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Two tandem multicomponent reactions for the synthesis of sequence-defined polymers

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Multicomponent polymerizations have become powerful tools for the construction of sequence-defined polymers. Although the Passerini multicomponent reaction has been widely used in the synthesis of sequence-defined polymers, the tandem usage of the Passerini multicomponent reaction and other multicomponent reactions in one-pot for the synthesis of sequence-defined polymers has not been developed until now. In this contribution, we report the tandem usage of the Passerini three-component reaction and the three-component amine-thiol-ene conjugation reaction in one pot for the synthesis of sequence-defined polymers. The Passerini reaction between methacrylic acid, adipaldehyde, and 2-isocyanobutanoate was carried out, affording a new molecule containing two alkene units. Subsequently, an amine and a thiolactone were added to the reaction system, whereupon the three-component amine-thiol-ene conjugating reaction occurred to yield a sequence-defined polymer. This method offers more rapid access to sequence-defined polymers with high molecular diversity and complexity.

multicomponent polymerizations, multicomponent reaction, sequence-defined polymers, Passerini reaction

1 Introduction

The development of efficient methods for the synthesis of polymers with novel structures and unique properties is of great academic significance and industrial implication [1–11]. There are numerous synthetic strategies that can control the topological [12–20] and sequence structures of polymers [16,21–23]. Among these strategies, multicomponent reactions have become powerful tools for the fabrication of macromolecules with controlled sequences because of their high efficiency, functional group tolerance, atom economy, and step economy [24–28]. Multicomponent reactions are performed in one pot and occur in a specific order. They do not require the isolation of intermediates, and reactive intermediates formed in the first step can directly undergo the next *in situ* reaction, thereby selectively affording complicated structures [4,8]. The Passerini reaction is a multicomponent reaction involving a carboxylic acid, an isocyanide, and an aldehyde. This reaction has many advantages, such as mild reaction conditions, high efficiency, functional group tolerance, and atom economy [8,26]. Since Meier first introduced the use of the Passerini multicomponent reaction for the synthesis polymers, Passerini reactions have been extensively used in the synthesis of sequence- defined polymers. For example, Meier *et al*. [8] combined the Passerini three-component reaction and olefin metathesis for the preparation of poly[1-(alkyl carbamoyl)alkyl alkanoates], a new class of polyesters with amide moieties in the side chain, from renewable resources. Li *et al*. [23] reported a facile method for the synthesis of multiblock copolymers consisting of poly(ethylene glycol) (PEG) and poly(esteramide) segments with defined side

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group sequences via multicomponent polymerization based on the Passerini reaction. On the other hand, the multicomponent reaction between a thiolactone, an amine and an alkene, which is an amine-thiol-ene conjugation, can be carried out with high efficiency under mild conditions. The reaction has high functional group tolerance as evidenced by Du Prez's [29–32] and our experiments [25,33,34], and is therefore a very promising method for the synthesis of functional and sequence-controlled polymers.

We envisaged that the Passerini three-component reaction and the three-component amine-thiol-ene conjugation reaction between a thiolactone, an amine and an alkene can be carried out in tandem in one pot because the reactions require similar reaction conditions, do not require any catalyst, and proceed with high efficiency. The two tandem multicomponent reactions would more rapidly afford sequence-defined polymers with more components, diversity and functionality.

