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Selenolactone as a Building Block toward Dynamic Diselenide-Containing Polymer Architectures with Controllable Topology

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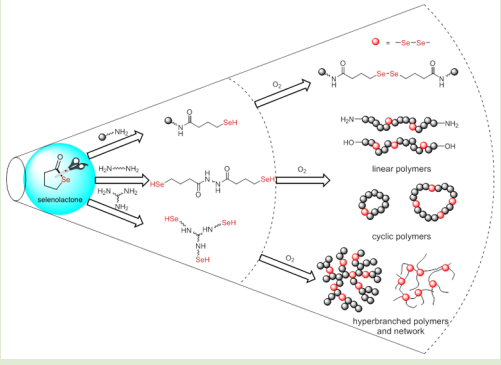
Supporting Information

ABSTRACT: A versatile protocol for the synthesis of a variety of multiresponsive diselenide-containing polymeric architectures was investigated. It consists of a one-pot, two-step process with the generation of a selenol by in situ nucleophilic ring opening of selenolactone with a broad range of amine-containing structures, followed by the transformation of the obtained compounds to the corresponding diselenide through a spontaneous oxidation coupling reaction. After elaboration of this one-pot reaction, a number of routes based on selenolactones have been developed for the successful synthesis of functional, linear, branched, cyclic, and cross-linked polymers via a mild, straightforward process. Moreover, the polymer end groups can be easily modified by changing the ratio of amine and selenolactone or sequential Michael addition of selenol to the methacrylic ester. At last, the self-healing properties of the diselenide-containing networks were determined by exposing a cut sample of the polymer to UV light.

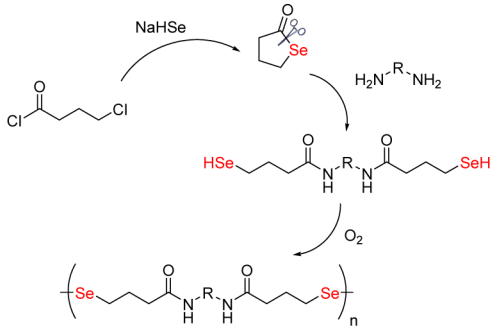


Diselenide-containing polymers recently attracted much interest in a wide range of applications as a result of their rapid response to external triggers, such as light or a reductive environment. Although reported for the first time almost 80 years ago,[1] these multiresponsive diselenide-containing polymers have only been developed in the past decade for their use in artificial enzymes,[2] controlled drug delivery,[3] and self-healing materials.[4] The synthetic routes toward diselenide-containing polymers include ring-opening polymerization of cyclic diselenide monomers,[5] polycondensation of alkalidiselenides with dihalides,[6] copolymerization of diisocyanate monomers with a diselenide-containing diol,[7] or A2+B3 type polycondensation of diselenide-containing diols.[8] Very recently, we also developed Se-RAFT synthesis to expand the synthetic utility of the valuable Se-containing polymers beyond the current state-of-the-art.[9]

Herein, we aimed for the in situ selenol generation, through a one-pot amine−oxidation coupling, which can serve as a new, quite versatile, and powerful protocol for the synthesis of diselenide-containing polymers with various architectures. In our methodology, selenolactone, which is the key precursor of selenol, is easily synthesized from sodium hydrogen selenide (NaHSe) on a multigram scale,[10] while the corresponding polymerizations with different commercial diamines are atom efficient, simple, and fast (Scheme 1).

Selenide monomers are exceptionally reactive intermediates with a rich history. In a related, but distinctly different,

Scheme 1. One-Pot Amine-Oxidation Conjugation for the Formation of Diselenide-Containing Polymer Architectures



approach, Mitchell,[11] Freda, and others have independently studied the ring-opening polymerization of cyclic diselenide monomers.[1b] However, these cyclic diselenide monomers have some disadvantages related to their synthesis, purification, and stability.

Similarly to selenolactone in this research, the thiolactone compound has become a famous synthon in polymer synthesis during the last 5 years, as it acts as a protected version of a thiol,

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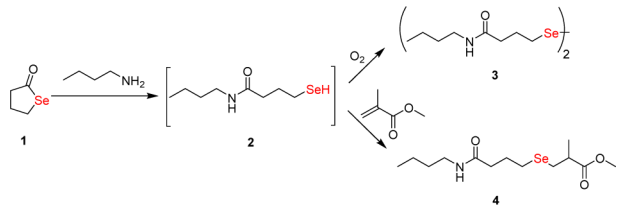
which after a ring-opening reaction by an amine can be further reacted by thiol−X reactions.[12] To the best of our knowledge, the use of selenolactones has never been explored in polymer synthesis, while it offers quite some potential in terms of the multiresponsive character of the obtained structures.

