Poly(vinyl ester) Star Polymers via Xanthate-Mediated Living Radical Polymerization: From Poly(vinyl alcohol) to Glycopolymer Stars

Julien Bernard, Arnaud Favier, Ling Zhang, Anastasia Nilasaroya, Thomas P. Davis, Christopher Barner-Kowollik, and Martina H. Stenzel*

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

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ABSTRACT: Poly(vinyl ester) stars have been synthesized via different macromolecular design via interchange of xanthate (MADIX)/reversible addition−fragmentation chain transfer (RAFT) polymerization methodologies. Two approaches were investigated. The first method involved attaching the xanthate functionality to the core via a nonfragmenting covalent bond (Z-group approach). The second approach involved attaching the xanthate functionality to the core via a fragmenting covalent bond (R-group approach). The R-group approach yielded well-defined poly(vinyl acetate), poly(vinyl pivalate), and poly(vinyl neodecanoate) stars with narrow polydispersities (PDI ≤ 1.4). In contrast, the molecular weight distributions of poly(vinyl acetate) stars prepared using the Z-approach tended to broaden at moderate to high conversions. We attribute this broadening to steric congestion around the xanthate functionality, restricting the access of monomer to the C=S bonds. The R-group approach was also found to be superior for preparing precursor stars suitable for hydrolysis to poly(vinyl alcohol). Hydrolysis of stars generated by the Z-group approach resulted in destruction of the architecture, as the process also cleaved the xanthate linkage at the nexus of the arms and core. Preliminary experiments on using the R-group approach to mediate the star-polymerization of vinyl-functional glycomonomers demonstrated the possibility of generating complex glycopolymer architectures. However, some significant problems were observed, and this synthetic approach requires further optimization.

Introduction

Reversible addition−fragmentation chain transfer (RAFT) and macromolecular design via interchange of xanthate (MADIX) polymerization methods[1−3] have been used extensively for creating novel complex architecture polymers.[4−9] In many instances, alternative living radical approaches, such as atom transfer radical polymerization (ATRP)[10−14] or nitroxide-mediated polymerization (NMP),[15−17] could also be adopted as synthetic pathways. However, when vinyl esters are utilized as the monomeric building blocks, this places a significant limitation on the synthetic methodology that can be adopted. Recently, we began a research program on using RAFT/MADIX with xanthates for mediating the living radical polymerization of vinyl acetate.[18,19] In the course of this work we found that narrow polydispersity polymers could be produced with molecular weights up to 50K.[18] We also found that the living radical polymerization of vinyl esters is extremely sensitive to impurities that can induce both retardation and inhibition.[18,19] The attraction of targeting poly(vinyl esters), particularly poly(vinyl acetate) (PVAc), is their potential use as precursors to poly(vinyl alcohol) (PVA). In an earlier Communication,[8] we demonstrated the feasibility of synthesizing 3- and 4-arm PVAc stars and then subsequently hydrolyzing them to PVA, a polymer with many biomedical applications.[20−23] The interest in developing synthetic methods to complex architecture PVA stems from some of the unique properties exhibited by hyperbranched polymers and stars (for example, low bulk and solution viscosity and high functionality).

The synthetic approaches to star polymers have been established for many years with major contributors such as Inoue,[24] Hadjichristidis[25] (anionic polymerization), the Warwick and CAMD groups (ATRP and RAFT),[4,6,8,26] and Hawker[16] and Gnanou (NMP, ATRP, and RAFT),[9,12,17] together with many others. There are essentially two routes to star polymers: (1) the arm first and (2) the core first method. The first strategy, "the arm first" method, requires the presynthesis of linear arms containing a terminal functional group that are subsequently covalently bonded to a multifunctional core. In contrast, the "core first" method involves the chain growth of linear arms from a plurifunctional initiating core.

In this study, we report the synthesis of two categories of multifunctional xanthate cores designed to prepare well-defined PVAc and other poly(vinyl esters) as precursors to PVA stars. The first strategy (R-approach) requires the synthesis of xanthates where the core of the multifunctional molecule is the leaving group (or R-group) of the RAFT agent. The arms are subsequently grown directly from the multifunctional core, and the xanthate functionality can be found either attached to the ends of the star arms or attached to free linear polymer in solution. In the second method (Z-approach), the core acts as the Z-group of the xanthate agent. The growth of the arms occurs at the nexus of the core and the arm, and as a consequence as the molecular weight builds up, steric congestion around the xanthate group can become a factor influencing the kinetics and control of the reaction. Both approaches have previously been studied for styrene polymerization.[4,6] The R-group approach generated some linear polystyrene RAFT functionalized chains as an impurity in the star polymer product and also generated some star−star coupled product from radical termination reactions via combination. The Z-group approach resulted in some loss of control at higher conversions (Scheme 1). However,

* Corresponding author: Fax + 61 2 9385-6250; e-mail camd@unsw.edu.au.

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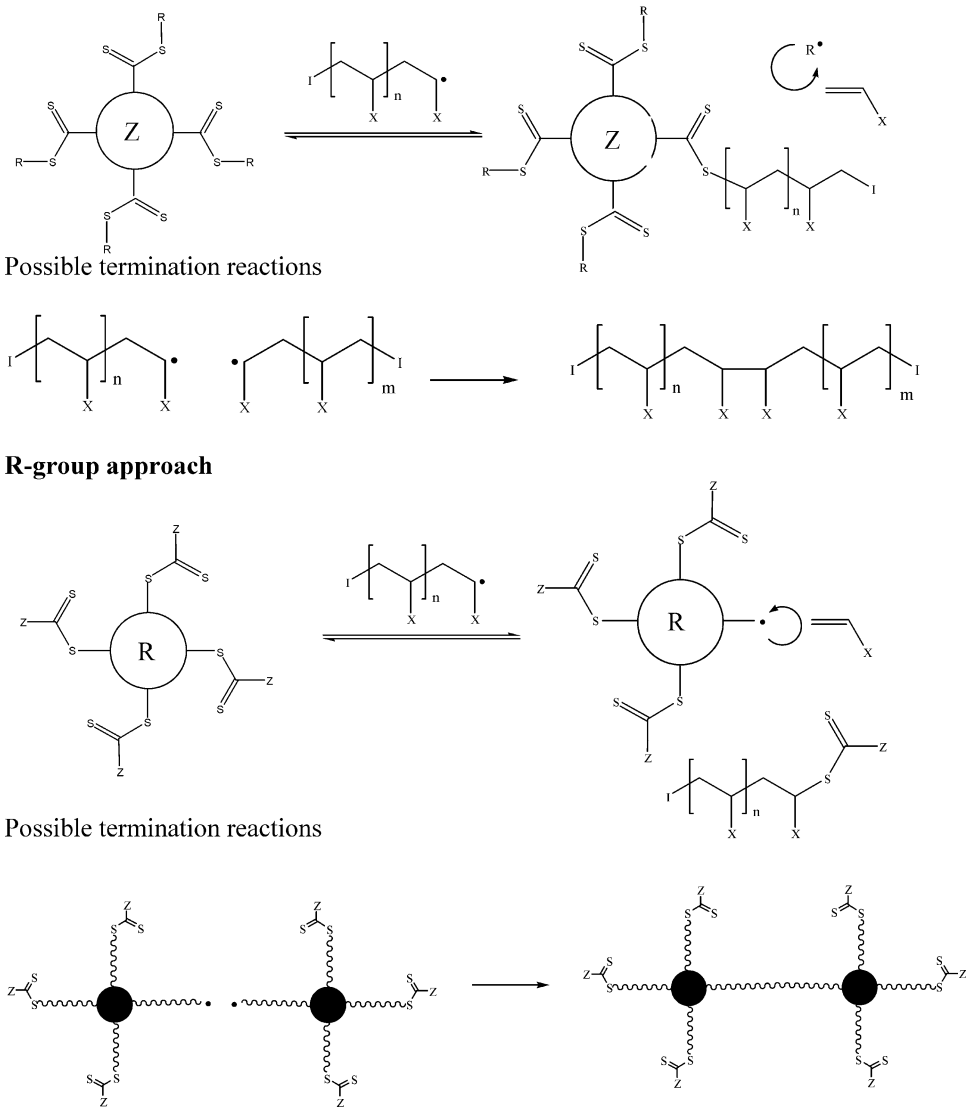
Scheme 1. Synthesis of Stars via RAFT Process with the R and Z Approach



some subsequent work on hyperbranched cores[27] indicated that the success of this synthetic strategy may depend on optimizing the precise chemical nature of the core and matching this to the monomer to be polymerized (suggesting that solvent effects and monomer partitioning need to be taken into account when optimizing the synthesis procedure). However, the rules to guide the synthetic method design are still unknown as the range of reports on this synthetic approach are relatively sparse at present.[28] In the present work we attempt to investigate both the R-approach and Z-approach to poly(vinyl esters) as precursors to PVA stars. As we also have a longer-term aim of controlling the architecture of glycopolymers from vinyl-functional monomers, we also included some preliminary results in the present publication.

