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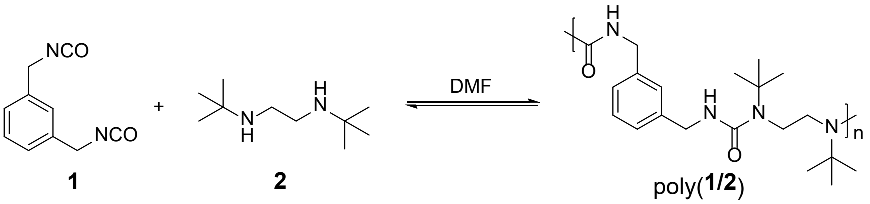
General

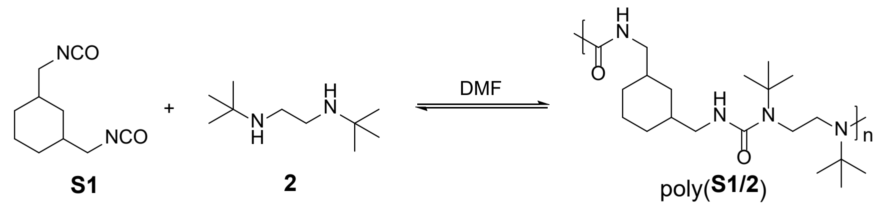
Materials. Anhydrous dimethylformamide (DMF) was dried by a column packed with 4Å molecular sieves. m-Xylylene diisocyanate was purchased from TCI America (Portland, OR, USA) and used as received. All deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and used as received. All 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. ESI mass spectra were recorded on Waters Quattro Ultima spectrometer (Milford, MA). 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.

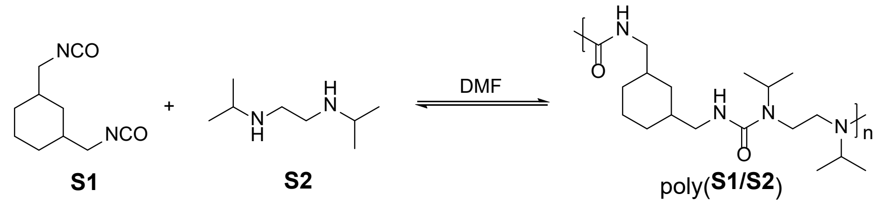
Synthesis of hindered polyurea



Synthesis of polymer (poly(1/2)): Equal molar m-xylylene diisocyanate (**1,** 1.88 g, 10.0 mmol) and *N,N′*-di-*tert*-butylethylene-diamine **(2,** 1.72 g, 10.0 mmol) were dissolved in DMF (10 g). The mixture was stirred at room temperature overnight vigorously. The polymer (M_n = 9.0 kDa, PDI=1.31) solution was directly used for GPC characterization and degradation study.



Synthesis of polymer (poly(S1/2)): Equal molar 1,3-bis(isocyanatomethyl)cyclohexane (**S1,** 1.94 g, 10.0 mmol) and *N,N′*-di-*tert*-butylethylene-diamine **(2,** 1.72 g, 10.0 mmol) were dissolved in DMF (10 g). The mixture was stirred at room temperature overnight vigorously. The polymer (M_n = 17 kDa, PDI=1.45) solution was directly used for GPC characterization and degradation study.



Synthesis of polymer (poly(S1/S2)): Equal molar 1,3-bis(isocyanatomethyl)cyclohexane (**S1,** 1.94 g, 10.0 mmol) and *N,N′*-di-*iso*-propylethylene-diamine **(S2,** 1.44 g, 10.0 mmol) were dissolved in DMF (10 g). The mixture was stirred at room temperature overnight vigorously. The polymer (M_n = 120 kDa, PDI=1.29) solution was directly used for GPC characterization and degradation study.

Degradation studies of hindered polyurea

polymer (poly(1/2)): To 136 mg as-prepared solution of poly(**1**/**2**), 10.2 μL hydrogen peroxide solution (30% water solution, about 0.05 equivalence to urea bond) was added. In another portion of the same solution (136 mg), 10.2 μL DI water was added as the control. Both mixtures were incubated at 37 °C. Aliquots were taken out and characterized by GPC at specific time points (see Figure 1 in text and Figure S1).

polymer (poly(S1/2)): To 137 mg as-prepared solution of poly(**S1**/**2**), 10.2 μL hydrogen peroxide solution (30% water solution, about 0.05 equivalence to urea bond) was added. In another portion of the same solution (137 mg), 10.2 μL DI water was added as the control. Both mixtures were incubated at 37 °C. Aliquots were taken out and characterized by GPC at specific time points (see Figure S2).

polymer (poly(S1/S2)): To 134 mg as-prepared solution of poly(**S1**/**S2**), 10.2 μL hydrogen peroxide solution (30% water solution, about 0.05 equivalence to urea bond) was added. In another portion of the same solution (134 mg), 10.2 μL DI water was added as the control. Both mixtures were incubated at 37 °C. Aliquots were taken out and characterized by GPC at specific time points (see Figure S3).

Mechanism Study of TBEU degradation by H_2O_2

Perhydrolysis of isocyanate by hydrogen peroxide: Benzyl isocyanante (**4**, 10.0 mg, 0.075 mmol) was dissolved in CD_3CN (0.55 mL) and added to the NMR tubes. Then hydrogen peroxide (30%, 10 μL) was added and the solution was monitored by ^1H NMR at 37ºC. In another experiment, the same solution was added water (10 μL) and also monitored by ^1H NMR at 37 ºC (Figure S4&5).

Oxidation of amine by hydrogen peroxide: *tert*-Butylethylamine (**5**, 7.4 mg, 0.073 mmol) was dissolved in CD_3CN (0.55 mL) and added to the NMR tubes. Then hydrogen peroxide (30%, 10 μL) was added and the solution was monitored by ^1H NMR at 37 ºC (Figure S6&7).

