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Supporting information

Controlled Ring-Opening Polymerization of α-amino acid *N*-carboxy-anhydride by Frustrated Amine/Borane Lewis Pairs

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Experimental Section.

General Methods.

All polymerizations were carried out under a dry and oxygen-free nitrogen atmosphere by using Schlenk techniques or under nitrogen atmosphere in a Vigor glovebox. Anhydrous dichloromethane (DCM), tetrahydrofuran (THF) and *N,N*-dimethy formamide (DMF) purchased from J&K SCIENTIFIC LTD were directly used without treatment. Aniline from Sinopharm Chemical (China) was dried with KOH for overnight, following distillation in vacuum. Bis-(2,4,6-tris-trifluoromethyl -phenyl) fluoroborane ($Fmes_2BF$) from Aldrich was sublimated several time prior to use. All other liquids were dried over activated 4 Å molecular sieves for a week and distilled before use. H-Glu(OBn)-OH was purchased from GL Biochem (shanghai) Ltd and used as received. γ-benzyl-$_L$-glutamate *N*-carboxyanhydride (BLG-NCA) and ε-benzyl-$_L$-lysine *N*-carboxyanhydride (Lys-NCA) were synthesized according to the reported procedure,[1] and the recrystallized four times before use. Di-*tert*-butyl dicarbonate (Boc_2O), $_L$-aspartic acid-4-benzyl ester, dicyclohexylcarbo diimide (DCC) and trifuoroacetic acid purchased from Aldrich was used without treatment.

Characterization.

The chemical structures of the monomer and polymers were characterized by ^{1}H NMR carrying out on a 400 MHz NMR instrument (Bruker Corporation, Germany) at room temperature using $CDCl_3$ and CD_2Cl_2 as solvent. The chemical shifts were measured against the solvent signal of $CDCl_3$ (δ = 7.26 ppm) and CD_2Cl_2 (δ = 5.32 ppm) as internal standard, respectively. GPC measurements of the synthetic polypeptides were carried out by Agilent 1260 LC equipped with a differential refractive-index detector. One guard column and two 7.5 x 300 mm PLgel MIXED-C columns were used. The measurements were performed using THF as eluent (flow rate of 1.0 mL/min at 35 ^{o}C), and polystyrene standards were employed for calibration. Polymer solutions with concentrations between 8.0 and 10.0 mg/mL were injected at an injection volume of 80 μL. *In situ* IR study of NCA polymerization was carried out by using ReactIR 15m with MCT Detector from METTLER TOLEDO AutoChem. DiComp (Diamond) probe was connected via AgX 6 mm x 2 m Fiber (Silver Halide). Spectra were taken from 2000 cm^{-1} to 650 cm^{-1} at 8 wavenumber resolution and the automatic sampling interval was 1 minute. The calibrated curves for calculating the conversion of Glu-NCA during

polymerization were plotted by the intensity ratio of the peaks at 1785 cm^{-1} (anhydride of monomer) to that at 1731 cm^{-1} (benzyl carbonyl group), based on the preparing the mixture solution of monomer Glu-NCA and polymer PBLG with the different molar ratio. In the process of polymerization, the polymerization solution was taken out from the system, and spotted on the KBr plate for scanning on FT-IR (Nicolet 6700, the accumulation rate was 16 times with 4 wavenumber resolution). The obtained intensity ratio at 1785 cm^{-1} and 1731 cm^{-1} was compared with the calibrated curves to afford the monomer conversion.

Polymerization procedure.

A typical procedure for polymerization of Glu-NCA was performed in a 25 mL Schlenk in a Vigor glovebox. The given amount of $Fmes_2BF$ and aniline was stirred in 140 μL anhydrous solvent (DMF, THF and DCM) for 10 min, followed by adding 200 mg Glu-NCA (0.76 mmol) in 1.2 CDM. The mixture was kept stirring at 25 °C. AutoChem. Dicomp probe of ReactIR 15m (METTLER TOLEDO) was connected to the reaction flask via AgX 6 mm x 2 m Fiber (Silver Halide) to monitor the conversion of monomer. After a specific time, 0.1 mL of the reaction mixture was taken out from the system and diluted to 10 mg/mL using THF. The solution was then analyzed by GPC to determine the molecular weight and PDI of the obtained polypeptides. The final reaction solution was precipitated in methanol, the obtained polymers were dried under vacuum.

The synthesis of Comp 2

The preparation of Comp 2 included three steps, as shown in Scheme S1. Firstly, preparation of Boc-$_L$-aspartic acid 4-benzyl ester was referred to the reported procedure.[2] To a solution of $_L$-aspartic acid-4-benzyl ester (2.0 g, 8.96 mmol) in 20 mL water/dioxane (v/v=1/1) was dropwise added anhydrous triethylamine (1.5 mL, 10.75 mmol), and then Boc (2.15 g, 9.86 mmol) at 0 °C in 0.5 h. The solution was stirred overnight at 25 °C. After that, the dioxane was evaporated under reduced pressure, the aqueous layer was acidified to pH 1 using HCl (1.0 M), and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo to give a white solid (2.11 g, 72.9% in yield) without further purification. ^{1}H-NMR ($CDCl_3$, δ ppm) 1.45 (9H, s), 2.86-3.12 (2H, m), 4.62-4.65 (1H, br), 5.15 (2H, d, *J* = 1.77 Hz), 5.53(1H, d, *J* = 8.16, -NH-), 7.32-7.36 (10H, m), 9.97 (1H, br, -COOH).

