Supporting Information

Facile Synthesis of Polypeptoid Bearing Bulky Sidechains via Urea Accelerated Ring-Opening Polymerization of α-Amino Acid *N*-Substituted *N*-Carboxyanhydrides

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Material

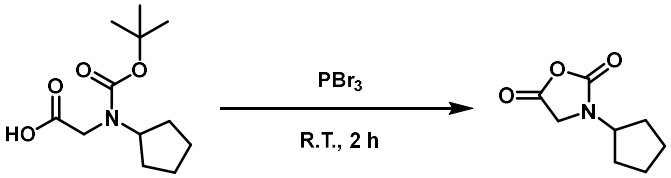
Anhydrous tetrahydrofuran (THF), n-hexylamine and *tert*-butylbenzylamine were purchased from Sigma-Aldrich and used without further purification. Bis(trifluoromethyl)aniline, 3,5-bis(trifluoromethyl)phenyl isocyanate and 1,3-bis(3,5-bis(trifluoro-ethyl)phenyl)thiourea (TU-S) were purchased from Shanghai Macklin Biochemical Technology Co., Ltd. Cyclopentylamine, cyclohexylamine, cyclooctylamine, ethyl 2-bromoacetate, glyoxylic acid, and solvents including dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc), hexane, acetonitrile (MeCN) were purchased from Adamas-beta®. All solvents used in synthesizing α-amino acid *N*-substituted *N*-carboxyanhydride

(NNCA) were freshly distilled or dried over $MgSO_4$ before use.

Instrumentation

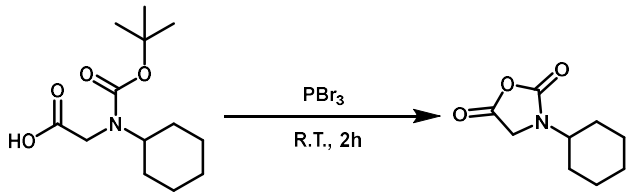
Gel permeation chromatography (GPC) was equipped with a Waters 1515 isocratic HPLC pump, a Brookhaven BI-MwA multi-angle light scattering detector, and a Waters 2414 refractive index detector. Tosoh TSKgel Alpha-2500 column (particle size 7 μm, 300 × 7.8 mm), Tosoh TSKgel Alpha-3000 column (particle size 7 μm, 300 × 7.8 mm) and Tosoh TSKgel Alpha-4000 column (particle size 10 μm, 300 × 7.8 mm) are connected in series for the separation of polypeptoids using 0.01 M LiBr in DMF as the mobile phase at a flow rate of 1 mL/min at 50°C. The calibration curve was determined using polymethylmethacrylate standards. A Shimadzu LC-20AR high-performance liquid chromatography (HPLC) system equipped with a Gemini 5 μm NX-C18 column was used for HPLC analysis. The intermediates of the monomer synthesis were purified using a SepaBean machine equipped with Sepaflash columns manufactured by Santai Technologies Inc. in China. Water content was measured by a Mettler Toledo V20 volumetric Karl-Fischer titrator. Nuclear magnetic resonance (NMR) spectra were obtained from a Bruker Avance III 400 MHz or an Ascend 600 MHz spectrometer. ^{1}H NMR chemical shifts were referenced to the resonance of the residual protonated solvent (δ 7.26 for $CDCl_3$, δ 3.31 for MeOD-d_4, δ 2.05 for acetone-d_6). High-resolution electrospray ionization mass spectroscopy (HRESI-MS) was tested by a Waters XEVO G2 TOF mass spectrometer and High-resolution EI Mass (HREI-MS) spectra were collected on a Waters GCT. Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectra were collected in a reflection mode and resolved using an AB SCIEX 5800plus MALDI-TOF analyzer.

Synthesis of *N*-cyclopentyl glycine *N*-carboxyanhydride (cyclopentyl-NNCA)



The product was synthesized by following a previously reported procedure.[1, 2] *N*-Boc-*N*-cyclopentyl-amino-acetic acid (2.0 g, 8.2 mmol) synthesized previously,[2] was dissolved in 80 mL anhydrous CH_2Cl_2 in a dry round-bottom flask charged with a magnetic stirring bar. Phosphorus tribromide (0.8 mL, 8.2 mmol) was added dropwise into the reaction flask in an ice bath under nitrogen protection. The reaction was stirred at room temperature for 2 h, and then the mixture was washed with cold deionization water rapidly and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the obtained crude product was recrystallized using dried CH_2Cl_2/hexane to afford a white solid (0.9 g, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30-4.41 (m, 1H), 4.06 (s, 2H), 1.93-2.04 (m, 2H), 1.50-1.78 (m, 6H). The ^{1}H NMR spectrum of this product was consistent to that in precedent literature.[2]

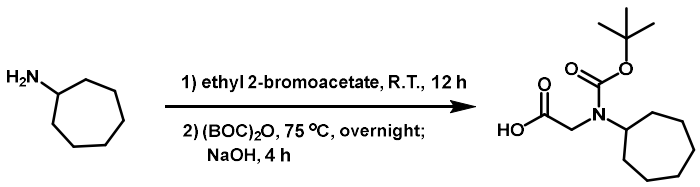
Synthesis of *N*-cyclohexyl glycine *N*-carboxyanhydride (cyclohexyl-NNCA)



The product was synthesized by following a previously reported procedure.[1, 2] *N*-Boc-*N*-cyclohexyl-amino-acetic acid (2.0 g, 7.8 mmol) synthesized previously,[2] was dissolved in 80 mL anhydrous CH_2Cl_2 in a dry round-bottom flask charged with magnetic stirring bar. Phosphorus tribromide (0.7 mL, 7.8 mmol) was added dropwise into the reaction flask in ice-water bath under nitrogen protection. The reaction was stirred at room temperature for 2 h. The mixture was washed with cold deionization water

rapidly and dried over anhydrous $MgSO_4$, and then the solvent was removed under vacuum and the obtained crude product was recrystallized using dried CH_2Cl_2/hexane to afford a white solid (0.8 g, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (s, 2H), 3.78-3.91 (m, 1H), 1.81-1.95 (m, 4H), 1.65-1.76 (m, 1H), 1.27-1.48 (m, 4H), 1.04-1.20 (m, 1H). The ^{1}H NMR spectrum of this product was consistent to that in precedent literature.[2]

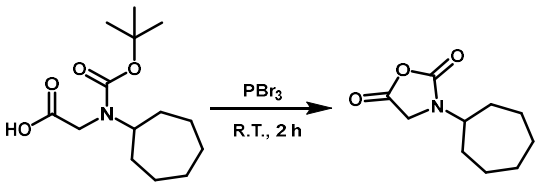
Synthesis of *N*-Boc-*N*-cycloheptyl-amino-acetic



The product was synthesized by following a previously reported procedure.[1, 2] Cycloheptylamine (12.0 mL, 94.2 mmol) was dissolved in 250 mL CH_2Cl_2 in a dry round-bottom flask charged with a magnetic stirring bar. Ethyl 2-bromoacetate (10.5 mL, 94.2 mmol) and triethylamine (39.2 mL, 282.7 mmol) were added dropwise, and the reaction mixture was stirred at room temperature for 12 h. The mixture was washed with deionization water (3 × 300 mL) and brine once (300 mL), then the residue was dried over anhydrous $MgSO_4$. After removing CH_2Cl_2 under vacuum, *N*-cycloheptylglycine ethyl ester was obtained and purified through silica gel column chromatography (5.6 g, 30% yield). Then Di-*tert*-butyl dicarbonate (6.4 mL, 27.6 mmol) was added dropwise into *N*-cycloheptylglycine ethyl ester (5.0 g, 25.1 mmol) in 100 mL MeOH, and heated to reflux overnight. After removing MeOH, the obtained oil was dissolved in a mixture of MeOH (120 mL) and THF (40 mL), and then NaOH (1 M, 75 mL) was added dropwise, followed by stirring the reaction at room temperature for 5 hours. After that, the mixture was adjusted to neutral pH using an HCl solution (1 M). After removing the organic solvent under vacuum, the residue was acidified to pH 3-4 by the HCl solution (4 M) at 0°C. The water

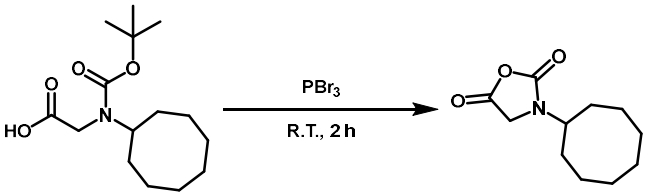
phase was extracted with CH_2Cl_2 three times. After dried over anhydrous $MgSO_4$, the CH_2Cl_2 solvent was removed under vacuum to obtain *N*-Boc-*N*-cycloheptyl-amino-acetic acid as a white solid (4.2 g, 61% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.67-4.28 (m, 3H), 1.30-1.93 (m, 21H).

Synthesis of *N*-cycloheptyl glycine *N*-carboxyanhydride (cycloheptyl -NNCA)



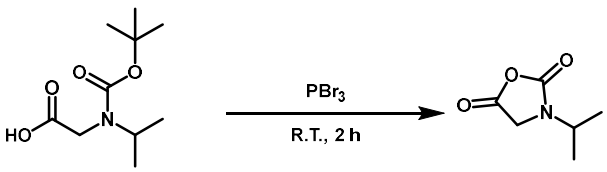
The product was synthesized by following a previously reported procedure.[1, 2] *N*-Boc-*N*-cycloheptyl-amino-acetic acid (2.0 g, 7.4 mmol) was dissolved in 70 mL anhydrous CH_2Cl_2 in a dry round-bottom flask charged with magnetic stirring bar. Phosphorus tribromide (0.7 mL, 7.4 mmol) was added dropwise into the reaction round-bottomed flask in ice-water bath under nitrogen protection. The reaction was stirred at room temperature for 2 h. The mixture was washed with cold deionization water rapidly and dried over anhydrous $MgSO_4$, and then the solvent was removed under vacuum and the obtained crude product was recrystallized using dried CH_2Cl_2/hexane to afford a white solid (0.8 g, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (s, 2H), 3.98-4.05 (m, 1H), 1.86-1.97 (m, 2H), 1.47-1.77 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.08, 151.27, 54.85, 45.68, 32.79, 27.56, 24.31. HREI-MS: m/z calculated for $C_{10}H_{15}NO_3$ $[M]^+$: 197.1052; Found: 197.1050.

Synthesis of *N*-cyclooctyl glycine *N*-carboxyanhydride (cyclooctyl-NNCA)



The product was synthesized by following a previously reported procedure.[1, 2] *N*-Boc-*N*-cyclooctyl-amino-acetic acid (2.0 g, 7.0 mmol) synthesized previously,[2] was dissolved in 70 mL anhydrous CH_2Cl_2 in a dry round-bottom flask charged with magnetic stirring bar. Phosphorus tribromide (0.7 mL, 7.0 mmol) was added dropwise into the reaction round-bottomed flask in ice-water bath under nitrogen protection. The reaction was stirred at room temperature for 2 h. The mixture was washed with cold deionization water rapidly and dried over anhydrous $MgSO_4$, and then the solvent was removed under vacuum and the obtained crude product was recrystallized using dried CH_2Cl_2/hexane to afford a white solid (0.9 g, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09-4.18 (m, 1H), 4.06 (s, 2H), 1.52-1.89 (m, 14H). The ^{1}H NMR spectrum of this product was consistent to that in precedent literature.[2]

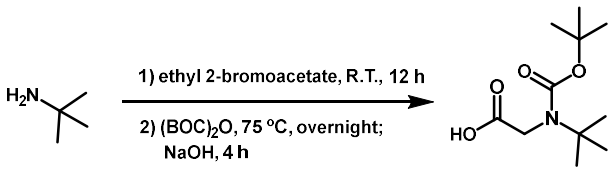
Synthesis of *N*-isopropyl glycine *N*-carboxyanhydride (isopropyl-NNCA)



The product was synthesized by following a previously reported procedure.[1, 2] *N*-Boc-*N*-isopropyl-amino-acetic acid (2.0 g, 9.2 mmol) was dissolved in 70 mL anhydrous CH_2Cl_2 in a dry round-bottom flask charged with magnetic stirring bar. Phosphorus tribromide (0.9 mL, 9.2 mmol) was added dropwise into the reaction round-bottomed flask in ice-water bath under nitrogen protection. The reaction was stirred at room temperature for 2 h. The mixture was washed with cold deionization water rapidly and dried over anhydrous $MgSO_4$, and then the solvent was removed under vacuum and the obtained crude

product was recrystallized using dried CH_2Cl_2/hexane to afford a white solid (0.7 g, 54% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 4.23-4.34 (m, 1H), 4.03 (s, 2H), 1.24-1.28 (m, 6H). The ^1H NMR spectrum of this product was consistent to that in precedent literature.[3]

