



pH-, thermo- and electrolyte-responsive polymer gels derived from a well-defined, RAFT-synthesized, poly(2-vinyl-4,4-dimethylazlactone) homopolymer via one-pot post-polymerization modification

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ABSTRACT

Well-defined stimulus-responsive polymer gels were prepared from poly(2-vinyl-4,4-dimethylazlactone) (PVDMA) via one-pot post-polymerization modification. VDMA homopolymers were reacted with diamine crosslinking agents and functional 1° or 2° amines to form polymer gels that swelled in organic solvents and, in many cases, aqueous solutions. A series of functional amine reagents, including *N,N*-dimethylethylenediamine (DMEDA), *N,N*-diethylethylenediamine (DEEDA), morpholine, 3-morpholinopropylamine (MPPA) and tetrahydrofurfurylamine (THFA), were chosen as functional amines to produce polymer gels containing environmentally sensitive species. ¹³C solid-state NMR and FTIR spectroscopic measurements confirmed complete conversion of the reactive scaffolds. pH-dependent swelling behavior at ambient temperature was observed in DMEDA-, DEEDA- and MPPA-modified hydrogels. Kinetic studies showed the swelling behaviors of DMEDA-modified hydrogels were regulated by cross-linker type and concentration in acidic water (pH = 4) at ambient temperature. The swelling ratio of hydrogels modified by DEEDA, MPPA and THFA also depended strongly on temperature, indicating successful synthesis of thermoresponsive gels. Furthermore, the concentration of added sodium sulfate played a significant role with respect to the swelling properties of MPPA-modified hydrogels. These smart materials may be of interest in the biomedical field as well as in other applications.

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1. Introduction

A gel may be defined as a three-dimensional network consisting of a liquid phase, either an organic solvent or aqueous solution, held in place by long-chain molecules

[1]. Polymer gels have received, and are still receiving, considerable attention due to their soft nature, excellent mechanical strength and capacity for sequestering small molecules [2–6]. Stimulus-responsive polymer gels are well-known “smart” materials that are capable of undergoing reversible volumetric phase transitions in response to changes in the environment [7,8]. Factors such as mechanical forces [9], pH [10–13], heat [14–18], humidity [19] and light [20,21] can induce phase transitions depending on the chemical composition of a given polymer gel. The incorporation of stimulus-responsive functionality in the fabrication of polymer gels has resulted in many interesting

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uses for such materials, including in protein delivery [22], sensors and actuators [23], and gating in microfluidic devices [24].

One of the most widely studied group of stimulus-responsive materials are those based on the methacrylic family of polymers containing tertiary amino functionality in the side chain [25]. This includes (co)polymers containing building blocks such as poly[2-(dimethylamino)ethyl methacrylate] (PDMAEMA) [26], poly[2-(diethylamino)ethyl methacrylate] (PDEAEMA) [27] and poly[2-(*N*-morpholino)ethyl methacrylate] (PMEMA) [26,28–32]. PDMAEMA and PDEAEMA have well-documented pH- and thermo-responsive properties in aqueous media. PDEAEMA, for example, is tunably hydrophilic/hydrophobic being readily water-soluble at low pH when the tertiary amine groups are protonated but water-insoluble when deprotonated. Such reversible pH-induced aqueous solubility has been exploited in the design and synthesis of AB diblock copolymers capable of reversible self-assembly in water as a function of solution pH.

With regards to PDMAEMA, the value of the apparent pK_a of the conjugate acid has been reported to vary between 6.2 and 7.8 [33]. As a weak cationic polyelectrolyte, above its apparent pK_a when PDMAEMA is largely deprotonated, it remains water-soluble but does exhibit inverse temperature dependent solubility characteristics with a reported lower critical solution temperature (LCST) in the range of ca. 32–47 °C, the exact value being dependent on the molecular weight of the polymer. Like PDEAEMA, when protonated, PDMAEMA is formally a weak cationic polyelectrolyte and loses its LCST characteristics. PMEMA homopolymers are versatile stimulus-responsive building blocks that are sensitive to both pH and temperature. The conjugate acid has a pK_a of 4.9 and LCSTs of homopolymers have been reported to lie between 34 °C and 47 °C at pH 7, again the exact value depending on the molecular weight of the homopolymer [34]. Its general aqueous solution behavior is similar to that exhibited by PDMAEMA. However, PMEMA can also be readily precipitated (salted out) from aqueous solution upon the addition of certain electrolytes, such as Na_2SO_4 [28], adding an extra level of complexity and potential responsive behavior. These few examples highlight the versatility and rich aqueous 'smart' behavior of copolymers containing specific tertiary amino functional groups as pendent side groups.

Post-polymerization modification is a particularly attractive strategy for synthesizing smart (co)polymers since it facilitates the introduction of a wide variety of functional groups (some of which may not be stable during polymerization and thus cannot be introduced directly) from a single precursor to suit many target applications [3,35–39]. Recently, there has been significant interest in the use of reactive (co)polymers such as those based on poly(2-vinyl-4,4-dimethylazlactone) (PVDMA) and poly(pentafluorophenyl (meth)acrylate) (PPFP(M)A) as scaffolds facilitating the straightforward preparation of a library of novel materials [30,39–46]. PVDMA precursors in particular show an extremely high reactivity toward primary amines, as well as alcohols and thiols, at ambient temperature via a nucleophilic ring-opening reaction [47]. For example, Zhu et al. [40] recently reported the

