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Precision Multisegmented Macromolecular Lineups: A Display of Unique Control over Backbone Structure and Functionality

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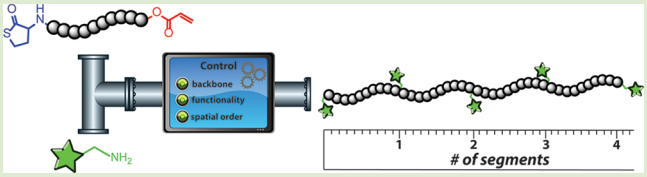
Supporting Information

ABSTRACT: A practical synthesis of unique, precisely decorated, multisegmented block copolymers was elaborated via amine-thiol−ene conjugation. By mixing the thiolactone-acrylate heterotelechelic precursor polymer with selected amines, a library of multisegmented species was obtained, featuring a high level of control over backbone structure and spatial arrangement of side chain residues. Ranging from glycosylated to amphiphilic materials, these macromolecular lineups have been analyzed by LCxSEC DOSY-NMR, and DLS, revealing the particular properties of these macromolecular structures.



Sustained development in polymer synthesis leading to groundbreaking innovations, including controlled polymerization methods and "click" chemistries, enabled scientists to master the exact structure and properties of synthetic macromolecules, and establish relevant structure−property relationships.[1−4] Hence, the polymer community developed a broad spectrum of complex macromolecular architectures for advanced material applications, ranging from block to cyclic to graft copolymers.[5,6] Within this research area, multisegmented block copolymers receive an increasing amount of attention because the possibility to regulate the polymer microstructure remains a challenging topic from a molecular perspective, intriguing synthetic chemists worldwide.[7,8]

Two distinct synthetic strategies to obtain well-controlled multisegmented block copolymers were developed. A first established procedure utilizes controlled radical polymerization techniques (CRP) through sequential addition of (different) monomers in a one-pot fashion.[9−11] Relying on the high end-group fidelity of these CRP strategies, structures ranging from deca- through icosa-blocks were obtained. However, as Sawamoto[12] and Meyer[13] expressed the necessity for the precision design of chemical functionalities throughout the polymer structure, it is practically impossible to incorporate strictly one functional handle between each segment, as exemplified by midchain functionalized block copolymers[14,15] or styrene-maleimide copolymerizations[16] and corresponding multisegmented block copolymers.[17] Therefore, our ongoing research focuses on a second methodology via efficient conjugation chemistries. Multisegmented block copolymers are indeed also obtained through step-growth coupling of the end-groups of a heterotelechelic macromonomer.[18] In spite of the synthetic simplicity this approach offers, already explored coupling reactions (e.g., CuAAC,[19] ATRC[20]) do not provide the option to incorporate in a straightforward manner any desired functionality into the macromolecular lineups. In this regard, we targeted a strategy that enables the synthesis of polymer chains, with a tailored backbone structure (segment length and composition) and readily diversified functionalities, positioned at each segment connection and thus equally spaced along the backbone. To the best of our knowledge, no synthetic procedure, yielding periodically functionalized precision block copolymers, has been reported.

Two main prerequisites for an effective synthesis of the targeted polymer structures are (*i*) the preparation of narrow-disperse heterotelechelic macromonomers, featuring a high end-group fidelity and (*ii*) the efficient coupling of the individual segments, with concomitant introduction of the desired functional residue. While Cu(0)-mediated polymerization was utilized in response to the former requirement,[21−23] the characteristics of the in-house developed amine−thiol−ene conjugation[24,25] match the second requirement. Indeed, the thiolactone group serves as a latent thiol functionality through nucleophilic lysis with a functional amine, while in the presence of an acrylate, the liberated thiol is consumed in a conjugate (Michael-) addition[26,27]

Application of this one-pot, additive-free, step-growth coupling protocol for the targeted species (Scheme 1) demands a multigram synthesis of a heterotelechelic thiolactone-acrylate macromonomer (Scheme 2). Following the large-scale synthesis of a thiolactone-containing initiator (Scheme S1 and Figure S1), the high-T_g polymer poly(isobornyl acrylate) (PiBA) was prepared for the first time via Cu(0)-mediated polymerization (Scheme S2 and Figure S2) to facilitate purification. Subsequently, the bromine end-group was transformed into an acrylate (Schemes S3 and S4), yielding the heterotelechelic polymer with the required stringent purity as

