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Hindered Urea Bond | *Very Important Paper* |

Hindered Urea Bond: A Bilaterally Responsive Chemistry to Hydrogen Peroxide

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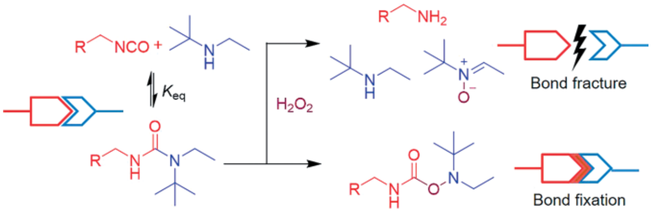
Abstract: As a type of safe, clean, and bio-relevant oxidant, hydrogen peroxide has been widely used as a trigger in the design of stimuli-responsive materials. Hindered urea bond (HUB) is a type of dynamic covalent bond which can reversibly dissociate into isocyanate and amine. Quenching of isocyanate or amine will shift the equilibrium and facilitate the degradation of HUB bond. Herein, we report that one of the HUB moiety – 1,1-*tert*-butylethylurea (TBEU) can react with hydrogen peroxide (H_2O_2) resulting in two opposing outcomes. Perhydrolysis of isocyanate and oxidation of amine lead to the bond fracture, while formation of urethane product with an oxygen inserted into the original TBEU structure was also observed giving a stabilized form of linkage. More precise kinetic control of the two distinct pathways are expected to make hydrogen peroxide a trigger to either degrade or fix the HUB based polymeric materials.

Introduction

Stimuli-responsive materials[1] have been widely used in the design of drug-delivery,[2–3] tissue engineering,[4] sensors,[5] and tunable catalysis.[6] A variety of external stimuli can be used for the triggered degradation, such as pH,[7] light,[8] temperature,[9] redox reagents,[10] enzyme,[11] etc. Hydrogen peroxide (H_2O_2) is gaining popularity in the designs of stimuli-responsive materials in recent years as a safe, clean, and massively-produced oxidant.[12] It is also a type of reactive oxygen species (ROS) existing in living creatures related to diseases such as cancer or inflammation.[13–14] Many drug carriers incorporate chemical bonds that are responsive to H_2O_2 to selectively release the drug.[15–16] A lot of chemistries have been developed that can selectively respond to H_2O_2, such as boron esters,[17–18] thioketal,[10] thioether,[19] oxalate,[20] benzil,[21] etc. Most of these chemistries show bond fracture (reduction of molecular size) when being treated by H_2O_2. However, other types of effects have rarely been reported.

Hindered urea bond (HUB) is a type of dynamic covalent bond (DCB),[22–24] which can reversibly dissociate into isocyanate and amine.[25–27] Among them, 1,1-*tert*-butylethylurea (TBEU) is one of HUBs that has both large equilibrium constant and fast exchange kinetics in ambient condition. Therefore, TBEU can be facilely incorporated into high molecular weight polymers (pTBEU) with swift chain exchange at low temperature. Due to the dynamic properties of TBEU, the polymeric state of pTBEU is responsive to a variety of chemical signals that can interact with its dissociative intermediates, such as amine, alcohol, water, etc. They were demonstrated to shift the chemical equilibrium and reduce the size of polymers. However, none of these triggers can stabilize (shut off the dynamicity of) the DCB without breaking the linkage. Such a type of reaction has been achieved for other DCBs such as hydrogenation of dynamic imine[28,29] or alkene bonds.[30] This reaction is very useful in the case that the bond dynamic exchange is required during the synthesis, but needs to be turned-off for the stabilized form of final products, such as in the synthesis of macrocycles.[28–30] Herein, we report H_2O_2 as the chemical trigger that can react with HUB in two distinct pathways leading to both bond fracture and fixation (Scheme 1).



Scheme 1. H_2O_2 induced degradation or fixation of TBEU bond.

