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New poly(acrylic acid) containing segmented copolymer structures by combination of "click" chemistry and atom transfer radical polymerization

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Dedicated to Professor Teiji Tsuruta on the occasion of his 88th birthday (Beiju).

Abstract

In this paper, the combination of atom transfer radical polymerization (ATRP) of 1-ethoxyethyl acrylate (EEA) and the copper(I) catalyzed "click" 1,3-dipolar cycloaddition reaction of azides and terminal alkynes was evaluated as a method to synthesize diverse amphiphilic copolymer structures. Using the 1-ethoxyethyl protecting group strategy, the application field was broadened with the synthesis of complex polymer structures containing poly(acrylic acid) (PAA) segments. A modular approach has been used: polymers with alkyne functionalities as well as azide functionalities have been synthesized. These polymers were subsequently "clicked" together to yield block copolymers. Furthermore, graft copolymers were synthesized by grafting alkyne-containing polymers onto a polymer backbone with multiple azide functions using the combination of ATRP and "click" reactions.

Keywords: Click chemistry; Atom transfer radical polymerization; Poly(acrylic acid); Block copolymer; Graft copolymer; pH-responsive

1. Introduction

Since their description as a new class of reactions by Sharpless et al., "click" reactions have gained an increasing success [1]. During the last five years, particularly the Cu(I) catalyzed "click" cycloaddition reaction of azides and terminal alkynes has become very popular in polymer chemistry, as a useful tool for functionalizing synthetic macromolecules and synthesizing a wide range of polymer architectures [2–6]. One of the most requested qualities for reactions used in polymer chemistry is that they proceed quantitatively, as otherwise a mixture of reaction products is obtained, leading to badly defined properties of the end products. The Cu(I) catalyzed

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"click" cycloaddition reaction of azides and terminal alkynes meets this requirement entirely. Moreover, these reactions proceed under mild reaction conditions and are tolerant to a broad variety of functional groups. The coupling of an azide and a terminal alkyne by a Cu(I) catalyzed 1,3-dipolar cycloaddition reaction leads to the selective formation of a 1,4 disubstituted triazole ring, a chemically very stable compound.

As within the field of polymer synthesis, atom transfer radical polymerization (ATRP) is probably one of the most powerful and most employed polymerization methods in modern material science [7–14], recently several research groups have reported on the combination of "click" chemistry and ATRP. The bromide chain ends of polymers prepared by ATRP can easily be transformed into azides by nucleophilic substitution [11,14,15] and subsequently reacted with functional alkynes [16]. This strategy was used for preparing either well-defined telechelic polymers or block copolymers [2,17–20]. Additionally, functional initiators or monomers (i.e., azide or alkyne functional molecules) can be used in ATRP for preparing well-defined "clickable" polymers [19–23]. Moreover, because both ATRP and azide–alkyne "click" reactions are catalyzed by Cu(I) compounds, the combination of these two techniques showed to be an attractive approach.

In this paper, amphiphilic poly(acrylic acid)-containing block copolymers and graft copolymers are synthesized for the first time using a combination of ATRP and "click" chemistry. To avoid complexation of the poly(acrylic acid) (PAA) segments with the Cu(I) species, a recently developed strategy, using 1-ethoxyethyl acrylate (EEA) as the protected monomer has been employed [24–27]. A modular approach has been used: first, polymers with alkyne functionalities as well as azide functionalities have been synthesized. These polymers were subsequently "click" coupled to obtain the desired block and graft copolymers (see Fig. 1). Finally the amphiphilic structures could be obtained by a simple heating step, without any further purification step.

To the best of our knowledge, this paper describes for the first time the preparation of polymers with PAA segments by "click" chemistry. As PAA is of great importance for a number of applications because of its pH-responsive nature, its hydrophilic properties and its interaction with metal ions and biomolecules, there is a continuous drive for the controlled synthesis of such polymer structures. Combining the 1-ethoxyethyl protecting group strategy and "click" reactions may contribute to the easy preparation of well-defined PAA containing polymer structures.

In addition, this contribution aims to further investigate the synthesis of graft copolymers by the combination of ATRP and "click" chemistry. Very recently, Matyjaszewski et al. reported on the copolymerization of glycidyl methacrylate and methyl methacrylate followed by the introduction of azide functionalities in a second step by ring-opening of the epoxide ring, and the graft copolymers were obtained by a "grafting onto" click process [28]. In another contribution, an alkyne-containing polymeric backbone was reacted with azido-terminated side chains [29]. The alkyne-containing polymeric backbone was obtained in two steps starting with the synthesis of poly(2-hydroxyethyl methacrylate), followed by esterification of the hydroxyl group with pentynoic acid. After "clicking" with azido-functionalized linear poly(ethylene oxide), poly(styrene) or poly(butyl acrylate), the corresponding graft copolymers were obtained with a varying grafting density according to the molecular weight, the chemical nature and the concentration of the linear side chains.

In contrast, our approach for the PAA-containing graft copolymers makes use of the opposite

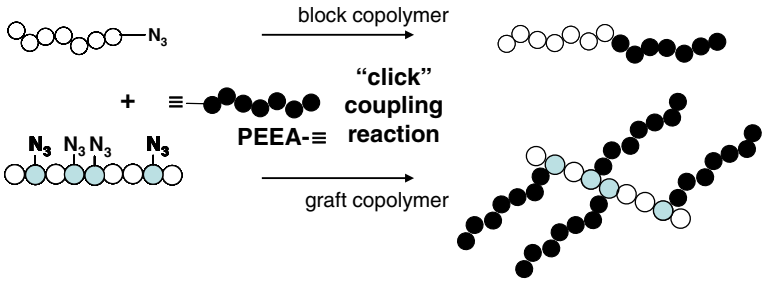

Fig. 1. Schematic depiction of the synthesis of block and graft copolymers using "click" chemistry.

strategy, which consists of the reaction of an azido-functionalized backbone with alkyne-terminated side chains. The azide-functionalized backbone was obtained in one step by direct copolymerization of an azide-containing monomer.

