polymeric scaffolds into multifunctional materials with well-defined properties has developed into a very expedient synthetic tool in polymer chemistry. The aqueous solution behavior of such products is a key factor for their applicability as advanced materials in a wide range of research fields. In this study we identified commercially available alcohols (e.g., di(ethylene glycol) monomethyl ether) and amines (e.g., ammonia) that transform pVDMA into water-soluble products, as well as alcohols (e.g., methanol) and amines (e.g., hexylamine) that transform pVDMA into water-insoluble products. Reactions of pVDMA with alcohols in the presence of a base must be carried out under anhydrous conditions to avoid hydrolysis of azlactone cycles yielding highly soluble carboxylates. Generally, for products species

dx.doi.org/10.1021/ma401096r | *Macromolecules* 2013, 46, 6475−6484

modified with amines, *N*-alkyl and *N*,*N*-dialkyl poly(2-acrylamido isobutyramide)s exhibited decreased solubility in water compared to the corresponding acrylamido analogues. *N*,*N*-Dialkyl species were better soluble than the constitutional isomers with an *N*-monoalkyl group of double length. Of a selection of products exhibiting an LCST in water, the species obtained from reacting pVDMA with tetrahydrofurfurylamine is, perhaps, most interesting, as its sharp phase separation occurs close to body temperature, is highly reproducible, and can easily be tuned. It is expected that the findings presented in this study will further advance pVDMA as a versatile platform for the development of novel smart materials.

■ ASSOCIATED CONTENT

Supporting Information

Exemplary ^{1}H NMR spectra of modified polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: (P.J.R.) P.Roth@unsw.edu.au.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

P.J.R. acknowledges the Australian Research Council (ARC) for funding through a Discovery Early Career Researcher Award (DE120101547).

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