Results and Discussion

The reaction between TBEU bond and H_2O_2 was first observed in a degradation study of linear pTBEU. Dynamic polymers pTBEUs were synthesized by polyaddition reaction of diisocyanate and diamine with 1:1 equivalence. Here, β-branched

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instead of linear isocyanates were used to synthesize pTBEU, which increased solubility of the resulting polymers in organic solvent. Compounds *m*-xylylene diisocyanate (**1**) and *N,N'*-di-*tert*-butylethylenediamine (**2**) were mixed with 1:1 equivalence in dimethylformamide (DMF, 25 % weight ratio) giving poly(**1**/**2**) (Figure 1a). Polymer with molecular weight of around 9.0 kDa was obtained as shown in gel permeation chromatography (GPC) characterization. We then did the polymer degradation study directly in DMF solution without purification. The polymer solution was added 0.05 mol/mol urea bond of H_2O_2 (as a form of 30 % aqueous solution) and incubated at 37 °C. The molecular weight reduction of polymer was monitored by GPC. Gradual right shift of GPC peaks was observed over time (Figure 1b). After 24 h, the molecular weight of poly(**1**/**2**) decreased from 9.0 kDa to 2.5 kDa (Figure 1c). To confirm that the degradation is not only from water in H_2O_2 solution, same weight of water was added to the polymer solution, and the molecular weight change was also monitored as a control study. Although water can also degrade the HUB by quenching the isocyanate dissociative intermediate, the degradation is much slower than H_2O_2. Little change of molecular weight for poly(**1**/**2**) was observed after 24 h (from 9.0 kDa to 8.2 kDa, Figure S1) at the same temperature. The degradation study was also performed on another pTEBU synthesized from 1,3-bis(isocyanatomethyl)cyclohexane (**S1**) and **2**, and the similar results were obtained (Figure S2). Also to demonstrate that the H_2O_2 interacts with TBEU bond rather than the other parts of polymeric chains, we synthesized a control polymer poly(**S1**/**S2**) by mixing **S1** with *N,N'*-di-isopropylethylenediamine (**S2**) in 1:1 molar ratio. In the new polymer, the urea bond is substituted with less hindered group (less dynamic, k_{-1} = 0.0015 h^{-1} compared with 0.21 h^{-1} for TBEU[25]). No matter the polymer was treated with H_2O_2 or water under the same condition, no reduction of molecular weight was shown, demonstrating that the reaction only happens at the urea bond with high bulkiness, and the rest part of the polymer backbone is stable to H_2O_2 (Figure S3).

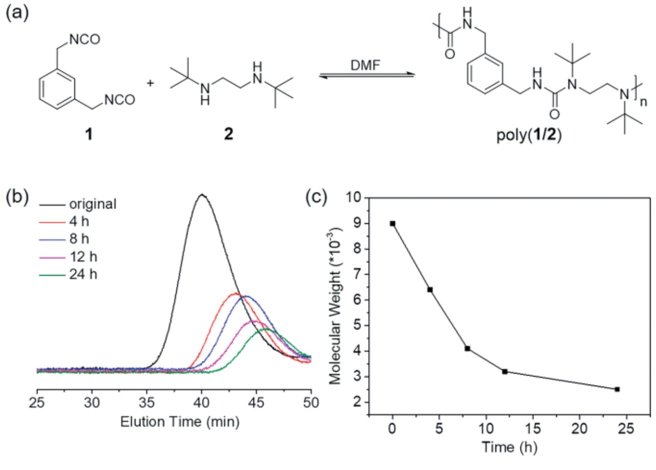
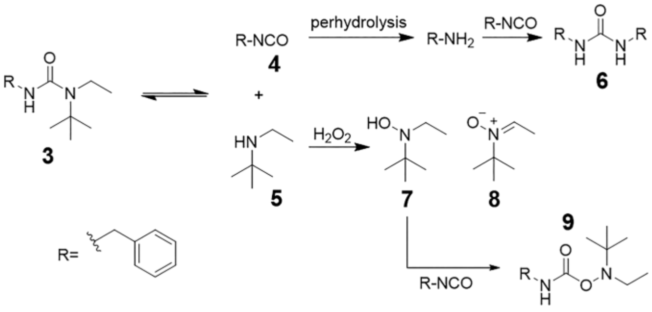