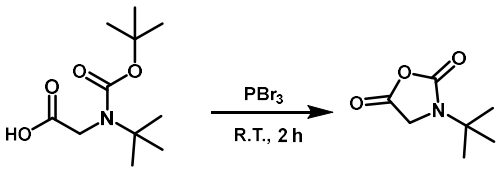
Synthesis of *N*-Boc-*N*-*tert*-butyl -amino-acetic



The product was synthesized by following a previously reported procedure.[1, 2] *Tert*-butylamine (12.0 mL, 114.1 mmol) was dissolved in 250 mL CH_2Cl_2 in a dry round-bottom flask charged with a magnetic stirring bar. Ethyl 2-bromoacetate (12.7 mL, 141.1 mmol) and triethylamine (47.5 mL, 342.6 mmol) were added dropwise, and the reaction mixture was stirred at room temperature for 12 h. The mixture was washed with deionization water (3 × 300 mL) and brine once (300 mL), then the residue was dried over anhydrous $MgSO_4$. After removing CH_2Cl_2 under vacuum, *N*-*tert*-butylglycine ethyl ester was obtained and purified through silica gel column chromatography (5.1g, 28% yield). Di-*tert*-butyl dicarbonate (7.9 mL, 34.5 mmol) was added dropwise into *N*-*tert*-butylglycine ethyl ester (5.0 g, 31.4 mmol) in 150 mL MeOH, and heated to reflux overnight. After removing MeOH , the obtained oil was dissolved in a mixture of MeOH (150 mL) and THF (50 mL), and then NaOH (1 M, 100 mL) was added dropwise, followed by stirring the reaction at room temperature for 5 hours. After that, the mixture was adjusted to neutral pH using an HCl solution (1 M). After removing the organic solvent under vacuum, the residue was acidified to pH 3-4 by the HCl solution (4 M) at 0°C. The water phase was extracted with CH_2Cl_2 three times. After dried over anhydrous $MgSO_4$, the CH_2Cl_2 solvent was removed under vacuum to obtain *N*-Boc-*N*-*tert*-butyl-amino-acetic acid as a white solid (3.0g, 41% yield). ^1H NMR

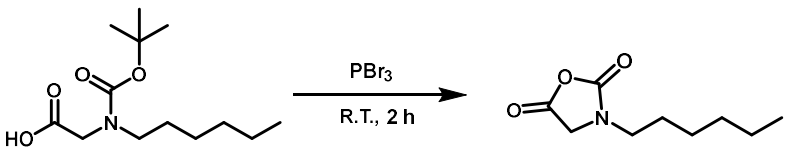
(600 MHz, $CDCl_3$) δ 4.08 (s, 2H), 1.46 (s, 9H), 1.41 (s, 9H). The ^{1}H NMR spectrum of this product was consistent to that in precedent literature.[4]

Synthesis of *N*-*tert*-butyl glycine *N*-carboxyanhydride (*tert*-butyl-NNCA)



The product was synthesized by following a previously reported procedure.[1, 2] *N*-Boc-*N*-*tert*-butyl-amino-acetic acid (2.0 g, 8.6 mmol) was dissolved in 70 mL anhydrous CH_2Cl_2 in a dry round-bottom flask charged with magnetic stirring bar. Phosphorus tribromide (0.8 mL, 8.6 mmol) was added dropwise into the reaction round-bottomed flask in ice-water bath under nitrogen protection. The reaction was stirred at room temperature for 2 h. The mixture was washed with cold deionization water rapidly and dried over anhydrous $MgSO_4$, and then the solvent was removed under vacuum and the obtained crude product was recrystallized using dried CH_2Cl_2/hexane to afford a white solid (0.6 g, 46% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.14 (s, 2H), 1.46 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.73, 150.46, 55.28, 47.98, 27.78. The ^{13}C NMR spectra were consistent to that in precedent literature.[5]

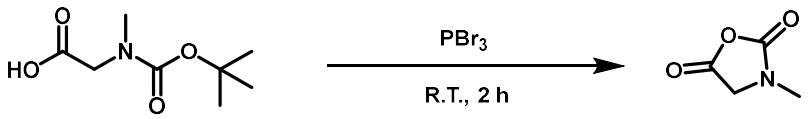
Synthesis of *N*-hexyl glycine *N*-carboxyanhydride (hexyl-NNCA)



The product was synthesized by following a previously reported procedure.[2, 6] *N*-Boc-*N*-hexyl-amino-acetic acid (2.0 g, 7.7 mmol) synthesized previously,[2] was dissolved in 100 mL anhydrous CH_2Cl_2 in a dry round-bottom flask charged with magnetic stirring bar. Phosphorus tribromide (0.7 mL, 7.7 mmol)

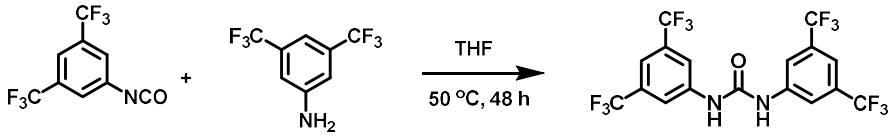
was added dropwise into the reaction round-bottomed flask in ice-water bath under nitrogen protection. The reaction was stirred at room temperature for 2 h. The mixture was washed with cold deionization water rapidly and dried over anhydrous $MgSO_4$, and then the solvent was removed under vacuum and the obtained crude product was recrystallized using dried CH_2Cl_2/hexane to afford a white solid (0.8 g, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (s, 2H), 3.40 (t, J = 7.3 Hz, 2H), 1.52-1.63 (m, 2H), 1.24-1.38 (m, 6H), 0.89 (m, 3H). The ^{1}H NMR spectrum of this product was consistent to that in precedent literature.[2]

Synthesis of *N*-methyl glycine *N*-carboxyanhydride (sarcosine-NCA)



The product was synthesized by following a previously reported procedure.[2, 6] *N*-Boc-*N*-methyl-amino-acetic acid (2.0 g, 10.6 mmol) synthesized previously,[2] was dissolved in 150 mL anhydrous CH_2Cl_2 in a dry round-bottom flask charged with magnetic stirring bar. Phosphorus tribromide (1.0 mL, 10.6 mmol) was added dropwise into the reaction round-bottomed flask in ice-water bath under nitrogen protection. The reaction was stirred at room temperature for 2 h. The mixture was washed with cold deionization water rapidly and dried over anhydrous $MgSO_4$, and then the solvent was removed under vacuum and the obtained crude product was recrystallized using dried CH_2Cl_2/hexane to afford a white solid (0.6 g, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 2H), 3.06 (s, 3H). The ^{1}H NMR spectrum of this product was consistent to that in precedent literature.[2]

Synthesis of 1,3-bis[3,5-bis(trifluoromethyl)phenyl]urea



This compound can be purchased or easily synthesized in a laboratory. The product was synthesized by following a previously reported procedure.[7] 3,5-bis(trifluoromethyl)aniline (0.3 g, 1.2 mmol) was dissolved in dry 10 mL THF in a dry round-bottom flask charged with magnetic stirring bar, then 3,5-bis(trifluoromethyl)phenyl isocyanate (0.7 mL, 3.91 mmol) was added dropwise. The reaction stirred at 50°C for 48 h. After that, the reaction mixture was cooled down to room temperature, followed by removing the solvent under reduced pressure and washed with CH_2Cl_2, and then dried under vacuum overnight. The product was obtained as white solid (0.5 g, 83% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.12 (s, 4H), 7.59 (s, 2H). The ^{1}H NMR spectrum of this product was consistent to that in precedent literature.[8]

General procedure for primary amine initiated NNCA polymerization

The procedure of typical NNCA polymerization was performed as follows. The cyclohexyl-NNCA (36.6 mg, 0.2 mmol) with 5% equivalent of 1,3-bis[3,5-bis(trifluoromethyl)phenyl]urea (U-O) was dissolved in anhydrous THF (160 μL), then a THF solution of n-hexylamine (40 μL, 0.25 M) was added to the mixture and stirred at room temperature inside a glove box. After the polymerization was complete (monitored by TLC), the resulting polypeptoid was precipitated out by hexane (45 mL). After centrifugated and dried under air flow, the collected solid was dissolved in THF (0.2 mL) and then was precipitated out again by hexane (45 mL). This dissolution-precipitation procedure was repeated two more times. The solid was washed with hexafluoroisopropanol three times to remove U-O and

precipitated by THF/hexane. The polymer was collected and dried under vacuum to provide polypeptoids (70−93% yield).

The procedure of sarcosine-NCA polymerization was performed as follows. The sarcosine-NCA (23.0 mg, 0.2 mmol) with 5% equivalent of U-O was dissolved in 160 μL anhydrous THF and DMF mixtures (THF:DMF = 90:10, v/v), then a THF solution of *tert*-butylbenzylamine (40 μL, 0.25 M) was added to the mixture and stirred at room temperature inside a glove box. After the polymerization was complete (monitored by TLC), the resulting polypeptoid was precipitated out by hexane (45 mL). After centrifugated and dried under air flow, the collected solid was dissolved in 0.2 mL methanol (MeOH) and then was precipitated out again by ether (45 mL). This dissolution-precipitation procedure was repeated two more times. The residue was washed with THF three times to remove U-O and precipitation by MeOH/ether. The poly(sarcosine) was collected and dried under vacuum to provide polypeptoids.

Kinetic study of the polymerization on cyclohexyl-NNCA

The procedure of typical kinetic study of the polymerization on cyclohexyl-NNCA was performed as follows. Cyclohexyl-NNCA (36.6 mg, 0.2 mmol), U-O (4.8 mg, 0.01 mmol) and internal standard triphenylmethane (5.0 mg, 0.02 mmol) were dissolved in anhydrous THF, and then mixed with a THF solution of n-hexylamine ([M]:[I] = 50:1, $[M]_0$ = 1 M). The reaction mixture was stirred at room temperature. HPLC quantified the unreacted NNCA by calculating the relative peak area ratio between the NNCA and the internal standard.[9] Then the rate constant for chain propagation was calculated by the equation below:

$$-\frac{d[M]}{dt} = k_p[I][M]$$

$$\ln\frac{[M]_0}{[M]} = k_p[I]t$$

$[M]_0$ is the initial concentration of the monomer, [M] is the residual concentration of the monomer, [I] is the concentration of initiator, k_p is the rate constant for chain propagation.

Mechanism studies

For the hydrogen bonding mechanism study, the ^{1}H NMR spectra of U-O organocatalyst and the ^{1}H NMR spectra of a 1:1 molar ratio mixture on the U-O and the cyclohexyl-NNCA were collected separately using $CDCl_3$/acetonitrile ($CDCl_3$:MeCN = 85:15, v/v) as the solvent. The ^{13}C NMR spectra of cyclohexyl-NNCA and the ^{13}C NMR spectra of cyclohexyl-NNCA mixing with U-O (1:2, molar ratio) after 20 min was collected separately using $CDCl_3$/acetonitrile ($CDCl_3$:MeCN = 85:15, v/v) as the solvent.

For HRESI-MS analysis, the cyclohexyl-NNCA (18.3 mg, 0.1 mmol) with 5% equivalent of U-O (2.4 mg, 0.005 mmol) was dissolved in anhydrous THF (100 μL), then a THF solution of *tert*-butylbenzylamine (100 μL, 1 M) was added to the mixture and were allowed to stir for 30 min. An aliquot of 5 μL reaction solution was diluted with HPLC grade acetonitrile for HRESI-MS analysis on a Waters XEVO G2 TOF mass spectrometer.

For MALDI-TOF-MS characterization, polypeptoid was prepared by *tert*-butylbenzylamine-initiated polymerization on cyclohexyl-NNCA catalyzed by 5% of U-O in THF at room temperature ([M]/[I] = 20, $[M]_0$ = 1 M). Then, the resulting polypeptoid was precipitated out three times using THF/hexane. Afterward, the polypeptoid was characterized by MALDI-TOF-MS using 2,5-dihydroxybenzoic acid (DHB) as a matrix and using THF as solvent.

Computational details

Density functional theory (DFT) calculations reported in this work were carried out in Gaussian 09 Revision E.01 package[10] using the exchange-correlation functional of B3LYP with different basis sets in the presence of SMD (Solvation Model Based on Density) describing THF at 298.15 K and 1.013×10^5 Pa.[11] Grimme's D3 dispersion correction was employed to improve the van der Waals interactions.[12] Specifically, 6-31G (d, p) basis set was used for structure optimization, and the vibrational frequencies of each structure have been calculated to verify the presence of zero imaginary frequency. 6-311+G (d, p) basis set was used to calculate the electronic energy of each structure and the Basis Set Superposition Error (BSSE) using the full counterpoise (CP) method. Energies and coordinates are given below.

