Graft block copolymers of propargyl methacrylate and vinyl acetate via a combination of RAFT/MADIX and click chemistry: Reaction analysis

6 AUTHORS, INCLUDING:

Damien Quémener
Université de Montpellier
33 PUBLICATIONS **711** CITATIONS

SEE PROFILE

Thomas P Davis
Monash University (Australia)
497 PUBLICATIONS **19,552** CITATIONS

SEE PROFILE

Martina H Stenzel
University of New South Wales
278 PUBLICATIONS **10,902** CITATIONS

SEE PROFILE

Graft Block Copolymers of Propargyl Methacrylate and Vinyl Acetate via a Combination of RAFT/MADIX and Click Chemistry: Reaction Analysis

DAMIEN QUÉMENER,* MAUDE LE HELLAYE, CARLA BISSETT, THOMAS P. DAVIS,
CHRISTOPHER BARNER-KOWOLLIK, MARTINA H. STENZEL

Centre for Advanced Macromolecular Design, School of Chemical Sciences and Engineering,
The University of New South Wales, New South Wales 2052, Sydney, Australia

ABSTRACT: Propargyl methacrylate with its acetylene function protected with a silyl group is polymerized via the reversible addition fragmentation chain transfer (RAFT) process, using cyanoisopropyl dithiobenzoate (CPDB) as RAFT agent, and subsequently deprotected to afford a polymer backbone where each repeated unit is decorated with an acetylene functionality ($1000 < M_n < 13,600$ g mol^{-1}, $1.07 <$ PDI < 1.29). In parallel, an azide functionalized xanthate (ethoxythiocarbonylsulfanyl-acetic acid 3-azido-propyl ester) was employed to prepare narrow polydisperse poly(vinyl acetate) ($M_n = 850$ g mol^{-1}, PDI $= 1.20$). The two polymers are conjugated by Huisgen 1,3-dipolar cycloaddition to afford narrow polydisperse comb polymer ($1.12 <$ PDI < 1.18, $3400 < M_n < 12,500$ g mol^{-1}, based on linear polystyrene calibration, $4500 < M_n^{theo} < 15,600$ g mol^{-1}). The study places special emphasis on following the copper catalyzed 1,3-dipolar cycloaddition via Fourier Transform Infrared Spectroscopy (FTIR) as well as via on-line UV–Vis photospectrometry on several model compounds, i.e. the nonmonomer inserted azido-xanthate RAFT/MADIX agent as well as a 2-propargyl-2-bromopropionate and 3-azidopropyl-2-bromopropionate model compounds. A suitable absorption band in the VIS at 666 nm (tentatively assigned to a charge transfer complex between copper(I) and the forming triazole moieties) is identified as a promising sensor for following the click reaction kinetics, thus allowing for the rapid assessment of reaction completion in an on-line fashion. © 2007 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 46: 155–173, 2008

Keywords: graft copolymers; Huisgen 1,3-dipolar cycloaddition; reversible addition fragmentation chain transfer (RAFT); UV-vis spectroscopy

INTRODUCTION

Novel polymeric materials regularly require well-defined properties. Often structural complexity is required in polymer architectures to achieve a certain set of properties, e.g., self-assembly in solution or phase separation in the solid state. Complex macromolecular architectures can be synthesized under relatively mild reaction conditions via living radical polymerization techniques. Especially polymer architectures based on poly(vinyl alcohol) (PVA) are highly desirable and open a large array of new applications, particularly in the area of polymer based (drug) delivery systems. PVA is typically

generated via the hydrolysis of poly(vinyl acetate) (PVAc) and is the largest volume water-soluble polymers produced industrially.[1] Originally, PVA was mainly employed in the textile and paper industries. However, in recent years, PVA has been increasingly used in biomedical applications due to its high water solubility. Hydrogels based on PVA have been investigated as carrier for the controlled delivery of hydrophilic drugs.[2,3] It is not only its biocompatibility that attracts the usage of PVA for biomedical application[4] but also its high hydroxy functional density, which allows the modification of the polymer via covalent linkages. For example, mono and oligonucleotides covalently bound to PVA have been tested as primers for the enzymatic synthesis of polynucleotides.[5] The interest in branched structures such as comb- and star-like polymers is partly motivated by their unusual properties regarding biomedical applications.[6] The higher binding affinity of end group functionalised star polymers compared with their linear counterparts is the results of multiple receptor/ligand interaction. Nature uses this so-called multivalency effect successfully in cell–cell interaction or in the targeting of cells by viruses.[7]

Reversible addition fragmentation chain transfer (RAFT) polymerization[8]/macromolecular design via the interchange of xanthates (MADIX)[9] have proven to be versatile tools in the synthesis of complex polymer architectures.[10] MADIX polymerization employs xanthate based controlling agents, which have been demonstrated to effectively control the polymerization of vinyl acetate.[11] Well-defined three- and four-arm star polymers were obtained[12–14] despite known complications that can arise during the synthesis of star polymers using the RAFT process.[15] Termination reactions such as star–star coupling can broaden the molecular weight distribution significantly. However, several avenues to optimize the star synthesis via RAFT have been suggested on the base of computational modeling,[16] which are in good agreement with experimental findings.[15] One important factor that results in the increased occurrence of side reactions is the increasing number of arms. Indeed, when attempting to synthesize PVAc comb polymers with 20–200 branches, the broadening reached catastrophic dimension with insoluble products being formed.[17] RAFT/MADIX polymerization reached consequently its limits.

Thus, there exists the need for novel synthetic strategies that allow for the synthesis of new complex architectures. Huisgen 1,3-dipolar cycloaddition, a particular reaction in a group of highly effective and orthogonal reactions often termed click chemistry is considered as a suitable pathway to complex polymer architectures effectively connecting the polymeric building blocks via 1,2,3-triazoles. Such 1,2,3-triazoles derived from alkynes and acetylenes were first prepared by Huisgen et al.[18] The synthesis approach was later modified by Meldal and coworkers[19] as well as Fokin and coworkers[20] by introducing Cu(I) ions. Cu(I) ions do not only direct the reaction leading to the formation of a single regioisomer, but also facilitate the cycloaddition enhancing the complete reaction at low temperatures.

Click chemistry has consequently been discovered as a tool not only to generate regioselective 1,2,3-triazoles, but also to build up complex architectures such as dendrimers. While traditional dendrimer synthesis can be subjected to low yields, high sensitivity towards functional groups, and steric hindrance, the click approach has been described as an easy and versatile alternative to build up dendrimers of many generations.[21–25]

The click reaction has recently been applied by polymer chemists, including our group, who recognized the opportunity for creating new polymer architectures by conjoining azide and alkyne endfunctionalized polymer pairs.[26–28] A range of complex structures including star polymers and block copolymers have been prepared by combining techniques such as atom transfer radical polymerization (ATRP),[29–32] ring opening metathesis polymerization (ROMP),[33] RAFT,[34–37] polycondensation and other polymerization methods[28] with the click approach.[38] In contrast, reports on the synthesis of comb polymers via click chemistry are rather sparse.[26,28] ATRP in combination with click chemistry has been employed to graft polymers onto a polymeric backbone,[39,40] but also to synthesize macromonomers to generate comb polymers via a combined ATRP/click approach.[41]

The investigation into the synthesis of comb polymers by click chemistry in combination with the versatility of the RAFT/MADIX process is the focus of the current contribution. MADIX polymerization has been demonstrated, thus far, as the most suitable pathway to control the polymerization of vinyl acetate. The difficulties arising during the synthesis of comb polymers via RAFT/MADIX polymerization makes the combined click/MADIX approach an ideal avenue to

access PVAc comb polymers, a polymer architecture that has not been prepared in a controlled fashion so far. The comb branches will be generated by MADIX polymerization followed by click reaction to a highly alkyne functionalized backbone. In an attempt to follow the progress of the click reaction in a more quantitative fashion, we have mimicked the reaction sequence via the use of click model compounds and followed the reaction kinetics via on-line UV–Vis photospectroscopy as well as FTNIR/MIR spectrometry.

EXPERIMENTAL

Materials

All reagents were purchased in the highest purity available and were used as supplied unless otherwise noted. Triethylamine (Et_3N, Aldrich, purum), diethyl ether (Et_2O anhydrous, Ajax Finechem, 99%), tetrahydrofuran (THF) (Ajax Finechem, 99.7%), were initially dried over calcium hydride and subsequently distilled. Styrene (Sigma-Aldrich, 99%) and vinyl acetate (Aldrich, 99%) were purified by passing over a column of basic alumina followed by distillation. Azobisisobutylnitrile (AIBN, Aldrich, 98%) initiator was purified by recrystallisation in methanol (Ajax Finechem, 99.8%) before use. 2-(2-Cyanopropyl) dithiobenzoate (CPDB),[42] 3-azido-1-propanol,[34] azido-xanthate RAFT agent (ethoxythiocarbonylsulfanyl-acetic acid 3-azido-propyl ester),[34] and trimethylsilyl propargyl methacrylate[43] were synthesized as previously reported. Caution: Azido-compounds are known to be unstable and potentially explosive. All polymerization reactions were performed in oven-dried Schlenk flasks fitted with a glass stopper or septum under a positive pressure of nitrogen.

Synthesis of Monomers and Polymers

Trimethylsilyl Propargyl Methacrylate, M_1

The experimental method used to synthesize the trimethylsilyl propargyl methacrylate monomer followed the method of Haddleton and coworkers[43] and was employed without alteration to produce an initial batch of protected monomer, using 10 g of trimethylsilyl propyn-1-ol starting reagent.

Propargyl Methacrylate, M_2

A solution of propargyl alcohol (5.0 g, 8.92 × 10^{-2} mol) and Et_3N (16.1 mL, 11.55 × 10^{-2} mol)

in Et_2O (100 mL) was cooled to −20 °C in an ice bath. A solution of methacryloyl chloride (10.3 mL, 10.54 × 10^{-2} mol) in Et_2O (50 mL) was added drop wise over a period of 30 min. The mixture was initially stirred at −20 °C for 45 min, then at ambient temperature overnight. The stirred mixture was filtered to remove the ammonium salts. The filtrate was recovered and the volatile solvent was evaporated under reduced pressure on a rotary evaporator. The clear yellow oily residue was passed through a flash chromatography column (CC, SiO_2, petroleum spirits BPt. 60–80 °C/Et_2O, 50:1). The clear, colourless solvent from the chromatography column was evaporated under reduced pressure leaving a clear oily liquid (1.7 g, 15%). δ_H (300 MHz, $CDCl_3$, 298 K) = 1.97 (3H, s, $CH_3C=CH_2$), 2.48 (1H, s, C≡CH), 4.76 (2H, s, OCH_2), 5.63 (1H, s, C=CHH), 6.18 (1H, s, C=CHH). δ_C (300 MHz, $CDCl_3$, 298 K) = 18.13 (1C, $CH_3C=CH_2$), 25.26 (1C, C≡CH), 52.08 (1C, OCH_2), 74.63 (1C, C≡CH), 126.44 (1C, $CH_3C=CH_2$), 135.54 (1C, $CH_3C=CH_2$).