Figure 1. Degradation of pTBEU by hydrogen peroxide (H_2O_2). (a) synthesis of poly(**1**/**2**); (b) GPC curves showing degradation by H_2O_2 over time at 37 °C. (c) Change of molecular weight of poly(**1**/**2**) after treating with H_2O_2 over time.

Next, we used dynamic urea model compound **3** to explore the degradation process of TBEU bond by H_2O_2 in molecular details. Urea **3** was synthesized by mixing isocyanate **4** and amine **5** in 1:1 equivalence. Due to the dynamic property of TBEU bond, **3** can dissociate, giving back the starting compounds **4** and **5** reversibly (Scheme 2). We postulated that the degradation of TBEU is caused by reaction of its dissociative intermediates with H_2O_2, so we first studied the reaction of H_2O_2 with **4** and **5**, separately. With [D$_3$]acetonitrile as the solvent, isocyanate **4** was treated with H_2O_2 or water and monitored by ^1H NMR spectroscopy. Hydrolysis product urea **6** was observed for both reactions. However, the reaction in H_2O_2 is much faster. In the NMR spectra, we also observed an intermediate during the hydrolysis process in H_2O_2, which was not found in the solution with only the addition of water (Figure S4). The intermediate was assumed to be formed by H_2O_2 attacking isocyanate, which was supported by ESI mass spectrum (Figure S5). Here H_2O_2 is a better nucleophile than water, which accelerates the hydrolysis kinetics of isocyanate group (also named as perhydrolysis).[31] Later, the reaction of H_2O_2 with another dissociative intermediate amine **5** was examined. We observed that the amine **5** could be oxidized to hydroxylamine **7** and further to amine oxide zwitterion **8** with the existence of H_2O_2 after 24 h at 37 °C in [D$_3$]acetonitrile (Figure S6–S7).[32]



Scheme 2. Proposed reaction process after treating TBEU with H_2O_2. Bond fracture products **5**~**8** and bond fixation product **9** were all observed at the same time.

After we learned that both dissociative intermediates of TBEU can react with H_2O_2, we then performed the experiments adding H_2O_2 to solution of urea compound **3** (Figure S8). As expected, we observed the production of **5**, **6** and **8** by treating **3** with H_2O_2. However, the formation of another product **9** was also detected, indicating an opposing result of this reaction that we did not expect initially. Compound **9** was identified as a urethane compound with an oxygen atom inserted between carbonyl and hindered nitrogen atom of the original urea **3**, which can possibly be formed from addition reaction between isocyanate **4** and hydroxylamine **7**. The reaction between isocyanate and hydroxylamine was demonstrated to be very fast (confirmed by model reaction between **4** and commercial available diethylhydroxylamine **10**, see Figure S11), which strongly drives the competition reaction towards the urethane side once the isocyanate **4** and hydroxylamine **7** is available from dissociation of **3** and oxidation of **5**. As control experiments, urea **3** was treated with same amount of water. No degradation was observed at 37 °C after 24 h, proving that the triggeredresponse effect was from hydrogen peroxide (Figure S9). Furthermore, we examined the reaction of less hindered urea **3′** under the same H_2O_2 reaction condition (Figure S10). No reaction was identified either, demonstrating that the reversibility of the bond is necessary for the reaction to happen.