2 Experimental

2.1 Materials

N,*N*-dimethyl-1,3-propanediamine (DMPDA, 99%), methacrylic acid (99%), 1-butanethiol (99%) and sodium periodate (98%) were purchased from Alfa Aesar (USA). *DL*-homocysteine thiolactone hydrochloride (99%), acetyl chloride (98%), and 4,7,10-trioxa-1,13-tridecanediamine (97%) were purchased from Sigma-Aldrich (USA). Allyl chloroformate (98%), adipoyl chloride (98%) and 1,2-cyclohexanediol (98%) were purchased from TCI. Triethylamine (99.5%) and 2,2-dimethoxy-2-phenylacetophenone (DMPA, 99%) were purchased from Aladdin (USA). Ethyl isocyanoacetate (99%) was purchased from Adamas-beta (China). DMSO-d_6 (99.8 atom% D) and chloroform-*d* (99.8 atom% D) were purchased from J&K (China). Anhydrous sodium sulfate (99%), sodium hydroxide (96%), *n*-hexane (97%), ethyl acetate (99.5%), methanol (99.7%), dichloromethane (99.5%), 1,4-dioxane (99%) and anhydrous diethyl ether (99.7%) were purchased from Sinopharm Chemical Reagent Co. Ltd. (SCRC, China). Tetrahydrofuran (SCRC, 99%) was purified by distillation. Other reagents were used as received.

2.2 Characterizations

All NMR spectra were recorded on a Bruker AV300 NMR (Germany) spectrometer (resonance frequency of 300 MHz for ^{1}H and 75 MHz for ^{13}C) operated in the Fourier transform mode. Molecular weights and molecular weight polydispersity indices (PDIs) were measured with a Size Exclusion Chromatography (SEC) instrument (Waters, USA). The system was equipped with a PL-RI Differential Refractive Index (DRI) detector, PL-BV 400RT Viscometer (Visc) and a Precision Detectors PD2020 Light Scattering (LS) Detector. LiBr/ DMF solution (0.1%) with a flow rate of 1.0 mL/min was used as the eluent. The molecular weights were calibrated against polystyrene standards. Mass spectrum analysis was performed by using a liquid chromatography-mass spectrometry (LC-MS) instrument (LTQ Orbitrap XL, Thermo Scientific, USA). The system was equipped with an electrospray ionization (ESI) source, and MS data were processed using Xcalibur software (2.1.0 SP1 build 1160).

2.3 Synthesis

2.3.1 Synthesis of *N*-acetylhomocysteine thiolactone

DL-homocysteine thiolactone hydrochloride (3.07 g, 20 mmol) was mixed with triethylamine (9.70 g, 96 mmol) in dichloromethane (50 mL) in ice bath, to form a suspension. Acetyl chloride (2.36 g, 30 mmol) was added dropwise over 30 min. The solution was stirred overnight at room temperature. Subsequently, the reaction mixture was diluted with dichloromethane (20 mL), filtered, washed with brine (30 mL×2), and extracted with dichloromethane (40 mL×2). The organic layer was dried with anhydrous Na_2SO_4. The product was further purified by silica gel column chromatography using ethyl acetate as the eluent. The yield was 65%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.931 (m, 1H), 2.029 (s, 3H), 2.895 (m, 1H), 3.301 (m, 2H), 4.527 (m, 1H), 6.171 (s, 1H).

2.3.2 Synthesis of *N*-(allyloxy)carbonylhomocysteine thiolactone

DL-homocysteine thiolactone hydrochloride (3.07 g, 20 mmol) was added to a suspension of $NaHCO_3$ (8.42 g, 100 mmol) in 1,4-dioxane/H_2O (1:1, *v*/*v*, 50 mL), and the mixture was stirred for 30 min. Subsequently, a solution of allyl chloroformate (4.85 g, 40 mmol) in 1,4-dioxane (5 mL) was added over 20 min. After the reaction mixture was stirred overnight at room temperature, the reaction mixture was washed with brine (100 mL) and extracted with ethyl acetate (150 mL×3). The organic layer was dried with anhydrous Na_2SO_4. The product was further purified by silica gel column chromatography using CH_2Cl_2/MeOH (49:1, *v*/*v*) as the eluent. The yield was 47%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.018 (m, 1H), 2.886 (m, 1H), 3.299 (m, 2H), 4.338 (m, 1H), 4.583 (d, 2H), 5.216–5.353 (m, 3H), 5.930 (m, 1H).