Alkyne-Based Polymer Backbone, P_1 and P_2

Monomer M_1 or M_2 ($2.55.10^{-3}$ mol) was combined with CPDB RAFT agent (0.04 g, 1.83 × 10^{-4} mol) and AIBN (6 mg, 3.71 × 10^{-5} mol) in toluene (0.5 mL) in a dry Schlenk tube. Four freeze-pump-thaw cycles were used to remove residual oxygen. The tubes were then placed in a constant temperature oil bath at 60 °C for 6 h, after which they were quenched in liquid nitrogen to stop the polymerization. The polymer solution was placed on a Schlenk line to remove the toluene and then redissolved in 3 mL THF. The dissolved polymer was precipitated as a pink powder in a methanol (anhydrous, Ajax Finechem, 99.8%)/distilled water 10:2 solution (80 mL), recovered by centrifugation and dried on a Schlenk line.

Kinetic Investigations. After the degassing process, the polymerization mixture was transferred via a cannula into an evacuated IR cuvette (1 mm). The cuvette was heated isothermally at 60 °C for 6 h, after which time the cuvette was quenched in liquid nitrogen to stop the polymerization.

Deprotected Polymer P_1-x_{depro}

Trimethylsilyl protected polymer P_1-x (0.230 g, 1.18 × 10^{-3} mol equiv of alkyne trimethylsilyl

groups) was dissolved in THF (16 mL). Nitrogen was bubbled (ca. 10 min) and the solution was cooled in an ice bath to −20 °C. A degassed 0.20 M solution of tetra-n-butyl ammonium fluoride hydrate (TBAF 3H$_2$O, 0.557 g, 1.77×10^{-3} mol) in THF (8.8 mL) was added drop wise via syringe (ca. 2–3 min). The mixture was stirred at −20 °C for 30 min, then warmed to ambient temperature and stirred for a further 3 h. The solution was passed through a short dry silica gel flash chromatography column and washed through with THF. The solution from the column was concentrated under reduced pressure using a rotary evaporator and the polymer was precipitated in cold methanol (Ajax Finechem, 99%)/distilled water 10:2. The precipitate was recovered by centrifugation and drying on a Schlenk line *in vacuo*.

Azido-Based Polyvinyl Acetate, PVAc-N₃

Vinyl acetate monomer (2.1 g, 2.38×10^{-2} mol) was combined with azido-xanthate RAFT agent (ethoxythiocarbonylsulfanyl-acetic acid 3-azido-propyl ester) (0.45 g, 1.64×10^{-3} mol) and AIBN (0.05 g, 3.33×10^{-4} mol) in a dry Schlenk tube. Four freeze-pump-thaw cycles were used to remove residual oxygen. The tubes were then placed in a constant temperature oil bath at 60 °C for 6 h, after which they were quenched in liquid nitrogen to stop the polymerization. The polymer was precipitated in cold distilled water, recovered by centrifugation and dried on a Schlenk line.

Synthesis of Model Compounds

2-Propargy-2-Bromopropionate

A solution of 2-bromopropionyl bromide (8.66 g, 4.01×10^{-2} mol) in THF (25 mL) was added drop wise to a solution of propargyl alcohol (1.52 g, 2.71×10^{-2} mol) and triethylamine (5.6 mL, 4.06 g, 4.01×10^{-2} mol) in THF (45 mL) at 0 °C. After complete addition, the reaction mixture was allowed to stir for 1 h at 25 °C. The excess of acid bromide was quenched by addition of methanol (7 mL). The formed triethylammonium bromide salt was filtered off and the solvent was removed *in vacuo*. The crude product was dissolved in dichloromethane and washed two times with a saturated ammonium chloride solution and two times with distilled water. The organic layer was dried with magnesium sulfate and the solvent removed *in vacuo*, yielding a yellow liquid, which was purified using flash chromatography (SiO$_2$, hexane/ethyl acetate, 20:1). The product was isolated as a bright yellow liquid, which was dried under vacuum (3.18 g, 61.5%). δ_H (300 MHz, CDCl$_3$, 298 K) = 1.85 (3H, d, CH–CH_3), 2.52 (1H, s, CH≡C), 4.40 (1H, q, CH—CH$_3$), 4.77 (2H, s, CH_2—O). δ_C (300 MHz, CDCl$_3$, 298 K) = 21.40 (1C, CH—CH$_3$), 39.11 (1C, CH—CH$_3$), 53.23 (1C, CH$_2$—O), 75.54 (1C, C≡CH), 169.32 (1C, CO). ν_max/cm^{-1} = 3294, 2955, 2131, 1736, 1445, 1375, 1333, 1246, 1215, 1147, 1094, 1072, 1057, 993, 971, 947, 927, 841, 673, 642.

3-Azidopropyl-2-Bromopropionate

A solution of 2-bromopropionyl bromide (9.43 g, 4.37×10^{-2} mol) in THF (25 mL) was added drop wise to a solution of 3-azido-1-propanol (3 g, 2.97×10^{-2} mol) and triethylamine (6.11 mL, 4.44 g, 4.37×10^{-2} mol) in THF (45 mL) at 0 °C. After complete addition, the reaction mixture was allowed to stir for 1 h at 25 °C. The excess of acid bromide was quenched by addition of methanol (7 mL). The formed triethylammonium bromide salt was filtered off and the solvent was removed *in vacuo*. The crude product was dissolved in dichloromethane and washed two times with a saturated ammonium chloride solution and two times with distilled water. The organic layer was dried with magnesium sulfate and the solvent removed *in vacuo*, yielding a yellow liquid, which was purified using flash chromatography (SiO$_2$, hexane/ethyl acetate, 20:1). The product was isolated as a bright yellow liquid, which was dried under vacuum (5.8 g, 83%). δ_H (300 MHz, CDCl$_3$, 298 K) = 1.80 (3H, d, CH—CH_3), 1.93 (2H, quint, CH$_2$—CH_2—CH$_2$), 3.41 (2H, t, CH_2—N$_3$), 4.24 (2H, m, CH_2—O—CO), 4.35 (1H, q, CH—CH$_3$). δ_C (300 MHz, CDCl$_3$, 298 K) = 21.42 (1C, CH—CH$_3$), 27.85 (1C, CH$_2$—CH$_2$—CH$_2$), 39.74 (1C, CH—CH$_3$), 47.71 (1C, CH$_2$—N$_3$), 62.57 (1C, CH$_2$—O—CO), 169.95 (1C, CO). ν_max/cm^{-1} = 2931, 2093, 1736, 1447, 1381, 1333, 1260, 1219, 1154, 1098, 1062, 1028, 986, 935, 904, 763, 673, 642.

Click Reactions

Click Coupling Between Propargyl Alcohol and 3-Azido-1-Propanol

Propargyl alcohol (0.072 g, 1.29×10^{-3} mol) and 3-azido-1-propanol (0.116 g, 1.14×10^{-3} mol)

were added to a solution of 1,8-diaza[5,4,0]bicycloundec-7-ene (DBU) (19 mg, 1.25×10^{-4} mol) in THF (1 mL). The resulting mixture was degassed with nitrogen (ca. 30 min) in an ice bath. Copper(I) iodide (CuI) (22 mg, 1.15×10^{-4} mol) was added to a separate round bottomed flask, which was then evacuated *in vacuo* and backfilled with nitrogen. A cannula was used to transfer the polymer solution into the flask containing CuI, which was also placed in an ice bath. The solution was transferred via cannula into a sealed, degassed 10-mm Q IR cell. The cell was placed in the sample holder of the FTNIR spectrometer and heated at 40 °C for 12 h, while NIR measurements were obtained every 2 min. For FTMIR measurements, samples were taken off regularly during the reaction and analysed by using an attenuated total reflection (ATR) unit.

Click Coupling Between 2-Propargyl-2-Bromopropionate and 3-Azidopropyl-2-Bromopropionate

A solution of 2-propargyl-2-bromopropionate (55.4 mg, 2.90×10^{-4} mol), 3-azidopropyl-2-bromopropionate (61.9 mg, 2.62×10^{-4} mol) and DBU (4.2 mg, 2.76×10^{-5} mol) in THF (12 mL) was degassed with nitrogen (ca. 30 min). CuI (6.8 mg, 3.57×10^{-5} mol) was added to a separate round-bottom flask, which was then evacuated *in vacuo* and backfilled with nitrogen. A cannula was used to transfer the solution into the flask containing CuI. The CuI did not completely dissolve. The round bottom flask was heated in a constant temperature oil bath at 40 °C for 24 h, without stirring. After 24 h, the solution that turned from yellow to clear brown was cooled down to room temperature, and then the solvent was removed under reduced pressure. The crude product was dissolved in dichloromethane and washed two times with an aqueous solution of ammonia (28%) (1:1), to remove the remaining copper complex, and one more time with distilled water. The organic layer was dried with magnesium sulfate and the solvent was removed *in vacuo*. The product was isolated as a clear brown liquid, which was dried under vacuum. δ_H (300 MHz, CDCl$_3$, 298 K) = 1.82 (6H, dd, CH—C*H$_3$*), 2.33 (2H, quint, CH$_2$—C*H$_2$*—CH$_2$), 4.21 (2H, m, CH$_2$—C*H$_2$*—O—CO), 4.38 (2H, dq, C*H*—CH$_3$), 4.49 (2H, t, CH$_2$—C*H$_2$*—N—CH), 5.32 (2H, s, OC*H$_2$*—C≡CH), 7.67 (1H, s, C=C*H*—N). δ_C (300 MHz, CDCl$_3$, 298 K) = 21.42 (2C, CH—*C*H$_3$), 28.98

(1C, CH$_2$—*C*H$_2$—CH$_2$), 39.65 (2C, *C*H—CH$_3$), 46.84 (1C, CH$_2$—*C*H$_2$—N—CH), 58.88 (1C, O*C*H$_2$—C≡CH), 61.96 (1C, CH$_2$—*C*H$_2$—O—CO), 124.14 (1C, C=*C*H—N), 142.08 (1C, *C*=CH—N), 169.88 (2C, *C*O). ν_{max}/cm^{-1} = 2962, 2923, 2854, 1736, 1447, 1377, 1332, 1257, 1216, 1151, 1050, 1005, 863, 793, 670.

