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Functional Degradable Polymers by Xanthate-Mediated Polymerization

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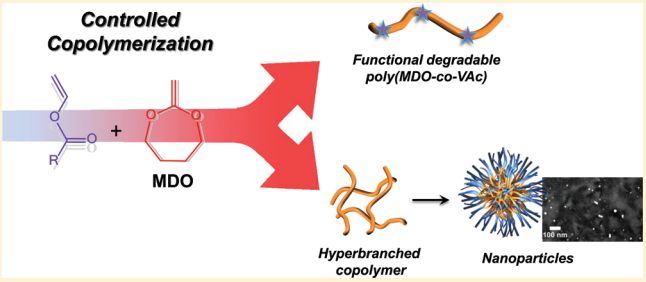
Supporting Information

ABSTRACT: Herein we report the first example of the controlled synthesis of linear and hyperbranched copolymers of 2-methylene-1,3-dioxepane (MDO) with functional vinyl monomers to deliver a range of functional, degradable polymers by reversible deactivation radical polymerization. The copolymerization was able to be tuned to vary the incorporation of degradable segments to create degradable materials with predictable molar mass, low dispersity values while also featuring side-chain functionality. The formation of nanoparticles by the addition of divinyladipate to form degradable hyperbranched copolymers was proven by DLS and TEM analyses.



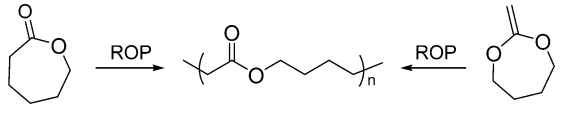
INTRODUCTION

Aliphatic poly(ester)s are an interesting class of polymers that are widely applied in the biomedical field as a consequence of their ability to undergo degradation in physiological conditions.[1−3] The most commonly used aliphatic poly(ester)s are synthesized via the ring-opening polymerization (ROP) of cyclic monomers such as β-butyrolactone, δ-valerolactone, ε-caprolactone, and cyclic diesters including lactide and glycolide in the presence of a catalyst and/or an initiator.[4−9] Poly(ε-caprolactone) (PCL) has been widely studied and applied in the biomedical field as a consequence of its excellent mechanical strength, thermal properties, biocompatibility and nontoxicity, which make it an ideal polymer candidate as an implantable carrier or in tissue engineering applications.[10,11] PCL is typically synthesized by anionic or metal-catalyzed ROP of ε-caprolactone, a process that requires rigorous synthetic procedures to enable the synthesis of polymers with predictable molar masses.[12,13]

A large amount of research has been focused on the incorporation of side chain functional groups onto the PCL-polymer backbone to increase the range of properties that can be targeted and diversify the chemistry of the materials.[14−18] However, such functional group incorporation remains synthetically challenging and is currently limited to only a few approaches: functionalization of ε-caprolactone (CL) monomers,[14,15,19,20] chain end modification[16,17] and/or copolymerization of CL with other monomers.[18,21] While chain end modification, based on manipulation of the initiator and ω-hydroxyl chain end structure, enables some functional group incorporation,[16,17] the approach is limited to low functional group density within the materials at higher molar masses. The synthesis of functionalized CL monomers has been reported, mainly in the γ- and α- positions; however, the ROP of these monomers is limited to those that contain functional groups that are compatible with the catalysts and process, hence requiring arduous and yield-lowering protection/deprotection steps.[15,22] Furthermore, copolymerization of CL with other readily available monomers that contain functional groups, such as epoxides, can also be a way of introducing side chain functional groups to the resultant polymer.[18,21] Such approaches can be limited by a poor match of reactivity ratios between the monomers or broad dispersities of the resultant polymers.

