Smart Morpholine-Functional Statistical Copolymers Synthesized by Nitroxide Mediated Polymerization

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ABSTRACT

Morpholine-functional homopolymers and copolymers (using 4-acryloylmorpholine (4AM), 2-N-morpholinoethyl acrylate (MEA) and 2-N-morpholinoethyl methacrylate (MEMA)) were synthesized by nitroxide-mediated polymerization (NMP) and tested for aqueous thermo-responsiveness. MEA homopolymerizations and MEMA/9-(4-vinylbenzyl)-9H-carbazole (VBK) were controlled as evidenced by linear increases in number average molecular weight, $\overline{M_n}$, versus conversion ($X < 0.75$) and relatively low polydispersities $\overline{M_w}/\overline{M_n}$ = 1.30-1.60. For MEMA/VBK copolymers, increases in copolymer $\overline{M_n}$, VBK content in the copolymer and polymer concentration in aqueous solution resulted in a decrease in the cloud point temperature, CPT (typically varied between 33.7-47.9°C). 2-(dimethylamino)ethyl methacrylate (DMAEMA)/4AM copolymerizations were controlled when initial 4AM molar composition $f_{4AM,0} > 0.10$; however, the resulting final copolymers exhibited a sharp and completely reversible CPT only when $f_{4AM,0} < 0.20$. Poly(MEA) was water-soluble but was not thermo-responsive.

Keywords: nitroxide mediated polymerization; morpholine-functional polymers; thermoresponsive polymers.

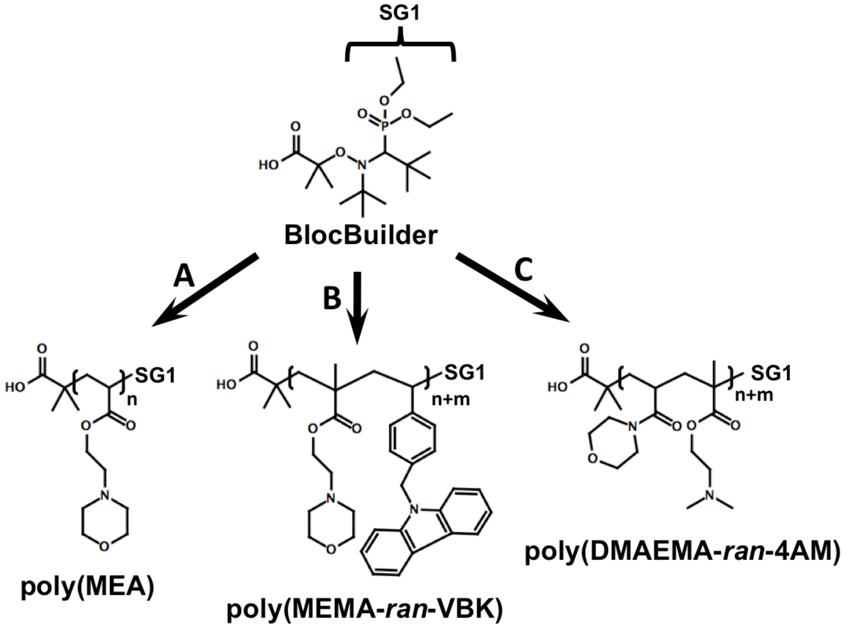
1. Introduction

Smart polymers undergo a significant physical change when exposed to a relatively modest environmental stimulus. Water-soluble statistical copolymers and block copolymers bearing pendant amine groups are of great interest as dual smart polymers due to the ionization potential of the amine group, resulting in a sensitivity to hydrogen bonding with the surrounding water molecules when experiencing a change in temperature or in pH.[1] For example, copolymers based on poly(N-isopropylacrylamide) (poly(NIPAM))[2-6] or poly(2-(dimethylamino)ethyl methacrylate) (poly(DMAEMA))[2,6-9] tend to be thermo/pH-responsive, experiencing a lower critical solution temperature (LCST) at approximately 32 °C and 46 °C, respectively. Morpholine-based statistical copolymers and block copolymers not only possess a tertiary amine, but also benefit from the presence of an oxygen group in its heterocyclic group, thereby providing high hydrophilicity.[1] Morpholine functional statistical and block copolymers have found application in a wide range of materials such as coatings for the reduction of calcium phosphate build-up,[10] hydrochloric acid (HCl) vapour sensors,[11] polychelatogens,[12] piezoelectric chemical sensors[13] and antimycotic nail varnish[14]. In addition, some applications, such as drug delivery systems, benefit from morpholine functional block copolymers that have good control of molecular weight distribution and copolymer composition.[15,16] In the last 20 years, several controlled radical polymerization (CRP) techniques have proven very successful in the synthesis of sophisticated molecular architectures for bio-functional materials.[17-19]

During the last decade, the use of second-generation nitroxide-mediated polymerization (NMP)[20-22] initiators based on alkoxyamines such as *N*-*tert*-butyl-*N*-

[1-diethylphosphono-(2,2-dimethylpropyl)] nitroxide (SG1, **Scheme 1**)[23,24] and 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (TIPNO)[25] have allowed the controlled polymerization of various monomers previously unattainable by first-generation nitroxide initiators, such as acrylates,[26-29] acrylamides, [30-33] and methacrylates (with the use of a low concentration of suitable controlling comonomer).[34-36] The controlled homopolymerization of 4-acryloylmorpholine (4AM, **Scheme 1**) has recently been demonstrated by our group[33] and by Eggenhuisen et al.[32] using 2-([*tert*-butyl[1-(diethoxyphosphoryl)-2,2-dimethylpropyl]amino]oxy)-2-methylpropanoic acid (BlocBuilder, **Scheme 1**) resulting in completely water-soluble homopolymers characterized by narrow molecular weight distributions.[32,33] In addition to being biocompatible, poly(2-*N*-morpholinoethyl methacrylate) (poly(MEMA)) homopolymers have been known to exhibit LCSTs ≈ 37°C,[37] making them ideal candidates for use as targeted drug delivery polymers or other biomaterials applications. However, very few examples regarding the controlled synthesis of acrylic or methacrylic-based morpholine-containing homopolymers or copolymers can be found in the literature[32,33,38], despite their desirable biocompatible properties. To the best of our knowledge there are no cases where acrylic or methacrylic-based morpholine functional polymers were synthesized by NMP. Here, for the MEMA polymerizations, a low fraction of 9-(4-vinylbenzyl)-9H-carbazole (VBK) was used as the controlling co-monomer, which also imparts hole-transport and fluorescent properties. VBK was earlier shown to be quite effective as a controlling co-monomer for BlocBuilder-mediated NMP of methacrylates. [9, 36]

In this manuscript, we report the controlled synthesis of several morpholine-based homopolymers and statistical copolymers by NMP with using BlocBuilder. The effect of copolymer composition, choice of monomer, concentration of copolymer in solution and heating rate on the thermo-responsive behaviour of the resulting morpholine functional copolymers is also discussed.