Click Coupling Between P$_1$-2$_{depro}$ and Azido-Xanthate RAFT Agent (Ethoxythiocarbonylsulfanyl-Acetic Acid 3-Azido-Propyl Ester)

Deprotected polymer (276.4 mg, 2.06×10^{-3} mol equiv of alkyne functionality) and azido-xanthate RAFT agent (602.7 mg, 2.28×10^{-3} mol) were added to a solution of DBU (33.9 mg, 2.23×10^{-4} mol) in THF (100 mL). The resulting mixture was cooled in an ice bath and degassed with nitrogen (ca. 30 min). CuI (45.2 mg, 2.37×10^{-4} mol) was added to a separate round-bottomed flask, which was then evacuated using a Schlenk line (ca. 10 min) and backfilled with nitrogen. A cannula was used to transfer the polymer solution into the flask containing CuI. The flask was placed in a constant temperature oil bath at 40 °C for 2 days, without stirring. After 2 days, the solution that turned from yellow to dark brown was cooled down to room temperature and then passed through a short dry silica gel flash chromatography column and washed with THF. The solution from the column was concentrated under reduced pressure using a rotary evaporator and the product was isolated as a dark brown solid, which was dried under vacuum.

Click Coupling Between P$_1$-x$_{depro}$ and Azido-Based Poly(Vinyl Acetate)

Deprotected polymer (76.2 mg, 5.68×10^{-4} mol equiv of alkyne functionality) and PVAc (499 mg, 6.23×10^{-4} mol) were added to a solution of DBU (8.6 mg, 5.65×10^{-5} mol) in THF (25 mL). The resulting mixture was cooled in an ice bath and degassed with nitrogen (ca. 30 min). CuI (11 mg, 5.77×10^{-5} mol) was added to a separate round-bottomed flask, which was then evacuated using a Schlenk line (ca. 10 min) and backfilled with nitrogen. A cannula was used to transfer the polymer solution into the flask containing CuI. The flask was placed in a constant temperature oil bath at 40 °C for 2 days, without stirring. After 2 days, the solution that turned from yellow to clear brown was cooled down to room temperature, and then the solvent

was removed under reduced pressure. The crude product was dissolved in dichloromethane and washed two times with an aqueous solution of ammonia (28%) (1:1), to remove the remaining copper complex, and one more time with distilled water. The organic layer was dried with magnesium sulfate and the solvent was removed *in vacuo*. The product was isolated as a clear brown solid, which was dried under vacuum.

Analytical Techniques

Fourier Transform Near/Mid Infrared Spectroscopy

The FTNIR measurements to follow monomer to polymer conversion were performed using a Bruker IFS66\S Fourier transform spectrometer equipped with a tungsten halogen lamp, a CaF_2 beam splitter and a liquid nitrogen cooled InSb detector. Each spectrum in the spectral region of 8000–4000 cm^{-1} was calculated from the coadded interferograms of 64 scans with a resolution of 4 cm^{-1}. A heated sample holder was used to obtain an isothermal reaction temperature. Monomer conversions were determined via on-line FTNIR spectroscopy by following the decrease of the intensity of the vinylic stretching overtone of the monomer at $v = 6200$ cm^{-1}. The FTNIR (model compound) experiments were prepared as follow: Propargyl alcohol (0.072 g, 1.29×10^{-3} mol) and 3-azido-1-propanol (0.116 g, 1.14×10^{-3} mol) were added to a solution of DBU (19 mg, 1.25×10^{-4} mol) in THF (1 mL). The resulting mixture was degassed with nitrogen (ca. 30 min) in an ice bath. CuI (22 mg, 1.15×10^{-4} mol) was added to a separate round bottomed flask, which was then degassed with nitrogen. A cannula was used to transfer the polymer solution into the flask containing CuI, which was also placed in an ice bath. The solution (and the majority of the undissolved CuI powder) was transferred via cannula into a sealed, degassed 10 mm Q-IR cell.

The FTMIR ATR measurements were performed using a Bruker IFS66\S Fourier transform spectrometer equipped with a tungsten halogen lamp, a KBr beam splitter and DTGS detector. Each spectrum in the spectral region of 4000–600 cm^{-1} was calculated from the coadded interferograms of 64 scans with a resolution of 4 cm^{-1}.

Size Exclusion Chromatography

Size exclusion chromatography (SEC) analyses of the polymers were performed in THF (Sigma Aldrich, anhydrous 99.9% inhibitor-free) at 50 °C (flow rate = 1 mL min^{-1}) with a Shimadzu modular system comprising an SIL-10AD auto-injector, a Polymer Laboratories 5.0-lm bead-size guard column (50 × 7.8 mm) followed by four linear PL (Styragel) columns (105, 104, 103, and 500 Å) and an RID-10A differential refractive-index detector. The SEC calibration was obtained from narrow polydisperse poly(styrene) standards ranging from 500 to 10^6 g mol^{-1}.

Nuclear Magnetic Resonance

^{1}H NMR and ^{13}C NMR spectra were recorded on a 300-MHz Bruker ACF300 spectrometer using deuterated chloroform solvent (Chloroform-d, Aldrich, 99.9%).

Electrospray Ionisation Mass Spectrometry

Electrospray ionisation mass spectrometry (ESIMS) was carried out using a Thermo Finnigan LCQDECA ion trap mass spectrometer (Thermo Finnigan, San Jose, CA). The ESIMS operates in nebuliser assisted electrospray mode using an atmospheric pressure ionisation source. Caffeine, MRFA, and Ultramark 1621 (all sourced from Aldrich) were used as calibration standards in the mass range 195–1822 Da. Spectra were obtained over the mass to charge ratio range m/z 100–2000 Da in positive ion and centroid modes using and instrumental resolution of 0.1 Da. The spray voltage was 6 kV, capillary voltage 19 V and capillary temperature of 275 °C. The sheath gas used was nitrogen with a flow of 35% of maximum. The auxiliary gas was helium, with a flow of 5% of maximum. Tube lens offset was −60 V and the eluent used was 4:6 v/v THF and 0.25 M sodium acetate in methanol solution at 60 mg mL^{-1}. Reported molecular weights were obtained using CS Chem-Draw 6.0 software and are monoisotopic values. Additionally, isotopic pattern prediction was carried out using Thermo Finnigan Xcalibur software.

Ultraviolet-Visible Spectroscopy

Ultraviolet-visible (UV–Vis) spectroscopy was carried out using a Cary 300 Bio UV–Vis spectrophotometer (Varian) featuring a thermostattable sample cell holder (±0.2 °C). Absorption spectra were measured in THF from 200 to 800 nm with a resolution of 1 nm in a 10 mm UV-cuvette.

Synthesis of poly(vinyl acetate) branch
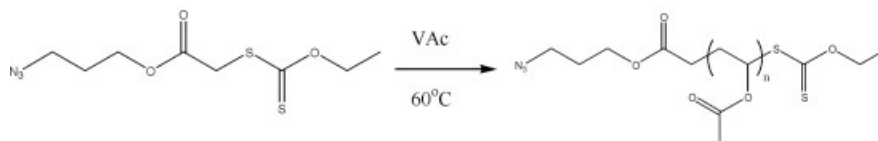
Synthesis of poly(vinyl acetate) comb polymer via *click* reaction
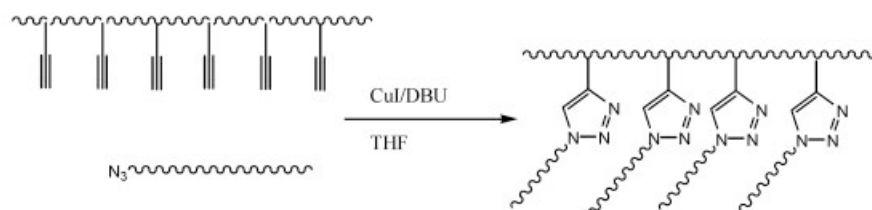
Scheme 1. Schematic representation of the general synthetic approach followed in the current study from monomer synthesis to the preparation of the final comb polymer.

RESULTS AND DISCUSSION

### Synthesis of the Acetylene Functionalized Polymer Backbone

The synthesis of the acetylene functionalized backbone was carried out with both the protected and nonprotected monomers M_1 and M_2, respectively. Protection of the acetylene function is in-principle required to avoid its potential addition of free radicals. However, in the present study we employed both the protected and unprotected monomer and evaluated their behaviour during RAFT/MADIX[44] mediated polymerization. CPDB was employed as the RAFT agent, as it allows for the mediation of methacrylates by virtue of its stabilizing Z-group and its tertiary leaving (R) group. The resulting structure of the RAFT polymer is depicted in Scheme 1. For the subsequent click reaction, the polymer backbone prepared via monomer M_2 has to be deprotected for the 1,3-dipolar cycloaddition to proceed, as shown in Scheme 1 and Scheme 2.

Initially, the rate of monomer to polymer conversion was followed via on-line FTNIR spectrometry by following the first overtone of the C—H stretching vibration on the vinylic bond in both monomers. The monomer to polymer conversions for each monomer at identical RAFT agent concentrations are depicted in Figure 1 alongside the first order rate plots (right hand *y*-axis of the graph). Inspection of the figure shows

that both polymerizations proceed with a constant concentration of radicals as indicated by the linear first order plots, yet the overall rates of polymerization of both monomers are vastly different, i.e. the silyl protected monomer polymerizes at a much lower rate than the nonprotected version. It is also important to note that the nonprotected monomer leads to polymer that is not soluble in a range of solvents including THF and *N,N*-dimethyl acetamide. The formation of insoluble crosslinked networks has been reported earlier and has been assigned to the involvement of acetylene moiety during the radical process.[45] It is for this reason that no molecular weighs are reported for the polymer generated from the nonprotected monomer. Thus, the difference in rate may be attributed to the fact the unprotected acetylene moieties engage in radical addition reactions that lead to crosslinking of the polymer and thus a stronger decrease in the free monomer concentration.