2.3.3 Synthesis of *N*,*N*-bis(2-oxotetrahydrothiophen-3-yl) adipamide

DL-homocysteine thiolactone hydrochloride (6.1 g, 40 mmol) was added to a suspension of $NaHCO_3$ (13.44 g, 150 mmol) in 1, 4-dioxane/H_2O (2:1, *v*/*v*, 120 mL), and the mixture was stirred for 30 min. After adipoyl chloride (3.4 g, 18.5 mmol) was added dropwise over 30 min, the mixture was stirred overnight at room temperature. After filtration, the residue was dissolved in water (250 mL). The product

was obtained as a white powder by filtration and dried in vacuum. Yield was 16%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.488 (s, 4H), 2.108 (m, 6H), 2.382 (m, 2H), 3.316 (m, 4H), 4.586 (m, 2H), 8.165 (d, 2H).

2.3.4 Synthesis of adipaldehyde

$NaIO_4$ (13.85 g, 65 mmol) in hot water (60 mL) was added to silica gel (50 g) and stirred vigorously. Subsequently, a solution of 1,2-cyclohexanediol (5.81 g, 50 mmol) in CH_2Cl_2 (250 mL) was added dropwise to the suspension, and the reaction was stirred for 24 h at room temperature. The mixture was filtered, and the silica gel was washed with CH_2Cl_2 three times. Adipaldehyde was obtained as colorless oil after the removal of CH_2Cl_2. The yield was 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.663 (m, 4H), 2.486 (m, 4H), 9.786 (s, 2H).

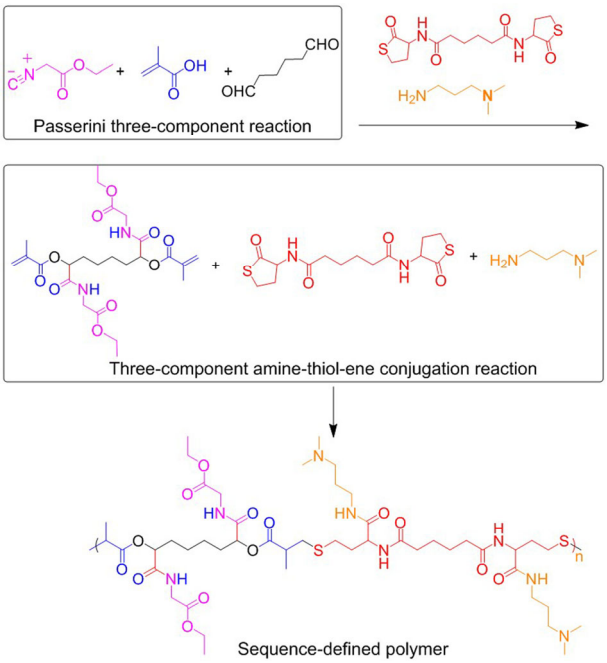
2.4 Two tandem multicomponent reactions in one pot

Methacrylic acid (86.0 mg, 1.0 mmol), adipaldehyde (57.0 mg, 0.50 mmol) and ethyl isocyanoacetate (135.0 mg, 1.2 mmol) were dissolved in CH_2Cl_2 (1 mL) and stirred at room temperature for 24 h. Subsequently, *N*,*N*-bis(2-oxotetrahydrothiophen-3-yl) adipamide (172.0 mg, 0.50 mmol) and *N*,*N*-dimethyl-1,3-propanediamine (122.0 mg, 1.2 mmol) in THF (4 mL) were added to the solution. After an additional 48 h at 40 °C, the polymer was isolated by precipitation in excess diethyl ether and dried under vacuum.