Experimental Section

Materials. 1,1,1-Tris(hydroxymethyl)ethane (Aldrich, 99%), pentaerythritol (Aldrich, 99%), 2-bromopropionyl bromide (Aldrich, 97%), triethylamine (Aldrich, 99%), *O*-ethylxanthic acid potassium salt (Aldrich), carbon disulfide (Aldrich, 99,9%), methyl bromoacetate (Aldrich, 97%), and trioxane (Aldrich, 99%) were used without further purification.

Dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), chloroform, and acetone were obtained from Ajax FineChem (Australia) and were dried over activated molecular sieves (4 Å) before use.

Vinyl acetate (VAc) (Aldrich, 99,9%), vinyl pivalate (VP) (Aldrich, 99%), and vinyl decanoate (VND) (Aldrich) were filtered prior to passing through a column of basic aluminum oxide to remove inhibitors. 2,2′-Azobis(isobutyronitrile) (AIBN) (Aldrich, 99%) was recrystallized twice from ethanol. 6-*O*-Vinyladipoyl-D-glucopyranose (VAG) was prepared according to a method described elsewhere.[29] Column chromatography was performed using silica gel (Kiesigel-60, Fluka).

Synthesis of R-Designed Trifunctional and Tetrafunctional Xanthate Agents. *(a) Reaction of the Hydroxyl-Functionalized Cores with 2-Bromopropionyl Bromide.* Pentaerythritol (tetrafunctional precursor) (2.72 g, 0.02 mol) was dissolved in anhydrous chloroform (30 mL) and pyridine (5 mL). 2-Bromopropionyl bromide (19.1 g, 0.09 mol) was added slowly to the ice-cooled solution. The ice bath was removed, and the mixture was stirred at ambient temperature for 48 h. Diluted hydrochloric acid (10%) was slowly added to the solution. The organic phase was then washed with 100 mL of aqueous $NaHCO_3$ (5 wt %) and finally dried with Na_2SO_4. After evaporation of the solvent under reduced pressure a colorless compound was obtained. The trifunctional bromide precursor was synthesized from 1,1,1-tris(hydroxymethyl)ethane following the same procedure.

Tetrafunctional Bromide Precursor. ^{1}H NMR ($CDCl_3$): 1.74 (CH_3−C−Br, 12H, d), 4.14 (CH−Br, 3H, q), 4.29 (CH_2−O, 6H, m). ^{13}C NMR ($CDCl_3$): 21.3 (*C*H_3−C−Br), 39.6 (CH−Br, 3H, q), 43.0 (C−*C*−C) 62.8 (CH_2−O, 6H, b), 169.4 (C=O). Yield: 70%.

Trifunctional Bromide Precursor. ^{1}H NMR ($CDCl_3$): 0.89 (CH_3−C, 3H, t), 1.76 (CH_3−C−Br, 9H, d), 4.14 (CH−Br, 3H, q), 4.33 (CH_2−O, 6H, b).^{13}C NMR ($CDCl_3$): 7.3 (*C*H_3−C), 21.4 (*C*H_3−C−Br), 39.6 (CH−Br), 41.5 (C−*C*−C) 65.2 (CH_2−O, 6H, b), 169.6 (C=O). Yield: 70%.

(b) Reaction of the Bromide Precursor with O-Ethylxanthic Acid, Potassium Salt. The tetrafunctional bromide precursor (10 g, 1.5×10^{-2} mol) was redissolved in chloroform (100 mL) and stirred with a 10-fold excess of *O*-ethylxanthic acid potassium salt (24 g, 1.5×10^{-1} mol) for 3 days. The suspended remaining sodium (*O*-ethyl) xanthate was filtered off and washed several times with chloroform. After evaporation of the solvent the product was purified using column chromatography on silica gel (hexane: ethyl acetate = 7:3). The trifunctional xanthate agent was synthesized from the trifunctional bromide agent following the same procedure.

R-Designed Tetrafunctional Xanthate Agent: Yellow Compound. ^{1}H NMR ($CDCl_3$): 1.43 (C*H*$_3$−CH_2−O, 12H, t), 1.58 (C*H*$_3$−CH−S, 12H, d), 4.17 (CH_2−O, 8H, m), 4.40 (CH−S, 4H, q), 4.63 (CH_3−C*H*$_2$−O, 8H, q). ^{13}C NMR ($CDCl_3$): 13.6 (*C*H_3−CH_2−O), 16.5 (*C*H_3−C−S), 44.0 (C−*C*−C), 47.0 (CH−S), 62.8 (CH_2−O), 70.4 (CH_3-*C*H_2−O), 171.2 (C=O), 211.9 (C=S). Yield: 40%.

LC-MS: accurate mass: 887.1 amu (theoritical mass of $C_{29}H_{44}S_8O_{12}$, Na^+ = 886.3 amu).

R-Designed Trifunctional Xanthate Agent: Yellow Compound. ^{1}H NMR ($CDCl_3$): 0.83 (CH_3−C, 3H, b), 1.42 (C*H*$_3$−CH_2−O, 9H, t), 1.56 (C*H*$_3$−CH−S, 9H, d), 4.07 (CH_2−O, 6H, m), 4.40 (CH−S, 3H, q), 4.63 (CH_3−C*H*$_2$−O, 6H, q). ^{13}C NMR ($CDCl_3$): 7.9 (*C*H_3−C), 13.6 (*C*H_3−CH_2−O), 16.8 (*C*H_3−C−S), 42.5 (C−*C*−C), 47.1 (CH−S), 65.2 (CH_2−O), 70.9 (CH_3-*C*H_2−O), 171.2 (C=O), 211.9 (C=S). Yield: 40%.

Synthesis of Z-Designed Trifunctional and Tetrafunctional Xanthate Agents. Pentaerythritol (2.72 g, 0.02 mol) was solubilized in DMSO at 60 °C. The clear solution became cloudy after addition at room temperature of a low volume of potassium hydroxide aqueous solution (6.72 g of KOH, 0.12 mol).

A large excess of carbon disulfide (48 mL, 0.8 mol) was then slowly added at 0 °C for 30 min, and the resulting dark red solution was stirred for 2 h at room temperature. Finally, methyl bromoacetate (18.36 g, 0.12 mol) was slowly added for 1 h at room temperature. The resulting yellow solution was stirred overnight.

After reaction, diethyl ether (250 mL) was added. To remove DMSO and the water-soluble side products, the organic phase was washed several times with water. The organic solution was then dried with magnesium sulfate and filtered, and the solvent was evaporated under vacuum. The multifunctional xanthate agents were finally purified by column chromatography on silica gel with hexane/ethyl acetate mixtures as eluent (80/20 v/v for the tetrafunctional xanthate agents and 60/40 for the trifunctional). The tetrafunctional control agent was further successfully recrystallized from diethyl ether.

Z-Designed Tetrafunctional Xanthate Agent: Light Green Powder. ^{1}H NMR ($CDCl_3$): δ (ppm) = 3.78 (CO_2*C*H_3, s, 12H,), 3.93 (*C*H_2−CO_2, s, 8H,), 4.81 (C-*C*H_2−O, s, 8H,). ^{13}C NMR ($CDCl_3$): 33.1 (CH_2−S), 43.9 (C−*C*−C), 52.9 (CH_3−O), 71 (CH_2−O), 167.9 (C=O), 211.8 (C=S). Yield: 60%.

LC-MS: accurate mass: 750.7 amu (theoritical mass of $C_{21}H_{28}S_8O_{12}$, Na^+ = 751.9 amu).

Z-Designed Trifunctional Xanthate Agent: Very Viscous Yellow Liquid. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.22 (C−*C*H_3, s, 3H,); 3.77 (CO_2*C*H_3, s, 9H) 3.94 (*C*H_2−CO_2, s, 6H), 4.61 (C-*C*H_2−O, s, 6H,). ^{13}C NMR ($CDCl_3$): 17.2 (*C*H_3−C), 37.8 (CH_2−S), 39.9 (C−*C*−C), 52.8 (CH_3−O), 67.8 (CH_2−O), 167.9 (C=O), 212.1 (C=S). Yield: 60%.

LC-MS: accurate mass: 586.9 amu (theoritical mass of $C_{17}H_{24}S_6O_9$,Na^+ = 587.7 amu).

Polymerizations. Bulk polymerization of VAc was performed using 2,2′-azobis(isobutyronitrile) (AIBN) as the initiator and the R or Z functional xanthate agents given in Scheme 1 as chain transfer agent (1.1×10^{-2}, 2.2×10^{-2}, or 4.3×10^{-2} mol L^{-1} of xanthate functions).