Table 1 gives the obtained molecular weights of the RAFT polymerization of the initially protected monomer as well as the molecular weights of the same polymer after hydrolysis of the silyl protecting group. Each of the polymerizations P-1 to P-4 was carried out with an individual RAFT agent concentration (going from 0.053 to 0.53 mol L^{-1}) and driven to close to 100% conversion. The table reports the molecular weight obtained via end group analysis by ^{1}H NMR as well as SEC based on linear styrene
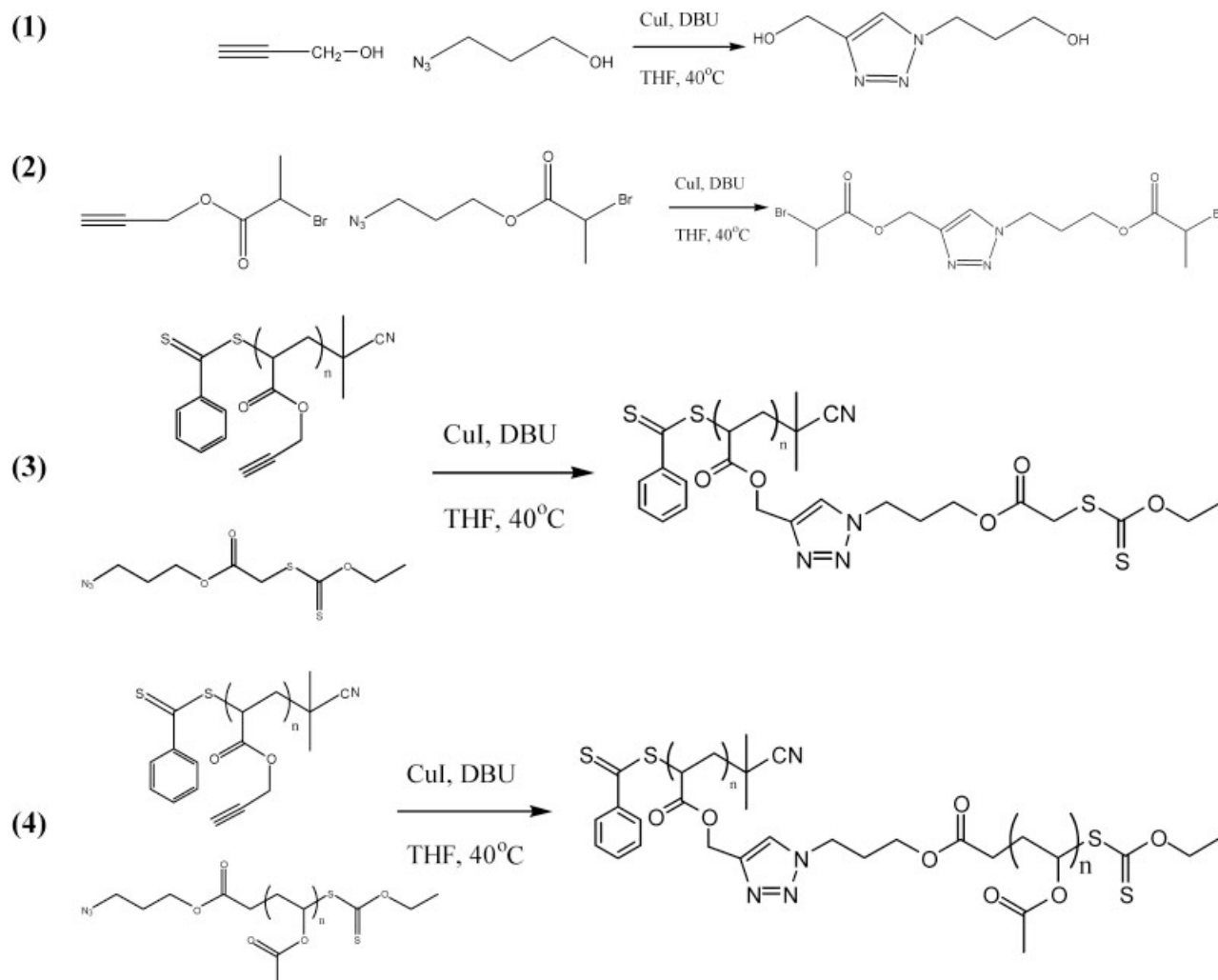
Scheme 2. Summary of (model) click reactions carried out using azide and alkyne groups (2.5×10^{-2} mol L^{-1}each), 2.5×10^{-3} mol L^{-1} of DBU and 2.5×10^{-3} mol L^{-1} of CuI in THF at 40 °C.

standards. The table also gives the theoretically expected molecular weight (at 100% conversion) before and after deprotection (assuming that all silyl groups are successfully cleaved off). The data in the table shows that the molecular weights obtained via NMR compare reasonably well with the targeted molecular weight before deprotection. Typical ^{1}H NMR spectra of the protected and deprotected polymers are depicted in Figures 2 and 3, respectively. The SEC determined molecular weight is more deviant and this is mainly due to the use of a linear polystyrene calibration as no Mark-Houwink parameters for the polymer is available. Unfortunately, the NMR determination of the molecular weight is not possible in the case of the deprotected polymers, as after hydrolysis

the RAFT end group was no longer detectable, probably due to the hydrolysis of the thiocarbonylthio group or the cyanoisopropyl group, or both. Inspection of the apparent molecular weights before and after deprotection shows a clear decrease in the number average molecular weight after deprotection for each polymer. While the molecular weight should indeed decrease after protection, the decrease when going from P$_1$-4 to P$_1$-4depro (see the last two row in Table 1) seems somewhat large. The drop in molecular weight can also be visualized via plotting the full molecular weight distributions of each polymer before and after deprotection as shown in Figure 4.

The arguably best method for verifying the deprotection of the acetylene group is via imag-
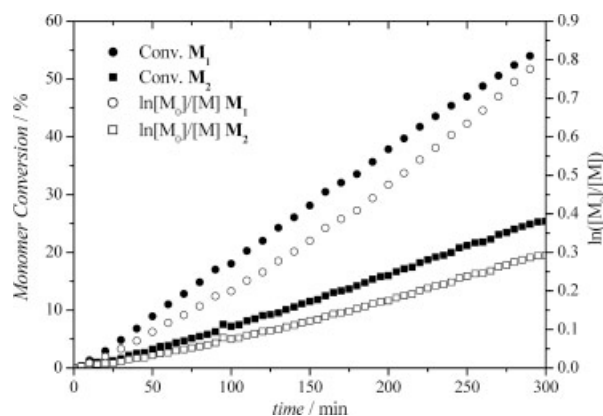
Figure 1. RAFT polymerization of the propargyl methacrylate monomers (M_1 and M_2) followed by on-line FTNIR spectroscopy. $n_{monomer} = 2.55 \times 10^{-3}$ mol; $n_{CPDB} = 1.85 \times 10^{-5}$ mol; $n_{AIBN} = 3.72 \times 10^{-6}$ mol, $V_{toluene} = 0.5$ mL, 60 °C.

ing each single chain via electrospray ionization coupled with a quadrupole ion trap detector.[47] The lower part of Figure 5 shows an ESIMS spectrum of the protected polymer (on the example of P_1). The theoretically expected repeat unit of the monomer in the protected polymers is 196.09 Da. Inspection of the MS spectrum indicates that the observed (average) repeat unit is 196.07 Da and thus in excellent agreement with the theoretical prediction. After deprotection, the observed repeat unit has decreased to 124.00 Da; the theoretically expected repeat unit after deprotection has a mass of 124.05 Da. Thus, again excellent agreement is observed.

However, the information contained in the MS spectra allows for further information to be deducted. Figure 6 shows the theoretically expected and experimentally observed isotopic patterns of the protected and unprotected polymer on the example of a particular molecular weight. Excellent agreement between the expected and simulated isotopic pattern distribution, which prevails throughout both entire distributions can be observed. It is noteworthy that, as one would expect, the protected polymer backbone features an intact thiocarbonylthio group on one end and a cyanoisopropyl group on the other. In contrast and in agreement with the NMR observations discussed above, the deprotected polymer backbone does not feature any thiocarbonylthio group, which has been replaced by a hydrogen; the cyanoisopropyl R-group is still attached to the polymer. Although the polymer endgroups have been altered, this suite of data demonstrates that a low PDI polymer backbone with one acetylene functionality per repeat unit has been constructed. The removal of the RAFT end group is inconsequential for the further decoration of the polymer with PVAc chains via click chemistry. During the processing of variable batches for deprotection, it was noticed that at short reaction times, the RAFT end group is not fully removed from the poly(propargyl methacrylate) backbone and residues of RAFT end group can remain. We will later on demonstrate this by the presence of an appropriate UV signal (see below). Yet, as mentioned

Table 1. Molecular Weight M_n Estimation of the P_1 Polymers Prepared from M_1 and P_1-Depro Obtained After the Deprotection of P_1

Exp.	Target M_n	M_n (^{1}H NMR)	M_n (GPC)[a]	PDI	c^0_{RAFT}[b]
P_1-1	1000[c]	1000[d]	1700	1.12	0.53
P_1-1depro	720[e]	[f]	1400	1.07	
P_1-2	2000[c]	1980[d]	2800	1.15	0.26
P_1-2depro	1350[e]	[f]	2100	1.13	
P_1-3	3000[c]	4750[d]	4200	1.16	0.18
P_1-3depro	1980[e]	[f]	3300	1.18	
P_1-4	10000[c]	13600[d]	19000	1.29	0.053
P_1-4depro	8600[e]	[f]	12300	1.18	

[a] Apparent molecular weight based on linear polystyrene standards.
[b] Initial RAFT agent concentration (CPDB) in mol L^{-1} based on an assumed monomer density of 1 g mL^{-1}. The RAFT agent to initiator ratio was 5:1 in all cases.
[c] Theoretical M_n value based on an assumed 100% monomer conversion.
[d] Obtained using the integration ratio between the benzyl group protons (δ, 7.9 ppm) from the RAFT agent end group and both the trimethylsilyl group protons (d, δ, 0.2 ppm) and the protons adjacent to the ester group (c, δ, 4.6 ppm).
[e] Theoretical M_n value based of ^{1}H NMR M_n of P_1.
[f] The RAFT agent end group was not detected by ^{1}H NMR after deprotection of the polymer backbone. All molecular weights are reported in g mol^{-1}.
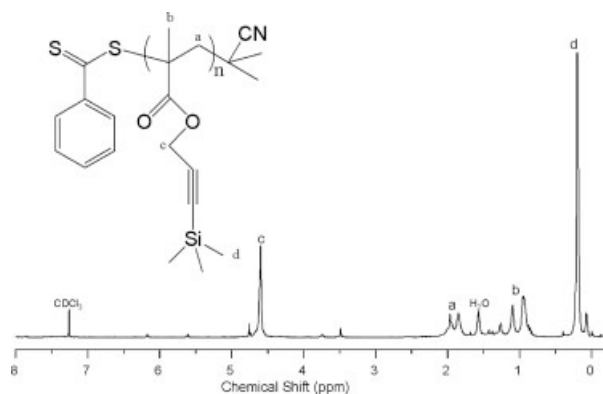
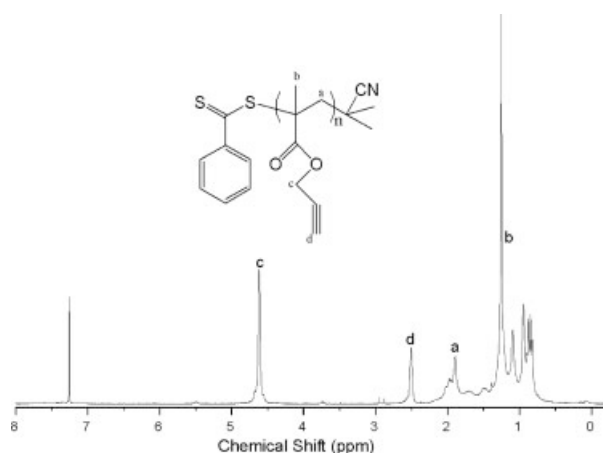**Figure 2.** ^{1}H NMR characterization of the RAFT prepared poly(propargyl methacrylate) (P_1-4 polymer, see Table 1).

above, whether or not the RAFT end group is fully removed from the backbone is of no consequence for the ensuing click reaction.