Scheme 1. Summary of the synthetic routes employed to make morpholine functional homopolymers and copolymers using the BlocBuilder unimolecular initiator: A) poly(2-*N*-morpholinoethyl acrylate) (poly(MEA)), B) poly(2-*N*-morpholinoethyl methacrylate-*ran*-9-(4-vinylbenzyl)-9H-carbazole) (poly(MEMA-*ran*-VBK)) and C) poly(2-(dimethylamino)ethyl methacrylate-*ran*-4-acryloylmorpholine) (poly(DMAEMA-*ran*-4AM)).

2. Experimental Section

2.1. Materials

N,N-Dimethylformamide (DMF, >95%), anhydrous ethyl ether (>95%, BHT stabilized), hexanes (>95%) and tetrahydrofuran (THF, >99.9%, HPLC grade) were obtained from Fisher Scientific and used as received. Deuterated chloroform ($CDCl_3$, >99%) was obtained from Cambridge Isotopes Laboratory and was also used as received. 2-N-Morpholinoethyl acrylate (MEA, 95%, inhibited with 100 ppm MEHQ) was obtained from Polysciences, Inc. calcium hydride (90-95%, reagent grade), basic alumina (Brockmann, type 1, 150 mesh), 4-acryloylmorpholine (4AM, 97%, inhibited with 1,000 ppm MEHQ), 2-(dimethylamino)ethyl methacrylate (DMAEMA, 98%, inhibited with 2,000 ppm MEHQ), and 2-N-morpholinoethyl methacrylate (MEMA, 95%, inhibited with 1,000-1,200 ppm MEHQ) were obtained from Aldrich. MEA, 4AM, DMAEMA, and MEMA were all purified by passage through a column of 5 wt. % calcium hydride relative to basic alumina and stored in a refrigerator in a sealed flask under a head of nitrogen until required. 9-(4-vinylbenzyl)-9H-carbazole (VBK) was synthesized according to the literature.[39] 2-([*tert*-butyl[1-(diethoxyphosphoryl)-2,2-dimethylpropyl]amino]oxy)-2-methylpropanoic acid, also known as BlocBuilder (99%), was obtained from Arkema and used without further purification. {*tert*-butyl[1-(diethoxyphosphoryl)-2,2-dimethylpropyl]amino}oxidanyl, also known as SG1 (>85%), was kindly donated by Noah Macy of Arkema and also used as received.

2.2. Polymer Synthesis

2.2.1 General

The syntheses of all homopolymers and copolymers were performed in a three-neck round bottom flask (50 mL) equipped with a condenser, a temperature well, and a magnetic stir bar. A thermocouple was inserted into the temperature well, and connected to a controller, which was used to modulate the reactor temperature using a heating mantle. To prevent monomer and solvent evaporation, the condenser was cooled using a Neslab 740 chiller unit and a 50 vol. % mixture of water/ethylene glycol. Prior to heating, the mixture was bubbled using a nitrogen purge, which was reduced but present throughout the entirety of the reaction. The condenser was capped with a rubber septum with needle to relieve the pressure build-up.

2.2.2. Synthesis of poly(2-N-Morpholinoethyl Acrylate) (poly(MEA)) Homopolymers

All MEA homopolymerizations were performed using a 50wt% dilute DMF solution where the amount of BlocBuilder was calculated to give a target molecular weight of approximately 25 kg·mol-1. The polymerization temperature varied from 100 to 120°C depending on the experiment. A formulation with MEA homopolymerization at 110°C with 10 mol % SG1 additional free nitroxide relative to BlocBuilder is given as an example: BlocBuilder (0.075 g, 0.195 mmol), SG1 (0.005 g, 0.018 mmol), MEA (4.94 g, 26.67 mmol), and DMF (5.03 g, 68.9 mmol) were added to the reactor prior to being sealed with a rubber septum. All other formulations and a summary of kinetic results for MEA homopolymerizations can be found in **Table S1** of the *Supporting Information*. The mixture was bubbled with nitrogen for 20 min at room temperature prior to being heated with a rate of 10°C·min^{-1}. The time when the temperature reached 110 °C was arbitrarily taken as the start of the reaction (t = 0 min). Samples were periodically withdrawn by syringe and precipitated in an excess of 50 vol% mixture of ethyl ether and hexanes after being cooled in a freezer. The final polymer was recovered after similar precipitation followed by being dried in the vacuum oven at 60 °C overnight. For the specific example cited, the polymerization was stopped after 23.7h and the final homopolymer was characterized by a yield of 0.70 g (39% conversion according to ^{1}H NMR) with $\overline{M_n}$ = 6.0 kg·mol^{-1} and $\overline{M_w}/\overline{M_n}$ = 1.37 according to GPC using poly(methyl methacrylate) standards in THF.

2.2.3. Synthesis of Poly(2-N-Morpholinoethyl Methacrylate-ran-9-(4-Vinylbenzyl)-9H-Carbazole) (poly(MEMA-ran-VBK)) Statistical Copolymers.

In all cases, the copolymerizations were executed at a constant temperature of 80 °C in a feed solution of 50 wt. % DMF using a similar molar ratio of SG1 relative to BlocBuilder (r = [SG1]$_0$/[BocBuilder]$_0 \approx$ 0.10). Depending on the copolymerization, the initial molar composition of VBK relative to MEMA was varied between $f_{VBK,0}$ = 0.01-0.20 and the amount of BlocBuilder was calculated to obtain a target molecular weight at complete conversion of approximately 10, 25 or 50 kg·mol^{-1} (see **Table S2** in *Supporting Information* for formulations). The formulation for MEMA/VBK-25-0.02 is given as an example. BlocBuilder (0.062 g, 0.162 mmol), SG1 (0.005 g, 0.016 mmol), MEMA (4.06 g, 20.4 mmol), VBK (0.11 g, 0.39 mmol), DMF (4.09 g, 56.0 mmol) and a stir bar were added to the reactor. The mixture was stirred, and bubbled for 20 min, prior to being heated to 80 °C. The nitrogen flow was reduced and t = 0 min was arbitrarily taken as the time at which the reactor reached 80 °C. Samples were periodically withdrawn by syringe and precipitated in an excess of hexanes. The crude polymer was recovered and dried in a vacuum oven at 60 °C overnight. For the specific example cited, the polymerization was stopped after 3 h. The final yield was 1.17 g (71% conversion according to ^{1}H NMR; final molar composition of VBK, F_{VBK} = 0.03 with $\overline{M_n}$ = 14.5 kg·mol^{-1} and $\overline{M_w}/\overline{M_n}$ = 1.53 by GPC relative to poly(methyl methacrylate) standards in THF).

2.2.4. Synthesis of Poly(4-Acryloylmorpholine-ran-2-(Dimethylamino)Ethyl Methacrylate) (poly(4AM-ran-DMAEMA)) Statistical Copolymers.