A few recent studies have presented an alternative route for the synthesis of a PCL-like polymer by the radical ring-opening polymerization (rROP) of the 7-membered cyclic ketene acetal (CKA), 2-methylene-1,3-dioxepane (MDO) (Scheme 1).[23−26] In comparison to the conventional ROP of CL, the rROP of MDO requires less stringent synthetic conditions in which to undertake polymerization. Furthermore, the wide range of

Scheme 1. Analogy between the Formation of PCL from the ROP of CL and PCL-Substitute from the ROP of MDO



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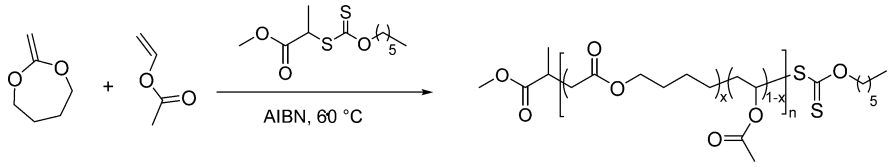
Scheme 2. Synthesis of Poly(MDO-*co*-VAc) Copolymers Mediated by RAFT/MADIX Polymerization



available vinyl monomers opens up potentially limitless possibilities for the synthesis of functional degradable PCL-type polymers. Indeed, the copolymerization of CKAs with vinyl monomers such as methyl methacrylate (MMA)[27] and propargyl acrylate (PA)[28] have been reported to form degradable polymers however as a consequence of the great difference in reactivity ratios, nonrandom copolymer structures result. Vinyl acetate (VAc) has also been copolymerized with CKAs and showed random incorporation of ester units in the polymeric backbone as a consequence of the similar reactivity ratios of the two monomers.[23,29] These copolymerizations have initially been performed by conventional free radical polymerization, however the use of controlled polymerization techniques has recently attracted a wide interest in an attempt to synthesize controlled and well-defined polymers from the rROP of CKA's.[30−36] Reversible deactivation radical polymerization (RDRP) techniques provide polymers with low dispersities, tunable molar mass and functional end-groups which can be used to produce complex polymer architectures. Among the most popular RDRP techniques are atom-transfer radical polymerization (ATRP),[37] nitroxide mediated polymerization (NMP)[38] and reversible addition−fragmentation chain transfer (RAFT) polymerization (also known as MADIX, macromolecular design via interchange of xanthates) when xanthate chain transfer agents are used.[39] Of these techniques, RAFT can be applied to a wider range of monomers and polymerization conditions. The use of RDRP techniques to produce degradable polymers from the rROP of cyclic ketene acetals has mostly been applied to two substituted CKAs, 5,6-benzo-2-methylene-1,3-dioxepane (BMDO)[31−35,40−42] and 2-methylene-4-phenyl-1,3-dioxolane (MPDL).[34,35] In all cases, controlled aspects of the polymerization were proven, as well as the incorporation of degradable units in the vinyl polymeric backbone. However, incorporation of aromatic groups (*e.g.*, BMDO) into the polymer backbone drastically alters the physical properties of the final polymer and does not provide a viable alternative route for the synthesis of PCL. As yet there have been limited examples of defined methodologies to produce controlled and well-defined PCL-substitute polymers from the nonfunctional CKA, MDO, and only few attempts were conducted using RDRP techniques.[34,35,42,43]

Herein, we report the first example of controlled copolymerization of the CKA, MDO with VAc and other vinyl monomers to produce well-defined, side-chain functional biodegradable polymers via the RAFT/MADIX polymerization method. Furthermore, we demonstrate the extension of this methodology to facilitate the synthesis of fully degradable hyperbranched copolymers.

RESULTS AND DISCUSSION

To demonstrate the potential of a controlled synthesis of poly(MDO-*co*-VAc) the use of the RAFT/MADIX technique was chosen as a consequence of its high tolerance to a range of conditions.[39,44,45] Good control over the polymerization of VAc has previously been reported using xanthates as a chain transfer agent (CTA).[46−48] Hence, *O*-hexyl-*S*-methyl-2-propionylxan-

Table 1. Characterization Data for the Copolymerization of MDO and VAc (30/70 mol %) Using CTA 1 for Different Time Points

time (h)	VAc convn (%)	MDO convn (%)	$M_{n\ theor}$[a] (kDa)	$M_{n\ obsd}$[b] (kDa)	$Đ_M$[c]
1	3	7	0.4	0.9	1.25
2	13	10	1.1	1.6	1.30
3	16	13	1.4	1.9	1.37
4	19	15	1.6	2.0	1.39
5	21	17	1.8	2.3	1.40
7	32	20	2.7	3.0	1.42
9	45	27	3.6	3.8	1.49
16	62	44	5.3	7.8	1.55

[a]Theoretical molar mass based on monomer conversion (^{1}H NMR spectroscopy). [b]Observed molar mass obtained by ^{1}H NMR spectroscopy end-groups analysis. [c]Dispersities obtained by SEC analyses in $CHCl_3$.