The second step was performed according to the reported method.[3] To a stirred solution of Boc-$_L$- aspartic acid 4-benzyl ester (1.0 g, 3.09 mmol) in anhydrous CH_2Cl_2 (20 mL) was

added a solution of DCC (0.763 g, 3.7 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 ℃ in 0.5 h. Then, anhydrous aniline (0.34 mL, 3.7 mmol) was added dropwise to the reaction mixture at 0 ℃. The mixture was stirred at 25 ℃ overnight and filtered through celite to remove insoluble material. The resulting liquid was evaporated, and purified by silica gel column with ethyl acetate and petroleum ether (v/v = 1/10). The light yellow solid (Boc-protecting Comp 2) was afforded in a yield of 89.3%. ^{1}H NMR ($CDCl_3$, δ ppm) 1.48 (9H, s), 2.76-3.13 (2H, m), 4.66 (2H, br), 5.16 (2H, d, *J* = 0.72 Hz), 5.81(1H, br -NH-), 7.08-7.49 (10H, m), 8.50 (1H, br, -NHPh)

Step 3, to a stirred solution of *t*-butoxycarbonyl-$_L$-aspartamylaniline γ-benzyl ester (Boc-protecting Comp 2) (400 mg, 1 mmol) in dichloromethane (0.6 mL) was added trifuoroacetic acid (1.14 g, 10 mmol) at 0 ℃, followed by stirring at 25 ℃ for 2.5 h. Then, the saturated $NaHCO_3$ was added into the resulting solution to adjust pH value to 8 at 0 ℃. The solution was extracted with DCM (3 × 50 mL), and the organic phase was dried over $MgSO_4$. A white solid was obtained by drying in vacuum with yield of 84%. ^{1}H NMR ($CDCl_3$, δ ppm) 1.83 (2H, br, NH_2-), 2.79-3.10 (2H, m), 2.80-3.84 (1H, dd, J_1 = 3.78 Hz, J_2 = 8.01 Hz), 5.16 (2H, d, *J* = 3.06 Hz), 7.08-7.58 (10H, m), 9.50 (1H, br, -NHPh).

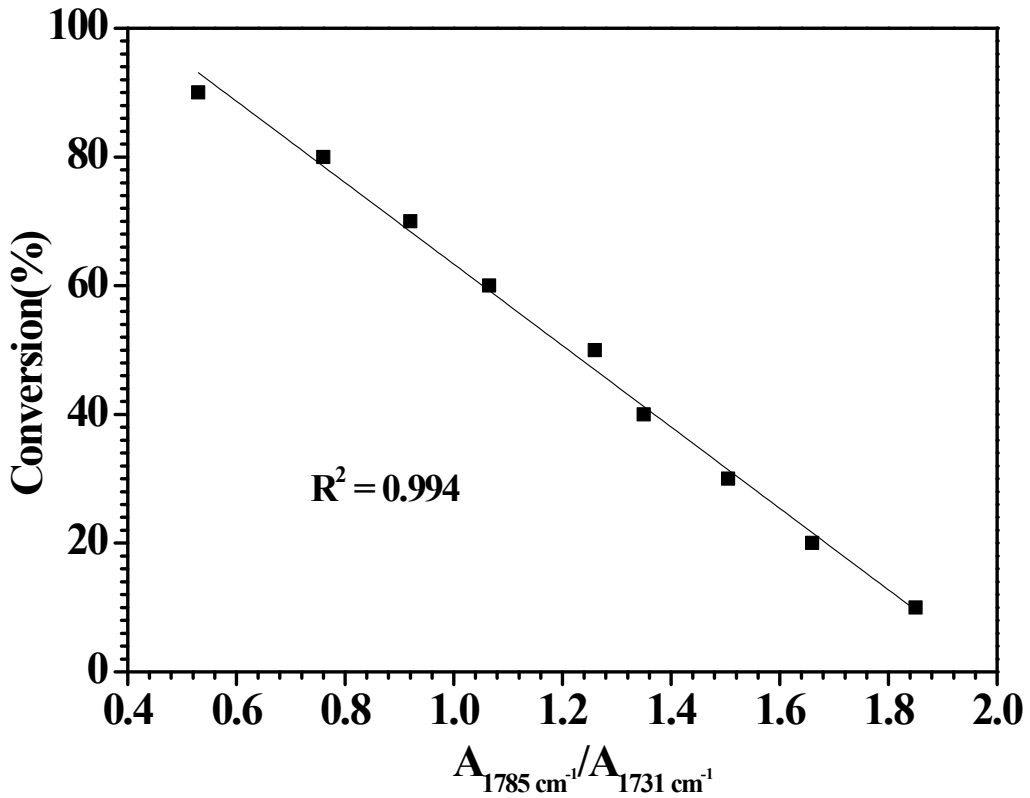


Figure S1. Calibrated curve of Glu-NCA conversion *vs* the peak intensity ratio at 1785 cm^{-1} and 1731 cm^{-1}.

