Supporting Information

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

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General. Anhydrous dimethylformamide (DMF) was dried by an aluminum column and stored with molecular sieves in a glove box. Anhydrous THF, anhydrous hexane, trimethylsilyl dimethylcarbamate (TMSDC) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) were purchased from Sigma (St. Louis, Mo) and used as received. Methylene chloride was purchased from J. T. Baker (Phillipsburg, NJ). Anhydrous DMSO-d_6 was prepared by treating regular DMSO-d_6 (Cambridge Isotope Laboratories, Andover, MA) with calcium hydride at 70°C under N_2 overnight followed by distillation under reduced pressure. H-Glu(OBn)-OH and H-Lys(Z)-OH were purchased from Chem-Impex International (Des Plaines, IL) and used as received. NMR spectra were recorded on a Varian 400 MHz or on a Varian VXR 500 MHz spectrometer. Tandem gel permeation chromatography (GPC) was performed on a system equipped with an isocratic pump (Model 1100, Agilent Technology, Santa Clara, CA), a DAWN HELEOS 18 angle MALLS light scattering detector (Wyatt Technology, Santa Barbara, CA) and an Optilab rEX refractive index detector (Wyatt Technology, Santa Barbara, CA). The detection wavelength of HELEOS was 658 nm. Separations were effected by 500 Å, 10^3 Å and 10^4 Å Phenogel columns (5 μm, 300 × 7.8 mm, Phenomenex, Torrance, CA) using DMF containing 0.1 M LiBr as the mobile phase at 60°C. Infrared spectra were recorded on a Perkin Elmer 1600 FT-IR spectrophotometer calibrated with polystyrene film. Low resolution FAB-MS was collected on a Micromass 70-VSE mass spectrometer. High resolution FAB-MS was collected on a Waters 70-SE-4F mass spectrometer.

Synthesis of (S)-γ-benzyl-glutamate-N-carboxyanhydride (Glu-NCA) A 250 mL round bottom schlenk flask charged with H-Glu(OBn)-OH (2.37 g, 10 mmol), triphosgene (1.49 g, 5 mmol) and a stir bar was vacuumed for 2 hrs at room temperature. Anhydrous THF (100 mL) was added under nitrogen. The mixture was stirred at 40°C for 2 hrs. The suspension gradually turned clear, which indicated the completion of the reaction. The solvent was removed under vacuum to give crude Glu-NCA. The crude NCA was purified by recrystallization in a glove box four times using a mixture of hexane and THF resulting inGlu-NCA in crystalline form (2.10 g, 83%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.11 (s, 1H, NH), 7.3-7.4 (m, 5H, ArH), 5.10 (s, 2H, $C_6H_5C\underline{H}_2$), 4.47 (dd, 1H, α-CH), 2.52 (t, 2H, β-CH_2), 2.05 (m, 1H, γ-CH), 1.92 (m, 1H, γ-CH). ^{13}C NMR (DMSO-d_6, 500 MHz): δ 172.4, 172.0, 152.6, 136.7, 129.1, 128.8, 128.7, 66.4, 57.0, 29.8, 27.1. The ^{13}C NMR, ^{1}H NMR and FTIR spectra of this material are identical to data found for the authentic sample of Glu-NCA.[1]

Synthesis of (S)-ε-carbobenzoxy-lysine-N-carboxyanhydride (Lys-NCA) The Lys-NCA was synthesized following the same procedure as the synthesis of the Glu-NCA (78%). ^{1}H NMR (DMSO-d_6, 500MHz): δ 9.08 (s, 1H, ring NH), 7.30-7.36 (m, 5H, ArH), 7.26-7.28 (m, 1H, side chain NH) 5.01 (s, 2H, $C_6H_5C\underline{H}_2$), 4.40 (dd, 1H, α-CH), 2.96 (m, 2H, N-C$\underline{H}_2$-), 1.63-1.71 (m, 2H, β-CH_2), 1.28-1.41 (m, 4H, -NHCH_2C$\underline{H}_2$C$\underline{H}_2$CH_2-). ^{13}C NMR (DMSO-d_6, 500MHz): δ 171.8, 156.1, 152.0, 137.3, 128.4, 127.8, 65.1, 57.0, 41.3, 31.1. 30.6, 28.7