2. Experimental

2.1. Materials

Isobornyl acrylate (iBA, Aldrich, tech.) was purified by vacuum distillation (121 °C/18 mmHg). 1-Ethoxyethyl acrylate (EEA) was synthesized by the acid catalyzed addition reaction of acrylic acid to ethyl vinyl ether as described previously [24,26,27], and purified by vacuum distillation (30 °C/7 mbar). Cu(I)Br (Aldrich, 98%) was purified by stirring with acetic acid, then by filtering and washing with ethanol and diethylether, and finally by drying in a vacuum oven at 70 °C [30]. *N*,*N*,*N*′,*N*″,*N*″-Pentamethyldiethylenetriamine (PMDETA, Acros, 99 +%) was distilled (85–86 °C/12 mm Hg). Methyl-2-bromopropionate (MBP, Acros, 99%), ethyl 2-bromoisobutyrate (Aldrich, 98%), dimethyl 2,6-dibromoheptanedioate (BHD, Aldrich, 97%), propargyl alcohol (Aldrich, 99%), 2-bromopropionic acid (Acros, 99%), *N*,*N*′-dicyclohexylcarbodiimide (DCC, Acros, 99%), 4-dimethylaminopyridine (4-DMAP, Acros, 99%), azidotrimethyl silane (Acros, 97%), tetrabutyl ammoniumfluoride (1.0 M solution in THF, 99 %), sodium azide (Aldrich, 99.5%), tetrabutyl ammonium hydrogen sulphate (Acros, 98%), hydroquinone (Fluka, 99%) and (trimethylsilyl)diazomethane (2.0 M solution in diethyl ether, Aldrich) were used as received. Solvents were purchased from Aldrich (HPLC grade) and used without purification. All other chemicals were used as received.

2.2. Characterization

^{1}H NMR spectra were recorded in $CDCl_3$ at room temperature, with a Bruker AM500 or a Bruker Avance 300 spectrometer.

Gel Permeation Chromatography (GPC) analysis was performed on a Waters instrument, using a refractive index detector (2410 Waters), equipped with Waters Styragel 10^3–10^4–10^5 Å serial columns (5 μm particle size) at 35 °C. Polystyrene standards were used for calibration and $CHCl_3$ as eluent at a flow rate of 1.5 mL/min. Samples were injected using a Gilson autoinjector type 234.

Preparative GPC was performed in $CHCl_3$ as the solvent at a flow rate of 5 mL/min at room temperature using an Alltech 426 HPLC pump and a PLgel 10 μ 10^3 Å column. Refractive index detection was done with a Melz RI LCD 212 detector.

Infrared spectra were obtained with a React-IR 4000 instrument from Mettler Toledo.

Thermogravimetric analysis (TGA) was performed with a Mettler Toledo TGA/SDTA851e instrument under air atmosphere at a heating rate of 10 °C/min from 25 °C to 800 °C.

2.3. Synthesis of propargyl 2-bromopropionate: alkyne-containing initiator

Ten milliliter (9.6 g, 0.17 mol) propargyl alcohol and 15.46 mL (26.3 g, 0.17 mol) 2-bromopropionic acid are dissolved in 100 mL of THF. The reaction mixture is cooled in an ice bath. A solution of 34.8 g DCC (0.17 mol) in 40 mL of THF is added slowly under continuous stirring. Next, a solution of 1.2 g 4-DMAP in 40 mL of THF is added during 10 min. The mixture is stirred during 1 h at 0 °C and followed by 24 h at room temperature. During the reaction, dicyclohexyl urea is formed and precipitates. After the reaction, the dicyclohexyl urea is filtered off and washed with THF. The solvent THF was removed, and propargyl 2-bromopropionate was obtained as a yellow viscous oil. Yield is 74%.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.83 (d, 3H, CH_3C), 2.52 (t, 1H, CH≡C) 4.38 (q, 1H, CH(Br)), 4.76 (s, 2H, OCH_2C≡).

IR: characteristic alkyne C–H stretch at 3296 cm^{-1}. Other characteristic absorptions: C–H stretch at 2860–3000 cm^{-1}, C=O (ester) at 1741 cm^{-1}, CH_3 bending at 1450 and 1375 cm^{-1}, C–O (ester) at 950–1300 cm^{-1}, and C–Br stretch at 670 cm^{-1}.

2.4. ATRP of EEA with propargyl 2-bromopropionate as the initiator

A typical polymerization procedure is as follows (e.g. Table 1, entry 4). A mixture of 0.0624 mol (9.0 mL) of the monomer EEA and 0.624×10^{-3} mol (0.130 mL) of PMDETA as the ligand was added to a reaction flask and was bubbled with N_2 for 1 h to remove oxygen from the reaction mixture. After that, Cu(I)Br (0.624×10^{-3} mol, 0.090 g) was added and the reaction flask was placed in an oil bath at 70 °C. When the reaction mixture reached the desired reaction temperature, the

Table 1
Summary of the reaction conditions and results of the polymerizations of EEA using propargyl 2-bromopropionate as the alkyne-containing initiator by ATRP

Entry[a]	$[M]_0/[In]_0/[Cu]_0/[ligand]$[b]	Temp. (°C)	Time (min)	Conv.[c] (%)	$M_{n,th}$ (g mol^{-1})	$M_{n,exp}$[d] (g mol^{-1})	M_w/M_n[d]
1	50/1/2/2	50	306	23	2000	3000	1.33
2	50/1/1/1	60	391	49	3700	5300	1.29
3	50/1/1/1	70	300	81	6000	8200	1.34
4	100/1/1/1	70	378	42	6200	6100	1.17
5	100/1/1/1	70	300	38	5600	6700	1.12
6	100/1/1/1	70	326	33	4900	4700	1.22
7	100/1/1/1	70	307	40	5900	4600	1.21
8	100/1/1/1	70	304	37	5500	6100	1.16

[a] All polymerizations were performed in bulk, with propargyl 2-bromopropionate as initiator, Cu(I)Br as catalyst and PMDETA as ligand.
[b] $[M]_0$, $[In]_0$, $[Cu]_0$ and [ligand] = initial concentration of monomer, initiator, copper catalyst and ligand, respectively.
[c] Calculated from ^{1}H NMR.
[d] Relative to polystyrene standards.

polymerization was started by adding 0.624×10^{-3} mol (0.086 mL) of propargyl 2-bromopropionate as the initiator. Samples were withdrawn periodically to monitor the monomer conversion (by ^{1}H NMR) and the average molecular weight (by GPC). The reaction was ended by cooling the reaction mixture in liquid nitrogen. The resulting polymer was dissolved in THF and the copper catalyst was removed by passing the diluted reaction mixture over a column of neutral Al_2O_3. After evaporating the excess of solvent, the residual monomer was removed by high vacuum.