Typically, the polymerization of VAc (3 mL, 3.25×10^{-2} mol) was carried out using AIBN (1.1 mg, 6.7×10^{-6} mol), the functional xanthate agent (23.4 mg of B or 27 mg of D, 1.2×10^{-4} mol of xanthate functions), and trioxane (243 mg, 2.7×10^{-3} mol) as an internal reference for the measurement of VAc consumption as previously reported.[19]

Six samples of the stock solution were transferred to Schlenk tubes which were thoroughly deoxygenated by five consecutive freeze−pump−thaw cycles. The tubes were then placed in a constant temperature water bath at 60 °C and were removed at regular time intervals. The reactions were stopped by plunging the tubes into iced water. The conversions were determined by ^{1}H NMR in $CDCl_3$ by relative integration of vinyl (unreacted VAc) and OCH_2 (trioxane) protons.[19] Molecular weights were also evaluated from dried polymers by ^{1}H NMR (in $CDCl_3$) from the following equation:

$$\bar{M}_{n,NMR} = M_{\text{xanthate agent}} + n(3I_{-CH-O}/I_{O-CH_3} \times M_{VAc})$$

with $M_{\text{xanthate agent}}$ the molecular weight of the xanthate agent, n the number of branches of the star, and I_{-CH-O} and I_{O-CH_3} relative integrations of the −C*H*−O protons of the PVAc backbone (δ (ppm) = 4.85) and of the O−C*H*$_3$ protons of the arm ends (δ (ppm) = 3.65).

Z Approach: 4-Arm PVAc Stars. 25% of conversion in 2 h; $\bar{M}_{n,GPC}$ = 11 800 g mol^{-1}; $\bar{M}_{n,NMR}$ = 25 100 gmol^{-1} ($\bar{M}_{n,th}$ = 22 400 g mol^{-1}); PDI = 1.2. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.73 (−C*H*$_2$−CH−), 2 (−C*H*$_3$−CO), and 4.85 (−CH_2−C*H*−).

R Approach : 4-Arm PVAc Stars. 10.5 % of conversion in 2 h, $\bar{M}_{n,GPC}$ = 7500 g mol^{-1}; $\bar{M}_{n,th}$ = 8600 g mol^{-1}); PDI = 1.24. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.73 (−C*H*$_2$−CH−), 2 (−C*H*$_3$−CO), and 4.85 (−CH_2−C*H*-).

Typically, the bulk polymerizations of VP (3 mL, 2.05×10^{-2} mol) or VND (3 mL, 1.34×10^{-2} mol) were performed using 2,2′-azobis(isobutyronitrile) (AIBN) (respectively 0.67 mg, 4.1×10^{-6} mol or 0.44 mg, 2.7×10^{-6} mol) and R-designed tetrafunctional xanthate agents (respectively 8.6 mg, 4.08×10^{-5} mol of xanthate functions or 5.6 mg, 2.66×10^{-5} mol of xanthate functions).

The mixture containing the monomer, the initiator, and the xanthate agent was transferred into several vials which were sealed with rubber septa and purged with nitrogen for 30 min. The vials were placed in a water bath at 60 °C and removed at predetermined time intervals, and polymerization was stopped by cooling the solutions in ice water. The conversions were determined using ^{1}H NMR in $CDCl_3$ by relative integration of the polymer backbone (−CH_2−CH−) and of the vinyl protons of the monomer (CH_2=CH−).

PVP: 64% of conversion in 24 h; $\bar{M}_{n,GPC}$ = 50 800 g mol^{-1}, $\bar{M}_{n,th}$ = 165 000 g·mol^{-1}; PDI = 1.09. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.16 (−*C*H_3−C−), 1.74 (−*C*H_2−CH), and 4.80 (−CH_2−*CH*−).

PVND: 45% of conversion in 22 h; $\bar{M}_{n,GPC}$ = 58 935 gmol^{-1}, $\bar{M}_{n,th}$ = 177 500 g mol^{-1}; PDI = 1.37. ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.8−2 (pendant alkyl chain, −*C*H_2−CH) and 4.82 (−CH_2−*CH*−).

Polymerizations of VAG were performed in solution (*N*,*N*-dimethylacetamide). Typically, 6-*O*-vinyladipoyl-D-glucopyranose monomer (1.34 g, 4×10^{-3} mol) was dissolved in a solution of *N*,*N*-dimethylacetamide (2 mL) containing 4,4′-azobis(cyanopentanoic acid) (3.3 mg, 1.2×10^{-5} mol) and D (42 mg, 2×10^{-4} mol of xanthate functions) and placed in a Schlenk tube. The tube was then sealed with greased glass stopper, degassed with six cycles of freeze−pump−thaw, and transferred to a preheated oil bath (70 °C) for 24 h. The reaction was stopped by quenching with ice cold water for 5 min. The conversion was determined using ^{1}H NMR in DMSO by relative integration of −*C*H_2−CH− protons of the polymer

Table 1. Main Characteristics of the Cleaved Arms from 3- and 4-Arm Stars

cleaved arms from 3-arm stars				cleaved arms from 4-arm stars			
conv (%)[a]	$\bar{M}_{n,th}$[b] (g mol^{-1})	$\bar{M}_{n,GPC}$ (g mol^{-1})	PDI[c]	conv (%)[a]	$\bar{M}_{n,th}$[b] (g mol^{-1})	$M_{n,GPC}$ (g mol^{-1})	PDI[c]
16.4	14 000	13 000	1.23	15.8	13 400	16 000	1.22
40	34 000	31 800	1.21	33.8	28 800	38 000	1.13
60	51 200	40 900	1.42	47	40 000	41 200	1.32
62	53 200	37 200	1.5	68.4	58 200	59 700	1.52

[a] Evaluated from ^{1}H NMR. [b] Calculated from the following equation: $\bar{M}_{n,th} = [VAc]/[RAFT] \times M_{VAc} \times$ conversion $+ M_{RAFT}$ with [VAc] and [RAFT], initial concentrations in monomer and RAFT agent, and M_{VAc} and M_{RAFT} molecular weights of VAc and RAFT agent. [c] Evaluated from GPC in THF.

backbone (δ (ppm) = 1.84) and of the vinyl proton CH_2=C*H*−O (H13) of the monomer (δ (ppm) = 7.30).

4-Arm PVAG Stars. 22% of conversion in 2.5 h; $\bar{M}_{n,GPC}$ = 26 600 g mol^{-1}; $\bar{M}_{n,th}$ = 22 400 g mol^{-1}; PDI = 1.33. ^{1}H NMR: see ref 29.

Cleavage of the Arms. Z-designed PVAc stars (500 mg) were dissolved in 5 mL of THF, and 1 mL of propylamine was added. The solution was stirred overnight at room temperature and dried under vacuum.

^{1}H NMR ($CDCl_3$): Similar to PVAc backbone; molecular weights of the cleaved arms collected in Table 1.

Hydrolysis of PVAc. Poly(vinyl acetate) was hydrolyzed to poly(vinyl alcohol) by dissolving 100 mg of polymer in methanol (10 mL). A solution of 200 mg of potassium hydroxide dissolved in methanol (10 mL) was added to the polymer solution. The solution was stirred for 2 h. The precipitated poly(vinyl alcohol) was then filtered off and washed several times with methanol prior to drying.

Yield of hydrolysis: 100% (total disappearance of the CO_2CH_3 peak δ (ppm) = 2 and shifting of the (−CH_2−*C**H*−) protons from 4.85 to 3.81). PVA: $M_{n,GPC(DMAc)}$ = 55 000 g mol^{-1}, PDI = 1.48 (PVAc precursor: $M_{n,GPC(THF)}$ = 42 000 g mol^{-1}, PDI = 1.20). ^{1}H NMR (D_2O): δ (ppm) = 1.34 (−*C**H*$_2$−CH−), 3.81 (−CH_2−*C**H*−), 4.17, 4.43, and 4.63 (CH−O*H*).

Poly(vinyl pivalate) (0.09 g) was dissolved in ethanol (1 mL), and then methanolic NaOH (1 wt %, 1 mL) was added. The mixture was heated at 60 °C for 24 h.

Yield of hydrolysis: 90% (calculated from the relative integrations of the −CH_2−*C**H*− protons of the hydrolyzed PVP units, δ (ppm) = 3.64, and of the −CH_3 protons of the nonhydrolyzed VP units of the polymer backbone, δ (ppm) = 1.16). PVA: $\bar{M}_{n,GPC(DMAc)}$ = 70 400 g mol^{-1}, PDI = 1.21 (PVP precursor: $\bar{M}_{n,GPC(THF)}$ = 85 600 g mol^{-1}, PDI = 1.33).

Poly(vinyl neodecanoate) was suspended in ethanol (1 mL), and then methanolic NaOH (1 wt %, 1 mL) was added. The mixture was heated at 60 °C for 24 h. No hydrolysis was observed.

Characterization. ^{1}H NMR spectra were recorded on a Bruker spectrometer (300 MHz) using $CDCl_3$ as solvent for PVAc materials and D_2O for PVA polymers. Gel permeation chromatography (GPC) analyses of PVAc, PVP, and PVND polymers were performed in THF at 25 °C (flow rate:1 mL/min) using a Shimadzu modular system comprising an autoinjector and a Polymer Laboratories 5.0 μm bead-size guard column (50 × 7.5 mm) followed by three linear PL columns (10^5, 10^4, and 10^3 Å) and a differential refractive index detector.

