

Supporting Information

Hydrolyzable Polyureas Bearing Hindered Urea Bonds

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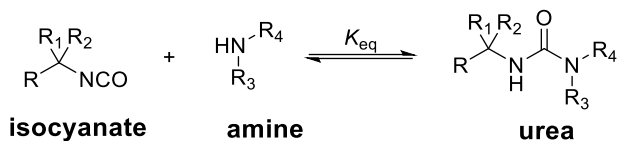
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General

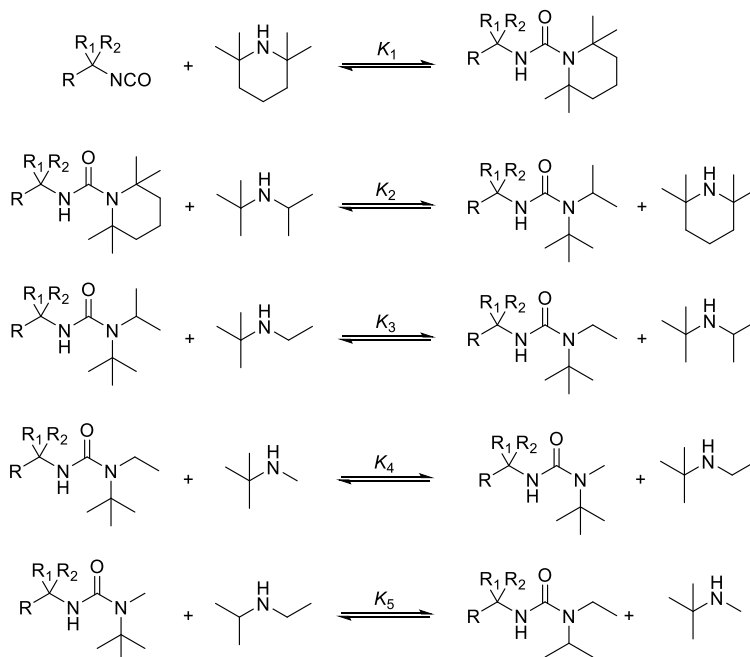
Materials. Anhydrous dimethylformamide (DMF) was dried by a column packed with 4Å molecular sieves. m-Xylylene diisocyanate was purchased from TCI America (Portland, OR, USA) and used as received. Tri-functional homopolymer of hexamethylene diisocyanate (HDI) (Desmodur N3900, Bayer MaterialsScience) was obtained from Innovadex. All deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and used as received. All other chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received unless otherwise specified.

Instrumentation. NMR spectra were recorded on Varian U400 (400 MHz), U500 (500 MHz), VXR-500 (500 MHz), UI500NB (500 MHz) spectrometer. Gel permeation chromatography (GPC) experiments were performed on a system equipped with an isocratic pump (Model 1100, Agilent Technology, Santa Clara, CA, USA), a DAWN HELEOS multi-angle laser light scattering detector (MALLS detector, Wyatt Technology, Santa Barbara, CA, USA) and an Optilab rEX refractive index detector (Wyatt Technology, Santa Barbara, CA, USA). The detection wavelength of TREOS was set at 658 nm. Separations were performed using serially connected size exclusion columns (10^2 Å, 10^3 Å, 10^4 Å, 10^5 Å and 10^6 Å Phenogel columns, 5 μm , 300×7.8 mm, Phenomenex, Torrance, CA, USA) using DMF as the mobile phase.

Determination of binding constants of hindered urea bonds



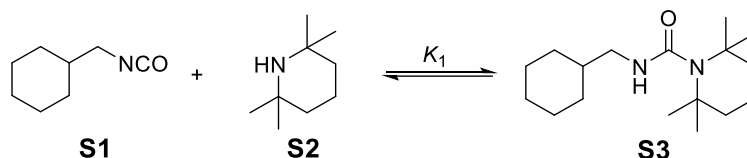
If the binding constant of urea is large, it is difficult to determine the binding constant K_{eq} directly through the equilibrium concentrations of isocyanate, amine and urea species. The K_{eq} of the hindered urea bond increases with the decrease of the substituents bulkiness. To accurately determine the binding constants, we used an ‘indirect’ method through equilibrium reactions between different urea species. (All used $CDCl_3$ as the solvent)



$K_1 \sim K_5$ are mostly in the range that can all be accurately determined by 1H NMR, we could determine K_{eq} by:

$$K_{eq} = K_1 \cdot K_2 \cdot K_3 \text{ (when } R_3=t\text{-Bu, } R_4=Et) \text{ or } K_{eq} = K_1 \cdot K_2 \cdot K_3 \cdot K_4 \cdot K_5 \text{ (when } R_3=i\text{-Pr, } R_4=Et)$$

Determination of binding constant of urea 2 (Determination of binding constant of urea 1 with similar methods has been reported in ref. 19a in text)



Cyclohexylmethyl isocyanate (**S1**, 11.1 mg, 0.080 mmol) and 2,2,6,6-tetramethylpiperidine (**S2**, 8.0 mg, 0.056 mmol) were dissolved in CDCl₃ (0.55 mL). ¹H NMR spectra were collected 0.5 h after **S1** and **S2** were mixed at room temperature when equilibrium was reached/peaks integral stopped changing (Figure S1). Concentration of each species was calculated based on the integral ratios of the ¹H NMR signals and the initial concentrations of **S1** and **S2**. The equilibrium constants were calculated as $K_1 = [\mathbf{S3}]_{\text{eq}} / ([\mathbf{S1}]_{\text{eq}} \cdot [\mathbf{S2}]_{\text{eq}})$.

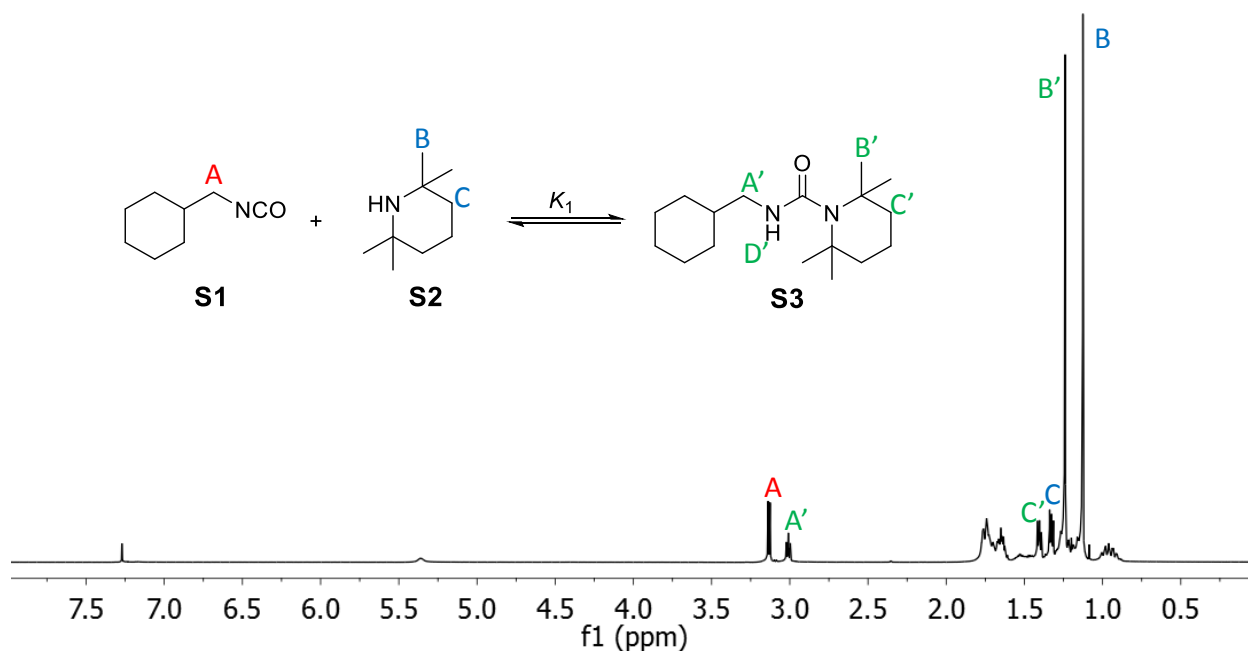
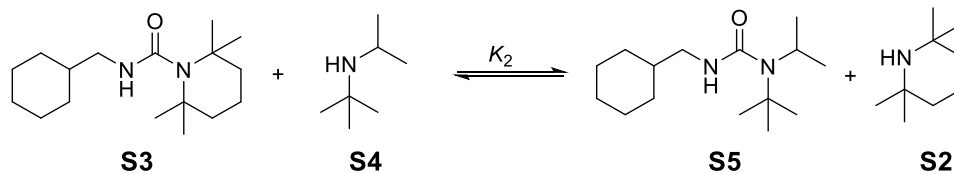


Figure S1. ¹H NMR spectrum of the mixture of compound **S1** and **S2**. Peaks are assigned to each compound except for the protons in cyclohexyl group. The spectrum was taken 30 min after

S1 and **S2** were mixed. Binding constant K_1 was determined as

$$K_1 = [\mathbf{S3}]_{\text{eq}} / ([\mathbf{S1}]_{\text{eq}} \bullet [\mathbf{S2}]_{\text{eq}}) = 0.067 / (0.078 \times 0.036) \text{ M}^{-1} = 24 \text{ M}^{-1}$$



Cyclohexylmethyl isocyanate (**S1**, 10.0 mg, 0.072 mmol), 2,2,6,6-tetramethylpiperidine (**S2**, 9.5 mg, 0.067 mmol) and *N*-tertbutyl-*N*-isopropyl amine (**S4**, 6.8 mg, 0.059 mmol) were dissolved in CDCl₃ (0.55 mL) and added to the NMR tubes. ¹H NMR spectra were collected 12 h after mixing at room temperature after equilibrium was reached/peaks integral stopped changing (Figure S2). The equilibrium constant of the reaction K_2 was calculated according to the concentration ratio of each species: $K_2 = ([\text{S5}]_{\text{eq}} \cdot [\text{S2}]_{\text{eq}})/([\text{S3}]_{\text{eq}} \cdot [\text{S4}]_{\text{eq}})$.

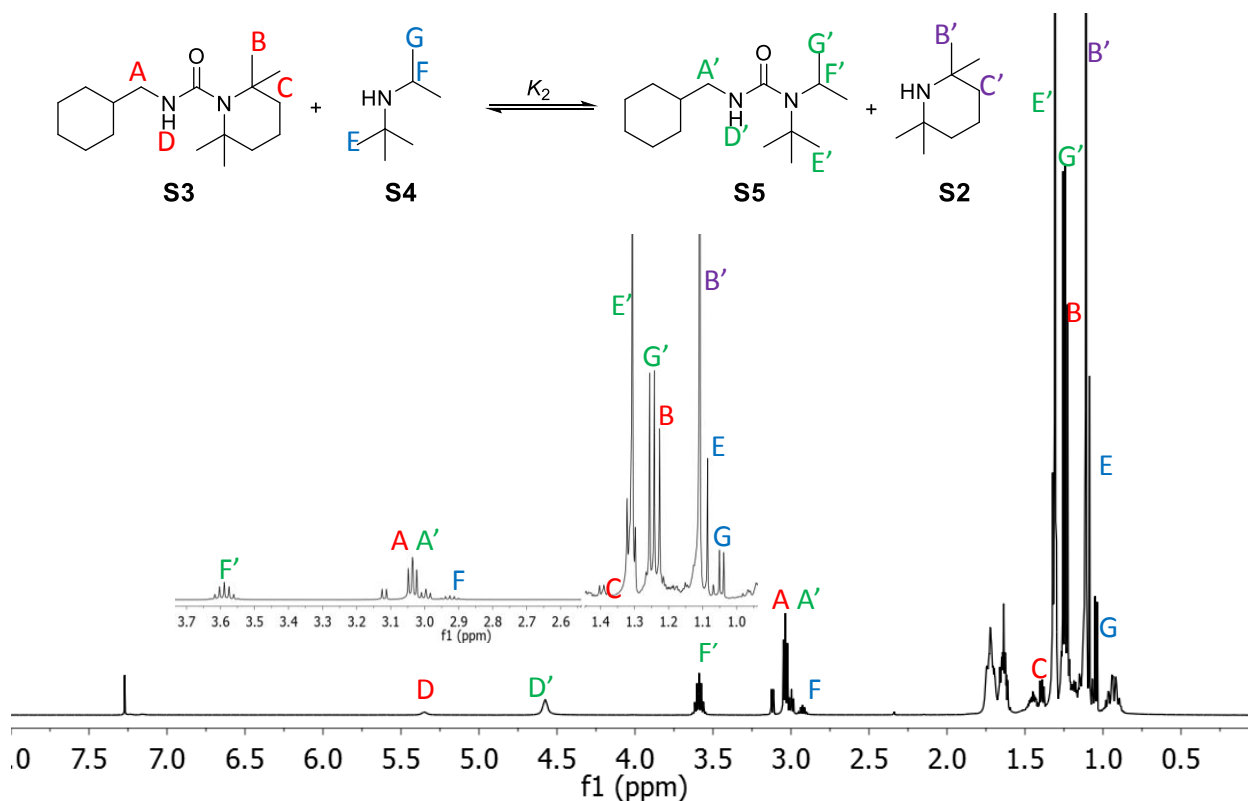
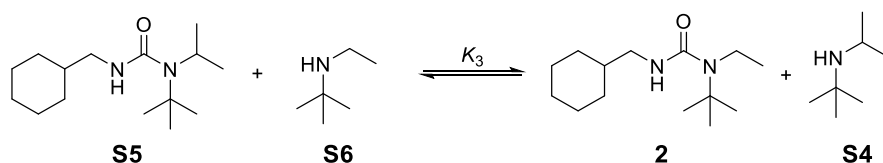


Figure S2. ¹H NMR spectrum of the mixture of compound **S1**, **S2**, and **S4** (and the produced compound **S3**, **S5**). Peaks are assigned to each compound except for the protons in

cyclohexyl group. The spectrum was taken 12 h after mixing. The region containing peaks B, B', F and F' for the calculation of the concentration of each species is zoomed in.

$$K_2 = ([\mathbf{S5}]_{\text{eq}} \cdot [\mathbf{S2}]_{\text{eq}} / ([\mathbf{S3}]_{\text{eq}} \cdot [\mathbf{S4}]_{\text{eq}})) = 25.$$



Cyclohexylmethyl isocyanate (**S1**, 10.2 mg, 0.073 mmol), *N*-tertbutyl-*N*-isopropyl amine (**S4**, 7.2 mg, 0.063 mmol) and *N*-tertbutyl-*N*-ethyl amine (**S6**, 6.7 mg, 0.066 mmol) were dissolved in CDCl₃ (0.55 mL) and added to the NMR tubes. ¹H NMR spectra were collected 12 h after mixing at room temperature after equilibrium was reached/peaks integral stopped changing (Figure S3). The equilibrium constant of the reaction K_2 was calculated according to the concentration ratio of each species: $K_3 = ([\text{2}]_{\text{eq}} \cdot [\text{S4}]_{\text{eq}}) / ([\text{S5}]_{\text{eq}} \cdot [\text{S6}]_{\text{eq}})$.

