Hydrolyzable Polyureas Bearing Hindered Urea Bonds

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S *Supporting Information*

ABSTRACT: Hydrolyzable polymers are widely used materials that have found numerous applications in biomedical, agricultural, plastic, and packaging industrials. They usually contain ester and other hydrolyzable bonds, such as anhydride, acetal, ketal, or imine, in their backbone structures. Here, we report the first design of hydrolyzable polyureas bearing dynamic hindered urea bonds (HUBs) that can reversibly dissociate to bulky amines and isocyanates, the latter of which can be further hydrolyzed by water, driving the equilibrium to facilitate the degradation of polyureas. Polyureas bearing 1-*tert*-butyl-1-ethylurea bonds that show high dynamicity (high bond dissociation rate), in the form of either linear polymers or cross-linked gels, can be completely degraded by water under mild conditions. Given the simplicity and low cost for the production of polyureas by simply mixing multifunctional bulky amines and isocyanates, the versatility of the structures, and the tunability of the degradation profiles of HUB-bearing polyureas, these materials are potentially of very broad applications.

Polymers with transient stability in aqueous solution, also known as hydrolyzable polymers, have been applied in many biomedical applications, such as in the design of drug delivery systems,[1] scaffolds for tissue regeneration,[2] surgical sutures,[3] and transient medical devices and implants.[4] These applications usually require short functioning time and complete degradation and clearance of materials after their use. Hydrolyzable polymers have also been applied in the design of controlled release systems in agriculture and food industries and used as degradable, environmentally friendly plastics and packaging materials.[5] Besides polyesters, a class of widely used, conventional hydrolyzable materials,[6] a large variety of other hydrolyzable polymers bearing anhydride,[7] orthoester,[8] acetal,[9] ketal,[10] aminal,[11] hemiaminal,[11,12] imine,[13] phosphoester,[14] and phosphazene[15] bonds have also been reported. Syntheses of these polymers usually involve condensation[2d] or ring-opening polymerization,[16] and these syntheses typically involve removal of byproducts[2d] and use of high reaction temperature[2d] and/or metal catalysts,[6b] which complicates materials preparation. In this study, we report the design of polyureas bearing hindered urea bonds (HUBs) as potentially one of the least expensive degradable polymers that can be easily synthesized by mixing multifunctional bulky amines and isocyanates, expanding the family of hydrolyzable polymers.

Polyureas are commonly used as fiber, coating, and adhesive materials.[17] They can be readily synthesized via addition reaction of widely available, di- or multifunctional isocyanates and amines that do not require the use of catalysts and extreme reaction conditions and do not produce any byproducts. Urea is one of the most stable chemical bonds against further reactions including hydrolysis due to the conjugation stabilization effects of its dual amide structure. However, urea bonds can be destabilized by incorporating bulky substituents to one of its nitrogen atoms, by means of disturbing the orbital coplanarity of the amide bonds that diminishes the conjugation effect (Scheme 1).[18] Urea bonds bearing a bulky substituent, or

Scheme 1. Illustration of Hydrolysis Mechanism of HUBs[a]
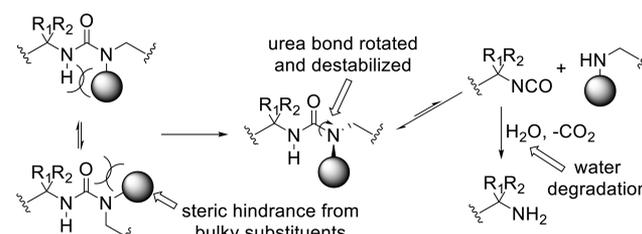
[a]Urea bond is destabilized by bulky substituents induced bond rotation and loss of conjugation effect.

HUBs, can reversibly dissociate into isocyanate and amines and show interesting dynamic property. The fast reversible reactions between HUBs and isocyanates/amines have been the basis in our recent design of self-healing polyureas.[19] Because isocyanates can be subject to hydrolysis in aqueous solution to form amines and carbon dioxide, an irreversible process that shifts the equilibrium to favor the HUB dissociation reaction and eventually lead to irreversible and complete degradation of HUBs (Scheme 1), we reason that HUBs can be used to design easily available hydrolyzable polymers potentially for the numerous applications above-mentioned. Herein, we report the development of HUB-based polyureas that can be hydrolyzed with hydrolytic degradation kinetics tunable by the steric hindrance of the HUB structures.