Degradation of hindered urea by hydrogen peroxide: Urea **3** (9.7 mg, 0.040 mmol, prepared by directly mixing **4** (5.5 mg, 0.040 mmol) and **5** (4.2 mg, 0.040 mmol)) was dissolved in CD_3CN (0.55 mL) and added to the NMR tubes. Then hydrogen peroxide (30%, 10 μL) was added and the solution was monitored by ^1H NMR at 37 ºC (Figure S8). Two control studies were set at the same time. In the first control experiment, same **3** solution in CD_3CN (9.7 mg in 0.55 mL) was added water (10 μL) and monitored by ^1H NMR at 37 ºC (Figure S9). In the second control experiment, less hindered urea **3’** (13.6 mg, 0.062 mmol, prepared by directly mixing **4** (8.2 mg, 0.062 mmol) and **5’** (5.4 mg, 0.062 mmol)) was dissolved in CD_3CN (0.55 mL) and added to the NMR tubes. Then hydrogen peroxide (30%, 10 μL) was added and the solution was monitored by ^1H NMR at 37 ºC (Figure S10).

Degradation of hindered urea with or without the existence of free amine: After careful analysis of the degradation mechanism, we figured out there are two parallel pathways for interaction between hindered urea **3** and hydrogen peroxide (see Figure 2). To further support the argument, we did the degradation of **3** by hydrogen peroxide with or without adding free amine **5**. For pathway 1, since the urea needs to dissociate first, addition of **5** greatly suppresses the dissociation so that the kinetics of pathway will be slowed down. However, for pathway 2, the addition of **5** has no effect to (or enhance) the direct oxygen insertion of urea. The experimental results shown in Figure 2 and S12~13 well proved our hypothesis.

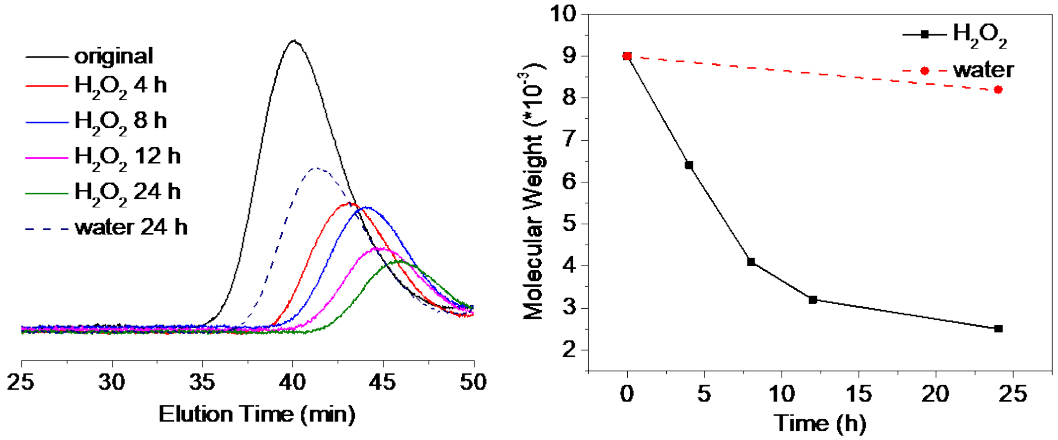


Figure S1. Degradation of poly(1/2) by hydrogen peroxide (H_2O_2). (a) GPC curves showing degradation by H2O2 or water over time at 37 oC. (c) Change of molecular weight of poly(1/2) after treating with H2O2 or water over time.

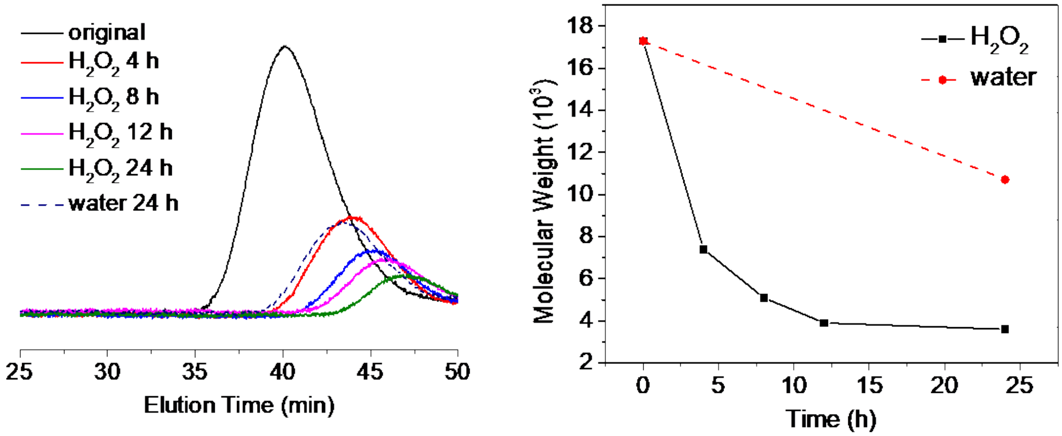


Figure S2. Degradation of poly(S1/2) by hydrogen peroxide (H_2O_2). (a) GPC curves showing degradation by H_2O_2 or water over time at 37 °C. (b) Change of molecular weight of poly(**S1**/**2**) after treating with H_2O_2 or water over time.

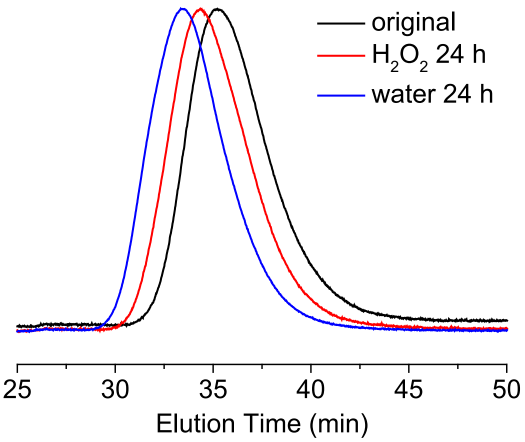


Figure S3. GPC curves showing degradation of poly(S1/S2) by H_2O_2 or water at 37 °C after 24 h.