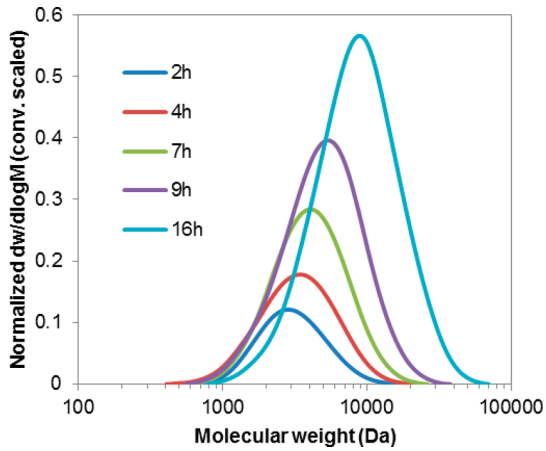


Figure 1. Size exclusion chromatograms of poly(MDO-*co*-VAc) (30/70 mol %) for different polymerization times.

Table 2. Characterization Data for the Copolymerization of MDO and VAc (70/30 mol %) Using CTA 1 for Different Time Points

time (h)	VAc convn (%)	MDO convn (%)	$M_{n\ theor}$[a] (kDa)	$M_{n\ obsd}$[b] (kDa)	$Đ_M$[c]
2	5	4	0.5	0.8	1.20
4	10	9	1.0	1.7	1.21
7	22	15	1.8	2.4	1.24
9	24	18	2.1	2.9	1.27
16	52	27	3.5	5.0	1.52

[a]Theoretical molar mass based on monomer conversion (^{1}H NMR spectroscopy). [b]Observed molar mass obtained by ^{1}H NMR spectroscopy end-groups analysis. [c]Dispersities obtained by SEC analyses in $CHCl_3$.

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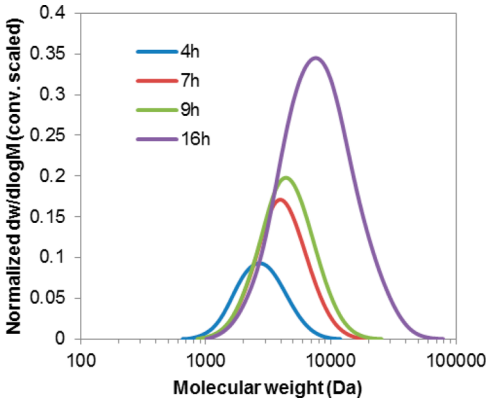

Figure 2. Size exclusion chromatograms of poly(MDO-*co*-VAc) (70/30 mol %) for different polymerization times.

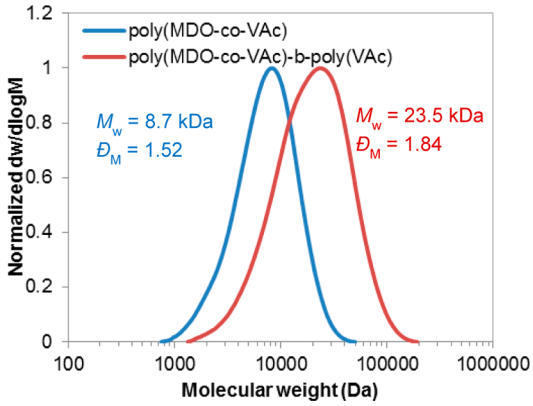

Figure 3. Size exclusion chromatograms of the chain extension of poly(MDO-*co*-VAc) (30/70 mol %) with VAc (RI detector, with $CHCl_3$ as the eluent).