GPC analyses of PVA and PVAG polymers were performed in *N*,*N*-dimethylacetamide (DMAc) (0.03% w/v LiBr, 0.05% BHT) at 40 °C (flow rate: 1 mL/min) using a Shimadzu modular system comprising a SIL-10AD autoinjector and a Polymer Laboratories 5.0 μm bead-size guard column (50 × 7.8 mm) followed by four linear PL (Styragel) columns (10^5, 10^4, 10^3, and 500 Å) and a RID-10A differential refractive index detector. Calibration of the GPCs was performed with narrow polydispersity polystyrene standards ranging from 500 to 10^6 g/mol. The experimental molecular weights were corrected for PVAc using the Mark−Houwink parameters (universal calibration): $K = 16 \times 10^{-5}$ mL g^{-1} and $\alpha = 0.70$ (PS, $K = 14.1 \times 10^{-5}$ mL g^{-1} and $\alpha = 0.70$).

Dual detection analyses were performed in THF on a modular system comprising a LC-10ATVP Shimadzu solvent delivery system, an in-line ERC-3415 degasser unit, a SIL-10ADVP Shimadzu autoinjector with a stepwise injection control motor with an accuracy of ±1 μL, a column set which consisted of a PL 5.0 μm bead size guard column and a set of 3 PL gel 5 μm linear columns (10^3, 10^4, 10^5 Å), and a DRI (Shimadzu RID-10A) and DV (Viscotek model 250) detector.

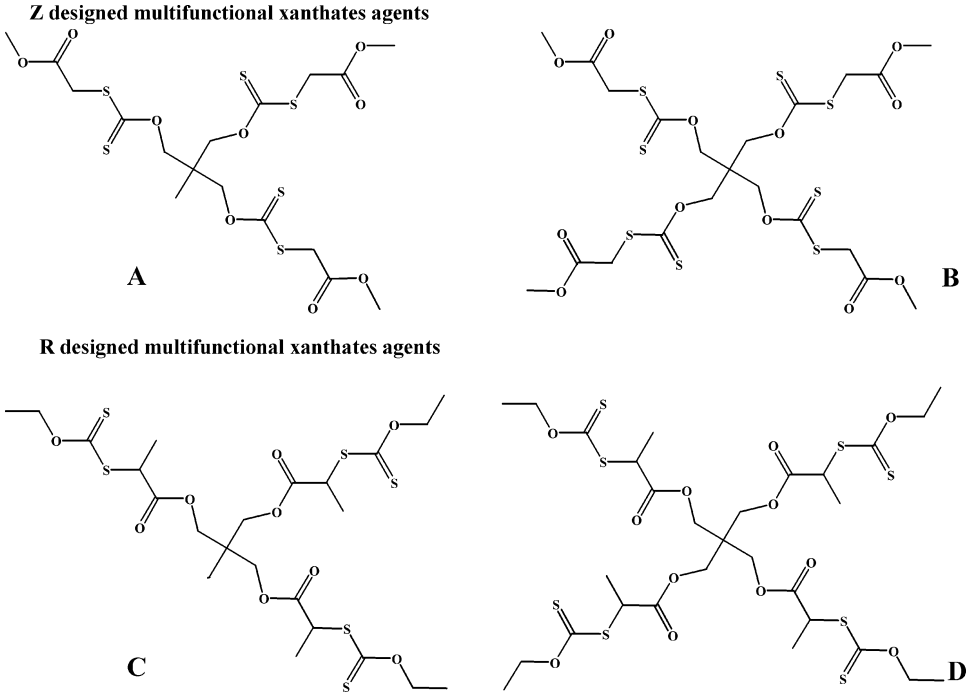
Liquid chromatography−mass spectrometry (LC−MS) analysis was carried out using a Thermo-MAT high-pressure liquid chromatography system consisting of a SCM1000 solvent degasser, a P4000 quaternary pump, an AS3000 autoinjector, a UV2000 dual-wavelength UV detector, and a C8 Luna reverse phase column (Phenomenex, 150 × 4.6 mm, 100 Å pore size, 5 μm particle size). The mobile phase was acetonitrile buffered with 1 mM acetic acid. The chromatography system was coupled to a Thermo Finnigan LCQ Deca ion-trap mass spectrometer equipped with an atmospheric pressured-ionization source operated in nebulizer-assisted electrospray mode (ESI). The instrument was calibrated with caffeine (Aldrich), MRFA (Thermo Finnigan), Ultramark 1621 (Lancaster), and poly(propylene glycol) (Aldrich, $\bar{M}_n$ = 2700 g mol^{-1}) in the mass range 195−3822 amu. All spectra were acquired in positive ion mode over the *m*/*z* range 100−1000 with a spray voltage of 5 kV, a capillary voltage of 5 V, a tube lens offset of −45 V, and a capillary temperature of 300 °C. Nitrogen was used as sheath gas at a flow rate of 0.5 L min^{-1} while helium was used as auxiliary gas.

Results and Discussion

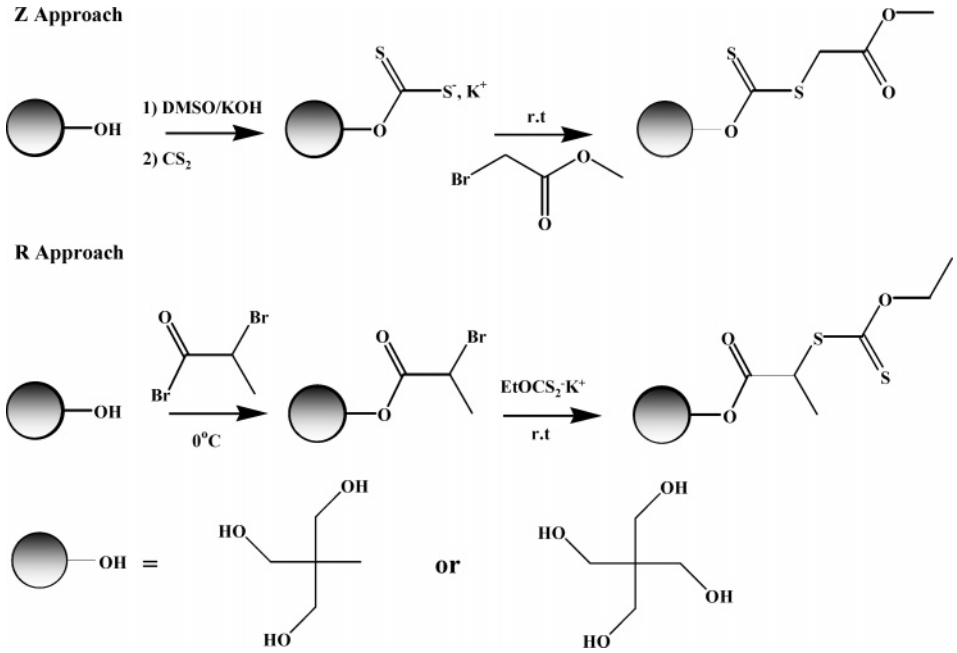
As in previous communications,[8,18,19] xanthate agents have been selected as chain transfer agents for this study (Scheme 2). Two simple experimental protocols were adopted to prepare multifunctional cores via either a one-pot (Z) or a two-step procedure (R) starting from hydroxyl-functionalized precursors, viz. 1, 1, 1-tris-(hydroxymethyl)ethane (3 OH) and pentaerythritol (4 OH) as illustrated in Scheme 3. The multifunctional core molecules were synthesized with acceptable yields, and they proved amenable to purification procedures.

Polymerization of VAc Mediated with Z-Designed Multifunctional RAFT Agents (A and B). The R and Z multifunctional xanthate agent mediated bulk polymerizations of VAc stars were investigated at different concentrations of xanthate functions (1.1×10^{-2}, 2.2×10^{-2}, and 4.3×10^{-2} mol L^{-1}) at 60 °C in the presence of AIBN (2.2×10^{-3} mol L^{-1}). Time vs conversion plots for the bulk polymerization of VAc mediated with A and B (Z-designed agents) are given in Figures 1 and 2. In accord with a previous report on PVAc synthesis mediated by monofunctional xanthate agents, prominent inhibition periods were observed for both multifunctional cores (A and B), with severity increasing as the xanthate concentration increased. However, the inhibition periods observed with B (less than 30 min) are much less pronounced than those polymerizations mediated by A, where inhibition periods up to 6 h were observed at the highest xanthate concentration (4.3×10^{-2} mol L^{-1}). The most likely origin of these inhibition periods is that, as reported earlier, trace levels of impurity (too low to be detected

Scheme 2. Structure of the R- and Z-Designed Multifunctional RAFT Agents



Scheme 3. Synthetic Approach to R- and Z-Designed Multifunctional RAFT Agents



on thin-layer chromatography plates) are responsible. This hypothesis is supported by the relative ease of purification of A and B, where core A (in contrast to B) could not be purified by recrystallization. Postinhibition, the polymerization rates (~60% conversion in 4 h) were independent of the RAFT agent concentration and only slightly lower than the rates observed either in the absence of xanthate functionality or in the presence of a monofunctional xanthate agent (~80% of conversion in 4 h).