To demonstrate the potential of this new synthetic strategy for the synthesis of Se-containing polymeric materials and complex macromolecular architectures, the one-pot two-step reaction sequence was first performed on low molar mass model compounds (Scheme 2).

Scheme 2. Model of Amine-Oxidation and Amine−Selenol−Ene Conjugation: One-Pot Reaction between Butylamine and Selenolactone



γ-Butyroselenolactone **1** was treated with butylamine in THF, and the reaction mixture was exposed to air for the subsequent oxidative coupling of the selenol groups. Due to the high reactivity of amines toward selenolactones, an online ^{1}H NMR experiment was performed to monitor the consumption of **1** by a large shift of the signals of the corresponding $-SeCH_2-$ protons (from 3.51 to 2.87 ppm) and $-NHCH_2-$ protons (from 2.48 to 3.03 ppm). The obtained results indicated that the presence of an excess of amine is advantageous to speed up the reaction. Compound **1** was fully consumed after a few minutes after addition of 12 equiv of *n*-butylamine, compared to 10 h reaction time when using only 2 equiv (Figure S1A). Furthermore, the reaction speed was increased using tetrahydrofuran instead of chloroform as solvent (from 8 to 2.5 h for full conversion). Interestingly, in contrast to thiolactones,[13] secondary amines can also open the selenolactone ring at room temperature, although at lower rates, as demonstrated by the reaction with diethylamine (Figure S1B). Similarly, the speed of the reaction is increased by adding an excess of diethylamine. The conversions are around 80% and 20% when 15 and 1.5 equiv of diethylamine were used, respectively.

After aminolysis, the diselenide was formed instantaneously as a result of the high sensitivity of the selenol group to air (oxidation step). Moreover, as selenols are known for their high nucleophilic reactivity, an excess of methyl methacrylate (MMA) was added to the initial reaction mixture to allow for a subsequent selenol−Michael addition. An important conclusion drawn from this model study is that the amine-oxidation can be performed in the absence of any catalyst and gave the compounds directly, avoiding complicated synthesis and purification steps. The structures of **3** and **4** were confirmed by NMR and MS analysis (Figures S2−4). In the ^{77}Se NMR spectra, the selenium signal shifts from 465 to 299 (Figure S2c) and 297 ppm (Figure S4c) in the amine-oxidation reaction, demonstrating that the diselenides were formed. Also, the selenide signal as a result of the amine−selenol−ene reaction was detected at 145 ppm (Figure S3c).

Encouraged by the successful model study, we investigated the design of polymeric structures containing both diselenide bonds and amide groups. In a related study, Xu et al. recently reported the alcoholysis of isocyanates for the synthesis of linear structures starting from diselenide monomers.[4] In our case, as a selenolactone moiety can be considered as a precursor for the selenol functionality, the polymerization and functionalization can easily proceed by controlling the oxidant (e.g., oxygen) concentration or addition of Michael acceptors. First, 1,6-hexanediamine and 1,8-octanediamine were screened for the synthesis of linear polymers. Unfortunately, the obtained polymers were insoluble in common organic solvents, which are ascribed to the short chain length of these diamines and high concentration of hydrogen bonds. The use of the more polar 4,9-dioxadodecanediamine and 4,7,10-trioxatridecanediamine to open the selenolactone ring yielded a yellow powder. The purified polymers were soluble in DMA or DMSO and analyzed by SEC and NMR (Figures S6−8). The SEC chromatogram in DMA displayed a multimodal distribution. For the linear polymer obtained with 4,9-dioxadodecanediamine, an M_n of 5.0 kDa and $Đ$ of 1.75 were measured, while for the one with 4,7,10-trioxatridecanediamine, an M_n of 4.1 kDa and $Đ$ of 1.41 was obtained. In the ^{77}Se NMR spectra, the selenium signal was detected around 300 ppm (Figures S6 and S7), confirming the formation of the diselenide function. During the reaction, it is assumed that the polymers are terminated with selenol groups due to a small excess of used selenolactone, leading to a complete consumption of the diamine (confirmed by ^{1}H NMR spectra in Figures S6 and S7). Furthermore, a small amount of cyclic oligomers was detected at higher retention time, similar to recently reported results on the synthesis of diselenide-labeled cyclic polystyrene,[9c] which displayed multiple responses.