General procedure for the polymerization of Glu-NCA In a glove box Glu-NCA (26 mg, 0.1mmol) was dissolved in DMF (0.5 mL). The Glu-NCA solution was added to a HMDS/DMF solution (10 μL, 0.1 mmol/mL). The reaction mixture was stirred for 15 hrs at room temperature. The real-time concentration of NCA was quantified by measuring the intensity of NCA's anhydride peak at 1790 cm^{-1} by FT-IR. The conversion of NCA was determined by comparing the NCA concentration in the polymerization solution with the NCA concentration at t = 0. After diluting the concentration of PBLG to 10 mg/mL using DMF (containing 0.1 M LiBr), the solution was analyzed by GPC to measure the molecular weight of PBLG. The remaining PBLG was precipitated with 8 mL methanol. The obtained PBLG was sonicated for 5 minutes and centrifuged to remove the solvent. After the sonication-centrifugation procedure was repeated two more times, PBLG was collected and dried under vacuum (17 mg, 78%).

Polymerizations of Glu-NCA initiated with diethylamine (DEA), triazabicyclodecene (TBD) and trimethylsilyl dimethylcarbamate (TMSDC), and characterization of the resulting PBLGs were similarly carried out.

General procedure for the synthesis of block polypeptides In a dry box, Lys-NCA (30 mg, 0.1 mmol) was dissolved in DMF (0.5 mL). The solution was then added to a HMDS solution in DMF (10 μL, 0.1 mmol/mL). The reaction mixture was stirred for 42 hrs. After the Lys-NCA was completely consumed (monitored by FT-IR), Glu-NCA (26 mg, 0.1 mmol) in 0.5 mL DMF was added to the mixture to make the second black. The polymerization of Glu-NCA was complete after 24 hrs. The molecular weights of first block (PZLL) and the block-copolymer (PZLL-*b*-PBLG) were analyzed by GPC.

References:

(1) Block, H. *Poly(gamma-benzyl-L-glutamate) and Other Glutamic Acid Containing Polymers.*; Gordon and Breach: New York, **1983**.

FT-IR analysis of equal molar mixture of Glu-NCA and HMDS

Procedure: Glu-NCA (26 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (600 μL) was added dropwise to an anhydrous CH_2Cl_2 solution containing HMDS (16 mg, 0.1 mmol). The solution was allowed to stir in glove box at room temperature overnight. The FT-IR spectrum was collected on a KBr salt plate (Figure S1).