Table S1. The coordinates and electronic energy of the optimized geometries

U-O
Electronic energy = -2036.211444 Hartrees

C	3.49153100	-1.45556700	-0.43194700
C	2.48118400	-0.49519700	-0.29020200
C	2.84663600	0.82369100	0.02205500
C	4.18871500	1.13655000	0.20942500
C	5.19502100	0.17863200	0.11171100
C	4.82207100	-1.12037100	-0.21273100
H	3.23504100	-2.46901400	-0.71414300
H	2.09002600	1.58579200	0.11130100
H	6.23119600	0.43822700	0.27500200
C	5.84084700	-2.22000100	-0.29893500
C	4.55685400	2.54095500	0.60371800
F	5.78877900	-2.87546300	-1.48169400
F	7.10330300	-1.78726900	-0.13486500
F	5.62182200	-3.16697600	0.66052900
F	5.78097000	2.89420400	0.15081400
F	3.68071000	3.45660700	0.13837800
F	4.58977400	2.68714700	1.95280700
N	1.16201500	-0.92999100	-0.44195600
H	1.04522500	-1.93106600	-0.55732600
C	0.00416900	-0.17824300	-0.31692300
O	-0.01551900	1.03838100	-0.23229600
N	-1.12552100	-0.97819500	-0.30331300

H	-0.98410600	-1.97936600	-0.23386700
C	-2.45563500	-0.55793300	-0.19163600
C	-2.87662600	0.75991400	-0.40498200
C	-3.41167400	-1.53369500	0.13286000
C	-4.22875200	1.07532400	-0.28626600
H	-2.15918800	1.52472700	-0.65484900
C	-4.75099300	-1.19042800	0.24427900
H	-3.10115500	-2.55723700	0.30422700
C	-5.18202900	0.11888800	0.03831000
H	-6.22635400	0.38124300	0.13098800
C	-4.63969200	2.50953400	-0.47426700
C	-5.76835300	-2.25542300	0.54417600
F	-6.33932700	-2.73803500	-0.58825800
F	-5.23454900	-3.31598900	1.18889100
F	-6.77884300	-1.79019100	1.31300600
F	-5.96372000	2.64328600	-0.70594500
F	-4.35885200	3.26039200	0.62022400
F	-3.99469400	3.09197200	-1.51143700

NNCA
Electronic energy = -631.477647 Hartrees

C	-1.56579600	1.16252100	-0.10144800
C	-1.31183600	-1.13471200	0.06472400
C	-2.77136500	-0.76177200	0.06977000
O	-2.87962900	0.57528100	-0.03004900
H	-1.05327000	-1.65303900	0.99192900
O	-1.43715900	2.34849000	-0.18728500
O	-3.72677200	-1.49395900	0.14754500
N	-0.67226600	0.15867800	-0.05429600
C	0.78424000	0.36583200	-0.07116700
C	1.41228400	-0.01853700	1.27693100
C	1.43420800	-0.39528600	-1.23537300
H	0.91845200	1.43818600	-0.23072200
C	2.93166700	0.20185300	1.25154400
H	1.20496600	-1.07470600	1.48143300
H	0.94673900	0.56930800	2.07379800
C	2.95220900	-0.16696100	-1.25174600
H	1.23815100	-1.46686800	-1.12044300
H	0.98090700	-0.07565100	-2.17855700
C	3.58890100	-0.55548200	0.08961900
H	3.36382800	-0.11152400	2.20660200
H	3.13770600	1.27442000	1.14646100
H	3.40018500	-0.74057600	-2.06868400
H	3.15653400	0.89123500	-1.45732600

H	4.66449700	-0.35443500	0.06905500
H	3.46755700	-1.63417600	0.24683800
H	-1.09898200	-1.79615500	-0.77913100

U-O and Cyclohexyl-NNCA
Counterpoise corrected energy = -2667.702869 Hartrees
BSSE energy = 0.002201652 Hartrees

C	2.24689800	1.30313400	-1.18706500
C	1.00943200	1.76355600	-0.71813800
C	0.96100000	2.99609300	-0.04803900
C	2.13624300	3.71078000	0.15736400
C	3.37575800	3.23967900	-0.26863400
C	3.40879800	2.02542700	-0.94410700
H	2.30042300	0.37575300	-1.74348000
H	0.01758200	3.38373400	0.29969500
H	4.27996200	3.80280700	-0.08693900
C	4.70850100	1.42881900	-1.40165900
C	2.07439300	4.99964700	0.93088900
F	4.69868900	1.12943800	-2.72133100
F	5.76643100	2.22833600	-1.17911300
F	4.96176300	0.25241000	-0.75573000
F	3.03005100	5.87417500	0.54322400
F	0.88541600	5.62575600	0.80085100
F	2.25970900	4.79256400	2.25952500
N	-0.09880600	0.93859000	-0.92676000
H	0.10589100	0.02929000	-1.32722500
C	-1.40726300	1.16330100	-0.52824800
O	-1.81498800	2.22465400	-0.08664600
N	-2.19338800	0.03634700	-0.69644100
H	-1.72027700	-0.82807600	-0.93330200
C	-3.55480100	-0.09455400	-0.40027300
C	-4.41471700	0.99042100	-0.19328400
C	-4.07425200	-1.39723800	-0.33242100
C	-5.76092500	0.75580200	0.07966200
H	-4.03663000	1.99883500	-0.24062900
C	-5.41883200	-1.60039000	-0.05882400
H	-3.42085300	-2.24730400	-0.48697200
C	-6.28417800	-0.52858900	0.15317200
H	-7.32997900	-0.69325400	0.37047100
C	-6.64612400	1.94210800	0.34476000
C	-5.96962500	-2.99873200	-0.03782500
F	-6.51247700	-3.34295900	-1.23287800
F	-5.02473500	-3.92442500	0.23727300
F	-6.94923200	-3.14478900	0.88286300

F	-7.95882600	1.64568100	0.22831900
F	-6.46796600	2.43219800	1.59721400
F	-6.39369800	2.96523000	-0.50405200
C	1.97580600	-4.27557300	0.46791400
C	2.22434900	-2.11956600	-0.34402700
C	0.83452300	-2.63169100	-0.61870500
O	0.72686100	-3.88136600	-0.13278700
H	2.72801900	-1.87727500	-1.28362300
O	2.09630200	-5.36068100	0.95623600
O	-0.07191600	-2.06339300	-1.17580000
N	2.82676300	-3.24166800	0.34449000
C	4.22099400	-3.27640700	0.81302100
C	5.20160400	-3.24715200	-0.36896700
C	4.49620100	-2.13694400	1.80449500
H	4.32362500	-4.23115600	1.33391900
C	6.65387200	-3.28513400	0.12824100
H	5.04211200	-2.32904200	-0.94510100
H	4.99467400	-4.09272400	-1.03189800
C	5.94987300	-2.18529200	2.29564500
H	4.32156000	-1.17624600	1.30801200
H	3.79774900	-2.20699600	2.64384100
C	6.93676200	-2.14915900	1.12077100
H	7.33558900	-3.22683800	-0.72555500
H	6.84091300	-4.24863500	0.61872800
H	6.13448700	-1.34910600	2.97668500
H	6.10622600	-3.10532400	2.87260700
H	7.96493400	-2.21797100	1.48938700
H	6.84567200	-1.18631600	0.60341300
H	2.17440400	-1.21734400	0.27112100

TU-S
Electronic energy = -2359.15798 Hartrees

C	3.32833100	-1.29487200	0.65665700
C	2.47752000	-0.55728600	-0.16476100
C	3.00093400	0.45465700	-0.97487000
C	4.36173700	0.73046100	-0.92962100
C	5.22314200	0.00669500	-0.10597600
C	4.69332200	-1.01254300	0.67411500
H	2.92396200	-2.08477100	1.27910000
H	2.35516800	1.00588300	-1.64116800
H	6.28124400	0.22630300	-0.08538500
C	5.57507800	-1.82618900	1.57903600
C	4.91121700	1.85649800	-1.76042400
F	5.44122700	-3.15475800	1.34746000

F	6.88277100	-1.52972100	1.43789900
F	5.26545800	-1.63660500	2.88524100
F	6.19215700	1.63741800	-2.13375700
F	4.19707100	2.05867400	-2.88981700
F	4.90290100	3.03044600	-1.08232100
N	1.11232400	-0.91290700	-0.19914800
H	0.93501400	-1.90755600	-0.10082400
C	0.01894800	-0.08845800	-0.15042400
N	-1.13499600	-0.80431900	-0.31050800
H	-1.01426500	-1.76977100	-0.61193600
C	-2.47773100	-0.41600700	-0.16177000
C	-2.91994200	0.48241000	0.81394300
C	-3.41400800	-1.04297400	-0.98943600
C	-4.28050000	0.74451100	0.93611800
H	-2.21452100	0.96408700	1.47245400
C	-4.77186100	-0.79291400	-0.82511400
H	-3.07430100	-1.72625200	-1.75776700
C	-5.22372000	0.10992100	0.13140100
H	-6.27905500	0.31601900	0.24656400
C	-4.75165900	1.67348000	2.02180900
C	-5.75879900	-1.57106900	-1.64606400
F	-5.27328500	-1.90689000	-2.86164100
F	-6.08253700	-2.74737100	-1.03321700
F	-6.91540000	-0.91022700	-1.83989200
F	-5.87551000	2.33689400	1.67201300
F	-5.04332800	0.99745800	3.16242700
F	-3.82483000	2.59826700	2.34832600
S	0.09332200	1.58102800	0.06402200

Cyclohexyl-NNCA
Electronic energy = -631.477643 Hartrees

C	1.56164400	1.16418400	-0.06226800
C	1.31864500	-1.13882400	0.02602600
C	2.77707400	-0.75843300	0.04083400
O	2.87823300	0.58127100	-0.01691900
H	1.10301400	-1.77112600	-0.83936300
O	1.42737300	2.35182100	-0.10635000
O	3.73797600	-1.48576000	0.09692700
N	0.67273100	0.15532700	-0.04488200
C	-0.78439200	0.35988100	-0.04739000
C	-1.43791400	-0.32341000	-1.25686500
C	-1.41065400	-0.10759700	1.27422800
H	-0.91790900	1.44050400	-0.13800300
C	-2.95615700	-0.09091800	-1.25463400

H	-1.24011000	-1.39992500	-1.21525000
H	-0.98751200	0.05902700	-2.17783100
C	-2.92799000	0.12835100	1.26709500
H	-1.21562600	-1.17747400	1.41042000
H	-0.93839400	0.42215400	2.10708700
C	-3.59444400	-0.55074400	0.06300900
H	-3.40796700	-0.61532600	-2.10197900
H	-3.15626600	0.97809900	-1.40009400
H	-3.36070600	-0.23980000	2.20215100
H	-3.12423800	1.20729600	1.22963000
H	-4.66760000	-0.33593200	0.05589600
H	-3.48654300	-1.63787900	0.15662200
H	1.06721200	-1.69049300	0.93540900

TU-S and Cyclohexyl-NNCA
Counterpoise corrected energy = -2990.649338 Hartrees
BSSE energy = 0.002260078 Hartrees

C	4.25319600	-1.22049000	0.69621500
C	3.70558600	-0.25646100	-0.14842200
C	4.54021400	0.47671300	-0.99702000
C	5.91097800	0.25308900	-0.96706600
C	6.47342900	-0.70171300	-0.12075000
C	5.62972900	-1.44041700	0.69814200
H	3.60546300	-1.79460300	1.34869300
H	4.12082000	1.19896400	-1.68059700
H	7.54086200	-0.87125700	-0.11223000
C	6.18069400	-2.48374700	1.62889300
C	6.81007300	1.08293900	-1.84062000
F	5.58083100	-3.68523800	1.44662600
F	7.50604500	-2.67534900	1.47203200
F	5.98001600	-2.15379700	2.92844700
F	7.92384400	0.41148300	-2.21054200
F	6.19537400	1.48808300	-2.97393900
F	7.22960100	2.20508400	-1.20592800
N	2.30260400	-0.10549900	-0.16458200
H	1.78591800	-0.96872000	-0.02923400
C	1.57338800	1.05436900	-0.14192600
N	0.23815300	0.78964900	-0.27131000
H	0.00385300	-0.16518200	-0.53764400
C	-0.87712500	1.63376800	-0.13179300
C	-0.95599700	2.66220000	0.81204300
C	-1.98839000	1.35292600	-0.93238800
C	-2.13311100	3.39384200	0.92970400
H	-0.11486100	2.88363400	1.44979400