preparation of a series of novel thermoresponsive (co)polymers via the modification of PVDMA-based precursors with a series of low molecular weight 1° and 2° amines as well as several alcohols. From a library of ca. 30 new materials, 11 exhibited inverse temperature solubility behavior in water with measured cloud points spanning the range 7.9–70.8 °C. The same team [30] also reported the synthesis of VDMA-based block copolymers with *N,N*-dimethylacrylamide and *N*-isopropylacrylamide as comonomers. Reaction of the VDMA repeat units with *N,N*-dimethylethylenediamine (DMEDA), *N,N*-diethylethylenediamine (DEEDA) or picolylamine (PA) yielded novel thermo- and pH-responsive block copolymers that were capable of undergoing reversible self-assembly in aqueous media as a function of changes in temperature or pH. Finally, and of specific relevance to the work reported herein, Zimmermann and co-workers [48] previously reported the synthesis of hydrogel supports for in vitro cell growth using azlactone-modified (meth)acrylamidopeptide macromonomers. Reaction of a poly(ethylene glycol)-based diamine with an azlactone monomer gave a difunctional bisamide species. Radical copolymerization, in aqueous media, of this difunctional species with a gelatin-based monofunctional monomer obtained from the reaction of gelatin with a polymerizable azlactone gave novel non-cytotoxic hydrogels capable of supporting the growth of fibroblasts.

Herein, we describe the efficient one-pot preparation of pH-, temperature- and electrolyte-sensitive polymer gels derived from a VDMA homopolymer, prepared by RAFT radical polymerization, employing a diamine crosslinking agent and various functional 1° and 2° amines via post-polymerization modification. The functional amines employed were DMEDA, DEEDA, morpholine, 3-morpholinopropylamine (MPPA) and tetrahydrofurfurylamine (THFA). ^{13}C solid-state NMR and FTIR spectroscopic measurements confirmed formation of the expected structures. We demonstrate that the swelling behavior of the resulting polymer gels strongly depends on one or several triggers: pH, temperature or added electrolyte. We also identify how the crosslinker type and concentration influence the swelling kinetics of the modified hydrogels under acidic conditions. These smart polymer gels have the potential to find applications as biomedical devices, in tissue engineering and in microfluidic devices.

2. Materials and methods

2.1. Materials

All reagents were purchased from the Sigma–Aldrich Chemical Company and used as received unless otherwise noted. Poly(2-vinyl-4,4-dimethylazlactone) (PVDMA) was prepared via RAFT polymerization according to a procedure described elsewhere [30].

2.2. Preparation of smart PVDMA polymer gels

The smart PVDMA polymer gels were prepared via post-polymerization modification of a PVDMA homopolymer

($\bar{D}_M = \bar{M}_w/\bar{M}_n = 1.16$, $\bar{M}_n = 13,200$) with various diamine crosslinkers and functional 1° and 2° amines. A general procedure for the preparation of a smart PVDMA-based polymer gel is as follows:

A solution of 0.08 g PVDMA in THF (8 wt%) was stirred rapidly while 2 μ L of 2,2'-(ethylenedioxy)bis(ethylamine) crosslinking reagent was injected into the solution. The reaction mixture was then continuously stirred at ambient temperature for 30 min until gel formation was observed. Subsequently, a solution of *N,N*-dimethylethylenediamine (90 μ L, 0.72 mmol) in 5 mL THF was added to the reaction vessel containing the PVDMA gel and the reaction was allowed to proceed under continuous stirring at ambient temperature overnight. The final PVDMA-based polymer gel was purified via Soxhlet extraction with chloroform for 24 h to completely remove residual small molecule reactants. The gel was subsequently dried *in vacuo* at 60 °C for 2 days.

2.3. Characterization of the polymer gels

¹³C solid-state CP-TOSS NMR spectroscopy was employed to characterize the structure of the modified PVDMA-derived polymer gel. The measurements were performed on a Bruker Avance III (300 MHz) spectrometer. The spectrum was calibrated using ¹³C labeled glycine with a chemical shift value of $\delta = 176.0$ ppm at the carbonyl position. The measurement was performed utilizing 12 kHz MAS, a 3 s recycle delay, 10 k scans and a 2 ms ramped crosspolarization time at 25 °C.

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

In order to study the swelling kinetics, dried polymer gel samples of known weights, W_d , were immersed in acidic water (pH = 4) for predefined time intervals at 25 °C. The swollen gels were periodically removed from the acidic solution and excess water removed using a filter paper. The weights of the swollen polymer gels, W_w , were recorded and the swelling ratio were calculated according to Eq. (1):

$$\text{Swelling ratio} = (W_w - W_d)/W_d \quad (1)$$

To assess the temperature-dependent equilibrium swelling ratio, the dry samples were placed in basic water (pH = 10) at a predetermined temperature between 5 °C and 95 °C for 24 h. The pH-dependent swelling behavior was evaluated in a similar fashion; the polymer gel samples were equilibrated in aqueous media of a predetermined pH range between 3 and 12 at 25 °C for 24 h. In order to investigate the electrolyte-dependent swelling behavior, the polymer samples were immersed in basic water (pH = 8) with a predetermined Na₂SO₄ concentration (up to 1.2 M) at 25 °C for 24 h.

To investigate the reversibility of the temperature-responsive swelling behavior, the THF amine-modified PVDMA-based dry sample was placed in basic water (pH = 10) at 5 °C for 24 h before switching to 95 °C for an additional 24 h. This heating-cooling cycle was repeated