2.5. Synthesis of PiBA–Br

A typical polymerization procedure is as follows (e.g. Table 2, entry 10). A mixture of 0.1136 mol (24.0 mL) of the monomer iBA and 2.84×10^{-4} mol (0.059 mL) of PMDETA as the ligand was bubbled with N_2 for 1 h to remove oxygen. Ethyl acetate as the solvent was also bubbled with N_2 for 1 h to remove oxygen and 8 mL (25 vol%) ethyl acetate was added to the reaction flask. Cu(I)Br (2.84×10^{-4} mol, 0.0407 g) was added under N_2 atmosphere, and the reaction flask was placed in an oil bath at 90 °C. When the reaction mixture reached the desired temperature, the polymerization was started by adding 5.68×10^{-4} mol (0.063 mL) of methyl-2-bromopropionate as the initiator. Samples were withdrawn periodically to monitor the monomer conversion (by ^{1}H NMR) and the average molecular weight M_n (by GPC). The reaction was ended by cooling the reaction mixture in liquid nitrogen. The resulting polymer was dissolved in THF and the copper catalyst was removed by passing the diluted reaction mixture over a column of neutral Al_2O_3. After evaporating the excess of solvent, the polymer was precipitated in methanol (10-fold excess). A detailed study on the synthesis of well-defined PiBA is described elsewhere [25].

2.6. Substitution of PiBA–Br to PiBA–N_3

A typical substitution procedure is as follows. PiBA is dissolved in THF. 10 equivalents of azidotrimethylsilane (Me_3SiN_3) and 10 equivalents of tetrabutylammonium fluoride (TBAF) relative to the amount of Br end groups are added to the polymer

Table 2
Summary of the reaction conditions and results of the polymerizations of iBA to yield PiBA–Br that was subsequently transformed to PiBA–N_3

Entry [a]	$[M]_0/[In]_0/[Cu]_0/[ligand]$ [b]	Temp. (°C)	Time (min)	Conv.[c] (%)	$M_{n,th}$ (g mol^{-1})	$M_{n,exp}$[d] (g mol^{-1})	M_w/M_n
9	100/1/0.5/0.5	90	60	33	7000	7700	1.32
10	200/1/0.5/0.5	90	120	33	13900	10400	1.31

[a] All polymerizations were performed in 25 vol% of ethyl acetate as solvent, with methyl 2-bromopropionate as initiator, Cu(I)Br as catalyst and PMDETA as ligand.
[b] $[M]_0$, $[In]_0$, $[Cu]_0$ and [ligand] = initial concentration of monomer, initiator, copper catalyst and ligand, respectively.
[c] Calculated from ^{1}H NMR.
[d] A conversion factor of 1.4 relative to polystyrene standards was applied.

solution. The reaction mixture is then stirred for 48 h at room temperature. Purification of the product is done by precipitation into a 10-fold excess of cold methanol. The precipitated polymer is filtered off and washed with cold methanol. This precipitation procedure was done twice. Finally the PiBA–N_3 was dried at room temperature under vacuum.

2.7. Synthesis of 3-azidopropyl methacrylate: azide-containing monomer

Step 1: synthesis of 3-azidopropanol. 30.0 mL (33.9 g, 0.358 mol) of 3-chloropropanol is added to a mixture of 40 mL water, 47 g (0.716 mol) sodium azide and 1 g tetrabutyl ammonium sulphate. The reaction flask is equipped with a reflux condenser and the reaction mixture is stirred at 80 °C during 24 h. Then it was stirred at room temperature during 14 h. The product is then extracted with diethyl ether (three times 100 mL) and the organic phase is dried using sodium sulphate. 3-Azidopropanol is obtained as a colourless liquid by vacuum distillation. Boiling point is 62 °C at 3–4 mbar.

Step 2: synthesis of 3-azidopropyl methacrylate. A mixture of 23.5 mL (0.253 mol) 3-azidopropanol, 45.0 mL (0.323 mol) triethylamine (dried with sodium sulphate), 0.1 g hydroquinone and 100 mL of diethyl ether (dried with sodium sulphate) is cooled to 0 °C in an ice bath. 29.0 mL (0.300 mol) of methacryloyl chloride is added dropwise during a period of 20 min. The reaction mixture is stirred at 0 °C for one more hour and stirring was continued for 14 h at room temperature. Hundred mL of diethyl ether is added to the reaction mixture and the mixture is extracted subsequently with an aqueous solution of HCl (10 vol%, 2 times 100 mL), water (two times 100 mL), an aqueous solution of NaOH (10 weight%, two times 100 mL), and again with water (two times 100 mL). The diethyl ether phase is dried with sodium sulphate. After removal of sodium sulphate and the solvent diethyl ether, 3-azidopropyl methacrylate was obtained as a yellow oil. Distillation of the monomer was not performed because of safety reasons. Sumerlin et al. reported that special care should be taken and recommended not to heat the azide compound above 75–80 °C because it becomes shock-sensitive at elevated temperatures [23]. Yield is 70%.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.91–2.00 (m, 5 H, overlap of $CH_3C{=}$ and CCH_2C), 3.41 (t, 2H, CH_2N_3), 4.24 (t, 2H, CH_2O), 5.57 (s, 1H, =CH), 6.10 (s, 1H, =CH).