Click Reactions

The Huisgen 1,3-dipolar cycloaddition between azides and alkynes is facilitated by the presence of Cu(I) ions. The advantage of the copper catalysis is not only the lowering of the required reaction temperature, but also the higher regiospecificity of the reaction leading only to 1,4 products while the conventional 1,3-cycloaddition results in a mixture of 1,4 and 1,5 regioisomers. Cu(I) salts are known to react with acetylene to form copper acetylide probably via π-complexation between the metal and the triple bond.[28] This reaction will also take place when using terminal alkynes, but is absent


Figure 3. ^{1}H NMR characterization of prepared and subsequently deprotected poly(propargyl methacrylate) (P_1-4depro polymer, see Table 1).
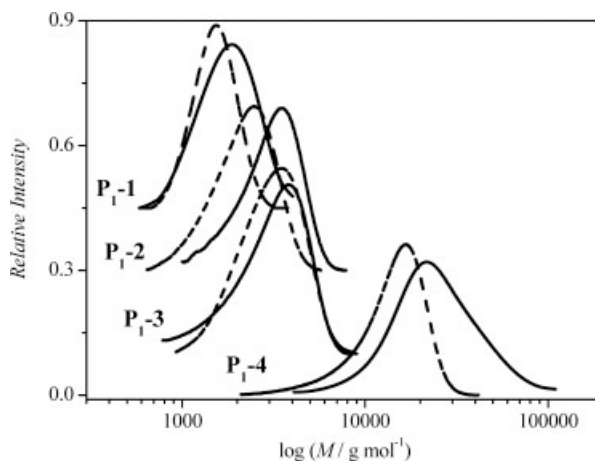

Figure 4. SEC traces of P_1 polymers. Solid lines correspond to protected polymers P_1 and dash lines correspond to deprotected polymers P_1 depro. The polymer to monomer conversion for each protected polymer was close to 100%.

when using disubstituted triple bonds (alkynes, where the triple bond is not located as an end-functionality).[20,48] In organic media, poor solubility of Cu(I) salt can be enhanced with a suitable ligand. The choice of ligand for Cu(I) was observed to be a rate determining factor in the synthesis of 1,2,3-triazoles, not only influencing the rate of reaction, but also the achievable overall conversion.[49] It should be noted that not only the ligand, but also the counterion of the
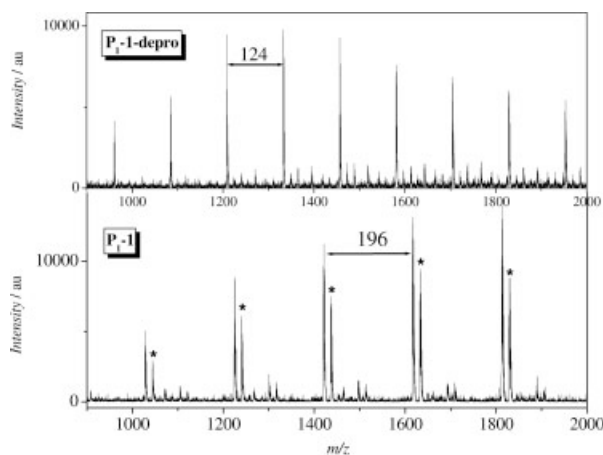
Figure 5. ESIMS analysis of the P_1 polymer, before (P_1-1) and after (P_1-1depro) deprotection of the backbone. The peaks denoted by an asterisk arise from oxidation of the C=S double bond into a C=O double bond due to the traces of peroxides present in the solvent (THF) employed during MS analysis and storing of the RAFT polymer.[47]
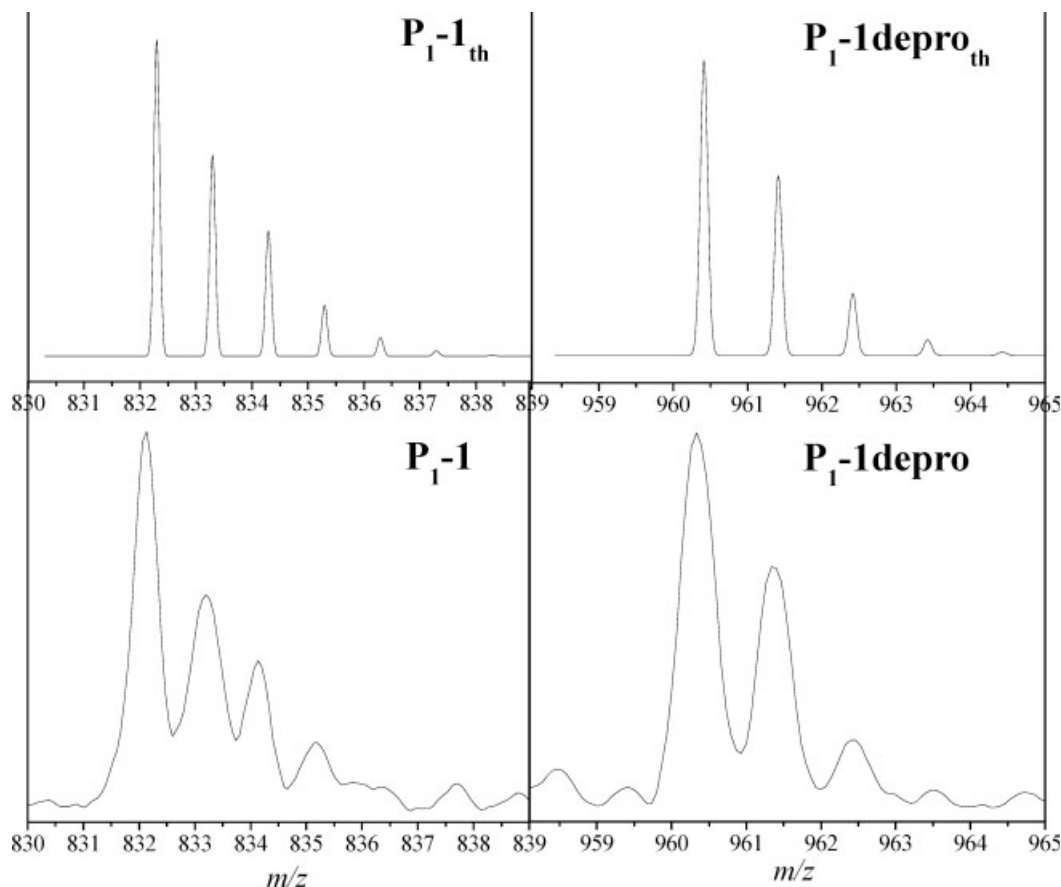
Figure 6. Isotopic pattern comparison between P_1-1 and P_1-1depro. Theoretical patterns were obtained from Xcalibur software and demonstrate the excellent agreement between the measured and predicted patterns.

Cu(I) salt may have a significant influence on solubility, reaction rate and conversion.

DBU in combination with CuI was found to be an appropriate ligand to facilitate the reaction between azides and alkynes. This system has been employed earlier to conjoint poly(vinyl acteate) with polystyrene[34] or glycopolymers[35] to generate block copolymers. High yields have been obtained using this catalyst system while being stable in the presence of other functional groups. Despite the high stability of Cu(I) complexes, the reaction was carried out under the exclusion of oxygen. While Cu(I) complexes are usually more stable against oxidation than free Cu(I) ions, the stability of a Cu(I) complex is usually dependent on the nature of the ligand such as the nucleophilicity and steric effects.[50] Prior to the click reaction between the two functional polymers (backbone and PVAc branch), we investigated the click reaction between two simple functionalized alcohols, as well as between the two reactive components of the RAFT agent and the monomer, and between the backbone and the RAFT agent (see Scheme 2).

All the compounds were combined using similar concentrations of 2.5×10^{-2} mol L^{-1} azide and alkyne groups, 2.5×10^{-3} mol L^{-1} of DBU and 2.5×10^{-3} mol L^{-1} of CuI in THF. The brown reaction mixture was allowed to react under the strict exclusion of oxygen at 40 °C for a preset time followed by an intensive washing step with aqueous ammonia. Aqueous ammonia facilitated the removal of copper-ions, which is necessary since the resulting 1,2,3-triazole is known to form a coordinative bond to copper,[51] especially in its oxidized state.[52] The resulting products may therefore appear colored if the copper is not removed properly.

Investigation into the rate of reaction or the completeness of the reaction was then carried out using a range of techniques including FTNIR and FTMIR, NMR, UV–Vis spectroscopy and SEC.
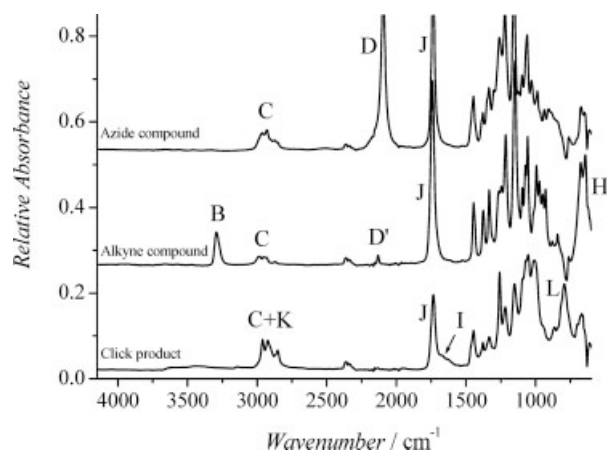
Figure 7. FTMIR analysis of the click product from the reaction between 2-propargyl-2-bromopropionate (Alkyne compound) and 3-azidopropyl-2-bromopropionate (Azide compound). B. ≡C—H stretch. C. Normal C—H stretch. D. R—N$_3$ stretch. D′. C≡C stretch. H. ≡C—H bend fundamental. I. triazole C=C stretch. J. C=O stretch. K. triazole =C—H stretch. L. triazole =C—H bend.