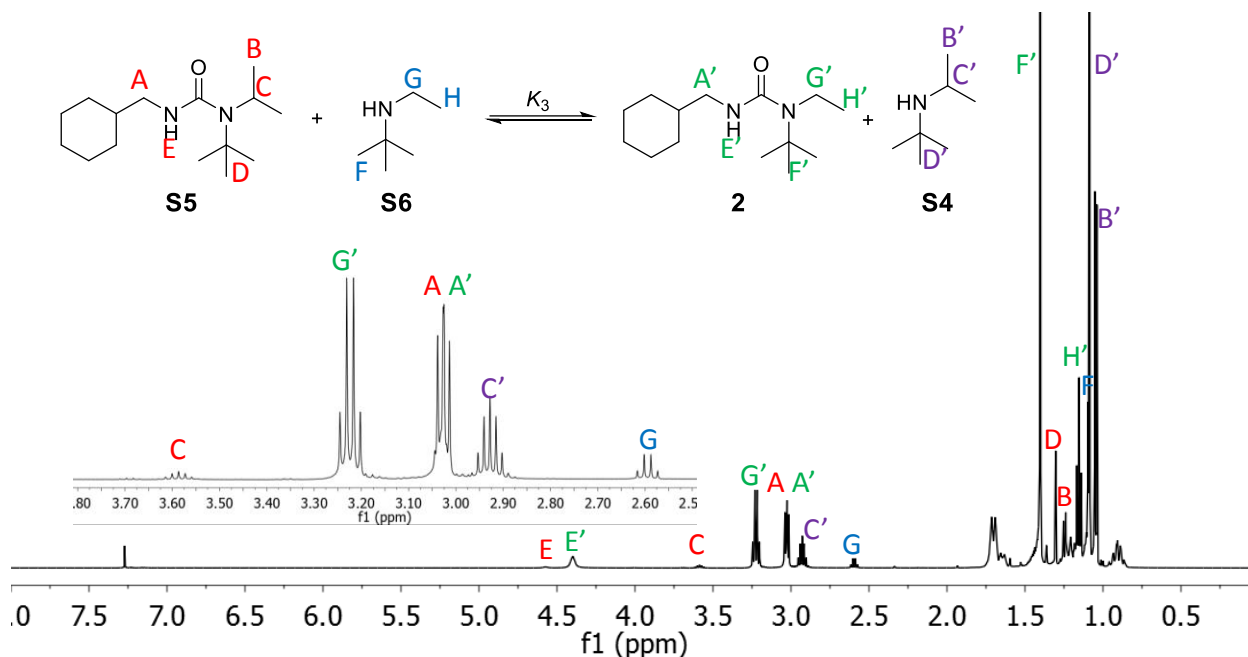
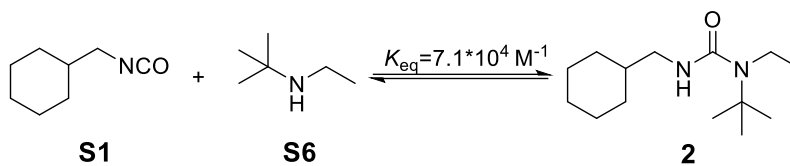


Figure S3. ¹H NMR spectrum of the mixture of compound **S1**, **S4**, and **S6** (and the produced compound **S5**, **2**). Peaks are assigned to each compound except for the protons in cyclohexyl group. The spectrum was taken 12 h after mixing. The region containing peaks C, C',

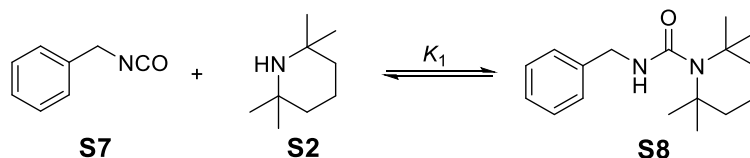
G and G' for the calculation of the concentration of each species is zoomed in.

$$K_3 = ([2]_{\text{eq}} \cdot [S4]_{\text{eq}} / ([S5]_{\text{eq}} \cdot [S6]_{\text{eq}})) = 118.$$

So, for urea **2**, $K_{\text{eq},2} = K_1 \cdot K_2 \cdot K_3 = 7.1 \times 10^4 \text{ M}^{-1}$



Determination of binding constant of urea 3



Benzyl isocyanate (**S7**, 11.1 mg, 0.083 mmol) and 2,2,6,6-tetramethylpiperidine (**S2**, 9.4 mg, 0.067 mmol) were dissolved in CDCl_3 (0.55 mL). ^1H NMR spectra were collected 0.5 h after **S7** and **S2** were mixed at room temperature when equilibrium was reached/peaks integral stopped changing (Figure S4). Concentration of each species was calculated based on the integral ratios of the ^1H NMR signals and the initial concentrations of **S7** and **S2**. The equilibrium constants were calculated as $K_1 = [\text{S8}]_{\text{eq}} / ([\text{S7}]_{\text{eq}} \cdot [\text{S2}]_{\text{eq}})$.

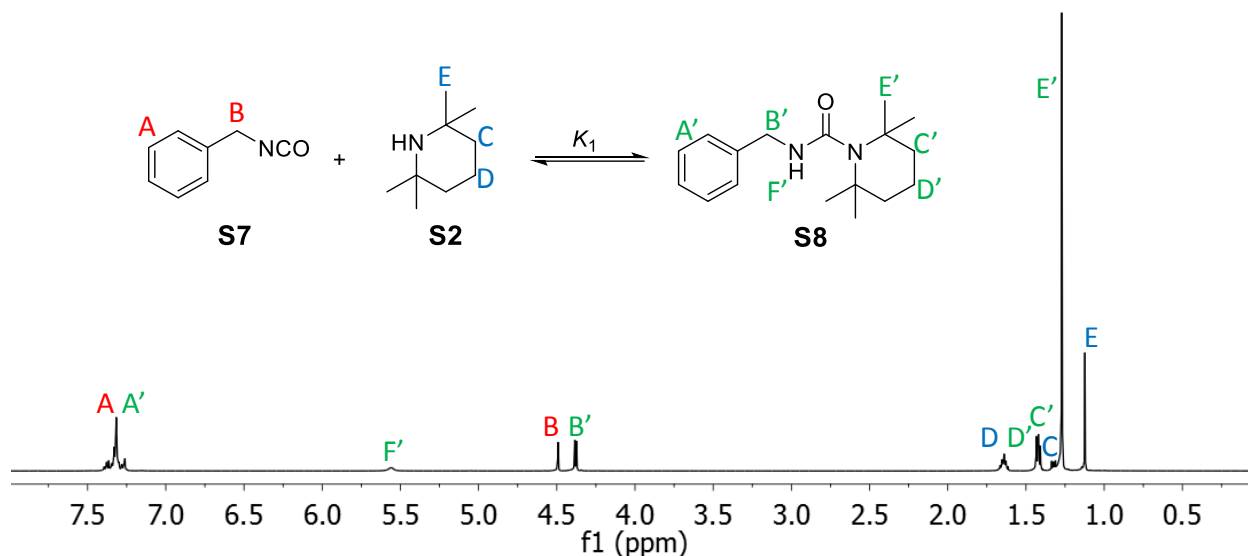
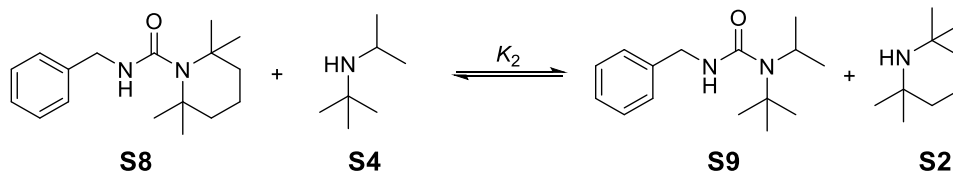


Figure S4. ^1H NMR spectrum of the mixture of compound **S7** and **S2**. Peaks are assigned to each compound. The spectrum was taken 30 min after **S7** and **S2** were mixed. Binding constant K_1 was determined as $K_1 = [\text{S8}]_{\text{eq}} / ([\text{S7}]_{\text{eq}} \cdot [\text{S2}]_{\text{eq}}) = 0.100 / (0.052 \times 0.021) \text{ M}^{-1} = 92 \text{ M}^{-1}$



Benzyl isocyanate (**S7**, 11.9 mg, 0.089 mmol), 2,2,6,6-tetramethylpiperidine (**S2**, 8.5 mg, 0.060 mmol) and *N*-tertbutyl-*N*-isopropyl amine (**S4**, 6.0 mg, 0.052 mmol) were dissolved in CDCl₃ (0.55 mL) and added to the NMR tubes. ¹H NMR spectra were collected 12 h after mixing at room temperature after equilibrium was reached/peaks integral stopped changing (Figure S5). The equilibrium constant of the reaction K_2 was calculated according to the concentration ratio of each species: $K_2 = ([\text{S9}]_{\text{eq}} \cdot [\text{S2}]_{\text{eq}}) / ([\text{S8}]_{\text{eq}} \cdot [\text{S4}]_{\text{eq}})$.

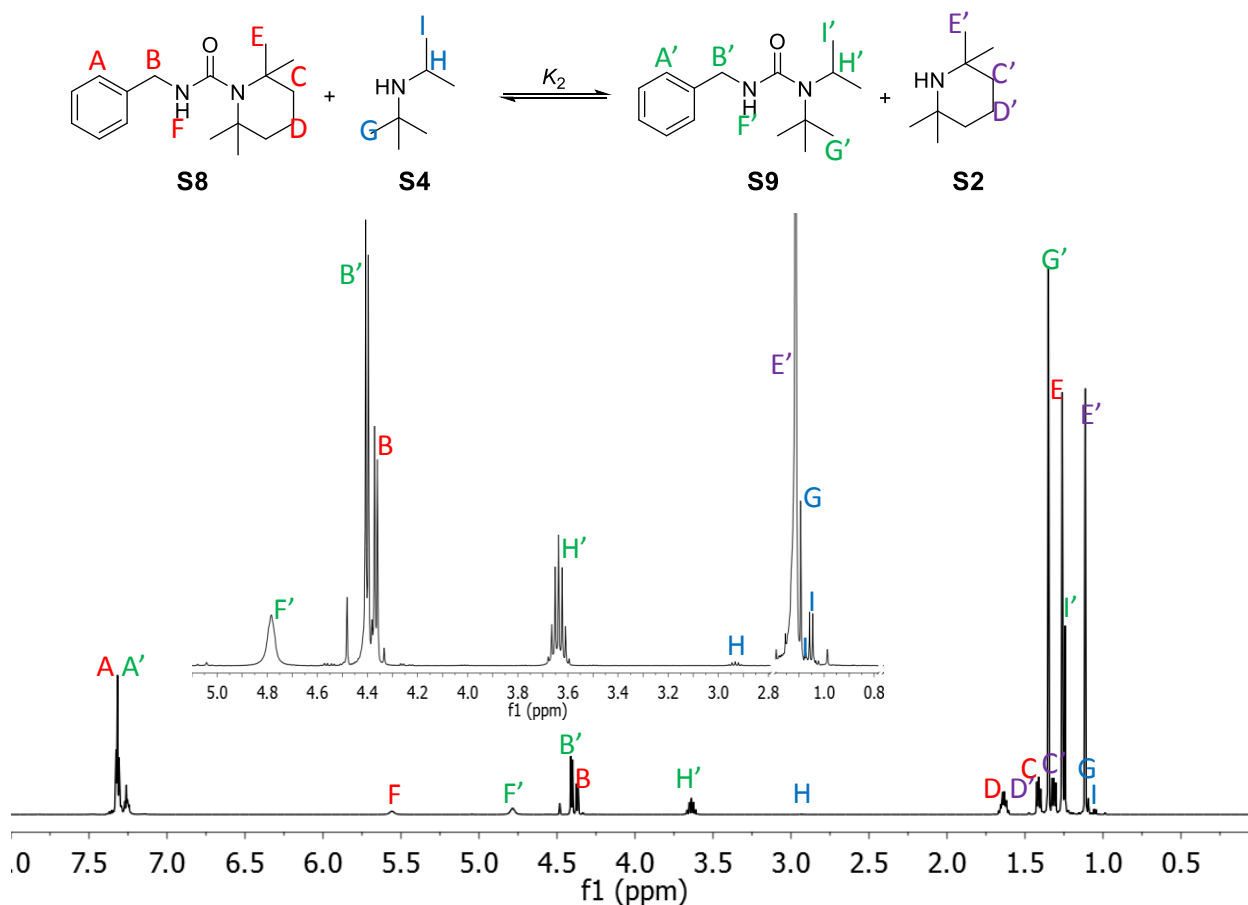
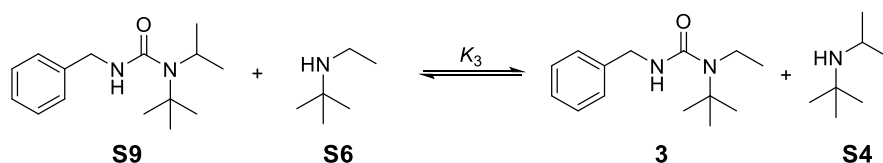


Figure S5. ^1H NMR spectrum of the mixture of compound **S7**, **S2**, and **S4** (and the produced compound **S8**, **S9**). Peaks are assigned to each compound. The spectrum was taken 12 h after mixing. The region containing peaks B, H, H' and E' for the calculation of the concentration of each species is zoomed in. $K_2 = ([\text{S9}]_{\text{eq}} \cdot [\text{S2}]_{\text{eq}} / ([\text{S8}]_{\text{eq}} \cdot [\text{S4}]_{\text{eq}})) = 43$.



Benzyl isocyanate (**S7**, 10.7 mg, 0.080 mmol), *N*-tertbutyl-*N*-isopropyl amine (**S4**, 7.5 mg, 0.065 mmol) and *N*-tertbutyl-*N*-ethyl amine (**S6**, 7.9 mg, 0.078 mmol) were dissolved in CDCl₃ (0.55 mL) and added to the NMR tubes. ¹H NMR spectra were collected 12 h after mixing at room temperature after equilibrium was reached/peaks integral stopped changing (Figure S6). The equilibrium constant of the reaction K_3 was calculated according to the concentration ratio of each species: $K_3 = ([\mathbf{3}]_{\text{eq}} \cdot [\mathbf{S4}]_{\text{eq}}) / ([\mathbf{S9}]_{\text{eq}} \cdot [\mathbf{S6}]_{\text{eq}})$.

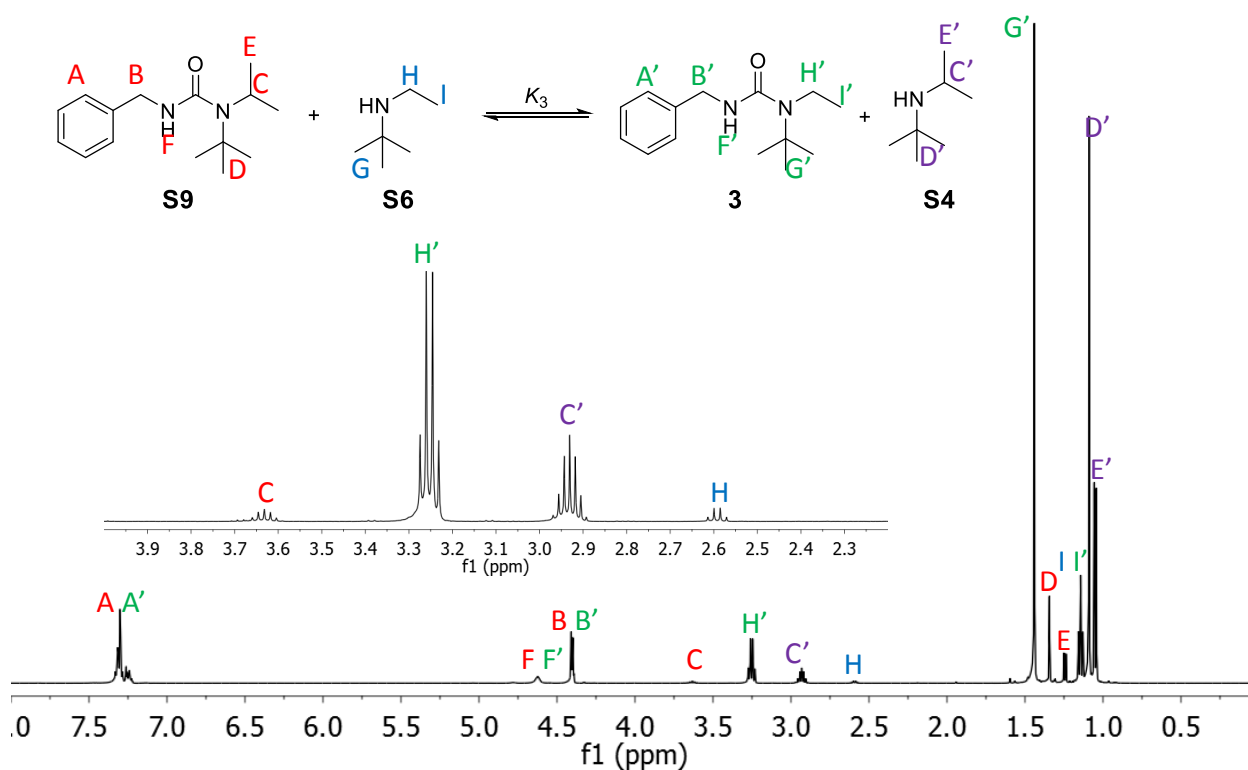
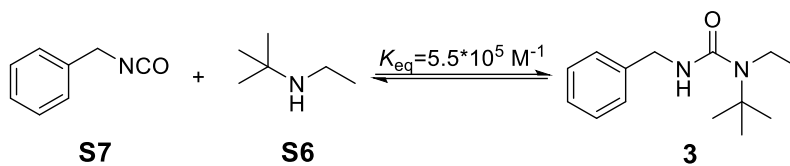


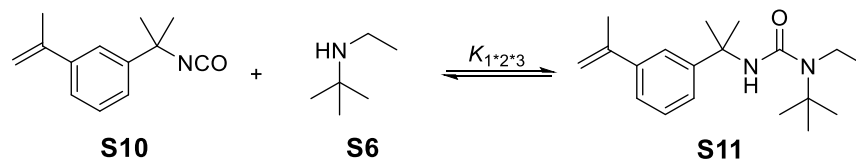
Figure S6. ¹H NMR spectrum of the mixture of compound **S7**, **S4**, and **S6** (and the produced compound **S9**, **3**). Peaks are assigned to each compound. The spectrum was taken 12

h after mixing. The region containing peaks C, C', H and H' for the calculation of the concentration of each species is zoomed in. $K_3 = ([\mathbf{3}]_{\text{eq}} \bullet [\mathbf{S4}]_{\text{eq}} / ([\mathbf{S9}]_{\text{eq}} \bullet [\mathbf{S6}]_{\text{eq}}) = 140$.