2.8. Copolymerization of MMA and AzMA

The copolymerization procedure of MMA and AzMA is as follows (Table 3, entry 11). 0.0928 mol (10.0 mL) of MMA, 0.0232 mol (3.93 g, 3.67 mL) of AzMA and 0.774×10^{-3} mol (0.134 g, 0.162 mL) of PMDETA were added to a reaction flask and the mixture was bubbled with N_2 for 1 h to remove oxygen from the reaction mixture. Acetone was degassed separately by bubbling with N_2 and 25 vol% (4.55 mL) of acetone was added to the reaction flask. After that, Cu(I)Br (0.5 equivalent to initiator, 0.774×10^{-3} mol, 0.111 g) was added and the reaction flask was placed in an oil bath at 50 °C. When the reaction mixture reached the desired reaction temperature, the polymerization was started by adding dropwise during 20 s 1.548×10^{-3} mol (0.3019 g, 0.227 mL) of ethyl 2-bromoisobutyrate as the initiator. Samples were withdrawn periodically to monitor the monomer conversion (by ^{1}H NMR) and the average molecular weight M_n (by GPC). The reaction was terminated by cooling the reaction mixture in liquid nitrogen. The resulting polymer was dissolved in THF and the copper catalyst was removed by pass-

Table 3
Summary of the reaction conditions and results of the copolymerization of MMA and AzMA by ATRP

Entry[a]	$[MMA]_0/[AzMA]_0/[In]_0/[Cu]_0/[ligand]$[b]	Temp. (°C)	Time (min)	Conv.[c] MMA (%)	Conv.[c] AzMA (%)	Composition[d]	$M_{n,exp}$[e] (g mol^{-1})	M_w/M_n
11	60/15/1/0.5/0.5	50	60	48	47	MMA_{39}/ $AzMA_9$	7000	1.25

[a] Polymerization was performed in 25 vol% of acetone as solvent, with ethyl 2-bromoisobutyrate as initiator, Cu(I)Br as catalyst and PMDETA as ligand.

[b] $[MMA]_0$, $[AzMA]_0$, $[In]_0$, $[Cu]_0$ and [ligand] = initial concentration of methyl methacrylate, 3-azidopropyl methacrylate, initiator, Cu catalyst and ligand, respectively.

[c] Calculated from ^{1}H NMR.

[d] Composition was determined from ^{1}H NMR analysis of the purified product, taking into account an initiator efficiency of 75%.

[e] Relative to polystyrene standards.

ing the diluted reaction mixture over a column of neutral Al_2O_3. After evaporating the excess solvent, the polymer was precipitated in cold hexane, and dried under vacuum. The recovery yield was about 50% after passing the polymer through a column of basic Al_2O_3 and after selective precipitation. On the other hand, the "click" reaction itself was complete under these conditions as no azide signal could be detected in infrared measurements.

2.9. Formation of block copolymer by "click" reaction of PiBA–N_3 with PEEA-≡

A typical "click" coupling procedure for the formation of a poly(iBA-*b*-EEA) block copolymer is as follows (Table 4, entry 12). The bromide end group of PiBA ($M_n = 10400\ g\ mol^{-1}$) was substituted to an azide end group as described before (Table 2, entry 10). Then, PiBA–N_3 (0.4 g, 3.77×10^{-5} mol) and PEEA-≡ (0.5 g, 7.46×10^{-5} mol, 2 equivalents to PiBA–N_3) were dissolved in 4 mL of THF. PMDETA ($2.23.10^{-4}$ mol, 0.047 mL, 3 equivalents to alkyne functions) was added and the mixture was bubbled with N_2 for 30 min. The "click" coupling reaction was started by adding Cu(I)Br (2.23×10^{-4} mol, 0.0319 g, 3 equivalents to alkyne functions). After completion of the "click" reaction, the resulting solution was further diluted in THF and the copper catalyst was removed by passing the reaction mixture over a column of neutral Al_2O_3. After evaporating the excess solvent, the excess of PEEA-≡ was removed by selective precipitation in cold methanol. The coupled product poly(iBA-*b*-EEA) was filtered off, washed with cold methanol, and dried under vacuum.

2.10. Formation of graft copolymer by "click" reaction of poly(MMA-co-AzMA) with PEEA-≡

The "click" coupling procedure for the formation of a poly(MMA-*g*-EEA) graft copolymer is as follows (e.g. Table 5, entry 13). Poly(MMA_{39}-*co*-$AzMA_9$) copolymer (0.046 g, 8.36×10^{-6} mol, 7.53×10^{-5} mol of N_3 groups) and PEEA-≡ (1.5 equivalents to N_3 groups, 1.17×10^{-4} mol, 0.54 g) were dissolved in 4 mL of THF. PMDETA (3.52×10^{-4} mol, 0.074 mL, 1 equivalent to Cu(I)Br) was added and the mixture was bubbled with N_2 for 30 min. The "click" coupling reaction was started by adding Cu(I)Br (3.52×10^{-4} mol, 0.0505 g, 3 equivalents to alkyne functions). After completion of the "click" reaction, the resulting solution was further diluted in THF and the copper catalyst was removed by passing the reaction

Table 4
Summary of the data and results of the "click" coupling reaction between PiBA–N_3 and PEEA-≡, yielding a block copolymer

Entry	M_n/M_p/PDI[a] PiBA–N_3[b]	M_n/M_p/PDI[a] PEEA-≡[c]	M_n/M_p/PDI[a] coupled product[d]	Composition[e] coupled product
12	7400/9000/1.30	6700/7500/1.12	11500/14100/1.25	$PiBA_{50}$-*b*-$PEEA_{43}$

[a] Relative to polystyrene standards.
[b] Table 2, entry 10.
[c] Table 1, entry 5.
[d] After purification (removal of excess PEEA).
[e] Determined *via* ^1H NMR analysis of the purified product by comparing the integration of PiBA and PEEA signals. DP_n of PiBA was found by GPC analysis (applying a conversion factor of 1.4 (calibration of GPC was done with polystyrene standards)).

Table 5
Summary of the results of the "click" coupling reaction between poly(MMA-*co*-AzMA) and PEEA-≡, yielding a graft copolymer

Entry[a]	M_n/M_p/PDI[b] copolymer poly(MMA_{39}-*co*-$AzMA_9$)[c]	M_n/M_p/PDI[b] PEEA-≡	[PEEA-≡]/[Cu(I)Br]/[PMDETA]	M_n/M_p/PDI[b] coupled product
13	7000/9900/1.25	4600/5400/1.21[d]	1/3/3	37100/46900/1.27
14	7000/9900/1.25	6100/7000/1.16[e]	1/3/3	42200/56800/1.23
15	7000/9900/1.25	4600/5400/1.21[d]	1/0.3/0.3	35200/41500/1.27

[a] For all "click" coupling reactions, the ratio of [copolymer poly(MMA_{39}-*co*-$AzMA_9$)]/[PEEA-≡] is 1/2, Cu(I)Br was used as catalyst and PMDETA as ligand, in THF as solvent.
[b] Relative to polystyrene standards.
[c] Table 3, entry 11.
[d] Table 1, entry 7.

mixture over a column of neutral Al_2O_3. The "clicked" product was isolated by preparative GPC.

