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Poly(2-oxazoline) with Pendant Hydroxyl Groups via a Silyl Ether-Based Protecting Group

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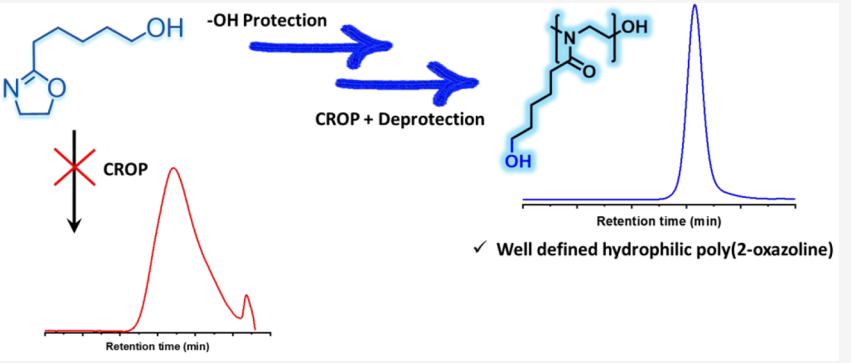

ABSTRACT: The introduction of a functionality onto a poly(2-oxazoline) (POx) chain has been widely explored, yet reports of POx bearing hydroxyl side chains in a well-defined manner have not. Here, we report a simple yet elegant approach for the synthesis of POx with pendant hydroxyl groups through use of silyl protecting groups. First, a hydroxyl group containing 2-oxazoline monomer was synthesized from ε-caprolactone, which on its own results in poorly defined polymers. Moreover, protecting the hydroxy group with silyl ether-based protecting group led to well-defined polymers with free hydroxyl groups on the side chains upon deprotection. Finally, copolymers with 2-ethyl-2-oxazoline resulted in polymers with tunable hydrophilicity, and copolymers with 2-*n*-propyl-2-oxazoline resulted in polymers with tunable thermoresponsive behavior in water.

INTRODUCTION

The increasing attention of poly(2-oxazoline)s (POx) in both biological and industrial applications has led to a plethora of research on this very interesting polymer class.[1−3] Numerous literature examples exist regarding the synthesis of POx via cationic ring-opening polymerization (CROP) and are very well summarized in several review articles.[4−7] Although the CROP of 2-oxazolines with alkyl side chains can be relatively straightforward in that there are no major interferences from the monomer that can result in chain transfer and/or termination reactions, monomers bearing certain functionalities are not so facile.[8,9] In particular, free amines and alcohols as well as acids can have detrimental effects on the pseudoliving nature of the polymerization leading to chain transfer reactions and poorly defined chains.[10,11] Therefore, it is important to either have a noninterfering functional group or have a suitable protecting group that will not hinder the polymerization. Alternatively, desirable functional groups can be introduced on the chain end through end-capping.[12−14] In general, functional groups on a POx chain can be introduced in three ways: on the α-end by using a functional initiator, on the ω-end through using a functional chain terminator, or by functional side chains.[12,15−18] Side chain functionalization can be introduced by either polymerization of a monomer containing the functional group or post-polymerization modification.[19,14,20−22]

POx bearing amines on the side chains have been synthesized through the use of a protected amine monomer—first by Cesana and co-workers where they synthesized a *tert*-butyloxycarbonyl (Boc)-protected amine 2-oxazoline monomer from 6-aminohexanoic acid.[23] Leiske and co-workers then demonstrated the use of the amino groups containing poly(2-oxazoline)s to introduce cationic charge for gene delivery,[24] and more recently, Zhou and co-workers reported the use of amino-functionalized POx for its abilities as an antimicrobial agent.[25] Other literature reports exist regarding synthesis and application of amino-functionalized POx, highlighting the diverse use of amine side chain bearing POx from further functionalization to introduction of cationic charge to the polymer.[26,27]

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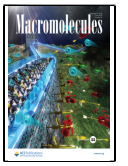
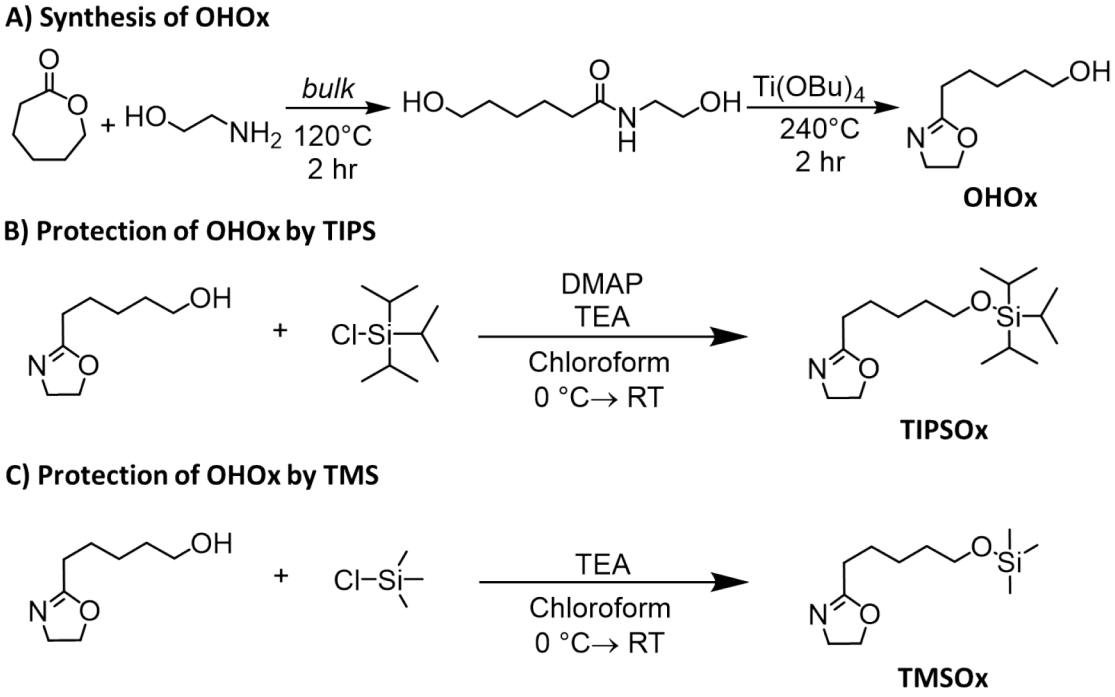


Scheme 1. (A) Synthesis of OHOx from ε-Caprolactone, (B) Synthesis of TIPSOx by TMSCl Protecting Group, and (C) Synthesis of TMSOx by a TMSCl Protecting Group



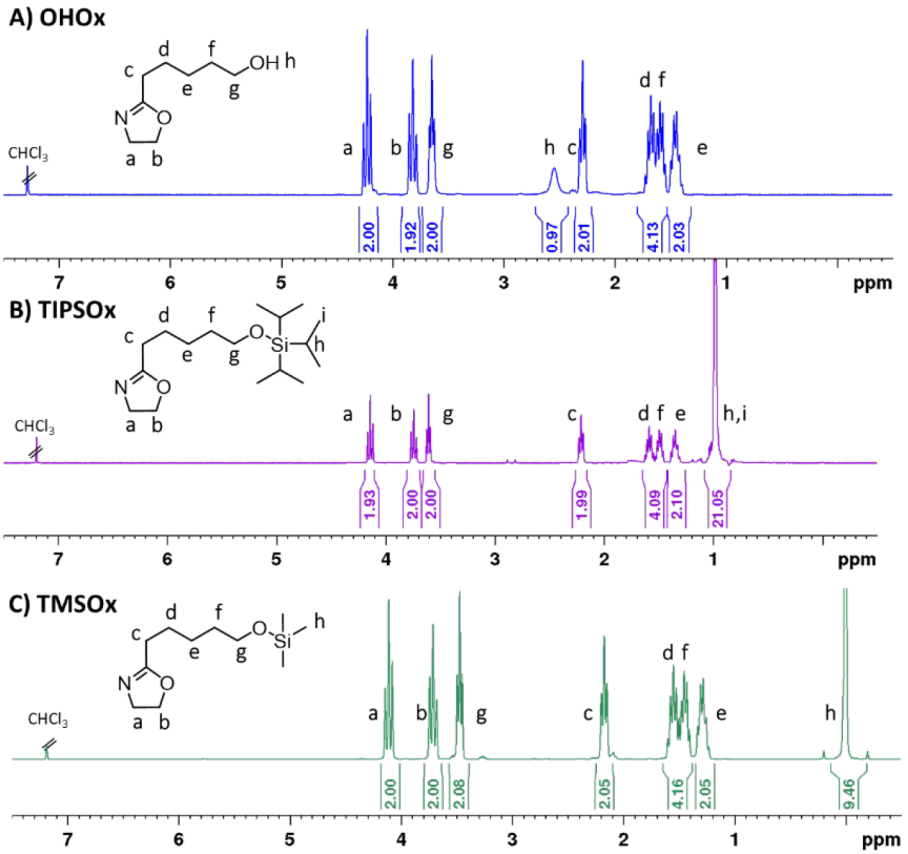


Figure 1. ^{1}H NMR spectra of OHOx, TIPSOx, and TMSOx, measured in $CDCl_3$.