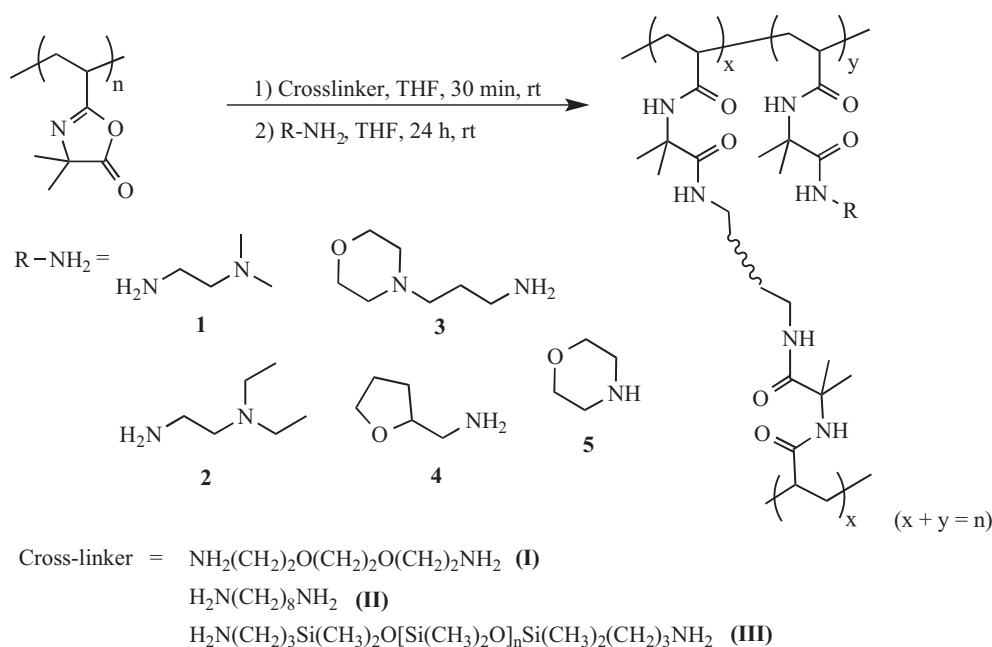
three times and the results are based on multiple trials (error < 2%) (see Supporting information).

To demonstrate that the PVDMA-based hydrogels possessed responsive properties, a series of swelling ratio measurements at different pH, temperature and salt concentrations were performed on individual gel samples as well as a single gel sample (to confirm that the gel samples possess uniform properties based on their assumed homogeneous structure).

3. Results and discussion

3.1. Preparation of modified PVDMA polymer gels

A VDMA homopolymer was synthesized via RAFT polymerization following a literature procedure [30]. The average molecular weight, as estimated by end-group analysis utilizing ¹H NMR spectroscopy, was 13,200 and the SEC-determined dispersity ($\bar{D}_M = \bar{M}_w/\bar{M}_n$) was 1.16. In the first step, a sample of the VDMA homopolymer was subjected to post-polymerization modification, employing THF as solvent, with three different crosslinking agents at varying mol fractions based on VDMA repeat units. The crosslinkers employed were 2,2'-(ethylenedioxy)bis(ethylamine), 1,8-diaminooctane and bis(aminopropyl)-terminated polydimethylsiloxane (PDMS) ($\bar{M}_n \approx 2500$). The short-chain diamine crosslinker, 2,2'-(ethylenedioxy)bis(ethylamine) was chosen to provide some hydrophilic character to the polymer gel systems whereas the more hydrophobic 1,8-diaminooctane was anticipated to give gels with more hydrophobic character and the diamine-functional PDMS was chosen to facilitate the formation of novel organogels. As expected, the concentration of reactive PVDMA homopolymer played an important role in the efficient formation of polymer gels with desirable mechanical properties [49]. Preliminary experiments indicated the minimum concentration of PVDMA required to form a gel was 8 wt%, and as such all further gel-forming reactions were conducted at 8 wt%. Under these conditions, gel formation occurred rapidly after the addition of the difunctional amine crosslinker at between 5 and 54 mol% based on VDMA repeat units. Following gel formation, a 1° or 2° amine species, Scheme 1, was added, in 2-fold excess based on remaining VDMA units, into the gel mixture and allowed to react at ambient temperature overnight with continuous stirring. The 1° amines *N,N*-dimethylethylenediamine (DMEDA), *N,N*-diethylethylenediamine (DEEDA), 3-(*N*-morpholino)propylamine (MPPA), tetrahydrofurfurylamine (THFA) and the 2° amine morpholine (MORP) were employed as functionalization agents. We hypothesized that employing these specific amines as functionalization agents to give the modified polymer gels, **g1–g7** Table 1, would yield materials with the potential to exhibit interesting stimulus-responsive properties in aqueous media in a manner similar to those exhibited by the 3° amine-containing (meth)acrylic species highlighted above and the recently reported 3° amine functional PVDMA-derived (co)polymers [30,40]. After extensive Soxhlet extraction followed by drying *in vacuo*, the modified PVDMA gel samples were obtained as white powders in



Scheme 1. Conditions employed for the preparation of the modified PVDMA hydrogels and organogels by sequential reaction with various crosslinkers followed by reaction with different small molecule primary and secondary amines at ambient temperature.

Table 1

List of polymer hydrogels (**g0–g5**) and organogels (**g6–g7**) prepared from a PVDMA homopolymer via one-pot post-polymerization modification, type of reagent and crosslinker, feed ratio of crosslinking agent, product yield and, where relevant, their observed stimulus-responsiveness in aqueous media.