So, for urea **3**, $K_{\text{eq},3} = K_1 \bullet K_2 \bullet K_3 = 5.5 \times 10^5 \text{ M}^{-1}$



Determination of binding constant of urea 4



3-Isopropenyl- α,α -dimethylbenzyl isocyanate (**S10**, 14.0 mg, 0.069 mmol) and N-tertbutyl-N-ethyl amine (**S6**, 7.8 mg, 0.077 mmol) were dissolved in CDCl_3 (0.55 mL). ^1H NMR spectra were collected 0.5 h after **S10** and **S6** were mixed at room temperature when equilibrium was reached/peaks integral stopped changing (Figure S7). Concentration of each species was calculated based on the integral ratios of the ^1H NMR signals and the initial concentrations of **S10** and **S6**. The equilibrium constants were calculated as $K_{1*2*3} = [\text{S11}]_{\text{eq}} / ([\text{S10}]_{\text{eq}} \cdot [\text{S6}]_{\text{eq}})$.

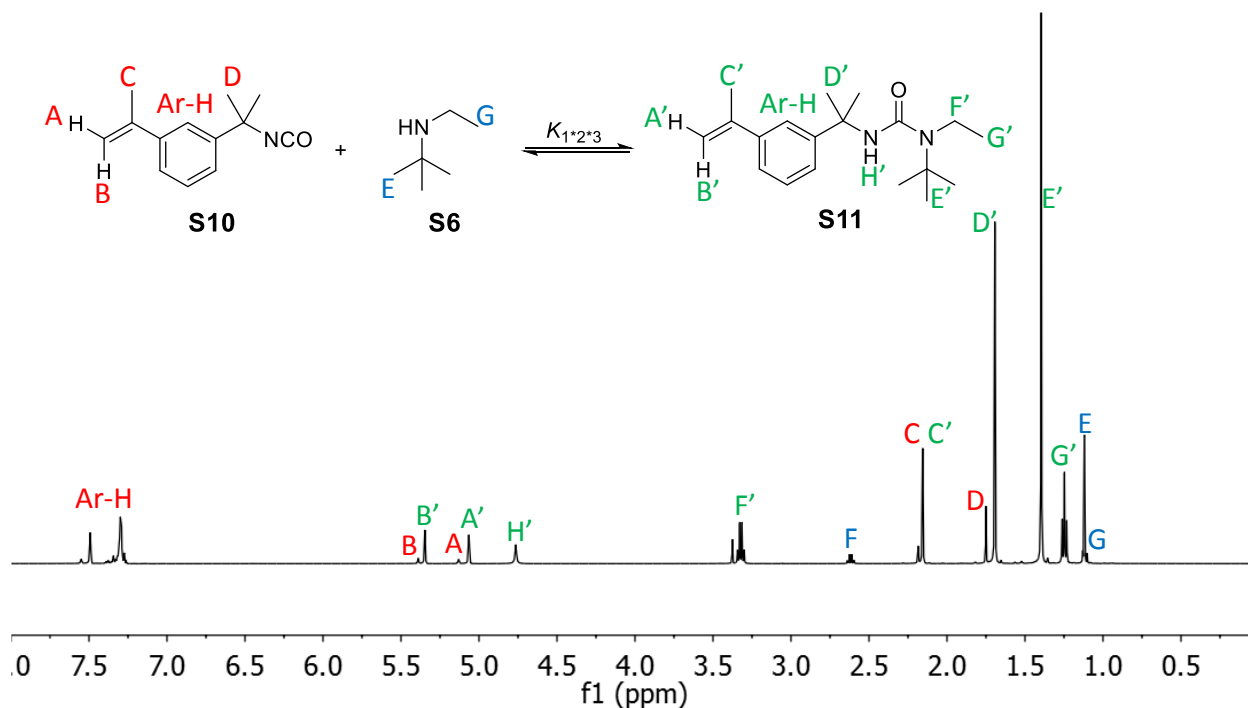
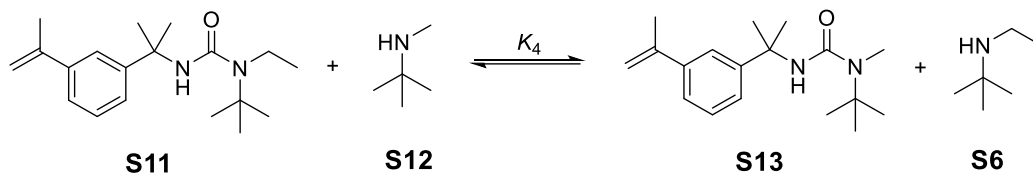


Figure S7. ^1H NMR spectrum of the mixture of compound **S10** and **S6**. Peaks are assigned to each compound. The spectrum was taken 0.5 h after **S10** and **S6** were mixed. Binding constant

K_{1*2*3} was determined as $K_{1*2*3} = [\mathbf{S11}]_{\text{eq}} / ([\mathbf{S10}]_{\text{eq}} \bullet [\mathbf{S6}]_{\text{eq}})$
 $= 0.107 / (0.018 \times 0.033) \text{ M}^{-1} = 180 \text{ M}^{-1}$



3-Isopropenyl- α,α -dimethylbenzyl isocyanate (**S10**, 14.1 mg, 0.070 mmol), N-tertbutyl-N-ethyl amine (**S6**, 14.3 mg, 0.142 mmol) and N-tertbutyl-N-methyl amine (**S12**, 8.9 mg, 0.102 mmol) were dissolved in CDCl_3 (0.55 mL) and added to the NMR tubes. ^1H NMR spectra were collected 15 d after mixing at room temperature after equilibrium was reached/peaks integral stopped changing (Figure S8). The equilibrium constant of the reaction K_4 was calculated according to the concentration ratio of each species: $K_4 = ([\mathbf{S13}]_{\text{eq}} \cdot [\mathbf{S6}]_{\text{eq}}) / ([\mathbf{S11}]_{\text{eq}} \cdot [\mathbf{S12}]_{\text{eq}})$.

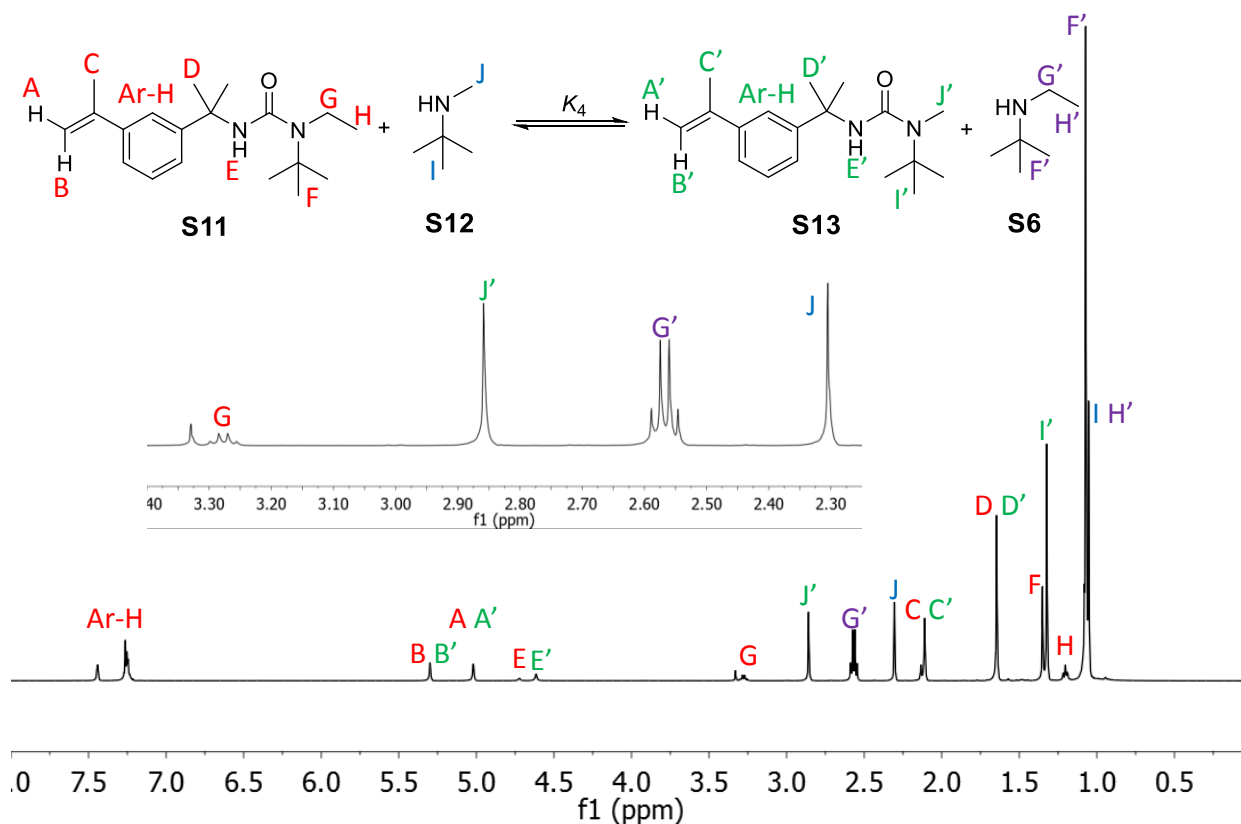
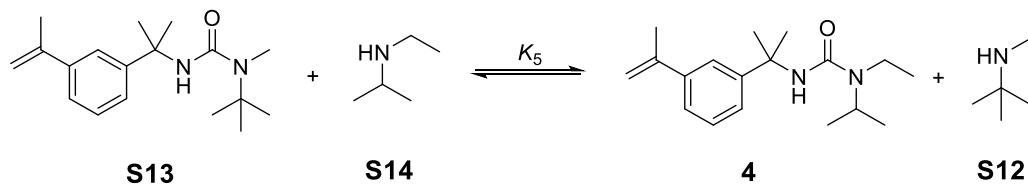


Figure S8. ^1H NMR spectrum of the mixture of compound **S10**, **S6**, and **S12** (and the produced compound **S11**, **S13**). Peaks are assigned to each compound. The spectrum was taken 15 d after mixing. The region containing peaks G, G', J and J' for the calculation of the concentration of each species is zoomed in. $K_4 = ([\text{S13}]_{\text{eq}} \bullet [\text{S6}]_{\text{eq}} / ([\text{S11}]_{\text{eq}} \bullet [\text{S12}]_{\text{eq}})) = 6.8$.



3-Isopropenyl- α,α -dimethylbenzyl isocyanate (**S10**, 10.1 mg, 0.050 mmol), N-tertbutyl-N-methyl amine (**S12**, 8.0 mg, 0.092 mmol) and N-isopropyl-N-ethyl amine (**S14**, 8.3 mg, 0.095 mmol) were dissolved in CDCl_3 (0.55 mL) and added to the NMR tubes. ^1H NMR spectra were collected 15 d after mixing at room temperature after equilibrium was reached/peaks integral stopped changing (Figure S9). The equilibrium constant of the reaction K_5 was calculated according to the concentration ratio of each species: $K_5 = ([\mathbf{4}]_{\text{eq}} \cdot [\mathbf{S12}]_{\text{eq}} / ([\mathbf{S13}]_{\text{eq}} \cdot [\mathbf{S14}]_{\text{eq}})$.

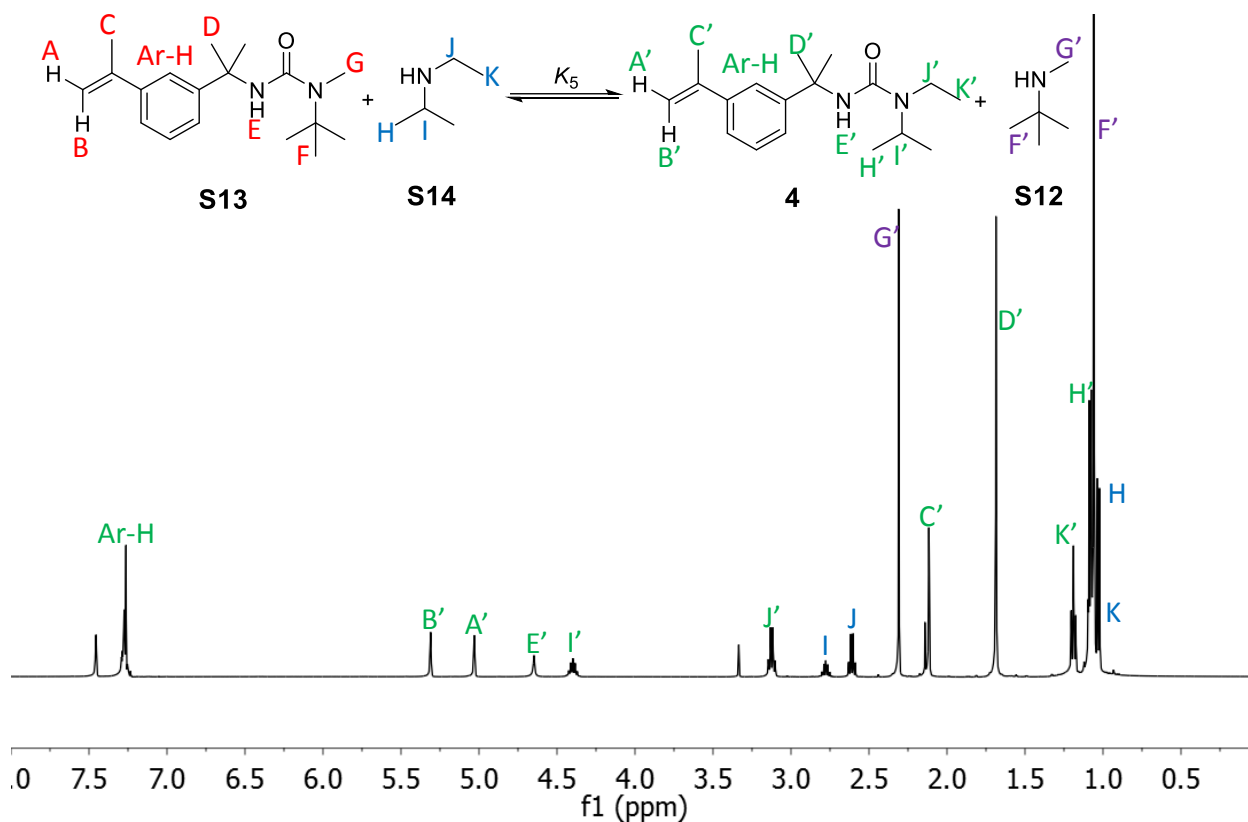
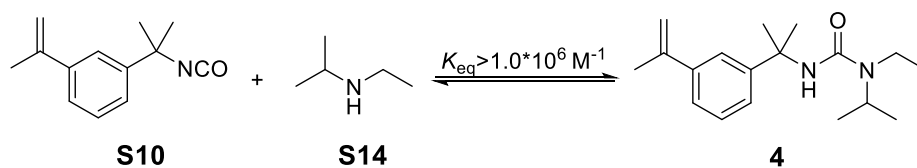
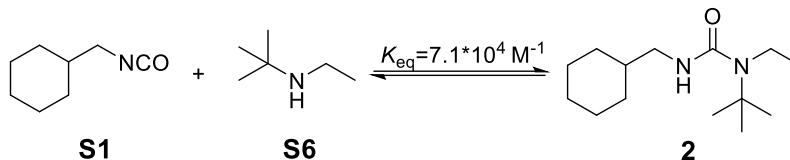


Figure S9. ^1H NMR spectrum of the mixture of compound **S10**, **S12**, and **S14** (and the produced compound **S13**, **4**). Peaks are assigned to each compound. The spectrum was taken 15 d after mixing. Here, no peaks for **S13** were observed. By integrating area of 2.83 ppm ~ 2.89 ppm where peak G for **S13** should be, we have $K_5 = ([\mathbf{4}]_{\text{eq}} \cdot [\mathbf{S12}]_{\text{eq}} / ([\mathbf{S13}]_{\text{eq}} \cdot [\mathbf{S14}]_{\text{eq}})) > 840$.

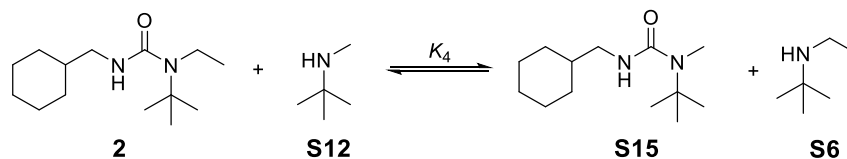
So, for urea **4**, $K_{\text{eq},4} = K_{1*2*3} \cdot K_4 \cdot K_5 > 1.0 \times 10^6 \text{ M}^{-1}$



Determination of binding constant of urea 5



We already have the binding constant for **2**: $K_{\text{eq},2} = K_1 \cdot K_2 \cdot K_3 = 7.1 \times 10^4 \text{ M}^{-1}$



Cyclohexylmethyl isocyanate (**S1**, 14.1 mg, 0.101 mmol), *N*-tertbutyl-*N*-ethyl amine (**S6**, 11.3 mg, 0.112 mmol) and *N*-tertbutyl-*N*-methyl amine (**S12**, 8.1 mg, 0.093 mmol) were dissolved in CDCl_3 (0.55 mL) and added to the NMR tubes. ^1H NMR spectra were collected 15 d after mixing at room temperature after equilibrium was reached/peaks integral stopped changing (Figure S10). The equilibrium constant of the reaction K_4 was calculated according to the concentration ratio of each species: $K_4 = ([\text{S15}]_{\text{eq}} \cdot [\text{S6}]_{\text{eq}}) / ([\text{2}]_{\text{eq}} \cdot [\text{S12}]_{\text{eq}})$.

