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Stabilization of the hindered urea bond through de-*tert*-butylation

Yingfeng Yang[a], Hanze Ying[a], Yunchao Jia[b], Yingying Chen[a], Jianjun Cheng[a]*

We report the discovery of acid-assisted de-*tert*-butylation reaction that can instantly "turn off" the dynamicity of hindered urea bond (HUB) and thus broaden its applications. The reaction is demonstrated to be widely applicable to different hindered urea substrates, leading to improved chemical stabilities and mechanical properties of HUB-containing materials.

Dynamic covalent chemistry (DCC),[1,2] characterized by the reversible breaking and formation of covalent bonds, is a powerful tool that enables the synthesis of novel macrocycles, molecular cages, knots and covalent organic frameworks.[3-11] It has also been incorporated into polymeric networks which endows materials with functions like self-healing, shape memory, stimuli responsiveness, reprocessability and recyclability.[12-17] Despite these interesting features, structures with DCC incorporated often suffer from low stability, because of the endogenous bond dynamicity. This problem can be circumvented, however, by "turning off" the bond dynamicity to achieve stabilized structures and substrate properties. However, only a few DCCs have the feasible chemistry tools to allow easy "turning off" of the DCC bond dynamicity, such as stabilizing the dynamic hydrazone bond at high pH,[18] or reduction of the dynamic olefin, alkyne and imine[19] bonds. Thus, new dynamic covalent reactions with facile stabilizing strategies are of great interest and importance.

Polyurea is one of the most widely used industrial materials for coating because it features multiple advantages such as high strength and toughness, and high thermal and chemical stability.[20] Despite these superior properties,

advancement in chemistry and applications are quite limited. Recently our group developed the hindered urea chemistry where the bulky *N*-substituent renders the urea bond dynamic.[21] Based on this chemistry, hindered polyurea materials which display some unique features as opposed to traditional polyurea were developed, such as materials with self-healing property, multiple shape-memory effect, reprocessability and recyclability, as reported by us[21-26] and others.[27-29] However, stability issue can sometimes severely limit their applications. Since the dynamicity of the hindered urea bond is induced by the bulky *N*-substituent, one relatively straightforward strategy to "turn off" the dynamicity could be removing the *tert*-butyl group as shown in **Scheme 1**. Here we report the discovery of acid-assisted de-*tert*-butylation reaction that can instantly "turn off" the reversibility of the hindered urea bond (HUB). With the use of acid, the carbonyl group of HUB is protonated, followed by formation of *tert*-butyl carbocation and rearrangement of proton for the formation of the urea bond that has no dynamicity. We demonstrated that this de-*tert*-butylation reaction is easily attainable in small molecules, and linear/crosslinked polymers.
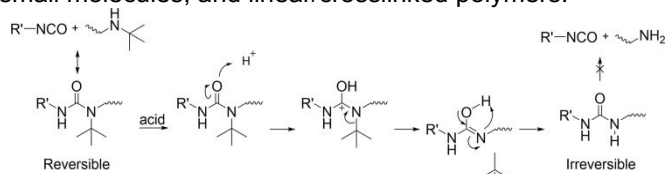
Scheme 1. Illustration for the acid-assisted de-*tert*-butylation of hindered urea bond.

The acid-assisted de-*tert*-butylation of HUB was discovered unexpectedly in our research. While we were studying the influence of electron effect on the hydrolysis kinetics of HUB, we selected **1** (**Figure 1**) as the model compound considering that its dimethylamino group would change from a weak electron donating group to a strong electron withdrawing group when pH drops from neutral to acidic. To assess the difference, **1** was dissolved in D$_2$O

a. *Department of Materials Science and Engineering, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, United States. E-mail: jianjunc@illinois.edu*
b. *School of Materials Science and Engineering, Henan University of Technology，100 Lianhua St, Zhongyuan District, Zhengzhou, Henan, China*