Methacrylic acid (86.0 mg, 1 mmol), adipaldehyde (57.0 mg, 0.5 mmol) and ethyl isocyanoacetate (135.0 mg, 1.2 mmol) were dissolved in CH_2Cl_2 (1 mL) and stirred at room temperature for 24 h. Subsequently, thiolactone (*N*-acetylhomocysteine thiolactone or *N*-(allyloxy) carbonylhomocysteine thiolactone, 1.0 mmol), 4,7,10-trioxa-1,13-tridecanediamine (110.0 mg, 0.5 mmol), and triethylamine (10 mg, 0.1 mmol) in THF (4 mL) were added to the reaction system. After an additional 48 h at 40 °C, the polymers were isolated by precipitation in excess diethyl ether and dried under vacuum.

3 Results and discussion

The tandem Passerini three-component reaction and three-component amine-thiol-ene conjugation reaction are outlined in Scheme 1. First, the Passerini three-component reaction between methacrylic acid, adipaldehyde and ethyl isocyanoacetate produced a new molecule with an alkene unit at both ends. Subsequently, a thiolactone and an amine were added to the reaction system. The amine can ring-open the thiolactone to give a thiol-containing molecule, which can immediately react with 4,7,14,17-tetraoxo-3,18-dioxa-6,15-diazaicosane-8,13-diyl bis(2-methylacrylate) (formed in the Passerini three-component reaction), thereby forming a sequence-defined polymer via two tandem three component



Scheme 1 Outline of the synthesis of a sequence-controlled polymer via tandem multicomponent reactions.

reactions in one pot. The Passerini three-component reaction between methacrylic acid, adipaldehyde and ethyl isocyanoacetate was carried out in CH_2Cl_2 at room temperature, and NMR spectroscopy was used to follow the progress of reaction, as shown in Figure 1. The Passerini three-component reaction involves a trimolecular reaction between the isocyanide, the carboxylic acid, and the aldehyde in a sequence of nucleophilic additions. After the nucleophilic additions, the chemical shift of the CH_2 unit (h) in adipaldehyde changes from 2.42 to 1.91 ppm, the chemical shift of the CH_2 unit (d) in ethyl isocyanoacetate changes from 4.25 to 4.19 ppm, and the chemical shifts of the methacrylic unit (b, a) change from 2.00, 5.58, 6.16 to 1.95, 5.61, 6.20 ppm, respectively, as shown in Figure 1(A). Based on integral values, the acid conversion reaches 94.6% after 24 h. In the ^{13}C spectra, after reaction for 24 h, the peaks for the carbons of Nos. 10, 11 and 12 in adipaldehyde almost completely move from 202.5, 43.3, 21.3 to 73.8, 31.7, 24.1 ppm, respectively. The chemical shifts of carbons Nos. 5 and 6 in ethyl isocyanoacetate change from 163.7, 63.1 to 170.1, 41.0 ppm, respectively, and the peak of the methacrylic unit (4) almost completely moves from 171.0 to 166.0 ppm, as shown in Figure 1(B). All of these results indicate that the Passerini three-component reaction between methacrylic acid, adipaldehyde, and ethyl isocyanoacetate *in situ* forms an intermediate molecule with two alkene units in a very high yield.

Du Prez's and our investigations have shown that primary amines do not react with the electron-deficient carbon-

carbon double bond of methacrylate without a catalyst. However, primary amines are able to ring-open a cyclic thiolactone, thereby releasing a thiol, whereas secondary and tertiary amines do not perform this reaction [25,31,35]. On the other hand, the thiol can react with methacrylate very efficiently in the presence of a nucleophile such as a tertiary amine [35,36]. Therefore, *N*,*N*-bis(2-oxotetrahydrothiophen-3-yl) adipamide and *N*,*N*-dimethyl-1,3-propanediamine (DMP-DA) were added to the completed Passerini three-component reaction system. We expected that the following would happen: DMPDA does not react with methacrylate [25], but it causes the ring-opening of *N*,*N*-bis(2-oxotetrahydrothiophen-3-yl) adipamide to give a thiol-intermediate. The latter is very likely to react with the double bond of methacrylate via a Michael addition reaction, thereby producing a sequence-defined polymer, as shown in Scheme 1 and Figure 2.