Based on the results above, we identified two distinct outcomes of the reaction between TBEU and H_2O_2. The TBEU bond dissociates into two intermediates – isocyanate and amine, both of which are quenched by H_2O_2 (product **5**, **6**, **8**) and cannot reform the TBEU bond (bond fracture). However, one of the oxidation products of amine – hydroxylamine can bind with isocyanate and reform the bond (product **9**) with dynamic property turned-off (bond fixation). These two pathways lead to completely different outcomes of pTBEU materials after the H_2O_2 triggered reaction. While the first pathway results in the reduction of chain length of polymers and weakening of materials, the second one maintains the degree of polymerization and eliminates the reversible property to strengthen the materials.

It will be significant if we can have a better control of the competition between these two pathways. Figure 2 shows one of the example that can tune the kinetics between two pathways. Two solutions of **3** in [D$_3$]acetonitrile were prepared, and one of them was added additional amine molecule **5** that was used to synthesize **3** (Figure S12–13). After treating both solutions with H_2O_2 for 24 h at 37 °C, all compound **3** were consumed. However, the ratios of bond fracture product **6** and bond fixation product **9** are quite different. For the solution without the addition of **5**, two pathways are almost equivalent ([**6**]/[**9**] = 53:47). In contrast, for the solution with the addition of **5**, the bond fixation pathway dominates ([**6**]/[**9**] = 17:83). The reason for the change of ratio is that the addition of amine molecule can suppress the urea hydrolysis process, which has been demonstrated in our previous work.[25–26] Although we have not achieved the complete elimination for one of the process, the experiment clearly showed that the kinetics of two pathways can be tuned through change of reaction conditions.

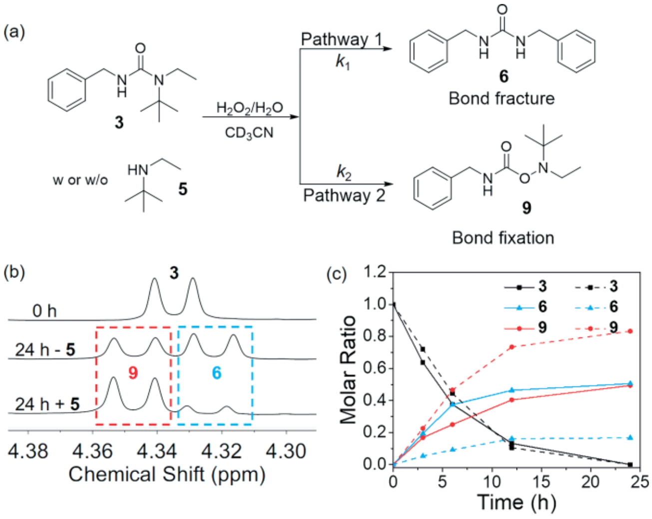


Figure 2. Kinetic control of two pathways through addition of free amine. (a) Reactions schemes showing the attempt to use the addition of amine **5** to control the selectivity between two pathways; (b) NMR spectra showing the change of signals corresponding to **3**, **6**, **9** after reaction for 24 h at 37 °C under two different conditions. (c) Plot showing the change of molar ratio of **3**, **6**, **9** over time (solid line: without the addition of **5**, dotted line: with the addition of **5**).

Conclusions

In summary, we demonstrated that H_2O_2 can be used as the trigger to change the bonding state of TBEU. Perhydrolysis of isocyanate and oxidation of amine quench the dissociative intermediates, shift the chemical equilibrium and degrade the TBEU bond. Besides the bond fracture process, an opposing result of the reaction was also identified. The binding of hydroxylamine and isocyanate gives a urethane product with an oxygen inserted into the TBEU bond, which retains the linkage and turns off the dynamic property. An example was shown that the kinetics ratio between the two pathways can be tuned to be more favored towards the fixation process through addition of hindered amine. Our work demonstrates the feasibility to use oxidation methods to either degrade or stabilize the TBEU selectively, which is expected to be further improved by discovering more finely-engineered oxidants or reaction conditions that can completely suppress either one of the process.[33]

Acknowledgments

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Keywords: Dynamic covalent bond · Hindered urea · Hydrogen peroxide · Degradation · Stabilization

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