The synthesis of 2-*n*-pentanol-2-oxazoline (OHOx) was first reported by Levy and Litt more than four decades ago but since then very little has been reported regarding the use of this monomer.[28] They reported that the polymerization of OHOx resulted in a hard, amorphous, insoluble material as the alcohol group interferes with the pseudoliving nature of the CROP reaction; the resulting polymer was poorly defined and was assumed that the material is highly cross-linked. Since then,

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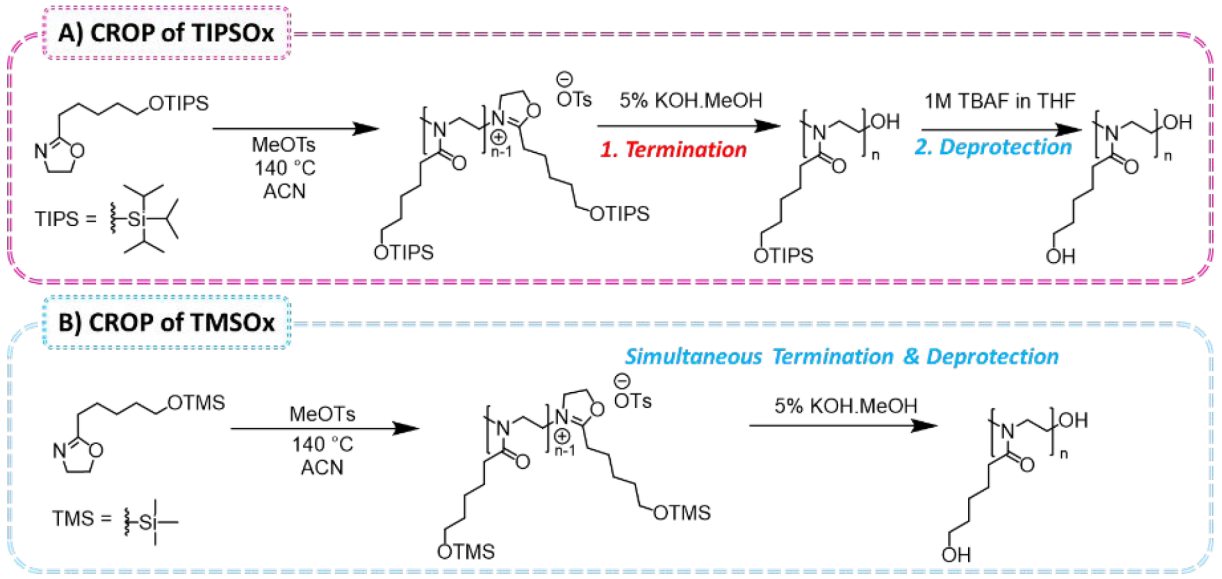
Scheme 2. (A) CROP of TIPSOx and Subsequent Termination with 5% KOH/MeOH Followed by Deprotection through TBAF and (B) CROP of TMSOx Followed by Simultaneous Termination and Deprotection with 5% KOH/MeOH



almost no reports contain the use of this monomer, only that the monomer can be synthesized from ϵ-caprolactone, but no further reports on its polymerization or the use of hydroxyl group bearing POx have been reported.[12,29] In addition, OHOx was reported in a patent whereby the molecule was used as a precursor to radiation curable compounds.[30] To the best of our knowledge, our group was the first to revitalise the use of this monomer for CROP through further functionalization by first introducing an initiator for Cu(0)-mediated RDRP[31] and then a chain transfer agent (CTA) for RAFT polymerization.[32] This allowed for graft copolymer synthesis, combining CROP with controlled radical polymerization in a *grafting from* manner. However, the hydroxyl group itself can be a useful functional group to have on a polymer; it can increase the hydrophilicity of the polymer,[33] can allow for further post-polymerization modification,[34] and can also function as an initiator for ring-opening polymerization (ROP). Therefore, the aim of this work was to find a suitable protecting group that would allow for the CROP of the monomer in a well-defined manner, fully deprotect the monomer leading to pendant OH groups on the polymer side chain, and characterization of the deprotected polymer and determine what properties they exhibit.

RESULTS AND DISCUSSION

Synthesis of Monomers OHOx, TIPSOx, and TMSOx. Following previous literature,[28] OHOx was synthesized from ϵ-caprolactone resulting in OHOx, the 2-oxazoline monomer with the −OH side group (Scheme 1A). The ^{1}H NMR and ^{13}C NMR of OHOx are shown in Figures 1A and S1, respectively. A plethora of alcohol protecting groups have been previously reported in the literature, and notably, a silyl ether-based protecting group is a common class in organic chemistry. Depending on the R group of the silyl group, it can be more or less robust against acidic/basic conditions, with the trimethylsilyl (TMS) being the least resilient under these conditions and *tert*-butyldiphenylsilyl (TBDS) being the most stable.[35] Triisopropylsilyl (TIPS) was the first choice for the protection of the alcohol, it being a common protecting group that is relatively stable across acidic/basic conditions and can be deprotected using tetrabutylammonium fluoride (TBAF) (Scheme 1B).

The TIPS-protected monomer (TIPSOx) was synthesized by reacting OHOx with triisopropylsilyl chloride under basic conditions (addition of TEA and DMAP) and was purified by column chromatography (see Figures 1B and S2 for ^{1}H and ^{13}C NMR spectrum, respectively). Next, TMSOx was synthesized from OHOx and trimethylsilyl (TMS) chloride. Rarely used as an alcohol protecting group as it is extremely acid/base labile,[35] the motivation was to take advantage of this so that the end-capping and deprotection of the polymer could happen in a simultaneous and rapid manner because the termination of CROP can be achieved by the addition of a base. Synthesis of the monomer proceed in a similar manner as TIPSOx, although the protection was successful without the addition of DMAP and monomer purification was achieved by vacuum distillation (see Figures 1C and S3 for ^{1}H and ^{13}C NMR spectra, respectively). TGA analysis of OHOx, TIPSOx, and TMSOx showed that all were thermally stable to at least 200 °C (Figure S4).

CROP of OHOx, TIPSOx, and TMSOx. Polymerization of OHOx was conducted under standard CROP conditions using methyl *p*-toluenesulfonate (MeOTs) as an initiator at 140 °C in dry acetonitrile (**P1**). As expected, the nucleophilicity of the terminal alcohol group resulted in unwanted side reactions as indicated by the SEC trace with relatively broad dispersity (Figure S5). Kinetics investigation of **P1** showed a linear semilogarithmic indicating "livingness" of the reaction; however, dispersity increased as conversion increased. In addition, the M_n determined by SEC started to deviate from the theoretical M_n, indicating that it was not a linear polymer. Copolymerization with the commercially available 2-ethyl-2-oxazoline (EtOx, **P2**) also reached to full monomer conversion with a dispersity value of 2.03 (Figure S6).

Subsequent polymerization of TIPSOx under the same reactions conditions as **P1** (the polymerization of the unprotected monomer, OHOx) resulted in a polymer with relatively narrow dispersity (Scheme 2A, Figure 2A). Upon

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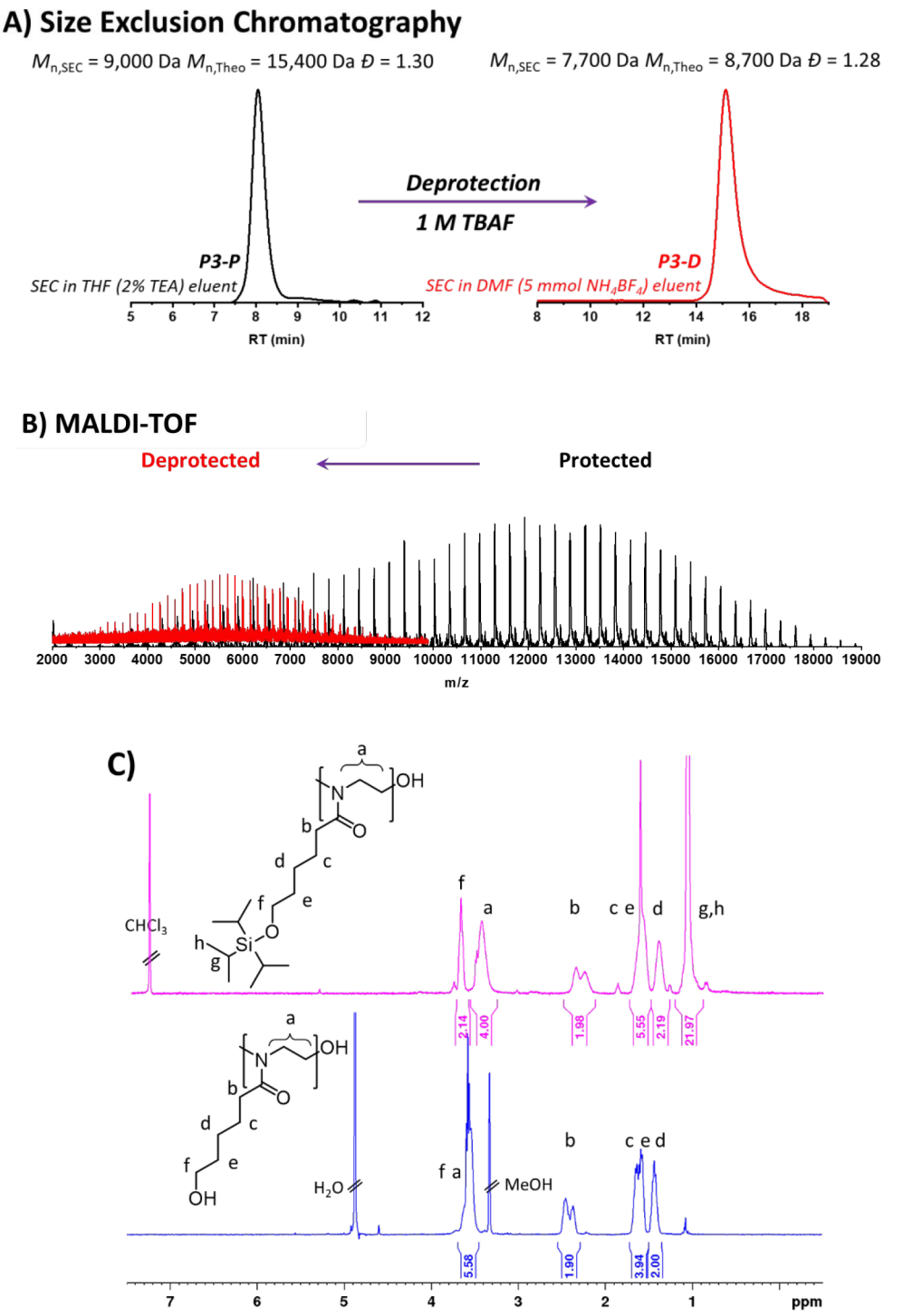