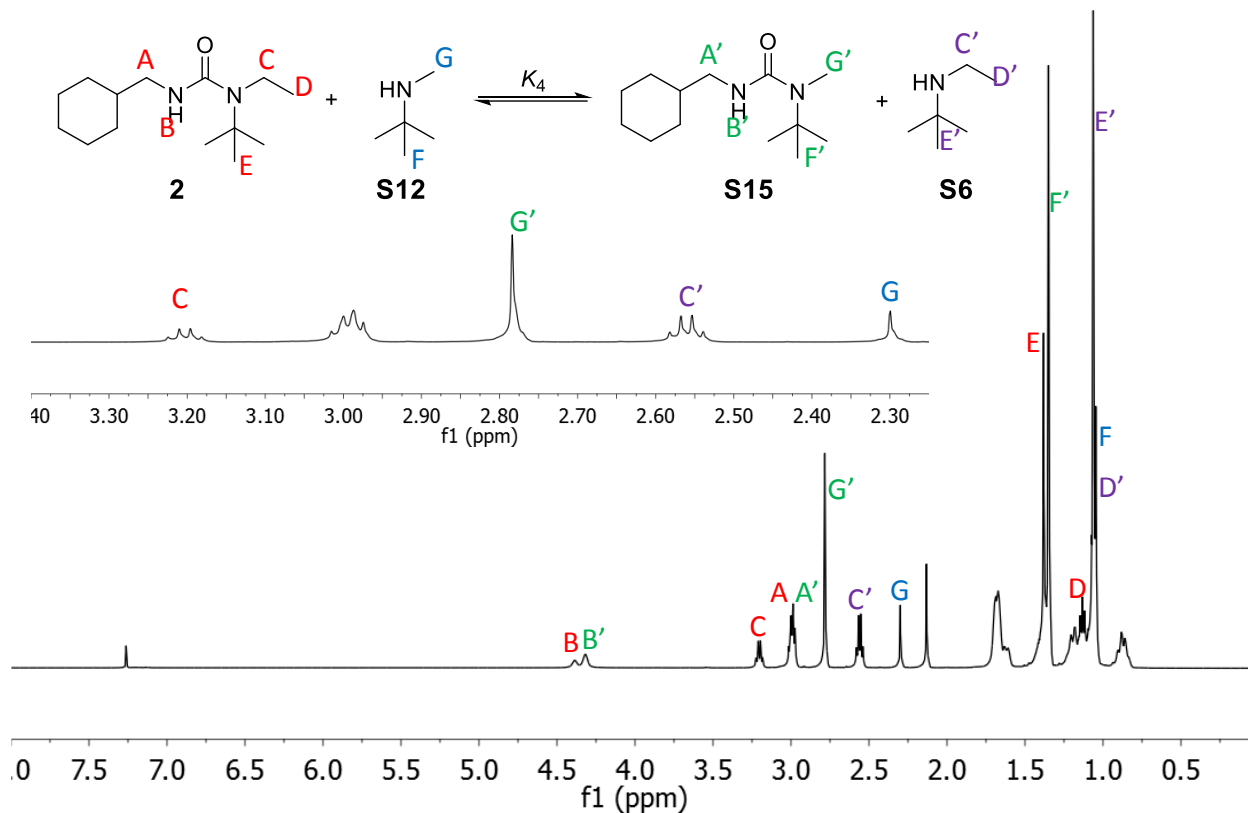
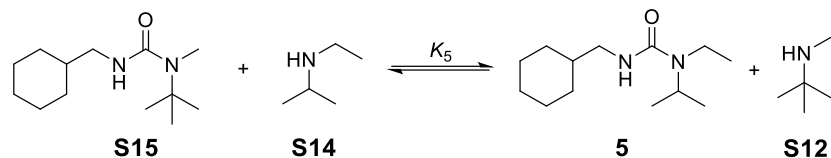


Figure S10. ^1H NMR spectrum of the mixture of compound S1, S6, and S12 (and the produced compound 2, S15). Peaks are assigned to each compound except for the protons in cyclohexyl group. The spectrum was taken 15 d after mixing. The region containing peaks C, C', G and G' for the calculation of the concentration of each species is zoomed in.

$$K_4 = ([\text{S15}]_{\text{eq}} \cdot [\text{S6}]_{\text{eq}}) / ([\text{2}]_{\text{eq}} \cdot [\text{S12}]_{\text{eq}}) = 5.7.$$



Cyclohexylmethyl isocyanate (**S1**, 9.4 mg, 0.068 mmol), *N*-tertbutyl-*N*-methyl amine (**S12**, 7.2 mg, 0.083 mmol) and *N*-isopropyl-*N*-ethyl amine (**S14**, 8.1 mg, 0.093 mmol) were dissolved in CDCl₃ (0.55 mL) and added to the NMR tubes. ¹H NMR spectra were collected 41 d after mixing at room temperature after equilibrium was reached/peaks integral stopped changing (Figure S11). The equilibrium constant of the reaction K_5 was calculated according to the concentration ratio of each species: $K_5 = ([\text{5}]_{\text{eq}} \cdot [\text{S12}]_{\text{eq}} / ([\text{S15}]_{\text{eq}} \cdot [\text{S14}]_{\text{eq}})$.

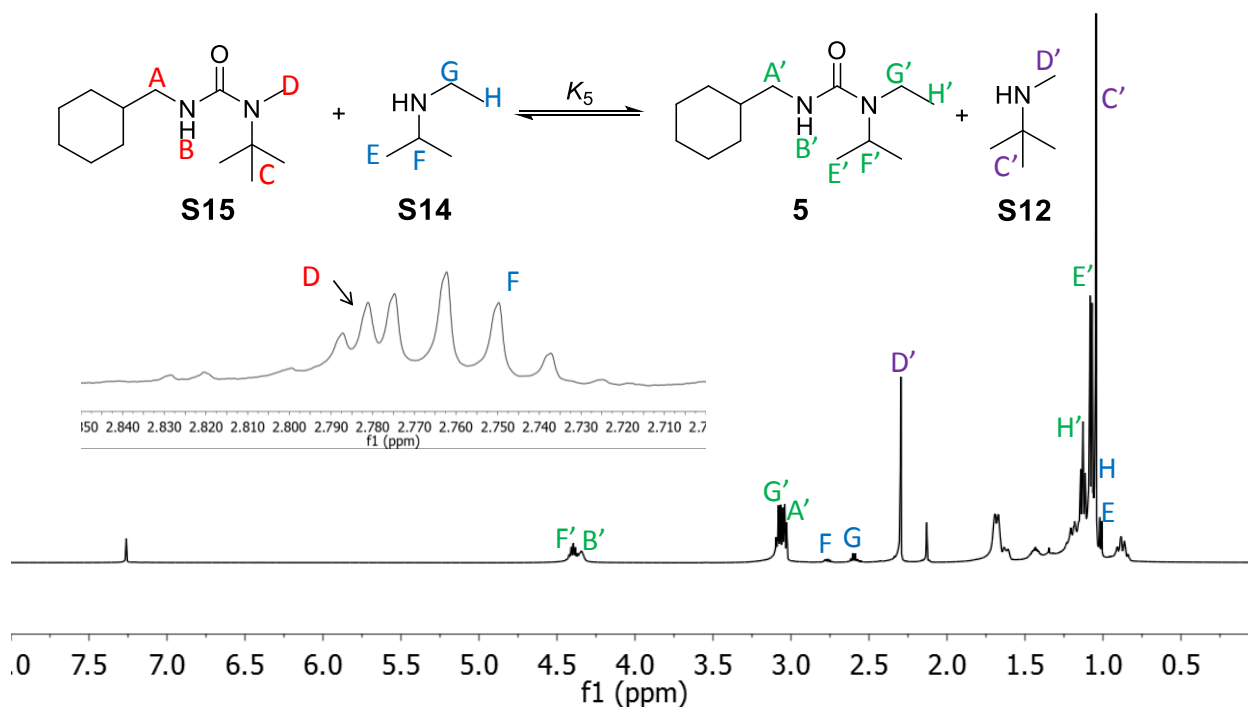
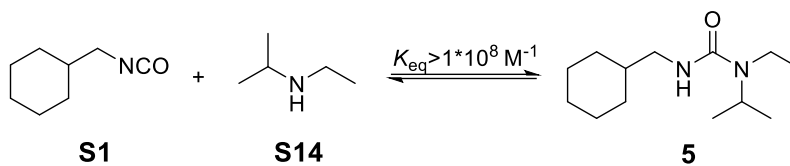


Figure S11. ¹H NMR spectrum of the mixture of compound **S1**, **S12**, and **S14** (and the produced compound **S15**, **5**). Peaks are assigned to each compound except for the protons in cyclohexyl group. The spectrum was taken 41 d after mixing. Here, no peaks for **S15** were

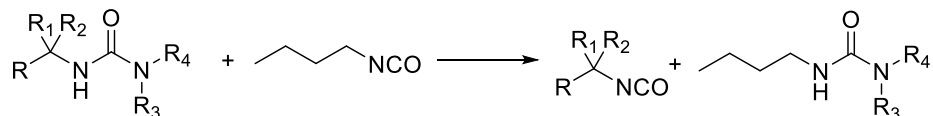
observed except for a very weak peak D as shown in zoomed in picture.

$$K_5 = ([\mathbf{5}]_{\text{eq}} \bullet [\mathbf{S12}]_{\text{eq}} / ([\mathbf{S15}]_{\text{eq}} \bullet [\mathbf{S14}]_{\text{eq}}) > 1130.$$

So, for urea **5**, $K_{\text{eq},5} = K_{\text{eq},2} \bullet K_4 \bullet K_5 > 1.0 \times 10^8 \text{ M}^{-1}$



Determinations of dissociation rates of hindered urea bonds (Determination of dissociation rate of urea **1** with similar methods has been reported in ref. 18 in text)



The dissociation kinetics (k_{-1}) of hindered urea compounds **2~5** were determined (Figure S12-15, respectively). To urea compounds were added butyl isocyanate to capture the released free amine. The rates of consumption of urea compounds were monitored by ^1H NMR at 37 °C and dissociation rates were calculated based on those data. (All used CDCl_3 as the solvent)

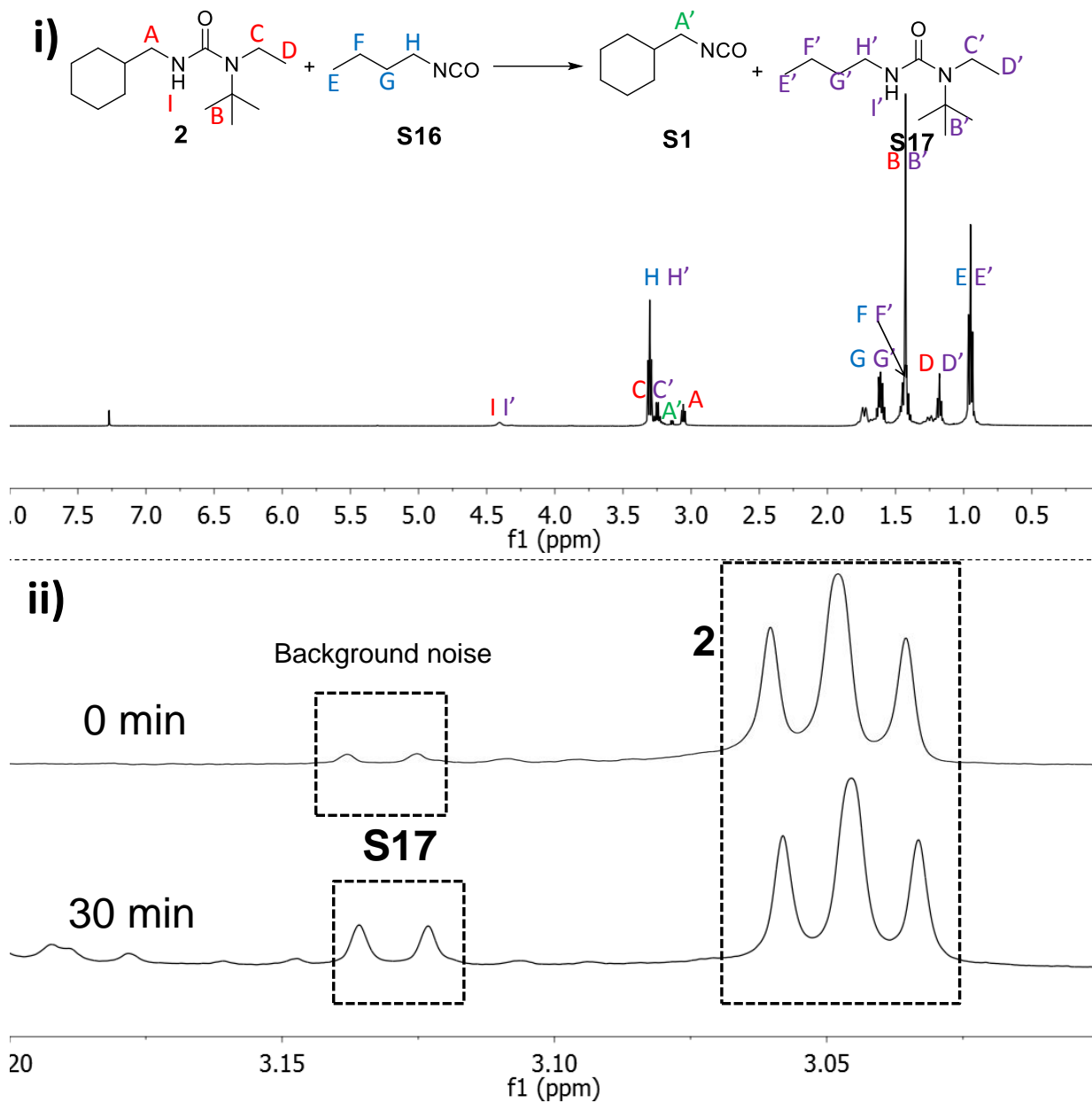


Figure S12 Dissociation rate of urea 2. i) ^1H NMR spectrum of the mixture of compound **2** (6.2 mg, 0.026 mmol) and **S16** (10.1 mg, 0.102 mmol, and the produced compound **S1** and **S17**) in CDCl_3 (550 μL). The spectrum was taken 30 min after **2** and **S16** were mixed at 37°C . Peaks are assigned to each compound except for the protons in cyclohexyl group. ii) ^1H NMR spectra showing exchange reaction between **2** and **S16** at 37°C . The rate of consumption of **2** was used to

calculate the dissociation rate with the following equation: $k_{-1} = -\frac{\ln \frac{[2]}{[2]_0}}{T} = -\frac{\ln 0.91}{0.5 \text{ h}} = 0.19 \text{ h}^{-1}$

(T: reaction time, peak A' used for the calculation overlapped with background noise in the same range, which has been deducted in the calculation)