The DMAEMA/4AM copolymerizations were performed under identical conditions to those of the MEMA/VBK copolymerizations. In all cases, a polymerization temperature of 80 °C, an initial solution concentration of 50 wt. %, $r \approx 0.10$ and a target molecular weight of 25 kg·mol^{-1} was used. Depending on the copolymerization, the initial molar composition of 4AM relative to DMAEMA was varied between $f_{4AM,0}$ = 0.02-0.50 (see **Table S2** in *Supporting Information* for all formulations). The formulation of DMAEMA/4AM-0.05 is given as an example. BlocBuilder (0.076 g, 0.200 mmol), SG1 (0.006 g, 0.020 mmol), DMAEMA (4.68 g, 29.8 mmol), 4AM (0.22 g, 1.57 mmol), DMF (4.90 g, 67.1 mmol) and a stir bar were added to the reactor and nitrogen was bubbled through the mixture for 30 min. The mixture was then heated to 80 °C (t = 0 min), samples were periodically withdrawn by syringe and precipitated in an excess of 5 vol % mixture of diethyl ether relative to hexanes (the composition of diethyl ether relative to hexanes would vary depending on the copolymer composition). After recovery, the crude polymer was dried in the vacuum oven at 60 °C overnight. For the specific example cited, the polymerization was stopped after 5.3 h. The final yield was 0.85 g (48% conversion according to ^{1}H NMR; final molar composition of 4AM, F_{4AM} = 0.02 with $\overline{M_n}$ = 10.3 kg·mol^{-1} and $\overline{M_w}/\overline{M_n}$= 1.63 by GPC relative to poly(methyl methacrylate) in THF).

2.2.5. Chain Extension of 9-(4-Vinylbenzyl-9H-Carbazole) (VBK) from *Poly(2-N-Morpholinoethyl Methacrylate-ran-9-(4-Vinylbenzyl)-9H-Carbazole) (poly(MEMA-ran-VBK)) Macroinitiators*

The ability of a MEMA/VBK statistical copolymer to be able to reinitiate a polymerization was tested by using MEMA/VBK-15-0.04 as the macroinitiator ($\overline{M_n}$ = 10.0 kg·mol^{-1}, $\overline{M_w}/\overline{M_n}$= 1.47, F_{VBK} = 0.04, see **Table 1**) to initiate a second batch of VBK. The same reactor set-up and procedure was used as in the previous section for the MEMA/VBK statistical copolymers. After adding the macroinitiator (0.42 g, 0.042 mmol) to the DMF solvent (4.01 g, 55 mmol) along with the VBK monomer (2.00 g, 7.1 mmol), the contents were stirred at room temperature while applying a nitrogen purge for 30 minutes. The reactor was then heated to a set-point of 110 °C while maintaining a light nitrogen purge. Samples were taken for molecular weight analysis after 20 minutes and when the solution started becoming much more viscous. The polymerization was stopped after 223 minutes and the reactor was cooled down to room temperature and the solution was poured into excess hexane to precipitate the polymer. After drying in a vacuum oven at 60°C overnight to remove the solvents, the crude product was re-dissolved in a minimal amount of THF and then purified by fractionation (to remove any dead macroinitiator) with the slow addition of methanol. After the solution turned cloudy, it was placed in a refrigerator to precipitate the purified block copolymer product.

The final product was significantly richer in VBK with F_{VBK} = 0.90 according to ^{1}H NMR and $\overline{M_n}$ = 34.5 kg·mol^{-1} and $\overline{M_w}/\overline{M_n}$ = 1.53 by GPC relative to PMMA standards in THF.

2.3. Polymer Characterization

2.3.1 Gel Permeation Chromatography (GPC)

The number average molecular weight, $\overline{M_n}$, and the dispersity, $\overline{M_w}/\overline{M_n}$, were determined using gel permeation chromatography GPC (Water Breeze), which was equipped with both ultra-violet (UV 2487) and differential refractive index (RI 2414) detectors. The mobile phase of HPLC grade THF with a flow rate of 0.3 mL·min^{-1} was applied. The GPC was equipped with a guard column and three Waters Styragel® HR columns (HR1, HR2, and HR4) with the particle size of 5 μm which were heated to 35 °C. The HR columns have molecular weight measurement ranges of 0.1 to 5 kg·mol^{-1}, 0.5 to 20 kg·mol^{-1}, and 5 to 500 kg·mol^{-1}, respectively. The GPC was calibrated using linear, narrow molecular weight distribution poly(methyl methacrylate) standards at 35 °C in THF.

2.3.2. Nuclear Magnetic Resonance Spectroscopy (NMR)

To track the progression of the polymerization, monomer conversion was determined with ^{1}H NMR spectroscopy from aliquots taken at various polymerization times. The samples were analyzed using a 400MHz Varian Gemini in $CDCl_3$. Conversion of the MEA homopolymerizations was determined by comparing the area associated to the vinylic proton peaks (average of δ = 5.8, 6.1, 6.4 ppm, corresponding to 3H in total) to the area associated to the non-vinylic protons (average of δ = 2.5 - 2.7, 3.7, 4.3 ppm, corresponding to 12H in total). Overall conversion of the MEMA/VBK and DMAEMA/4AM copolymerizations was calculated according to $X = X_a f_{a,0} + X_b f_{b,0}$, where X_a and X_b are the individual monomer conversions and $f_{a,0}$ and $f_{b,0}$ are the initial molar fractions for monomers *a* and *b,* respectively. The conversion of the MEMA monomer, X_{MEMA}, was determined by comparing the area associated to the vinyl proton peaks (average of δ = 5.5, 6.1 ppm, corresponding to 2H in total) to the area associated to the protons in the morpholine ring (δ = 3.5-3.8 ppm, corresponding to 8H). Conversion of the VBK monomer, X_{VBK}, was determined by comparing the area associated to the vinyl proton peaks (average of δ = 6.6, 5.65, 5.2 ppm, corresponding to 3H in total) to the area corresponding to the protons associated to the methylene protons adjacent to the carbazole group (δ = 5.55 ppm, corresponding to 2H). Conversion of the DMAEMA monomer, X_{DMAEMA}, was determined by comparing the area associated to the vinyl proton peaks (average of δ = 5.5, 6.1 ppm, corresponding to 2H in total) to the area corresponding to the methylene protons next to the ester bond (δ = 4.0-4.2 ppm, corresponding to 2H). Conversion of the 4AM monomer, X_{4AM}, was determined by comparing the area associated to the vinyl proton peaks (average of δ = 5.7, 6.3, 6.5 ppm, corresponding to 3H in total) to the area associated to the protons in the morpholine ring (δ =3.5-3.8 ppm, corresponding to 8H). The final molar composition of VBK (F_{VBK}) in the MEMA/VBK copolymers was determined by determining the ratio of the area associated to the protons in the morpholine ring associated with MEMA (δ = 3.5-3.8 ppm, corresponding to 8H) relative to the area corresponding to the protons associated with the methylene protons adjacent to the carbazole group of the VBK units (δ = 5.55

ppm, corresponding to 2H). The final molar composition of 4AM (F_{4AM}) in the DMAEMA/4AM copolymers was found by determining the ratio between the area associated to the protons in the morpholine ring associated to 4AM units (δ = 3.5-3.8 ppm, corresponding to 8H) and the area associated to the methylene protons next to the ester bond associated to the DMAEMA units (δ = 4.0-4.2 ppm, corresponding to 2H)

2.3.3. Measurement of Cloud Point Temperature (CPT)

The cloud point temperatures (CPTs) were determined by two different methods: UV-Vis spectroscopy and dynamic light scattering (DLS). UV-Vis spectroscopy measurements were performed using a Cary 5000 UV−Vis−NIR spectrometer (Agilent Technologies) equipped with a Peltier thermostatted (6 × 6) multicell holder with temperature controller, magnetic stirring and a heating rate of 0.5 $°C \cdot min^{-1}$. The CPT was noted as the temperature at which the normalized absorbance of a 500 nm wavelength through the sample reached 0.5. In the case of the poly(MEMA-*ran*-VBK) copolymers, the CPT value was taken as the average of 2-3 heat-cool cycles (average deviation 0-2 °C).