C	-3.16654600	2.07374400	-0.77217800
H	-1.92567000	0.56870100	-1.67647100
C	-3.25318900	3.10909500	0.15234800
H	-4.16490500	3.67988700	0.26389400
C	-2.22639900	4.46470800	1.98243500
C	-4.37865000	1.66983300	-1.56033400
F	-4.06385600	1.14381800	-2.76463400
F	-5.08811200	0.70575500	-0.90360400
F	-5.22897600	2.69128800	-1.77383500
F	-3.04777400	5.47181700	1.61285300
F	-2.71983300	3.97405200	3.14813900
F	-1.02669800	5.01069400	2.27135200
C	-2.67844400	-4.27602400	0.32892300
C	-2.53132600	-2.03654400	-0.24880800
C	-1.15810400	-2.65003400	-0.14969800
O	-1.28322100	-3.94470100	0.19170600
H	-2.62586900	-1.20833800	0.45853800
O	-3.01018300	-5.38776400	0.61950400
O	-0.08928200	-2.12240500	-0.33601100
N	-3.38493500	-3.15953200	0.07877000
C	-4.85553200	-3.11209600	0.09108400
C	-5.36850800	-2.08863100	1.11391400
C	-5.41166700	-2.83707800	-1.31337100
H	-5.16788900	-4.11106500	0.40457500
C	-6.90411400	-2.05887000	1.12609500
H	-4.99282800	-1.09399900	0.85064100
H	-4.97671900	-2.33719100	2.10488300
C	-6.94683600	-2.80881300	-1.29129000
H	-5.04109900	-1.86840400	-1.66773100
H	-5.04648100	-3.60260000	-2.00470000
C	-7.47333600	-1.78836600	-0.27313600
H	-7.24985000	-1.29884800	1.83317500
H	-7.27942200	-3.02390300	1.48921400
H	-7.32378600	-2.57995400	-2.29260900
H	-7.32144700	-3.80692500	-1.03152300
H	-8.56714900	-1.81409200	-0.24538400
H	-7.18517100	-0.77947400	-0.59151800
H	-2.69835500	-1.65588100	-1.25961600
S	2.23819400	2.59493900	0.01096600

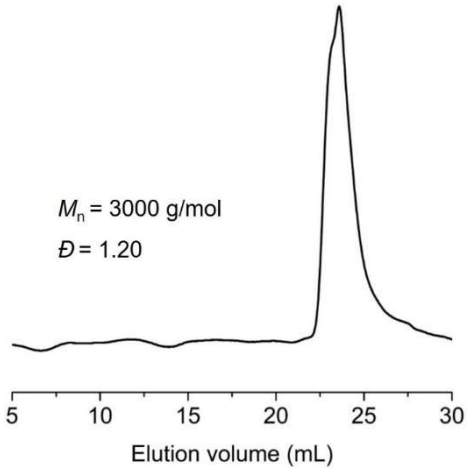


Figure S1. GPC trace of polypeptoid synthesized by n-hexylamine-initiated cyclohexyl-NNCA polymerization with 20% TU-S (molar ratio) in THF ([M]/[I] = 20, $[M]_0$ = 1 M, Table 1, entry 2).

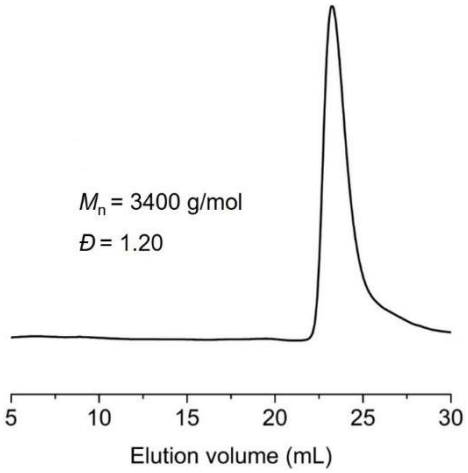


Figure S2. GPC trace of polypeptoid synthesized by n-hexylamine-initiated cyclohexyl-NNCA polymerization with 20% U-O (molar ratio) in THF ([M]/[I] = 20, $[M]_0$ = 1 M, Table 1, entry 3).

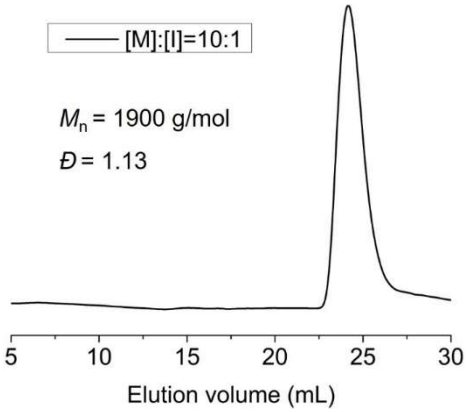


Figure S3. GPC trace of polypeptoid synthesized by n-hexylamine-initiated cyclohexyl-NNCA polymerization with 5% U-O (molar ratio) in THF ([M]/[I] = 10, $[M]_0$ = 1 M, Table 1, entry 4).

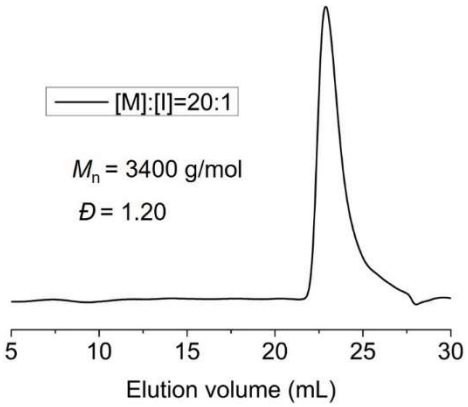


Figure S4. GPC trace of polypeptoid synthesized by n-hexylamine-initiated cyclohexyl-NNCA polymerization with 5% U-O (molar ratio) in THF ([M]/[I] = 20, $[M]_0$ = 1 M, Table 1, entry 5).

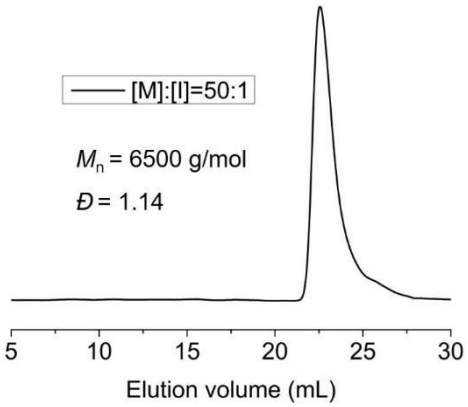


Figure S5. GPC trace of polypeptoid synthesized by n-hexylamine-initiated cyclohexyl-NNCA polymerization with 5% U-O (molar ratio) in THF ([M]/[I] = 50, $[M]_0$ = 1 M, Table 1, entry 6).

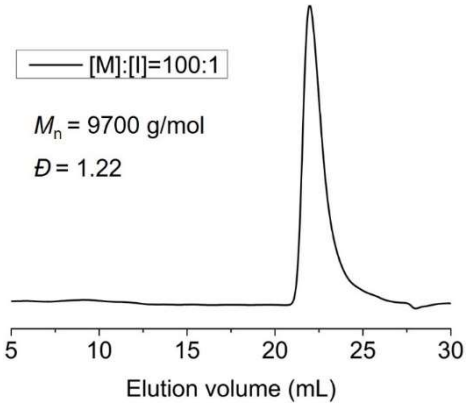


Figure S6. GPC trace of polypeptoid synthesized by n-hexylamine-initiated cyclohexyl-NNCA polymerization with 5% U-O (molar ratio) in THF ([M]/[I] = 100, $[M]_0$ = 1 M, Table 1, entry 7).

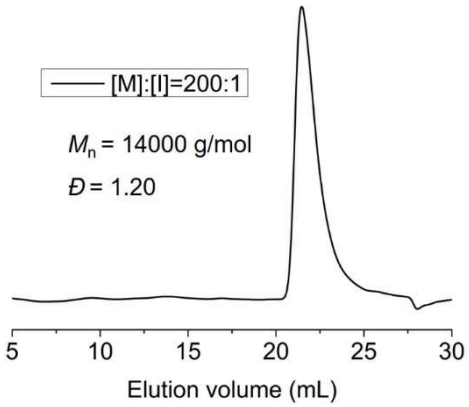


Figure S7. GPC trace of polypeptoid synthesized by n-hexylamine-initiated cyclohexyl-NNCA polymerization with 5% U-O (molar ratio) in THF ([M]/[I] = 200, $[M]_0$ = 1 M, Table 1, entry 8).

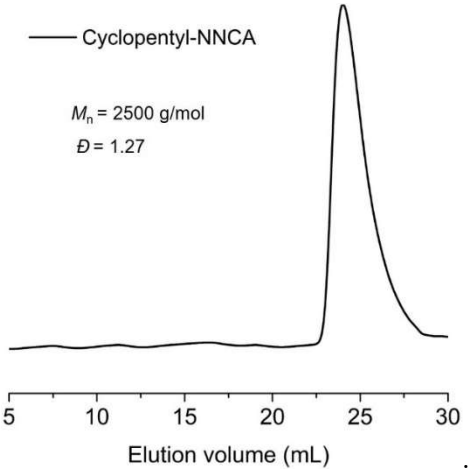


Figure S8. GPC trace of polypeptoid synthesized by *tert*-butylbenzylamine-initiated cyclopentyl-NNCA polymerization with 5% U-O (molar ratio) in THF ([M]/[I] = 20, $[M]_0$ = 1 M, Table 2, entry 1)

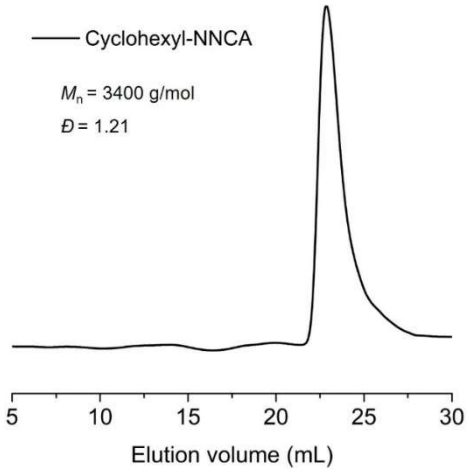


Figure S9. GPC trace of polypeptoid synthesized by *tert*-butylbenzylamine-initiated cyclohexyl-NNCA polymerization with 5% U-O (molar ratio) in THF ([M]/[I] = 20, $[M]_0$ = 1 M, Table 2, entry 2)

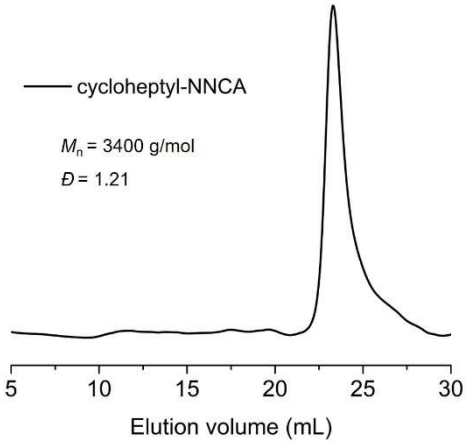


Figure S10. GPC trace of polypeptoid synthesized by *tert*-butylbenzylamine-initiated cyclohetpyl-NNCA polymerization with 5% U-O (molar ratio) in THF ([M]/[I] = 20, $[M]_0$ = 1 M, Table 2, entry 3)

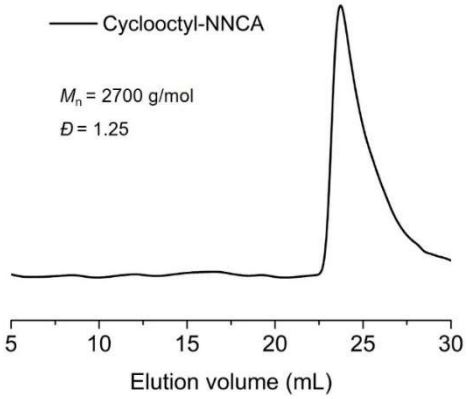


Figure S11. GPC trace of polypeptoid synthesized by *tert*-butylbenzylamine-initiated cyclooctyl-NNCA polymerization with 5% U-O (molar ratio) in THF ([M]/[I] = 20, $[M]_0$ = 1 M, Table 2, entry 4)

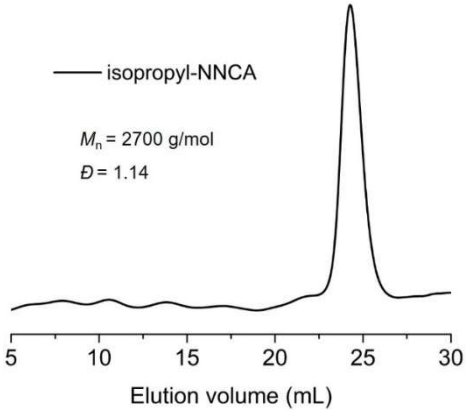


Figure S12. GPC trace of polypeptoid synthesized by *tert*-butylbenzylamine-initiated isopropyl-NNCA polymerization with 5% U-O (molar ratio) in THF ([M]/[I] = 20, $[M]_0$ = 1 M, Table 2, entry 6).