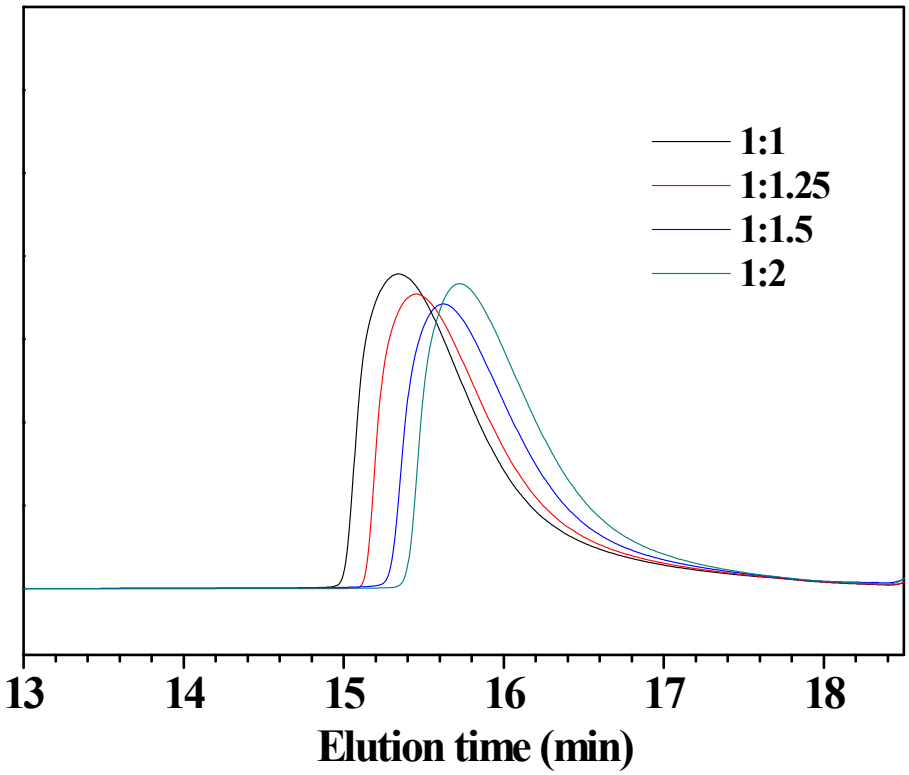


Figure S2. GPC profiles of PBLG with varying the molar ratio of $Fmes_2BF$ and aniline as initiator. [$Fmes_2BF$]/[aniline] = 1/1～1/2, [Glu-NCA] = 0.5 M, at 25 ºC in DCM.

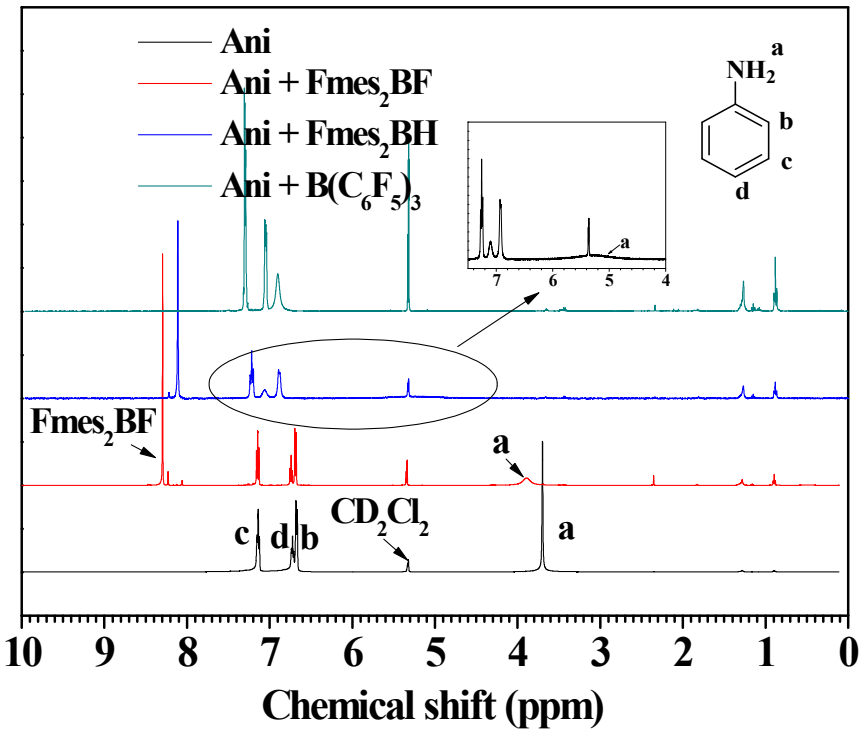


Figure S3. ^1H NMR spectra of chemical structures of aniline interacting with $Fmes_2BF$, $Fmes_2BH$ and $B(C_6F_5)_3$.