The property of a dynamic covalent bond can be expressed by its K_{eq}, the binding constant showing the thermodynamic stability of the dynamic bond, and its k_{-1}, the dissociation rate of the dynamic bond. According to the hydrolytic degradation mechanism of a HUB shown in Figure 1a, the rate of hydrolysis equals to the rate of the formation of product **D**, which can be expressed by eq 1 considering addition of **B** and water is the rate-determining step:
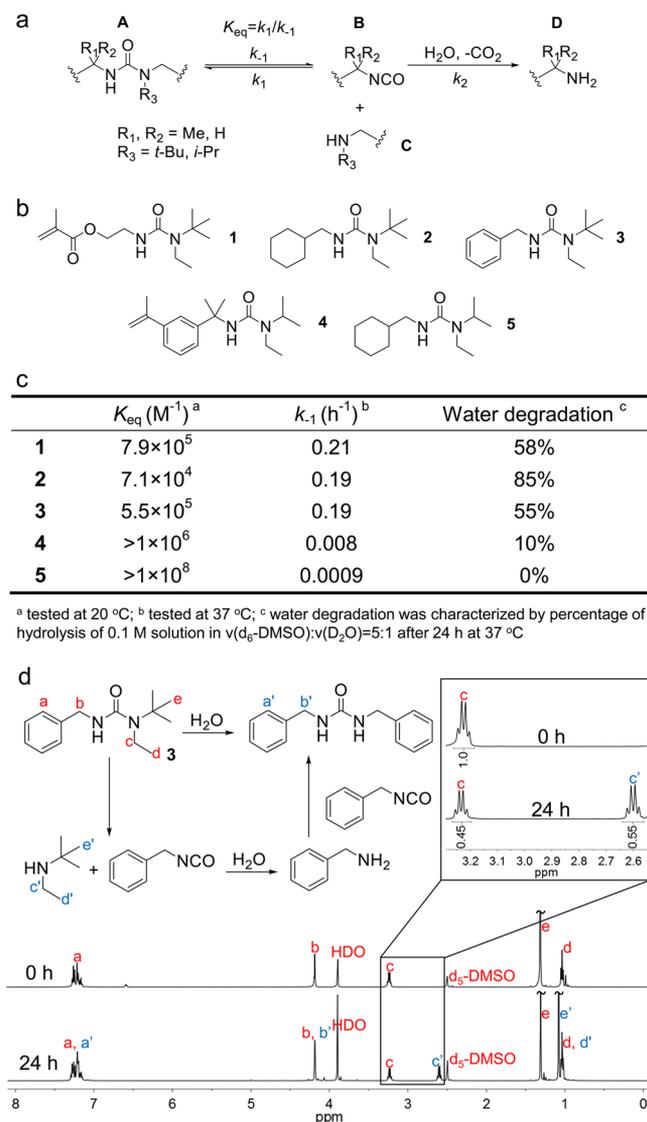
Figure 1. Dynamicity and hydrolytic degradation of HUB-containing model compounds. (a) Parameters related to the hydrolytic degradation of HUBs. (b) Structures of five HUB-containing model compounds. (c) Binding constants (K_{eq}), dissociation rates (k_{-1}), and water degradation kinetics of five HUB-containing model compounds shown in (b). (d) Representative NMR spectra showing the degradation of **3**. The percentage of hydrolysis was determined by the integral ratio of peaks corresponding to starting compounds and hydrolysis products as shown in the inset.

$$r(\text{hydrolysis}) = \frac{d[\mathbf{D}]}{dt} = k_2[\mathbf{B}][\text{H}_2\text{O}] \tag{1}$$

Since the isocyanate **B** is a dissociative intermediate with very low concentration, a steady-state approximation expressed as eq 2 is thus deduced:

$$k_2[\mathbf{B}][\text{H}_2\text{O}] + k_1[\mathbf{B}][\mathbf{C}] = k_{-1}[\mathbf{A}] \tag{2}$$