Figure 2. (A) Normalized SEC trace of **P3-P** in THF eluent with 2% TEA and normalized SEC trace of **P3-D** in DMF (5 mmol of NH_4BF_4) eluent. (B) MALDI-TOF spectra of **P3-P** and **P3-D**. (C) ^{1}H NMR spectra of **P3-P** (measured in $CDCl_3$) and **P3-D** (measured in MeOD).

addition of 5% KOH/MeOH to the reaction mixture, the polymer chains were terminated resulting in −OH-terminated chains. The TIPS group, however, was robust enough to withstand these basic conditions, and therefore it was possible to isolate the protected polymer by precipitation in cold methanol, resulting in **P3-P** (Figure 2). As expected, the protected polymer was not soluble in polar solvents such as DMF, methanol, or water but more soluble in other organic solvents such as THF. MALDI-TOF analysis was performed on **P3-P** showing a distribution with an average repeating unit of 316 Da, closely matching the molecular weight of the monomer repeating unit (Figure S7).

Deprotection of the TIPS group was then performed by stirring the polymer solution in a 1 M tetrabutylammonium fluoride (TBAF) solution in THF and was directly dialyzed against water, resulting in a fully deprotected polymer with pendant −OH groups on the side chains (Figure 2C). This was evident from the polymer becoming fully soluble in polar solvents such as MeOH, DMF, and water. Analysis of the deprotected polymer, **P3-D**, by ^{1}H NMR spectroscopy

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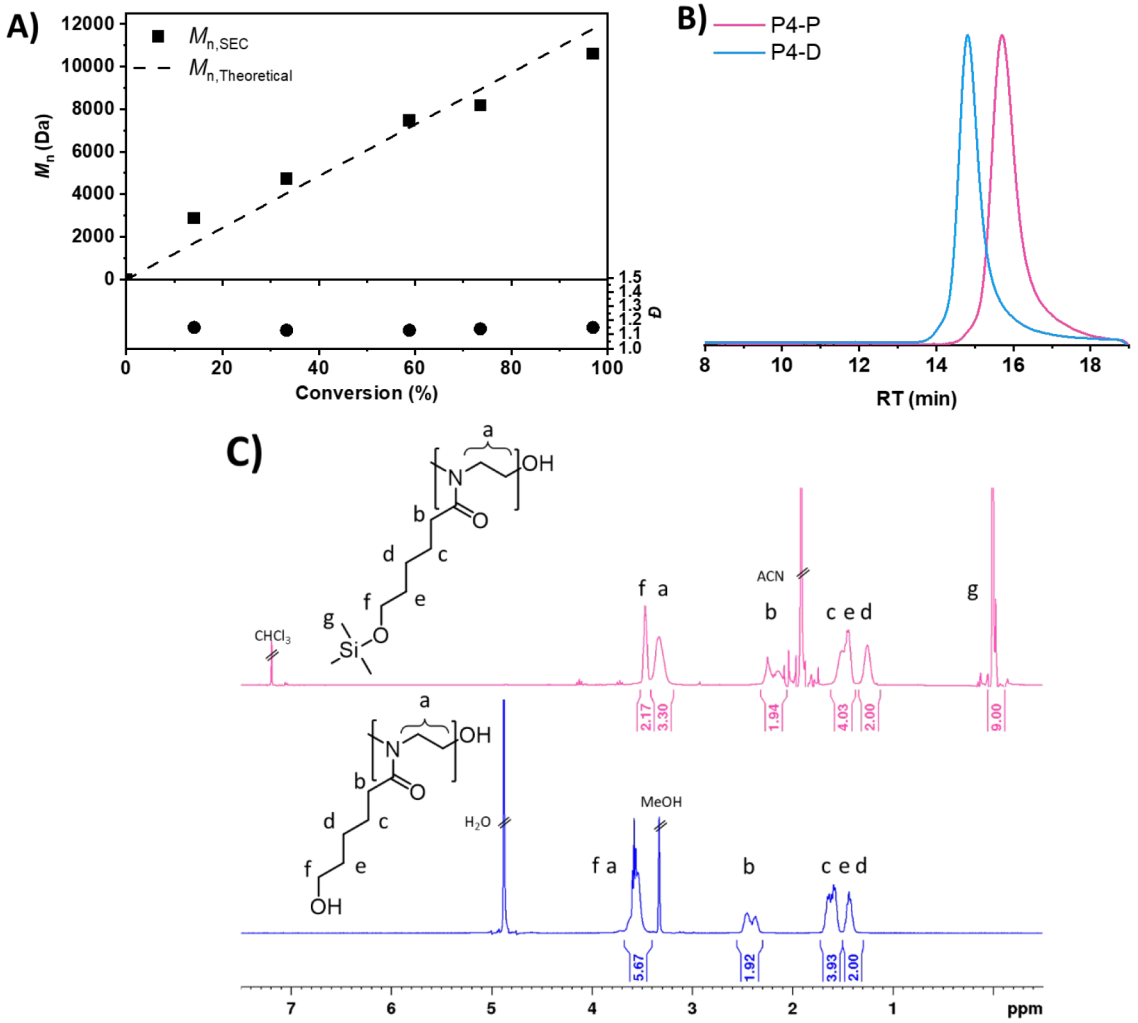

Figure 3. (A) Evolution of molecular weight and dispersity over conversion for CROP of **P4-P**. (B) Normalized RI SEC traces of **P4-P** and **P4-D** measured in DMF (5 mmol of NH_4BF_4) eluent. (C) ^{1}H NMR spectra of **P4-P** (measured in $CDCl_3$) and **P4-D** (measured in MeOD).

indicated that all side chains had undergone deprotection since the peaks associated with the TIPS protons had disappeared (Figure 2C). The SEC trace measured in DMF eluent showed that the polymer still showed relatively narrow dispersity. In addition, FT-IR analysis showed a strong, broad absorption at around 3400 cm^{-1}, indicating the presence of −OH groups in the polymer (Figure S8). Analysis of **P3-D** by MALDI-TOF spectrometry showed a clear shift in the molecular weight distribution with an average repeat unit of 157 Da (Figure 2). The synthesis and polymerization of TIPSOx are, to the best of our knowledge, the first demonstration of forming poly(2-oxazoline)s containing pendant hydroxyl groups with relatively good control over molecular weight and dispersity via a silyl ether-based protecting group. The synthesis of TIPSOx in relatively good overall yield as well as the facile polymerization and deprotection of the TIPS group highlights the advantages of using the TIPSOx monomer.

Polymerization of TMSOx at 140 °C again resulted in polymers with relatively narrow dispersity, and kinetics investigations showed that it proceeded in a pseudoliving manner. Direct injection of 5% KOH/MeOH solution into the polymerization mixture followed by dialysis of the polymer against water both fully terminated and deprotected the polymer, which was confirmed by SEC, NMR spectroscopy, and FT-IR. FT-IR analysis of the deprotected polymer, **P4-D**, compared to the protected polymer, **P4-P**, showed a strong, broad absorption at around 3400 cm^{-1}, indicating the presence of −OH bonds in the polymer (Figure S8). This along with ^{1}H NMR spectra showing complete disappearance of the TMS group would suggest complete deprotection, resulting in pendant −OH units across the polymer (Figure 3).