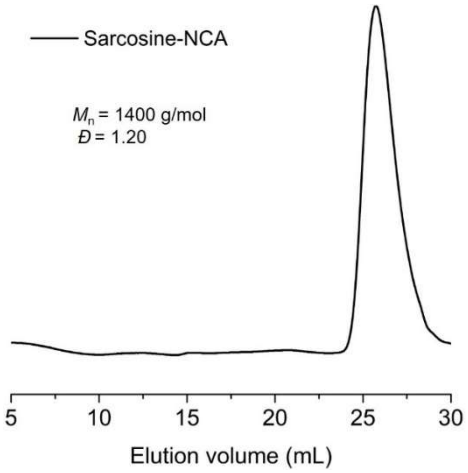


Figure S13. GPC trace of polypeptoid synthesized by *tert*-butylbenzylamine-initiated Sarcosine-NCA polymerization with 5% U-O (molar ratio) in THF ([M]/[I] = 20, $[M]_0$ = 1 M, Table 2, entry 5).

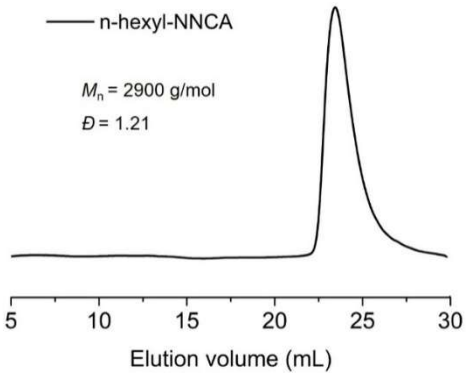


Figure S14. GPC trace of polypeptoid synthesized by *tert*-butylbenzylamine-initiated hexyl-NNCA polymerization with 5% U-O (molar ratio) in THF ([M]/[I] = 20; $[M]_0$ = 1 M, Table 2, entry 7).

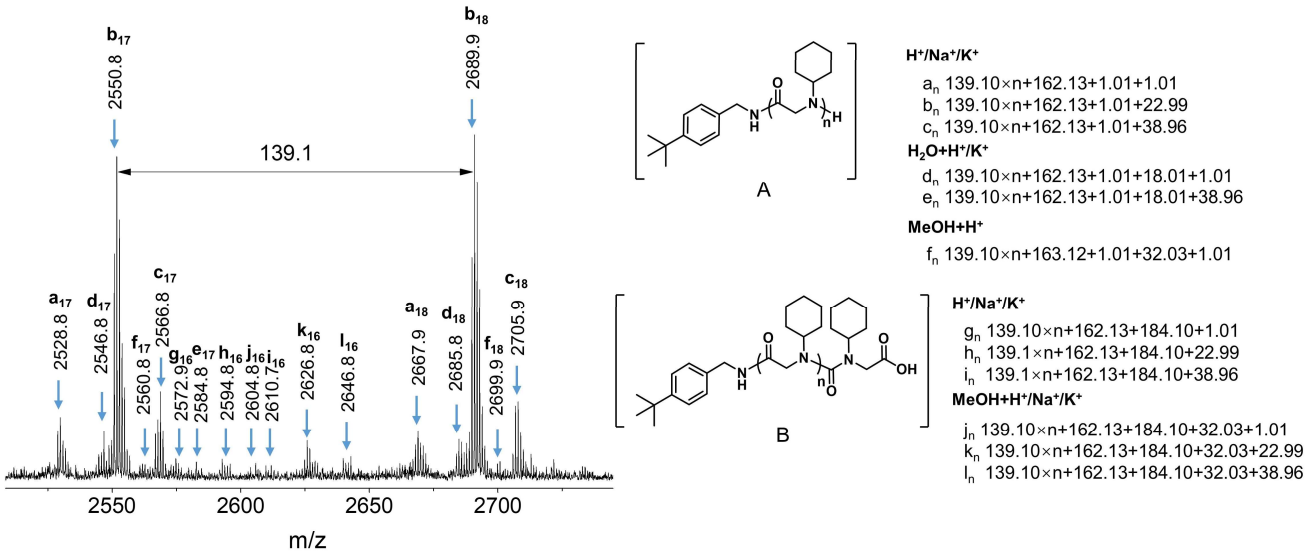


Figure S15. MALDI TOF spectrum of polypeptoid prepared from tert-butylbenzylamine-initiated polymerization on cyclohexyl-NNCA catalyzed by 5% of U-O (molar ratio) in THF at room temperature after purification ([M]/[I] = 20, $[M]_0$ = 1 M) and the detailed structural assignment for the observed mass ions corresponding to Figure 3. Note: many small peaks belong to structure B that come from a side reaction of the NNCA polymerization, similar to the report of side reaction for NCA polymerization in precedent literatures,[13] via nucleophilic addition to the C2 carbonyl by the amine as the reactive center during polymerization.

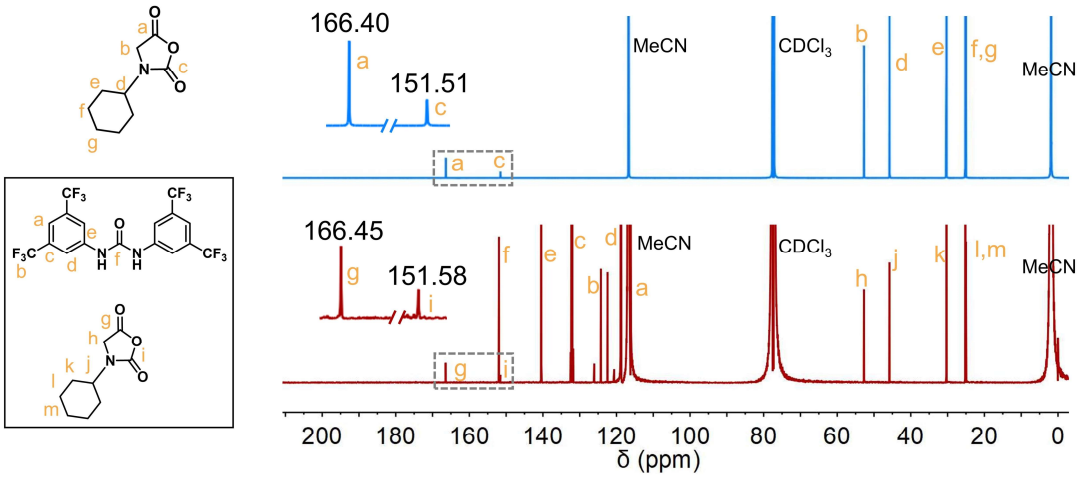


Figure S16. ^{13}C NMR spectra of cyclohexyl-NNCA and cyclohexyl-NNCA mixing with U-O (1:2, molar ratio) after 20 min in $CDCl_3$/MeCN ($CDCl_3$:MeCN = 85:15, v/v).

Table S2. The *tert*-butylbenzylamine-initiated ring-opening polymerization of *tert*-butyl-NNCA.[a]

Entry	Monomer	[M]:[I]:[Cat]	Time	$M_{n,calcd}$ (g/mol)	$M_{n,SEC}$[b] (g/mol)	$Đ$[b]
1	*Tert*-butyl-NNCA	20/1/4	48 h	2400	N/A	N/A

[a] The *tert*-butylbenzylamine-initiated ring-opening polymerization on *tert*-butyl-NNCA in THF catalyzed by 20% U-O (molar ratio) at 76°C ($[M]_0$ = 4 M).

[b] $M_{n,SEC}$ of obtained oligomer is below the GPC detection limit.

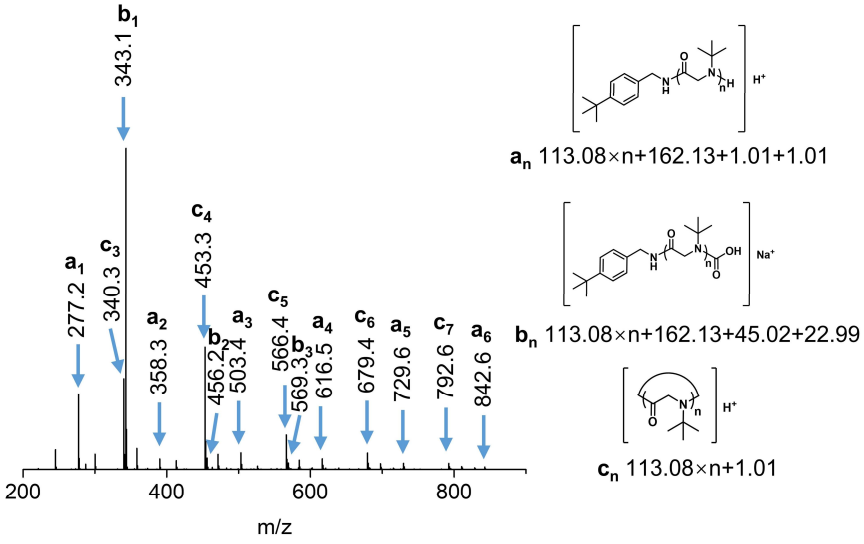


Figure S17. ESI spectrum of oligomer synthesized by *tert*-butylbenzylamine-initiated *tert*-butyl-NNCA polymerization with 20% U-O (molar ratio) in THF at 76°C without furthering purification ([M]/[I] = 20, $[M]_0$ = 4 M).

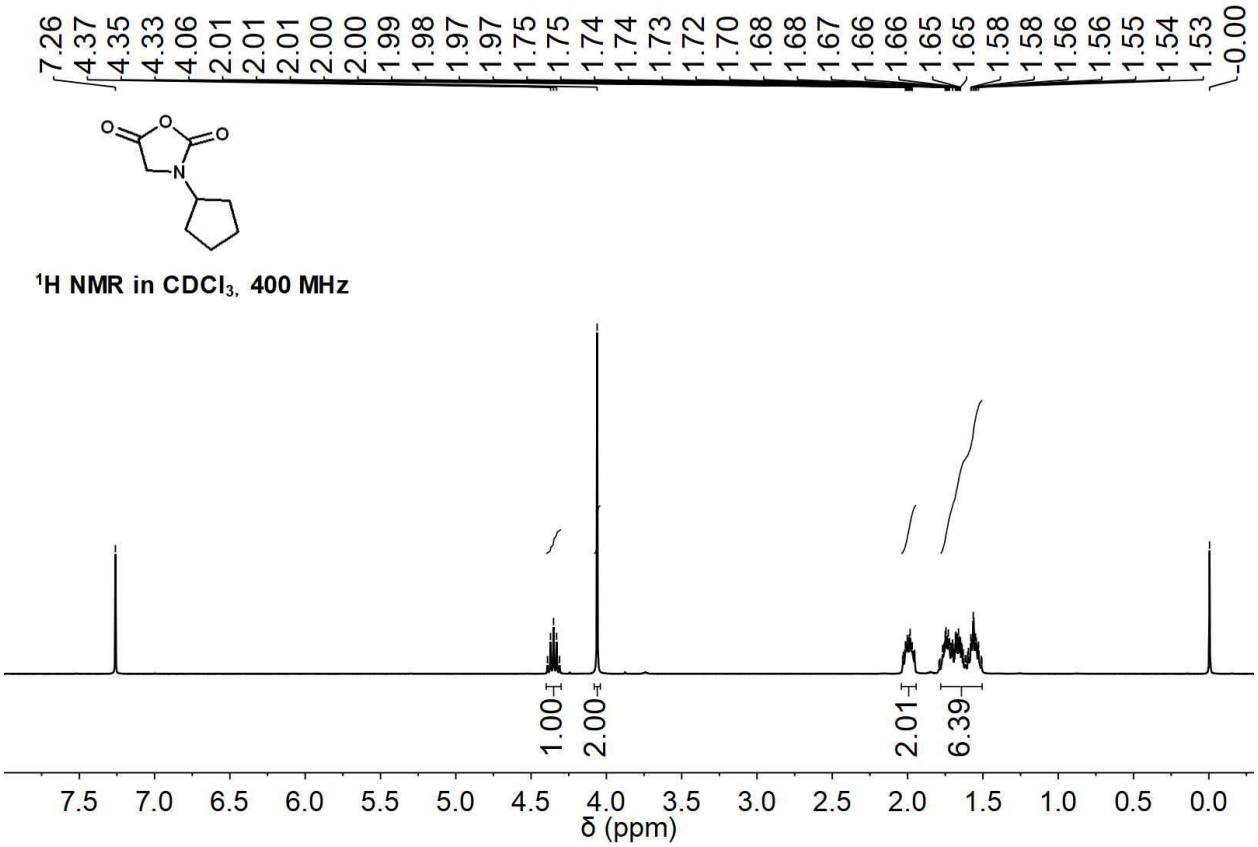


Figure S18. ^{1}H NMR spectrum of cyclopentyl-NNCA in $CDCl_3$, 400 MHz.