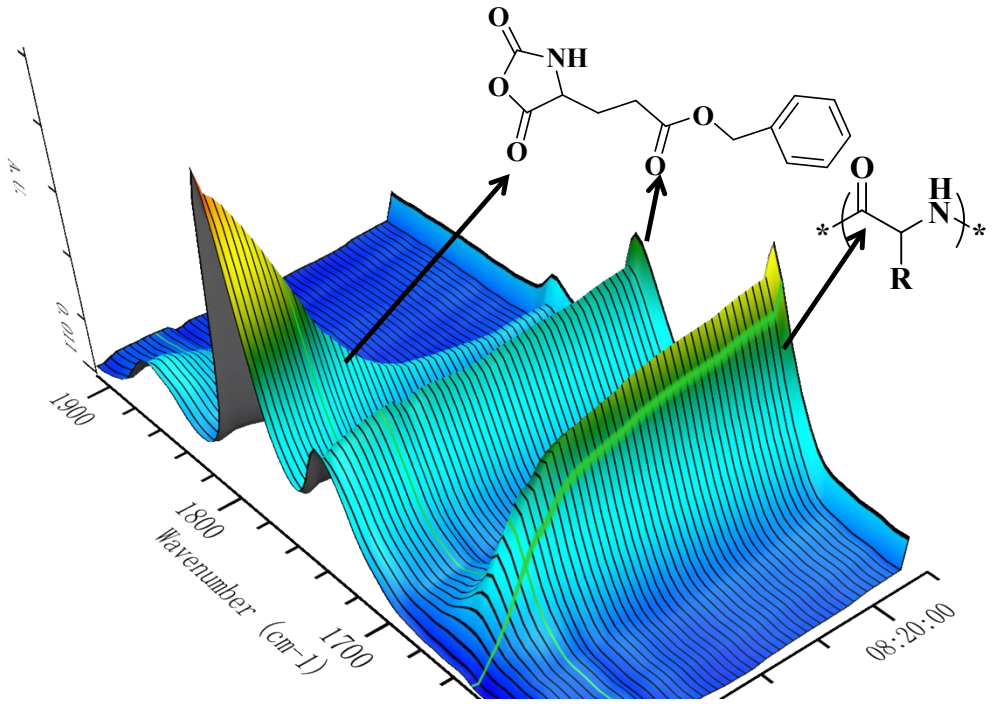


Figure S4. 3D kinetic behavior profile from *in situ* IR (the sampling interval is 1 min).

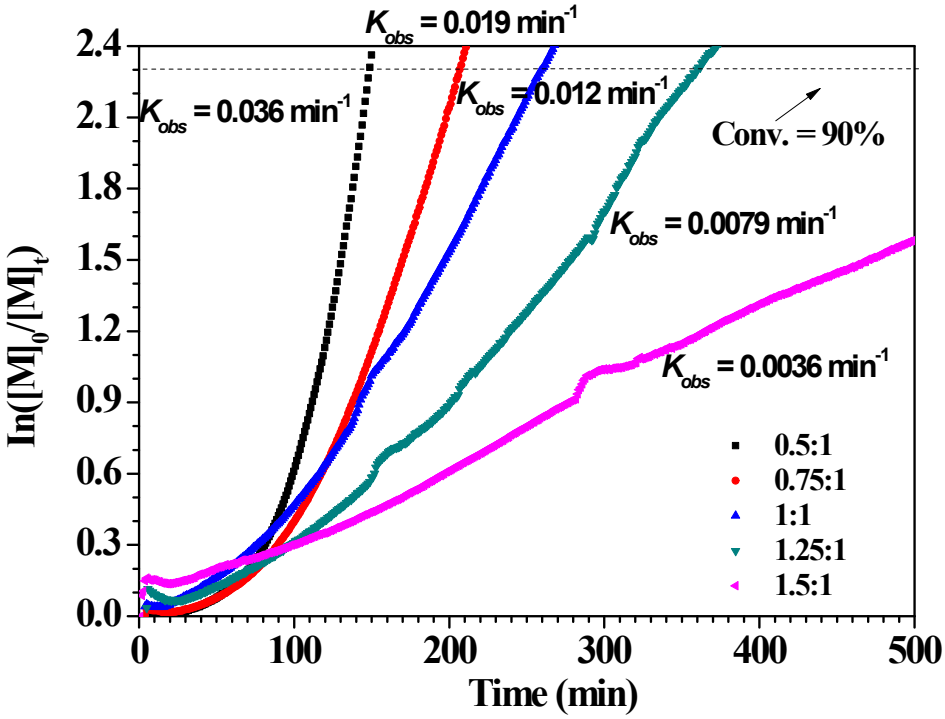


Figure S5. Kinetics of the ROP of Glu-NCA initiated by the aniline and $Fmes_2BF$ system ([Glu-NCA] = 0.50 M, [Glu-NCA]/[aniline] = 50, [$Fmes_2BF$]/[aniline] = 0.5, 0.75, 1.0, 1.25 and 1.5, 25 °C in DCM, the automatic sampling interval of in situ IR is 60 seconds).