P4-P was analyzed in both THF and DMF eluent SEC, and although both showed SEC traces with relatively narrow dispersity, the SEC trace of the DMF eluent displayed lower molecular weight than the theoretical molecular weight and the SEC trace measured in THF eluent matched more closely with the theoretical molecular weight (Figure S9). Comparison of the protected polymer (**P4-P**) and the deprotected polymer (**P4-D**) by DMF SEC, with narrow PMMA calibration, showed an apparent higher molecular weight for the deprotected polymer even though there is inevitable mass loss from the deprotection procedure. Potential discrepancies between the theoretical and calculated molecular weight of **P4-P** could be that DMF is a poor solvent for the protected polymer, leading to a smaller hydrodynamic volume, resulting in the $M_{n,SEC}$ being much lower than $M_{n,Theo}$. Calculation of absolute molecular weight of **P4-D** using universal calibration by use of RI, viscometry, and light scattering data matched

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closely to that of the theoretical molecular weight of the polymer but was not possible to do the same with **P4-P** as it was challenging to isolate the protected polymer.

As mentioned above, the SEC trace of **P1**, when OHOx was polymerized with no protecting group, showed a polymer with a broad dispersity. This was presumed to be because of the interfering nature of the alcohol group on the pseudoliving cationic mechanism resulting in chain transfer reactions as well as premature chain termination, ultimately resulting in a nonlinear chain. Multidetector SEC analysis in DMF eluent was therefore performed to compare **P1** and **P4-D** to determine what effects the protection−deprotection steps had on the polymer architecture. Direct comparison of the two polymers showed differing intrinsic viscosities between **P4-D** and **P1** as shown in the Mark−Houwink plots (Figure S10). The intrinsic viscosity of **P1** is much lower than that of **P4-D** at the same molecular weight values. Also, the alpha values, as calculated from the slopes of the plots, were determined to be 0.46 and 0.70, respectively. This indicates that **P4-D** behaves like a linear polymer in the DMF eluent whereas **P1** behaves more like a branched structure. This would also correlate with the proposed mechanism of CROP for the OHOx monomer on its own, with no protecting group, where the −OH group would lead to many termination and side reactions, resulting in some form of branching. Overall, comparison of **P1** and **P4-D** by SEC highlights the advantages of the TMSOx CROP route for linear polymer structures with narrow dispersity.

Finally, MALDI-TOF spectrometry analysis of the deprotected polymer, **P4-D**, showed a major distribution that matched closely to the calculated molecular weight, with the molecular weight between the repeating units being that of the molecular weight of OHOx (Figure 4).

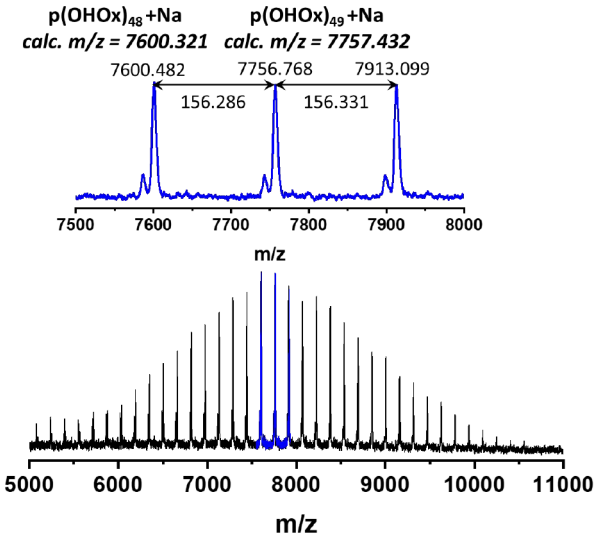

Figure 4. MALDI-TOF spectrum of **P4-D** measured in reflector mode.

MALDI-TOF spectrometry analysis was also attempted on **P4-P**, but no clear spectrum was obtained under various sample preparation methods. Therefore, a shorter DP polymer (DP = 10, **P5**) was prepared to see if the protected monomer could be analyzed by MALDI, and indeed, at smaller molecular weight, MALDI spectra were observed with multiple distributions (Figure S11). Detailed analysis of the spectra showed that some of the peak distances were associated with the molecular weight of the protecting group, whereas some had a peak difference of roughly m/z = 157 Da, which is the molecular weight of the unprotected monomer, OHOx. Therefore, it could be theorized that the TMS groups can undergo a degree of degradation by laser irradiation in the MALDI-TOF spectrometer or is cleaved off during sample preparation.

Because of the facile nature of the deprotection step, as well as the relatively straightforward synthesis and purification, TMSOx was chosen as the ideal monomer to continue using compared to TIPSOx. Following the demonstration of TMSOx in CROP, copolymers of TMSOx and other 2-oxazoline monomers were targeted, mainly 2-ethyl-2-oxazoline (EtOx) and 2-*n*-propyl-2-oxazoline (*n*PropOx), as outlined in Table 1. All polymers showed relatively narrow dispersities before and after purification.

Determination of Hydrophilicity. Because of the side chain structure of the polymers containing OHOx, where the long alkyl chain (C_5) would be contribute to the polymers' overall hydrophobicity but the alcohol group would increase the hydrophilicity, the polymers were analyzed by high-performance liquid chromatography (HPLC) on a reversed phase column to determine their hydrophilicity with respect to poly(EtOx) and poly(MeOx). The signal at 210 nm was used to compare the retention times because the polymers have a very low UV absorption and the signal at 210 nm gave the clearest peak in the chromatogram. In a gradient eluent of water and methanol, poly$(EtOx)_{50}$ eluted at a retention time of 14.3 min. In comparison, **P4-D**, a polymer of relatively similar repeating units, had a much faster elution time of 6.8 min, indicating that the addition of pendant −OH units in a linear fashion resulted in a dramatic increase in hydrophilicity. Compared to poly$(EtOx)_{100}$, which as a similar molecular weight to **P4-D**, it again showed to be more hydrophilic; the longer poly(EtOx) chain has a slightly higher retention time than the shorter poly(EtOx) chain.

P1, which was previously shown the have a branched structure, had a slightly longer retention time of 8.5 min but was still shown to be much more hydrophilic than p$(EtOx)_{50}$. As expected, **P7-D**, which contained 50% OHOx and 50% EtOx, had a retention time of 10.3 min, which was approximately halfway between **P4-D** and p$(EtOx)_{50}$ (Figure 5). **P9-D**, which is a copolymer with the more hydrophobic PropOx, showed the highest retention time of the measured polymers of 15.8 min. However, it must be noted that this was still similar to poly$(EtOx)_{100}$, indicating that incorporation of OHOx increases polymer hydrophilicity. Analysis of poly(MeOx), which can be considered the most hydrophilic poly(2-oxazoline),[36] showed the shortest retention time of 0.97 and 0.98 min for poly$(MeOx)_{50}$ and poly$(MeOx)_{100}$, respectively. Although poly(MeOx) was shown to be more hydrophilic compared to **P4-D**, considering the longer alkyl chain of OHOx (C_5), its hydrophilic behavior in solution is an interesting property.

Thermoresponsive Properties of Copolymers Containing OHOx. Thermoresponsive polymers that have a lower critical solution temperature (LCST) behavior in solution can undergo an entropy driven change in conformation that is temperature induced.[37] Polymers that have an LCST will therefore be miscible in solution below the critical temperature but will become immiscible/partially immiscible above the critical temperature. Poly(2-oxazoline)s with ethyl (EtOx), *n*-propyl (PropOx), and isopropyl side groups are known to

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Table 1. List of Homo- and Copolymers Synthesized Using OHOx, TIPSOx, and TMSOx

polymer[a]	Mon 1	DP[b]	Mon 2[c]	Mon 2 DP	RT/min[d]	conv/%[e]	$M_{n,Theo}$/Da	$M_{n,SEC}$/Da[f]	$Đ$[f]
P1	OHOx	53			20	>99	9600	7900	1.98
P2	OHOx	28	EtOx	30	20	>99	7400	9400	2.03
P3-P	TIPSOx	47			30	>99	15400	9000[g]	1.30
P3-D							7700	8700	1.28
P4-P	TMSOx	54			18	96	11600	6100	1.22
P4-D							8200	8200	1.14
P5	TMSOx	10			5	90	2300	3320	1.20
P6-P	TMSOx	100			40	96	21400	14300	1.14
P6-D							15100	14220	1.18
P7-P	TMSOx	34	EtOx	32	20	92	10100	8000	1.22
P7-D							8500	9500	1.32
P8-P	TMSOx	6	*n*PropOx	46	20	96	6600	7800	1.11
P8-D							6200	8900	1.11
P9-P	TMSOx	26	*n*PropOx	25	20	>99	8500	6800	1.30
P9-D							6700	6800	1.42
P10-P	TMSOx	47	*n*PropOx	5	20	>99	10900	1300	1.04
P10-D							7700	8900	1.33

[a]P denotes protected polymer, and D denotes deprotected polymer. [b]DP denotes degree of polymerization. [c]Mon **2** denotes comonomer used where EtOx is 2-ethyl-2-oxazoline and *n*PropOx is 2-*n*-propyl-2-oxazoline. [d]Denotes reaction time. [e]Conversion as calculated by ^{1}H NMR. [f]$M_{n,SEC}$ and $Đ$ from DMF (5 mmol of NH_4BF_4) eluent SEC. [g]$M_{n,SEC}$ and $Đ$ from SEC in THF (2% TEA) measured with narrow PMMA standards. All polymerizations are conducted in acetonitrile in a sealed vial at 140 °C in an oil bath.