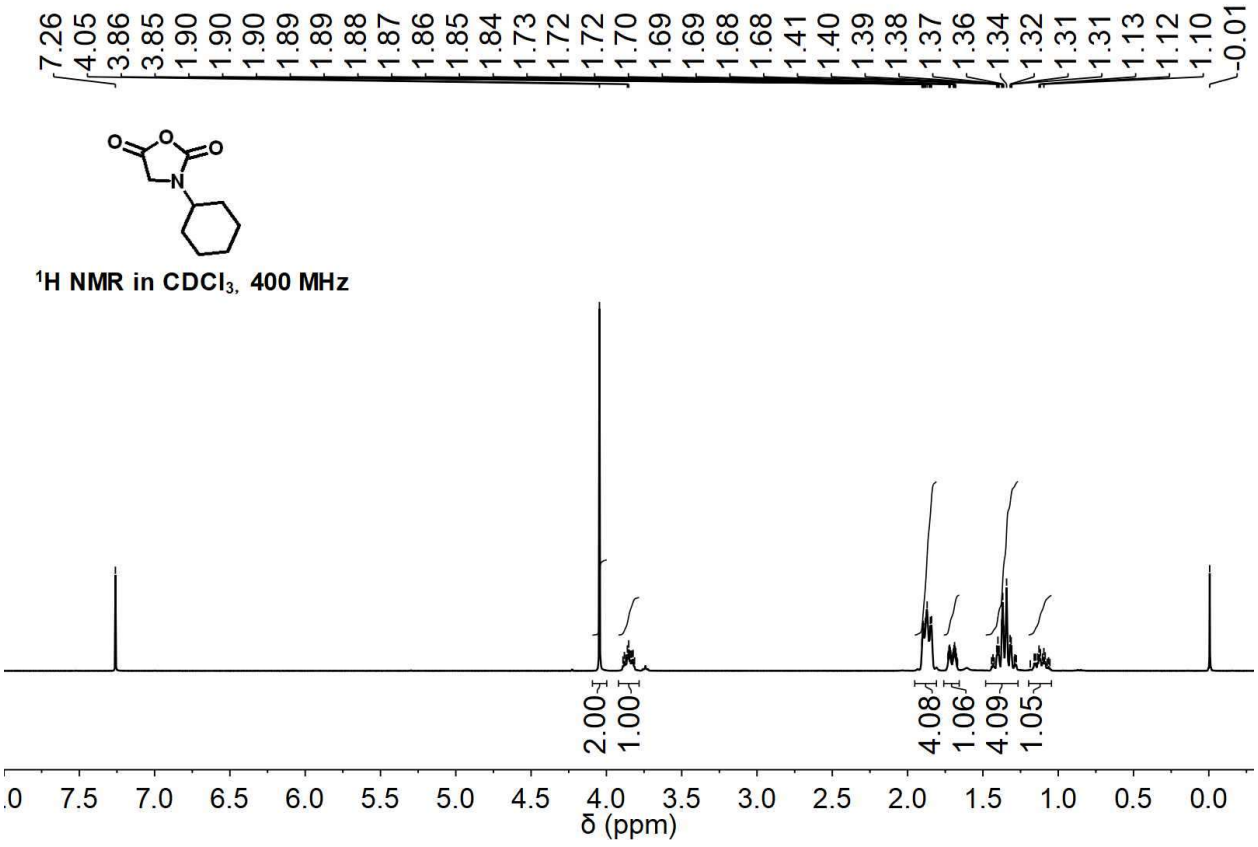


Figure S19. ^{1}H NMR spectrum of cyclohexyl-NNCA in $CDCl_3$, 400 MHz.

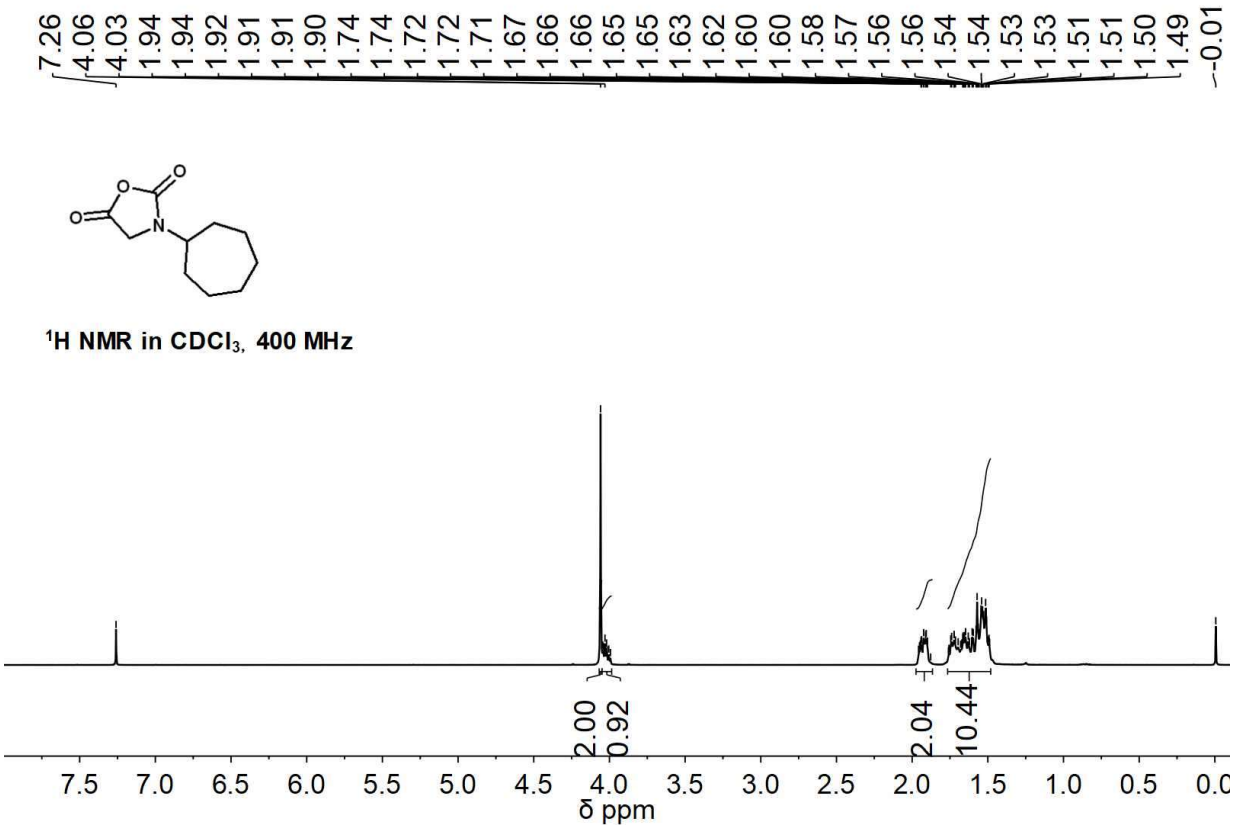


Figure S20. ^{1}H NMR spectrum of cycloheptyl-NNCA in $CDCl_3$, 400 MHz.

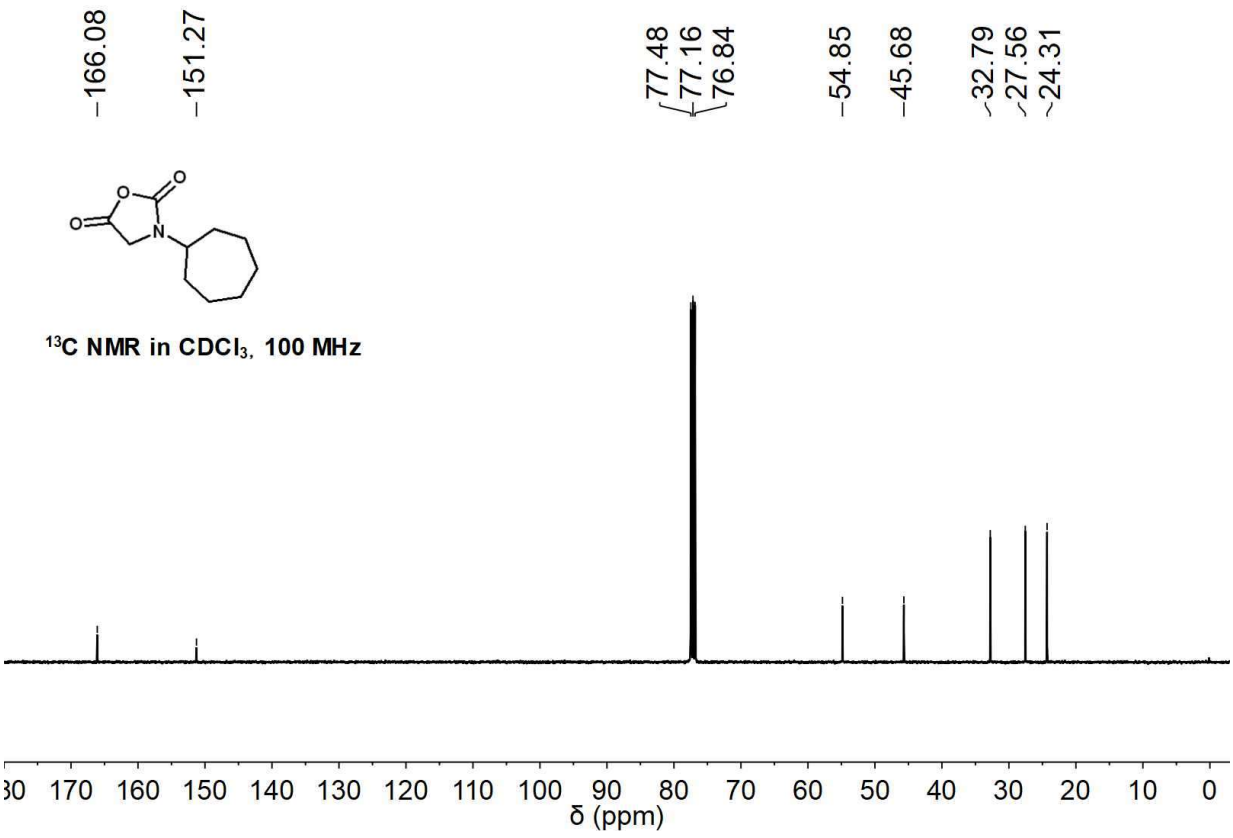


Figure S21.^{13}C NMR spectrum of cycloheptyl-NNCA in $CDCl_3$, 100 MHz.