and the hydrolysis profile was monitored by ^{1}H NMR with or without addition of DCl. For **1** with the addition of DCl, we observed the appearance of a new set of peaks (**Figure 1-i**, red peaks) in addition to **1** (**Figure 1-i**, black peaks). Compound **1** completely disappeared after 2h (**Figure 1-ii**). However much to our surprise, the ^{1}H NMR of the products in the neutral and acidic groups were different. To further confirm this, compound **2**, which was a hydrolysis product, was added to the acidic group (**Figure 1-iii**). The new set of peaks did not coincide with that of compound **2** (**Figure 1-iii, blue peaks**), implying a degradation process different from hydrolysis. MS analysis showed that the acid-induced reaction of **1** resulted in **3**, the *tert*-butyl group depleted form of **1** instead of the hydrolysed product (**2**).
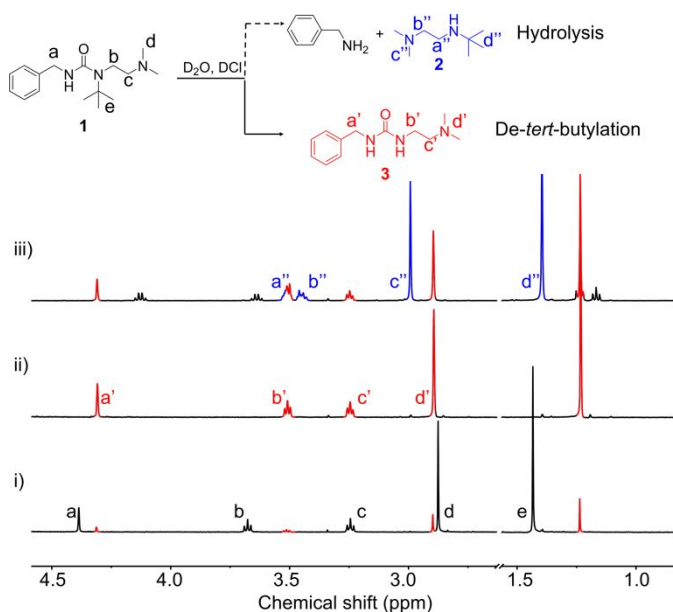
Figure 1. ^{1}H NMR spectrum of compound **1** in D_2O i) shortly after adding DCl (2 µL in 600 µL D_2O); ii) 2 h after adding acid; iii) with further addition of compound **2** after acid treatment.

We next explored if the de-*tert*-butylation is generally applicable in hindered urea compounds. Different *tert*-butyl based hindered ureas prepared from either aliphatic or aromatic isocyanates and *tert*-butyl amines (**Figure 2a, Scheme S1, Figures S1-S10**) were tested in either D_2O or $CDCl_3$, with either DCl or methanesulfonic acid/ trifluoroacetic acid added, respectively. The products were confirmed by NMR and MS (**Figures S13-S23**). All compounds showed very fast and exclusive de-*tert*-butylation with barely any hydrolysis product observed. These results demonstrated that the acid assisted de-*tert*-butylation reaction was achievable in a wide range of compounds bearing hindered urea bond in both aqueous and organic solvents with added inorganic/organic acids. What's more, excessive acid would not cause degradation of the urea linkage under our experimental conditions. We also tested two urea compounds bearing *N*-adamantyl substituent (**Figure S11-12**). With no surprise, the

adamantyl group can also be readily removed by acid (**Figure 2b, Figures S24-S26**), implying any substituents on HUB that can form a stable tertiary carbocation upon acidification would undergo similar depletion process, resulting in stable urea structure.
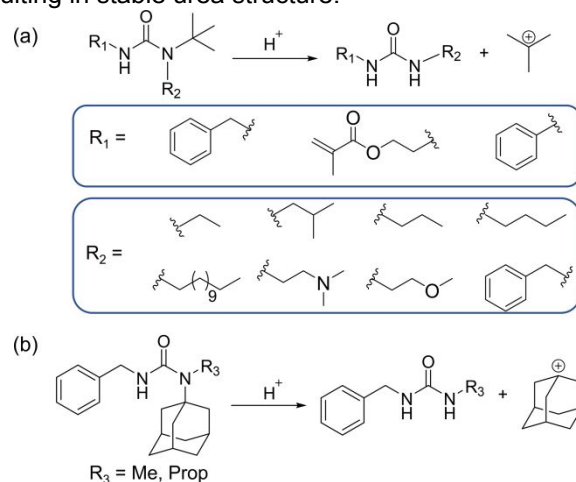

Figure 2. (a) Structures of the different hindered urea compounds used to confirm the feasibility of the de-*tert*-butylation reaction. (b) Hindered urea structures bearing *N*-adamantyl substituent can also be stabilized by acid.