Code	Reagent	Cross-linker	Cross-linker (%) ^b	Yield (%) ^c	Stimulus-responsiveness
g0	–	2,2'-(Ethylenedioxy)bis(ethylamine) (I)	100	33.9	–
g1a	<i>N,N</i> -Dimethylethylenediamine (1)	2,2'-(Ethylenedioxy)bis(ethylamine) (I)	5	68.9	pH
g1b	<i>N,N</i> -Dimethylethylenediamine (1)	2,2'-(Ethylenedioxy)bis(ethylamine) (I)	10	62.3	pH
g1c	<i>N,N</i> -Dimethylethylenediamine (1)	2,2'-(Ethylenedioxy)bis(ethylamine) (I)	33	79.4	pH
g1d	<i>N,N</i> -Dimethylethylenediamine (1)	2,2'-(Ethylenedioxy)bis(ethylamine) (I)	54	69.7	pH
g2	<i>N,N</i> -Diethylethylenediamine (2)	2,2'-(Ethylenedioxy)bis(ethylamine) (I)	10	77.3	pH, temperature
g3	3-Morpholinopropylamine (3)	2,2'-(Ethylenedioxy)bis(ethylamine) (I)	10	62.4	pH, temperature, salt
g4	Tetrahydrofurfurylamine (4)	2,2'-(Ethylenedioxy)bis(ethylamine) (I)	10	63.4	Temperature
g5a	<i>N,N</i> -Dimethylethylenediamine (1)	1,8-Diaminooctane (II)	5	92.6	–
g5b	<i>N,N</i> -Dimethylethylenediamine (1)	1,8-Diaminooctane (II)	33	89.1	–
g5c	<i>N,N</i> -Dimethylethylenediamine (1)	1,8-Diaminooctane (II)	54	86.0	–
g6a^a	<i>N,N</i> -Dimethylethylenediamine (1)	Poly(dimethylsiloxane), bis(3-aminopropyl) terminated (III)	5	65.7	–
g6b^a	<i>N,N</i> -Dimethylethylenediamine (1)	Poly(dimethylsiloxane), bis(3-aminopropyl) terminated (III)	10	66.8	–
g7a^a	Morpholine (5)	Poly(dimethylsiloxane), bis(3-aminopropyl) terminated (III)	5	60.8	–
g7b^a	Morpholine (5)	Poly(dimethylsiloxane), bis(3-aminopropyl) terminated (III)	25	59.2	–

^a Organogels swell in solvents such as THF and chloroform.

^b Molar percentage of crosslinking reagents in feed.

^c Yield refers to recovered material based on total amount of PVDMA, crosslinker and reagents: $\text{yield}\% = \frac{\text{Mass(RecoveredMaterial)}}{\text{Mass(PVDMA + Crosslinker + Reagent)}} \times 100\%$.

relatively high yields of approximately 70% with the exception of the THFA-modified gel, which had a somewhat lower yield. Additionally, unmodified polymer gel **g0** was prepared and employed as a control sample.

Even though the body of literature dealing with smart hydrogels is growing there are still remarkably few reports of multi-stimuli responsive gels [50–52]. To demonstrate the versatility of our approach, amine-functionalized organogels **g6–g7** were prepared via one-pot post-polymerization modification. These organogels readily swell in THF and chloroform. In the case of organogel **g6a**, modified with DMEDA and 5% crosslinker, more pronounced

swelling characteristics were found compared to the morpholine-modified gel sample **g7a** in THF and chloroform (see SI). However, the swelling behavior of these smart materials in response to changes of surrounding environment is unclear and we are currently investigating this in more detail.

3.2. Characterization of the copolymer gels

Basic structural characterization of the modified gels was accomplished using a combination of ¹³C solid-state NMR and FTIR spectroscopies. As a representative example,

Fig. 1 shows the solid-state ^{13}C NMR spectrum of the modified PVDMA gel, **g2**, obtained from the reaction of PVDMA with *N,N*-diethylethylenediamine (DEEDA) and 10 mol% 2,2'-(ethylenedioxy)bis(ethylamine) as the crosslinker. The resonance at $\delta = 175.2$ ppm associated with the carbon atoms of the amide carbonyl groups (CONH) is clearly distinct. The peak at $\delta = 69.3$ ppm, assigned to the carbon chains ($-\text{CH}_2-\text{O}-\text{CH}_2-$) of the ethylenedioxy groups associated with the crosslinker, confirms successful post-polymerization modification of the parent PVDMA polymer. Another significant peak at $\delta = 56.8$ ppm is associated with the carbon atoms from both ethylenedioxy ($-\text{NH}-\text{CH}_2-\text{CH}_2-\text{O}$) carbons and diethylethylenediamine ($-\text{CH}_2-\text{N}(-\text{CH}_2-\text{CH}_3)_2$) carbons. A small sharp peak at $\delta = 45.0$ ppm represents the quaternary carbons ($-\text{COO}-\text{C}(\text{CH}_3)_2-$) that are present after the ring opening reaction. The neighboring peak at $\delta = 40.4$ ppm can be assigned to carbon chains of the polymer backbone as well as the diethylethylenediamine ($-\text{CH}_2-\text{CH}_2-\text{N}(-\text{CH}_2-\text{CH}_3)_2$) carbons. The two split peaks at $\delta = 27.1$ ppm and $\delta = 23.5$ ppm are representative of carbon atoms of ($-\text{COO}-\text{C}(\text{CH}_3)_2$) methyl groups near the quaternary carbons and those ($-\text{CH}_2-\text{N}(-\text{CH}_2-\text{CH}_3)_2$) carbons from *N,N*-diethylethylenediamine, respectively. Collectively, these data confirm the formation of the anticipated functional gel.

The PVDMA homopolymer precursor and the modified hydrogels were also characterized by FTIR spectroscopy to further confirm their anticipated chemical structure. Fig. 2 shows the recorded FTIR spectra for the PVDMA homopolymer, unmodified polymer gel **g0** and tertiary amine-modified gels **g1a**, **g2**, **g3**, **g4**, **g7a**. In the absorbance spectrum of PVDMA, weak bands at 2989, 2939 and