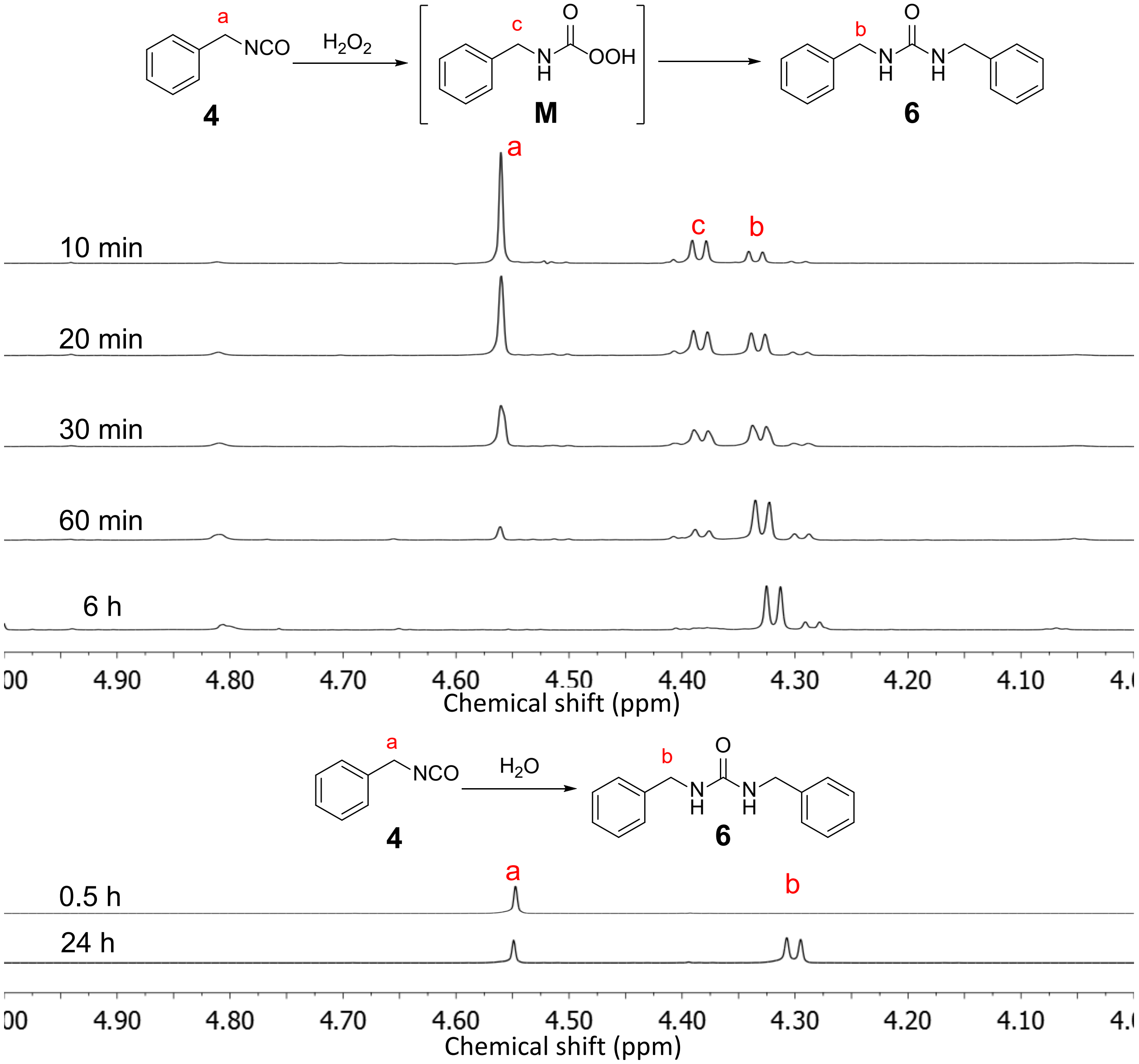


Figure S4. ^{1}H NMR spectra of isocyanate hydrolysis with various time at 37 ºC. i) ^{1}H NMR spectra shows fast hydrolysis of isocyanate (compound **4**) with the existence of hydrogen peroxide going through peroxy acid intermediate. ii) Slow hydrolysis of isocyanate without hydrogen peroxide shown by ^{1}H NMR spectra.