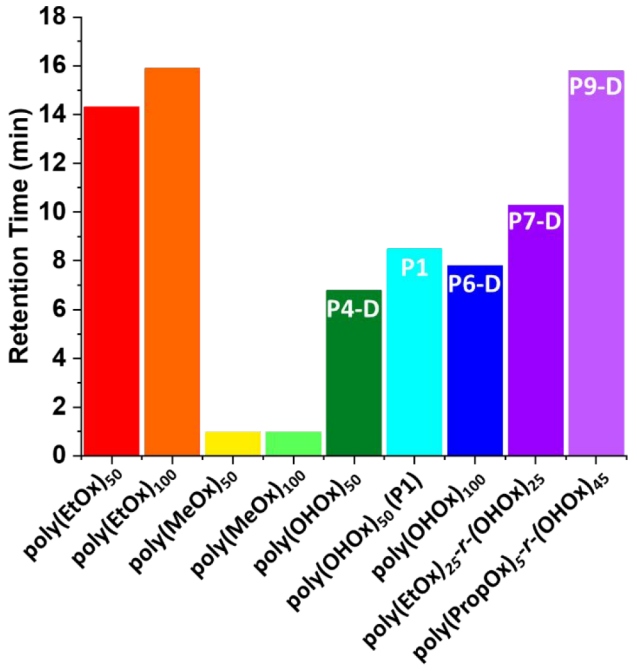

Figure 5. Retention times of polymers measured by HPLC with a DAD detector at 210 nm.

display LCST behavior in water;[38] however, poly(2-oxazoline)s with longer alkyl chains can be characterized as hydrophobic and do not generally dissolve in water.[10] Hoogenboom et al. had previously reported the tuning of the LCST of copolymers of EtOx and PropOx whereby increasing the content of PropOx in a polymer chain decreased the cloud point.[38]

For a polymer in solution, the LCST is also dependent on the chain length (or DP), dispersity, and branching.[39] Linear poly(EtOx), for example, does not have an LCST below 100 °C in water when DP < 100, and the lowest cloud point temperature (T_{CP}) was reported to be 66 °C when DP = 500, whereas poly(*n*PropOx) has a T_{CP} = 42.9 °C for a DP = 15.[38] OHOx, which has a relatively long alkyl chain (C_5) but also contains a hydroxyl functional group, could therefore be seen as hydrophobic or hydrophilic depending on its structure. Therefore, polymers containing OHOx were investigated to see if they would display any thermoresponsive behavior in water and if it could be tuned by incorporating different 2-oxazoline monomers, mainly EtOx and *n*PropOx.

First, turbidity measurements for **P4-D**, which from the Mark–Houwink plot is presumed to be a linear poly(OHOx)$_{50}$ chain, were performed at concentrations of 5 and 10 mg/mL in water. At both concentrations, it showed no cloud point below 85 °C (Figure 6), which given the cuvettes used and the solution it was measured in was determined to be the upper measurement limit.

P1, on the other hand, is presumed to have a somewhat branched architecture from the SEC analysis. As discussed above, the Mark–Houwink plot for **P1** showed that its intrinsic viscosity was lower than that of **P4-D**. Therefore, **P1** was also investigated to determine if the architecture had any effects on their solution behavior in water. Interestingly, **P1** did show a cloud point temperature of 57.5 °C at 5 mg/mL in water; however, the transmittance did not fully reach 0%, indicating that it only became partially immiscible at higher temperatures (Figure 6). At a higher concentration of 10 mg/mL in water, the cloud point increased to 54.5 °C but still did not fully reach 0% transmittance.

The same comparison measurements were performed for copolymers of EtOx to determine if the composition, as well as architecture, affected the thermoresponsive properties of the polymer. **P7-D**, which is determined to be a linear copolymer of OHOx and EtOx, did not have a T_{CP} in water between 20 and 85 °C (Figure S16). However, **P2**, which is also a copolymer of EtOx and OHOx of the same ratio as **P7-D** albeit not a linear structure, showed a T_{CP} of 66.5 °C (Figure S16). The transmittance for **P2** at higher temperatures reached 0%, unlike in **P1**, and some hysteresis between the heating and cooling cycle. Cloud point measurements of polymers of OHOx and copolymers with EtOx showed that the linear

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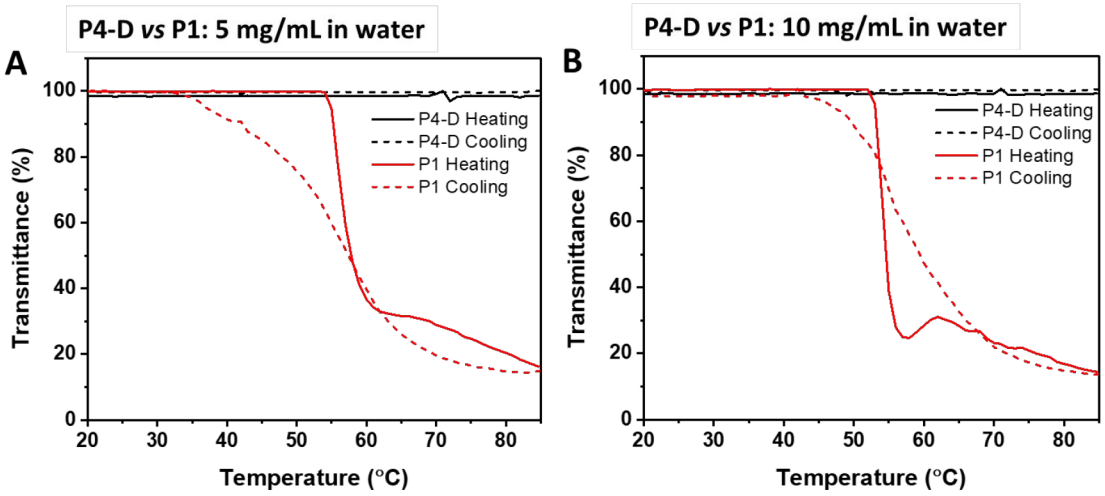

Figure 6. Turbidity measurements of **P4-D** and **P1** at (A) 5 mg/mL in water and (B) 10 mg/mL in water.

polymers had no thermoresponsive behavior whereas the branched structures did. This would indicate that with polymers of OHOx and OHOx-EtOx, architecture had a greater influence than composition on its solution behavior. This is also in line with literature reports on poly(EtOx) not having a cloud point below 100 °C at low DPs, and the hydroxyl groups of the OHOx would only make it more, not less, soluble in water.

Copolymers containing *n*PropOx and OHOx were then investigated to determine if incorporation of OHOx units would result in tunable thermoresponsive behavior, poly(*n*PropOx) having a much lower LCST than poly(EtOx). With an overall target DP = 50, three polymers were synthesized with varying degrees of TMSOx incorporated with *n*PropOx (Table 1). Turbidity measurements of *n*PropOx (DP = 50) showed a T_{CP} of 33.5 °C. When there was 10% incorporation of OHOx, the T_{CP} was not affected (**P10-D**, Figure 7). However, at 50% incorporation of OHOx, the T_{CP} increased to 45.5 °C (**P9-D**, Figure 7), and finally when OHOx incorporation was 90%, the T_{CP} increased to 72.5 °C (**P8-D**, Figure 7).

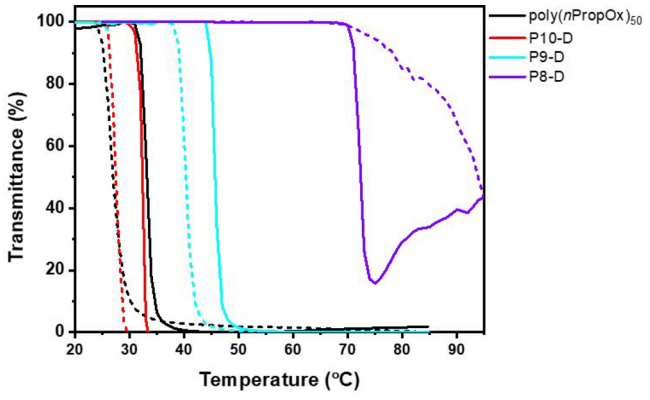

Figure 7. Cloud point measurements of **P10-D**, **P9-D**, and **P8-D** compared to poly(*n*PropOx)$_{50}$ all measured in water at 10 mg/mL. The solid line shows the second heating cycle, and the dotted line shows the second cooling cycling.

CONCLUSION

We demonstrate a facile approach to linear poly(2-oxazoline) polymers with pendant hydroxyl groups by using a silyl ether-based protected 2-oxazoline monomer during the polymerization. When using TMS as the protecting group, simultaneous termination and deprotection were achieved, resulting in a fast track access to poly(2-oxazoline)s bearing alcohol units on the side chains. Homopolymers containing hydroxyl groups were shown to be relatively hydrophilic compared to linear poly(EtOx), and the hydrophilicity could be tuned depending on the ratio of OHOx units in the polymer. Finally, the thermoresponsive behavior of OHOx containing polymers was investigated. It showed that branched poly(OHOx) structures formed from the polymerization of the unprotected monomer resulted in thermoresponsive behavior, whereas linear poly(OHOx) form the polymerization of the protected monomer did not. This would indicate that branching has an effect on their solution behavior in water. Finally, copolymers containing OHOx and *n*PropOx resulted in tunable cloud point temperatures.