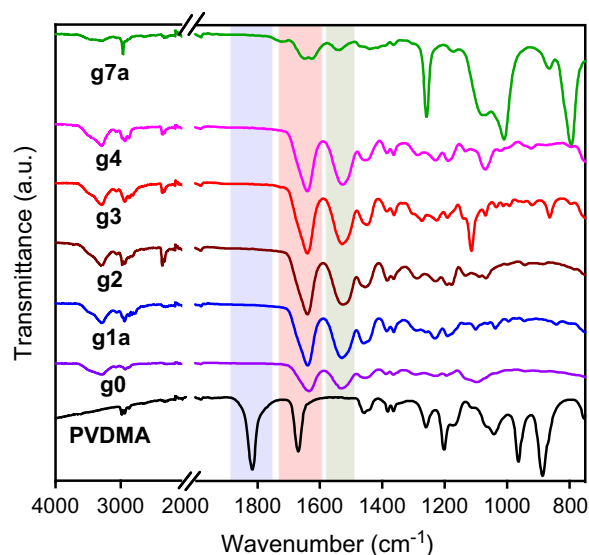


Fig. 2. FT-IR spectra of PVDMA homopolymer (**PVDMA**, black), unmodified (**g0**, purple), DMEDA- (**g1a**, blue), DEEDA- (**g2**, brown), MPPA- (**g3**, red), and THFA-modified PVDMA gels (**g4**, pink), with 2,2'-(ethylenedioxy)bis(ethylamine) as crosslinking agent and MORP-modified PVDMA organogel (**g7a**, green) with bis(3-aminopropyl) terminated polydimethylsiloxane as the crosslinking agent. The characteristic carbonyl $\text{C}=\text{O}/\text{C}=\text{N}$ stretching bands of the azlactone (blue), ester (red) and amide (green) are marked by colored columns. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2864 cm^{-1} are observed which can be associated with the methyl groups on the azlactone ring and the methylene and methine groups on the polymer backbone respectively.

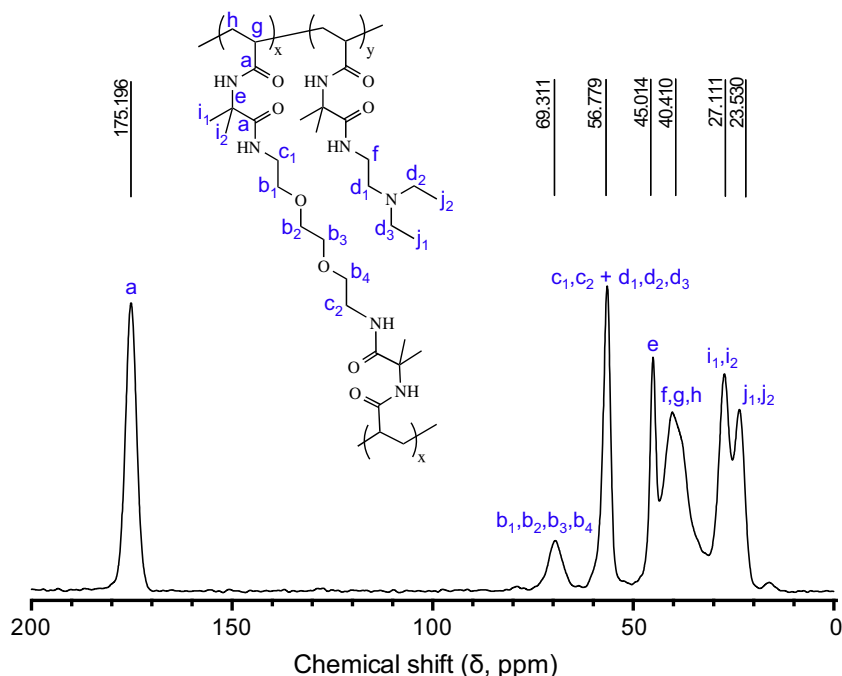


Fig. 1. Solid state ^{13}C NMR spectrum of the polymer gel, **g2**, derived from PVDMA by reaction with *N,N*-diethylethylenediamine (DEEDA) and 10 mol% 2,2'-(ethylenedioxy)bis(ethylamine) as the crosslinking agent.

In the carbonyl region, the characteristic lactone C=O and imine C=N stretching bands appear at 1822 and 1672 cm^{-1} respectively. The quantitative nature of the ring opening modification in the PVDMA polymer gels, **g0**, **g1a**, **g2**, **g3**, **g4** and **g7a**, is evident from the complete disappearance of the distinctive C=N imine band and the clear appearance of amide bands at ~ 3290 (N–H stretch), ~ 1640 (amide C=O stretch) and ~ 1530 cm^{-1} (N–H bend). Furthermore, the increase of the absorbance at ~ 2970 cm^{-1} , compared to the PVDMA reactive precursor, suggests the presence of further methylene groups in the modified polymer gels. In addition, the absorbance spectrum of the MPPA-modified polymer gel, **g3**, showed a strong absorbance at 1116 cm^{-1} attributed to the stretching C–O–C band of the morpholine ring. Moreover, the spectrum of the MORP-modified poly(dimethylsiloxane)-crosslinked PVDMA organogel, **g7a**, possesses characteristic peaks at ~ 1260 (CH_3 symmetric bend in Si– CH_3), ~ 1013 (Si–O–Si stretching) and ~ 798 cm^{-1} (Si–C stretching and CH_3 rocking) [53].

3.3. Stimulus-responsive properties of the tertiary-amine modified polymer gels

The small molecule amines employed as functionalization agents after initial crosslinking were chosen based on the hypothesis that their associated tertiary amine functional groups would impart ‘smart’ behavior to the polymer gels. Specifically, and based on our prior work [30,40], it was anticipated that incorporation of DMEDA and DEEDA would confer pH- and temperature-responsiveness, THFA thermal responsiveness and MPPA pH, thermal and electrolyte responsive behavior. Unlike discreet (co)polymers in homogeneous solution, such ‘smart’ characteristics in the gels would manifest in the swelling behavior of the individual hydrogels in aqueous media as a function of the applied stimulus.