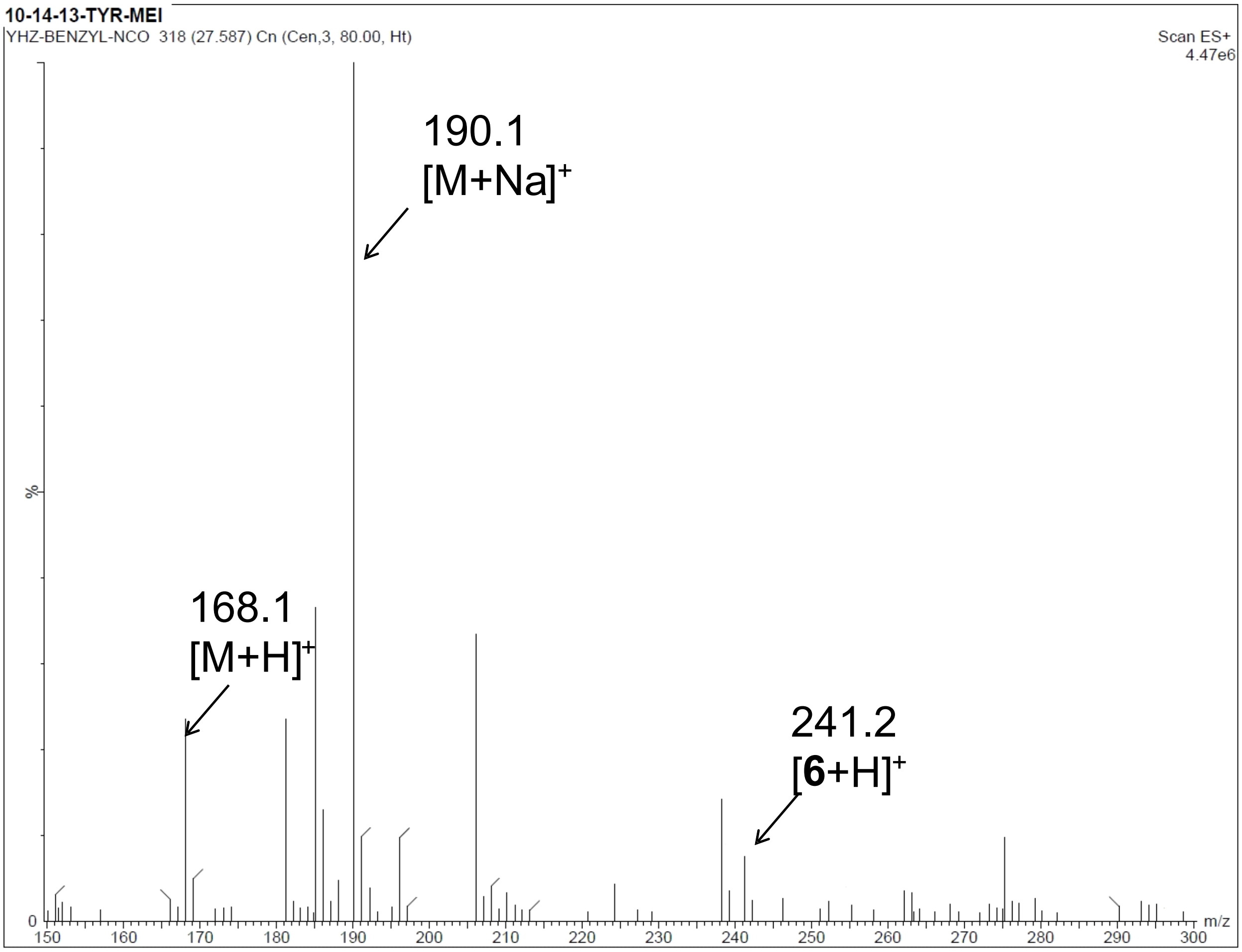


Figure S5. ESI spectrum of 4 solution (10 mg in 550 µL CH_3CN) treated by H_2O_2 for 10 min at room temperature. Peaks for peroxy acid intermediate **M** and hydrolysis product **6** were identified.

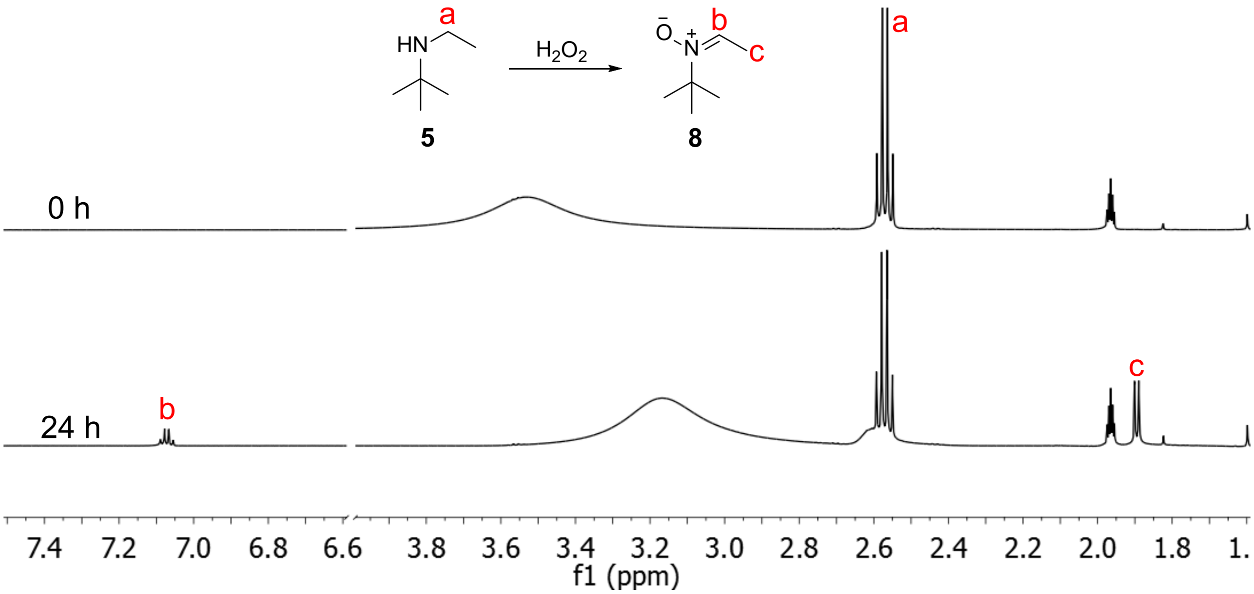


Figure S6. ^{1}H NMR spectra of oxidation of 5 at 37 °C. The structure of amine oxide 8 was identified in ^{1}H NMR (peaks b & c)