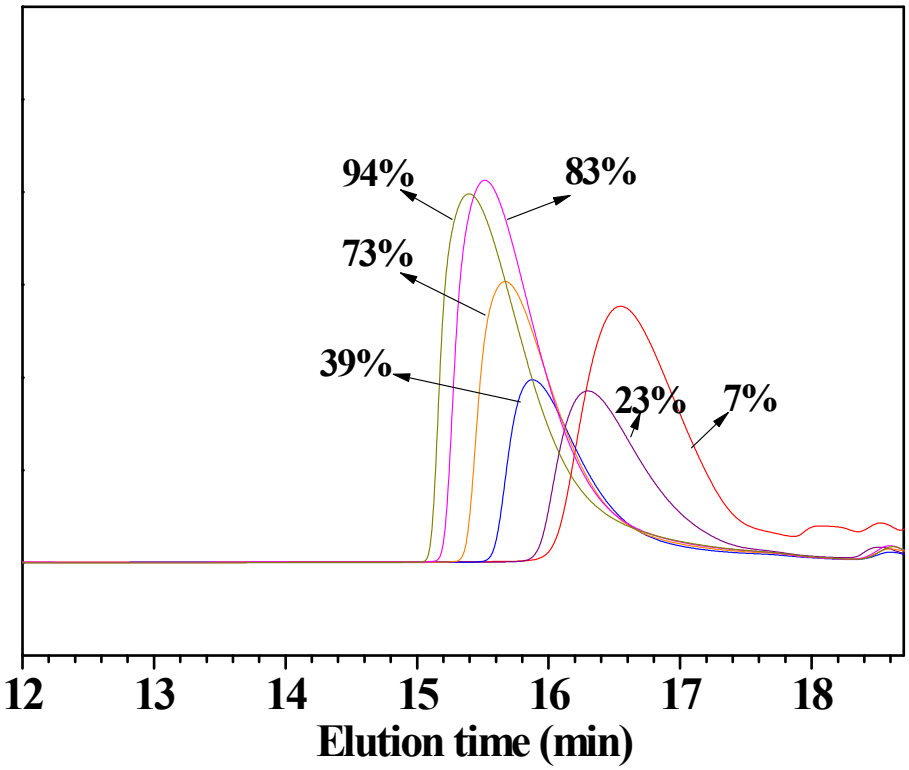


Figure S6. GPC profiles of PBLG depending on the different monomer conversion. [Glu-NCA]/[$Fmes_2BF$]/[aniline] = 50/1/1, [Glu-NCA] = 0.5 M, at 25 °C in DCM.

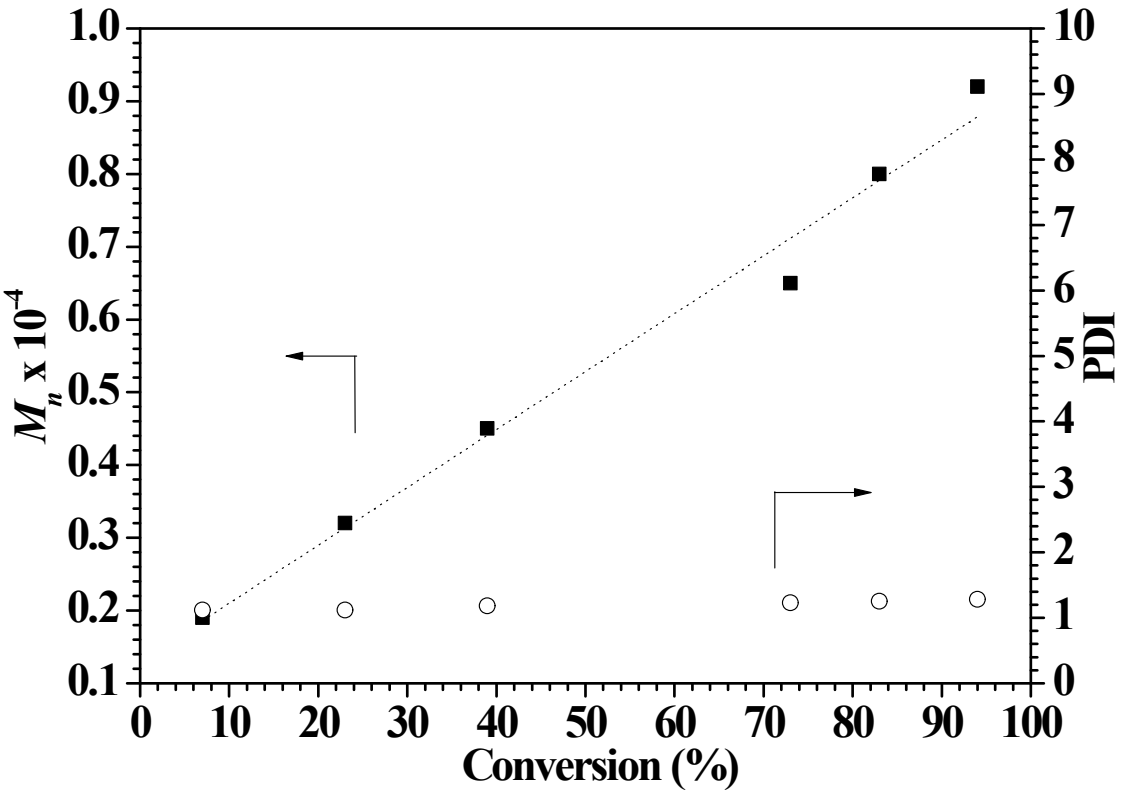
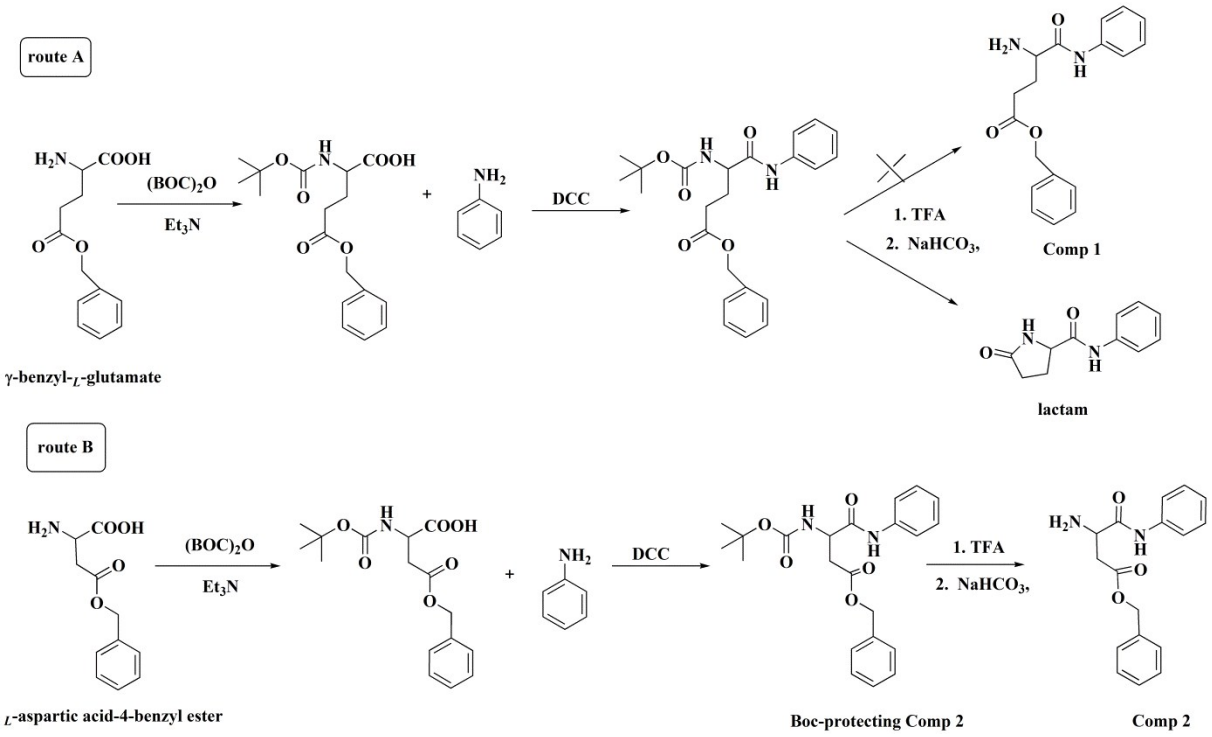