3. Results and Discussion

3.1. Homopolymer and Copolymer Synthesis by NMP

3.1.1. Homopolymerization of 2-N-Morpholinoethyl Acrylate (MEA)

A series of MEA homopolymerizations were performed using polymerization temperatures between 100 °C and 120 °C (see the *Supporting Information*, **Table S1** for details on the formulation, the experimental setup, the kinetics and the control of the MEA homopolymerizations). The final homopolymers were characterized by a relatively narrow molecular weight distribution ($\overline{M_w}/\overline{M_n}$ < 1.4, **Table S1** of *Supporting Information*) and were completely water-soluble. As mentioned in the introduction, the poly(methacrylate) analogue, poly(MEMA), exhibits a sharp LCST ≈ 37 °C, however poly(MEA) did not exhibit a LCST between 20 and 95 °C in a neutral aqueous solution. The subtle change in monomer structure often greatly affects the solubility and thermo-responsive behaviour in such systems. Cai and coworkers reported a decrease in LCST of as much as 37°C from the acrylic-based pyrrolidone functional homopolymer (CPT ≈ 66.5 °C, poly[N-(3-acryloyloxypropyl) pyrrolidone]) to the methacrylic-based pyrrolidone functional homopolymer (CPT ≈ 29.5 °C, poly[N-(3-methacroyloxypropyl) pyrrolidone]).[40,41] In another example of subtle changes in structure resulting in drastic changes in LCST, simply changing the *N′*-group to ethyl or methyl resulted in water-soluble polymers with no LCST while poly(*N*-acryloyl-*N′*-propylpiperazine) had an LCST of 37 ºC. [42,43] Due to the lack of thermo-responsiveness of the poly(MEA) homopolymers between 20 and 95 °C, no further investigations were performed here.

3.1.2. Copolymerization of 2-N-Morpholinoethyl Methacrylate (MEMA) and 9-(4-vinylbenzyl)-9H-carbazole (VBK)

Originally, the controlled synthesis of low polydispersity poly(MEMA) homopolymers was accomplished by oxyanionic polymerization[44,45] or by group transfer polymerization.[46] As mentioned, very few examples of MEA or MEMA homopolymerizations by CRP techniques have been found in the literature.[38] To the best of our knowledge, in terms of CRP techniques, the homopolymerization of MEMA has only been accomplished using ATRP.[38] The controlled homopolymerization of acrylates, such as MEA, is possible using BlocBuilder as shown in the previous section. However, to apply NMP via BlocBuilder, the methacrylate analogue to MEA, MEMA, must be copolymerized with a suitable controlling comonomer.[35,36,46,48] Recently, our group has established that 9-(4-vinylbenzyl)-9H-carbazole (VBK) can be used as an effective controlling comonomer for various methacrylates, requiring as little as 1 mol % of VBK relative to methacrylate in the initial feed to give a linear increase in $\overline{M_n}$ versus X and a final copolymer characterized by a relatively narrow molecular weight distribution ($\overline{M_w}/\overline{M_n}$> 1.4).[36] VBK has since been used as a controlling comonomer for the methacrylate-rich copolymerizations of not only methyl methacrylate (MMA),[36] but also 2-(dimethylamino) ethyl methacrylate (DMAEMA),[9] oligo(ethylene glycol)methacrylate (OEGMA)[49] and methacrylic acid (MAA)[50]. The copolymerization of MEMA was therefore sought out by using VBK as a controlling comonomer resulting in poly(2-*N*-morpholinoethyl methacrylate-*ran*-9-(4-vinylbenzyl)-9H-carbazole) (poly(MEMA-*ran*-VBK)) statistical copolymers. Characteristic $\ln(1-X)^{-1}$ versus time plots are shown in **Fig. 1a** for MEMA/VBK copolymerizations with various VBK feed compositions. The plot of $\overline{M_n}$ and $\overline{M_w}/\overline{M_n}$ versus X for the copolymerizations described in **Fig. 1a** is shown in **Fig. 1b**. A typical set of GPC chromatograms at various polymerization times is shown in **Fig. 1c** for an MEMA/VBK copolymerization with $f_{VBK,0}$ = 0.10 and $\overline{M_n}_{Target}$~ 25 kg·mol^{-1}. The complete summary for the kinetics and control of the MEMA/VBK copolymerization is listed in the *Supporting Information,* **Table S3** while **Table S4** lists the evolution of molecular weight during the polymerization. Noticeable in **Fig. 1a** tis that in some cases there is conversion of monomer already present at the initial time. In some cases, there can be monomer converted due to the choice of initial time (i.e. when a certain temperature is reached). Here, 80oC was taken to be when t = 0, which is above the temperature for the BlocBuilder initiator to decompose and begin the polymerization. However, at very low VBK feed compositions $f_{VBK,0} \leq 0.02$, the conversion is exceedingly high with $X \sim 0.3$-0.4 and this suggests that there could have significant early chain termination occurring in addition to the choice of initial polymerization time. For compositions $f_{VBK,0} \geq 0.05$, the $\overline{M_n}$ versus X remained linear up to about 50% conversion, indicating relatively good control and the $\overline{M_w}/\overline{M_n}$~ 1.3-1.5 except for very low loadings of VBK ($f_{VBK,0} < 0.02$). Thus, VBK enabled the controlled copolymerization ($\overline{M_w}/\overline{M_n}$= 1.35) of MEMA at $\overline{M_n}_{Target}$ up to ~ 25 kg·mol^{-1} and $f_{VBK,0} \geq 0.05$.

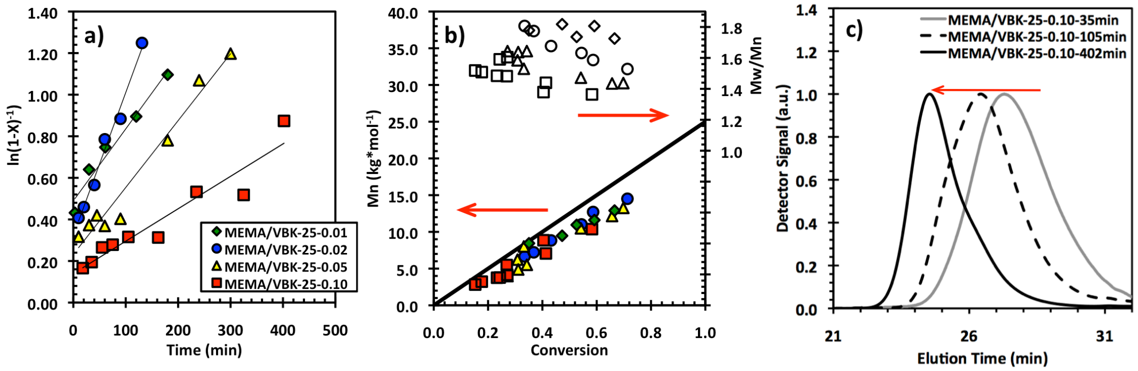


Fig. 1. a) The semi-logarithmic plots of scaled conversion (ln[(1 - X)$^{-1}$]) (X = conversion) versus time, b) the number-average molecular weight, $\overline{M_n}$ versus X plots and c) GPC chromatogram for characteristic copolymerizations of 9-(4-vinylbenzyl)-9H-carbazole with 2-*N*-morpholinoethyl methacrylate (MEMA/VBK). All corresponding experimental formulations can be found in **Table S2**.