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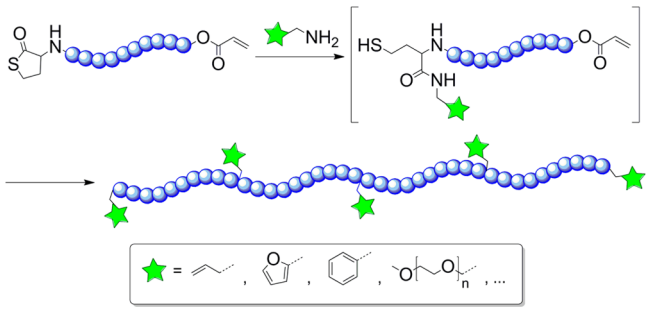
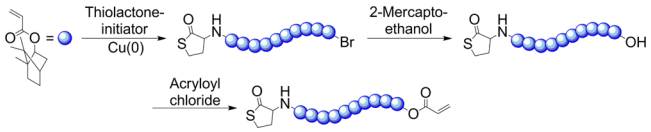
Scheme 1. General Concept for the Synthesis of Functionalized Multisegmented, Macromolecular Lineups via the Amine−Thiol−ene Conjugation from a Thiolactone-Acrylate Hetero-Telechelic Macromonomer



Scheme 2. Synthetic Strategy To Obtain the Hetero-Telechelic Thiolactone-Acrylate Macromonomer, Starting from a Thiolactone Initiator and a Two-Step Modification Reaction



confirmed by NMR, SEC, and MALDI-TOF analysis (Figures S3−12).

Consequently, the macromonomers were effectively connected by treatment with the preferred amine in an equimolar ratio, or in small excess in case more volatile amines are used (Scheme S5), in a minimal amount of THF or chloroform (160 mg/0.1 mL). The success of this unassisted segment linking was featured by an increase in molar mass and broadening of the dispersity (Figure 1). Independently, diffusion-ordered NMR spectroscopy (DOSY) and differential scanning calorimetry (DSC) denoted the same result, respectively, by a decrease in diffusion coefficient (Figure 1) and an increase in glass transition temperature (T_g; Figure S13).

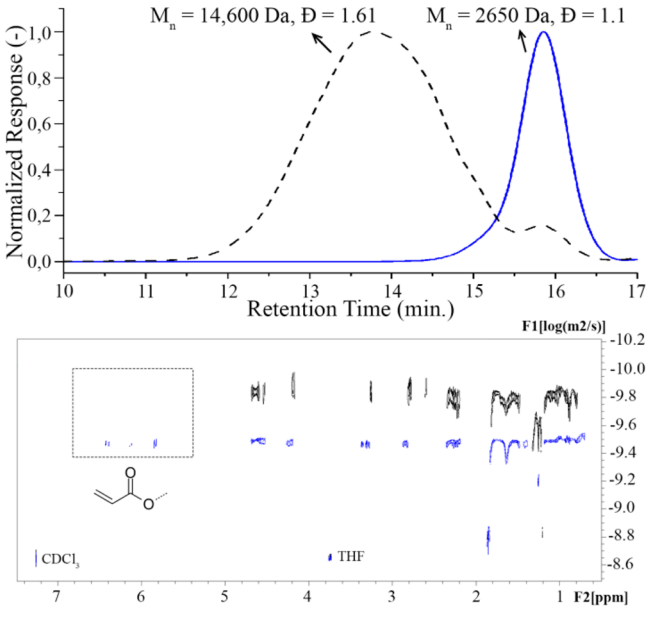


Figure 1. Corresponding SEC traces (top) and DOSY-NMR (bottom) for the thiolactone-acrylate heterotelechelic macromonomer (solid blue) and the *n*-octylamine (Table 1, entry 1) functionalized multisegmented block copolymer (dashed black).

To determine the average number of segments in those periodically functionalized precision polymers, size exclusion chromatography (SEC, universal calibration) was applied, evidencing a multisegmented block copolymer with a number-average molecular weight corresponding to about 10 linked precursor units. The prepolymer, obtained by CRP methods, inherently introduces a small distribution effect of side-chain functionalities. A polymeric library of on-demand precisely decorated polymers was created, strengthening the general applicability of this strategy. For this, different functionalized amines have been used, enabling the direct introduction of double bonds, furan, aromatic or PEGylated moieties at each segment connection, without the need for protection and deprotection strategies and with no interference of the polymerization process. The latter illustrates the functional group tolerance of this conjugation approach (Table 1).

Table 1. Molecular Weights and Dispersities of Functionalized Multisegmented Block Copolymers Using Different Amines

entry	amine	M_n[a] (kDa)	$Đ$[a]
1	*n*-octylamine	14.6	1.61
2	allylamine	11.1	1.62
3	2-(1-cyclohexenyl)ethylamine	10.8	1.61
4	furfurylamine	8.9	1.52
5	benzylamine	10.6	1.58
6	PEG-amine (800 Da)	9.2	1.51
7	PEG-amine (2000 Da)	6.2	1.62

[a]Molecular weights and dispersities determined by SEC in THF vs polystyrene standards.