The evolution of experimental molecular weights and molecular weight distributions of A and B based stars with conversion was investigated by GPC analysis in THF. Each chromatogram exhibited a monomodal distribution, and no molecular weight peak corresponding to dead linear polymers was observed, indicating a low proportion of termination products (single or double arms depending on the termination mode). The molecular weights of the 3- and 4-arm Z-designed PVAc stars increased linearly with conversion, as shown in Figures 3 and 4. As the branched/star structures have lower hydrodynamic volumes than the equivalent linear polymers, the experimental molecular weights of the stars determined by GPC (see Figure 5) with linear PS standards appeared lower than the theoretical molecular weights calculated from the conversion (^{1}H NMR) according to the following equation: $\bar{M}_{n,th}$ = [VAc]/[xanthate] × M_{VAc} × conversion + $M_{xanthate}$ with [VAc] and [RAFT], initial concentrations of monomer and multifunctional xanthate agent, and M_{VAc} and $M_{xanthate}$ molecular weights of VAc and xanthate agent.

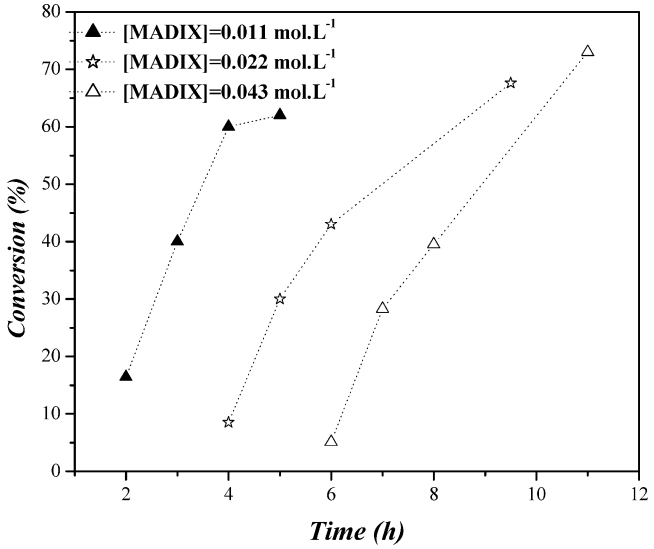


Figure 1. Conversion vs time plots obtained by ^{1}H NMR for the RAFT bulk polymerization of VAc at 60 °C with various concentrations of A. [AIBN] = 2.2×10^{-3} mol L^{-1}. Dotted lines are only a guide to the eye.

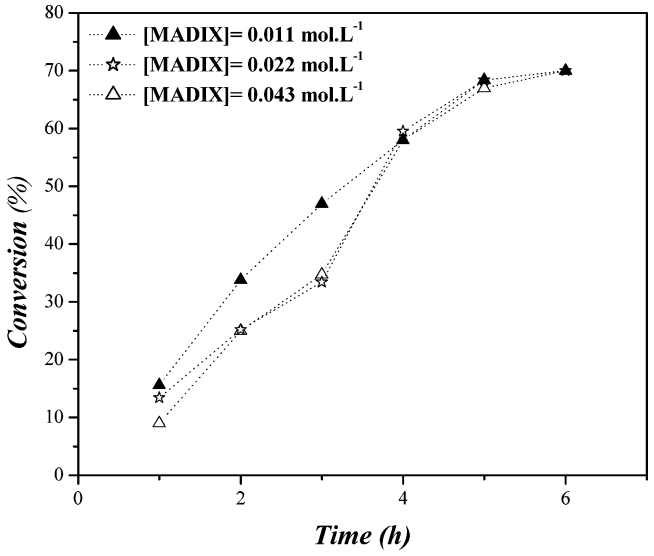


Figure 2. Conversion vs time plots obtained by ^{1}H NMR for the RAFT bulk polymerization of VAc at 60 °C with various concentrations of B. [AIBN] = 2.2×10^{-3} mol L^{-1}. Dotted lines are only a guide to the eye.

The molecular weight distributions were shown to broaden significantly at moderate to high conversions (40−70%), in agreement with previous results on linear living radical PVAc polymerizations. This observation can be attributed in part to the occurrence of irreversible transfer reactions (transfer to monomer and polymer) involving the very reactive VAc propagating radical. However, other processes may also be playing a role, as the initial concentration of xanthate agent has a significant effect on the broadening of polydispersities. The arm growth process occurs in the vicinity of the core, resulting in an increasing polymer segment density around the xanthate functionality. It has been speculated previously that this has the potential to reduce the efficiency of the addition−fragmentation process,[6] resulting in an increased probability of radical−radical termination.

Consistent with this explanation, the polydispersity of the stars prepared at the lowest concentration of xanthate functions ([xanthate] = 1.1×10^{-2} mol L^{-1}), targeting higher molecular weights (~80 000 g mol^{-1} per arm with 100% of conversion), tended to broaden at lower conversions (PDI ≥ 1.5 at 40% of conversion) than stars prepared at higher concentrations of xanthate functions (PDI ≥ 1.5 at 70% of conversion with [xanthate] = 2.2×10^{-2} and 4.3×10^{-2} mol L^{-1}) (Figures 3 and 4). In addition, the broadening was slightly more pronounced for the 4-arm star syntheses where the polymer segment density around the core is higher.

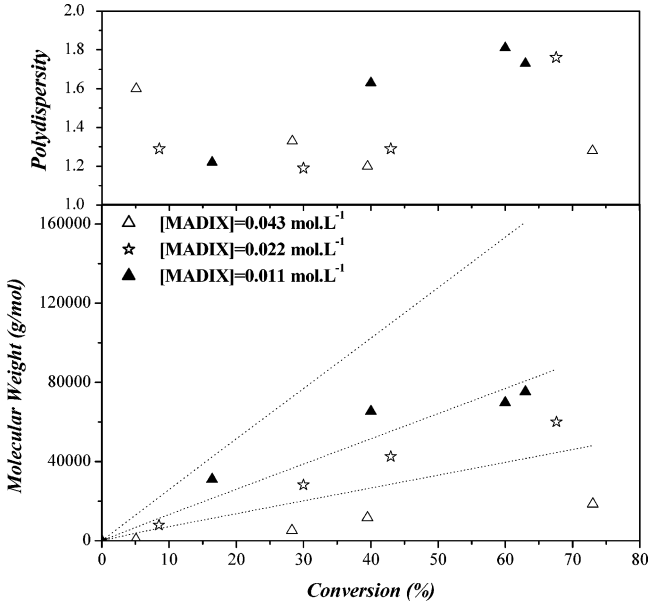


Figure 3. Evolution of the molecular weight and polydispersity with conversion for the RAFT bulk polymerization of VAc at 60 °C in the presence of A. [AIBN] = 2.2×10^{-3} mol L^{-1}. Dashed lines indicate the theoretical values.

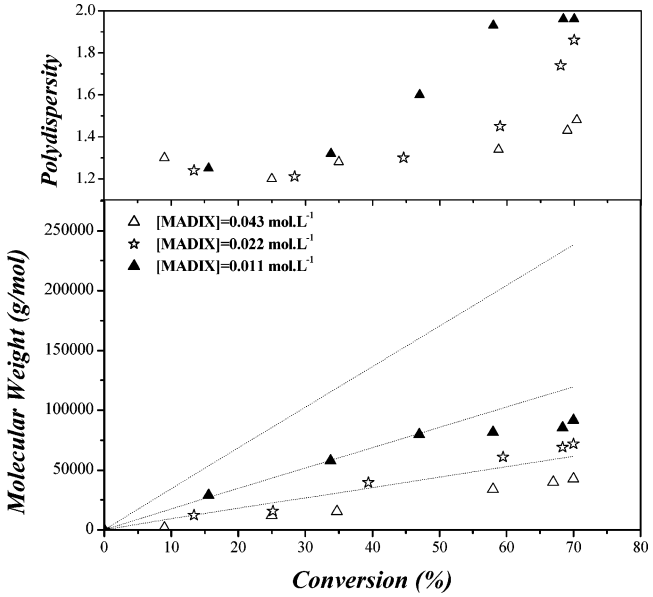


Figure 4. Evolution of the molecular weight and polydispersity with conversion for the RAFT bulk polymerization of VAc at 60 °C in the presence of B. [AIBN] = 2.2×10^{-3} mol L^{-1}. Dashed lines indicate the theoretical values.

To overcome problems with accurate molecular weight analysis and to confirm that each thiocarbonylthio function located on the multifunctional cores yields a PVAc chain, we cleaved the fragile xanthate links located between the core and the arms using a strong nucleophile, viz. by aminolysis with propylamine.

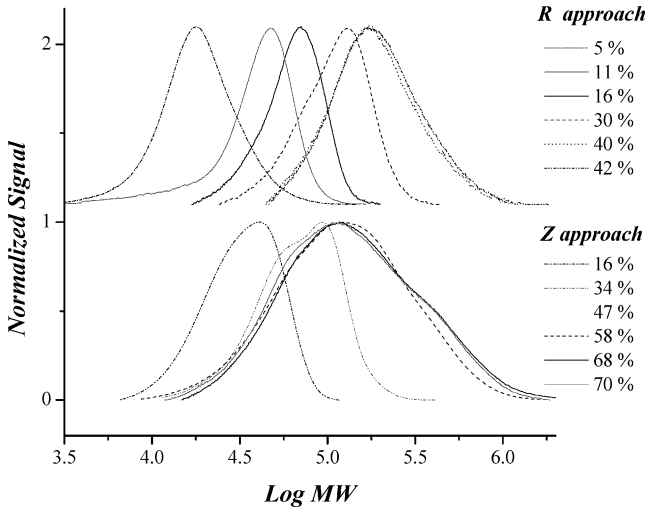


Figure 5. Evolution of GPC chromatograms for the RAFT bulk polymerization of VAc at 60 °C in the presence of Z-designed multifunctional core B (bottom) ([AIBN] = 2.2×10^{-3} mol L^{-1}; [B] = 1.1×10^{-2} mol L^{-1}) and in the presence of R-designed multifunctional core D (top) ([AIBN] = 2.2×10^{-3} mol L^{-1}; [B] = 1.1×10^{-2} mol L^{-1}).