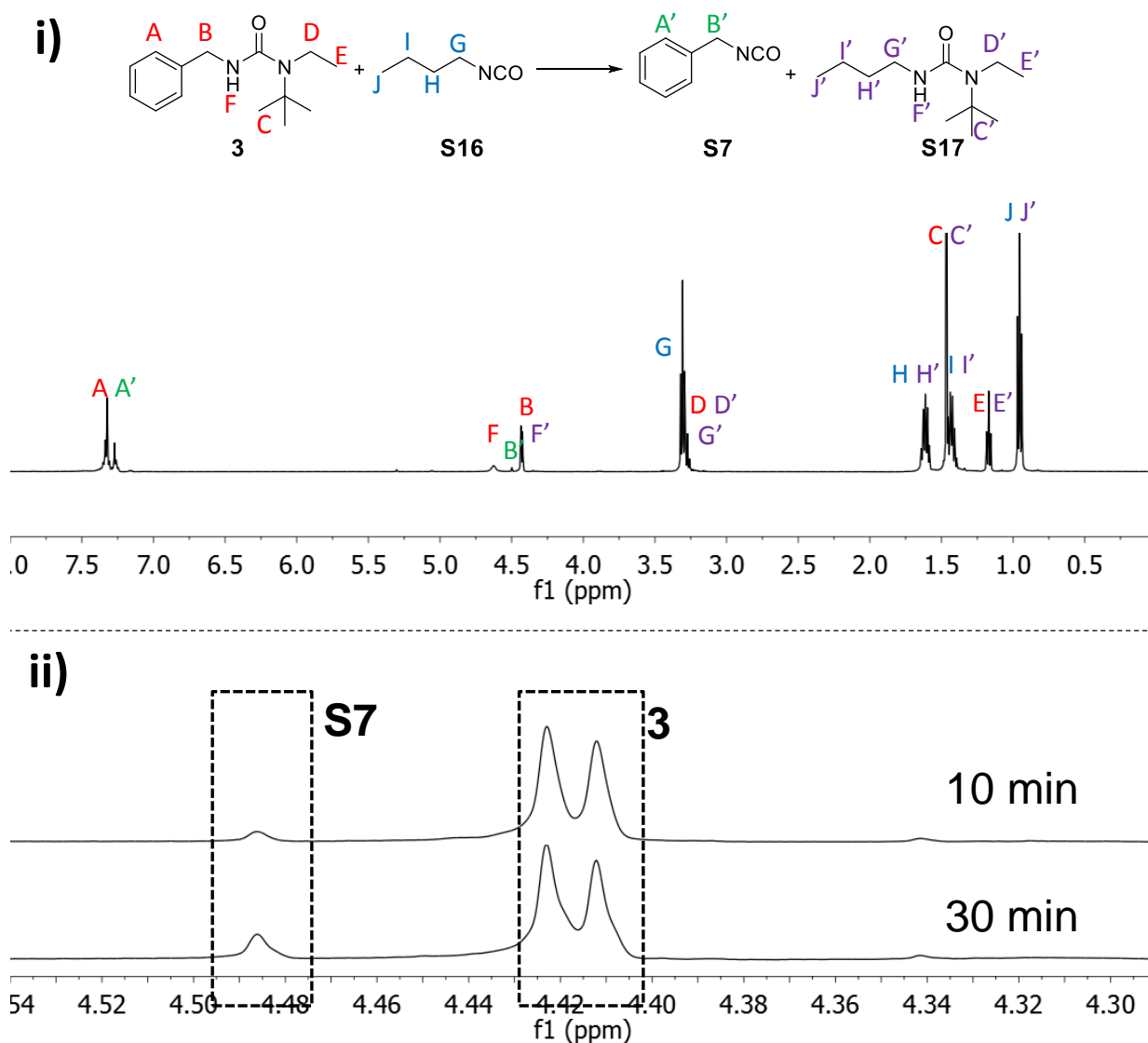


Figure S13. Dissociation rate of urea 3. i) ^1H NMR spectrum of the mixture of compound **3** (7.4 mg, 0.032 mmol) and **S16** (11.9 mg, 0.120 mmol, and the produced compound **S7** and **S17**) in CDCl_3 (550 μL). The spectrum was taken 30 min after **3** and **S16** were mixed at 37°C . Peaks are assigned to each compound. ii) ^1H NMR spectra showing exchange reaction between **3** and

S16 at 37°C. The rate of consumption of **3** was used to calculate the dissociation rate with the

following equation: $k_{-1} = -\frac{\ln \frac{[\mathbf{3}]}{[\mathbf{3}]_0}}{T} = -\frac{\ln 0.91}{0.5 \text{ h}} = 0.19 \text{ h}^{-1}$ (T: reaction time)

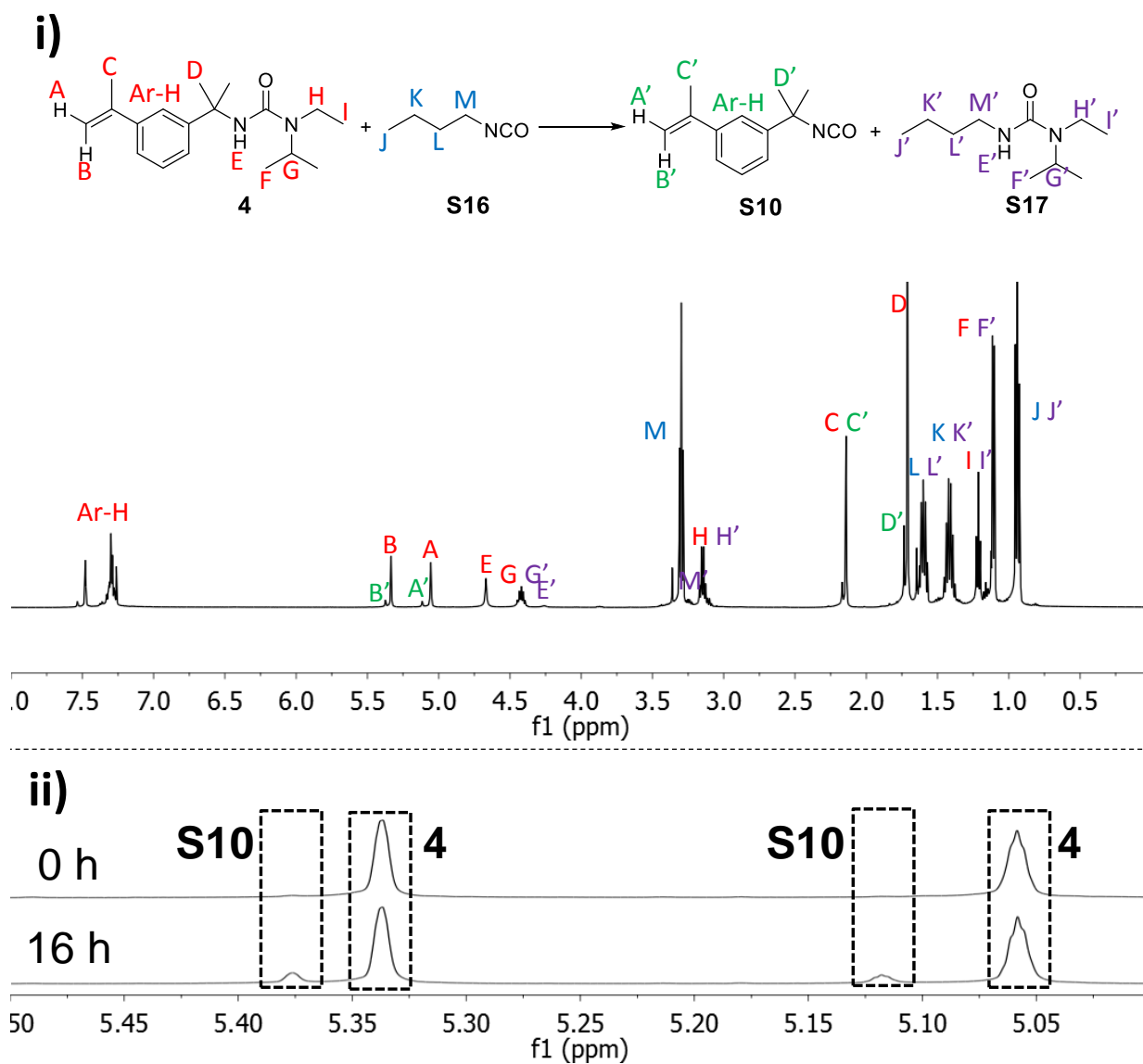


Figure S14. Dissociation rate of urea 4. i) ^1H NMR spectrum of the mixture of compound **4** (8.3 mg, 0.029 mmol) and **S16** (9.6 mg, 0.097 mmol, and the produced compound **S10** and **S17**) in CDCl_3 (550 μL). The spectrum was taken 16 h after **4** and **S16** were mixed at 37°C . Peaks are assigned to each compound. ii) ^1H NMR spectra showing exchange reaction between **4** and **S16** at 37°C . The rate of consumption of **4** was used to calculate the dissociation rate with the

following equation:
$$k_{-1} = -\frac{\ln \frac{[\mathbf{4}]}{[\mathbf{4}]_0}}{T} = -\frac{\ln 0.88}{16 \text{ h}} = 0.008 \text{ h}^{-1} \quad (\text{T: reaction time})$$

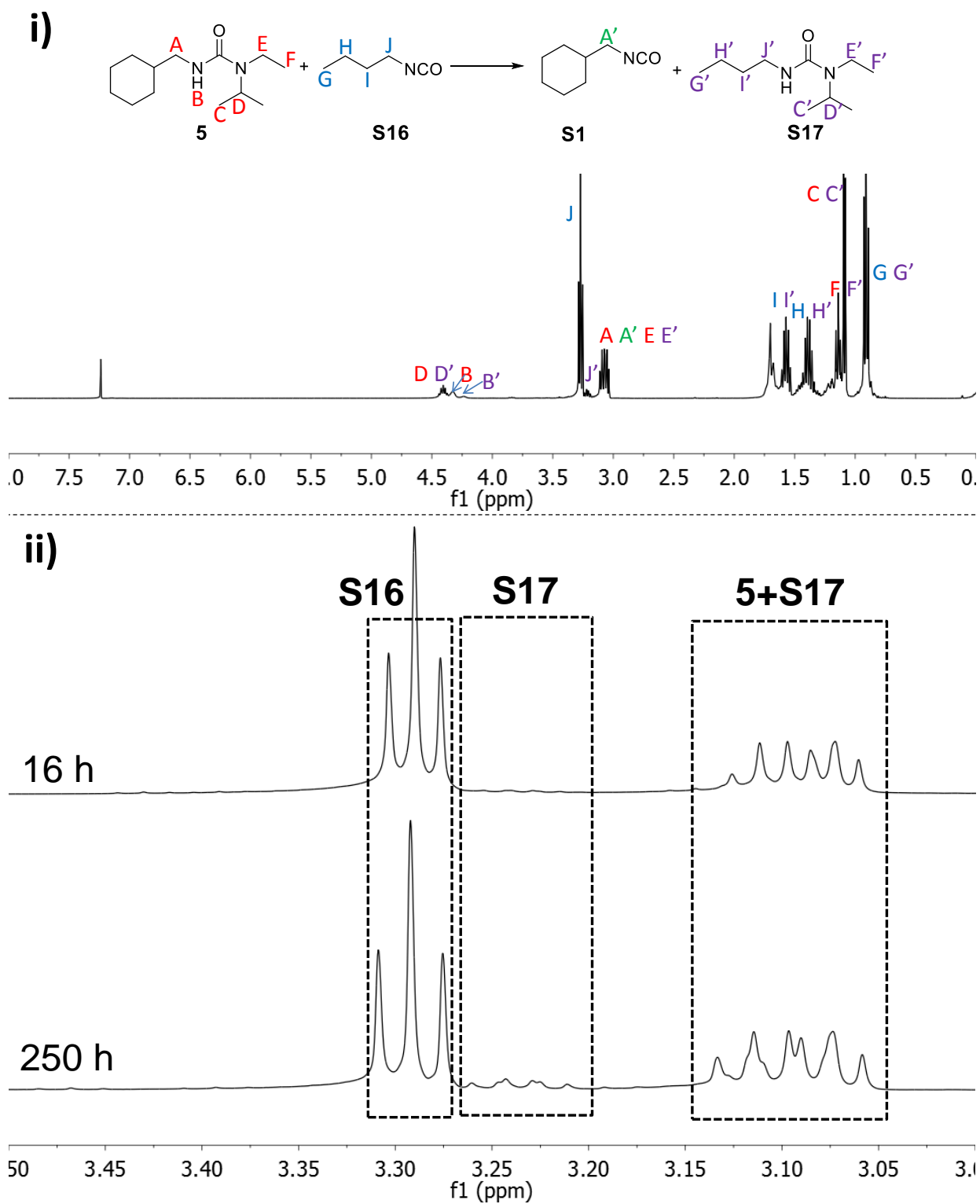


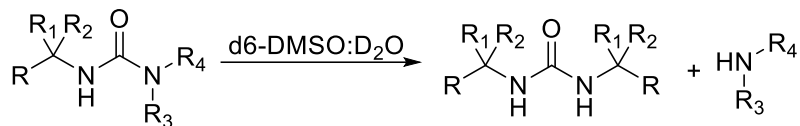
Figure S15. Dissociation rate of urea 5. i) ^1H NMR spectrum of the mixture of compound **5** (6.4 mg, 0.028 mmol) and **S16** (8.3 mg, 0.084 mmol, and the produced compound **S1** and **S17**) in

CDCl₃ (550 μL). The spectrum was taken 250 h after **5** and **S16** were mixed at 37°C. Peaks are assigned to each compound except for the protons in cyclohexyl group. ii) ¹H NMR spectra showing exchange reaction between **5** and **S16** at 37°C. The rate of consumption of **5** was used to

calculate the dissociation rate with the following equation: $k_{-1} = -\frac{\ln \frac{[\mathbf{5}]}{[\mathbf{5}]_0}}{T} = -\frac{\ln 0.79}{250 \text{ h}} = 0.0009 \text{ h}^{-1}$

(T: reaction time)

Determination of hydrolysis kinetics of hindered urea bonds



We compared the hydrolysis kinetics of urea **1~5** by comparing the percentage of hydrolysis after 24 h at 37 °C environment. Urea **1~5** were dissolved in mixture of d6-DMSO and D₂O (v(d₆-DMSO):v(D₂O)=5:1) with concentration of 0.1 M. After incubation at 37 °C for 24 h, ¹H NMR spectra were collected to characterize the percentage of hydrolysis (through the ratio of produced amine and original urea).

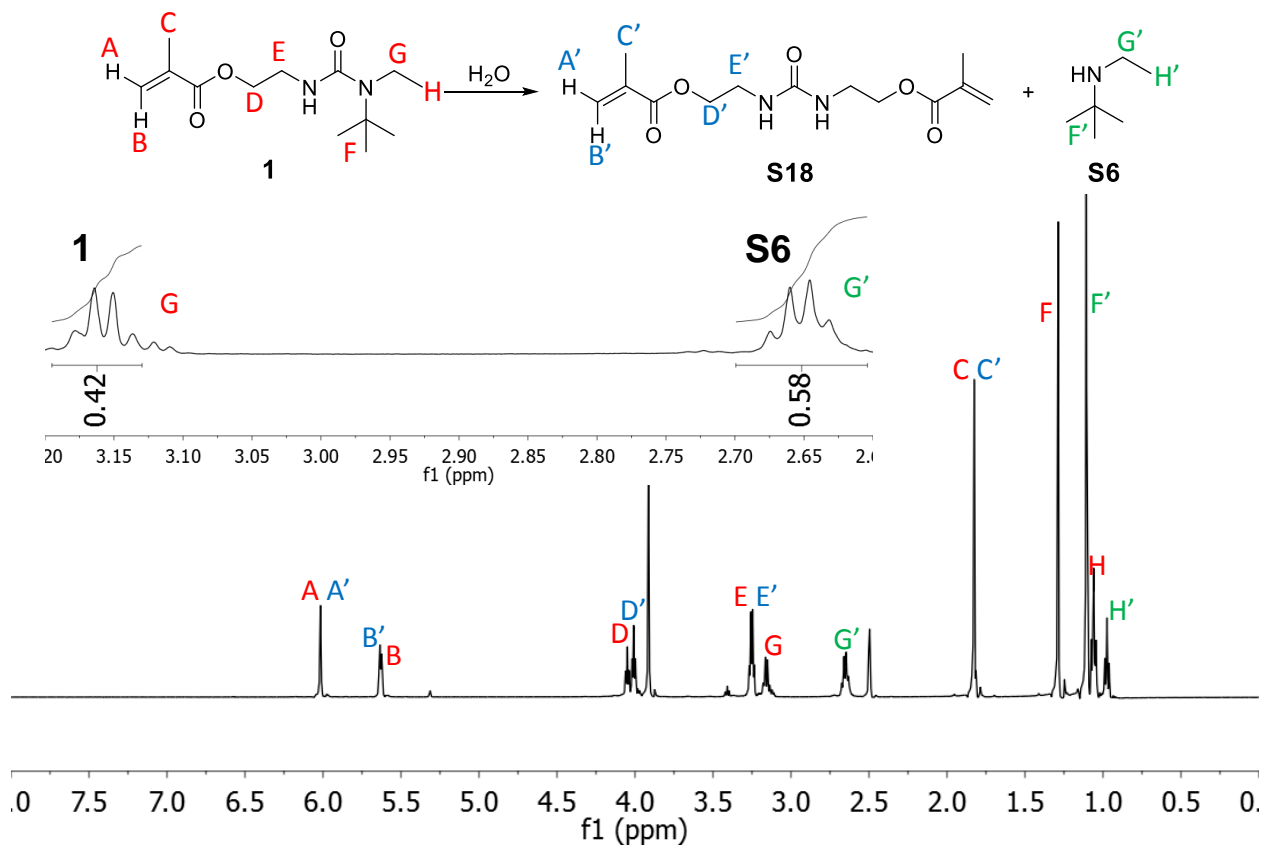


Figure S16. Hydrolysis of urea 1. Peaks are assigned to each compound. The spectrum was taken 24 h after dissolving in mixture of d₆-DMSO and D₂O (v(d₆-DMSO):v(D₂O)=5:1) at 37 °C. The region containing peaks G, G' for the calculation of the percentage of hydrolysis is zoomed in. The percentage of hydrolysis was determined as 58%.