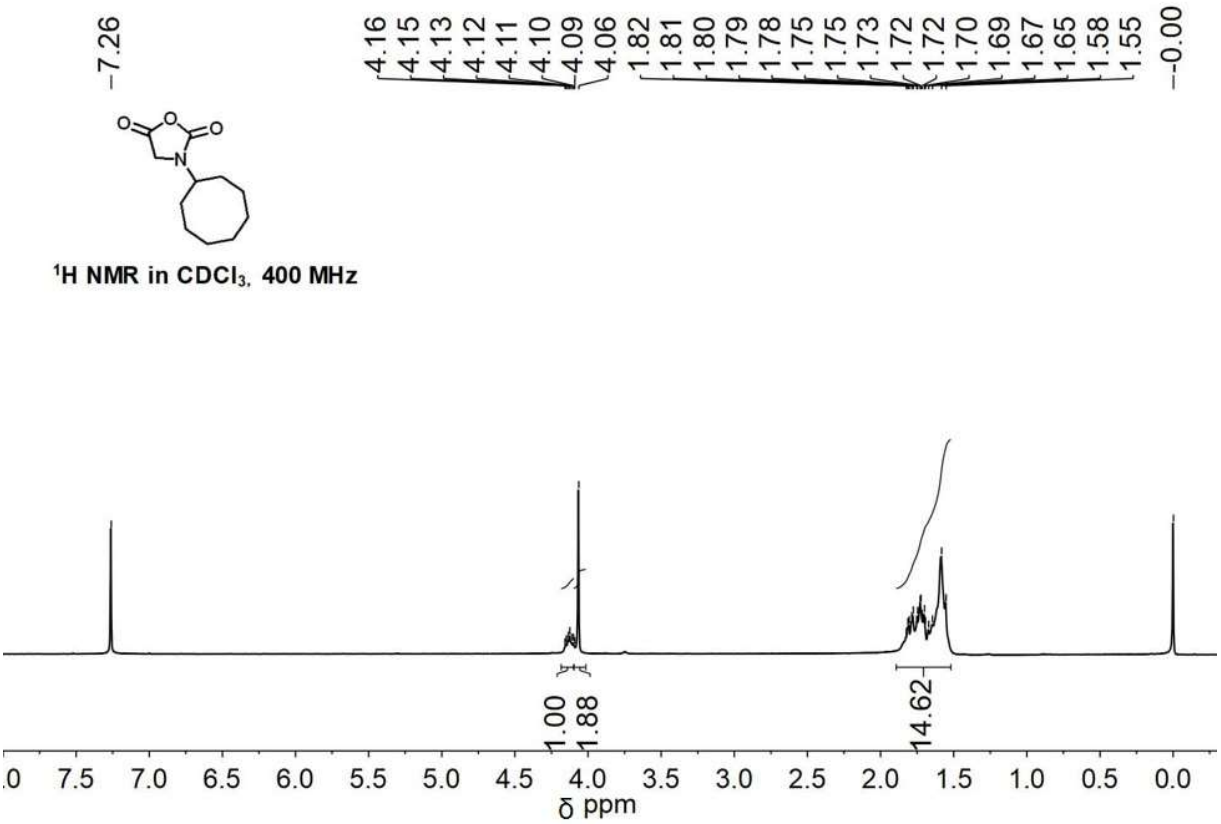


Figure S22. ^{1}H NMR spectrum of cyclooctyl-NNCA in $CDCl_3$, 400 MHz.

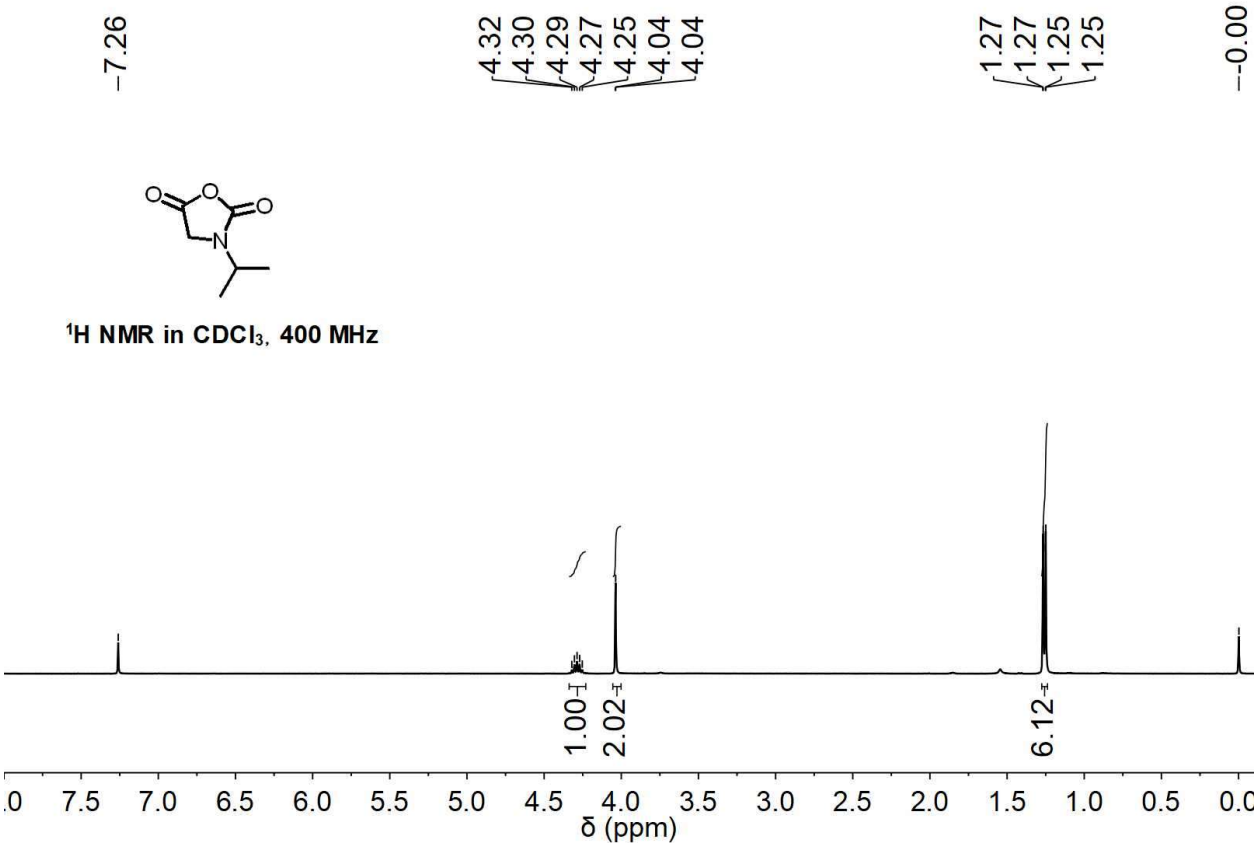


Figure S23. ^{1}H NMR spectrum of isopropyl-NNCA in $CDCl_3$, 400 MHz.

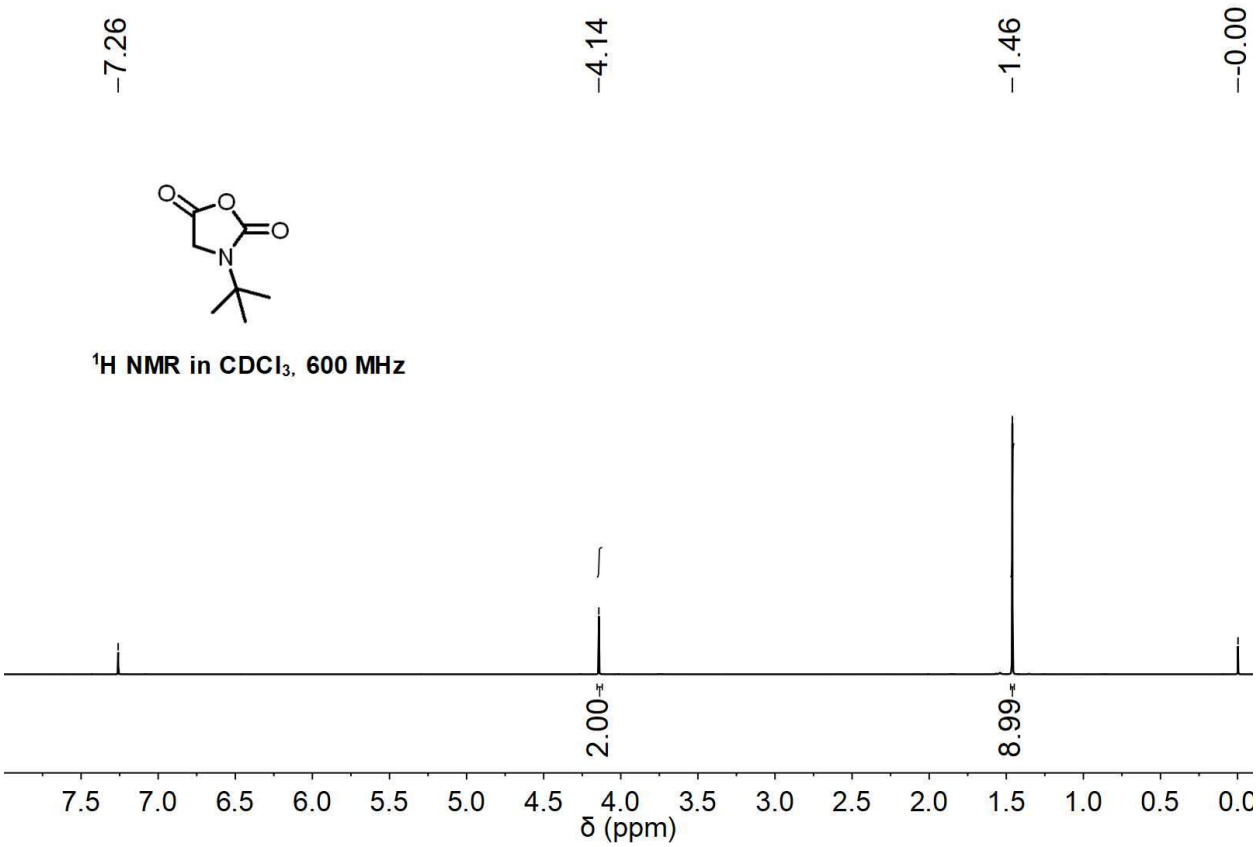


Figure S24. ^{1}H NMR spectrum of *tert*-butyl-NNCA in $CDCl_3$, 600 MHz.

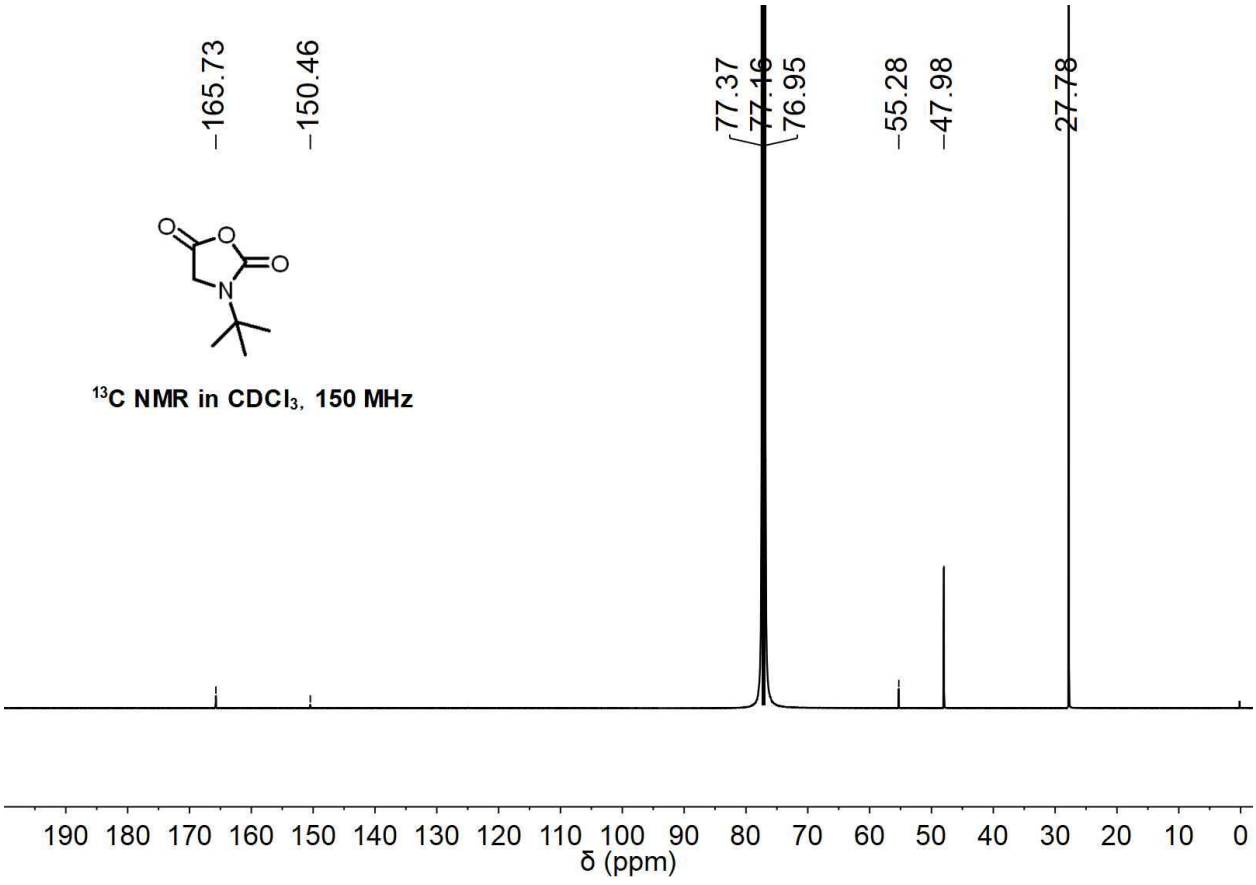


Figure S25.^{13}C NMR spectrum of *tert*-butyl -NNCA in $CDCl_3$, 150 MHz.