3.1.3. Copolymerization of 2-(Dimethylamino) ethyl methacrylate (DMAEMA) and 4-Acryloylmorpholine (4AM)

As mentioned, the controlled homopolymerization of 4AM has recently been demonstrated by our group[33] and by Eggenhuisen et al.[32] using BlocBuilder. While the resulting homopolymers were water-soluble, they exhibited no LCST between 25 °C and 90 °C in a neutral aqueous solution. Due to the seemingly similar homopolymerization kinetics between 4AM and styrene, it was thought that 4AM could act as a controlling comonomer for a thermo-responsive methacrylate, such as DMAEMA (**Scheme 1**). In addition to potentially controlling the copolymerization of DMAEMA, 4AM could introduce more hydrophilicity into the final copolymers, thereby also manipulating the thermo-responsive behaviour of the final copolymers. A similar type of behaviour would be expected when acrylonitrile is used as the controlling comonomer for methacrylates, which resulted in more hydrophilic copolymers when acrylonitrile was used instead of styrene as the controlling comonomer [46]. For a complete discussion on the kinetics and the control of the DMAEMA/4AM copolymerizations, please see **Tables S3-S4** of the *Supporting Information*. It was determined that 4AM can be used as a water-soluble controller for DMAEMA but to obtain a relatively well-controlled copolymerization, a minimum of 10 mol. % of 4AM relative to DMAEMA is required. A similar protocol was attempted by Phan et al. using *N, N* dimethylacrylamide (DMA) as a controlling co-monomer for MMA.[51] This potential to act as a controlling co-monomer was suggested by the good control of DMA homopolymerizations by SG1 type initiators previously [52-54]. Phan et al. found that statistical MMA/DMA copolymers could be attained which exhibited narrow molecular weight distributions $\overline{M_w}/\overline{M_n}$= 1.25-1.40 with DMA initial feed compositions from 0.4-0.9. [51] We observed significant termination at low 4AM loadings but control improved as the 4AM feed composition increased to greater than 0.1. Still, our molecular weight distributions were broader ($\overline{M_w}/\overline{M_n}$= 1.51-1.70 for 4AM initial feed compositions from 0.02-0.50; see **Table 1**) compared to Phan et al. [51] but this could be due to absorption issues with DMAEMA-rich copolymers to GPC columns as we [9] and others have observed previously. [55]

3.1.4. Block Copolymer Formation

The livingness of characteristic poly(MEMA-*ran*-VBK) macroinitiators was performed by initiating a fresh batch of VBK using a typical MEMA-rich macroinitiator (MEMA/VBK-15-0.04, $\bar{M}_n$= 10.0 kg·mol^{-1}, $\overline{M_w}/\overline{M_n}$= 1.47, F_{VBK} = 0.04). The final molecular weight characteristics of the macroinitiator and final block copolymers can be found in **Table 2**. GPC chromatograms clearly illustrate the growth of the block copolymers by a shift in elution time with the peaks staying relatively monomodal, thereby suggesting that most of the macroinitiator chains were able to re-initiate (**Fig. 2**). The GPC chromatograms also indicate a tailing which could indicate that some of the poly(MEMA-*ran*-VBK) macroinitiators were irreversibly terminated. The crude block copolymer product had $\bar{M}_n$= 26.2 kg·mol^{-1}, $\overline{M_w}/\overline{M_n}$= 1.70. We attempted to fractionate this crude product to remove any dead macroinitiator. After performing the GPC, the low molecular weight tail was not as prominent (see **Fig. 2d**) and the molecular weight distribution narrowed with the fractionated product having $\bar{M}_n$ = 34.5 kg·mol^{-1}, $\overline{M_w}/\overline{M_n}$= 1.54. It was also quite-rich in VBK with F_{VBK} = 0.90 since the VBK segment added was quite long compared to the macroinitiator and the product was no longer water-soluble.

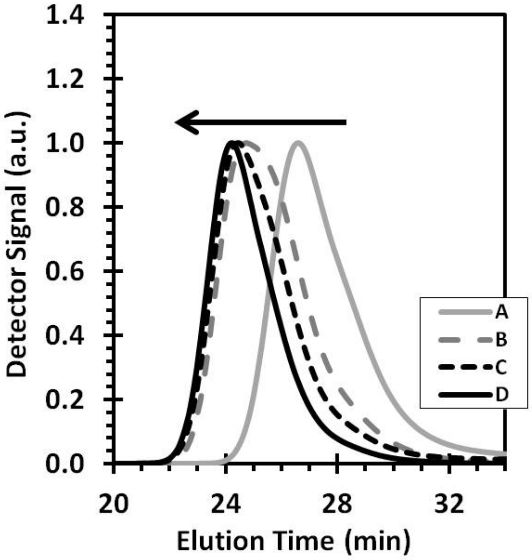


Fig. 2. Gel permeation chromatograms (GPC) of VBK chain extension done in a 50 wt% solution in DMF at 110 ºC from a poly(MEMA/VBK) macroinitiator: A) MEMA/VBK-15-0.04 macroinitiator ($\bar{M}_n$= 10.0 kg·mol^{-1}, $\overline{M_w}/\overline{M_n}$= 1.47); B) MEMA/VBK-15-0.04-b-VBK with sample taken at t = 20 min ($\bar{M}_n$= 20.9 kg·mol^{-1}, $\overline{M_w}/\overline{M_n}$= 1.76; C) MEMA/VBK-15-0.04-b-VBK final product with sample taken at t = 233 min ($\bar{M}_n$= 26.2 kg·mol^{-1}, $\overline{M_w}/\overline{M_n}$= 1.70 and D) MEMA/VBK-15-0.04-b-VBK$_F$, which is the final fractionated product ($\bar{M}_n$= 34.5 kg·mol^{-1}, $\overline{M_w}/\overline{M_n}$= 1.54). Please See **Table 2** for summary of molecular weight and compositions of the macroinitiator and chain-extended products.