Table 3. Characterization Data of Poly(MDO-*co*-VAc) for DP 200 to 600, (30/70 mol % VAc/MDO)

target DP	VAc convn (%)	MDO convn (%)	$M_{n\ theor}$[a] (kDa)	$M_{n\ obsd}$[b] (kDa)	$Đ_M$[c]
200	41	27	6.8	6.1	1.49
400	40	19	11.4	8.1	1.63
600	36	21	17.4	11.3	1.73

[a]Theoretical molar mass based on monomer conversion (^{1}H NMR spectroscopy). [b]Observed molar mass obtained by ^{1}H NMR spectroscopy end-groups analysis. [c]Dispersities obtained by SEC analyses in $CHCl_3$.

thate, **1**, an analogous structure to a CTA previously reported in our group for the polymerization of "less-activated" vinyl monomers including the biocompatible thermoresponsive polymers of poly(*N*-vinylpiperidone), was prepared.[49]

Copolymerization of MDO and VAc at 60 °C in bulk, using 2,2′-azobis(isobutyronitrile) (AIBN) as the radical initiator, and **1** as the CTA (Scheme 2), was conducted such that $[MDO]_0/[VAc]_0/[AIBN]_0/[\mathbf{1}]_0$ = 50:50:0.1:1. After 5 h reaction time, the resultant polymer displayed a dispersity, $Đ_M$, < 1.60 when analyzed by size-exclusion chromatography (SEC) with ^{1}H NMR spectroscopic analysis revealing monomer conversions of 62 and 44% for VAc and MDO respectively and a molar mass close to that expected on the basis of the monomer:CTA ratio which indicates high retention of chain end fidelity. These observations suggest that the CTA is well-suited to

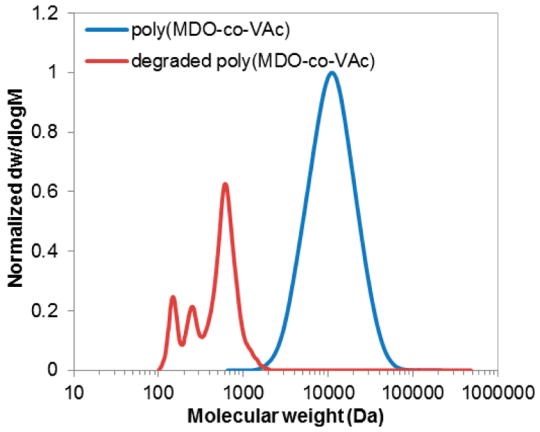

Figure 4. Size exclusion chromatograms of the poly(MDO-*co*-VAc) (30/70 mol %) before and after degradation in potassium hydroxide in methanol for 5 h at 40 °C, (SEC $CHCl_3$, RI detector, PS used as standard.

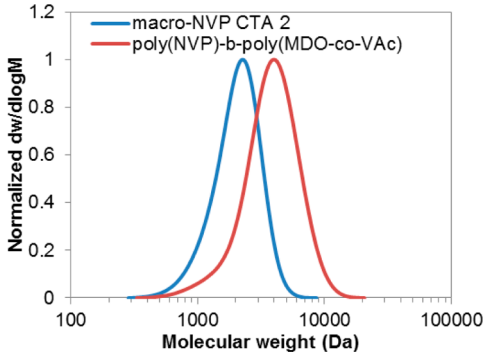

Figure 5. Size exclusion chromatograms of the chain extension of the macro-NVP CTA **2** with MDO (30 mol %) and VAc (70 mol %) to form the block copolymer: poly(NVP)-*b*-poly(MDO-*co*-VAc) (SEC DMF, PMMA used as standard.

copolymerize the MDO/VAc system. In an attempt to reduce the viscosity of the polymerization mixture, the polymerizations were also performed in solution. Benzene was chosen as the polymerization solvent as a consequence of its low chain transfer constant ($K_c = 3.6 \times 10^5$) toward vinyl acetate.[50]