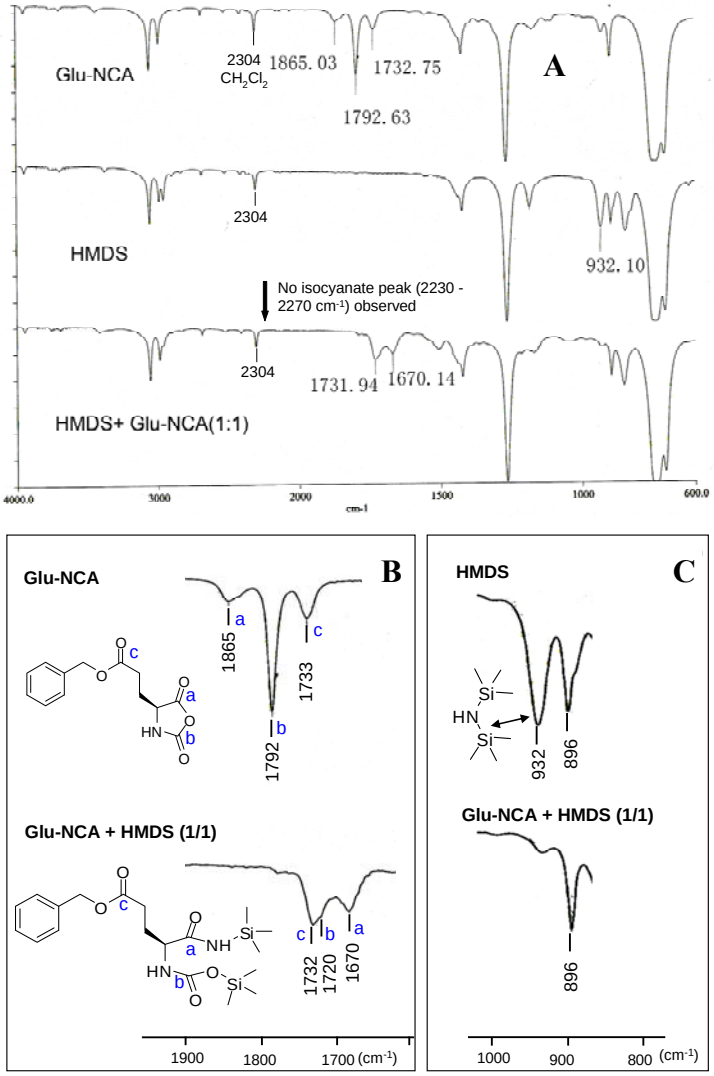


Figure S1. FT-IR analysis of equal molar mixture of Glu-NCA and HMDS. (A) overall spectra (600-4000 cm^{-1}) overlay; (B) carbonyl groups (1600-1900 cm^{-1}); (C) HMDS groups (800-1000 cm^{-1})

Data analysis: After the mixture was stirred in a glove box at room temperature for 16 hrs, both the characteristic anhydride peaks of Glu-NCA (1865 cm^{-1} and 1792 cm^{-1}) (Figure S1B) and the Si-N-Si peak of HMDS (932 cm^{-1}) (Figure S1C) disappeared, indicating NCA ring opening and cleavage of the Si-N bond in HMDS, respectively. The peaks of 1670 cm^{-1} (a) and 1720 cm^{-1} (b) are due to the formation of the N-TMS amide (a) and TMS carbamate bonds (b). No isocyanate peak (~ 2230-2270 cm^{-1}) was observed after mixing HMDS and Glu-NCA (The peak 2304 cm^{-1} was from the solvent (CH_2Cl_2), not from isocyanate).

^{13}C-NMR analysis of equal molar mixture of Glu-NCA and HMDS

Procedure: An anhydrous DMSO-d_6 solution (600 μL) containing 26 mg Glu-NCA (0.1 mmol) was added dropwise to an anhydrous DMSO-d_6 solution (400 μL) containing 16 mg HMDS (0.1 mmol). The solution was allowed to stir in a glove box at room temperature for 16 hrs. The reaction solution was transferred to a NMR tube in glove box. The NMR tube was capped, sealed with parafilm to avoid exposure to moisture, and analyzed on a Varian VXR-500 MHz spectrometer. ^{13}C NMR (DMSO-d_6) (carbonyl peaks only) δ 177.8, 174.0, 173.5, 172.9, 156.3, 155.2.