3.2. Thermo-Responsive Behavior of Copolymers in Water.

3.2.1 Cloud Point Temperature (CPT) Measurements for poly(2-N-Morpholinoethyl Methacrylate-ran-9-(4-vinylbenzyl)-9H-carbazole) (poly(MEMA-ran-VBK)) Statistical Copolymers

When dissolved in water, homopolymers and block copolymers containing either poly(DMAEMA) or poly(MEMA) have been known to exhibit lower critical solution temperatures (LCST)s ≈ 32-50°C[37,56] and LCST ≈ 34-53°C[37], respectively. Changes in solution concentration, solution pH, molecular weight and even the addition of hydrophilic/hydrophobic comonomers all have a significant effect on the corresponding LCST.[37,56] A series of poly(MEMA-*ran*-VBK) copolymers, with a range of VBK molar compositions F_{VBK} = 0.01-0.03, and molecular weights from $\overline{M_n}$ = 5.6-21.7 kg·mol^{-1}, were dissolved in water at various concentrations between 0.1 and 2 wt. % and their characteristic cloud point temperatures (CPTs) were determined using UV-Vis spectroscopy (see **Table S5,** *in Supporting Information*). As a comparison, the corresponding CPTs were plotted as a function of solution concentration in **Fig. 3**. The inclusion of VBK, a relatively hydrophobic comonomer, in the statistical copolymers resulted in a decrease in the CPT. However, when the statistical copolymer had F_{VBK} = 0.06, it was barely water-soluble. Once heated, the copolymer completely precipitated out of solution. When F_{VBK} > 0.06, the resulting copolymer was completely water-insoluble. Similar results have previously been observed when adding a hydrophobic co-monomer, such as VBK, to the final copolymer.[9,49,50] The solution concentration also appears to have a significant effect on the CPT (**Fig. 3**). As the solution concentration increases, the apparent CPT decreases until reaching a plateau (**Fig. 3**). For example, MEMA/VBK-10-1 (F_{VBK} = 0.01) exhibited a sharp decrease in CPT from 47.9 °C to 41.7

°C when increasing the solution concentration from 0.1 wt. % to a 0.5 wt. %. However, very little change in CPT is observed upon further increasing the concentration to 1.0 wt. % and 2.0 wt. %, which resulted in CPTs leveling to about 40.5°C. (**Fig. 3, Table S5** in *Supporting Information*). Similar drops in CPT with increase in solution concentration have previously been observed for other thermo-responsive statistical copolymers such as 4AM/2-hydroxypropyl acrylate (4AM/HPA), [32] HPA/DMA [32] and 2-hydroxyethyl acrylate/HPA (HEA/HPA)[27] copolymers. Note that when heating the relatively concentrated solutions (≥ 2 wt. %) above their respective LCST, a significant fraction of copolymer would precipitate out of solution (taking 12-24 hours below the LCST to completely re-dissolve in many cases) resulting in a lack of thermo-reversibility. Finally, between 5.6 kg·mol^{-1} and 21.7 kg·mol^{-1} it would appear that generally a decrease in CPT was observed with the increase of copolymer molecular weight (**Fig. 3**). For example, MEMA/VBK-10-2 ($\overline{M_n}$ = 5.6 kg·mol^{-1}, F_{VBK} = 0.03) had a CPT = 46.7°C and 36.6°C at a solution concentration of 0.1 and 1.0 wt. %, respectively, while MEMA/VBK-50-2 ($\overline{M_n}$ = 21.7 kg·mol^{-1}, F_{VBK} = 0.02) had a CPT = 38.8°C and 35.4°C at the same solution concentrations (**Table S5** in *Supporting Information*, **Fig. 3**). Therefore, depending on the solution concentration, poly(MEMA-*ran*-VBK) statistical copolymers experienced a difference in CPT of as much as 8°C when manipulating the final copolymer $\overline{M_n}$ between 5.6 kg·mol^{-1} and 21.7 kg·mol^{-1}. These values are consistent with those determined by Armes and coworkers who established, for poly(MEMA) homopolymers, a decrease in CPT from 53.4°C to 34.0°C when increasing the molecular weight from 1.8 kg·mol^{-1} to 32.0 kg·mol^{-1} (when keeping the solution concentration equal to 0.5 wt. %).[37] The poly(MEMA-*ran*-VBK) copolymers exhibited a slight discrepancy in CPT between the heating and the cooling cycles, which is common for thermo-responsive polymers bearing tertiary amines.[9,57,58] It is generally understood that this hysteresis effect is a result of inter-polymer hydrogen bonding of the amine groups. For example, the hysteresis experienced when cooling poly(NIPAM) results in multiple thermodynamically stable phase changes between coil and globule[59] which take place due to the hydrogen bonding formed between the ethylamide and the carbonyl group when aggregated above the LCST[40,58]. The tertiary amine groups present in both poly(DMAEMA) and poly(MEMA) are known to be strong hydrogen bond acceptors, resulting in hydrogen bonding with water molecules that are trapped in the globule above the LCST.[58,60]

It should also be noted that the LCST is strongly dependent on the heating rate.[61-64] Thus, a series of solutions were prepared and run under different heating rates to observe the kinetic effect on the thermo-reversible transition. We observed that as the heating rate increased, the transition became more diffuse and the resulting CPT was found to increase. For example, for a 0.5 wt% solution of MEMA-10-1, the CPT increased from 40.2°C to 43.8°C when increasing the heating rate from 0.1 $°C \cdot min^{-1}$ to 2.0 $°C \cdot min^{-1}$, respectively. While very low heating rates, such as 0.1 $°C \cdot min^{-1}$, afforded the sharpest thermal transition, the polymer also began to precipitate out of solution due to being held above the LCST for extended periods of time, resulting in a loss of thermo-reversibility (**Fig. 4**).

In summary, the CPT for poly(MEMA-*ran*-VBK) statistical copolymers studied here can be modulated between 34 °C and 48 °C by manipulating the VBK content in the final copolymer between F_{VBK} = 0.01 and 0.03, by adjusting the solution concentration between 0.1 wt. % and 2 wt. % and by increasing the $\overline{M_n}$ from 5.6 kg·mol^{-1} to 21.7 kg·mol^{-1}.

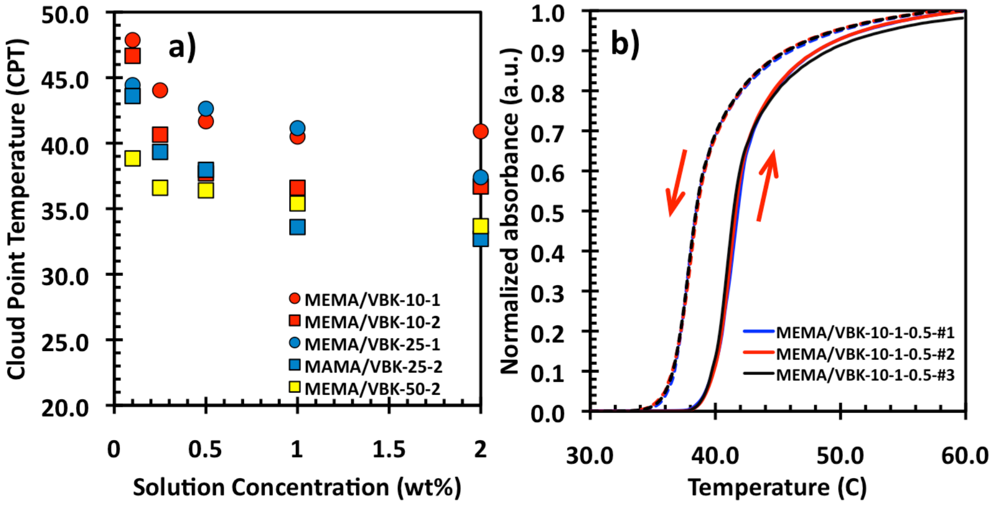


Fig. 3. a) Cloud point temperature (CPT) versus solution concentration for various poly(MEMA-*ran*-VBK) statistical copolymers and b) normalized absorbance versus temperature for a characteristic UV-Vis spectrogram corresponding to an average triplicate to determine the CPT value (the characteristic spectrogram corresponds to a 0.5 wt. % solution of MEMA/VBK-10-1). The molecular weight characteristics and copolymer composition of the statistical copolymers can be found in **Table 1**. CPTs were determined as the midpoint on the heating ramp of the scaled absorbance at 500 nm using UV-Vis spectroscopy.