A detailed RAFT/MADIX copolymerization study of MDO and VAc was conducted at 60 °C in benzene (15 wt %) such that $[MDO]_0/[VAc]_0/[AIBN]_0/[\mathbf{1}]_0$ = 30:70:0.1:1. Poly(MDO-*co*-VAc) with well-controlled number-average molar mass (M_n) and low dispersities ($Đ_M$ = 1.21−1.60) were synthesized (Table 1). The conversion of MDO was found to be lower than VAc over the course of the polymerization which is in agreement with its lower reactivity ratio as reported by previous studies carried out using conventional free radical polymerization technique.[23,29] This observation was also confirmed by the determination of the reactivity ratios in the presence of the CTA using the nonlinear least-squares (NLLS) method (Figure S11). The observed polymer molar masses ($M_{n\ obsd}$) were obtained by integration of the protons from the VAc and MDO polymer backbone at δ = 4.8−5.2 and 4.2 ppm respectively and referenced to the characteristic resonance of the CH_2 protons adjacent to the xanthate group at δ = 4.5 ppm. The theoretical molar masses ($M_{n\ theor}$) were based on monomer conversions as determined by ^{1}H NMR spectroscopy. The $M_{n\ obsd}$ values showed good correlation to the $M_{n\ theor}$ values over the first 9 h of the polymerization, which indicates

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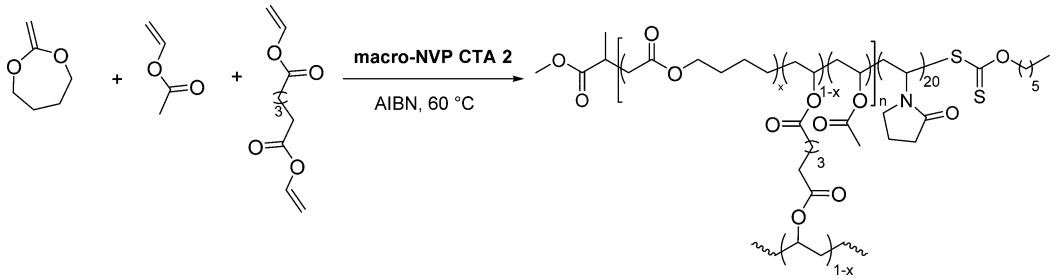
Scheme 3. Synthesis of the Hyperbranched Poly(MDO-*co*-VAc) Using the Macro-NVP CTA 2



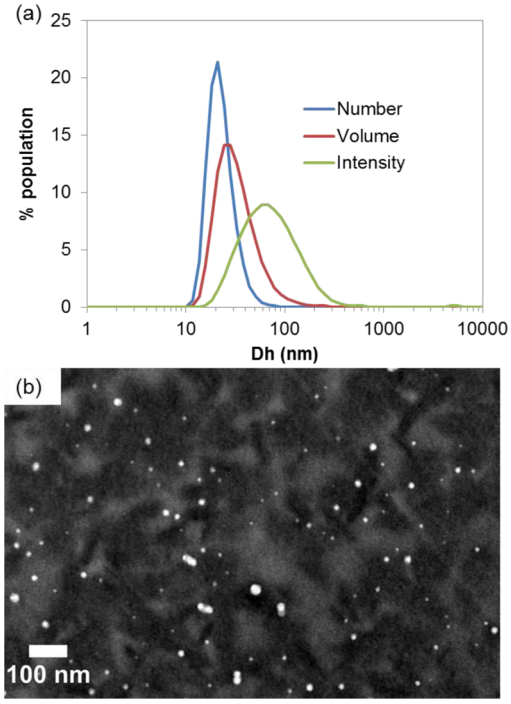


Figure 6. DLS traces (a) and TEM image (b) for the particles obtained from hyperbranched poly(MDO-*co*-VAc)-*b*-poly(NVP) (at DP = 50).

retention of the active xanthate group at the polymer chain end. Beyond 9 h of polymerization, however, there was a deviation in the values of $M_{n\ obsd}$ and $M_{n\ theor}$, which indicated that termination reactions were occurring, in turn leading to a loss of the CTA end group and a resultant loss of polymerization control and a broadening of the dispersity of the resultant copolymer (Figure 1).