EXPERIMENTAL SECTION

Materials. 2-Ethyl-2-oxazoline (EtOx) (>99%, Sigma-Aldrich) and 2-methyl-2-oxazoline (MeOx) (>98%, Sigma-Aldrich) were distilled over calcium hydride prior to use and stored over 3 Å molecular sieves. ε-Caprolactone (97%, Sigma-Aldrich) and methyl *p*-toluenesulfonate (MeOTs) (>97%, Fisher Scientific) were distilled prior to use and stored over 3 Å molecular sieves. Ethanolamine (≥99.0%, Sigma-Aldrich), titanium(IV) *tert*-butoxide (97%, Sigma-Aldrich), butyronitrile (≥99%, Sigma-Aldrich), zinc acetate dihydrate (≥98%, Sigma-Aldrich), triethylamine (≥99.5%, Sigma-Aldrich), anhydrous acetonitrile (>99.9%, Sigma-Aldrich), triisopropylsilyl chloride (97%, Sigma-Aldrich), chlorotrimethylsilane (>98.0%, Sigma-Aldrich), *n*-hexane (Fischer Chemicals), potassium hydroxide pellets (85%, Thermo Scientific), tetrahydrofuran (contains 250 ppm BHT as inhibitor, >99.0%, Sigma-Aldrich), methanol (MeOH) (HPLC grade, Fischer Chemical), dichloromethane (DCM) (≥99.0%, Sigma-Aldrich), ethyl acetate (≥99.5%, Sigma-Aldrich), diethyl ether (≥99.0%, Sigma-Aldrich), (tetrabutylammonium fluoride (TBAF) solution (1.0 M in THF, Sigma-Aldrich), prewetted standard RC dialysis tubing (1 kDa MWCO, Spectrum), *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) (≥99.0%, Sigma-Aldrich), α-cyano-4-hydroxycinnamic acid (≥99.0%, Sigma-Aldrich), and sodium trifluoroacetate (98%, Sigma-Aldrich) were all used as received.

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^{1}H NMR and ^{13}C NMR Spectroscopy. NMR spectra were recorded either on a Bruker Avance III HD 300 or 400 MHz spectrometer at room temperature using deuterated chloroform and deuterated methanol. The resonance signal of residual $CHCl_3$ at 7.26 ppm and MeOH at 3.31 ppm served as a reference for the chemical shift, δ.

Size Exclusion Chromatography (SEC). Two different SEC systems were used in this study due to the solubility differences between the protected and deprotected polymers. The first system was run at 40 °C with an Agilent 1260 infinity system with a THF + 2% TEA (triethylamine), and 0.1% BHT (butylated hydroxytoluene) eluent, equipped with a refractive index detector and variable wavelength detector, 1 × PLgel 5 mm Mixed-C column (300 × 7.5 mm^2) and autosampler. Narrow linear poly(methyl methacrylate) standards were used for calibration between 121600 and 550 g mol^{-1}. All samples were filtered through 0.2 μm PTFE filters before injection.

The second SEC system was an Agilent Infinity II MDS instrument that was equipped with differential refractive index (DRI), viscometry (VS), dual angle light scatter (LS), and variable wavelength UV detectors. The system was equipped with 2 × PLgel Mixed D columns (300 × 7.5 mm^2) and a PLgel 5 μm guard column. The eluent is DMF with 5 mmol of NH_4BF_4 additive. Samples were run at 1 mL/min at 50 °C. Poly(methyl methacrylate) standards (Agilent EasiVials) were used for calibration between 955000 and 550 g mol^{-1}. All samples were filtered through 0.2 μm nylon filters before injection.

Cloud Point Measurements by UV−Vis Spectroscopy. Cloud point measurements were performed on an Agilent Technologies Cary 3500 UV−vis spectrophotometer equipped with an air-cooled Peltier temperature control. The samples were prepared so that they were 10 or 5 mg/mL solutions in water in a disposable cuvette (UV grade PMMA). Each sample underwent three heating and cooling cycles between 15 and 85 °C at a heating/cooling rate of 1 °C/min at λ = 600 nm.

Thermogravimetric Analysis (TGA). Thermal degradation was analyzed on a Mettler-Toledo TGA equipped with an autosampler under an air flow of 50 mL min^{-1} from 25 to 550 °C with a heating rate of 1 °C min^{-1}. The samples (5−10 mg) were prepared using aluminum pans.

MALDI-TOF Spectrometry. MALDI-TOF samples for **P3-P** and **P5** were prepared by making a 10 mg/mL solution in THF. Twenty μL of the sample solution was then mixed with 20 μL of the matrix solution (50 mg/mL of DCTB in THF) and 8 μL of the salt solution (5 mg/mL sodium trifluoroacetate in ethanol). This was then spotted onto a 384 ground steel multitarget plate and left to dry. **P3-D and P4-D** samples were prepared by making a 10 mg/mL solution in MeOH. 20 μL of the sample solution was then mixed with 20 μL of the matrix solution (50 mg/mL of α-cyano-4-hydroxycinnamic acid in MeOH) and 8 μL of the salt solution (5 mg/mL sodium trifluoroacetate in ethanol). The dried spots were then analyzed using a Bruker Autoflex, equipped with a 337 nm N_2 laser, operating in reflectron positive mode with an ion source voltage of 19 kV. Data analysis was then performed on Bruker flexAnalysis software.

Fourier-Transform Infrared (FT-IR). FT-IR was performed on a Bruker ALPHA II FT-IR spectrometer fitted with a crystal plat and a pressure tower running at 65 scans per sample with a speed of 0.5 cm s^{-1}.

High-Performance Liquid Chromatography (HPLC). HPLC chromatograms were measured using an Agilent 1260 Infinity II LC system equipped with an InfinityLab Poroshell 120 EC-C18 column (4.6 × 100 mm^2) with 2.7 μm packing. Water and methanol were used as mobile phases A and B, respectively, and both contained 0.04 vol % TFA. Samples were prepared in water (with 0.04 vol % TFA), and the injection volume was 10 μL. A gradient elution was used where B was increased from 50% to 95% in 20 min and held at that ratio for 5 min and the UV absorbance at 210 nm was measured.

Synthesis of 2-*n*-Propyl-2-oxazoline (PropOx). Butyronitrile (50.3 mL, 579 mmol), ethanolamine (38.5 mL, 637 mmol), and zinc acetate (12.7 g, 57.9 mmol) were refluxed at 130 °C overnight. The reaction mixture was then cooled to room temperature, and DCM was added. The organic layer was washed with water and brine three times, and the solvent was removed under vacuum. The monomer was then purified by distillation *in vacuo* (3.5 × 10^{-3} bar, 20 °C) three times, resulting in the purified PropOx as a clear colorless liquid (22.5 g, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (t, J = 9.5 Hz, 2H), 3.83 (t, J = 9.4 Hz, 2H), 2.26 (t, J = 7.5 Hz, 2H), 1.67 (d, J = 7.5 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ = 167.75, 66.57, 54.14, 29,60, 19.12, 13.23 ppm. ESI-MS (m/z) found 114.1; calcd 114.09 [M + H].

Synthesis of 2-*n*-Pentanol-2-oxazoline (OHOx). ε-Caprolactone (50.1 g, 438 mmol) was added to a flask and heated to 80 °C under inert conditions. The same equivalent of ethanolamine (26.8 g, 438 mmol) was then added to the flask and subsequently heated at 120 °C for 2 h. Titanium(IV) butoxide (7.00 mL, 21.9 mmol) was then added to the reaction mixture and heated *in vacuo* at 230 °C for 2 h. The reaction mixture was then distilled *in vacuo* (3.5 × 10^{-3} bar, 110 °C) four times to obtain the purified 2-*n*-pentanol-2-oxazoline as a clear pale-yellow oil (42.7 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (t, J = 9.5 Hz, 2H), 3.81 (t, J = 9.4 Hz, 2H), 3.65 (q, J = 5.2 Hz, 2H), 2.29 (t, J = 7.3 Hz, 2H), 1.62 (m, J = 6.0 Hz, 6H), 1.45 (q, J = 7.1 Hz, 2H) ppm.^{13}C NMR (400 MHz, $CDCl_3$) δ = 168.93, 67.12, 61.20, 53.50, 31.77, 27.28, 24.22 ppm. ESI-MS (m/z) found 158.1; calcd 158.12 [M + H].