Figure S7. M_n vs. Glu-NCA conversion with the molar ratio of monomer, aniline and $Fmes_2BF$ to 50:1:1 at 25 ºC in DCM.

Table S1. ROP of Glu-NCA initiated by different Lewis base in DCM.

Run	LB	[M]:[LB][a]	Time (h)	Conv. (%) [b]	$M_{n,cal}\times10^{-4}$ [c]	$M_{n,mea}\times10^{-4}$ [d]	$Đ$[d]
1	*p*-MeO-Ani	50:1	1	>99	1.10	0.91	1.46
2	*p*-Br-Ani	50:1	3	>99	1.10	1.22	1.64
3	BA	50:1	1	>99	1.10	0.89	1.37

[a] Indicating that the molar ratio of monomer (Glu-NCA) to Lewis base (LB). [b] Determined by monitoring the change of the NCA anhydride absorption peak at 1785 cm^{-1} in FT-IR spectroscopy. [c] Calculated by [Glu-NCA]/[LB]×(M_{NCA}-44)×monomer conversion. [d] Determined by gel-permeation chromatography (GPC), Đ represents molecular weight distribution.



Scheme S1. Preparation route of Comp 2.

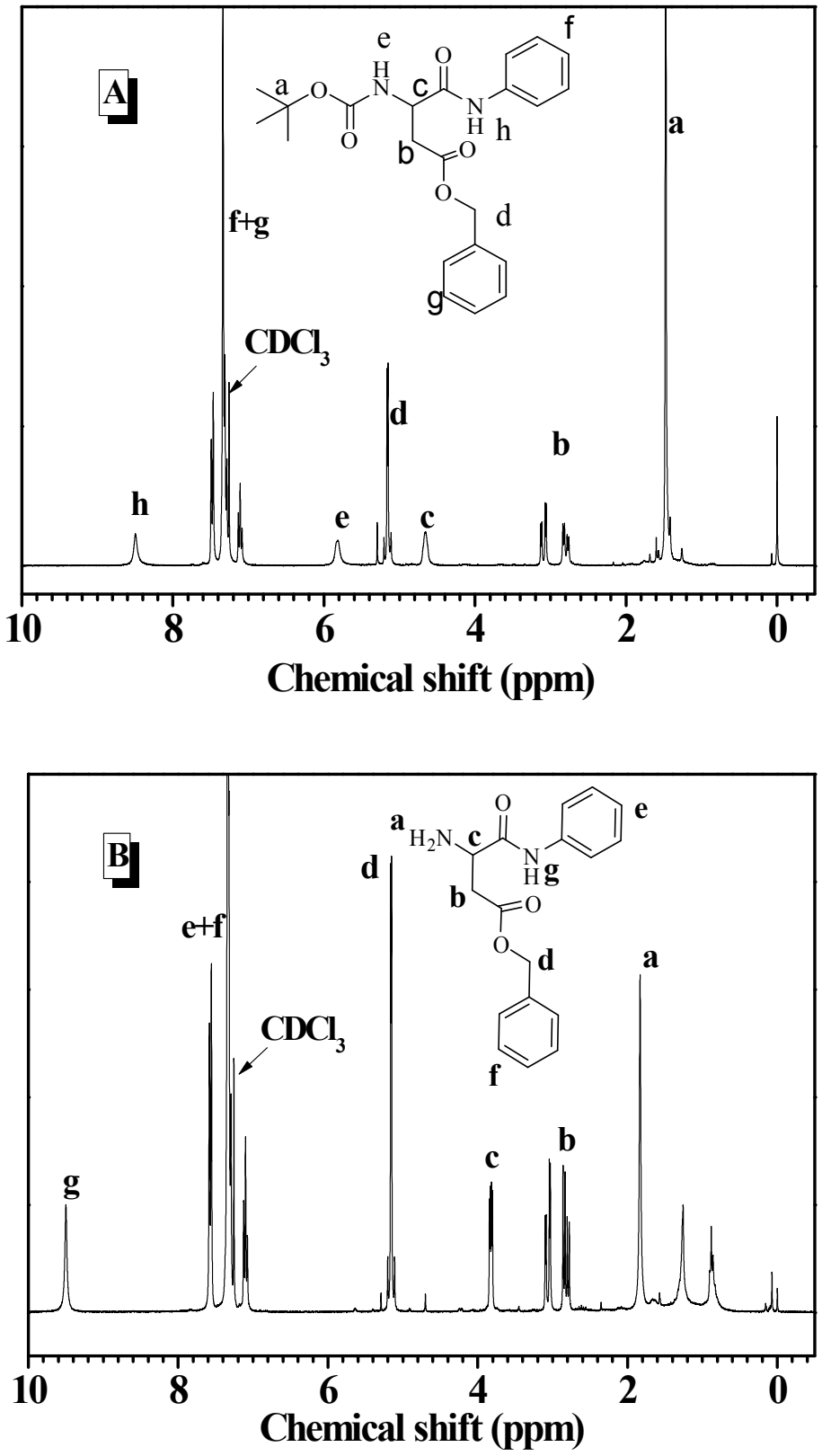


Figure S8. ^{1}H NMR spectra of Boc-protecting Comp 2 (A) and Comp 2 (B).

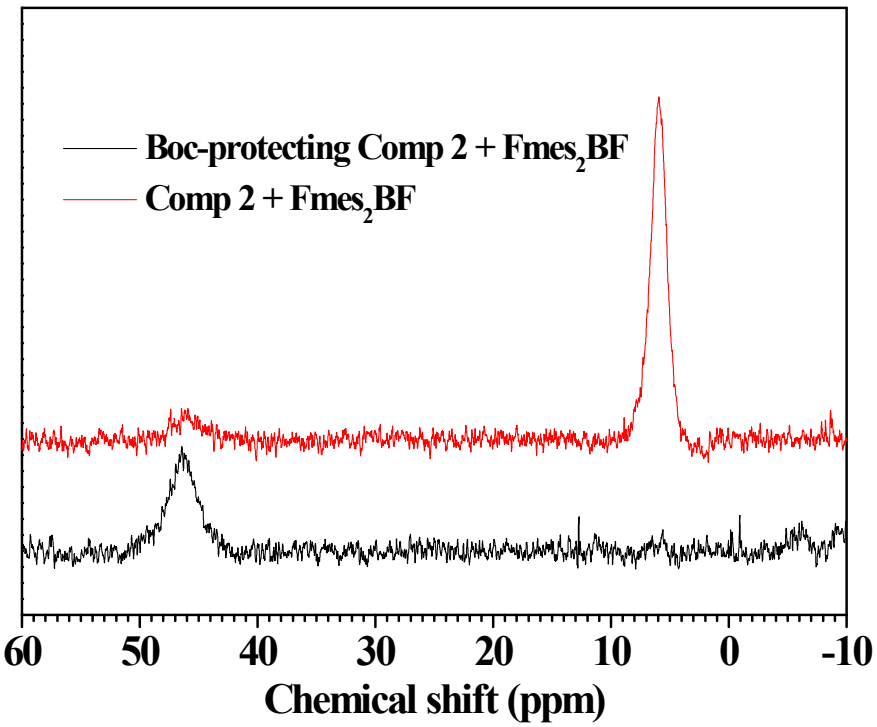
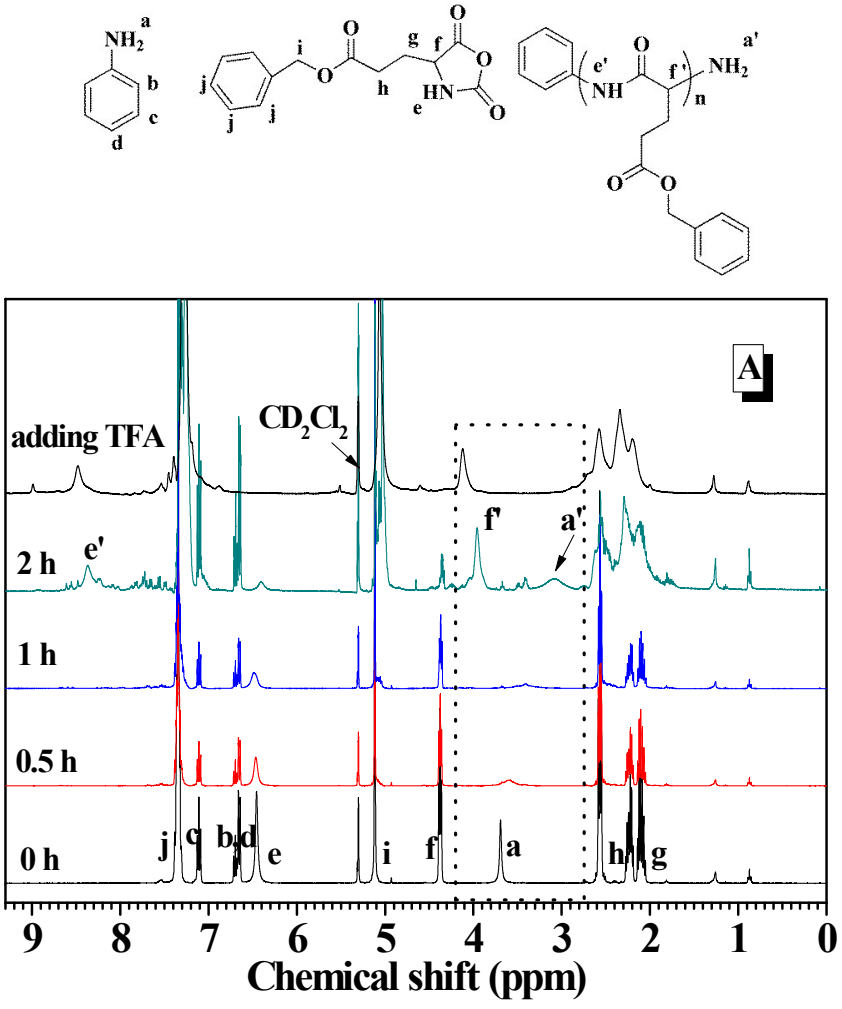