The thiol unit is very reactive toward the carbon–carbon double bond of the methacrylate unit [36,37]. In the Michael addition based thiol-ene click reaction, a proton is abstracted from the thiol unit to give a thiolate anion. The thiolate anion is generally a strong nucleophile, and it readily adds to the electron-deficient carbon-carbon double bond of methacrylate, yielding a carbon-centered anionic intermediate. The latter can abstract a hydrogen to yield a thioether as the product, as shown in Scheme 1 [36]. The signals due to the methylene unit of methacrylate (at 5.7, 6.2 ppm) are very weak in 48 h, as shown in Figure 2. Additionally, the peaks at 135 and 127 ppm for the carbons involved in the C=C double bond of methacrylate almost shift to 40 (j) and 35 (l) ppm as shown in the ^{13}C NMR spectrum (Figure 2(B)). Based on the integral values in the ^{1}H NMR spectrum, the conversion of the double bond of methacrylate reaches ~95% after 48 h. We also used SEC to trace the sequence-defined polymer obtained after performing the amine-thiol-ene conjugation for 48 h. The corresponding sequence-defined polymer has a molecular weight of 13.7 kDa and a polydispersity of 3.1, as shown in Figure 2(C).

Moreover, these tandem three-component reactions can be extended to prepare sequence-defined polymers with functional side units (such as a clickable alkene unit) as shown in Scheme 2. When *N*-(allyloxy) carbonylhomocysteine thiolactone and 4,7,10-trioxa-1,13-tridecanediamine are used in the second multicomponent amine-thiol-ene conjugation reaction, the sequence-defined polymer formed has clickable alkene side units as shown in Scheme 2. The sequence-defined polymer with clickable alkene side unit obtained via two tandem multicomponent reactions has a molecular weight of 49.8 kDa and polydispersity of 2.03 after a reaction time of 48 h, as shown in Figure 3. It should be noted that, although the alkene units can readily react with thiols via a radical-mediated thiol-ene click reaction, here the thiol-intermediate does not react with the alkene side units because there is no radical source in the three-component polymerization system [33,36]. As shown in Figure 4, it is very clear that the signals for the alkene unit at 5.8 and 5.2 ppm survive after reaction for 48 h. These clickable alkene side units can be used as reacting units for the modification of the sequence-defined polymer via thiol-ene click reaction. Here we used benzene thiol as a model molecule to modify the polymer. It is clear that all of the signals arising from the benzene thiol molecule appear in the sequence-defined polymer after modification.