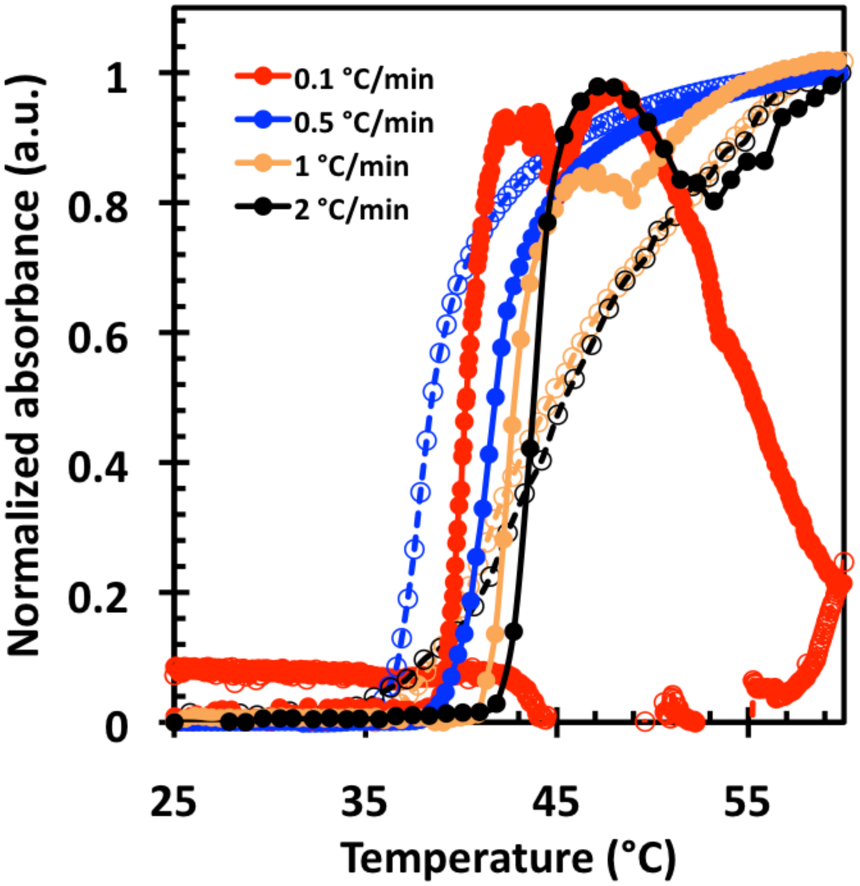


Fig. 4. UV-Vis spectrogram corresponding to a 0.5 wt. % solution of MEMA/VBK-10-1 performed at 0.1 °C·min^{-1}, 0.5 °C·min^{-1}, 1.0 °C·min^{-1} and 2.0 °C·min^{-1}. CPTs were determined as the midpoint on the heating ramp of the scaled absorbance at 500 nm using UV-Vis spectroscopy. The solid lines indicating the heating ramp while the corresponding dashed lines represent the cooling.

3.2.2. Cloud Point Temperature (CPT) Determination for Poly(2-(dimethylamino) ethyl methacrylate-ran-4-acryloylmorpholine) (poly(DMAEMA-ran-4AM)) Statistical Copolymers

As mentioned, poly(4AM) homopolymers are completely water-soluble and do not exhibit any apparent LCST when dissolved in water. However, the inclusion of 4AM, a hydrophilic comonomer, can increase the apparent LCST of a thermo-responsive homopolymer, such as poly(HPA).[32] A series of poly(DMAEMA-*ran*-4AM) statistical copolymers were synthesized with varying compositions of 4AM in the final copolymer between F_{4AM} = 0.01-0.27 (**Table 1**). 1.0 wt. % solutions of the poly(DMAEMA-*ran*-4AM) statistical copolymers in water were heated and their respective CPTs were determined by UV-Vis spectroscopy (**Fig. 5**). As the 4AM content increased, the CPT tended to increase. For example, DMAEMA/4AM-0.02 (F_{4AM} = 0.01) exhibited a CPT = 44.8°C while DMAEMA/4AM-0.05 (F_{4AM} = 0.02) exhibited a CPT = 47.5°C (**Fig. 5**). These results are consistent with the addition of hydrophilic comonomers which help to increase the overall hydrophilicity of the copolymer and thus requires more energy to phase-separate.[56,65] Similarly to the MEMA/VBK copolymers, DMAEMA/4AM-0.02 (F_{4AM} = 0.01) exhibited a hysteresis ≈ 3 °C between the precipitation and the dissolution of the copolymers in water (**Fig. 5**). However, as the content of 4AM in the copolymer increases, the copolymer solution begins to lose its sharp thermo-reversible transition, resulting in a less distinct phase transition and a drop in overall relative absorbance (**Fig. 5**). Similar diffuse transitions have been observed for poly(HPA-*ran*-4AM) copolymers when F_{4AM} > 0.50.[32] To maintain a sharp thermal transition for the DMAEMA/4AM copolymers, the copolymer composition must be F_{4AM} < 0.07 (eg. DMAEMA/4AM-

0.20). These results indicate that when performing the DMAEMA/4AM copolymerizations, $0.10 \leq f_{4AM,0} \leq 0.20$ was necessary to obtain a final copolymer that is characterized by a relatively narrow molecular weight distribution while still exhibiting a sharp thermo-reversible transition.

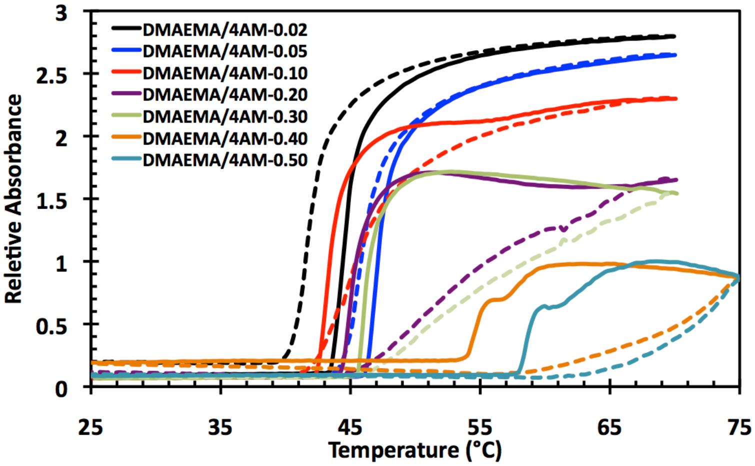


Fig. 5. Characteristic temperature modulated UV-Vis spectrograms used to determine the cloud point temperature (CPT) for various poly(DMAEMA-*ran*-4AM) statistical copolymers. The molecular weight characteristics and copolymer composition of the statistical copolymers can be found in **Table 1**. CPTs were determined using 1.0 wt. % solutions in water.