3.3.1. pH-dependent swelling properties

Swelling ratios of ‘smart’ polymer gels, **g1b**, **g2**, **g3**, were measured to establish the effect of pH on hydrogels containing tertiary amines (DMEDA, DEEDA and MPPA) with established pH-responsive properties. All samples were immersed in aqueous solutions with pH's ranging from 3 to 12 at 25 °C for 24 h to allow the materials to approach their equilibrium state. Fig. 3 shows the swelling ratio results for unmodified hydrogel **g0** and modified hydrogels **g1b**, **g2** and **g3** containing 10 mol% 2,2'-(ethylenedioxy)bis(ethylamine) crosslinker respectively. Broadly, the swelling ratio of these tertiary amine-modified polymer gels decreased with increasing solution pH while unmodified polymer gel **g0** exhibited a small negligible volume transition over the entire pH range. Among these, the DMEDA-modified product **g1b** exhibited the largest volume transition from a swelling ratio of 77–21 upon changing the solution pH from 4 to 10. The inset image shows the size change of DMEDA-modified polymer gel in acidic and neutral water. Interestingly, above pH 4 there is a monotonic decrease in the swelling ratio up to a pH of 10 after which there is no apparent change.

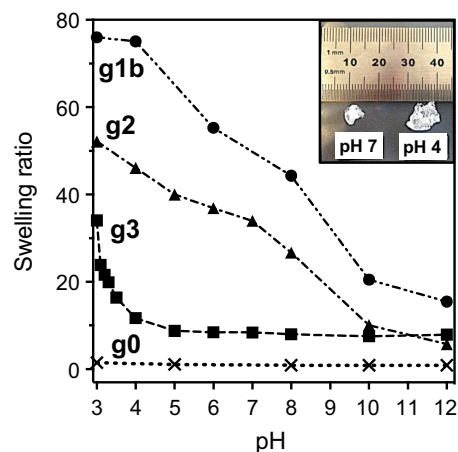


Fig. 3. pH-dependent swelling ratio of unmodified (×, **g0**) and modified PVDMA polymer gels by reacting with (●, **g1b**) DMEDA, (▲, **g2**) DEEDA, and (■, **g3**) MPPA. All the modified PVDMA gels were prepared with 10 mol% crosslinker. All measurements were performed in aqueous media at 25 °C and equilibrated for 24 h. Inset image illustrates a drastic size change of DMEDA-modified hydrogel in neutral and acidic water after 24 h.

The DEEDA-functionalized sample **g2** presented similar pH-dependent behavior although the swelling/contraction characteristics were less pronounced compared to the DMEDA hydrogel. However, **g2** still exhibited an essentially linear decrease in its swelling/contraction characteristics up to pH 12. Such a difference in swelling characteristics between dimethyl vs. diethyl derivatives is consistent with our recent findings regarding the significant difference in cloud points for DMEDA- vs. DEEDA-modified VDMA homopolymers, which is attributed to the significantly more hydrophilic nature of DMEDA side chain groups [30,40]. The swelling/contraction behavior of the MPPA-modified polymer gel, **g3**, with 10% crosslinker, exhibited very different behavior compared to **g1b** and **g2**.

For any given pH the maximum swelling ratio of MPPA-modified PVDMA gel **g3** is significantly lower than **g1b** or **g2**. However, and in stark contrast to **g1b** and **g2**, the swelling ratio drops dramatically over a very narrow pH range (between ca. 3 and 4) after which it plateaus and does not change over the remainder of the examined pH values. Such distinct differences in swelling/contraction behavior highlight how structurally small changes in the chemical nature of pendent functional groups can influence the bulk behavior of hydrogels. The shrinking behavior of these hydrogels can be rationalized in terms of the various degrees of ionization of the pendent 3° amine groups and the resulting electrostatic repulsions coupled with the changes in osmotic pressure due to the changes in the concentration of negatively charged counterions. All gels are expected to be in their most swollen state at low pH [54] where the majority of 3° amino groups are in their protonated cationic form with the gels also containing the highest concentration of counterions. As the solution becomes more basic both of these features decrease leading to a decrease in the swelling. The most

remarkable feature with this series of three hydrogels, however, is the rapid change associated with the swelling/deswelling of the morpholino functional material **g3**. This material reaches its plateau-swelling ratio at ca. pH 5, vs. ca. 10 for **g1b** and **g2**.

Rapid swelling and shrinkage kinetics triggered by a specific external stimulus is clearly of practical interest. The pH-dependent swelling/contraction phenomenon of modified PVDMA-hydrogels raises another interesting question. Specifically, the effect of cross-linker type, and density, on the pH-dependent swelling kinetics of these novel functional polymer gels is not known. To address this question, DMEDA-modified polymer gels with two different types of crosslinker and at various crosslinking concentrations were exposed to acidic water (pH 4) at ambient temperature for varying lengths of time, and the rate and degree of swelling of the gel samples quantified using Eq. (1) (see Fig. 4). The modified polymer gels were prepared using 5, 33 or 54 mol% of 2,2'-(ethylenedioxy)bis(ethylamine) (**g1a**, **g1c**, **g1d**) or the more hydrophobic species 1,8-diaminooctane (**g5a–g5c**) as the crosslinking agents.

Consider first the **g1** series of hydrogels prepared using 2,2'-(ethylenedioxy)bis(ethylamine) as the crosslinker and DMEDA as the functionalization species. Fig. 4 clearly shows the swelling ratio of the polymer gels decreased with increasing crosslinker concentration (**g1a** → **g1c** → **g1d**). **g1a**, with a feed ratio of 5% 2,2'-(ethylenedioxy)bis(ethylamine), exhibited a rapid increase in swelling to a ratio value of 62 in the first 5 h and finally reached a value of 78 after 1 day. However, hydrogels **g1c** and **g1d**, with 33% and 54% crosslinking agent respectively, leveled off after 24 h at very low values of ca. 10 and 5. The strong dependence of crosslinker density on swelling behavior of a polymer gel is not uncommon. For example, it has been reported that the mechanical properties of chemically crosslinked hydrogels can be tightly regulated by crosslinking density [55,56].