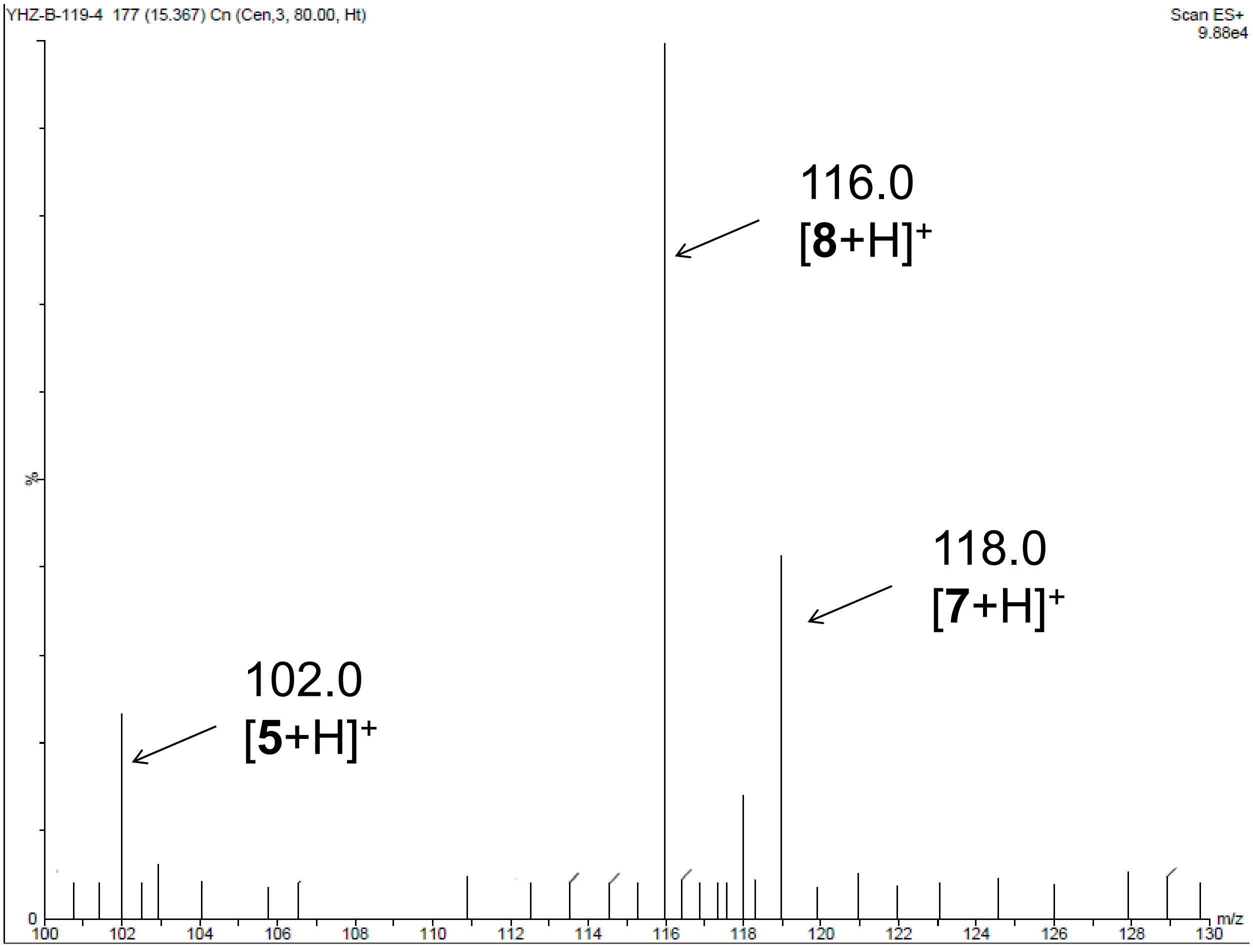


Figure S7. ESI spectrum of 5 solution (7.0 mg in 550 μL CH_3CN) treated by H_2O_2 for 24 h at 37 °C. Peaks for starting compound **5** and oxidized amine species **7** and **8** were identified.