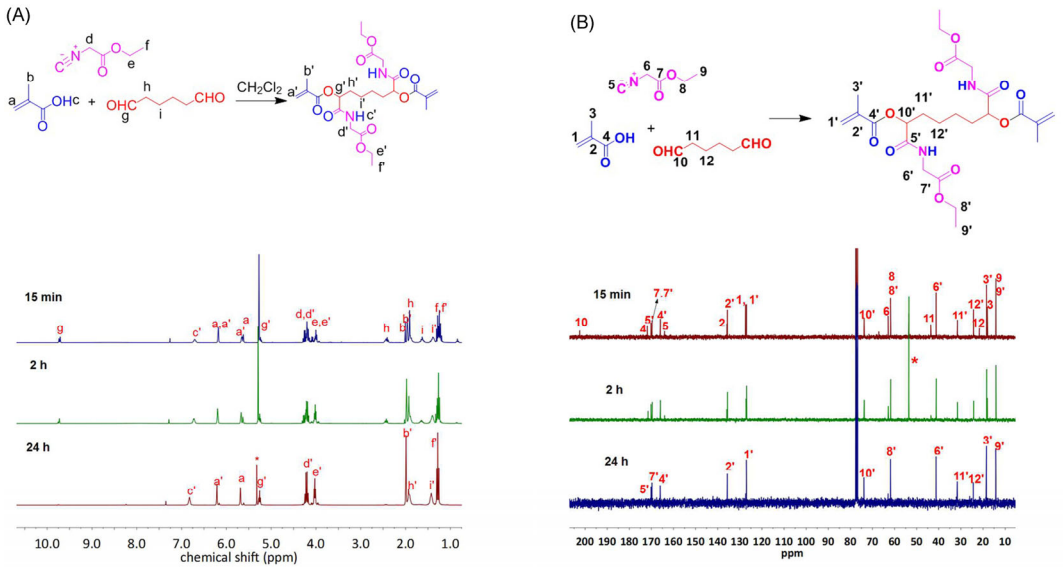


Figure 1 ^{1}H NMR (A) and ^{13}C NMR (B) spectra in $CDCl_3$ regarding the Passerini three-component reaction between methacrylic acid, adipaldehyde, and ethyl isocyanoacetate at different reaction times. * is CH_2Cl_2.

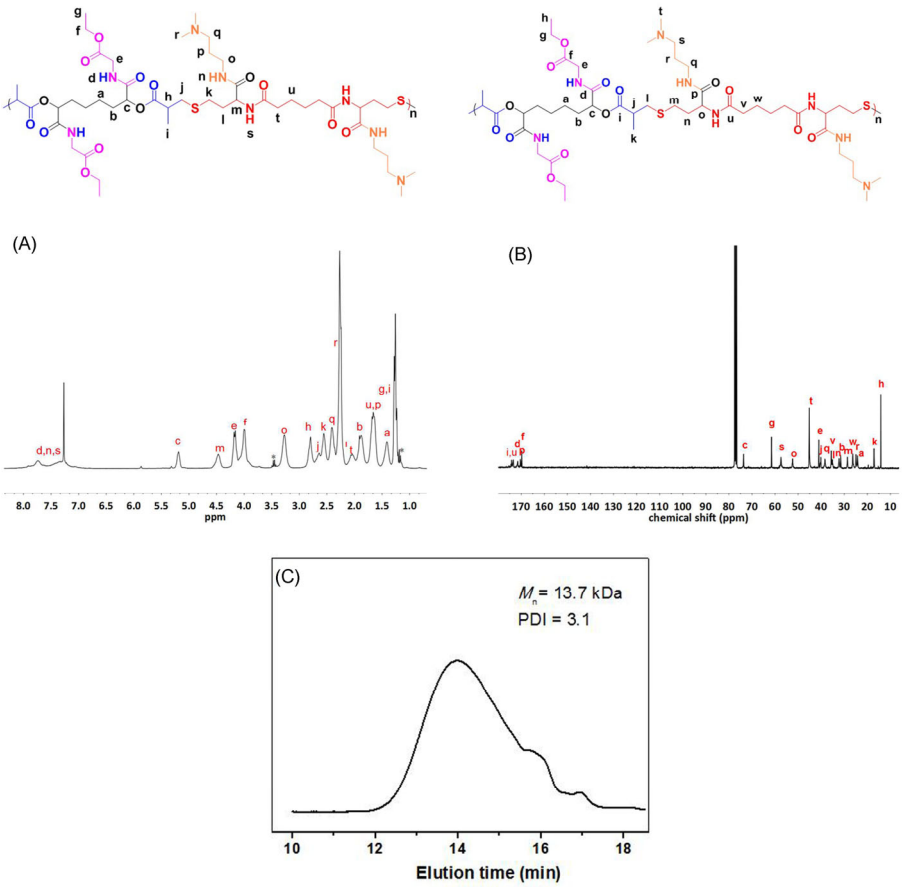
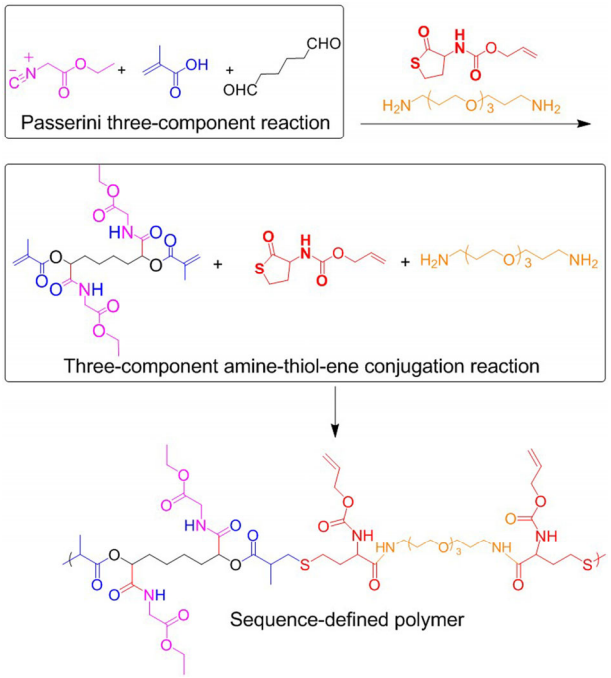


