Polypeptides have been extensively utilized in drug delivery, tissue engineering, sensing, and catalysis. To prepare polypeptides for these applications, it is essential to control their molecular weights (MWs) as well as their end groups during the ring-opening polymerizations (ROPs) of amino acid N-carboxyanhydrides (NCAs). We recently reported hexamethyldisilazane (HMDS)-mediated, controlled NCA polymerization. This polymerization proceeds via a unique, trimethylsilyl carbamate (TMS-CBM) propagating group (Scheme 1a), which involves cleavage of the Si–N bond of HMDS during the initiation step. The resulting TMS-amine (red, Scheme 1a) opens the NCA ring at its CO-5 position to form a TMS-amide at the C-end while the TMS group (blue, Scheme 1a) is attached to the N-end to form a TMS-CBM (the propagating chain end). The propagation of polypeptide chains proceeds through the transfer of the TMS group from the terminal TMS-CBM to the incoming monomer and forms a new TMS-CBM propagating chain end (Scheme 1a). We postulate that when a N-TMS amine is used as the initiator, cleavage of its Si–N bond will generate an amine and a TMS group (Scheme 1b) that will subsequently form the corresponding amide at the C-end and a TMS-CBM at the N-end after NCA ring opening (Scheme 1b). Thus, chain propagation should proceed in the same manner as HMDS-mediated polymerization (Scheme 1a). Because a large variety of N-TMS amines are readily available, this method should allow facile functionalization of the C-termini of polypeptides (Scheme 1b).

To demonstrate this concept, N-TMS allylamine (1-TMS, 1 = allylamine, Scheme 1c) was utilized as the initiator for the polymerization of γ-benzyl-l-glutamate NCA (Glu-NCA) (Scheme 1b). As shown in Figure 1a, 1-TMS had remarkable control of Glu-NCA polymerization and gave poly(γ-benzyl-l-glutamate) (PBLG) with the expected MWs and narrow MWDs over a broad range of monomer/initiator (M/I) ratios (M/I = 20–300). The obtained M_n’s of PBLG at an M/I ratio of 20 and 300 were 4.6 × 10^3 and 7.01 × 10^3 g/mol, respectively, both of which were nearly identical to the expected M_n’s (4.4 × 10^3 and 6.57 × 10^3 g/mol, respectively). All polymerizations were finished within 12–24 h at room temperature under atmospheric pressure, in contrast to a few recently reported controlled polymerizations that require either reduced temperature or vacuum. The M_n’s of PBLG showed a linear correlation with the conversions of Glu-NCA, which were in good agreement with the expected M_n’s (Figure 1b). This experiment demonstrated that the propagation of PBLG chains proceeded through a living chain end. 1-TMS also showed remarkable control of polymerizations of ε-Cbz-l-lysine NCA (Lys-NCA) and resulted in poly(ε-Cbz-l-lysine) (PZLL) with the expected MWs and very narrow MWDs (Figure S1). Block copolypeptides, such as PZLL-b-PBLG, can also be readily prepared with the anticipated MWs and narrow MWDs via sequential addition of Lys- and Glu-NCA (Table S1 and Figure S2).

We next compared the polypeptides obtained through 1-initiated and 1-TMS-initiated Glu-NCA polymerizations. The PBLG resulting from 1-initiated polymerization at an M/I ratio of 20 had a broad MWD (M_w/M_n = 1.52) based on the MALDI-TOF MS analysis (red, Figure 1c). In contrast, a similar polymerization mediated by 1-TMS resulted in PBLG with a much narrower MWD (M_w/M_n = 1.17). The MALDI-TOF MS spectrum of the latter polymer showed a Poisson distribution centered at the exact number of repeating units of PBLG (Figure 1d).
N-TMS amines for Glu-NCA polymerization (M/I = 100)

<table>
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<tr>
<th>Initiator</th>
<th>Expected M_n (g/mol)</th>
<th>Obtained M_n (g/mol)</th>
<th>M_n/M_i</th>
<th>Conv. of NCA (%)</th>
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<tr>
<td>(2-TMS) N-HNTMS</td>
<td>21,900</td>
<td>23,500</td>
<td>1.26</td>
<td>&gt;99</td>
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<td>1.21</td>
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<td>1.18</td>
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References


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Figure 2. ESI-MS of equal molar mixture of 1-TMS and Lys-NCA.

Table 1. N-TMS Amines for Glu-NCA Polymerization (M/I = 100)

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References


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