^{1}H NMR spectroscopic analyses of the copolymers revealed the presence of resonances at δ = 0.90 and 3.65 ppm, characteristic of side-chain reactions that result from the 1,4- and 1,7-hydrogen transfer or backbiting during the ROP of MDO.[25] Further ^{1}H NMR spectroscopic analysis led to an estimation of the side-chains that occurred from these processes to be 10−15% of the MDO repeat unit contained in the copolymer backbone. The estimation was obtained after comparison of the alkyl side-chain integrals (δ = 0.90 and 3.65 ppm) with the CH_2 (δ = 4.00 ppm) close to the MDO carbonyl group. ^{13}C NMR spectroscopic analysis was undertaken to estimate the degree of ring-opening of MDO in the different copolymers synthesized, as this is also a known side-reaction in previously reported free radical copolymerizations of MDO monomers.[51,52] In all cases, total ring-opening of the cyclic MDO monomer was observed as quantified by the absence of characteristic signals for the acetal quaternary carbon peak at δ = 100−110 ppm (Figure S7).[51,52]

To increase the degradability of the synthesized copolymers, the incorporation of ester repeat units was altered by increasing the ratio of MDO in the monomer feed to 70 mol %. Following the polymerization, as previously described the final composition of the copolymer revealed an incorporation of 61% of MDO and 39% of VAc in the polymer, as determined by ^{1}H NMR spectroscopy. Again the copolymerizations were all well-controlled with dispersities between 1.20 and 1.52 with a controlled process maintained up to 16 h as noted for the copolymerizations. Once again a loss of the CTA end group was observed after 16 h of polymerization (Table 2 and Figure 2). By terminating the polymerization before this time, a well-controlled and well-defined copolymer with increased content of degradable linkages was obtained.

Chain growths from the obtained copolymers were performed in order to test the "living" character of the polymerization technique and retention of the CTA end group. Extension of poly(MDO-*co*-VAc) (30:70 mol %) with VAc was performed to create a block copolymer of poly(MDO-*co*-VAc)-*b*-poly(VAc). ^{1}H NMR spectroscopy and SEC analyses confirmed the controlled character of this polymerization process, with complete shift of the distribution and the absence of a shoulder on the SEC analysis indicating successful chain extension (Figure 3) after the addition of the second block of poly(VAc).

Further extension of this system to target increased degrees of polymerization (DPs) by varying the initial amount of CTA was also investigated. SEC and ^{1}H NMR spectroscopic analyses of polymers with targeted DPs between 200 and 600 again showed polymerization control with characteristic signals of the CTA end group observed both in the ^{1}H NMR spectra and in all SEC UV-detected (280 nm) chromatograms. The number-average molar masses obtained were found to be between 6.8 and 17.4 kDa (Table 3); however, the dispersities were found to increase as the targeted molar masses were increased. Although this is indicative of a possible loss of control in the polymerization, a broadening of the dispersities can also be attributed to a consequence of increased target DP, which is commonly observed for controlled radical polymerization techniques.[48,53,54]

The degradability of poly(MDO-*co*-VAc) was proven by the hydrolysis of the copolymer sample (VAc75/MDO25) in a solution of potassium hydroxide (KOH, 1.5 M) in methanol at 40 °C for 5 h. These conditions have been shown to provide simulated accelerated *in vivo* conditions for the degradation of PCL.[55] In all cases, a decrease in the molar mass of the samples was observed by SEC analyses (Figure 4). This result proves

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the efficient insertion of degradable ester units in the polymer backbone through the copolymerization of MDO with VAc.