As $K_{eq} = k_1/k_{-1}$, eq 3 can thus be deduced from eq 1 and 2:

$$r(\text{hydrolysis}) = \frac{k_2[\mathbf{A}][\text{H}_2\text{O}]}{K_{eq}[\mathbf{C}] + \frac{k_2}{k_{-1}}[\text{H}_2\text{O}]} \tag{3}$$

According to eq 3, the hydrolysis kinetics is related to both K_{eq} and k_{-1}, with smaller K_{eq} and larger k_{-1} giving faster

hydrolysis. This is consistent with the notion that more dynamic HUBs (more bulky N-substituents) give faster hydrolytic degradation. To confirm this, we analyzed the dynamic parameters[19a] and the hydrolysis kinetics of five different HUB-containing model compounds (**1**−**5**, Figure 1b) with their dynamicity and hydrolytic degradation parameters summarized in Figure 1c (see all the measurement details in Figures S1−S20). All five compounds were synthesized by mixing the corresponding isocyanates and amines at 1:1 molar ratio. Compounds **1**−**3** have similar bulkiness, which are all based on 1,1-*tert*-butylethylurea (TBEU, $R_3 = tert$-butyl) structure. They show nearly identical k_{-1}. Compounds **4** and **5** have less bulky 1-*iso*-propyl-1-ethylurea (IPEU, $R_3 = iso$-propyl) structure, which show lower dynamicity than **1**−**3** (higher K_{eq} and lower k_{-1}). For these two IPEU-based compounds, **4** shows higher dynamicity than **5** with lower K_{eq} and higher k_{-1} due to its more bulky isocyanate structure (more bulky R_1 and R_2).

We went on to analyze the hydrolytic degradation profiles of **1**−**5** by ^{1}H NMR. The compound was dissolved in a mixture of d_6-DMSO and D_2O (v(d_6-DMSO)/v(D_2O) = 5:1). The percentage of the hydrolyzed products was analyzed after the mixture was incubated for 24 h at 37 °C (Figure 1d; the hydrolytic degradation of **3** was shown as an example). All three TBEU-based compounds (**1**−**3**) showed over 50% of hydrolytic degradation of their urea bonds, with **2** showing the fastest degradation (85%) due to its lowest K_{eq}. Compound **4**, bearing less bulky (less dynamic) IPEU structure, showed slower hydrolytic degradation (∼10%) compared to **1**−**3**. No detectable hydrolysis was observed for compound **5** because of its least substituent bulkiness (lowest dynamicity, Figure 1c). These results are consistent with the conclusion drawn from eq 3.

We next examined if polymers bearing HUBs (pHUBs) could also be degraded by water. Linear pHUBs were synthesized by mixing diisocyanates and diamines at 1:1 molar ratio in DMF. Although the bulky substituents in HUBs destabilize the urea bond, the HUBs still have sufficiently large binding constants ($K_{eq} \sim 10^5$, see Figure 1c) to form high molecular weight polymers. Poly(**6**/**9**), poly(**7**/**9**), poly(**8**/**10**), and poly(**6**/**10**), four different pHUBs with descending dynamicity, were prepared by mixing the corresponding diisocyanate (1,3-bis(isocyanatomethyl)cyclohexane (**6**), 1,3-bis(isocyanatomethyl)benzene (**7**) or 1,3-bis(1-isocyanato-1-methylethyl)benzene (**8**)), and diamine (*N,N'*-di-*tert*-butylethylenediamine (**9**) or *N,N'*-di-*iso*-propylethylenediamine (**10**)). The HUB structure of poly(**6**/**9**), poly(**7**/**9**), poly(**8**/**10**), and poly(**6**/**10**) resembles the corresponding model compounds **2**−**5** (Figure 2a). The M_n's of these four polymers were 22, 22, 44, and 120 kDa, as characterized by gel permeation chromatography (GPC), and showed correlation with their K_{eq}'s. To study the hydrolytic degradation of these pHUBs, 5% of water was added to the DMF solutions of each polymer. These solutions were vigorously stirred and incubated at 37 °C, and the molecular weights were monitored by GPC at selected time. MW decrease was observed for TBEU-based poly(**6**/**9**) and poly(**7**/**9**) (Figure 2b). For IPEU-based polymers, poly(**8**/**10**) showed limited degradation, while poly(**6**/**10**) barely showed any change of its M_n after 24 h (Figures 2c and S25−S28). After incubation for 48 h, the percentages of MW reduction for poly(**6**/**9**), poly(**7**/**9**), and poly(**8**/**10**) were 88%, 81%, and 43%, respectively. The MW of poly(**8**/**10**) did not further decrease for elongated incubation