To further extend the scope of this methodology and demonstrate its versatility, the use of postpolymerization modification (PPM) reactions on those structures was envisaged. After the connection of the segments, the crude reaction mixture essentially consists of the targeted species and a minor amount of residual amine. Without intermediate purification, two metal-free PPM reactions were examined in this context: on the one hand, the radical thiol−ene reaction between *n*-octanethiol and an alkene-containing multisegmented block copolymer (Scheme S6 and Table 1, entry 2), and on the other hand, the Diels−Alder reaction between *N*-benzylmaleimide and the furan containing copolymer analogue (Scheme S7 and Table 1, entry 4). The disappearance of the distinct signals in the ^{1}H NMR spectra and the apparent shift of the SEC traces indeed confirm the successful outcome of both PPM reactions (Figures S14 and S16).

Finally, pushing the boundaries of this strategy to material design, two different applications were set forth. In a first case, the synthesis of a glycosylated macromolecular lineup was intended. Through specific interactions with lectins, these materials have acquired an intriguing interest due to their ability to mimic biological functions of natural carbohydrate-containing polymers.[28] As the applied galactopyranose-based sugar moieties are not well soluble in the concentrated polymerization mixture, when introduced directly via the step-growth coupling, these functionalities were anchored onto the polymer chain via the radical thiol−ene PPM reaction.

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SEC- and NMR-analysis demonstrated again the success of this synthetic strategy (Figure S15).

A second appealing application of these structures is located within the field of amphipilic polymer materials. As was shown that sophisticated polymeric structures are beneficial at stabilizing emulsions or dispersions,[29] we focused on the synthesis of amphiphilic graft copolymers by the use of our newly developed strategy. In this way, the hydrophobic PiBA-precursor was directly solubilized in THF and reacted with an amine-derived PEG-compound (800 or 2000 Da, entries 6 and 7). To analyze this mixture of three different polymer structures (precursor polymer, PEG-amine and the PEG-functionalized multisegmented block copolymer), LCxSEC measurements were performed.

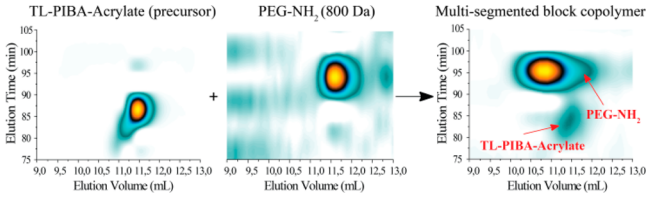

Figure 2. LCxSEC analysis of the separate polymers (TL-PiBA-acrylate and PEG-amine) and the obtained amphiphilic multi-segmented block copolymer with precisely grafted PEO-segments (Table 1, entry 6).

Figure 2 displays both the precursor and PEG(800)-amine starting materials, clearly showing the difference in molecular weight (*x*-axis) and polarity (*y*-axis) between both segments. A clear increase in molecular weight and dispersity, compared to the starting precursor polymer, can be observed along with an increase in polarity. It should be noted that, in the corresponding amphiphilic multisegmented block copolymer, only trace amounts of the residual starting materials remain (<1%), demonstrating the high yield and coupling efficiency. To evidence the assembly behavior of the targeted amphiphiles (entry 6), the aqueous aggregate solution was analyzed by dynamic light scattering (DLS), showing an average hydrodynamic volume of 130 nm (PDI = 0.127; Figure S17).

In conclusion, this paper describes the first synthesis of precision functionalized multisegmented block copolymers. By the preparation of a thiolactone-acrylate heterotelechelic polymer in an upscalable way, a multisegmented macromolecular lineup was obtained via the nucleophilic ring-opening of the thiolactone unit by a functionalized amine and consecutive thiol-Michael addition. By the choice of the amine, a library of macromolecular compounds, with functionalities equally spaced across the polymeric backbone and ranging from PEG chains to reactive functional handles, were obtained. Moreover, PPM reactions provided access to a plethora of tailor-made, multisegmented lineups. Finally, these materials were applied in the construction of glycosylated and amphiphilic polymers. Due to these remarkable results, the presented methodology is considered as a breakthrough result in the precision design of macromolecular materials. Future work will focus on incorporating chemical handles that can induce self-organization of the polymer structure through supramolecular interactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; synthesis of initiator and polymers; kinetic study; and NMR, DOSY-NMR, MALDI-TOF, SEC, and DLS data are included. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.5b00231.

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Notes

The authors declare no competing financial interest.

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