Fourier Transform Near/Mid Infrared Spectroscopy

FTIR spectroscopy allows for the effortless observation of changes of functional groups during the click reaction by following the receding intensity of the IR signal of alkyne and azide groups. Typical IR vibration within the MIR region for alkynes and azides, respectively, can be found at 3300 cm^{-1} (alkyne) and 2100 cm^{-1}

(azide). The complete disappearance of these bands is expected to be accompanied by increasing triazole bands. Figure 7 displays typical FTMIR spectra, here of the reactants 2-propargyl-2-bromopropionate (alkyne compound) and 3-azidopropyl-2-bromopropionate (azide compound), as well as the final purified 1,2,3-triazole [reaction (2), see Scheme 2] derivative were recorded. The successful synthesis after allowing the components to react for 24 h at 40 °C was evidenced by the disappearance of the strong azide signal at ∼ 2100 cm^{-1} and alkyne signal at ∼ 3300 cm^{-1}, which were replaced by triazole bands at ∼ 800, 1650, and 2800 cm^{-1}.

The versatility of FTMIR lies in the possibility of confirming the completeness of the reaction without prior removal of the copper complex. A sample of the reaction solution is investigated using FTMIR ATR purely by evaporation of the solvent. The FTMIR spectrum of all components of model reaction (1) from Scheme 2 clearly displays the strong azide band (see Fig. 8, right), while the alkyne band in this model reaction is hidden below the strong signals corresponding to the hydroxyl groups. The progress of the reaction can conveniently be followed by the disappearance of the azide band at ∼ 2100 cm^{-1}. After a reaction time of 24 h this signal vanished fully, while the formation of triazole becomes evident (∼ 1650 cm^{-1}).

A more refined way of investigating the click reaction is FTNIR analysis, which allows moni-
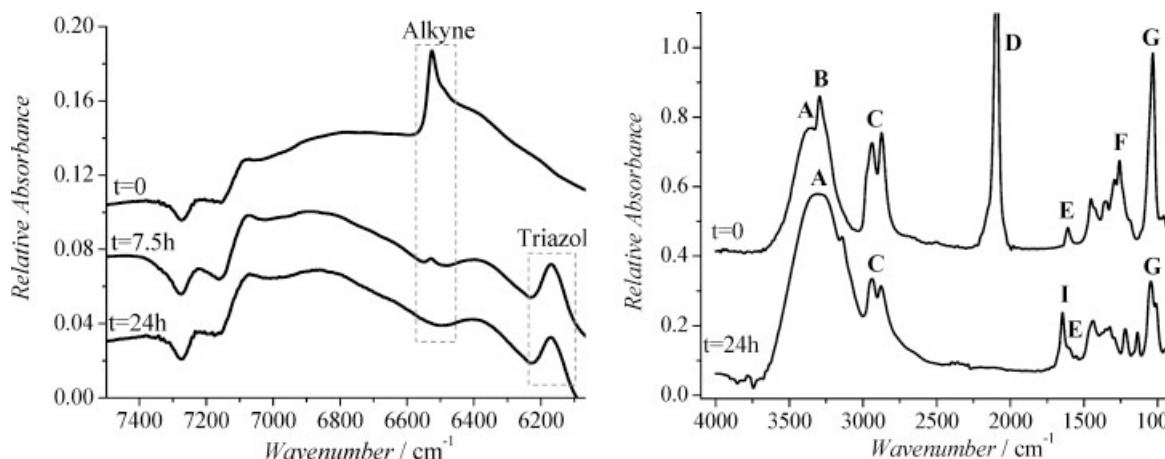
Figure 8. FTNIR (left, in THF) and FTMIR (right, after solvent evaporation) analysis of the click model reaction between propargyl alcohol and 3-azido-1-propanol including CuI/DBU. A. O—H stretch. B. ≡C—H stretch. C. Normal C—H stretch. D. C≡C stretch + R—N$_3$ stretch. E. C=N stretch of DBU (ligand). F. ≡C—H bend overtone. G. C—O stretch. H. ≡C—H bend fundamental. I. triazole C=C stretch.
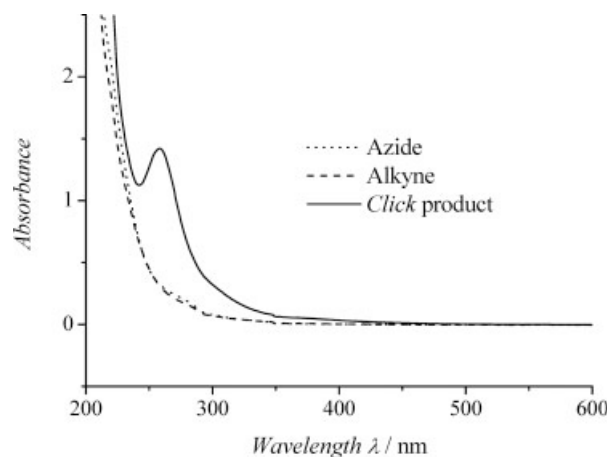
Figure 9. UV–Vis spectra of 2-propargyl-2-bromo-propionate (2.40×10^{-4} mol L^{-1}) and 3-azidopropyl-2-bromopropionate (2.17×10^{-4} mol L^{-1}) and the click model compound (2.24×10^{-4} mol L^{-1}) in THF.

toring the reaction without the need of solvent evaporation prior to analysis (see Fig. 8). The initial alkyne signal at $\sim$6500 cm^{-1} is replaced by a triazole peak at $\sim$6150 cm^{-1} during the course of the click reaction in THF. It becomes evident that under the current experimental conditions a reaction (at 40 °C) time of at least 10 h is necessary to ensure the complete cyclo-addition between both components. The reaction curve displayed at 7.5 h reveals some remaining alkyne functionality, which fully disappears after further reaction. A reaction time of 24 h was therefore chosen for further experiments to ensure completeness of the reaction.

Following the investigation of the model components, the click reactions were carried out using the xanthate RAFT agent as well as PVAc-N_3 with a molecular weight of 850 g mol^{-1} by reacting all the components for 24 h (see Table 3). The products were investigated using FTIR spectroscopy confirming the absence of azide and alkyne functionalities. The accuracy of the FTIR analysis is however reduced by the weak signal intensities of the functional groups in contrast to the strong intensity of the polymer signals.

Nuclear Magnetic Resonance

NMR studies of both purified model products show the appearance of a singlet at 7.7 ppm, which corresponds to the triazole ring indicative for the exclusive formation of the 1,4 cycloaddition product. Investigation of the polymeric

products was, however, less conclusive due to the relatively small intensity of the functional endgroups compared with the polymer product.

UV–Vis Photospectroscopy

Further analysis was carried out with model reaction (2) (in Scheme 2) as well as the click reaction between PVAc-N_3 and P1-2depro [see Scheme 2, reaction (4)] employing UV–Vis spectroscopy in THF. The spectra of the purified model product (reaction (2) as well as the reactants are displayed in Figure 9. While the reactants do not show significant absorptions above a wavelength $\lambda = 250$ nm, the resulting triazole product is evidenced by an absorption maximum at 258 nm and a molar extinction coefficient of 6200 L cm^{-1} mol^{-1}.

UV–Vis spectra were recorded of the reaction mixture, which combines all the principal reactants of the click reaction as model compounds. With the addition of the copper-DBU complex a shoulder at around 280 nm appears (see Fig. 10). DBU alone does not show any absorption above 250 nm, while the mixture of CuI and DBU complex, which is measured in THF without the addition of alkyne and azide, has absorption maxima at 294, 366, and 462 nm. Samples were then taken directly from the reaction mixture at different time intervals and further
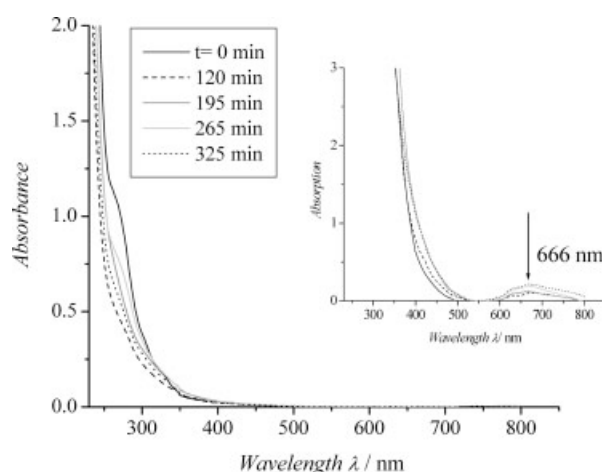
Figure 10. UV–Vis spectra of a mixture of 2-propargyl-2-bromopropionate (5.0×10^{-4} mol L^{-1}) and 3-azidopropyl-2-bromopropionate (5.0×10^{-4} mol L^{-1}) with added [Cu(DBU)]I (5.0×10^{-5} mol L^{-1}) taken from a click reaction mixture (40 °C) after certain time intervals and diluted with THF; the inserted figure shows the UV–Vis spectra of the undiluted reaction mixture.
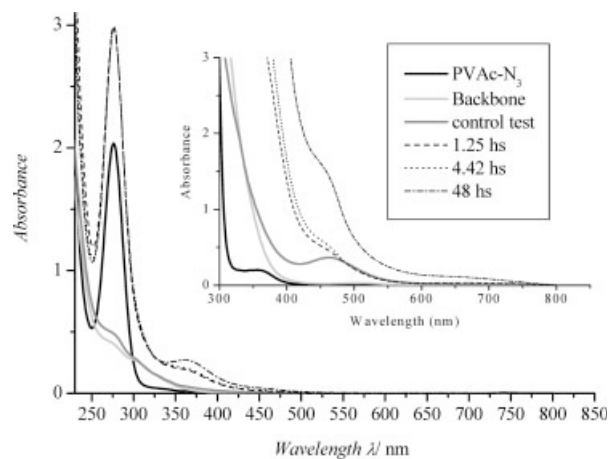
Figure 11. Click reaction between PVAc-N$_3$ and P$_1$-2depro followed by UV–Vis spectrometry. Solutions have been diluted by a factor of 100 and 5 (see inset figure) before analysis. (Concentration of click reaction: [Backbone, P$_1$-2depro] = 2.3 × 10^{-2} mol L^{-1}, [PVAc-N$_3$] = 2.5 × 10^{-2} mol L^{-1}, [DBU] = 2.3 × 10^{-3} mol L^{-1}, [CuI] = 2.3 × 10^{-3} mol L^{-1}). The control test corresponds to a mixture of P$_1$-2depro (backbone), DBU and CuI, heated at 40 °C during 48 h.

investigated using UV–Vis spectroscopy. As illustrated in Figure 10, the shoulder, which was assigned to the added Cu-complex, decreases in intensity with reaction time just to increase again at an extended reaction time. The correlation between reaction time and the absorption at around 280 nm will not be further discussed here, but it certainly reflects the intricacies of the complicated click mechanism. This includes the above mentioned interaction between the copper(I) ion and the terminal triple bond as well as intermediate complexes involving Cu(I), azides, and alkynes.[19,20,44] In addition, triazole with a strong absorption at 258 nm is formed and will potentially interact with Cu(I) ions.[45] Instead, attention should be drawn to an emerging UV–Vis band at 666 nm, which is not present in the beginning of the reaction. This band is also absent in the purified product after removal of the copper-ion and can therefore potentially be assigned to a charge transfer complex between Cu(I) ions and the forming triazole.