In comparison, PVDMA-based hydrogels **g5a–g5c** prepared with 1,8-diaminooctane as the crosslinking agent

showed much lower swelling ratios under the same conditions. For example, **g5a** with 5% crosslinker reaches a maximum swelling ratio of only ca. 30 compared to 78 for the same hydrogel prepared with the 2,2'-(ethylenedioxy)bis(ethylamine) as crosslinker. We ascribe such different behavior to the hydrophobic nature of the 1,8-diaminooctane crosslinker vs. the hydrophilic 2,2'-(ethylenedioxy)bis(ethylamine) species, which reinforces the idea that the swelling characteristics are not only governed by crosslink density but also by the chemical nature of the crosslinking species.

3.3.2. Temperature-dependent swelling properties

While varying aqueous solution pH is a convenient method for inducing volume changes in hydrogels, temperature is, arguably, a more straightforward approach for affecting a similar response. Given our previous studies with DMEDA, DEEDA, THFA and MPPA-modified (co)polymers in which we demonstrated that under certain pH conditions homopolymers and copolymers containing such functional groups exhibit inverse temperature solubility behavior in aqueous media we also evaluated the temperature dependent swelling characteristics of the novel functional hydrogels [30,40].

Importantly, (co)polymers containing 3° amino functional groups only exhibit inverse temperature dependent solubility (cloud points, CP) when the amine groups are deprotonated, while THFA derivatised PVDMA exhibits a CP of ca. 31 °C, independent of solution pH, with some observed dependence on molecular weight. As such, all temperature-dependent swelling measurements were made in basic water at pH = 10. Hydrogels were prepared from the samples with the 2,2'-(ethylenedioxy)bis(ethylamine) crosslinker at a concentration of 10 mol%. All hydrogels were initially immersed in deionized water (pH = 10) for 24 h at a predetermined temperature between 5 and 95 °C to reach their equilibrium-swelling ratio.

At 5 °C, DMEDA-, DEEDA-, THFA- and MPPA-modified polymer gels reached their maximum swelling ratio of 32, 28, 12 and 10, respectively after 24 h. Consider first **g1b**, the hydrogel modified with DMEDA and 10 mol% crosslinker. Under these conditions its maximum equilibrium-swelling ratio is significantly lower than that observed in acidic media (ca. 76), reaching a maximum value of 32. Gradually heating the hydrogel to 95 °C results in a small negative change at ca. 60 °C after which it plateaus. This is broadly consistent with the measured CP of ~70 °C of a PVDMA homopolymer of molecular weight 35,160 modified with DMEDA at a concentration of 1 wt% in 0.1 M NaOH [30]. However, while there is a small drop, overall this hydrogel appears relatively temperature insensitive. In stark contrast to **g1b**, **g2** (hydrogel modified with DEEDA) undergoes a rapid contraction between ca. 28 and 45 °C, reaching a swelling ratio of 27. Such behavior is consistent with the more temperature-sensitive nature of DEEDA vs. DMEDA and the more hydrophobic nature of DEEDA in its non-protonated state. The onset of the rapid swelling is also consistent with the reported CP of a PDEEDA-based homopolymer of ca. 24 °C in 0.1 M NaOH [40]. As mentioned in the introduction, this characteristic of hydrogels can be attributed to a unique volume phase transition

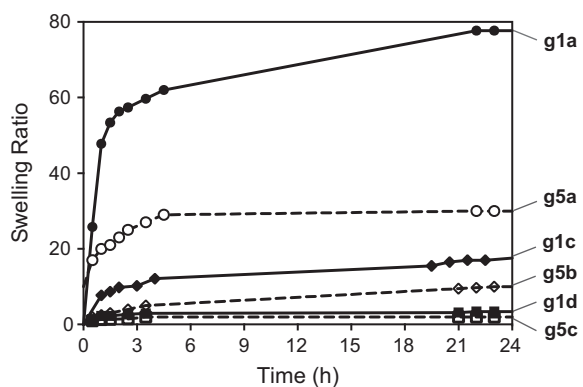


Fig. 4. Effect of crosslinker type and concentration on swelling ratio curves for DMEDA-modified PVDMA polymer gels, **g1a**, **g1c**, **g1d** and **g5a–g5c**, prepared with either 2,2'-(ethylenedioxy)bis(ethylamine) (solid lines) or 1,8-diaminooctane (dotted lines) as a cross-linker: (●, ○) 5 mol%, (◆, ◇) 33 mol% and (■, □) 54 mol%. All measurements were performed in acidic water (pH 4) at 25 °C.

between hydrophilic and hydrophobic states: below the CP, water molecules form hydrogen-bonds with polar groups in the gel, causing its expansion; as the surrounding temperature increases above LCST, the hydrophobic interactions of the hydrophobic groups and polymer backbone begin to dominate, causing gel shrinkage and expelling water from the networks (see Fig. 5).

In the case of the **g3** gel, modified with MPPA and 10% crosslinker, there is no evidence of a change in volume until the temperature reaches ca. 25 °C. Above this temperature there is a linear, monotonic decrease in the swelling ratio to a value of essentially 0 at 95 °C. The THFA-modified gel, **g4**, exhibited gel shrinkage spanning the range 25 – 40 °C, reaching its lowest value at ca. 50 °C after which there was little change. Again, volume contraction over this, albeit rather broad, range is inline with our previously reported CP of a THFA-based homopolymer of 32 °C. Importantly, while thermoresponsive hydrogels are well known [57–59] the results presented here highlight how a range of novel functional hydrogels with tunable swelling and shrinkage characteristics can be prepared from a single common reactive PVDMA scaffold by simple judicious choice of crosslinking agent and small molecule functional amine modifying reagent. Without a suitable amine modifier, as seen here in the example of gel **g0**, non-responsive gels with, albeit small, temperature-independent swelling ratios are obtained. Reversibility of the temperature-sensitive swelling behavior of the “smart” hydrogels is another interesting property in the field of stimulus-responsive polymers and gels. In the example of the **g4** gel, modified with THFA and 10% crosslinker, reversibility measurements were conducted at 5 °C or 95 °C over several heating–cooling cycles. Under such condition, the swelling behavior of the THFA-modified gels is indeed reversible. However, there is a large hysteresis of the swelling ratio after the second heating–cooling cycle (see SI).