Synthesis of TIPSOx. OHOx (7.10 g, 44.6 mmol) was added to a flask with 150 mL of chloroform. TEA (12.0 mL, 89.1 mmol) and DMAP (0.550 g, 4.45 mmol) were added to the stirred solution, and the reaction mixture was then cooled in an ice bath. TIPSCl (11.4 mL, 53.5 mmol) was added dropwise into the cooled reaction mixture and was left to stir overnight. The reaction was then quenched with water, and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (EA:hexane 9:1), resulting in a clear, colorless oil (5.09 g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (t, J = 9.5 Hz, 2H), 3.74 (t, J = 9.4 Hz, 2H), 3.61 (t, J = 6.4 Hz, 2H), 2.21 (t, J = 7.6 Hz, 2H), 1.59 (m, J = 7.6 Hz, 2H), 1.49 (m, J = 7.0 Hz, 2H), 1.36 (m, J = 4.0 Hz, 2H), 0.98 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ = 169.13, 67.82, 63.33, 54.47, 33.34, 28.63, 25.85, 17.64, 11.79 ppm. ESI-MS (m/z) found 314.2; calcd 314.25 [M + H].

Synthesis of TMSOx. OHOx (15.0 g, 95.5 mmol) was added to a flask with 250 mL of chloroform. TEA (20.0 mL, 143 mmol) was added to the stirring solution and the reaction mixture was then cooled in an ice bath. TMSCl (14.5 g, 143.2 mmol) was added dropwise into the cooled reaction mixture and was left to stir overnight. The reaction was then quenched with water and the organic layer was washed with brine and dried over $MgSO_4$ and purified by distillation *in vacuo* (3.5 × 10^{-3} bar, 100 °C) resulting in a clear colorless oil (15.7 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (t, J = 9.5 Hz, 2H), 3.71 (t, J = 9.4 Hz, 2H), 3.47 (t, J = 6.5 Hz, 2H), 2.17 (t, J = 7.6 Hz, 2H), 1.55 (d, J = 15.2 Hz, 2H), 1.46 (m, J = 7.0, 14.3 Hz, 4H), 1.29 (t, J = 7.1 Hz, 2H), 0 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ = 168.96, 67.59, 61.88, 54.87, 32.83, 28.44, 26.28, 26.02, 0.004 ppm. ESI-MS (m/z) found: 230.1, 252.1; calcd 230.2 [M + H], 252.1 [M + Na].

CROP of EtOx (DP = 50, DP = 100). To an oven-dried microwave vial, EtOx (1.62 g, 16.0 mmol) and dry ACN were added to make a 4 M solution. The reaction vial was then capped and degassed, after which MeOTs (DP = 50:48 μL, 0.320 mmol; DP = 100:24.0 μL, 0.160 mmol) was added to the reaction mixture using a microsyringe. After taking a small aliquot for ^{1}H NMR analysis, the microwave vial was placed in an oil bath at 140 °C and was left to stir for 20 min. Upon reaction completion, the vial was cooled in an ice bath to stop the polymerization, and the reaction mixture was diluted in DCM. The organic layer was then washed with saturated $NaHCO_3$ and brine and subsequently precipitated in cold diethyl ether.

CROP of MeOx (DP = 50, DP = 100). To an oven-dried microwave vial, MeOx (2.72 g, 32.0 mmol) and dry ACN were added to make a 4 M solution. The reaction vial was then capped and degassed, after which MeOTs (DP = 50:97.0 μL, 0.640 mmol; DP = 100:48.0 μL, 0.320 mmol) was added to the reaction mixture using a

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microsyringe. After taking a small aliquot for ^{1}H NMR analysis, the microwave vial was placed in an oil bath at 140 °C and was left to stir for 20 min. Upon reaction completion, the vial was cooled in an ice bath to stop the polymerization and subsequently precipitated in cold diethyl ether.

CROP of PropOx (DP = 50). To an oven-dried microwave vial, PropOx (0.680 g, 6.00 mmol) and dry ACN were added to make a 4 M solution. The reaction vial was then capped and degassed, after which MeOTs (18.0 μL, 0.120 mmol) was added to the reaction mixture using a microsyringe. After taking a small aliquot for ^{1}H NMR analysis, the microwave vial was placed in an oil bath at 140 °C and was left to stir for 20 min. Upon reaction completion, the vial was cooled in an ice bath to stop the polymerization, and the reaction mixture was diluted in DCM. The organic layer was then washed with saturated $NaHCO_3$ and brine and subsequently precipitated in cold MeOH.

CROP of OHOx. To an oven-dried microwave vial, OHOx (0.620 g, 4.00 mmol) and dry ACN were added to make a 4 M solution. The reaction vial was then capped and degassed, after which MeOTs (12.0 μL, 0.060 mmol) was added to the reaction mixture using a microsyringe. After taking a small aliquot for ^{1}H NMR analysis, the microwave vial was placed in an oil bath at 140 °C and was left to stir for 20 min. Upon reaction completion, the vial was cooled in an ice bath to stop the polymerization, and the solvent was removed under vacuum.

CROP of TIPSOx. To an oven-dried microwave vial, TIPSOx (0.630 g, 2.00 mmol) and dry ACN were added to make a 2 M solution. The reaction vial was then capped and degassed, after which MeOTs (6.00 μL, 0.050 mmol) was added to the reaction mixture using a microsyringe. After taking a small aliquot for ^{1}H NMR analysis, the microwave vial was placed in an oil bath at 140 °C and was left to stir for 20 min. Upon reaction completion, the vial was cooled in an ice bath to stop the polymerization. 5% KOH in MeOH was added to the reaction mixture to end-cap the polymers, and the polymer was washed with saturated $NaHCO_3$ to remove tosylates and subsequently precipitated in cold MeOH to remove the solvent and unreacted monomer. The purified protected polymer was then analyzed by ^{1}H NMR and SEC and FT-IR.

Deprotection of P(TIPSOx). To a stirring solution of **P2-P** in THF, a 1 M solution of TBAF in THF was added and left to stir overnight. The reaction mixture was then placed in an RC MWCO 1000 Da dialysis tubing and dialyzed against water for 3 days. The polymer was then freeze-dried and analyzed by ^{1}H NMR, SEC, and FT-IR.

CROP of TMSOx and Deprotection of P(TMSOx). To an oven-dried microwave vial, TMSOx (1.38 g, 6.00 mmol) and dry ACN were added to make a 2 M solution. The reaction vial was then capped and degassed, after which MeOTs (18.0 μL, 0.120 mmol) was added to reaction mixture using a microsyringe. After taking a small aliquot for ^{1}H NMR analysis, the microwave vial was placed in an oil bath at 140 °C and left to stir for 20 min. Upon reaction completion, a small aliquot was taken for ^{1}H NMR and SEC analysis. A 5% KOH in MeOH solution was then added to the reaction mixture and left to stir for 10 min to terminate and deprotect the polymer. The reaction mixture was then placed in an RC MWC 1000 Da dialysis tubing and dialyzed in water for 3 days. The polymer was then freeze-dried and analyzed by ^{1}H NMR, SEC, and FT-IR.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.2c02050.

^{13}C NMR spectra, TGA, SEC, FT-IR, and HPLC traces as well as supporting analysis of the polymers presented in the paper (PDF)

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Author Contributions

J.K. performed the experiments. J.K. and V.B. analyzed the results and wrote the manuscript. C.R.B. supervised the project.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Estabrook, D. A.; Chapman, J. O.; Yen, S.-T.; Lin, H. H.; Ng, E. T.; Zhu, L.; van de Wouw, H. L.; Campàs, O.; Sletten, E. M. Macromolecular Crowding as an Intracellular Stimulus for Responsive Nanomaterials. *J. Am. Chem. Soc.* **2022**, *144* (37), 16792−16798.

(2) Romio, M.; Grob, B.; Trachsel, L.; Mattarei, A.; Morgese, G.; Ramakrishna, S. N.; Niccolai, F.; Guazzelli, E.; Paradisi, C.; Martinelli, E.; Spencer, N. D.; Benetti, E. M. Dispersity within Brushes Plays a Major Role in Determining Their Interfacial Properties: The Case of Oligoxazoline-Based Graft Polymers. *J. Am. Chem. Soc.* **2021**, *143* (45), 19067−19077.

(3) Finnegan, J. R.; Davis, T. P.; Kempe, K. Heat-Induced Living Crystallization-Driven Self-Assembly: The Effect of Temperature and Polymer Composition on the Assembly and Disassembly of Poly(2-oxazoline) Nanorods. *Macromolecules* **2022**, *55* (9), 3650−3660.

(4) Sedlacek, O.; Hoogenboom, R. Drug Delivery Systems Based on Poly(2-Oxazoline)s and Poly(2-Oxazine)s. *Advanced Therapeutics* **2020**, *3* (1), 1900168.

(5) Delaittre, G. Telechelic poly(2-oxazoline)s. *Eur. Polym. J.* **2019**, *121*, 109281.

(6) Wilson, P.; Ke, P. C.; Davis, T. P.; Kempe, K. Poly(2-oxazoline)-based micro- and nanoparticles: A review. *Eur. Polym. J.* **2017**, *88*, 486−515.

(7) Jana, S.; Uchman, M. Poly(2-oxazoline)-based stimulus-responsive (Co)polymers: An overview of their design, solution properties, surface-chemistries and applications. *Prog. Polym. Sci.* **2020**, *106*, 101252.

(8) Concilio, M.; Nguyen, N.; Becer, C. R. Oxazoline-methacrylate graft-copolymers with upper critical solution temperature behaviour in Yubase oil. *Polym. Chem.* **2021**, *12* (30), 4359−4371.