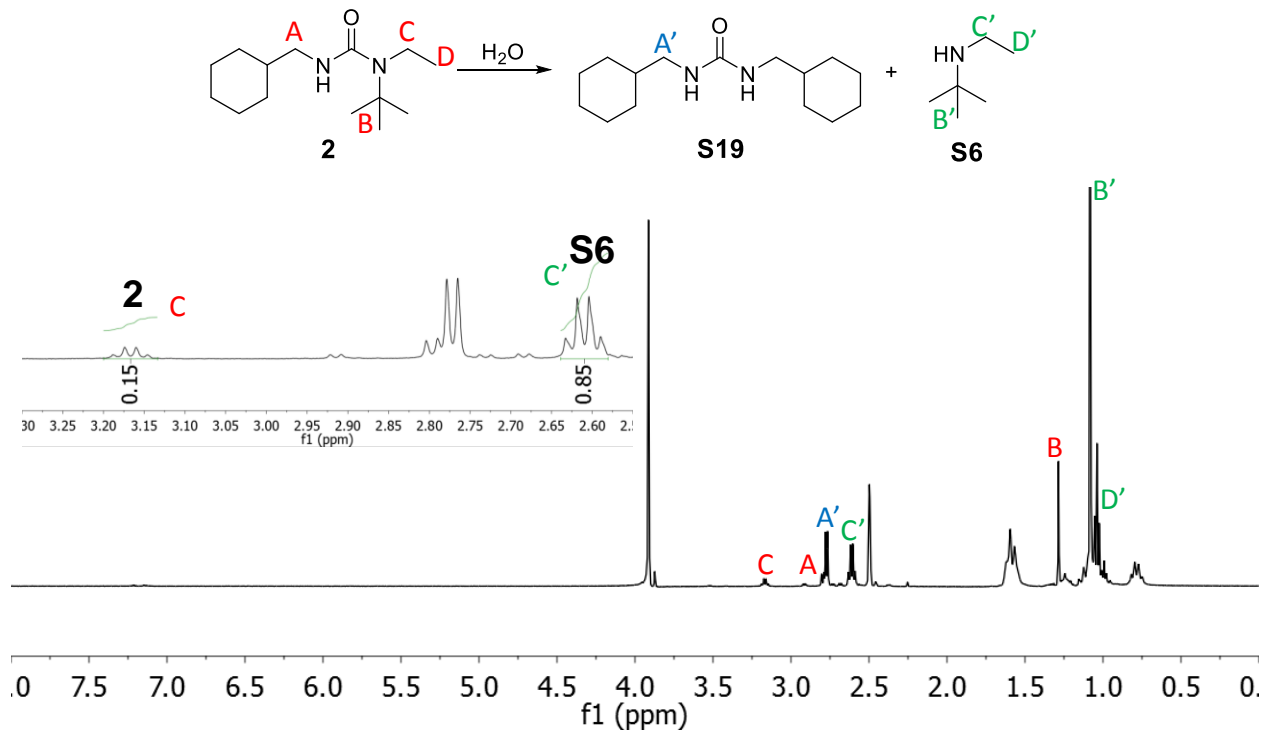


Figure S17. Hydrolysis of urea 2. Peaks are assigned to each compound except for the protons in cyclohexyl group. The spectrum was taken 24 h after dissolving in mixture of d_6 -DMSO and D_2O ($v(d_6\text{-DMSO}):v(D_2O)=5:1$) at 37 °C. The region containing peaks C, C' for the calculation of the percentage of hydrolysis is zoomed in. The percentage of hydrolysis was determined as 85%.

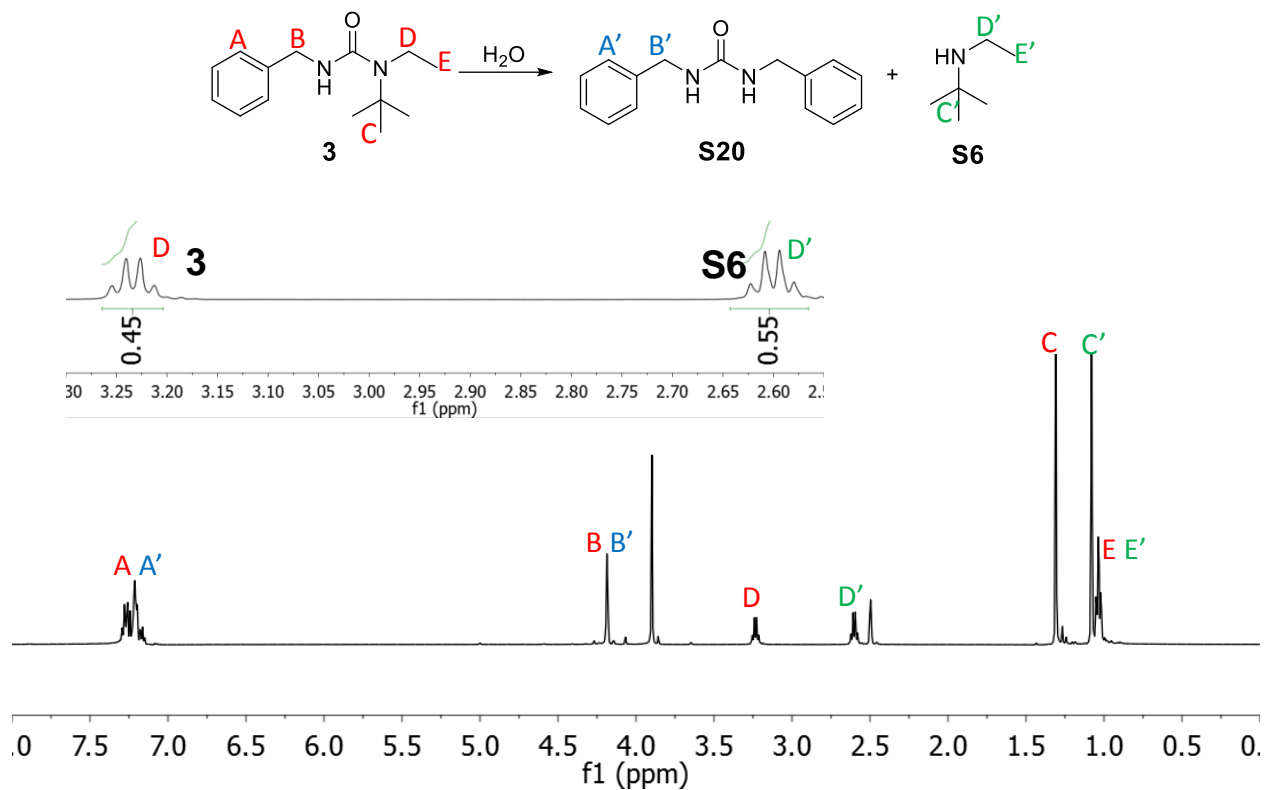


Figure S18. Hydrolysis of urea 3. Peaks are assigned to each compound. The spectrum was taken 24 h after dissolving in mixture of d₆-DMSO and D₂O (v(d₆-DMSO):v(D₂O)=5:1) at 37 °C. The region containing peaks D, D' for the calculation of the percentage of hydrolysis is zoomed in. The percentage of hydrolysis was determined as 55%.

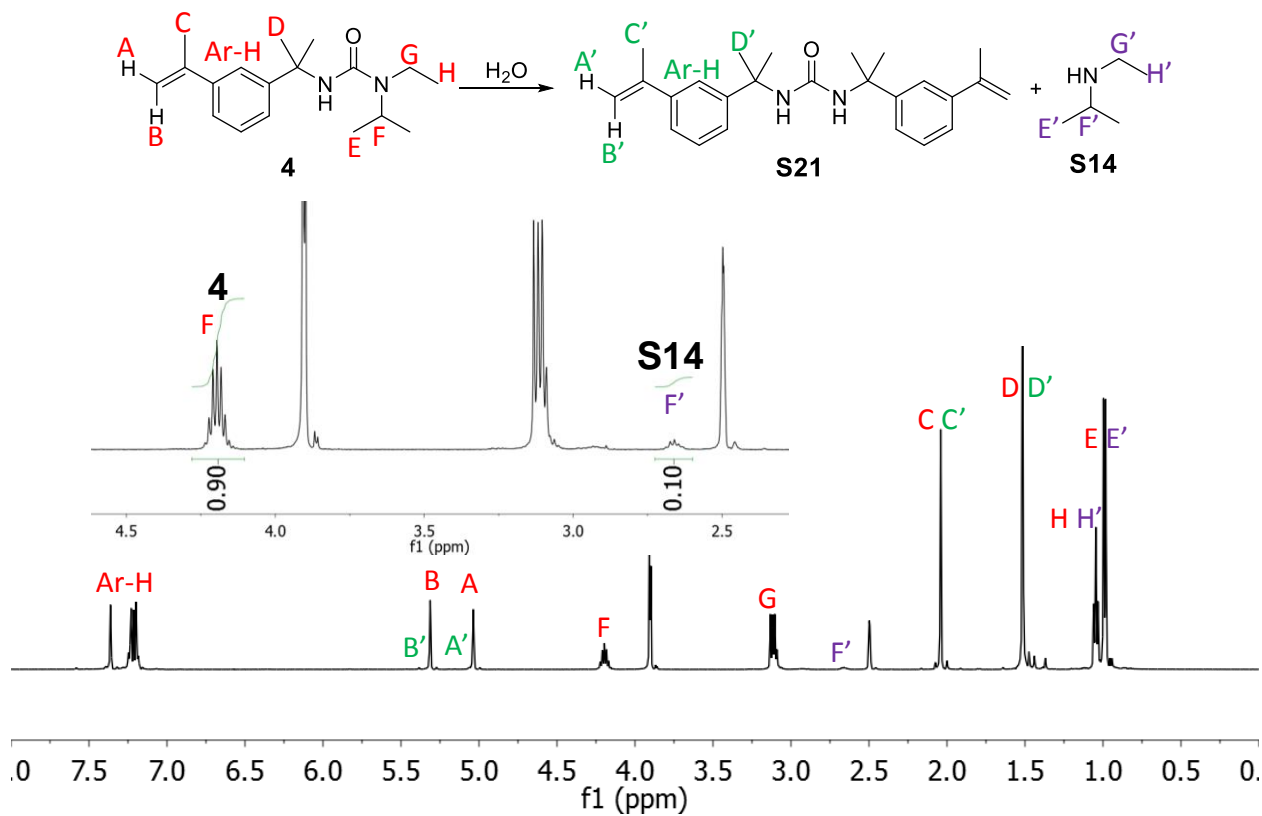


Figure S19. Hydrolysis of urea 4. Peaks are assigned to each compound. The spectrum was taken 24 h after dissolving in mixture of d₆-DMSO and D₂O (v(d₆-DMSO):v(D₂O)=5:1) at 37 °C. The region containing peaks F, F' for the calculation of the percentage of hydrolysis is zoomed in. The percentage of hydrolysis was determined as 10%.

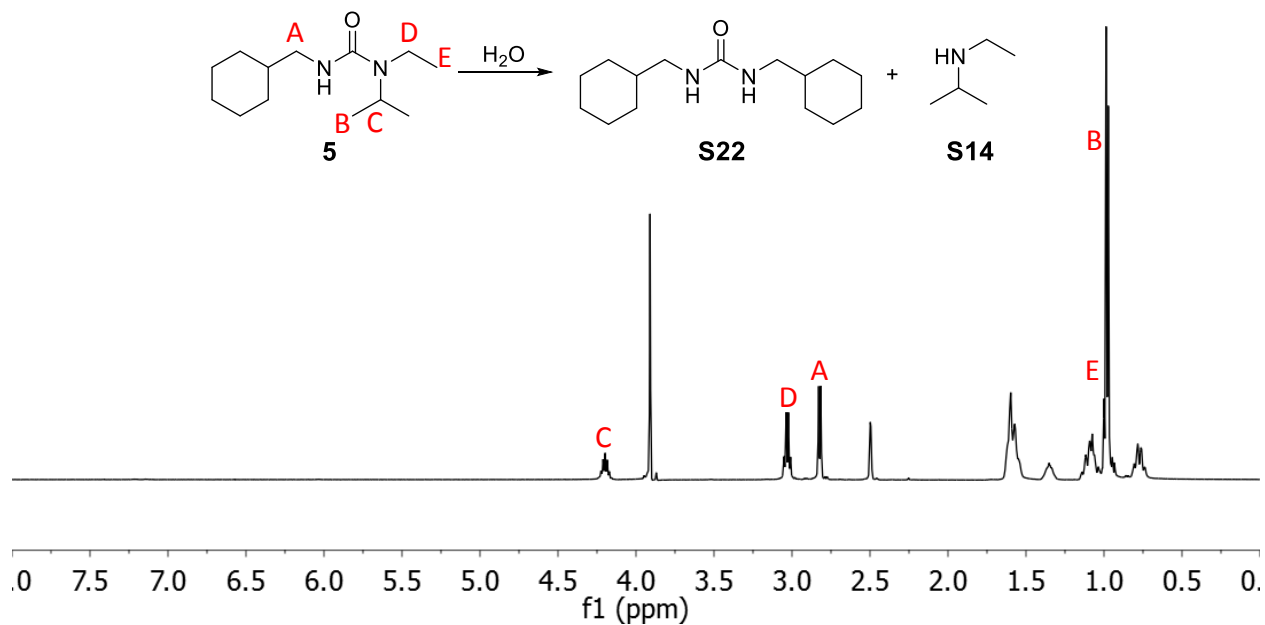


Figure S20. Hydrolysis of urea 5. Peaks are assigned to each compound except for the protons in cyclohexyl group. The spectrum was taken 24 h after dissolving in mixture of $\text{d}_6\text{-DMSO}$ and D_2O ($v(\text{d}_6\text{-DMSO}):v(\text{D}_2\text{O})=5:1$) at 37°C . No detectable hydrolysis was observed.

Synthesis of hindered polyurea

Synthesis of polymer (poly(6/9)): Equal molar 1,3-bis(isocyanatomethyl)cyclohexane (**6**, 1.94 g, 10.0 mmol) and *N,N'*-di-*tert*-butylethylene-diamine (**9**, 1.72 g, 10.0 mmol) were dissolved in DMF (10 g). The mixture was stirred at room temperature overnight vigorously. The polymer solution was directly used for GPC characterization and degradation study. Equal molar of **6** (0.194 g, 1.0 mmol) and **9** (0.172 g, 1.0 mmol) were mixed in CDCl₃ (1.0g). The solution was stirred at room temperature overnight vigorously, diluted by a factor of 10, and directly characterized by NMR without purification. Polymer solution in DMF was precipitated by ether (100 mL × 3). The white solid was collected by centrifuge and dried by vacuum oven overnight (yield: 90%, Mn = 22K, PDI = 1.55). The obtained solid was used for TGA and DSC characterizations.

Synthesis of polymer (poly(7/9)): Equal molar *m*-xylylene diisocyanate (**7**, 1.88 g, 10.0 mmol) and *N,N'*-di-*tert*-butylethylene-diamine (**9**, 1.72 g, 10.0 mmol) were dissolved in DMF (10 g). The mixture was stirred at room temperature overnight vigorously. The polymer solution was directly used for GPC characterization and degradation study. Equal molar of **7** (0.188 g, 1.0 mmol) and **9** (0.172 g, 1.0 mmol) were mixed in CDCl₃ (1.0g). The solution was stirred at room temperature overnight vigorously, diluted by a factor of 10, and directly characterized by NMR without purification. Polymer solution in DMF was precipitated by ether (100 mL × 3). The white solid was collected by centrifuge and dried by vacuum oven overnight (yield: 92%, Mn = 22K, PDI = 1.33). The obtained solid was used for TGA and DSC characterizations.

Synthesis of polymer (poly(8/10)): Equal molar 1,3-Bis(1-isocyanato-1-methylethyl)benzene (**8**, 2.44 g, 10.0 mmol) and *N,N'*-di-*iso*-propylethylene-diamine (**10**, 1.44 g, 10.0 mmol) were dissolved in DMF (10 g). The mixture was stirred at room temperature overnight vigorously. The polymer solution was directly used for GPC characterization and degradation study. Equal molar of **8** (0.244 g, 1.0 mmol) and **10** (0.144 g, 1.0 mmol) were mixed in CDCl₃ (1.0g). The solution was stirred at room temperature overnight vigorously, diluted by a factor of 10, and directly characterized by NMR without purification. Polymer solution in DMF was precipitated by ether (100 mL × 3). The white solid was collected by centrifuge and dried by vacuum oven overnight (yield: 87%, Mn = 44K, PDI = 1.45). The obtained solid was used for TGA and DSC characterizations.