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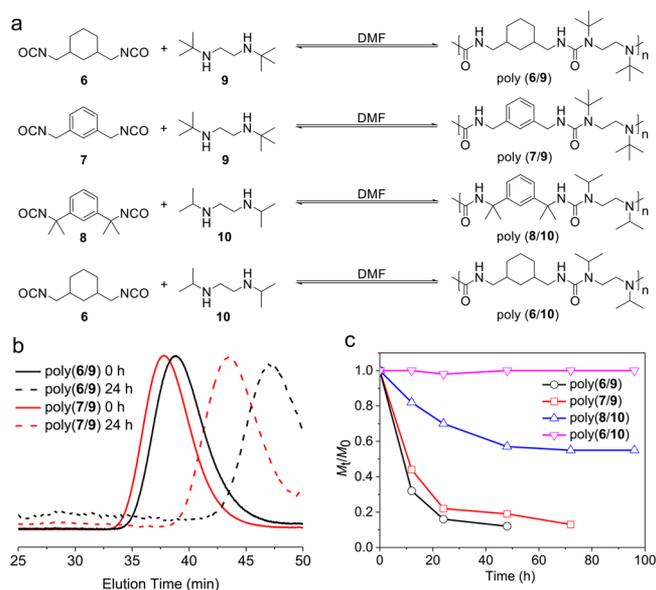dx.doi.org/10.1021/ja5093437 | *J. Am. Chem. Soc.* 2014, 136, 16974−16977

Figure 2. Water degradation of pHUBs. (a) Synthesis of four different types of pHUBs by simply mixing diisocyanates and diamines. (b) GPC curves showing water degradation of poly(**6/9**) and poly(**7/9**) in H_2O/DMF = 5:95 after 24 h incubation at 37 °C. (c) Plot showing molecular weight reduction of four polymers drawn in (a) in H_2O/DMF = 5:95 for various incubation time at 37 °C.

(Figure 2c), which could be attributed to the increase of free amine concentration that inhibits degradation (see eq 3, larger [**C**] gives lower degradation rate). The alteration of polymer hydrolysis kinetics with the change of HUB bulkiness was consistent with the results derived from the study of small molecular model compounds **1–5**.

To further demonstrate the hydrolytic degradation of TBEU-based polymer, we prepared a cross-linked organogel by mixing tri-isocyanate **11** with diamine **9** in DMF containing 5% water. Because isocyanate reacts with amine much faster than with water, **9** and **11** first reacted to form polyurea gel. The added water slowly hydrolyzed the TBEU bond, which led to the collapse of the gel after the gel was incubated 24 h at 37 °C (Figure 3a,c).