4. Conclusion

A series of morpholine-based homopolymers and copolymers were synthesized by NMP using BlocBuilder unimolecular initiator to produce thermo-responsive statistical copolymers in most cases. The synthesis of poly(2-N-morpholinoethyl acrylate) (poly(MEA)) resulted in final homopolymers characterized by a relatively narrow molecular weight distributions ($\overline{M_w}/\overline{M_n} < 1.40$) and were completely water-soluble but did not exhibit any transition in a reasonable temperature range. Secondly, a series of poly(2-*N*-morpholinoethyl methacrylate-*ran*-9-(4-vinylbenzyl)-9H-carbazole) (poly(MEMA-*ran*-VBK)) statistical copolymers were synthesized using $f_{VBK,0}$ = 0.01 to 0.1. The resulting poly(MEMA-*ran*-VBK) statistical copolymers exhibited cloud point temperatures (CPTs) between 33.7 and 47.9 °C. Increasing the copolymer $\overline{M_n}$, the final VBK copolymer composition, F_{VBK}, as well as the solution concentration resulted in a decrease in the CPT. Increases in the heating rate from 0.1 to 2.0 $^{\circ}\mathrm{C}\cdot\mathrm{min}^{-1}$ resulted in an increase in CPT ~ 4 °C. Finally, 4-acryloylmorpholine (4AM) was tested as a controlling comonomer for the copolymerization of 2-(dimethylamino) ethyl methacrylate (DMAEMA) using a variety of initial molar feed compositions, $f_{4AM,0}$ = 0.02-0.50. It was found that $0.10 \leq f_{4AM,0} \leq 0.20$ was necessary in obtaining relatively good control over the copolymerization ($\overline{M_w}/\overline{M_n} < 1.6$, linear increase in $\overline{M_n}$ versus *X*) and final statistical copolymers which would exhibit a sharp/completely reversible thermo-transition (CPTs ≈ 45-47 °C). These results demonstrate the versatility of NMP to incorporate morpholine functional groups into well-defined statistical copolymers exhibiting thermo-responsive behaviour.

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Table 1. *Molecular Weight Characterization for poly(2-N-Morpholinoethyl Methacrylate -ran-9-(4-Vinylbenzyl)-9H-Carbazole) (poly(MEMA-ran-VBK) and poly(2-(Dimethylamino)Ethyl Methacrylate-ran-4-Acryloylmorpholine) (poly(DMAEMA-ran-4AM) Statistical Copolymers.*

Exp. ID[a]	$f_{\mathrm{VBK},0}$	F_{VBK}[b]	X[c]	$\overline{M_n}$[d] (kg·mol^{-1})	$\overline{M_w}/\overline{M_n}$[d]
MEMA/VBK-10-0.01	0.01	0.01	0.66	5.7	1.78
MEMA/VBK-10-0.02	0.02	0.03	0.69	5.6	1.73
MEMA/VBK-15-0.04	0.04	0.04	0.76[e]	10.0	1.47
MEMA/VBK-25-0.01	0.01	0.02	0.68	12.9	1.73
MEMA/VBK-25-0.02	0.02	0.03	0.71	14.5	1.53
MEMA/VBK-25-0.05	0.05	0.06	0.70	13.3	1.44
MEMA/VBK-25-0.10	0.10	0.12	0.58	10.4	1.36
MEMA/VBK-50-0.02	0.02	0.02	0.69	21.7	1.64

Exp. ID[a]	$f_{\mathrm{4AM},0}$	F_{4AM}[b]	X[c]	$\overline{M_n}$[d] (kg·mol^{-1})	$\overline{M_w}/\overline{M_n}$[d]
DMAEMA/4AM-0.02	0.02	0.01	0.46	10.1	1.70
DMAEMA/4AM-0.05	0.05	0.02	0.48	10.3	1.63
DMAEMA/4AM-0.10	0.10	0.04	0.45	10.3	1.56
DMAEMA/4AM-0.20	0.20	0.07	0.44	8.4	1.62
DMAEMA/4AM-0.30	0.30	0.13	0.56	9.1	1.65
DMAEMA/4AM-0.40	0.40	0.21	0.55	9.6	1.51
DMAEMA/4AM-0.50	0.50	0.27	0.49	9.1	1.57

[a] Experimental identification (Exp. ID) for MEMA/VBK and DMAEMA/4AM copolymerizations are given by MEMA/VBK-Z-Y, and DMAEMA/4AM-Y, respectively, with MEMA representing 2-N-morpholinoethyl methacrylate, VBK representing 9-(4-vinylbenzyl)-9H-carbazole, 4AM representing 4-acryloylmorpholine, DMAEMA representing 2-(dimethylamino)ethyl methacrylate, Z representing the $\overline{M_n}_{Target}$ used and Y representing the initial molar fraction of VBK or 4AM in the feed..

[b] F_{VBK} and F_{4AM} are the molar fractions of VBK and 4AM, respectively, in the final copolymer as determined by ^{1}H NMR spectroscopy.

[c] Monomer conversion determined by ^{1}H NMR spectroscopy.

[d] Number-average molecular weight ($\overline{M_n}$) and polydispersity index ($\overline{M_w}/\overline{M_n}$) were determined by gel permeation chromatography (GPC).

[e] The conversion was not determined by NMR. It was estimated based on the gravimetric yield as this sample was targeted for solution properties of the copolymer and not kinetic data.

Table 2. *Molecular Weight Characterization for poly(2-N-Morpholinoethyl Methacrylate -ran-9-(4-Vinylbenzyl)-9H-Carbazole) (poly(MEMA-ran-VBK) Chain Extensions with VBK.*

Exp. ID[a]	$f_{\mathrm{VBK},0}$	$F_{VBK}{}^{b}$	$\overline{M_n}{}^{c}$ (kg·mol^{-1})	$\overline{M_w}/\overline{M_n}{}^{c}$
MEMA/VBK-15-0.04	0.04	0.04	10.0	1.47
MEMA/VBK-15-0.04-b-VBK	-	-	26.4	1.70
MEMA/VBK-15-0.04-b-VBK$_F$	-	0.90	34.5	1.54

[a] The experiment ID MEMA/VBK-15-0.04 means that the polymer is a MEMA/VBK statistical copolymer that was formulated to have a target molecular weight at full conversion of 15 kg·mol^{-1} with an initial molar fraction of VBK in the feed, $f_{VBK,0}$, of 0.04. The second entry MEMA/VBK-15-0.04-b-VBK is the chain extension of the copolymer with a batch of VBK. The last entry in the table refers to the fractionated sample of MEMA/VBK-15-0.04-b-VBK.

[b] F_{VBK} is the molar fraction of VBK in the final copolymer as determined by ^{1}H NMR.

c Number-average molecular weight ($\overline{M_n}$) and polydispersity index ($\overline{M_w}/\overline{M_n}$) were determined by gel permeation chromatography (GPC) relative to poly(methyl methacrylate) standards in THF at 40ºC.

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