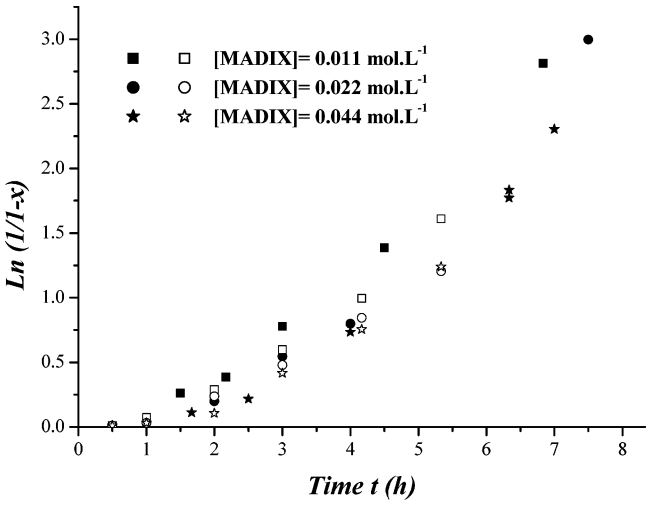


Figure 6. Conversion vs time plots obtained by ^{1}H NMR for the RAFT bulk polymerization of VAc at 60 °C with various concentrations of C and D. [AIBN] = 2.2×10^{-3} mol L^{-1}.

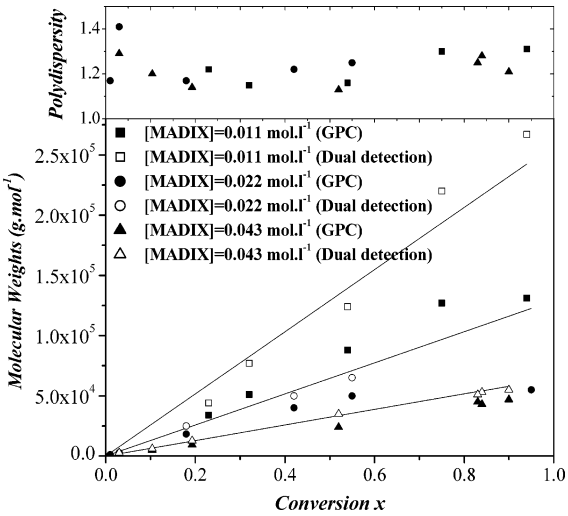


Figure 7. Evolution of the molecular weight and polydispersities with conversion for the RAFT bulk polymerization of VAc at 60 °C in the presence of C. [AIBN] = 2.2×10^{-3} mol L^{-1}. Lines indicate the theoretical values.

The resulting linear polymers were dried and subsequently characterized by GPC in THF; the results are given in Table 1. The complete absence of acetate group hydrolysis was confirmed by ^{1}H NMR of the polymer. All the arms cleaved from cores A and B exhibited monomodal distributions (PDI ≤ 1.6), and there was no indication of higher molecular weight byproducts (twice the molecular weight of one arm) that may have originated from arm−arm coupling. The theoretical and experimental molecular weights of the cleaved arms were in good accord, providing strong evidence that each thiocarbonylthio function located on the cores was involved in the growth of a PVAc chain. Consistent with the observations already made indicating star polydispersity broadening, the polydispersities of the cleaved arms also broadened significantly at moderate conversions. However, contrary to expectation,[30] the polydispersities of the linear polymer arms were systematically narrower in comparison with the corresponding star polymers at moderate and high conversions. This may simply reflect the error in GPC analysis of the stars distorting the polydispersity indices, or it is possible that the original star molecular weight distributions did include some linear chains that were not resolved by the chromatographic process.

Following the successful syntheses of star architecture PVAc molecules using the Z-approach, we attempted to generate PVA via hydrolysis reactions (MeOH/NaOH 1 wt % or EtOH/K_2CO_3). Unfortunately, it was not possible through these strategies to hydrolyze the acetate functionalities without cleaving the arms and the core (destruction of the xanthate linkages). Alternative routes (possibly enzymatic) may be adopted in the future to overcome this problem.

Polymerization of VAc Mediated with R-Designed Multifunctional RAFT Agents (C and D). Some preliminary results using this approach (using C and D) were reported in an earlier Communication.[8] This more detailed investigation, using reagent concentrations comparable with the preceding Z-group approach, reveals that the rate of polymerization is independent of the number of arms emanating from the core (Figure 6). Following an initial inhibition period of 30 min, the polymerization proceeds with pseudo-first-order kinetics consistent with a constant radical concentration. The inhibition time was observed to be slightly dependent on the xanthate concentration. There may be an underlying elementary reaction contributing to the inhibition; however, as discussed earlier in this particular system (vinyl acetate), it is very difficult to rule out a significant influence of minor impurities introduced as minor byproducts of the core syntheses.

An analysis of the GPC curves (Figure 5) clearly indicates the absence of either star−star coupling or linear polymers that may have been expected on consideration of the mechanism (Scheme 1).[28] The molecular weight of the stars prepared by MADIX polymerization mediated by C and D evolves linearly with conversion, consistent with a living process (Figures 7 and 8). As expected the measured molecular weights deviate from the theoretical values, attributable to the restricted hydrodynamic volume of the stars. To ensure an accurate analysis, we adopted an on-line viscometer to determine the intrinsic viscosities of the polymers allowing us to construct a universal calibration. The results clearly reveal that the experimental molecular

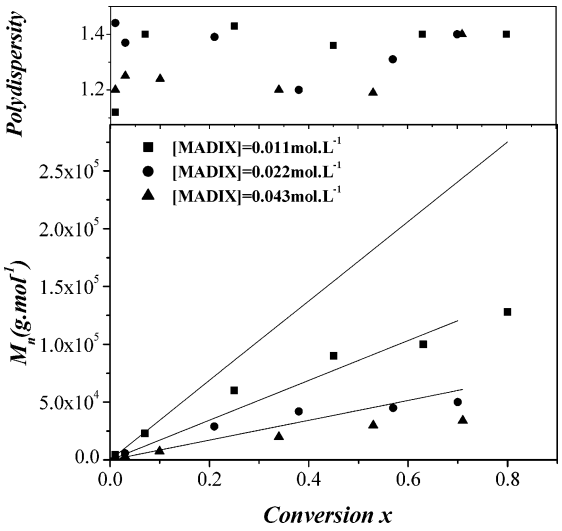


Figure 8. Evolution of the molecular weight and polydispersities with conversion for the RAFT bulk polymerization of VAc at 60 °C in the presence of D. [AIBN] = 2.2×10^{-3} mol L^{-1}. Lines indicate the theoretical values.

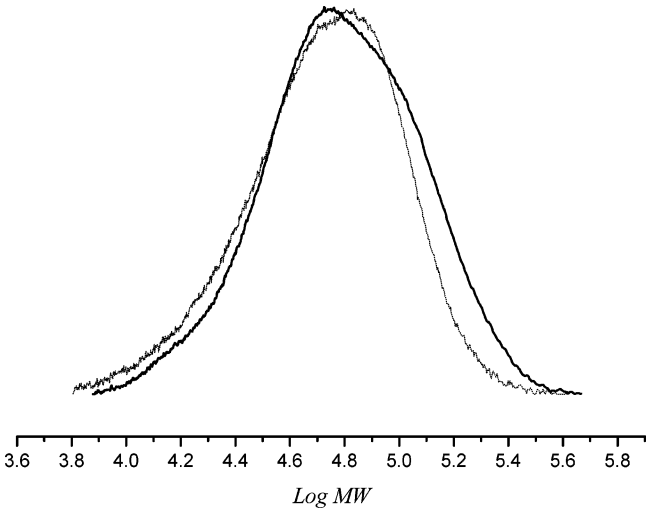


Figure 9. GPC chromatograms of 4-arm PVAc star and resulting PVA star after hydrolysis.

weights concur with the theoretical values (Figure 7). However, it should be noted here that the molecular weight as obtained using the universal calibration result in viscosity-average molecular weights and therefore slightly deviate from the number-average molecular weight. Since the polydispersity indices (PDI) remain below 1.4, even reducing to values of 1.1 at medium conversions, the deviations between these two molecular weights are rather small.

Hydrolysis of these poly(vinyl acetate) star polymers results in the formation of poly(vinyl alcohol) stars. The linkage between the branch and core is (in contrast to the Z-group approach) a stable ester linkage, which can only be hydrolyzed under very aggressive conditions. Despite the poor solubility of PVA in DMAc, GPC analysis indicates a slight increase in molecular weight due to the altered hydrodynamic radius while low molecular weight products are absent (Figure 9). The formation of a small shoulder on the distribution can be attributed to the formation of disulfide bonds, which may be obtained after hydrolysis of the branch end functionality, the xanthate group.