To study pHUBs degradation in aqueous solution and explore the potential of pHUBs for biomaterials applications, we designed hydrophilic polymers bearing HUB cross-linkers. To poly(ethylene glycol) methyl ether methacrylate monomer ($M_n \sim 500$), we added HUB containing dimethacrylate **13–14** as cross-linkers and Irgacure 2959 as the photoinitiator. The HUBs structures in **13–14** are TBEU and IPEU, respectively. The mixtures were irradiated by UV light (365 nm) to prepare the cross-linked polymers **G1** and **G2** (Figure 3b). We first did dynamic exchange study of **G1** and **G2** by immersing them in DMF in the presence or absence of hexylamine. In the absence of hexylamine, both gels swelled, demonstrating they are cross-linked polymers. In the presence of hexylamine, only **G1** was dissolved, while **G2** stayed intact. This experiment demonstrated that TBEU-containing **G1** has much faster dynamic exchange than **G2**, which is the requisite for efficient water degradation. For the water degradation study, we immersed **G1** and **G2** into phosphate buffered saline (PBS) and monitored the weight change at various time with the incubation at 37 °C (gels were pretreated with deionized water with short time to remove all the unreacted monomers).[2d] The weights of **G2** remained nearly unchanged after incubation for 9 days. In
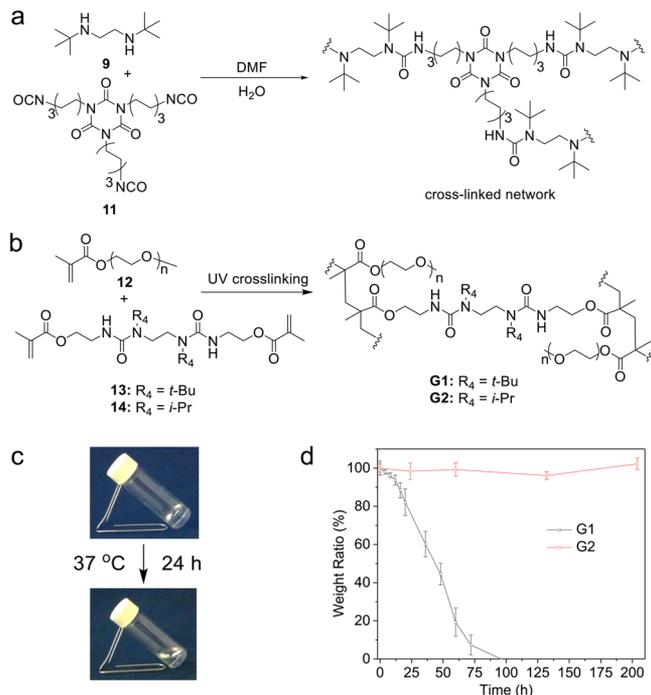

Figure 3. Water degradation of pHUBs. (a) Triisocyanate and diamine cross-linked into organogel in DMF with the preaddition of water. (b) Synthesis of urea-based cross-linked hydrophilic polymer **G1** and **G2** by UV polymerization. (c) Organogel synthesized from (a) collapsed into solution after 24 h incubation at 37 °C. (d) Weight change of **G1** (black curve) and **G2** (red curve) after immersing in PBS for variant time. Data represent averages of triplicate experiments. Error bars are standard deviation (n = 3).

contrast, **G1** showed consistent weight decrease and completely disappeared after incubation for 4 days (Figure 3b). We should notice that the degradation of TBEU might give a stable urea as the product since the amine from hydrolysis of isocyanate might react with another isocyanate molecule (as shown in the example in Figure 1d), which will hold the network without complete degradation. However, we observed complete degradation of **G1** in PBS, which meant that the formation of stable urea rarely happened in this case. Several reasons might explain the reduced probability of urea coupling: (i) much higher water concentration in pure water environment than organic solvent environment; (ii) protonation of amine groups in buffered neutral pH reduces reactivity; and (iii) amine groups are embedded by long oligo-ethylene glycol chains, which block their reaction of the exposed isocyanate.

In conclusion, we demonstrated the potential of HUBs for the design of water degradable polymeric materials. Kinetic analyses of small molecule model compounds prove that more bulky HUBs lead to faster water degradations. The same trend applies to the polymeric materials, with TBEU as one of the HUBs having the appropriate bulkiness for both sufficient binding stability for polymer formation and efficient dynamicity for water degradation. TBEU-based linear polymers degrades to 10–20% of their original size within 2 days. TBEU is also incorporated into cross-linked hydrogel materials which render complete water dissolution of the hydrogel within 4 days, making pHUBs alternative building blocks of hydrolyzable hydrogels. pHUBs provide a great new platform for the engineering of hydrolyzable materials. First, the degradation kinetics could be directly controlled by substituents bulkiness.

While we have demonstrated the use of TBEU for water degradable materials within days under mild conditions, less bulky urea might be used for applications which need longer lasting time or harsher degradation conditions (such as poly(8/10) or its derivatives). Second, different from traditional hydrolyzable polymers, pHUBs could be synthesized by simple mixing of amine and isocyanate at ambient condition with no catalyst and further purification needed and no byproducts generated, which made it possible for end-users to control the copolymer recipe for specific use without the need of complicated synthesis apparatus. Additionally, a large number of isocyanates monomers have been developed for use in the polyurethane and polyurea plastic industry, which can be used to react with amines with N-bulky substituents to give a very large library of hydrolyzable polymers with versatile structures and functions.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Binding constants, dissociation rates, and hydrolysis kinetics of model compounds, polymer synthesis, hydrolysis characterization procedures and data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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