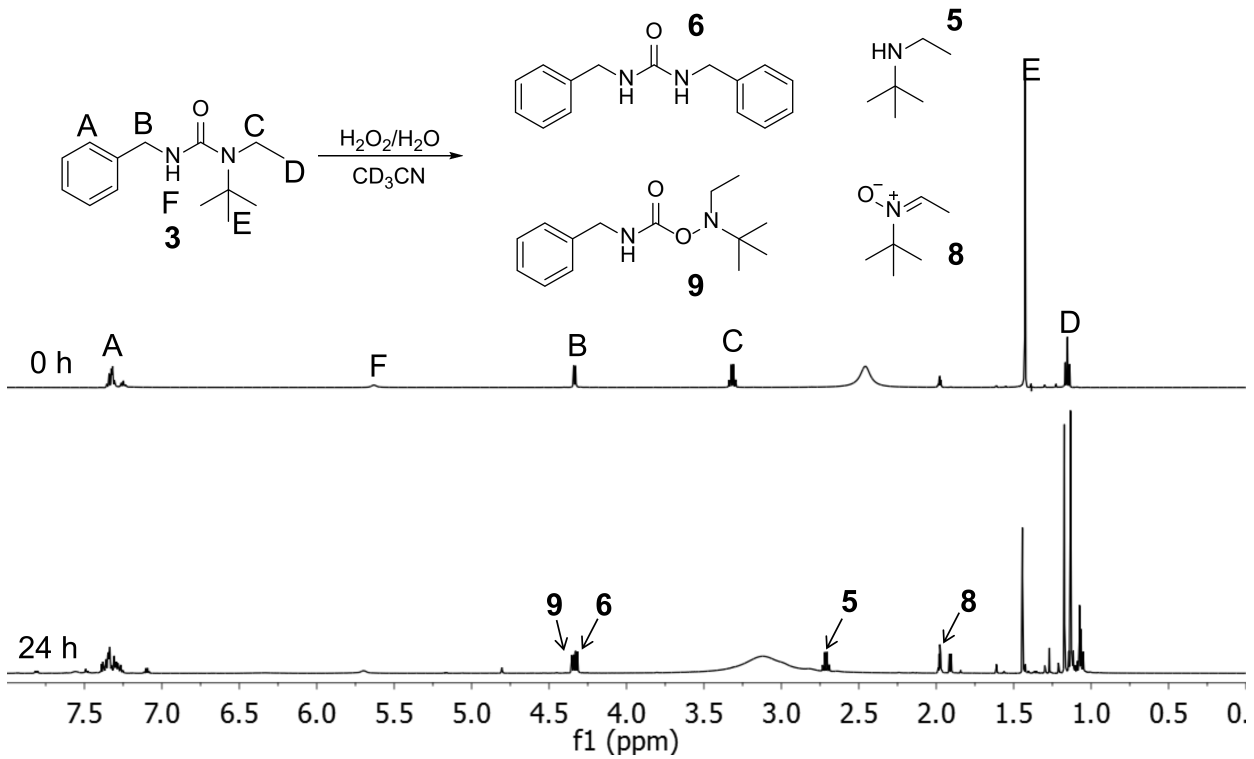


Figure S8. ^{1}H NMR spectra showing degradation of TBEU 3 by hydrogen peroxide at 37 °C.

Peaks for **3** completely disappeared after 24 h.

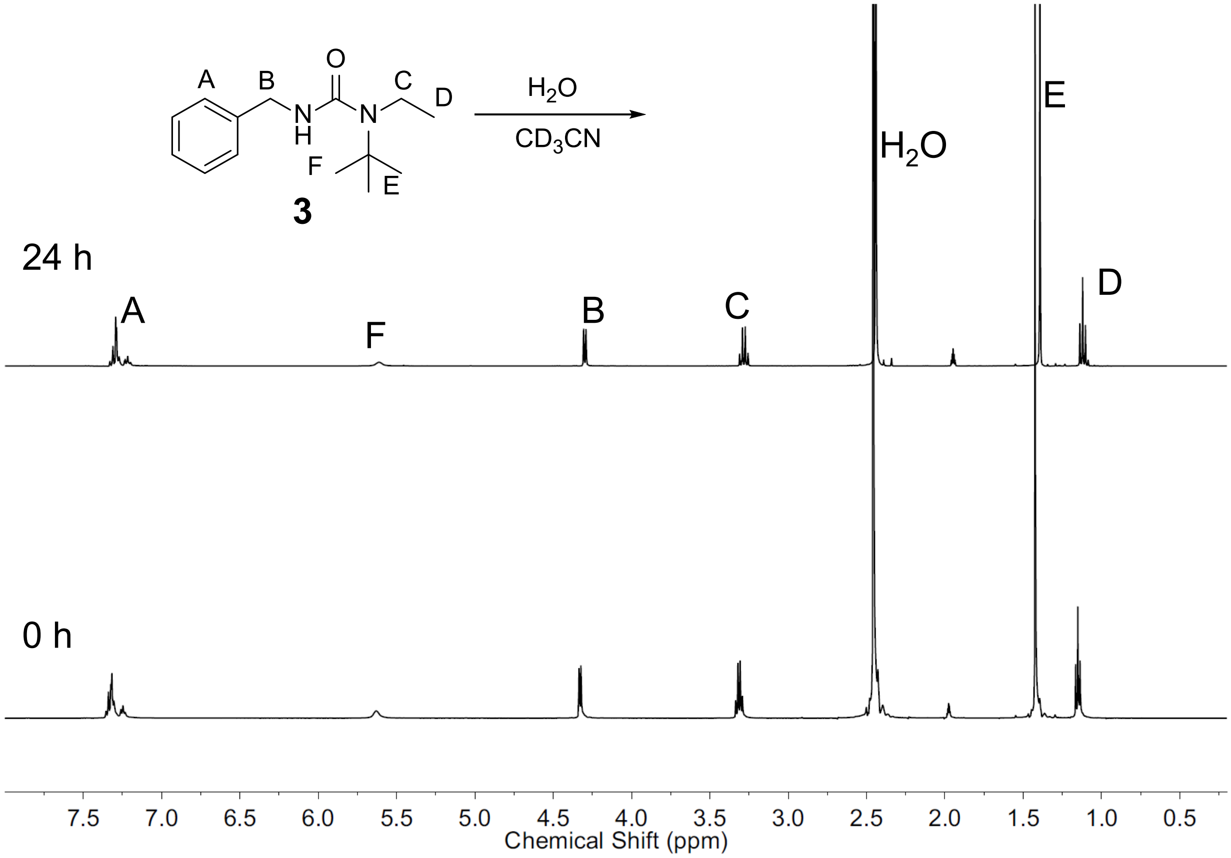


Figure S9. ^{1}H NMR spectra showing no degradation of TBEU by water at 37 ^{o}C. Almost no changes of peaks were shown after 24 h.