Synthesis of polymer (poly(6/10)): Equal molar 1,3-bis(isocyanatomethyl)cyclohexane (**6**, 1.94 g, 10.0 mmol) and *N,N'*-di-*iso*-propylethylene-diamine (**10**, 1.44 g, 10.0 mmol) were dissolved in DMF (10 g). The mixture was stirred at room temperature overnight vigorously. The polymer solution was directly used for GPC characterization and degradation study. Equal molar of **6** (0.194 g, 1.0 mmol) and **10** (0.144 g, 1.0 mmol) were mixed in CDCl₃ (1.0g). The solution was stirred at room temperature overnight vigorously, diluted by a factor of 10, and directly characterized by NMR without purification. Polymer solution in DMF was precipitated by ether (100 mL × 3). The white solid was collected by centrifuge and dried by vacuum oven overnight (yield: 95%, Mn = 120K, PDI = 1.72). The obtained solid was used for TGA and DSC characterizations.

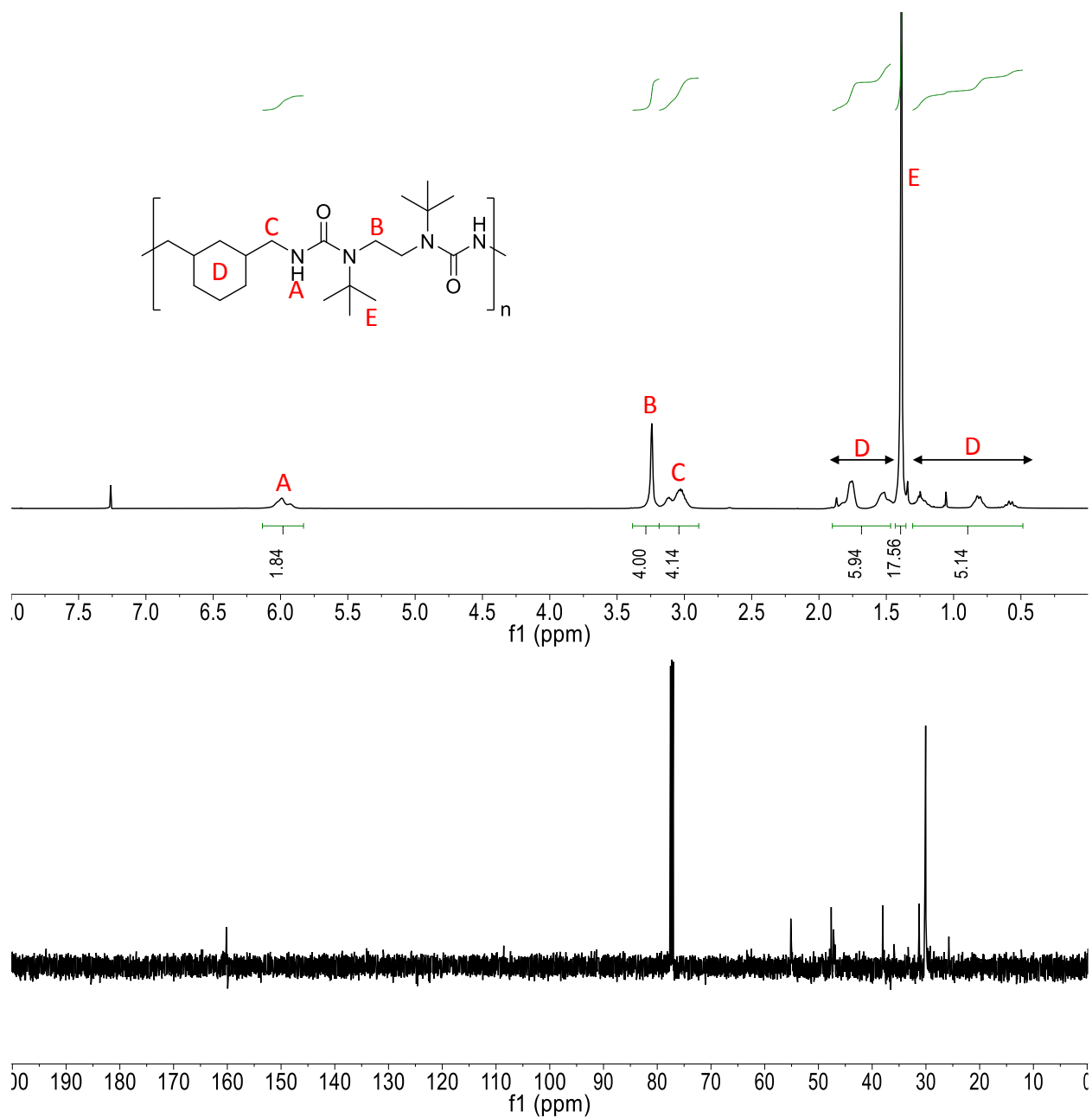


Figure S21. ^1H NMR and ^{13}C NMR spectra of poly(6/9)

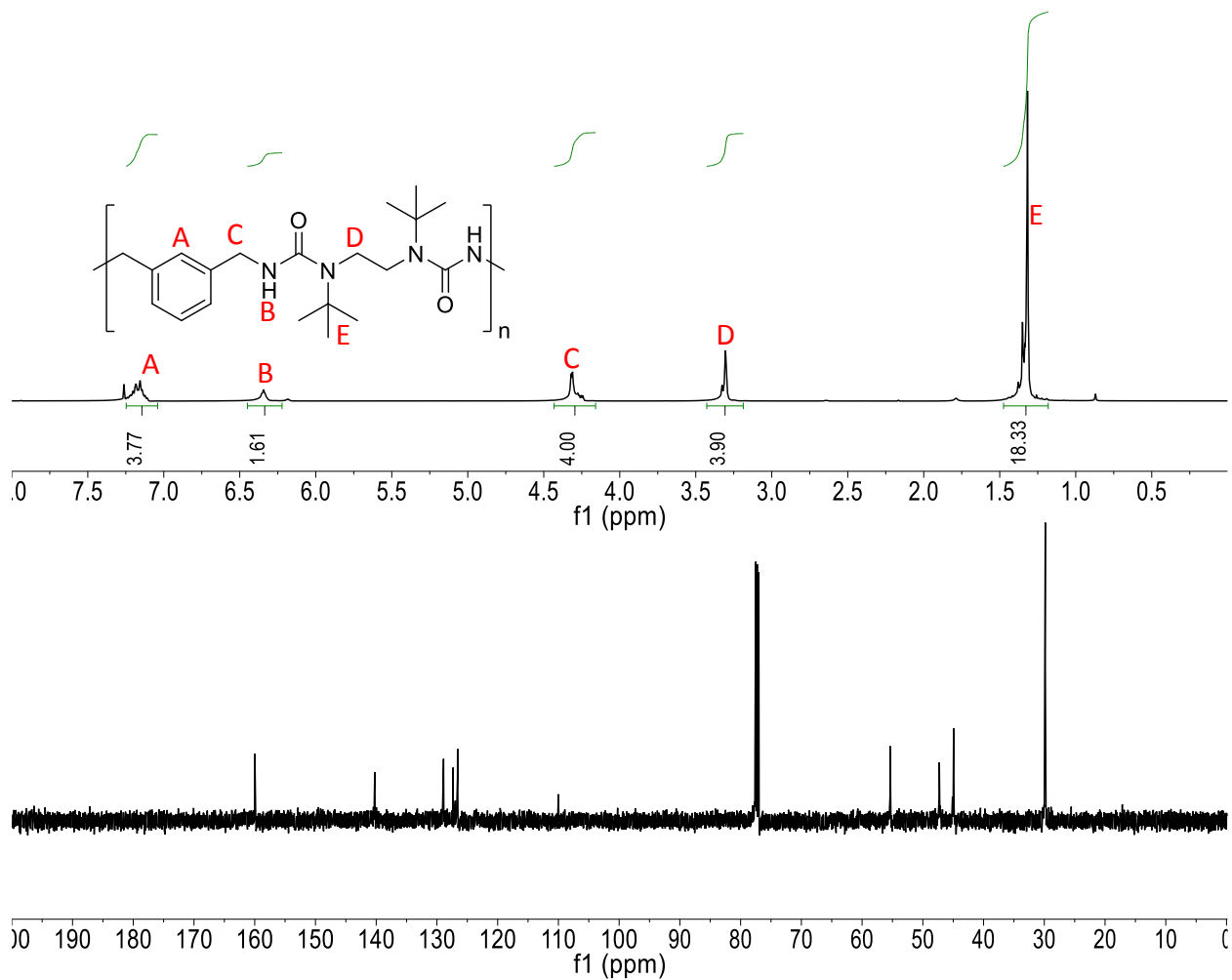


Figure S22. ¹H NMR and ¹³C NMR spectra of poly(7/9)

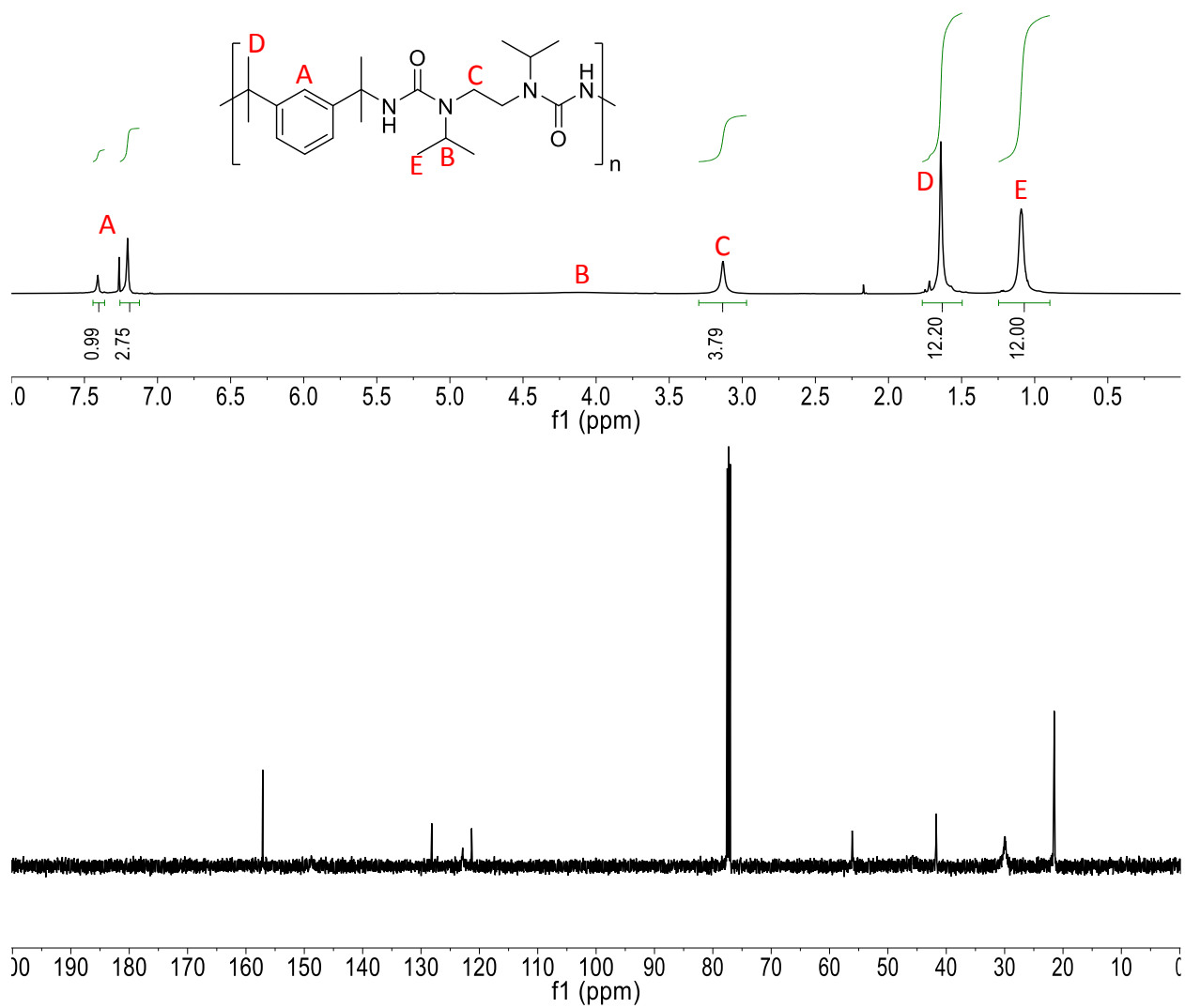


Figure S23. ¹H NMR and ¹³C NMR spectra of poly(8/10)

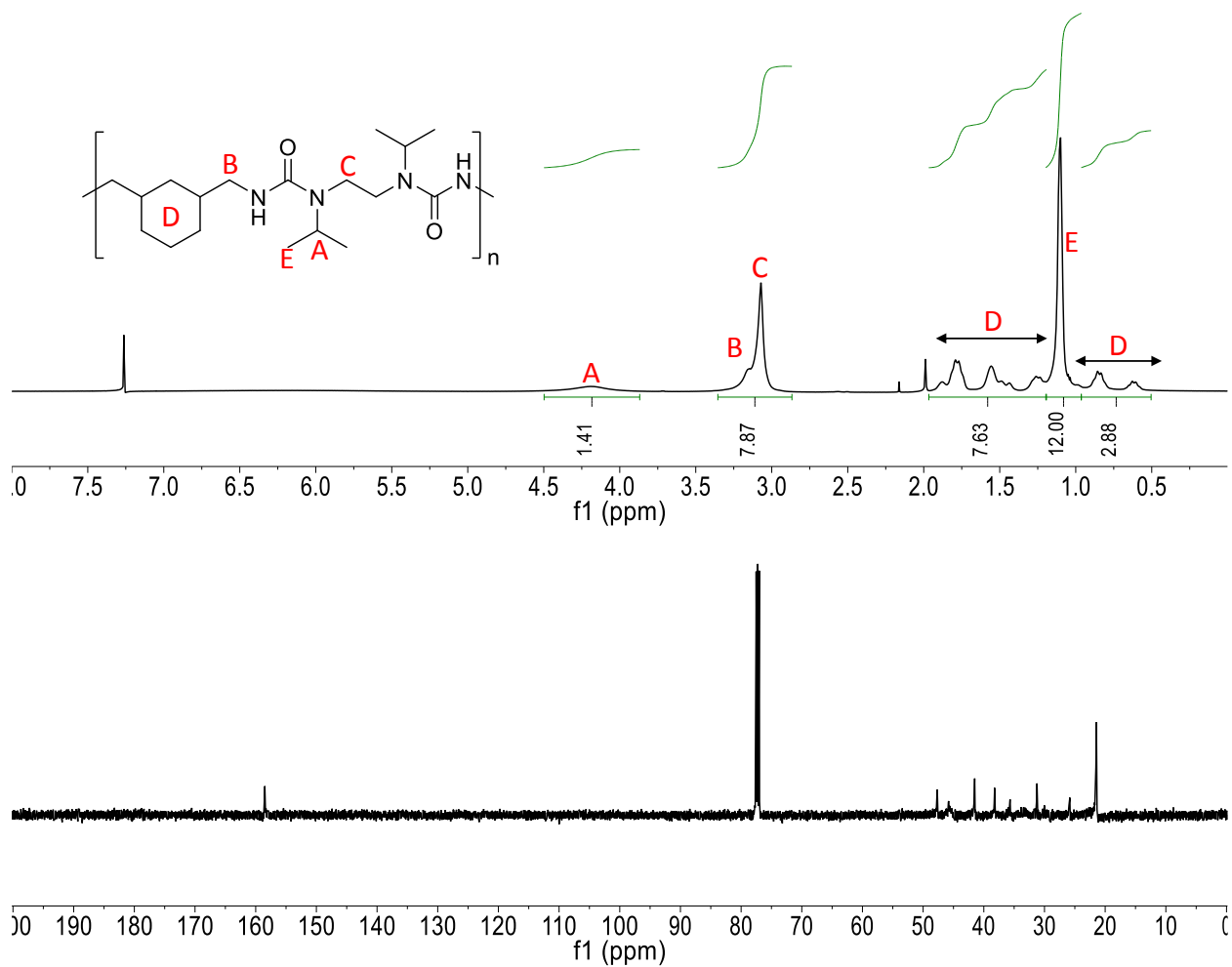


Figure S24. ^1H NMR and ^{13}C NMR spectra of poly(6/10)

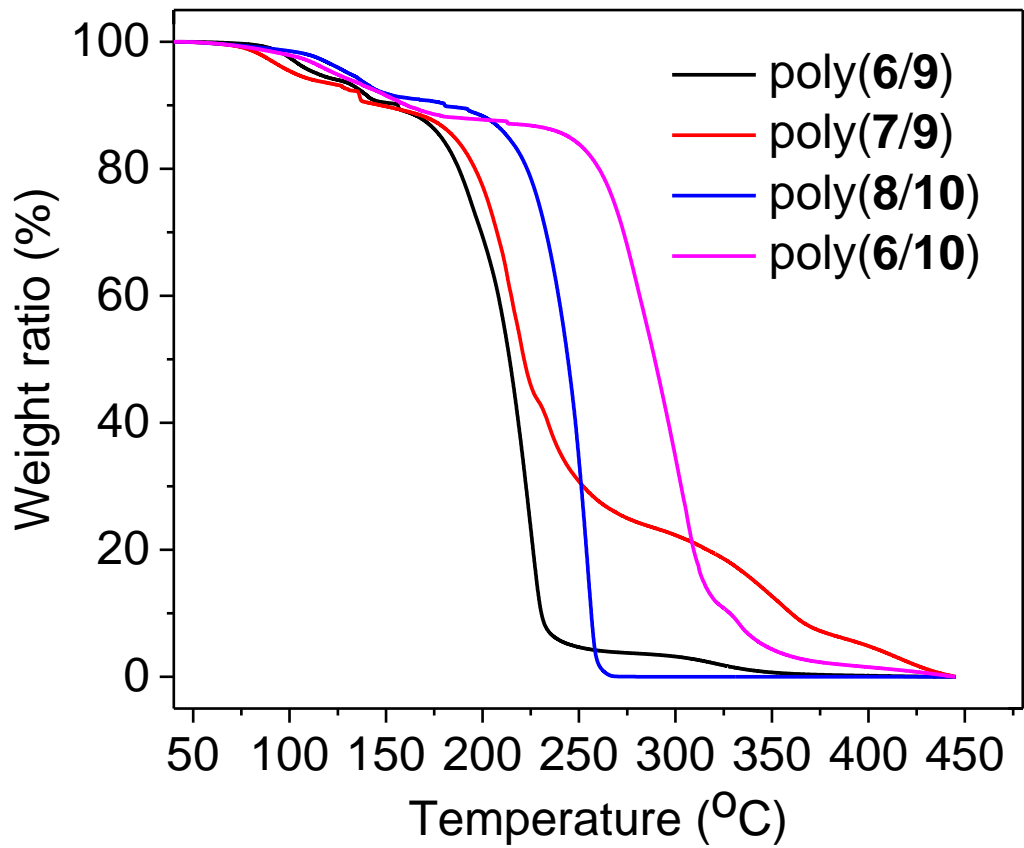


Figure S25. Thermo gravimetric analysis (TGA) of linear polymers.