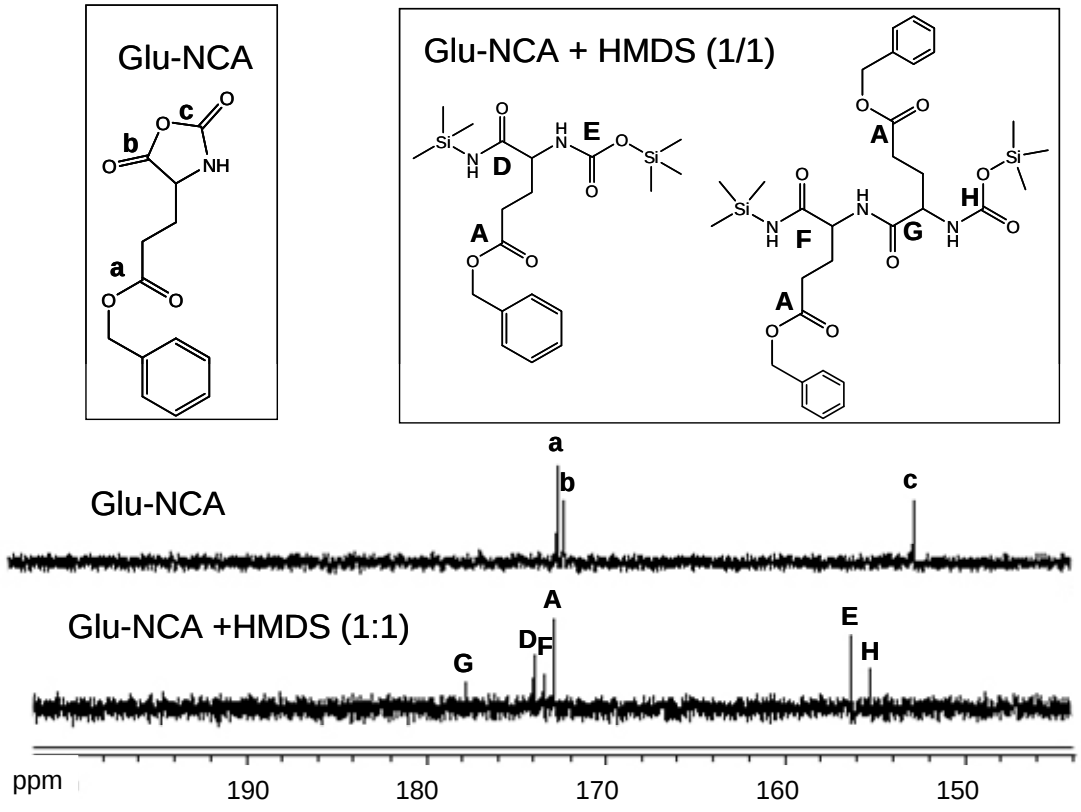


Figure S2. ^{13}C-NMR spectrum of equal molar mixture of Glu-NCA and HMDS.

Data analysis: Two sets of ^{13}C NMR carbonyl peaks were identified. Peaks **A**, **D** and **E** were the carbonyl of TMS carbamate-Glu(Bn)-NHTMS. Peaks **A**, **E**, **F** and **G** were the carbonyl of TMS carbamate-Glu(Bn)Glu(Bn)-NHTMS due to the chain propagation.

High-Resolution FAB-MS analysis of equal molar mixture of Glu-NCA and HMDS

Procedure: An anhydrous DMSO-d_6 solution (600 μL) containing 26 mg Glu-NCA (0.1 mmol) was added dropwise to an anhydrous DMSO-d_6 solution (400 μL) containing 16 mg HMDS (0.1 mmol). The solution was allowed to stir in a glove box at room temperature for 16 hrs. The reaction solution was analyzed on a Waters 70-SE-4F mass spectrometer for high-resolution FAB-MS.

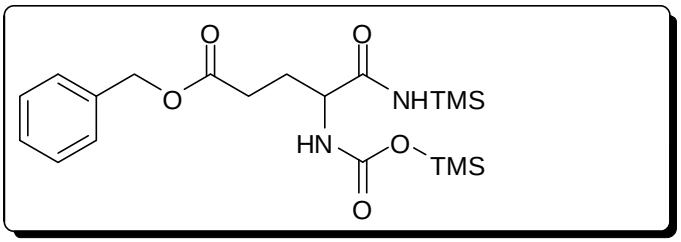
Selected isotopes: $CHO_{0-6}N_{0-4}Si_{0-2}$
Measured Mass **425.19260**
Error Limit: 5 mmu
Unsaturation Limits: -0.5 to 30

Formula	Calculated Mass	Error	Unsaturation
$C_{32}H_{25}O$	425.19055	2.1	20.5
$C_{25}H_{29}O_6$	425.19642	-3.8	21.0
$C_{30}H_{23}N_3$	425.18920	3.4	21.0
$C_{23}H_{27}O_5N_3$	425.19507	-2.5	12.0
$C_{28}H_{29}O_2Si$	425.19369	-1.1	15.5
$C_{23}H_{29}O_4N_2Si$	425.18967	2.9	11.5
$C_{26}H_{27}ON_3Si$	425.19235	0.2	16.0
$C_{24}H_{33}O_3Si_2$	425.19684	-4.2	10.5
$C_{19}H_{33}O_5N_2Si_2$	**425.19281**	-0.2	6.5
$C_{22}H_{31}O_2N_3Si_3$	425.19549	-2.9	11.0

Figure S3. High-resolution FAB-MS analysis of the peak of m/z = 425.2.

Data analysis: The only possible structure that contains 19 carbons is the intermediate **4** (Figure 2A) with a MW of m/z = 425.19281 and a formula of $C_{19}H_{33}O_5N_2Si_2$.