The use of a linear polyetheramine (Jeffamine D-2000) as macromolecular diamine was explored at different concentrations, and polymers with distinct M_n and $Đ$ were obtained (Figures S9−10). Based on the effective aminolysis of the selenolactone and subsequent spontaneous oxidative coupling of diselenols, a multiblock cyclic copolymer linked by several diselenide bonds and a monoblock cyclic polymer linked by only one diselenide bond were prepared in bulk and dilute conditions, respectively. These polymers could also be degraded under reductive or oxidative conditions (Figure S11).[9b] The SEC curve of the diselenide-labeled monoblock cyclic polymer was shifted to higher molecular weights under either reductive ($NaBH_4$) or oxidative conditions (H_2O_2), which also confirmed the cyclic topological structure. On the other hand, under the same conditions, the SEC curve of the diselenide-labeled multiblock cyclic copolymer was shifted to lower molecular weight but higher than the curve of the starting polymer. It should be noted that the degradation of the multiblock polymer, reduced by $NaBH_4$, was not perfect as indicated by SEC after several trials, due to side reactions during the reduction step.

This mild and efficient one-pot polycondensation process yielded a polymer with a polyamide/polydiselenide backbone and variable terminal groups by changing the ratio between the involved reagents. For example, when less than 2 equiv of selenolactone was used in the one-pot polycondensation reaction, amine end groups were obtained. On the other hand, the presence of an excess of 2-hydroxyethyl methacrylate (HEMA) yielded a hydroxyl-terminated polyamine/polydiselenide (Figure 1). While the residual trace of amine resonances in the ^{1}H NMR spectra (Figure 1A) confirmed the amine end group functionalities of the polymer, both the disappearance of

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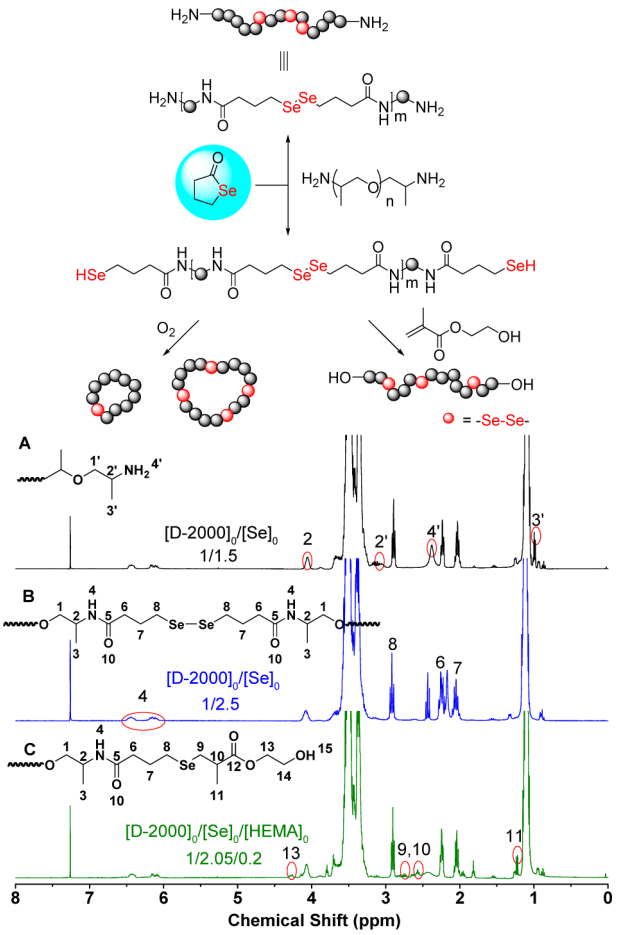

Figure 1. Stepwise polymerization of the selenolactone and Jeffamine D-2000 with or without HEMA in a one-pot process, yielding cyclic or linear polymers containing on the one hand diselenides and amide in the backbone and on the other hand different end groups (NH_2, OH).

the methacrylic signals and the presence of CH_3 signals originating from 2-hydroxyethyl methacrylate (labeled as 11 in Figure 1C) as a double peak demonstrated the hydroxyl end group functionalities. Moreover, the molecular weight of the polymer (M_n) can be controlled from 2.1 to 11.4 kDa by varying the ratio of amine and selenolactone. The polymers were further characterized by IR and SEC (Figures S13 and S15). It should be noted that MALDI-TOF analysis is not possible due to the instability of the diselenide bond during the ionization process.