To have a better understanding of the role acid plays in the reaction, **1** was used to study the pH dependence of the de-*tert*-butylation reaction. Four solutions of **1** were prepared with citrate buffer of pH 3, 4, 5, and 6, and the de-*tert*-butylation process of **1** at different pH was monitored by HPLC (**Figure S27**). It was observed that the hydrolysis product predominated at higher pH and the de-*tert*-butylated species only emerged at pH 3. This result indicates that high acidity is necessary for the de-*tert*-butylation reaction. We also studied the reaction kinetics with different urea and acid concentration. As shown in **Figure 3a**, a model reaction was chosen at either fixed acid concentration (50 mM) with the variation of the urea concentration (**Figure 3b**) or fixed urea concentration (0.5 mM) with the variation of the acid concentration (**Figure 3c**). A first order correlation to both the urea and acid concentration was observed, which explains why there was almost no hydrolyzed product observed in **Figure 1-ii**. As shown in **Figure 3d**, the dissociation (k_{-1}) and de-*tert*-butylation (k_{dt}) are two competing processes. The former is acid independent[30] while the latter accelerates with increased acid concentration. When subject to high acidity, the de-*tert*-butylation would be much faster than the dissociation process. Once de-*tert*-butylated, the hindered urea concentration would decrease, further reversing the dissociation reaction towards the formation of hindered urea, which explained why only de-*tert*-butylated species was observed at high concentration of acid. For aromatic HUB compounds with much greater dissociation constants, higher concentration of acid was required to drive the de-*tert*-butylation process and prevent the formation of hydrolyzed species (**Figures S22-S23**).

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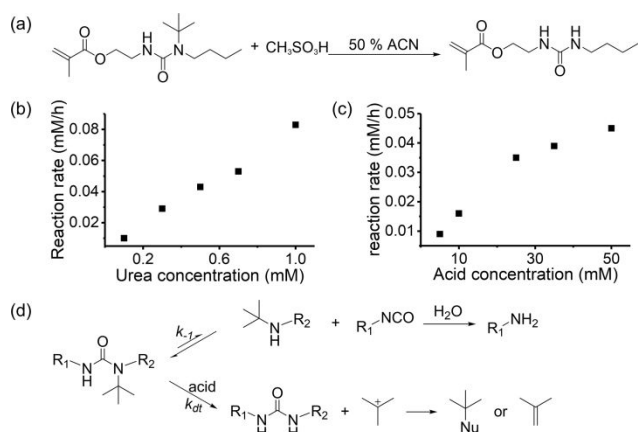
Figure 3. (a) Scheme for the model reaction. (b) The relationship between reaction rate and urea concentration (acid concentration: 50 mM). (c) The relationship between reaction rate and acid concentration (urea concentration: 0.5 mM). (d) Illustration for the relationship between dissociation and de-*tert*-butylation.
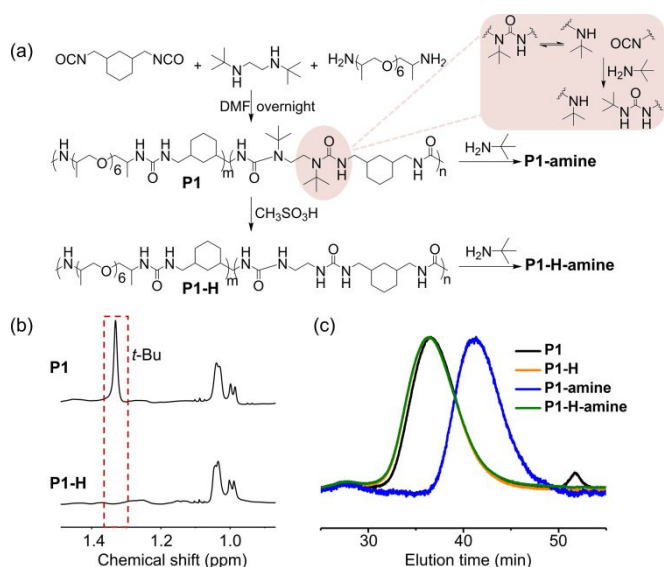
Figure 4. (a) De-*tert*-butylation of **P1** and amine treatment of **P1** and **P1-H**, the de-*tert*-butylated **P1**. (b) Partial ¹H NMR spectra of **P1** and **P1-H**. (c) GPC overlay of **P1**, **P1-H**, **P1-H-amine**, and **P1-H-amine**.