Figure 2 ^{1}H NMR (A) and ^{13}C NMR (B) spectra in $CDCl_3$ and SEC trace (C) of the polymer obtained via two tandem multicomponent reactions.



Scheme 2 Outline of the synthesis of a sequence-controlled polymer with functional side units.

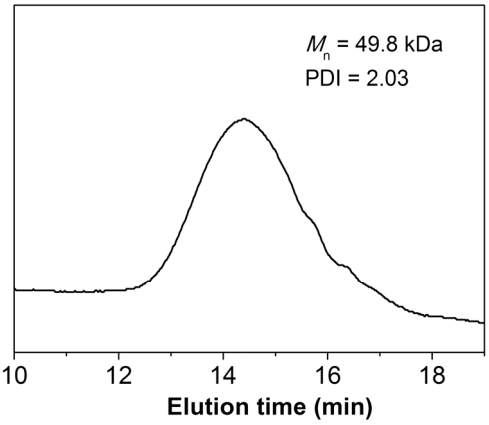


Figure 3 SEC trace of the sequence-defined polymer with clickable alkene side units obtained via two tandem multicomponent reactions.

4 Conclusions

In summary, we have reported a strategy consisting of tandem two multicomponent reactions for the synthesis of sequence-controlled polymers. Moreover, the novel multicomponent reactions can be extended to multicomponent polymerizations for the preparation of a series of sequence-

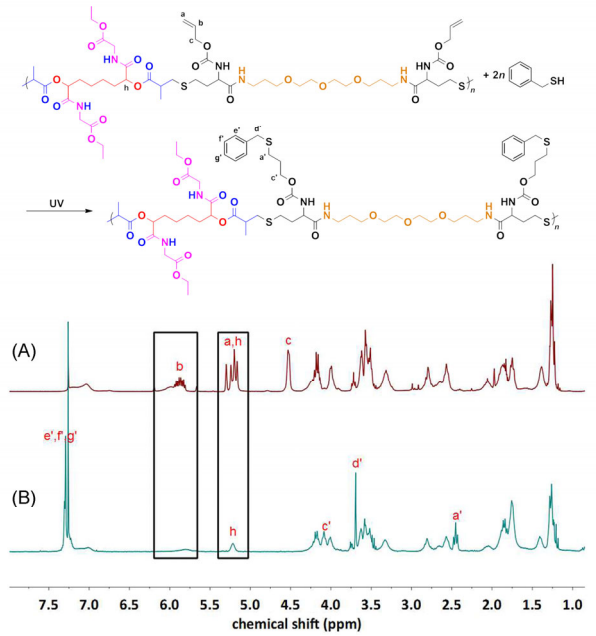


Figure 4 ^{1}H NMR spectra of the obtained sequence-defined polymer before (A) and after (B) modification by thiol-ene click chemistry.

defined functional polymers with high molecular weights. Functional side groups could easily be introduced into the polymers by effective post modification.

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