3. Results and discussion

3.1. Synthesis of alkyne-containing polymers

Propargyl 2-bromopropionate has been used for the synthesis of PAA segments with a terminal alkyne functionality. This alkyne-containing initiator is prepared by esterification of propargyl alcohol with 2-bromopropionic acid in the presence of DCC and 4-DMAP as catalyst [31].

The PAA segments for the synthesis of the block and graft copolymers are prepared starting from 1-ethoxyethyl acrylate (EEA) as the protected monomer. Polymerizations were carried out using Cu(I)Br as the catalyst in combination with PMDETA as the ligand. Propargyl 2-bromopropionate was used to introduce the desired alkyne functionalities. The amount of catalyst relative to the initiator concentration, the theoretical degree of polymerization ($DP_{th} = [M]_0/[In]_0$) and the polymerization temperature were varied to optimize the polymerization conditions (see Table 1).

For polymers with $DP_{th} = 50$, higher conversions were obtained (up to about 80%) with increasing polymerization temperature (Table 1, entry 1–3). Nevertheless, termination reactions during the early stages of the polymerization could not be avoided, as evidenced by the experimental average molecular weight ($M_{n,exp}$) being higher than the theoretical one ($M_{n,th}$) and the rather high polydispersity index. By increasing the DP_{th}, the overall concentration of radicals in the reaction medium is lowered and thus termination reactions are suppressed, as evidenced by a better accordance with the $M_{n,th}$. Best results for the polymerization were obtained at a temperature of 70 °C, with a ratio of initial concentration of monomer/initiator/catalyst/ligand $[M]_0/[In]_0/[Cu]_0/$[ligand] equal to 100/1/1/1. With these conditions, polymers with a low polydispersity index and a controlled molecular weight were obtained (Table 1, entry 4–8).

A kinetic study was carried out to further investigate the controlled behavior of the polymerization reaction using this alkyne-containing initiator. Although the first order kinetic plot shows some deviation from linearity, the linear increase of the average molecular weight (M_n) as a function of

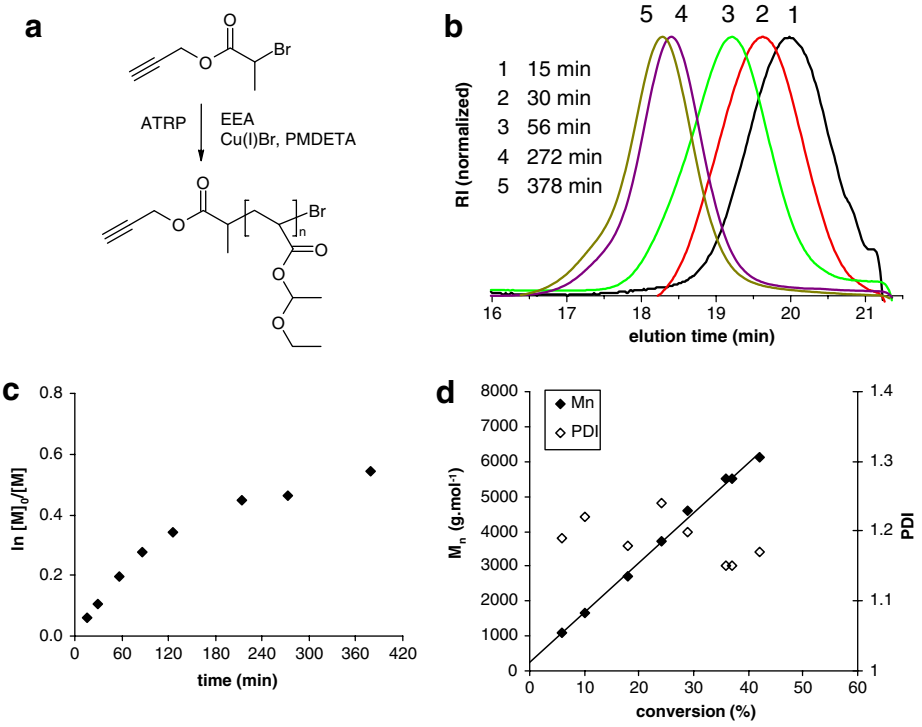

Fig. 2. ATRP of EEA using an alkyne-containing initiator (Table 1, entry 4). (a) schematic depiction, (b) GPC analysis, (c) first order kinetic plot, (d) increase of M_n and evolution of PDI as a function of conversion. (With trend line in graph (d)).

conversion, narrow molecular weight distribution, and the symmetrical GPC curves reveal the controlled character of the polymerization (see Fig. 2). The deviation of the first order kinetic plot could be ascribed to poisoning of the Cu catalyst because of complexation of a small fraction of deprotected carboxylic acid monomer or polymer with the copper species.

In conclusion, the polymerization of EEA initiated with propargyl 2-bromopropionate shows to be an appropriate route for the preparation of polymers with a terminal alkyne functionality.

3.2. Synthesis of azide containing polymers

Besides alkyne-functionalized polymers, also azide-containing polymers have to be prepared in order to be able to perform a "click" coupling reaction.

In case of the synthesis of block copolymers, the polymer segments should bear one azide end group. By "click" coupling with a polymer with a terminal alkyne function, a block copolymer is formed. The terminal azide group can be introduced in the polymer by nucleophilic substitution of the bromide end group.

One important issue for the synthesis of azide-terminated polymers *via* nucleophilic substitution of the bromide end group is that the polymers need to have a high degree of end group functionality. It is known that this can be obtained by ATRP of acrylates. Therefore, in this work, isobornyl acrylate (iBA) was used as the monomer. This particular acrylate was selected because the corresponding polymer is characterized by a high glass transition temperature ($T_g = 94$ °C [32]), which makes purification of the polymers easier, as they can be isolated by simple precipitation. Although polystyrene (PS) and poly(methyl methacrylate) (PMMA) also exhibit a similar T_g, there are a number of limitations to obtain a high degree of end group functionality with the ATRP process [2,33,34].

