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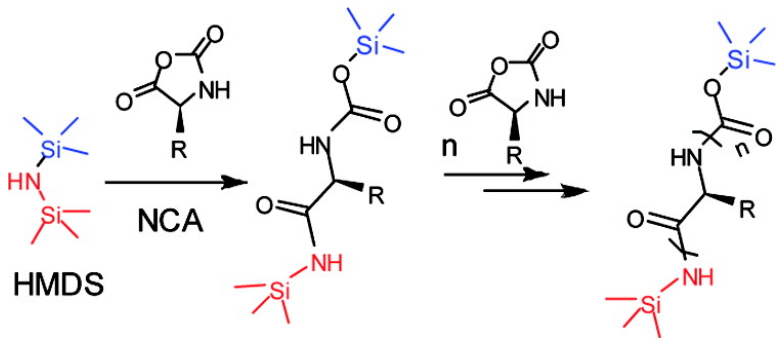

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Hexamethyldisilazane-Mediated Controlled Polymerization of α-Amino Acid *N*-Carboxyanhydrides

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Polypeptides are a class of important biomaterials that are extensively utilized in drug delivery,[1] tissue engineering,[2] sensing,[3] and catalysis.[4] They are usually prepared through amine-initiated ring-opening-polymerizations (ROP) of α-amino acid *N*-carboxyanhydrides (NCAs). Although large-scale, high molecular weight (MW) polypeptides can be readily synthesized using this method, the resulting polypeptides typically have uncontrolled MWs and broad MW distributions (MWDs).[5] In the past decade, a few controlled NCA polymerizations were reported using ammonium[6] or a transition metal complex as initiators,[7,8] or using conventional amine initiators under high vacuum.[9] In conjunction with these achievements, we report in this communication a surprising finding of controlled, living NCA polymerizations mediated by hexamethyldisilazane (HMDS) (Scheme 1) and the identification of trimethylsilyl carbamate (TMS-CBM) as an unusual chain-propagation group.

In a screen of amine initiators for the polymerizations of γ-benzyl-L-glutamate NCA (Glu-NCA), we found HMDS showed remarkable control of polymerizations and led to formation of poly(γ-benzyl-L-glutamate) (PBLG) with expected MWs (entries 1−3, Table 1). The NCA polymerizations initiated with HMDS were in sharp contrast to those initiated with conventional amine initiators in which elevated PBLG MWs by several folds were observed (entries 4−6). The obtained PBLG MW ($M_n = 2.18 \times 10^4$ g/mol) at *M*/*I* of 100, for instance, agreed perfectly with the expected PBLG MW ($M_n = 2.19 \times 10^4$ g/mol) in this HMDS-mediated polymerization (entry 2, Table 1). On the contrary, Glu-NCA polymerization initiated with diethylamine (DEA) gave PBLG with a M_n more than 3 times higher than the expected M_n (entry 4, Table 1). Polymerizations initiated by HMDS usually complete within 24 h at room temperature with quantitative monomer conversions and narrow MWDs (Table 1). The MWs of PBLG showed linear correlation with the conversions of Glu-NCA and agreed well with the expected MWs (Figure 1), demonstrating that PBLG chains were propagated through living chain ends. Block co-polypeptides, such as poly(γ-benzyl-L-glutamate)-*block*-poly(ε-Cbz-L-lysine) (PBLG-*b*-PZLL), can be readily prepared with predictable MWs and narrow MWDs (entry 7, Table 1).

Though numerous amines have been explored for NCA polymerizations, none of them gives controlled polymerizations close to what we observed with HMDS. In a typical amine-initiated polymerization, the initiations involve either the "amine mechanism" by nucleophilically attacking CO-5 with primary amines and some secondary amines or the "activated monomer mechanism" by deprotonating NH-3 with tertiary amines and some secondary amines (Scheme 1).[5] Initiations are usually slower than chain propagations. Therefore, only a small fraction of active chains is responsible for NCA polymerizations and results in polypeptides with elevated MWs (entries 4−6, Table 1). The well-controlled polymerizations observed with HMDS demonstrate that their initiation and chain propagation mechanisms differ from either the "amine" or the "activated monomer" mechanism. The excellent control of polymerization was originally attributed to the higher basicity of HMDS ($pK_a = 14$)[10] as compared to that of other aliphatic amines that have been previously used in NCA polymerization ($pK_a = 10-12$).[11] However, polymerizations of Glu-NCA initiated with triazabicyclodecene, a very basic secondary amine with a pK_a around 26,[12] did not show any control of PBLG MWs (entries 5 and 6, Table 1). Both HMDS and DEA are secondary amines and differ only in the substituents attached to the nitrogen, but their capabilities of controlling polymer MWs are dramatically different (entry 1 vs entry 4, Table 1). Thus, HMDS's unusual