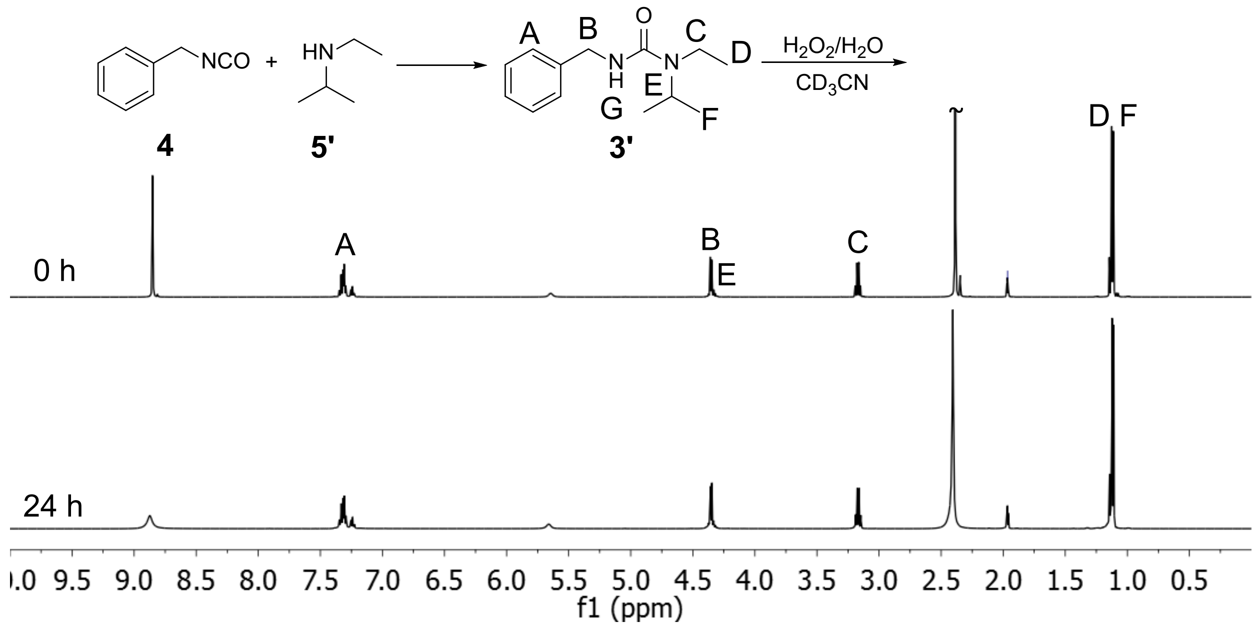


Figure S10. ^{1}H NMR spectra showing no degradation of less hindered urea 3' by hydrogen peroxide at 37 ^{o}C. Almost no changes of peaks were shown after 24 h.