After studying the reaction in small molecules, we went on to study the feasibility of the de-*tert*-butylation chemistry in linear hindered urea polymers (HUPs) using **P1** (**Figure 4a**) as the model polymer. Poly (propylene glycol) was added to increase the solubility of the de-*tert*-butylated polymer. The NMR studies revealed complete removal of the *tert*-butyl group with acid treatment of **P1** (**Figure 4b**). To assess the effectiveness of the de-*tert*-butylation reaction, both the original (**P1**) and acid-treated polymers (**P1-H**) were incubated in amine solution and then characterized by GPC. **P1** bears hindered urea bond, which will dissociate giving an isocyanate intermediate. The intermediate will be trapped by free amine, leading to degradation of the urea backbone and thus decrease of the MW (**Figure 4a**, pink highlight). However **P1-H** contains

only regular urea bond, which is stable towards free amine. Thus the urea backbone remained intact. As shown in **Figure 4c**, the GPC curve of **P1-H** matched well with that of **P1**, showing that acid treatment did not cleave the backbone of the polymer. After incubation with amine, as expected, **P1** showed a significant molecular weight decrease (the **P1-amine** blue curve, **Figure 4c**), while the MW of **P1-H** did not change after the amine treatment (the **P1-H-amine** green curve, **Figure 4c**). These experiments demonstrated the high efficiency of the de-*tert*-butylation reaction in HUPs and its utility in stabilizing the HUPs without degrading their backbones. We also studied the acid-induced de-*tert*-butylation reaction in aromatic HUPs, which gave similar results (**Figure S36**).
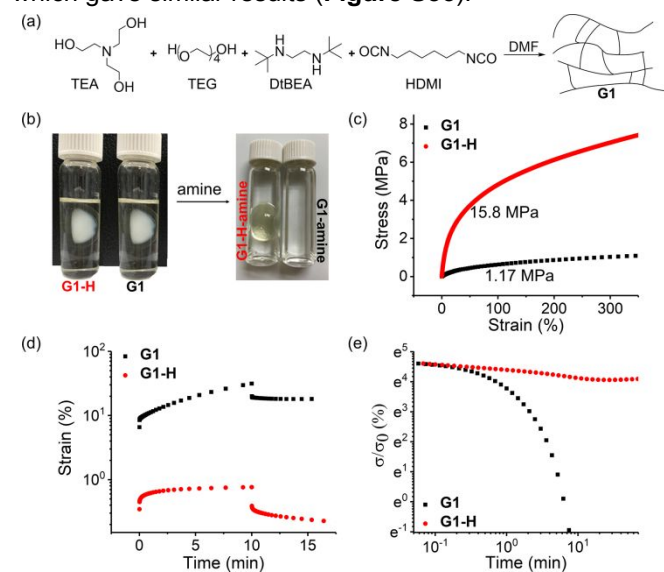
Figure 5. (a) Preparation of the HUB containing organogel in 30 wt% DMF (TEA:TEG:DtBEA:HMDI=1:6.5:4:12) . (b) **G1** and **G1-H** (acid-treated **G1**) after incubation with amine overnight in CHCl₃. (c) Stress-strain curve of **G1** and **G1-H** thin film (d) Creep behavior of **G1** and **G1-H** thin film (e) Stress relaxation of **G1** and **G1-H** thin film