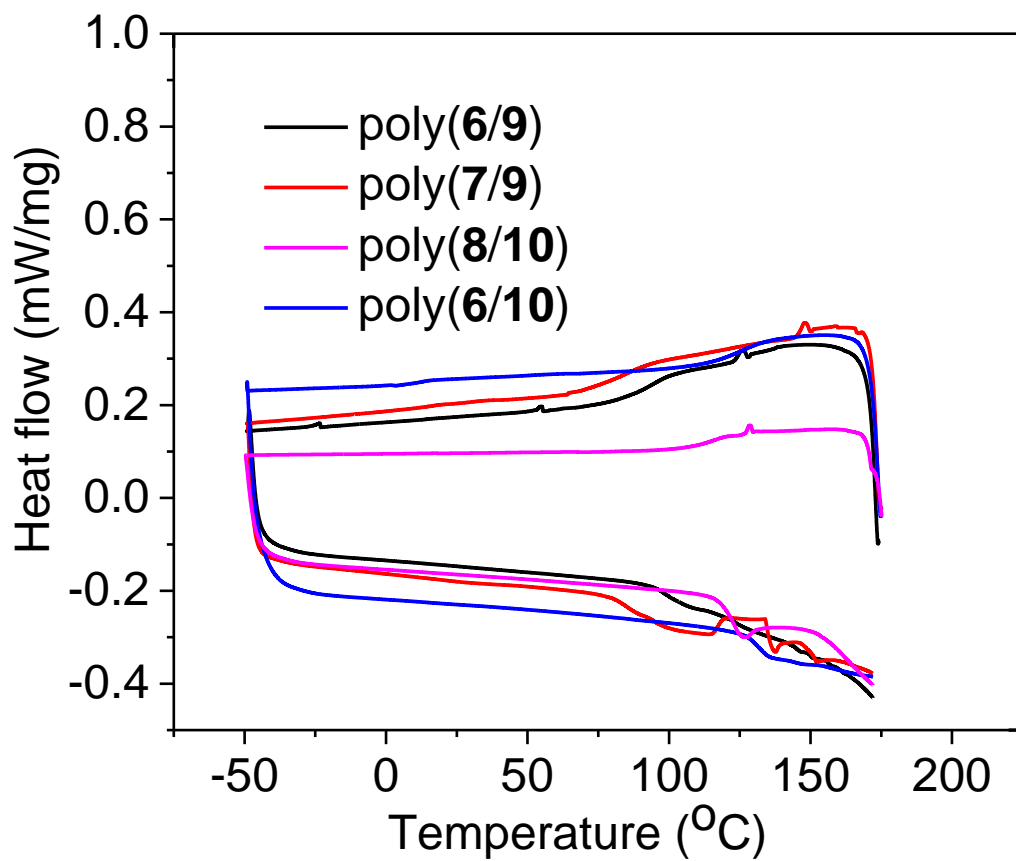


Figure S26. Differential scanning calorimetry (DSC) of linear polymers. Second heating curve from -50 °C to 175 °C were shown.

Water degradation of linear hindered polyurea

To 500 μL as prepared DMF solution of each polymer (see page S38-39), 25 μL water was added. The mixture was incubated at 37 $^{\circ}\text{C}$ with vigorous stirring. Samples were taken out at different time intervals for monitoring of molecular weight change by GPC.

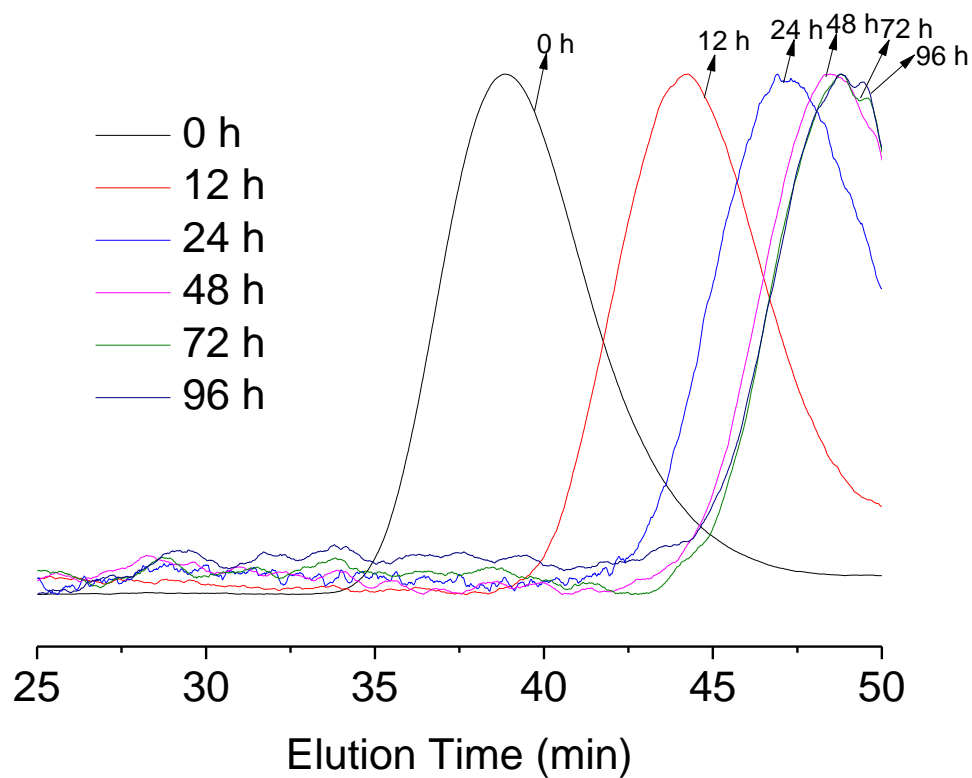


Figure S27. Water degradation of poly(6/9). GPC curves from light scattering detector showing water degradation of poly(6/9) after incubation in DMF (containing 5% water) at 37 °C for variant time intervals.

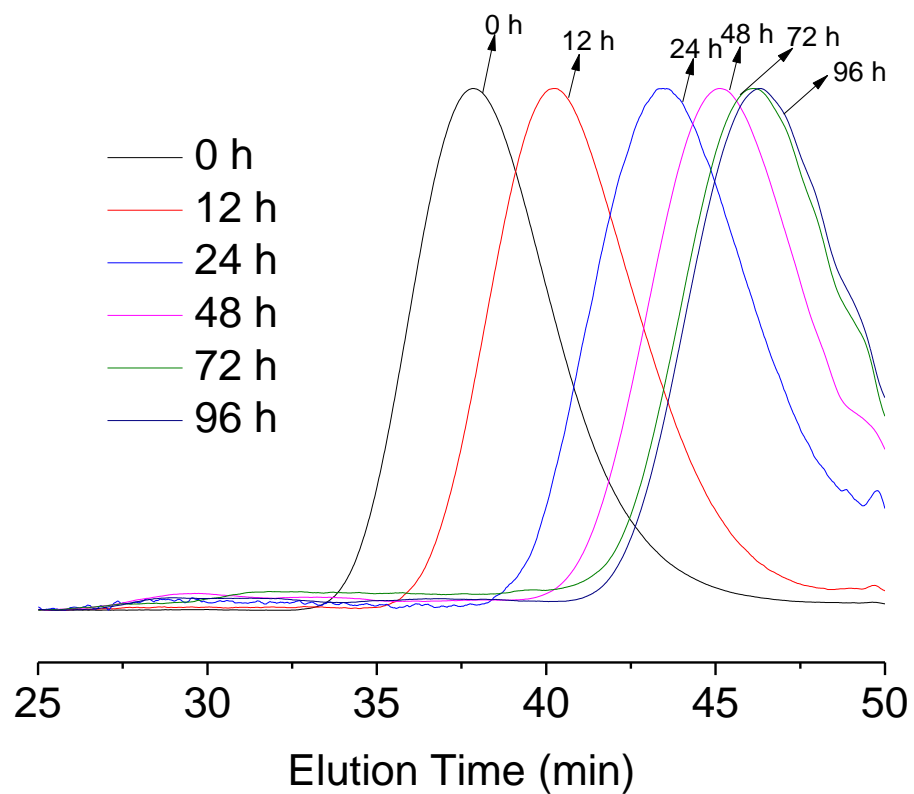


Figure S28. Water degradation of poly(7/9). GPC curves from light scattering detector showing water degradation of poly(7/9) after incubation in DMF (containing 5% water) at 37 °C for variant time intervals.

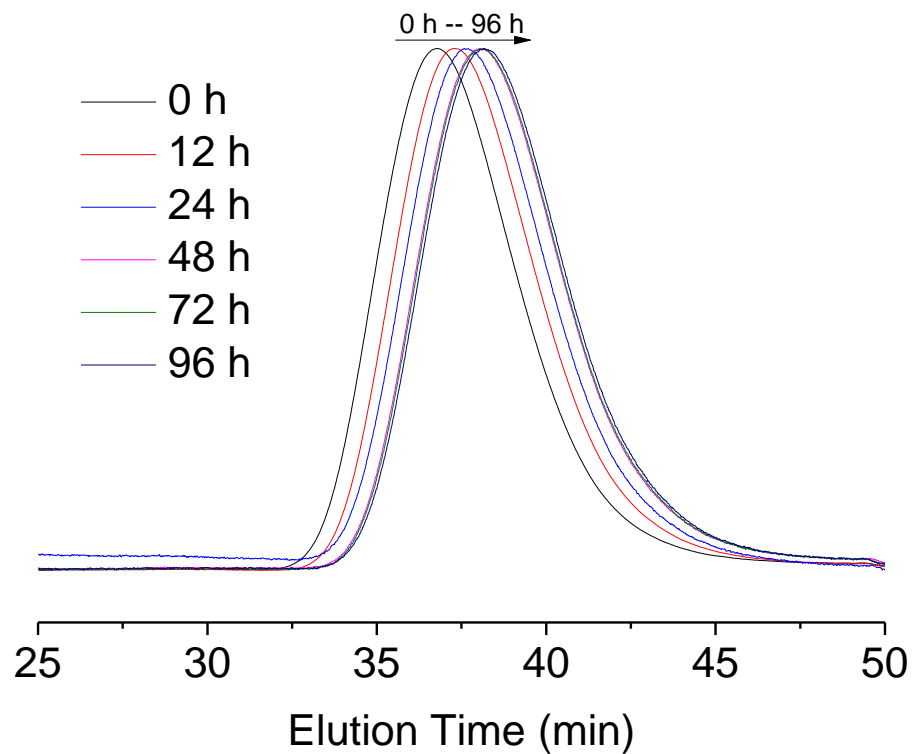


Figure S29. Water degradation of poly(8/10). GPC curves from light scattering detector showing water degradation of poly(8/10) after incubation in DMF (containing 5% water) at 37 °C for variant time intervals.

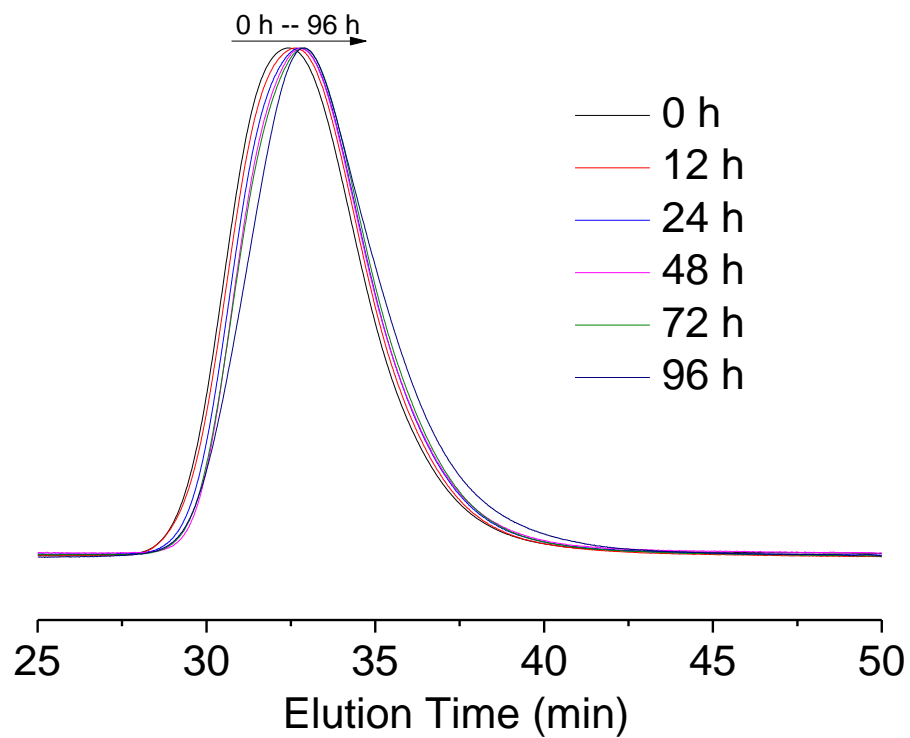


Figure S30. Water degradation of poly(6/10). GPC curves from light scattering detector showing water degradation of poly(6/10) after incubation in DMF (containing 5% water) at 37 °C for variant time intervals.

Water degradation of cross-linked hindered polyurea

Water degradation of hydrophobic cross-linked hindered polyurea. Tri-functional homopolymer of hexamethylene diisocyanate (**11**, 100 mg, 0.198 mmol) was dissolved in DMF (650 μ L). A solution of *N,N'*-di-*tert*-butylethylene-diamine (**9**, 51.4 mg, 0.299 mmol) in DMF (205 μ L) and water (50 μ L) was added. The mixture was homogenized for 5 s and let sit for 1 min at room temperature for gelation to happen. After that, the gel was incubated at 37 $^{\circ}$ C for degradation study.

Water degradation of hydrophilic cross-linked hindered polyurea. Poly(ethylene glycol) methyl ether methacrylate (**12**, 4.13 g, 8.26 mmol), 2-Isocyanatoethyl methacrylate (**S23**, 128 mg, 0.826 mmol), *N,N'*-di-*tert*-butylethylene-diamine (**9**, 71.2 mg, 0.413 mmol) and 2-Hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone (**S24**, 40 mg, dissolved in 40 μ L DMSO) were mixed and irradiated by UV (365 nm, 40 mW/cm²) for 15 min to yield cross-linked polymer **G1**. **G1** was divided and transferred into 15 mL centrifuge tubes with each one containing 300 mg polymer. Polymer was first immersed in deionized water for 12 h at 37 $^{\circ}$ C to remove all the unreacted monomers, solvent and photo initiator. After that the tubes were filled with PBS and incubated at 37 $^{\circ}$ C to start water degradation study. At different time point, samples were taken out and washed with deionized water for 3 times and weighed after drying by lyophilization. Degree of weight loss was used to characterize the degradation kinetics. The experiments were repeated in triplicate. As negative control, *N,N'*-di-iso-propylethylene-diamine (**10**, 59.5 mg, 0.413 mmol) instead of *N,N'*-di-*tert*-butylethylene-diamine were used to synthesize cross-linked polymer **G2**. Water degradations of **G2** were characterized with the same procedures.