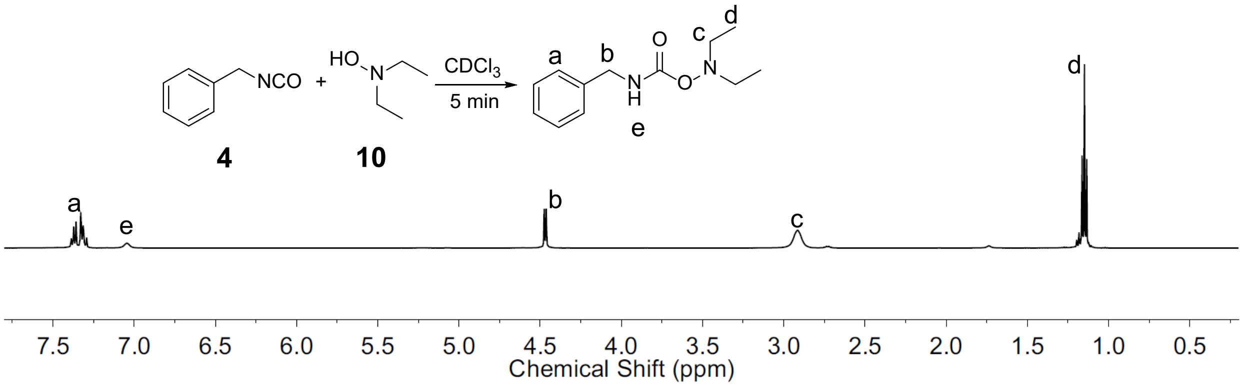


Figure S11. ^{1}H NMR spectra of model urethane compound

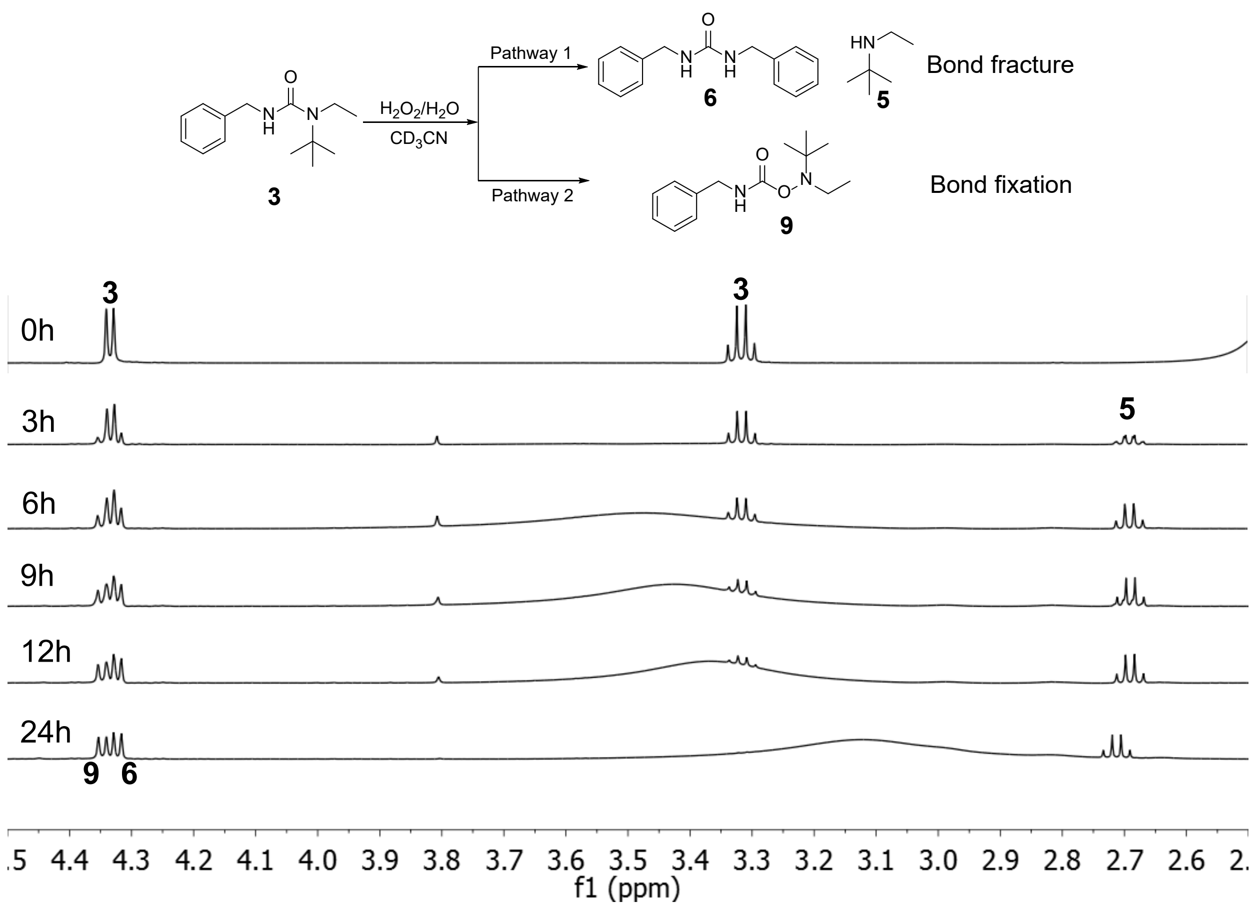


Figure S12. Part of ^{1}H NMR spectra showing degradation of hindered urea 3 by hydrogen peroxide at 37 ^{o}C with various time. Starting solution: **3** (9.7 mg) + H_2O_2 (30%, 10 μL) in 550 μL CD_3CN.

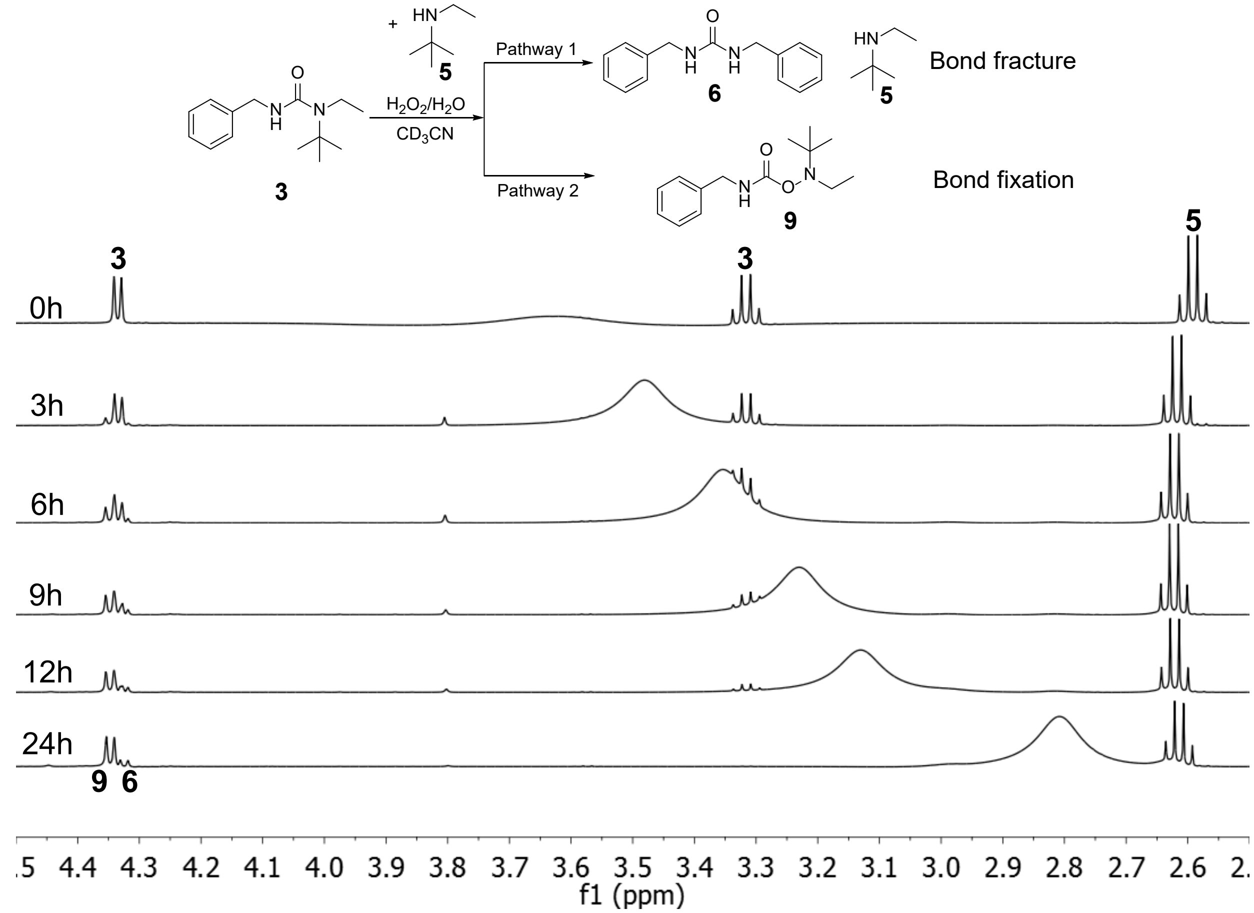


Figure S13. Part of ^{1}H NMR spectra showing degradation of hindered urea 3 by hydrogen peroxide at 37 ^{o}C over time with the addition of free amine 5. Production of **9** is dominant compared with **6** showing that pathway 1 is greatly suppressed with the existence of free amine. Starting solution: **3** (9.7 mg) + H_2O_2 (30%, 10μL) + **5** (8.7 mg) in 550 μL CD_3CN.