(9) Yilmaz, G.; Uzunova, V.; Hartweg, M.; Beyer, V.; Napier, R.; Becer, C. R. The effect of linker length on ConA and DC-SIGN binding of S-glucosyl functionalized poly(2-oxazoline)s. *Polym. Chem.* **2018**, *9* (5), 611−618.

(10) Verbraeken, B.; Monnery, B. D.; Lava, K.; Hoogenboom, R. The chemistry of poly(2-oxazoline)s. *Eur. Polym. J.* **2017**, *88*, 451−469.
(11) Paulus, R. M.; Becer, C. R.; Hoogenboom, R.; Schubert, U. S. Acetyl Halide Initiator Screening for the Cationic Ring-Opening Polymerization of 2-Ethyl-2-Oxazoline. *Macromol. Chem. Phys.* **2008**, *209* (8), 794−800.
(12) Glassner, M.; Vergaelen, M.; Hoogenboom, R. Poly(2-oxazoline)s: A comprehensive overview of polymer structures and their physical properties. *Polym. Int.* **2018**, *67* (1), 32−45.
(13) Weber, C.; Becer, C. R.; Hoogenboom, R.; Schubert, U. S. Lower Critical Solution Temperature Behavior of Comb and Graft Shaped Poly[oligo(2-ethyl-2-oxazoline)methacrylate]s. *Macromolecules* **2009**, *42* (8), 2965−2971.
(14) Zhao, T.; Drain, B.; Yilmaz, G.; Becer, C. R. One-pot synthesis of amphiphilic multiblock poly(2-oxazoline)s via para-fluoro-thiol click reactions. *Polym. Chem.* **2021**, *12* (44), 6392−6403.
(15) Krieg, A.; Weber, C.; Hoogenboom, R.; Becer, C. R.; Schubert, U. S. Block Copolymers of Poly(2-oxazoline)s and Poly(meth)-acrylates: A Crossover between Cationic Ring-Opening Polymerization (CROP) and Reversible Addition−Fragmentation Chain Transfer (RAFT). *ACS Macro Lett.* **2012**, *1* (6), 776−779.
(16) Becer, C. R.; Paulus, R. M.; Höppener, S.; Hoogenboom, R.; Fustin, C.-A.; Gohy, J.-F.; Schubert, U. S. Synthesis of Poly(2-ethyl-2-oxazoline)-b-poly(styrene) Copolymers via a Dual Initiator Route Combining Cationic Ring-Opening Polymerization and Atom Transfer Radical Polymerization. *Macromolecules* **2008**, *41* (14), 5210−5215.
(17) Kempe, K.; Hoogenboom, R.; Jaeger, M.; Schubert, U. S. Three-Fold Metal-Free Efficient ("Click") Reactions onto a Multifunctional Poly(2-oxazoline) Designer Scaffold. *Macromolecules* **2011**, *44* (16), 6424−6432.
(18) Hayes, G.; Remzi Becer, C. Hyperbranched poly(2-oxazoline)s via bisfunctional crosslinker. *Eur. Polym. J.* **2022**, *181*, 111678.
(19) Van Guyse, J. F. R.; Leiske, M. N.; Verjans, J.; Bernhard, Y.; Hoogenboom, R. Accelerated Post-Polymerization Amidation of Polymers with Side-Chain Ester Groups by Intramolecular Activation. *Angew. Chem., Int. Ed.* **2022**, *61* (29), e202201781.
(20) Drain, B. A.; Becer, C. R. Synthetic approaches on conjugation of poly(2-oxazoline)s with vinyl based polymers. *Eur. Polym. J.* **2019**, *119*, 344−351.
(21) Hayes, G.; Drain, B.; Becer, C. R. Multiarm Core Cross-Linked Star-Shaped Poly(2-oxazoline)s Using a Bisfunctional 2-Oxazoline Monomer. *Macromolecules* **2022**, *55* (1), 146−155.
(22) Drain, B. A.; Beyer, V. P.; Cattoz, B.; Becer, C. R. Solvent Dependency in the Synthesis of Multiblock and Cyclic Poly(2-oxazoline)s. *Macromolecules* **2021**, *54* (12), 5549−5556.
(23) Cesana, S.; Auernheimer, J.; Jordan, R.; Kessler, H.; Nuyken, O. First Poly(2-oxazoline)s with Pendant Amino Groups. *Macromol. Chem. Phys.* **2006**, *207* (2), 183−192.
(24) Leiske, M. N.; Sobotta, F. H.; Richter, F.; Hoeppener, S.; Brendel, J. C.; Traeger, A.; Schubert, U. S. How To Tune the Gene Delivery and Biocompatibility of Poly(2-(4-aminobutyl)-2-oxazoline) by Self- and Coassembly. *Biomacromolecules* **2018**, *19* (3), 748−760.
(25) Zhou, M.; Qian, Y.; Xie, J.; Zhang, W.; Jiang, W.; Xiao, X.; Chen, S.; Dai, C.; Cong, Z.; Ji, Z.; Shao, N.; Liu, L.; Wu, Y.; Liu, R. Poly(2-Oxazoline)-Based Functional Peptide Mimics: Eradicating MRSA Infections and Persisters while Alleviating Antimicrobial Resistance. *Angew. Chem., Int. Ed.* **2020**, *59* (16), 6412−6419.
(26) Blakney, A. K.; Yilmaz, G.; McKay, P. F.; Becer, C. R.; Shattock, R. J. One Size Does Not Fit All: The Effect of Chain Length and Charge Density of Poly(ethylene imine) Based Copolymers on Delivery of pDNA, mRNA, and RepRNA Polyplexes. *Biomacromolecules* **2018**, *19* (7), 2870−2879.
(27) Mazrad, Z. A. I.; Lai, M.; Davis, T. P.; Nicolazzo, J. A.; Thurecht, K. J.; Leiske, M. N.; Kempe, K. Protected amine-functional initiators for the synthesis of α-amine homo- and heterotelechelic poly(2-ethyl-2-oxazoline)s. *Polym. Chem.* **2022**, *13* (30), 4436−4445.
(28) Levy, A.; Litt, M. Polymerization of cyclic iminoethers. V. 1,3-oxazolines with hydroxy-, acetoxy-, and carboxymethyl-alkyl groups in the 2 position and their polymers. *Journal of Polymer Science Part A-1: Polymer Chemistry* **1968**, *6* (7), 1883−1894.
(29) Litt, M.; Levy, M. Polymerization of cyclic iminoethers. V. 1, 3-oxazolines with hydroxy-, acetoxy-, and carboxymethyl-alkyl groups in the 2 position and their polymers. *Journal of Polymer Science Part A-1: Polymer Chemistry* **1968**, *6* (7), 1883−1894.
(30) Jansen, J.; Dias, A.; Tijssen, P. Radiation Curable Compound. 2001000170, 2001.
(31) Kim, J.; Waldron, C.; Cattoz, B.; Becer, C. R. An ϵ-caprolactone-derived 2-oxazoline inimer for the synthesis of graft copolymers. *Polym. Chem.* **2020**, *11* (42), 6847−6852.
(32) Kim, J.; Cattoz, B.; Leung, A. H. M.; Parish, J. D.; Becer, C. R. Enabling Reversible Addition-Fragmentation Chain-Transfer Polymerization for Brush Copolymers with a Poly(2-oxazoline) Backbone. *Macromolecules* **2022**, *55* (11), 4411−4419.
(33) Hatakeyama, H.; Hatakeyama, T. Interaction between water and hydrophilic polymers. *Thermochim. Acta* **1998**, *308* (1), 3−22.
(34) Moulay, S. Review: Poly(vinyl alcohol) Functionalizations and Applications. *Polym.-Plast. Technol. Eng.* **2015**, *54* (12), 1289−1319.
(35) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; John Wiley & Sons, Inc.: Hoboken, NJ, 2006.
(36) Sedlacek, O.; Janouskova, O.; Verbraeken, B.; Hoogenboom, R. Straightforward Route to Superhydrophilic Poly(2-oxazoline)s via Acylation of Well-Defined Polyethylenimine. *Biomacromolecules* **2019**, *20* (1), 222−230.
(37) Ougizawa, T.; Inoue, T. UCST and LCST Behavior in Polymer Blends and Its Thermodynamic Interpretation. *Polym. J.* **1986**, *18* (7), 521−527.
(38) Hoogenboom, R.; Thijs, H. M.; Jochems, M. J.; van Lankvelt, B. M.; Fijten, M. W.; Schubert, U. S. Tuning the LCST of poly(2-oxazoline)s by varying composition and molecular weight: alternatives to poly(N-isopropylacrylamide)? *Chem. Commun.* **2008**, No. 44, 5758−60.
(39) Rimmer, S.; Carter, S.; Rutkaite, R.; Haycock, J. W.; Swanson, L. Highly branched poly-(N-isopropylacrylamide)s with arginine−glycine−aspartic acid (RGD)- or COOH-chain ends that form submicron stimulus-responsive particles above the critical solution temperature. *Soft Matter* **2007**, *3* (8), 971−973.

https://doi.org/10.1021/acs.macromol.2c02050
Macromolecules 2022, 55, 10651−10661