Figure S9. ^{11}B NMR spectra of $Fmes_2BF$ and α-amino-β-benzyl-$_L$-aspartamyl aniline before and after Boc removal with molar ratio of 1 to 1.



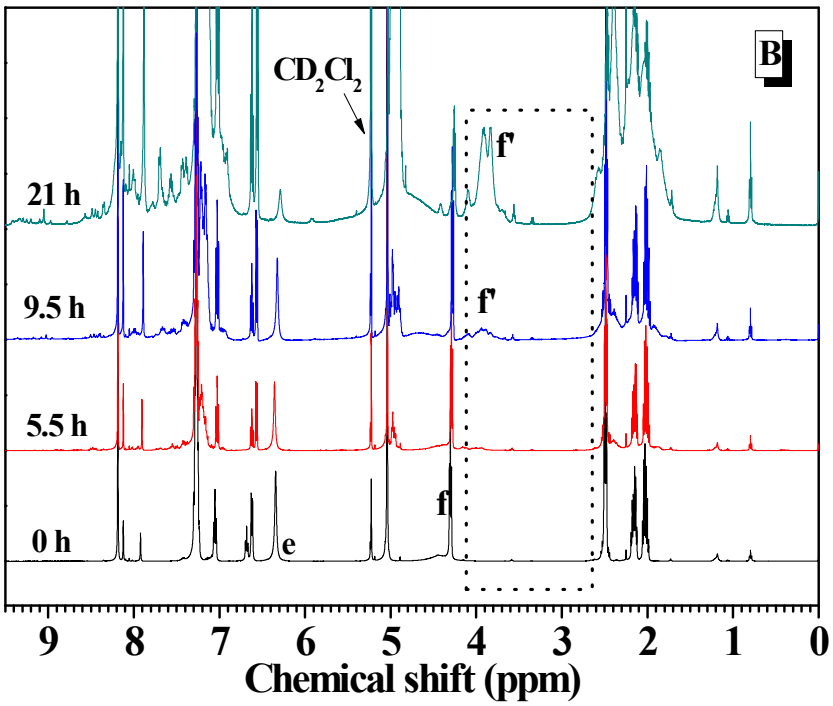


Figure S10. ^{1}H NMR spectra of polymerization process of Glu-NCA in the presence of aniline, [Glu-NCA]/[aniline] = 5/1 (A); in the presence of FLPs consisting of $Fmes_2BF$ and aniline (B), [Glu-NCA]/[aniline]/ [$Fmes_2BF$]=5:1:1, 25 °C in CD_2Cl_2.

References.

1. Daly, W. H.; Poché, D. *Tetrahedron Lett*. **1988**, *29(46)*, 5859-5862.
2. Koerber-Plé, K.; Massiot, G. J. Hetero. Chem. 1995, 32 (4), 1309–1315.
3. Senokuchi, K.; Nakai, H. Nagao, Y.; Sakai, Y.; Katsube, N.; Kawamura， M. Bioorg.& Med. Chem. 1998, 6, 441-463.