Table 2 summarizes the reaction conditions and the results for the PiBA polymers that were subsequently used for the further transformation of the bromide end group to an azide end group. A detailed study on the preparation of well-defined PiBA polymers is described elsewhere [25].

Nucleophilic substitution of the bromide end groups of PiBA was performed by reaction with azidotrimethylsilane (Me_3SiN_3) and tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) as the solvent (see Fig. 3) [15]. The role of TBAF is to transfer the azide anion in the organic phase so that substitution of the bromide can occur. This increases the reaction rate and makes the reaction proceed at room temperature.

^{1}H NMR spectroscopy was used to check the transformation of the bromide into an azide functionality. The ^{1}H NMR spectra of PiBA–Br and PiBA–N_3 are shown in Fig. 4.

The multiplet that arises from the proton next to the bromide group of PiBA–Br (4.15–4.25 ppm) completely disappears after the azidation reaction. On the other hand, the ^{1}H NMR spectrum of the PiBA–N_3 shows a signal that arises from the proton next to the azide group (3.75–3.95 ppm).

For the synthesis of graft copolymers, our approach starts with the synthesis of a polymer backbone with multiple (pendant) azide groups. The polymer backbone is prepared by copolymerization of methyl methacrylate (MMA) and 3-azidopropylmethacrylate (AzMA).

AzMA is synthesized in two steps [23]. The first step is the preparation of 3-azidopropanol by reaction of 3-chloropropanol *via* reaction with sodium azide. In a second step AzMA is formed by reaction of 3-azidopropanol with methacryloyl chloride.

3.3. Copolymerization of AzMA

For the preparation of the polymer backbone of the graft copolymer, MMA and AzMA were copolymerized to yield a random copolymer (see discussion further) containing multiple azide functionalities (see Fig. 5).

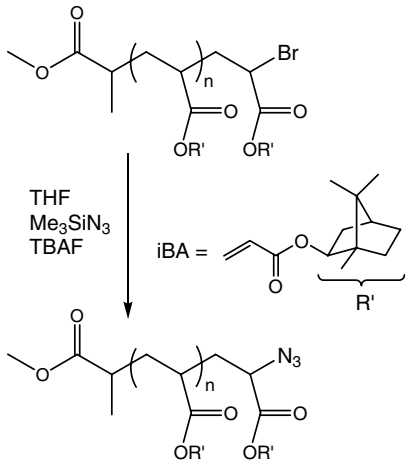

Fig. 3. Transformation of the bromide end group of PiBA to an azide by nucleophilic substitution.

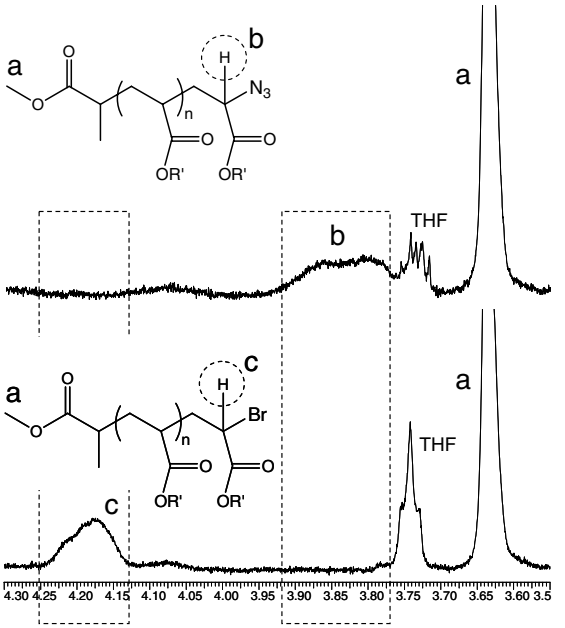

Fig. 4. Transformation of PiBA–Br into PiBA–N_3(Table 2, entry 9), as evidenced by ^{1}H NMR ($CDCl_3$, 500 MHz).

A copolymer of MMA and AzMA was synthesized with a ratio of 4/1 in the starting mixture (Table 3, entry 11). The reactions were performed in acetone as the solvent (25 vol%) and Cu(I)Br/PMDETA was used as the catalyst complex. Although a complete copolymerization study has not been performed, the expected similar reactivity ratios of both methacrylate monomers was confirmed by the similar conversions that were obtained for both monomers (see Table 3). As a result, the copolymerization of MMA and AzMA yields a polymer with an equal distribution of AzMA units along the PMMA backbone.

3.4. "Click" reactions with azide- and alkyne-containing polymers

After the synthesis of azide-terminated and alkyne-containing polymers, the synthesis of block and graft copolymers using the Cu(I) catalyzed "click" cycloaddition reaction was investigated. By combining hydrophilic PAA segments with hydrophobic polymer segments, we aimed to further extend the application of "click" chemistry toward the synthesis of amphiphilic polymer structures. Just like for ATRP, the "click" 1,3-dipolar cycloaddition reaction is catalyzed by Cu(I) species and consequently PAA poisons the catalyst, thus preventing the reaction to take place. The use of 1-ethoxyethyl acrylate (EEA) as monomer circumvents this problem.

An additional advantage of the "click" chemistry method is the intrinsic modular approach. This approach enables full analysis (e.g. molecular weight distribution) of the individual segments prior to coupling. This is in contrast to the synthesis of these polymers using the so-called macroinitiator approach or the sequential monomer addition method, where complete formation of block copolymers is often hard to assess and characterization of the individual blocks is difficult.

In addition to the above mentioned advantages of the "click" chemistry approach, the synthesis of comb or graft copolymers may be simplified as well. For example, one way to obtain graft copolymers is the (co)polymerization of macromonomers by ATRP, which is often complicated due to viscosity reasons and problems with quantitative end group transformations [35]. Using the "click" chemistry strategy, the synthesis of graft copolymers consists of (i) the synthesis of a (co)polymer containing "clickable" groups (the "backbone"), and (ii) the synthesis of a linear polymer containing a complimentary "clickable" end group (the actual brushes attached to the "backbone") (see Fig. 1).