Equivalent reaction concentrations and conditions were now employed to attach azide functionalized PVAc to poly(progargyl methacrylate) to generate well-defined PVAc comb polymers (see Scheme 2, reaction (4)).

The UV–Vis spectra in THF of both polymers PVAc-N$_3$ and P$_1$-2depro are displayed in Figure 11. Both polymers show now additional absorp-

tions below 300 nm, indicative of typical n-π^* transitions of carbonyl groups, which are abundant especially in PVAc-N$_3$. Furthermore, absorptions in the visible area emerge corresponding to the RAFT endgroup of the polymer.

The presence of transitions unique to the RAFT group allow UV–Vis spectroscopy to be a suitable tool to determine the concentration of RAFT groups in the polymer, consequently allowing additional molecular weight confirmation (assuming that no RAFT groups have been lost). For this purpose, molar absorption coefficients of both RAFT agents were determined and summarized in Table 2. 2-(2-Cyanopropyl) dithiobenzoate CPDB, the RAFT agent employed for the synthesis of the poly(propargyl methacrylate) backbone has a strong absorption at λ = 516 nm with a molar absorption coefficient ε_{CDBD} of 100 L mol^{-1} cm^{-1} (the absorption at 300 nm was found to be concentration dependent and consequently no molar absorption coefficient can be determined). Comparing this absorption with the spectrum obtained from the backbone polymer P$_1$-2depro (see Table 2 and Fig. 11) the molecular weight can theoretically be determined using

$$\overline{M_n} = \frac{m_{\text{polymer}} \times \varepsilon(\lambda = 515 \text{ nm})_{\text{RAFTagent}} \times d_{\text{cuvette}}}{A(\lambda = 515 \text{ nm})_{\text{Polymer}} \times V\text{solvent}},$$

where m is the mass of polymer in the solution, $\varepsilon_{\text{RAFTagent}}$ is the molar absorption coefficient of CPDB at λ = 515 nm, d the path length of the cuvette, A_{Polymer} is the absorption at λ = 515 nm of the polymer solution and V is the volume of the solution. The molecular weight of the backbone was found to be higher than the theoretical value confirming substantial cleavage of the RAFT endgroup during hydrolysis in good agreement with the above discussed mass spectra and the absence of noticeable RAFT end group signals in the ^{1}H NMR spectra.

A similar approach has been carried out with PVAc-N$_3$ using the absorption of the RAFT agent at 354 nm (see Table 2). The molecular weight obtained was calculated to be 900 g mol^{-1}, which is in good agreement with the theoretical molecular weight of 850 g mol^{-1}.

Similar to the model compound UV–Vis spectra were recorded by taking samples from the click reaction mixture after certain time intervals (see Fig. 11). With the onset of the click reaction additional transition maxima at 365

Table 2.   UV–Vis Absorption Maxima of Model Compounds and RAFT Agents Alongside Their Respective Molar Absorption Coefficients (Where Available) at Ambient Temperature

| Endgroup	Compound	UV–Vis Absorption Max/nm
N_3		<250
		276 ($\varepsilon = 21000$ L mol^{-1} cm^{-1}) 353 ($\varepsilon = 70$ L mol^{-1} cm^{-1})
		276 (RAFT endgroup and polymer) 354 (initial RAFT agent)
$C\equiv C$		<250
		300 (conc. dependent) 515 ($\varepsilon = 100$ L mol^{-1} cm^{-1})
		298 (RAFT endgroup and polymer) 505 (initial RAFT agent)

and 466 nm appear and grow in intensity. These band are clearly absent in all three reaction components, PVAc-N$_3$ and P$_1$-2depro and catalyst, and do not form when only two of these three ingredients are allowed to react at 40 °C. Both transitions are absent in the model reaction and at the current stage it can only be speculated about the origin of this effect.

However, similar to the model reaction a band at 666 nm is observed, which increases in intensity with reaction time. Overlaying the UV–Vis spectra of the click reaction of the model compound with the click reaction mixture of the comb synthesis at the same reaction time reveal that the absorption maximum at 666 nm reached a similar intensity (see Fig. 12). This observation strengthens the hypothesis that the origin of this transition may be the effect of formed 1,2,3-triazole.

The observation of the absorption at 666 nm seems to be a suitable to determine the rate of reaction. The click model reaction was therefore monitored spectroscopically via on-line UV–Vis using a heated chamber and typical click reaction conditions. As displayed in Figure 13 the absorption measured at $\lambda = 666$ nm reached a maximum after a reaction time of around 12 h. This time frame is in good agreement with FTIR
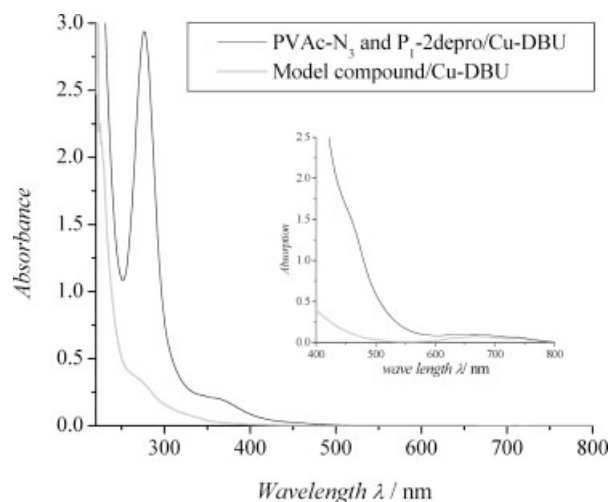
Figure 12. UV–Vis spectra obtained after click reaction in THF at 40 °C for 265 min. The solution has been diluted by a factor 100 prior to analysis while the inserted Figure shows the spectra of the undiluted click reaction mixture.

studies carried out earlier suggesting that a small percentage of reactants are still available after 7.5 h (see Fig. 8), which then fully disappear after further reaction. For comparison, the evolution of the absorption of the comb click reaction was added to the graph. The rate of comb click reaction seems to be of similar order. Deviations can be explained by the slight excess of azide groups during the comb synthesis, but also by problems arising due to uncertainties regarding absolute polymer concentrations.

FTIR, NMR, and UV–Vis studies therefore confirmed the complete click reaction of the model compound. The comb click reaction does seem to be complete and the click reaction seems to follow similar reaction rates. However, the investigation of the polymeric material is subject to greater uncertainties due the low concentration of azide or alkyne groups within the reaction mixture.

Size Exclusion Chromatography

The formation of well-defined products with monomodal molecular weight distributions was confirmed using SEC. As depicted in Figure 14 (left) and summarized in Table 3, the click reaction between the xanthate RAFT agent and the poly(propargyl methacrylate) backbone (reaction (3), see Scheme 2) results in a molecular weight

shift with a molecular weight close to the calculated value (see Table 3).

The click reaction between PVAc-N_3 was carried out with various backbones resulting in PVAc combs with close to 11 and 16 branches, respectively. A clear molecular weight shift was observed (see Fig. 14), which is close to the theoretical molecular weight (see Table 3). Unreacted PVAc-N_3 can be found in the reaction mixture, which is due to the fact that an excess of it was used to ensure the completion of the reaction in this particular case. These remaining side products can easily be removed by dialysis of the polymer against ethanol using dialysis tubing with a molecular weight cut-off of 5000 g mol^{-1} resulting in pure PVAc comb polymers with a molecular weight distribution below 1.2.

The synthesized PVAc comb polymer could now be hydrolyzed to well-defined PVA comb polymers. Earlier studies show that typical hydrolysis conditions (potassium hydroxide in methanol) only hydrolyses PVAc to PVA, whereas other ester bonds are stable under these conditions.[12,13]
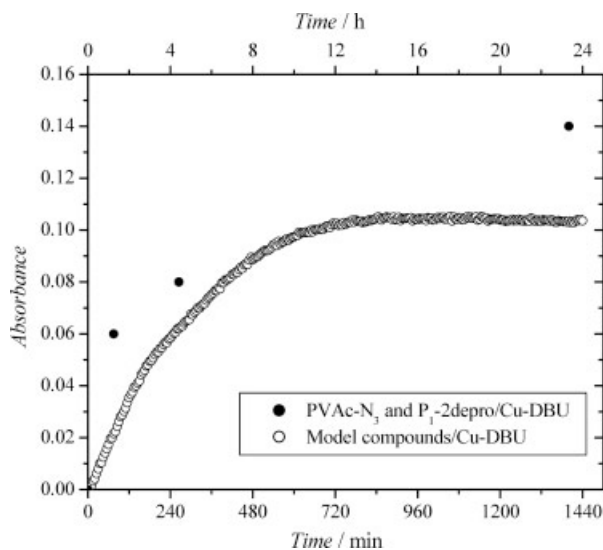
Figure 13. Evolution of the absorbance at 666 nm as a function of the reaction time in the model reaction of 2-propargyl-2-bromopropionate (2.5×10^{-2} mol L^{-1}) and 3-azidopropyl-2-bromopropionate (2.5×10^{-2} mol L^{-1}) with added [Cu(DBU)]I (2.5×10^{-3} mol L^{-1}) (open circles) at 40 °C in aqueous solution. The evolution of the same absorbance with time (probed at three time points) of the azide functionalized PVAc with deprotected poly(propargyl methacrylate) ($M_n = 1350$ g mol^{-1}, PDI = 1.15) is also depicted.
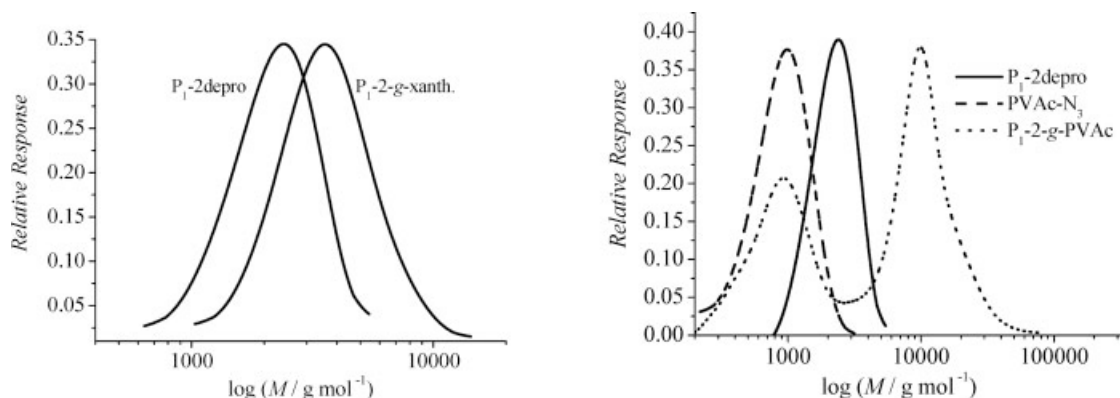
Figure 14. Left: SEC traces before (P$_1$-2depro, M_n = 2100 g mol^{-1}, PDI = 1.13) and after click reaction of azido-xanthate RAFT agent molecules onto the polymer backbone (P$_1$-2-g-xanth., M_n = 3400 g mol^{-1}, PDI = 1.18). Right: SEC traces before (P$_1$-2depro, M_n = 2100 g mol^{-1}, PDI = 1.13; PVAc-N$_3$, M_n = 850 g mol^{-1}, PDI = 1.19) and after the click grafting of PVAc-N$_3$ (P$_1$-2-g-PVAc, $M_{n,1}$ = 760 g mol^{-1}, PDI$_1$ = 1.20, $M_{n,2}$ = 9500 g mol^{-1}, PDI$_2$ = 1.18).