We then went on to explore the de-*tert*-butylation reaction in a crosslinked organogel. **G1**, a model HUB containing crosslinked polymer, was synthesized at the TEA:TEG:DtBEA:HMDI ratio of 1:6.5:4:12 in 30 wt% DMF (**Figure 5a**). Half of the gel was treated with methanesulfonic acid in CHCl₃ for 1 h and then washed with CHCl₃ three times to remove acid (**G1-H**). **G1-H** was then immersed in CHCl₃ overnight to ensure further removal of the acid. The washed **G1-H** and **G1** were immersed in CHCl₃, and then incubated with excessive amount of amine. The acid treated gel **G1-H** remained structurally intact while the gel **G1** was completely dissolved (**Figure 5b**), demonstrating that acid treatment can efficiently stabilize the gel bearing dynamic HUB presumably due to the acid-induced de-*tert*-butylation.

To further demonstrate the acid-induced de-*tert*-butylation in HUB containing materials, thin films were made from **G1** and the mechanical properties of the films were analyzed

pre- and post-acid treatment. As shown in **Figure 5c**, the Young's modulus of the gel increased by one order of magnitude after acid treatment. The acid-treated material also showed much improved creep resistance (**Figure 5d**) and negligible stress relaxation (**Figure 5e**). We attributed these observations to the increased number of hydrogen-bonding motifs (regular urea bond) after de-*tert*-butylation and therefore stronger bond strength in the acid-treated materials. These experiments clearly show that the de-*tert*-butylation reaction work very well in both gel and solid HUB-containing materials and can efficiently stabilize the urea bonds by removing the dynamicity of the HUB and thus improve the mechanical property of the materials.