3.4.1. Formation of block copolymers

In order to synthesize block copolymers *via* "click" chemistry, PiBA–N_3 should be "click" coupled with a polymer chain that contains one alkyne functionality, in this case poly(1-ethoxyethyl acrylate) (PEEA-≡). After deprotection of the

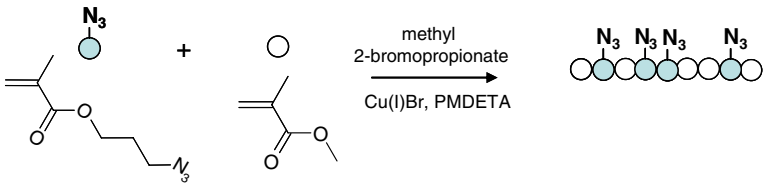

Fig. 5. Schematic depiction of the copolymerization of MMA and AzMA to yield a random copolymer containing multiple azide functionalities.

PEEA segment to PAA, the desired block copolymer is obtained.

The results and data of the performed "click" reaction are given in Table 4. A model experiment was performed at room temperature in THF using a Cu(I)Br/PMDETA catalyst system, with an initial ratio of [PiBA–N_3]/[PEEA-≡] = 1/2. Cu(I)Br/PMDETA was chosen as the catalyst complex as it was found that this catalyst system shows the highest catalytic activity relative to those of other metal complexes [16]. A three-fold excess of Cu(I)Br and ligand relative to alkyne end groups was used, according to literature conditions [2].

Effective coupling of the two polymer segments was proved by GPC analysis, as the peak molecular weight (M_p) of the coupled product reveals a shift towards higher molecular weight in comparison to the starting products. Fig. 6a shows the GPC traces of the "click" coupling reaction of PiBA–N_3 and PEEA-≡ (Table 4, entry 12) before the coupling reaction (0′, mixture of start products), after 5 min (5′), and after 16 h. The GPC trace of the coupled product has a bimodal character, which is due to the excess of PEEA-≡ in the reaction mixture. Note that the coupling reaction is complete after 5 min, as there is no difference between the GPC analysis of a sample taken after 5 min or 16 h.

After removal of the copper by filtration through an Al_2O_3 column, the excess of PEEA-≡ was removed by selective precipitation of the reaction mixture in cold methanol (methanol is a non-solvent for PiBA, and a good solvent for PEEA). The unimodal shape of the GPC analysis (Fig. 6b) of the purified product proves that the excess of PEEA was removed successfully.

The ^{1}H NMR spectrum of the purified "click" coupled product clearly shows the signals of the triazole link between both polymer segments at 5.0–5.1, 5.15–5.3 and 7.65–7.75 ppm (see Fig. 7). No signals arising from azide functionalities could be detected in the IR spectrum of the purified "click" coupled product, demonstrating quantitative coupling.

TGA analysis of poly(iBA-*b*-EEA) showed a weight loss of 18% (see Fig. 8, solid line) arising from the loss of ethyl vinyl ether during the deprotection of poly(iBA-*b*-EEA) to poly(iBA-*b*-AA) [24–27]. Integration of characteristic ^{1}H NMR signals of PiBA (at 4.4–4.8 ppm) and PEEA (at 5.8–6.1 ppm) revealed a relative composition of PiBA/PEEA of 1 to 0.86. Taking into account the molar mass of PiBA, the relative composition of iBA and EEA in the block copolymer and the respective molecular weight of the monomers, a theoretical weight loss of 18.6% should be obtained.

The good agreement between experimental and theoretical weight loss confirms the quantitative deprotection. For the large scale thermal treatment, the polymer was spread out on a glass plate and was put in an oven at 80 °C during 24 h. Complete deprotection of the poly(iBA-*b*-EEA) to poly(iBA-*b*-AA) is confirmed by TGA analysis of the deprotected sample, as no weight loss arising from additional deprotection could be observed (see Fig. 8, dotted line).

3.4.2. Formation of graft copolymers

Subsequently, graft copolymers were synthesized by the "click" coupling reaction of PEEA-≡ with a poly(MMA_{39}-*co*-$AzMA_9$) backbone, under similar

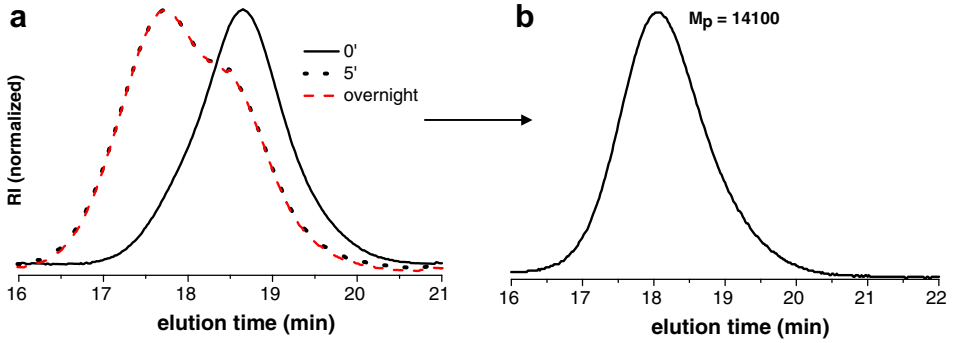

Fig. 6. (a) GPC traces of "click" coupling reaction (Table 4, entry 12) of a PiBA–N_3 and a PEEA-≡ polymer, before the coupling reaction (0′, mixture of start products), after 5 min (5′), and overnight. (b) GPC trace of the same "click" coupling reaction (Table 4, entry 12) after removal of the excess PEEA-≡ by selective precipitation in methanol.