R- vs Z-Group Approach. In contrast to earlier studies utilizing styrene, the R-group approach seems to result in better defined star products. A narrower molecular weight distribution is observed throughout the polymerization with a single GPC peak increasing in size with conversion. Single chains and significant star−star coupling as reported earlier are not clearly visible. A detailed investigation of the mechanism of the R-group approach indicates that the formation of linear polyxanthate agents as well as the formation of star−star termination products can be minimized if the radical concentration is kept low during the polymerization.[28] In these reactions, we maintain a high rate of polymerization relative to the rate of initiator decomposition. (Only around 16% of the initial AIBN concentration has decomposed after a reaction time of 4 h.) The Z-group approach, in contrast, exhibits monomodal molecular weight distributions that broaden significantly with conversion. In earlier studies this has been explained by an increased presence of termination products resulting from recombination or disproportionation of propagating chains. In this study, the molecular weight data obtained for the severed arms are consistent with the theoretical molecular weight values. Therefore, the observed broadening of the distribution may be explained by a decreased chain transfer activity between the linear macroradical that is now entangled within the star polymer and the xanthate groups. The limited mobility of the macroradical combined with the low accessibility of the thiocarbonylthio functions might lead to a preferred propagation of vinyl acetate, resulting in a hybrid behavior that is known to broaden the molecular weight distribution.

The R-group methodology seems more apposite as a synthetic approach to well-defined poly(vinyl alcohol) star polymers as it is possible to hydrolyze the acetate functionality without causing any destruction of the basic polymer structure (this contrasts with the Z-approach).

Polymerization of Bulky Vinyl Esters Mediated with R-Designed Multifunctional RAFT Agents (D). Given our ability to generate well-defined PVAc and subsequently PVA stars after hydrolysis, attempts were made to extend the scope of the R-designed multifunctional xanthate agents to the polymerization of vinyl esters with bulky pendant group such as vinyl pivalate (VP) or vinyl neodecanoate (VND) which may produce highly syndiotactic polymers.[31,32] Bulk polymerizations of VP and VND were carried out with D (respectively 1.37×10^{-2} and 8.97×10^{-3} mol L^{-1} of xanthate functions) in the presence of AIBN (respectively 1.37×10^{-3} and 8.97×10^{-4} mol L^{-1}) as initiator. The polymerization rates of VP and VND were significantly lower (respectively 64% of conversion in 24 h and 45% of conversion in 22 h) than comparable VAc polymerizations. This can be attributed to both the bulkiness of the side chains affecting monomer and radical reactivity and their lower concentrations in bulk (6.85 and 4.48 mol L^{-1} for VP and VND, respectively). MW vs conversion plots for the polymerization of these two monomers mediated by D are given in Figure 10. In both cases, experimental molecular weights determined by GPC exhibited as expected a strong deviation from the theoretical molecular weights calculated from conversion because of the star-shaped structure of the polymers and the PS standard calibration. However, the molecular weights were shown to increase linearly with conversion (up to 50%), and the samples exhibited

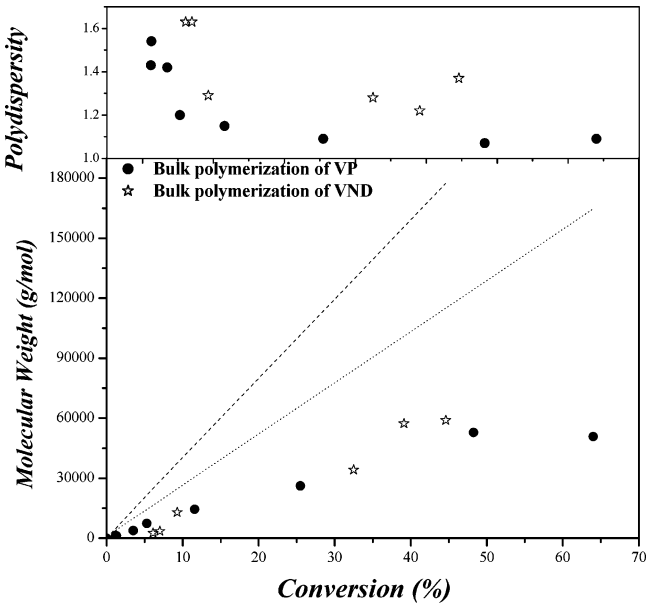


Figure 10. Evolution of the molecular weight and polydispersities with conversion for the RAFT bulk polymerization of VP at 60 °C in the presence of D. VP: [D] = 1.37×10^{-2} mol L^{-1}; [AIBN] = 1.37×10^{-3} mol L^{-1}; VND: [D] = 8.97×10^{-3} mol L^{-1}; [AIBN] = 8.97×10^{-4} mol L^{-1}. Dashed lines indicate the theoretical values.

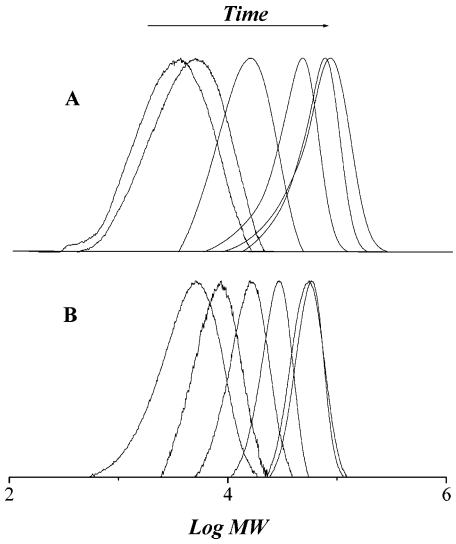


Figure 11. GPC chromatograms for the RAFT bulk polymerization of VND (top) and VP (bottom) at 60 °C in the presence of D. Top: [D] = 8.97×10^{-3} mol L^{-1}; [AIBN] = 8.97×10^{-4} mol L^{-1}; Bottom: [D] = 1.37×10^{-2} mol L^{-1}; [AIBN] = 1.37×10^{-3} mol L^{-1}.

narrow polydispersity indices (below 1.2 for VP and 1.4 for VND) indicating typical features of living radical polymerization (see Figure 11).

Glycopolymer Stars from 6-*O*-Vinyladipoyl-D-glucopyranose (VAG). The degradation of glucose-functionalized poly(vinyl ester)s[33,34] has been reported to lead to hydrolytic cleavage of the glucose moiety and the adipic acid spacer arm, leaving behind a biocompatible poly(vinyl alcohol) main chain. This potentially allows the design of degradable biocompatible polymers via a chain polymerization process. We extended our studies to the RAFT/MADIX polymerization of a glucose-functionalized vinyl ester monomer, namely 6-*O*-vinyladipoyl-D-glucopyranose, in the presence of multifunctional xanthate agent D.

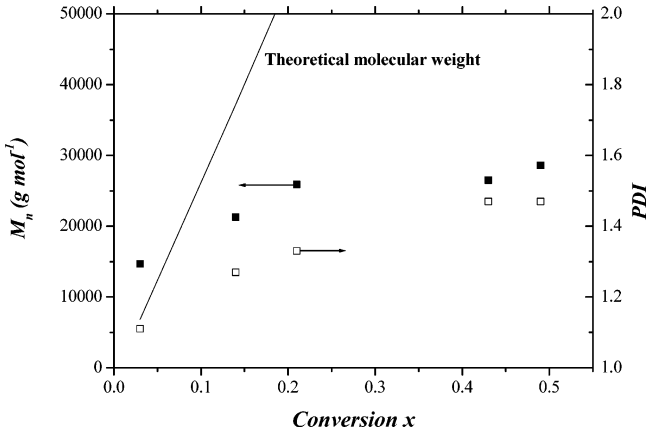
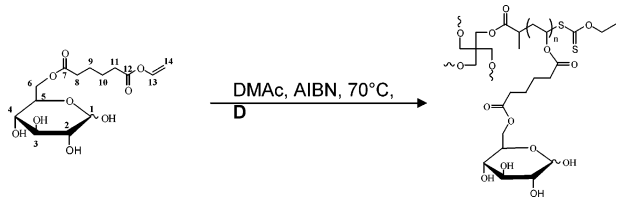


Figure 12. Evolution of the molecular weight and polydispersities with conversion for the RAFT bulk polymerization of VAG at 70 °C in the presence of D. [VAG] = 2 mol L^{-1}; [D] = 1×10^{-2} mol L^{-1}; [AIBN] = 6×10^{-3} mol L^{-1}.