Scheme 1. HMDS-Mediated NCA Polymerization

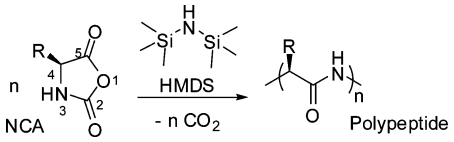

Table 1. Polymerization of Glu-NCA (Entries 1−6, 8, and 9) Initiated with Hexamethyldisilazane, Diethylamine, Triazabicyclodecene, and Trimethylsilyl Dimethylcarbamate, and Block Copolymerization of Lys-NCA and Glu-NCA (Entry 7) Initiated with HMDS

entry	initiator (equiv of NCA)[a]	obtained M_n (g/mol)	expected M_n (g/mol)	M_n (obt.)/ M_n (exp.)	M_w/M_n	conv.[b]
1	HMDS (50 Glu)	8500	10950	0.78	1.26	>99
2	HMDS (100 Glu)	21800	21900	0.99	1.2	>99
3	HMDS (200 Glu)	42800	43800	0.98	1.19	>99
4	DEA (50 Glu)	36600	10950	3.34	1.78	98
5	TBD (100 Glu)	98800	21900	4.51	1.33	86
6	TBD (150 Glu)	102300	32850	3.11	1.3	86
7[c]	HMDS (100 Lys/ 100 Glu)	20200/ 44600	26800/ 48700	0.75/ 0.92	1.04/ 1.03	>99
8	TMSDC (100 Glu)	24200	21900	1.11	1.19	>99
9	TMSDC (200 Glu)	42000	43800	0.96	1.14	>99

[a] DEA = diethylamine, TBD = triazabicyclodecene, TMSDC = trimethylsilyl dimethylcarbamate ($((CH_3)_2NC(O)OSi(CH_3)_3)$, Glu = Glu-NCA, Lys = Lys-NCA. [b] The conversion of NCA was determined using FT-IR by analyzing the intensity of the NCA anhydride absorption band at 1790 cm^{-1}. [c] Synthesis of (PBLG-*b*-PZLL) block co-polypeptide via the sequential addition of Lys-NCA and Glu-NCA to a HMDS solution, and determination of M_n and M_w/M_n (MWD) of PZLL/PBLG-*b*-PZLL.

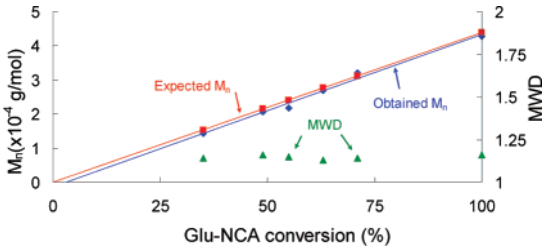

Figure 1. HMDS-mediated NCA polymerization terminated at selected monomer conversion.

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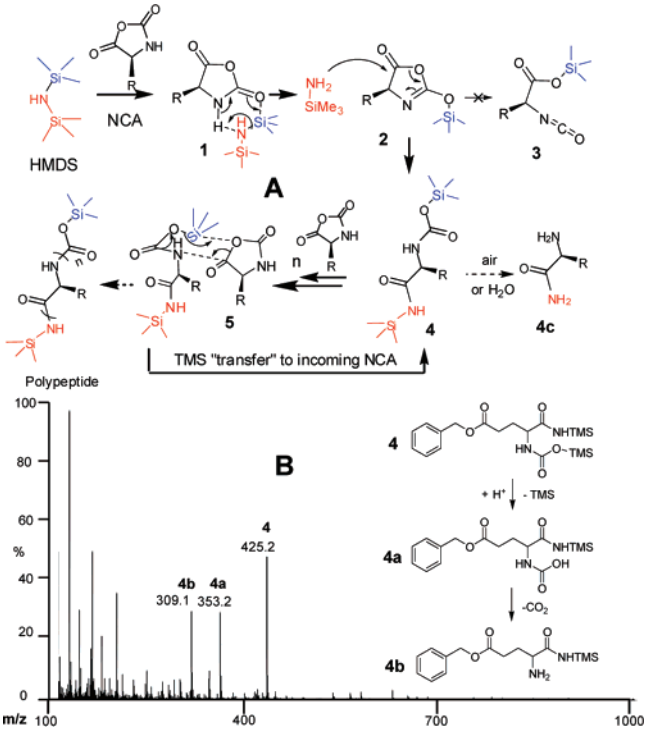

Figure 2. (A) HMDS-mediated NCA polymerization through TMS carbamate group. (B) FAB-MS spectrum of the reaction mixture of equal molar amounts of HMDS and Glu-NCA.

capability of controlling NCA polymerization should be related to its TMS group.