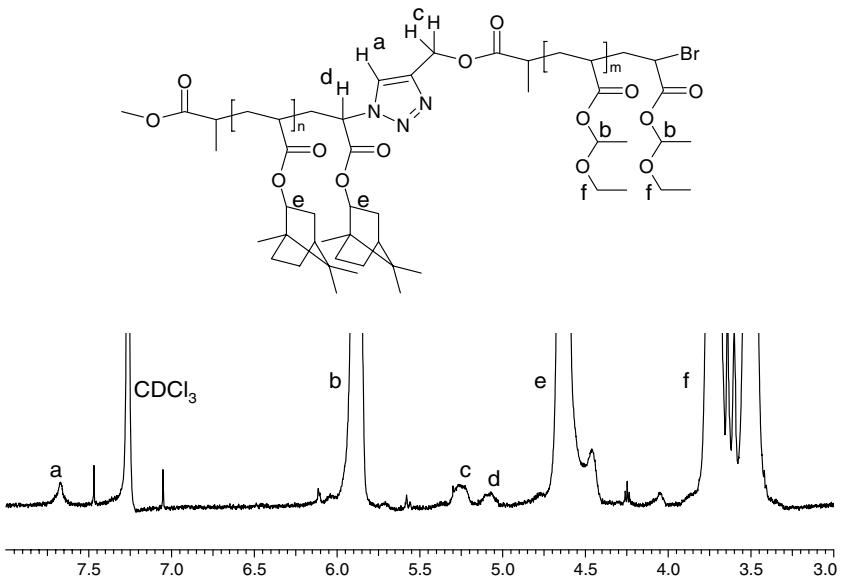

Fig. 7. ^{1}H NMR spectrum of the product of "click" coupling reaction (Table 4, entry 12) of PiBA–N_3 (Table 2, entry 10) and PEEA-≡ (Table 1, entry 6) to yield a poly(iBA-*b*-EEA) block copolymer (in $CDCl_3$, 500 MHz).

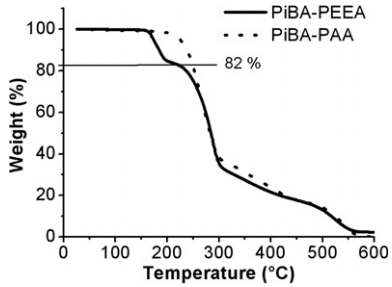

Fig. 8. TGA analysis of the "click" coupled poly(iBA-*b*-EEA) block copolymer before (solid line) and after deprotection (dotted line) by a heating process at 80 °C during 24 h (Table 4, entry 12). Heating rate: 10 °C/min; air atmosphere.

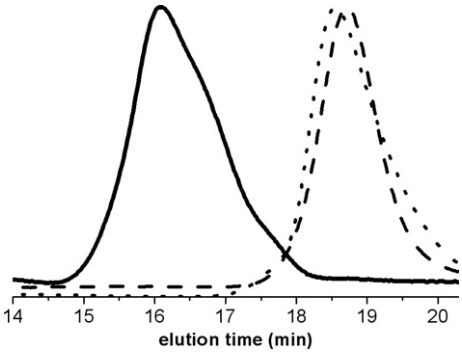

Fig. 9. GPC traces of "click" coupling reaction (Table 5, entry 14) of a poly(MMA-*co*-AzMA) copolymer (Table 3, entry 11, dotted line) and a PEEA-≡ polymer (Table 1, entry 8, dashed line), before the coupling reaction, and after the "click" reaction (solid line, after purification by preparative GPC).

conditions as the previous reactions (see Table 5). After the "click" reaction, deprotection of the PEEA segments to the corresponding PAA segments by heating is expected to provide the desired amphiphilic graft copolymer structures.

GPC analysis reveals the formation of a high molecular weight product (see Fig. 9). Also from a comparison of the M_n or M_p values of the poly-(MMA_{39}-*co*-$AzMA_9$) copolymer, the PEEA-≡ and the coupled product (Table 5), it can be concluded that the "click" coupling reaction proceeded successfully. Just as for the block copolymers, it was found that the "click" reaction was again completed in a short time interval. Also in this case, a bimodal GPC curve is obtained after the coupling reaction because an excess of PEEA-≡ was used (not shown). Unfortunately, because of the high PEEA content of the resulting graft copolymer, selective precipitation to separate the graft copolymer from PEEA-≡ was not possible, but the pure graft copolymer was finally obtained by removing the excess of PEEA-≡ by preparative GPC.

In a next "click" coupling reaction (see Table 5, entry 15), the copper concentration was lowered 10 times in comparison to entry 13, while the exper-

iment was still performed at room temperature. In this case, the coupling reaction is not fully completed after 5 min, as a (small) additional increase of M_p can be noted in the analysis of the samples taken at a longer reaction time (not shown). GPC analysis indicates similar molecular weights for both reactions (Table 5, entry 13 and 15).

To our knowledge, this is the first example of the controlled synthesis of a graft copolymer using ATRP and the "click" coupling strategy, starting from an azide-containing polymeric backbone. Although other groups have reported on the combination of controlled ring-opening polymerization and "click" chemistry [36–38], using ATRP significantly broadens the range of accessible graft copolymers. Moreover, using ATRP for the preparation of the side chain polymer offers the opportunity to introduce various architectures (e.g. block copolymers) as the side chain of the graft copolymers.

4. Conclusions

In this paper, it was confirmed that ATRP is a particularly suitable polymerization technique for combination with the "click" 1,3-dipolar cycloaddition reaction of azides and terminal alkynes, as it permits to introduce both alkyne and azide functionalities into a polymer chain. Alkyne end group functionalities were introduced *via* an alkyne-containing initiator, while azide end group functionalities can be obtained *via* nucleophilic substitution of the bromide end group into an azide. Pendant azide groups can be introduced by copolymerization with an azide containing monomer. In the present study, the azide containing monomer AzMA was copolymerized with MMA, yielding a random copolymer. The controlled behavior of the (co)polymerization reactions was demonstrated.

Block copolymers were obtained by "clicking" PEEA-≡ with PiBA–N_3. The reaction showed to be both quantitative and fast. After selective precipitation (PEEA-≡ was used in excess) and deprotection of the PEEA segment by a heating step, the desired amphiphilic PAA-containing block copolymer was obtained. *Amphiphilic graft copolymers* were prepared by "clicking" linear PEEA-≡ onto a polymer containing multiple azide functions, followed by deprotection of the PEEA side chains. Effective coupling of the PEEA-≡ chains onto the poly(MMA-*co*-AzMA) copolymer was observed. The "click" coupling reactions were found to be surprisingly fast even at lower copper concentration (0.3 equivalent to alkyne functions).

In summary, it has been shown that the combination of ATRP and the copper(I) catalyzed 1,3-dipolar cycloaddition reaction of azides and terminal alkynes is a powerful tool for the modular synthesis of block copolymers and graft copolymers. Using the 1-ethoxyethyl protecting group, the application field was broadened with the synthesis of amphiphilic polymer structures with PAA segments.

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