CONCLUSIONS

The Click Huisgen 1,3-dipolar copper catalyzed cycloaddition reaction in combination with RAFT/MADIX chemistry was found to be straight forward pathway to generate well-defined PVAc comb polymers. The initial RAFT polymerization of the propargyl methacrylate monomer has to proceed in its protected state as otherwise crosslinking reactions interfere. The subsequent deprotection can lead to a concomitant loss of RAFT endgroup functionality that is however inconsequential for the ensuing click functionalization. The click reaction itself leads to well defined comb block copolymers of poly(propargyl methacrylate) and PVAc of low PDI. The click reaction has been mimicked by a range of model reactions to assess a way to on-line monitor the reaction kinetics. The reaction progression can be followed via a kinetic sensor at 666 nm in the UV–Vis that is tentatively assigned to the formation of a charge transfer complex of the Cu(I) with the forming triazoles. The use of the 666 nm absorption band holds potential promise to be a simple and reliable indicator for monitoring click reactions for completeness. We refrain from deriving, even apparent, reaction rate coefficients from the kinetic data as the mechanistic underpinning are complex and certainly do not represent a single elementary reaction. Further investigation into the efficient monitoring of copper catalyzed 1,3-dipolar cylcoaddition reactions via on-line spectroscopic methods are underway in our laboratories.

Table 3. Click Grafted Copolymers Characteristics

Experiment	M_n Backbone (SEC)	M_n PVAc-N3 (SEC)	M_n Copolymer, Theoretical[a]	M_n Copolymer (SEC)	PDI
P1-2-g-xanthate	2100	263	4500	3400	1.18
P1-2-g-PVAc	2100	850	10,700	9500	1.18
P1-3-g-PVAc	3000	850	15,600	12,500	1.12

[a] Calculated using the theoretical molecular weight of the backbone.

REFERENCES AND NOTES

1. Chiellini, E.; Corti, A.; Antone, S. D'.; Solaro, R. Prog Polym Sci 2003, 28, 963.

2. Orienti, I.; Di Pietra, A.; Luppi, B.; Zecchi, V. Arch Pharm Pharm Med Chem 2000, 333, 421.

3. Rump, A. F. E.; Woschee, U.; Theisohn, M.; Fischbach, R.; Heindel, W.; Lackner, K.; Klaus, W. Eur J Clin Pharmacol 2002, 58, 459.

4. Nagano, K.; Yamane, S.; Toyoschima, K. Polyvinyl Alcohol; Kobunshi Kankokai: Tokyo, 1970.

5. Roychoudhury, R.; Kühn, S.; Schott, H.; Kössel, H. FEBS Lett 1975, 50, 140.

6. Merrill, E. W. J Biomed Sci Polym 1993, 5, 1.

7. Mammen, M.; Choi, S. K.; Whitesides, G. M. Angew Chem Int Ed 1998, 37, 2754.

8. (a) Barner-Kowollik, C.; Davis, T. P.; Heuts, J. P. A.; Stenzel, M. H.; Vana, P.; Whittaker, M. J Polym Sci Polym Chem 2003, 41, 365; (b) Moad, G.; Rizzardo E.; Thang, S. H. Aust J Chem 2005, 58, 379; (c) Perrier, S.; Takolpuckdee, P. J Polym Sci Polym Chem 2005, 43, 5347.

9. Destarac, M.; Brochon, C.; Catala, J. M.; Wilczewska, A.; Zard, S. Z. Macromol Chem Phys 2002, 203, 2281.

10. Barner, L.; Davis, T. P.; Stenzel, M. H.; Barner-Kowollik, C. Macromol Rapid Commun 2007, 28, 539.

11. Stenzel, M.; Cummins, L.; Roberts, G. E.; Davis, T. P.; Vana, P.; Barner-Kowollik, C. Macromol Chem Phys 2003, 204, 1160.

12. Stenzel, M. H.; Davis, T. P.; Barner-Kowollik, C. Chem Commun 2004, 13, 1546.

13. Bernard, J.; Favier, A.; Zhang, L.; Nilasaroya, A.; Davis, T. P.; Barner-Kowollik, C.; Stenzel, M. H. Macromolecules 2005, 38, 5475.

14. Boschmann, D.; Vana, P. Polym Bull 2005, 53, 231.

15. Barner-Kowollik, C.; Davis, T. P.; Stenzel, M. H. Aust J Chem 2006, 59, 719.

16. Chaffey-Millar, H.; Stenzel, M. H.; Davis, T. P.; Coote, M. L.; Barner-Kowollik, C. Macromolecules 2006, 39, 6406.

17. Bernard, J.; Favier, A.; Davis, T. P.; Barner-Kowollik, C.; Stenzel M. H. Polymer 2006, 47, 1073.

18. Huisgen, R.; Moebius, L.; Müller, G.; Stangl, H.; Szeimies, G.; Vernon, J. M. Chem Ber 1965, 98, 3992.

19. Tornøe, C. W.; Christensen, C.; Meldal, M. J Org Chem 2002, 67, 3057.

20. Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B. Angew Chem Int Ed 2002, 41, 2596.

21. Antoni, P.; Nystroem, D.; Hawker, C. J.; Hult, A.; Malkoch, M. Chem Commun 2007, 22, 2249.

22. Wu, P.; Malkoch, M.; Hunt, J. N.; Vestberg, R.; Kaltgrad, E.; Finn, M. G.; Fokin, V. V.; Sharpless, K. B.; Hawker, C. J. Chem Commun 2005, 46, 5775.

23. Joralemon, M. J.; O'Reilly, R. K.; Matson, J. B.; Nugent, A. K.; Hawker, C. J.; Wooley, K. L. Macromolecules 2005, 38, 5436.

24. Helms, B.; Mynar, J. L.; Hawker, C. J.; Frechet, J. M. J. J Am Chem Soc 2004, 126, 15020.

25. Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V. Angew Chem Int Ed 2004, 43, 3928.

26. Evans, R. A. Aust J Chem 2007, 60, 384.

27. Lutz, J. F. Angew Chem Int Ed 2007, 46, 1018.

28. Binder, W. H.; Sachsenhofer, R. Macromol Rapid Commun 2007, 28, 15.

29. Sumerlin, B. S.; Tsarevsky, N. V.; Louche, G.; Lee, R. Y.; Matyjaszewski, K. Macromolecules 2005, 38, 7540.

30. Mantovani, G.; Ladmiral, V.; Tao, L.; Haddleton, D. M. Chem Commun 2005, 2089.

31. Lutz, J.-F.; Boerner, H. G.; Weichenhan, K. Macromolecules 2006, 39, 6376.

32. Opsteen, J. A.; Van Heest, J. C. M. Chem Commun 2005, 57.

33. Binder, W. H.; Kluger, C. Macromolecules 2004, 37, 9321.

34. Quemener, D.; Davis, T. P.; Barner-Kowollik, C.; Stenzel, M. H. Chem Commun 2006, 5051.

35. Ting, S. R.; Granville, A.; Quémener, D.; Davis, T. P.; Stenzel, M. H.; Barner-Kowollik, C. Aust J Chem 2007, 60, 405.

36. Gondi, S. R.; Vogt, A. P.; Sumerlin, B. S. Macromolecules 2007, 40, 474.

37. Vogt, A. P.; Gondi, S. R.; Sumerlin, B. S. Aust J Chem 2007, 60, 396.

38. Hawker, C. J.; Vokin, V. V.; Finn, M. G.; Sharpless, K. B. Aust J Chem 2007, 60, 381.

39. Tsarevsky, N. V.; Bencherif, S. A.; Matyjaszewski, K. Macromolecules 2007, 40, 4439

40. Gao, H.; Matyjaszewski, K. J Am Chem Soc 2007, 129, 6633.

41. Liu, Q.; Chen, Y. J Polym Sci Part A: Polym Chem 2006, 44, 6103.

42. (a) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. Macromolecules 1998, 31, 5559; (b) Perrier, S.; Barner-Kowollik, C.; Quinn, J. F.; Vana, P.; Davis, T. P. Macromolecules 2002, 35, 8300.

43. Ladmiral, V.; Mantovani, G.; Clarkson, G. J.; Cauet, S.; Irwin, J. L.; Haddleton, D. M. J Am Chem Soc 2006, 128, 4823.

44. In the current study RAFT/MADIX are used interchangeably. The term RAFT is used merely as a mechanistic label.

45. Malkoch, M.; Thibault, R. J.; Drockenmuller, E.; Messerschmidt, M.; Voit, B.; Russell, T. P.; Hawker, C. J. J Am Chem Soc 2005, 127, 14942.

46. Barner-Kowollik, C.; Davis, T. P.; Stenzel, M. H. Polymer 2004, 45, 7791.

47. Vana, P.; Albertin, L.; Davis, T. P.; Barner, L.; Barner-Kowollik, C. J Polym Sci Polym Chem 2002, 40, 4032.

48. Manchot, W. J Soc Chem Ind Lond 1912, 30, 1302.

49. Meng, J.-C.; Fokin, V. V.; Finn, M. G. Tetrahedron Lett 2005, 46, 4543.

50. Munakata, M.; Kitagawa, S.; Kosome, S.; Asahara, A. Inorg Chem 1986, 25, 2622.

51. Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. Org Lett 2004, 6, 2853.

52. Reedijk, J.; Siedle, A. R.; Velapoldi, R. A.; van Hest, J. A. M. Inorg Chim Acta 1983, 74, 109.