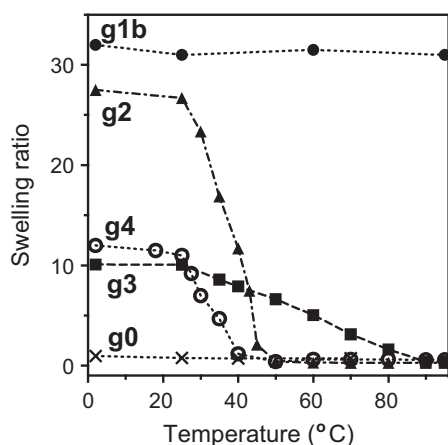


Fig. 5. Temperature-dependent swelling ratio of unmodified (×, **g0**) and modified PVDMA gels by reacting with (●, **g1b**) *N,N*-dimethylethylenediamine, (▲, **g2**) *N,N*-diethylethylenediamine, (■, **g3**) 3-morpholinopropylamine and (○, **g4**) THF amine. All measurements were performed in aqueous media at pH 10 for 24 h. All the modified PVDMA gels were prepared with 10 mol% crosslinker.

3.3.3. Salt-responsive characteristics

Certain classes of polymers, predominantly ionic polymers such as polyelectrolytes, polyampholytes and polybetaines [60], are sensitive to the presence of low molecular weight electrolytes. The response of such polymers to changes in electrolyte concentration typically manifests as changes in conformation and associated hydrodynamic diameters of the polymers and such behavior is described as the ‘polyelectrolyte’ and ‘anti-polyelectrolyte’ effects [61–64]. In the case of certain polybetaines, the effect of added electrolyte can be more pronounced [65]. In fact, the majority of such (co)polymers are insoluble in water in the absence of salts due to extensive intra- and intermolecular ionic interactions but become soluble upon addition of electrolytes due to screening of these ionic ‘crosslinks’. In addition to ionic (co)polymers there are examples of nonionic species that can undergo soluble-insoluble transitions through the addition of certain electrolytes. Of particular relevance here, and as detailed in the introduction, the morpholino group is one such salt-sensitive species as exemplified by the work on morpholino-based methacrylic (co)polymers that are sensitive to salts such as Na_2SO_4 in alkaline media and can be salted-out of aqueous solution [26,28,66]. It is this documented salt-responsive behavior that prompted us to prepare the MPPA-functional gels with the anticipation that similar electrolyte sensitive properties would be conferred. The swelling ratio of the MPPA-modified gel, **g3**, in basic water (pH = 8), at ambient temperature where the 3° amine residues are deprotonated was examined as a function of [Na_2SO_4], Fig. 6.

As hypothesized, the swelling ratio of the **g3** hydrogel decreased steadily with increasing [Na_2SO_4]. Addition of Na_2SO_4 reduced the water solubility of MPPA-modified polymer chains leading to the shrinkage of the hydrogel in basic water – in stark contrast to the unmodified, non-salt responsive, polymer gel **g0**. This is consistent with salt concentration-dependent aqueous solution properties of morpholino-modified (co)polymers [28,34,67–69], where

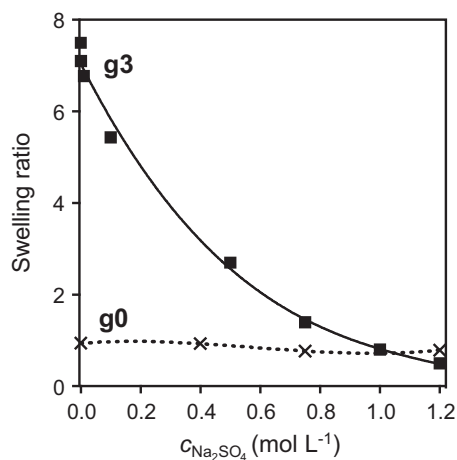


Fig. 6. Salt-dependent swelling ratio of unmodified (×, **g0**) and MPPA-modified PVDMA hydrogels (■, **g3**) in aqueous media at pH 8 and 25 °C for 24 h. A cubic polynomial regression fit was employed in data analysis.

it was reported that a critical salt concentration ($C_{Na_2SO_4}$) > 0.6 M was required to “salt out” a homopolymer of *N*-(morpholino)ethyl methacrylate from an aqueous solution at neutral or alkaline pH [34].

4. Conclusion

In summary, the synthesis and swelling properties of novel pH-, temperature- and salt-sensitive polymer gels are reported. The use of 2-vinyl-4,4-dimethylazlactone (VDMA) homopolymers as a reactive platform to yield smart polymeric gels provides a facile method to introduce desirable functionality to gel networks. A series of amine-functional groups, including *N,N*-dimethylethylenediamine (DMEDA), *N,N*-diethylethylenediamine (DEEDA), morpholine, 3-morpholinopropylamine (MPPA) and tetrahydrofurfurylamine (THFA), were utilized to produce various polymer hydrogels and organogels. The modified PVDMA hydrogels exhibit reversible volume phase transitions by applying single or multiple triggers: pH, temperature or added electrolyte. In acidic water, the swelling kinetics of the DMEDA-modified polymer gels strongly depended on cross-linker type and concentration. These smart polymer gels may find applications in tissue engineering and biological fields.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eurpolymj.2014.11.025>.

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