$C_{19}H_{33}O_5N_2Si_2$=



FAB-MS study of 5:1 ratio of Glu-NCA and HMDS

Procedure: Glu-NCA (26 mg, 0.1 mmol) was dissolved in anhydrous DMF (500 μL). The solution was added dropwise to a DMF solution (200 μL) containing 3.2 mg HMDS (0.02 mmol). The reaction mixture was stirred overnight at room temperature and then analyzed with FAB-MS under anhydrous conditions.

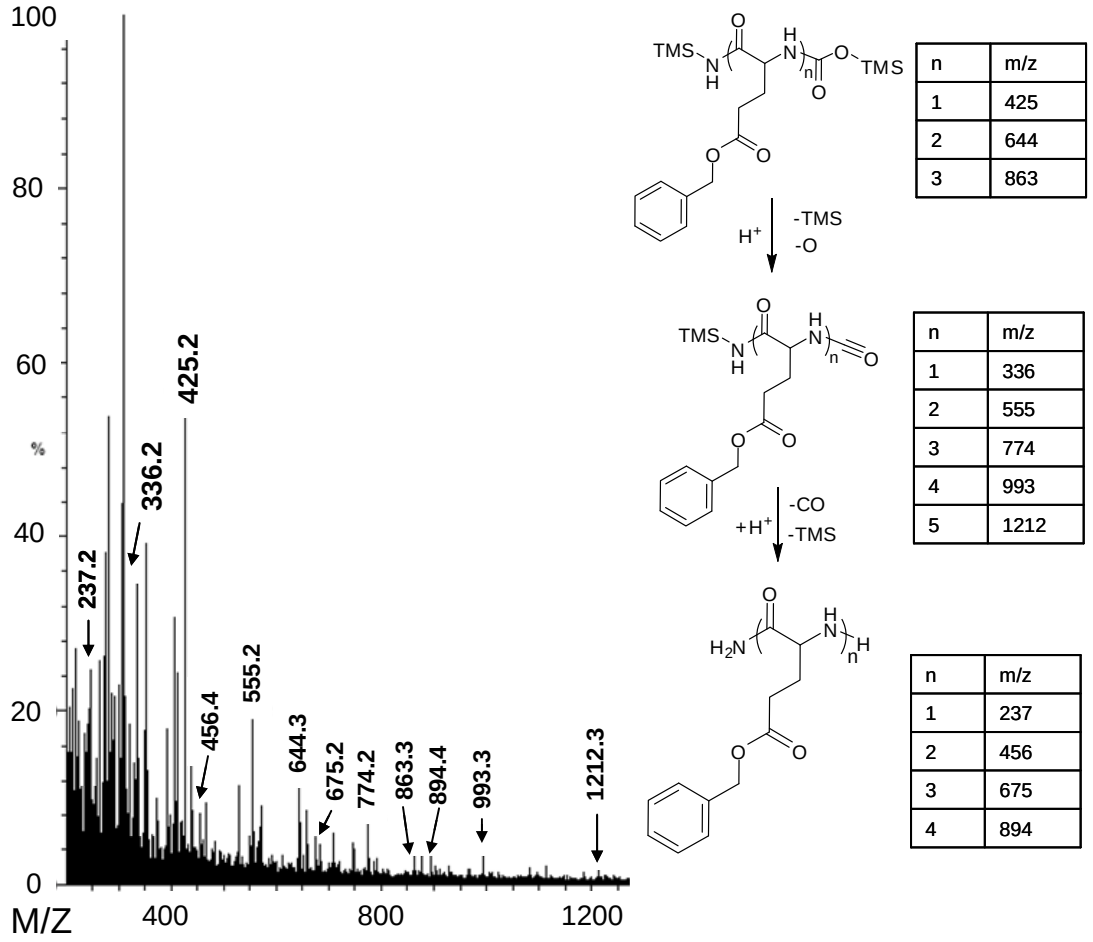


Figure S4. FAB-MS spectrum of a mixture of Glu-NCA and HMDS (M/I = 5/1). Major peaks were assigned according to the proposed decomposition of oligopeptides containing TMS carbamate end groups.

Data analysis: OligoGlu(Bn)s (n = 1 to 3) with TMS amide on the C-terminal and TMS-carbamate on the N-terminal were identified (425 Da, 644 Da, 863 Da), suggesting that TMS-carbamate was the active propagating group controlling chain elongation.