By variation of the end group composition and molecular weight, different properties can be obtained leading to novel materials, e.g., the synthesis of hyperbranched and cross-linked structures, which have shown their potential use as anticancer agents and mild-responsive drug delivery vehicles.[8a,14] To further extend the scope of this methodology in material science, the synthesis of these structures was targeted by the use of the trifunctional Jeffamine T (400 $g \cdot mol^{-1}$) as a model compound. By application of the above-mentioned process, hyperbranched polymers containing amine or hydroxyl end group functionalities were synthesized by addition of the Jeffamine T to less than 2 equiv of selenolactone **I** or by adding HEMA (Figure 2).

The molecular weight of the hyperbranched polymers and thus their degree of functionality could be varied with the ratio of amine/selenolactone/HEMA (Figure S14). Interestingly,

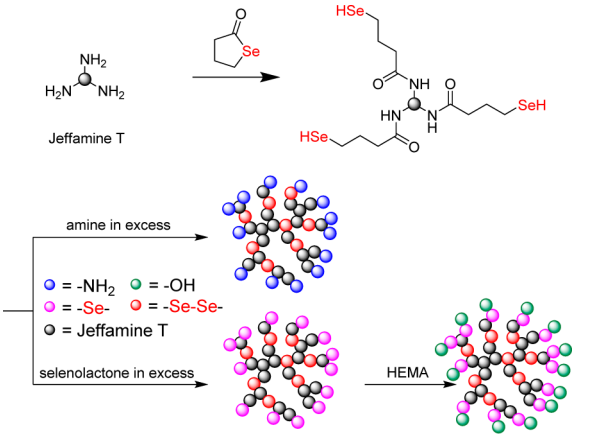

Figure 2. Schematic illustration of the formation of amine- or hydroxyl end-capped hyperbranched polymers starting from Jeffamine T.

when a ratio of the selenolactone/triamine higher than two was used, insoluble but swellable networks could be obtained. To explore the dynamic character of the diselenide bonds when exposed to UV light,[4,15] the self-healing properties of the networks, starting from Jeffamine T-5000, were determined by exposing a cut sample of the polymer to UV light for 10 min. Optical microscopy shows the disappearance of the applied cut (Figure 3). On the other hand, no healing occurred when the

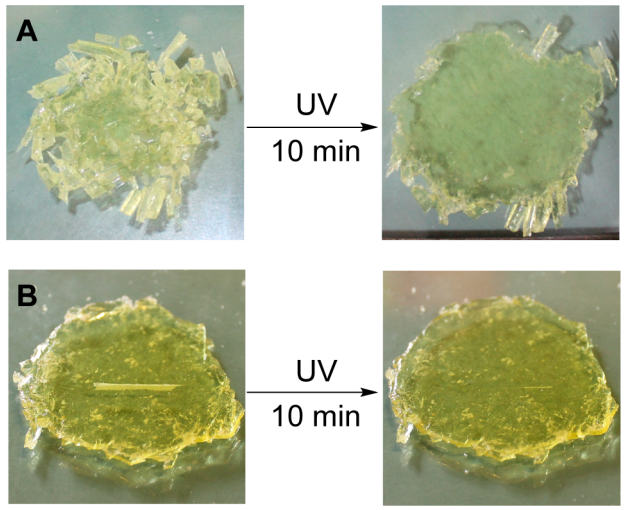

Figure 3. Photographs of the self-healing behavior of a cross-linked polymer network ($[Jeffamine\ T\text{-}5000]_0$/ $[Selenolactone]_0$ = 1:3.3) in air at room temperature. (A) Shred (left) and mended (right) states after irradiation for 10 min in a UV box. (B) Damaged sample and complete scar healing after irradiation for 10 min in a UV box.

fragments were stored in the dark for 12 h, which further indicates the fast photostimulated self-healing process of the material. The structure of these polymers was also confirmed by FTIR analysis (Figure S15). Additionally, thermogravimetric analysis (TGA) indicated that most of these polymers are stable up to 250 °C (Figure S16).

In conclusion, our process provides a straightforward and generally applicable method in which diselenide bonds can be easily introduced in several types of polymer architectures, avoiding thorough synthetic procedures including active diselenide intermediates. Furthermore, the high nucleophilic reactivity of the selenol offers multiple possibilities for

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postfunctionalization modifications. Besides the use of readily available low and high molar mass amines, this strategy could also be directly applied to many bioderived macromolecules with the formation of diselenide-containing biocompatible biopolymers. In general, in comparison to disulfide-containing polymers, diselenide-containing polymers display an increased bioactivity[16] and sensitivity to redox, light, and radiation.[14] Their further application in many responsive materials is therefore predicted.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.6b00944.

Experimental procedures; synthesis of diselenides and polymers; kinetic study; and IR, NMR, SEC, and TGA data (PDF)

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Notes

The authors declare no competing financial interest.

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