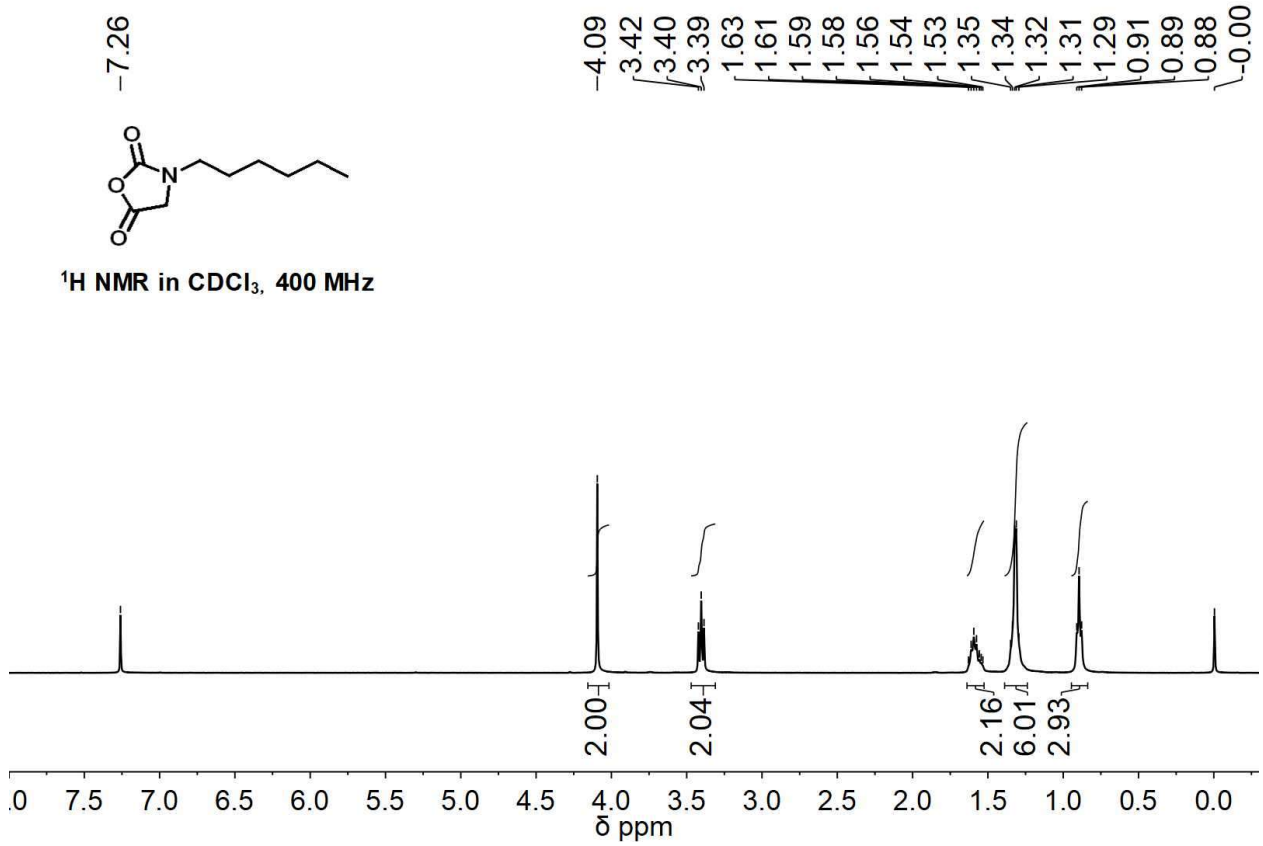


Figure S26. ^{1}H NMR spectrum of hexyl-NNCA in $CDCl_3$, 400 MHz.

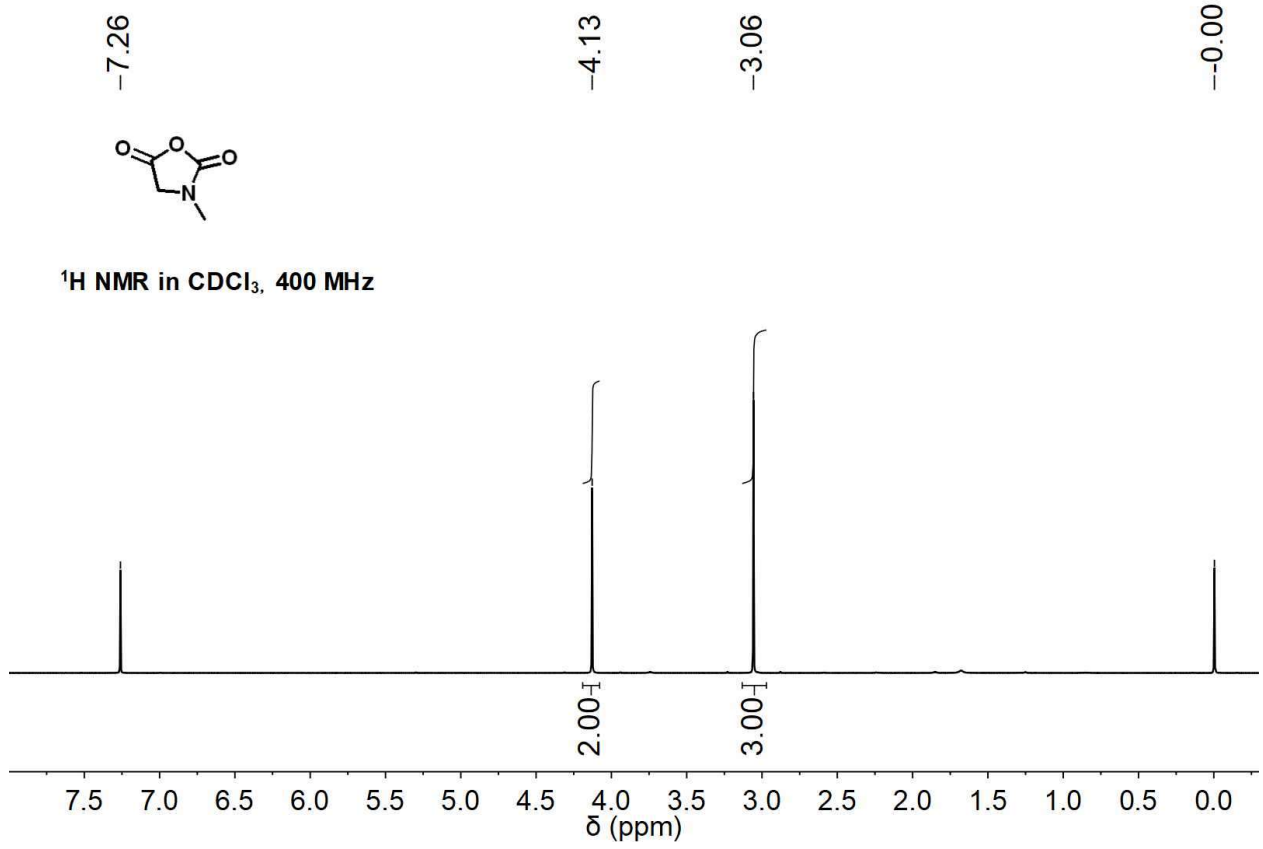


Figure S27. ^{1}H NMR spectrum of sarcosine-NCA in $CDCl_3$, 400 MHz.

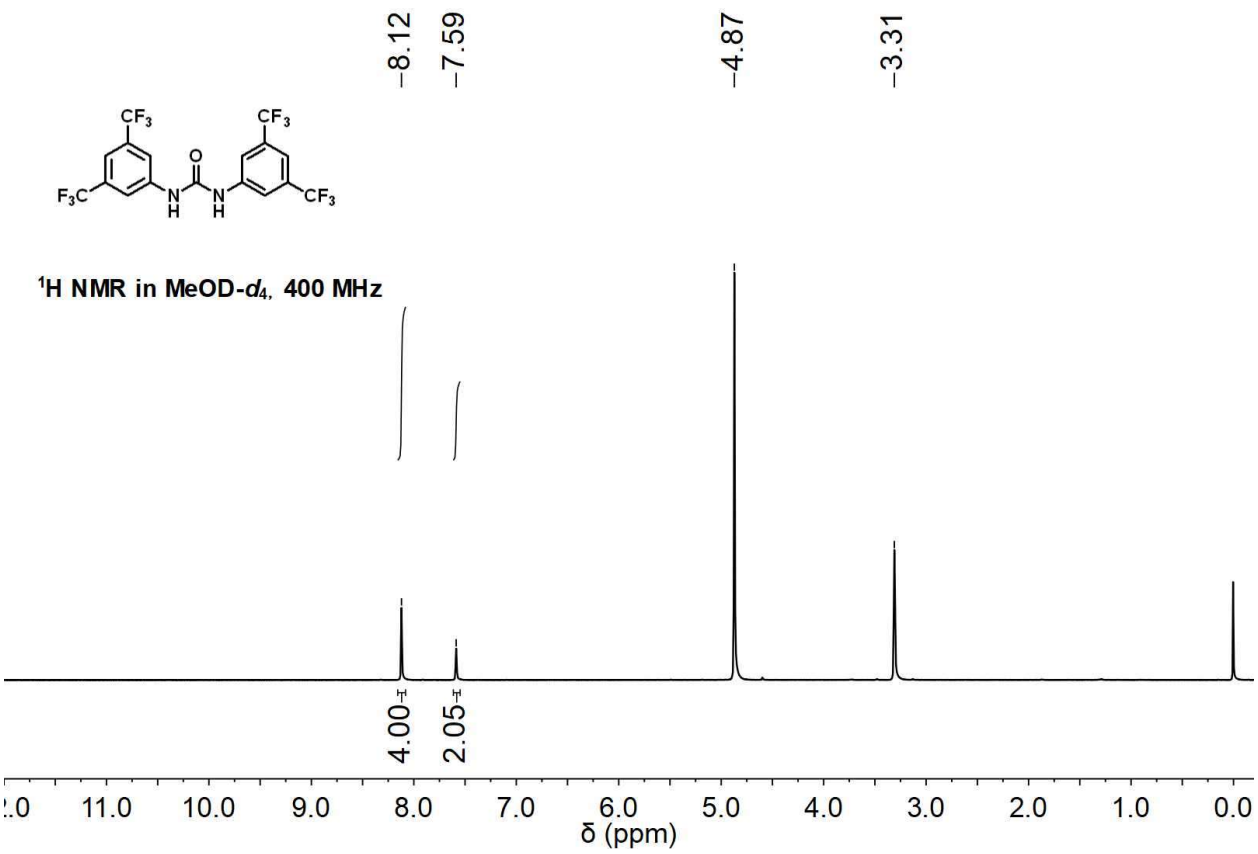


Figure S28. ^{1}H NMR spectrum of 1,3-bis[3,5-bis(trifluoromethyl)phenyl]urea in MeOD-d_4, 400 MHz.

Reference

1. L. Guo and D. Zhang, *J. Am. Chem. Soc.*, 2009, **131**, 18072-18074.
2. Y. Wu, M. Zhou, K. Chen, S. Chen, X. Xiao, Z. Ji, J. Zou and R. Liu, *Chin. Chem. Lett.*, 2021, **32**, 1675-1678.
3. J. W. Robinson, C. Secker, S. Weidner and H. Schlaad, *Macromolecules*, 2013, **46**, 580-587.
4. J. C. Pineiro, K. Dinnell, J. M. Elliott, G. J. Hollingworth, D. E. Shaw and C. J. Swain. Cyclohexane derivatives and their use as therapeutic agents. 2006. US, US7105507 B2.
5. H. R. Kricheldorf, *Die Makromolekulare Chemie*,1977, **178**, 905-939.
6. C. Baldauf, R. Günther and H.-J. Hofmann, *Helv. Chim. Acta*, 2003, **86**, 2573-2588.
7. T. Liedtke, P. Spannring, L. Riccardi and A. Gansäuer, *Angew. Chem. Int. Ed.*, 2018, **57**, 5006-5010.
8. L. Sun, X. Wu, D.-C. Xiong and X.-S. Ye, *Angew. Chem. Int. Ed.*, 2016, **55**, 8041-8044.
9. Y. Wu, D. Zhang, P. Ma, R. Zhou, L. Hua and R. Liu, *Nat. Commun.*, 2018, **9**, 5297.
10. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaranillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09 Rev. E.01,* Wallingford, CT, 2009.
11. S. Miertus and J. J. C. p. Tomasi, *Chem. Phys.*, 1982, **65**, 239-245.
12. S. Grimme, J. Antony, S. Ehrlich and H. Krieg, *J. Phys. Chem. Lett.*, 2010, **132**, 154104.
13. G. J. M. Habraken, M. Peeters, C. H. J. T. Dietz, C. E. Koning and A. Heise, *Polym. Chem.*, 2010, **1**, 514-524.