Conclusions

We report the acid assisted de-*tert*-butylation reaction of HUB, which enables effective removal of the *tert*-butyl group from the hindered urea, thus "turning off" the dynamicity of HUB and rendering urea bond stable. We demonstrated the feasibility of the reaction with different hindered urea compounds in different solvents. The de-*tert*-butylation reaction is dependent on acid concentration and high acidity is required for effective and exclusive de-*tert*-butylation. What's more, excessive acid would not cause degradation of the urea linkage. We also tested the de-*tert*-butylation reaction of HUB in polymers and organogels, both displaying complete removal of the *tert*-butyl group and increased materials stability. The de-*tert*-butylation reaction was also demonstrated to increase the mechanical property of materials bearing HUB. These results indicate that this de-*tert*-butylation reaction can be effectively used in combination with the dynamic covalent chemistry, acting as a stabilizing or curing step. From materials perspective, it provides a new way to construct regular polyurea materials through synthesizing hindered polyurea with isocyanate and hindered amine precursors, which is much easier to control, and processing the formed hindered polyurea to the desired stable forms following the removal of the hindered substituents. With this new strategy, polyurea processes that are difficult to achieve with conventional methods are readily attainable, and many new applications of polyurea could be possible. The de-*tert*-butylation chemistry also resembles the widely used deprotection chemistry of *tert*-butoxycarbonyl and *tert*-butyl ester and may have the potential in organic synthesis, such as the synthesis of macrocycles. Thus, this de-*tert*-butylation chemistry is a great tool to manipulate the stability of dynamic materials and enable the synthesis of functional molecules and materials.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1   J. M. Lehn, *Chemical Society reviews*, 2007, **36**, 151-160.
2   S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders and J. F. Stoddart, *Angew Chem Int Edit*, 2002, **41**, 898-952.
3   Y. H. Jin, C. Yu, R. J. Denman and W. Zhang, *Chemical Society reviews*, 2013, **42**, 6634-6654.
4   M. E. Belowich and J. F. Stoddart, *Chemical Society reviews*, 2012, **41**, 2003-2024.
5   C. S. Diercks and O. M. Yaghi, *Science*, 2017, **355**, eaal1585.
6   J. L. Segura, M. J. Mancheno and F. Zamora, *Chemical Society reviews*, 2016, **45**, 5635-5671.
7   T. Hasell and A. I. Cooper, *Nat Rev Mater*, 2016, **1**, 1-14.
8   F. Beuerle and B. Gole, *Angew Chem Int Edit*, 2018, **57**, 4850-4878.
9   S. Lee, A. Yang, T. P. Moneypenny and J. S. Moore, *J Am Chem Soc*, 2016, **138**, 2182-2185.
10 S. D. P. Fielden, D. A. Leigh and S. L. Woltering, *Angew Chem Int Edit*, 2017, **56**, 11166-11194.
11 J. J. Danon, A. Kruger, D. A. Leigh, J. F. Lemonnier, A. J. Stephens, I. J. Vitorica-Yrezabal and S. L. Woltering, *Science*, 2017, **355**, 159-162.
12 W. Zou, J. Dong, Y. Luo, Q. Zhao and T. Xie, *Adv Mater*, 2017, **29**, 1606100.
13 R. J. Wojtecki, M. A. Meador and S. J. Rowan, *Nat Mater*, 2011, **10**, 14-27.
14 Z. Wei, J. H. Yang, J. X. Zhou, F. Xu, M. Zrinyi, P. H. Dussault, Y. Osada and Y. M. Chen, *Chemical Society reviews*, 2014, **43**, 8114-8131.
15 T. Xie, *Nature*, 2010, **464**, 267-270.
16 P. Chakma and D. Konkolewicz, *Angew Chem Int Edit*, 2019, **58**, 9682-9695.
17 D. Roy, J. N. Cambre and B. S. Sumerlin, *Prog Polym Sci*, 2010, **35**, 278-301.
18 E. Moulin, G. Cormos and N. Giuseppone, *Chemical Society reviews*, 2012, **41**, 1031-1049.
19 Y. Jin, Q. Wang, P. Taynton and W. Zhang, *Accounts of chemical research*, 2014, **47**, 1575-1586.
20 D. K. Chattopadhyay and K. V. S. N. Raju, *Prog Polym Sci*, 2007, **32**, 352-418.
21 H. Ying, Y. Zhang and J. Cheng, *Nature communications*, 2014, **5**, 1-9.
22 H. Z. Ying, J. Yen, R. B. Wang, Y. Lai, J. L. A. Hsu, Y. H. Hu and J. J. Cheng, *Biomater Sci-Uk*, 2017, **5**, 2398-2402.
23 Y. Zhang, H. Ying, K. R. Hart, Y. Wu, A. J. Hsu, A. M. Coppola, T. A. Kim, K. Yang, N. R. Sottos, S. R. White and J. Cheng, *Adv Mater*, 2016, **28**, 7646-7651.
24 Y. C. Jia, H. Z. Ying, Y. F. Zhang, H. He and J. J. Cheng, *Macromol Chem Phys*, 2019, **220**, 1900148.
25 H. Z. Ying and J. J. Cheng, *J Am Chem Soc*, 2014, **136**, 16974-16977.
26 S. J. Wang, Y. F. Yang, H. Z. Ying, X. L. Jing, B. Wang, Y. F. Zhang and J. J. Cheng, *Acs Appl Mater Inter*, 2020, **12**, 35403-35414.
27 L. F. Chen, L. H. Zhang, P. J. Griffin and S. J. Rowan, *Macromol Chem Phys*, 2020, **221**, 1900440.
28 S. Zechel, R. Geitner, M. Abend, M. Siegmann, M. Enke, N. Kuhl, M. Klein, J. Vitz, S. Grafe, B. Dietzek, M. Schmitt, J. Popp, U. S. Schubert and M. D. Hager, *Npg Asia Mater*, 2017, **9**, e420.
29 G. Y. Kim, S. Sung, M. P. Kim, S. C. Kim, S. H. Lee, Y. I. Park, S. M. Noh, I. W. Cheong and J. C. Kim, *Appl Surf Sci*, 2020, **505**, 144546.
30 K. M. Cai, H. Z. Ying and J. J. Cheng, *Chem-Eur J*, 2018, **24**, 7345-7348.