Scheme 4. Preparation of Poly(6-*O*-vinyladipoyl-D-glucopyranose) 4-Arm Stars



Recently, initial results on the controlled radical polymerization of the same glucose-functionalized vinyl ester monomer using a linear xanthate agent were reported by our group.[29]

In these earlier studies water or methanol was adopted as the solvent for the polymerization of 6-*O*-vinyladipoyl-D-glucopyranose. In this study we used *N,N*-dimethylacetamide to ensure the solubilization of the multifunctional xanthate agent D (see Scheme 4). The polymerization of 6-*O*-vinyladipoyl-D-glucopyranose was therefore carried out in the presence of D and 4,4′-azobis(cyanopentanoic acid) at 70 °C. The polymerization proceeded without any inhibition time to a conversion of 35% within 4 h; thereafter, the rate starts to reduce until after 9 h a limiting conversion of 50% was attained. This result was reproducible. This limiting conversion occurs even though radicals are still being produced by the initiator.

The molecular weights were found to increase with conversion (Figure 12). The initial molecular weights are slightly higher than expected, and they further deviate from theoretical expectations at higher conversions. Some of this behavior may be explained by the poor calibration; however, we believe that the broadening polydispersity index is indicative of side reactions. The GPC analysis reveal that the initial distribution is rather narrow but this broadens considerably at higher conversions resulting in ill-defined and bimodal distributions (Figure 13). A ^{1}H NMR analysis of low conversion polymer confirmed that the multifunctional xanthate agent is incorporated into the polymer structure. Utilizing a method reported earlier,[19] the shifts of the peaks corresponding to the multifunctional xanthate agents were analyzed. Unfortunately, as there is a significant overlap of these with the glucose signals, we cannot confidently state that all branches are activated during the polymerization. Nonetheless, the GPC chromatograms recorded using UV detection at 350 nm

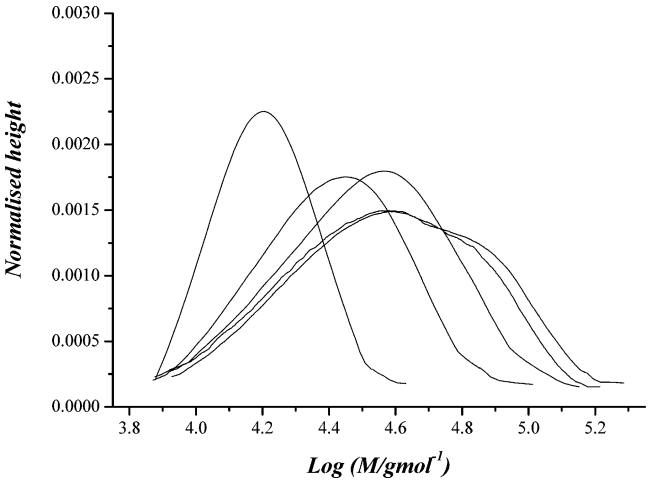


Figure 13. GPC chromatograms for the RAFT bulk polymerization of VAG at 70 °C in the presence of D. [VAG] = 2 mol L^{-1}; [D] = 1×10^{-2} mol L^{-1}; [I] = 6×10^{-3} mol L^{-1}.

(specific to a chromophore generated by the macroxanthate agent) confirm the incorporation of all available xanthate agents in the glycopolymer, and all multifunctional xanthate agents are involved in the polymerizations. Despite some problems, this approach does seem promising for generating complex biodegradable glycopolymer architectures.

Conclusions

Well-defined poly(vinyl alkanoate) star polymers were synthesized using multifunctional xanthates. Both methodologies (Z-group and R-group) result in a living polymerization with molecular weight increasing linearly with conversion. The R-group approach was found to be more suitable for the preparation of poly(vinyl alkanoate) star polymers, leading to small molecular weight distributions (1.1−1.4) throughout the polymerization. The hydrolysis of the polymers prepared via the R-group approach was found to be suitable to generate poly(vinyl alcohol) star polymers. Initial results on the polymerization of 6-*O*-vinyladipoyl-D-glucopyranose suggest that it is possible to utilize RAFT/MADIX to create complex biodegradable architectures; however, the presence of sugar functionality appears to cause some additional synthetic problems. We are currently pursuing further research in order to optimize this synthetic strategy.

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References and Notes

(1) Le, T. P.; Moad, G.; Rizzardo, E.; Thang, S. H. PCT Int. Appl. WO9801478 A1 19980115; *Chem. Abstr.* **1998**, *128*, 115390.
(2) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H *Macromolecules* **1998**, *31*, 5559−5562.
(3) Destarac, M.; Charmot, D.; Franck, X.; Zard, S. Z. *Macromol. Rapid Commun.* **2000**, *21*, 1035−1039.
(4) Stenzel-Rosenbaum, M.; Davis, T. P.; Chen, V.; Fane, A. G. *J. Polym. Sci., Part A* **2001**, *39*, 2777−2783.
(5) Mayadunne, R. T. A.; Jeffery, J.; Moad, G.; Rizzardo, E. *Macromolecules* **2003**, *36*, 1505−1513.
(6) Stenzel, M. H.; Davis, T. P. *J. Polym. Sci., Part A* **2002**, *40*, 4498−4512.
(7) Ming, C.; Ghiggino, K. P.; Launikonis, A.; Mau, A. W. H.; Rizzardo, E.; Sasse, W. H. F.; Thang, S. H.; Wilson, G. J. *J. Mater. Chem.* **2003**, *13*, 2696−2700.
(8) Stenzel, M. H.; Davis, T. P.; Barner-Kowollik, C. *Chem. Commun.* **2004**, *13*, 1546−1547.
(9) Dureault, A.; Taton, D.; Destarac, M.; Leising, F.; Gnanou, Y. *Macromolecules* **2004**, *37*, 5513−5519.
(10) Matyjaszewski, K.; Wang, J. S. PCT Int. Appl. WO9630421 A1 19961063.
(11) Ueda, J.; Matsuyama, M.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **1998**, *31*, 557−562.
(12) Angot, S.; Murthy, K. S.; Taton, D.; Gnanou, Y. *Macromolecules* **1998**, *31*, 7218−7225.
(13) Hedrick, J. L.; Trollsas, M.; Hawker, C. J.; Claesson, A. H.; Heise, A.; Miller, R. D.; Mecerreyes, D.; Jerome, R.; Dubois, P. *Macromolecules* **1998**, *31*, 8691−8705.
(14) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101*, 2921−2990.
(15) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661−3688.
(16) Hawker, C. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1456−1459.
(17) Robin, S.; Guerret, O.; Couturier, J. L.; Gnanou, Y. *Macromolecules* **2002**, *35*, 2481−2486.
(18) Stenzel, M. H.; Cummings, L.; Roberts, G. E.; Davis, T. P.; Vana, P.; Barner-Kowollik, C. *Macromol. Chem. Phys.* **2003**, *204*, 1160−1168.
(19) Favier, A.; Barner-Kowollik, C.; Davis, T. P.; Stenzel, M. H. *Macromol. Chem. Phys.* **2004**, *205*, 925−936.
(20) Uhrich, K. E.; Cannizarro, S. M.; Langer, R. S.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181−3198.
(21) Orienti, I.; Di Pietra, A.; Luppi, B.; Zecchi, V. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 421−424.
(22) Hassan, C. M.; Peppas, N. A. *Eur. J. Pharmacol. Biopharm.* **2000**, *49*, 161−165.
(23) Rump, A. F. E.; Woschee, U.; Theisohn, M.; Fischbach, R.; Heindel, W.; Lackner, K.; Klaus, W. *Eur. J. Clin. Pharmacol.* **2002**, *58*, 459−465.
(24) Inoue, K. *Prog. Polym. Sci.* **2000**, *25*, 453−571.
(25) Hadjichristidis, N.; Pitsikalis, M.; Pispas, S.; Iatrou, H. *Chem. Rev.* **2001**, *101*, 3747−3792.
(26) Haddleton, D. M.; Edmonds, R.; Heming, A. M.; Kelly, E. J.; Kukulj, D. *New J. Chem.* **1999**, *23*, 477−479.
(27) Jesberger, M.; Barner, L.; Stenzel, M. H.; Malmstrom, E.; Davis, T. P.; Barner-Kowollik, C. *J. Polym. Sci., Part A* **2003**, *41*, 3847−3861.
(28) Chaffey-Millar, H.; Busch, M.; Davis, T. P.; Stenzel, M. H.; Barner-Kowollik, C. *Macromol. Theory Simul.* **2005**, *14*, 143−157.
(29) Albertin, L.; Kohlert, C.; Stenzel, M. H.; Foster, J. L. R.; Davis, T. P. *Biomacromolecules* **2004**, *5*, 255−260.
(30) Schaefgen, J. R.; Flory, J. *J. Am. Chem. Soc.* **1948**, *70*, 2709−2718.
(31) Yamada, K.; Nakano, T.; Okamoto, Y. *Macromolecules* **1998**, *31*, 7598−7605.
(32) Yamada, K.; Nakano, T.; Okamoto, Y. *J. Polym. Sci., Part A* **2000**, *38*, 220−228.
(33) Tokiwa, Y.; Fan, H.; Hiraguri, H.; Kurane, R.; Kitagawa, M.; Shibatani, S.; Maekawa, Y. *Macromolecules* **2000**, *33*, 1636−1639.
(34) Kitagawa, M.; Raku, T.; Shimakawa, H.; Fan, H.; Tokiwa, Y. *Macromol. Biosci.* **2002**, *2*, 233−237.

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