As a secondary amine, HMDS can either function as nucleophile to open the NCA ring at CO-5 or behave like a base to deprotonate the NH-3 proton (Scheme 1).[11] Previous studies showed that secondary amines with bulky alkyl groups (e.g., diisopropylamine) exclusively deprotonated NCAs.[13] Therefore, it was unlikely that HMDS, a secondary amine containing two bulky TMS groups, attacked the CO-5 of Glu-NCA (Scheme 1). If the first step involved the deprotonation of the NH-3 proton of NCA by HMDS, an *N*-TMS NCA would form and should undergo rapid rearrangement to form α-isocyanatocarboxylic acid TMS esters.[14] However, no isocyanate peak (~2230−2270 cm^{-1}) was observed when the mixture of equal molar Glu-NCA and HMDS was analyzed by FT-IR (Figure S1). Interestingly, the Si−N band of HMDS at 932 cm^{-1} in FT-IR disappeared (Figure S1), indicating the cleavage of N−Si bond during initiation. It seemed more reasonable that a TMS group transferred to CO-2 from HMDS and formed intermediate **2** in a coordinated manner (**1**, Figure 2A). Instead of forming isocyanate **3**, **2** underwent rapid ring opening by the in situ generated TMS amine (Figure 2A) to form a TMS carbamate **4** (TMS-CBM).

To confirm the formation of **4**, we mixed equal molar amounts of Glu-NCA and HMDS in DMSO-d_6 and analyzed the mixture using ^{13}C NMR (Figure S2) and FAB-MS (Figure 2B). The anhydride carbon peak of Glu-NCA at 152.6 ppm disappeared; a new peak at 156.3 ppm appeared (Figure S2) that was attributed to the formation of a carbamate group. Interestingly, when the FAB-MS study was carried out with minimum exposure to air, **4** and its decomposed derivatives **4a** and **4b** were detected (Figure 2B); while after **4** was exposed to air for an extended period of time or when D_2O was added to **4**, only **4c** (Figure 2A) was detected (by FAB-MS analysis; data not shown). These experiments demonstrated that **4** contained an active, moisture-sensitive group. Using high-resolution FAB-MS, we determined the molecular formula of **4** to be $C_{19}H_{33}O_5N_2Si_2$ (Figure S3). The MS analysis of a mixture of Glu-NCA and HMDS (5:1 molar ratio) showed peaks of 644 and 863 Da (Figure 4S) that corresponded to the dimer and trimer of Glu peptides, respectively, with identical TMS-CBM terminal groups as **4**.

From these studies, it is evident that polypeptide chains were propagated through the transfer of the TMS group from the terminal TMS-CBM to the incoming monomer to form a new TMS-CBM terminal propagating group (**4** to **5**, Figure 2A). To demonstrate that controlled NCA polymerizations were mediated by a TMS-CBM group, we tested Glu-NCA polymerizations using trimethylsilyl dimethylcarbamate (TMSDC) as the initiator. As expected, polymerizations proceeded smoothly to yield PBLGs with anticipated MWs and narrow MWDs (entries 8 and 9, Table 1).

These HMDS-mediated NCA polymerizations resemble to some extent the group transfer polymerizations (GTPs) of acrylic monomers initiated by similar organosilicon compounds.[15] Unlike GTPs that typically require Lewis acid activators or nucleophilic catalysts to facilitate the polymerization,[16] HMDS-mediated NCA polymerizations do not require any additional catalysts or activators. However, it is unclear whether the TMS transfer proceeds through an anionic process as GTP[16] or through a concerted process tentatively illustrated as **5** (Figure 2A).

In conclusion, we discovered an unusual TMS-CBM propagating group that can control the living polymerization of NCAs. This organosilicon reagent mediated NCA polymerization offers a metal-free strategy for the convenient synthesis of homo- or block polypeptides with predictable MWs and narrow MWDs.

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Supporting Information Available: Experimental procedures and the FT-IR, MS, and NMR of HMDS-mediated polymerizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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