Other Functional Copolymers. The controlled copolymerization of MDO was applied to a broader range of vinyl monomers to enable the incorporation of functional groups into the degradable polymer backbone. Such a task remains challenging for conventional ROP techniques on account of the difficult functional monomer syntheses and drying processes. To this end, the copolymerization of *N*-vinylpyrrolidone (NVP), *N*-vinylpiperidone (VPip), and commercially available vinyl chloroacetate (VClAc) with MDO was studied. In all cases, the controlled aspect of the polymerization process was retained with low dispersities (1.30, 1.26, and 1.48 for poly(MDO-*co*-NVP), poly(MDO-*co*-VPip) and poly(MDO-*co*-VClAc) respectively) being observed in each case, demonstrating the broader utility of this approach for the synthesis of well-defined degradable polymers. The use of VClAc as a comonomer also enables access to a much broader range of materials through the substitution of the chloro group with sodium azide to yield a polymer with pendant azides, through which "click chemistry" can be performed to attach specific molecules required for a range of desired applications.[56,57]

Thermoresponsive, Degradable, Hyperbranched Polymers. Following the promising results obtained for the synthesis of well-defined copolymers of MDO, further experiments were performed to produce thermoresponsive, degradable, hyperbranched copolymer nanoparticles. The thermoresponsive portion of the polymer was obtained by RAFT/MADIX polymerization of NVP to form a poly(NVP) macro-CTA, **2** (DP_{NMR} = 20, M_w TD-SEC = 2.2 kDa, $Đ_M$ = 1.19).[58] In initial experiments, the chain growth of a MDO/VAc copolymer from macro-NVP CTA **2** (Figure 5) was found to form well-defined poly(NVP)-*b*-poly(MDO-*co*-VAc) block copolymers, with a net increase in molar mass being observed by SEC analysis alongside dispersity values of 1.28 and 1.49 after chain growth.

Extension of the concept to synthesize higher molar mass thermoresponsive hyperbranched polymers was undertaken using similar conditions but with the addition of a cross-linking monomer, divinyl adipate (DVA). Beyond the previous report of the synthesis of hyperbranched copolymers of VAc/DVA, reported by Poly et al.[59] in which the synthesis of nanogels was demonstrated also using a xanthate mediated polymerization technique, the incorporation of MDO in the (co)monomer system enables the synthesis of a degradable hyperbranched copolymer of poly(MDO-*co*-VAc) (Scheme 3). To this end, hyperbranched polymers with DP's of 20, 50, and 100 were synthesized with a comonomer feed ratio of MDO10/VAc90, (*i.e.*, $[MDO]_0/[VAc]_0/[DVA]_0/[AIBN]_0/[$macro-NVP CTA **2**$]_0$ = 2:18:1:0.1) for DP = 20. In all samples, successful chain growth was confirmed by SEC analyses by the observation of a net increase in M_w, using light scattering detection, from 3.0 kDa (macro-NVP CTA **2**) to 13.4, 26.1, and 42.2 kDa, respectively. Furthermore, examination of the SEC chromatograms revealed a multimodal peak which is consistent with the formation of hyperbranched polymers (Figure S23).[60,61] The behavior of the hyperbranched block copolymers was studied by the formation of particles using the solvent switch technique from THF to water such that a final concentration of 0.5 mg mL^{-1} was achieved. This process enabled the formation of particles composed of a poly(NVP) corona and a poly(MDO-*co*-VAc) core. The morphology and size of the particles formed were assessed by dynamic light scattering (DLS) and transmission electron microscopy (TEM). DLS results showed that particles formed from the hyperbranched copolymers were found to show diameters, D_{av}, of 9.3, 24.4, and 30.0 nm for DPs of 20, 50, and 100 respectively with TEM images confirming the presence of spherical particles in each solution with similar size profiles (Figure 6 and Figure S24−S31).

CONCLUSIONS

In summary, we report the first example of the synthesis of copolymers of MDO mediated by RAFT/MADIX in order to produce a functionalized degradable copolymer based on broadly applicable PCL. Well-defined and well-controlled copolymers with different degrees of degradability were successfully synthesized, as seen by ^{1}H NMR spectroscopy and SEC analysis, where good control over molar mass and end group fidelity was observed. Importantly, the incorporation of side chain functional groups was shown to be possible which extends the utility of this technique. Further chain growth of the MDO/VAc copolymers to produce degradable, thermoresponsive block and hyperbranched copolymers proved the efficient living character of the process presented. These results illustrate the great potential of the controlled process on CKAs and vinyl monomers where a wide range of properties can be readily targeted.

ASSOCIATED CONTENT

Supporting Information

Experimental section and characteriazation. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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