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Dynamic urea bond for the design of reversible and self-healing polymers

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Abstract

Polymers bearing dynamic covalent bonds may exhibit dynamic properties, such as self-healing, shape memory and environmental adaptation. However, most dynamic covalent chemistries developed so far require either catalyst or change of environmental conditions to facilitate bond reversion and dynamic property change in bulk materials. Here we report the rational design of hindered urea bonds (urea with bulky substituent attached to its nitrogen) and the use of them to make polyureas and poly(urethane-ureas) capable of catalyst-free dynamic property change and autonomous repairing at low temperature. Given the simplicity of the hindered urea bond chemistry (reaction of a bulky amine with an isocyanate), incorporation of the catalyst-free dynamic covalent urea bonds to conventional polyurea or urea-containing polymers that typically have stable bulk properties may further broaden the scope of applications of these widely used materials.

Differing from polymers formed with strong, irreversible covalent bonds and stable bulk properties, polymers prepared through reversible non-covalent interactions or covalent bonds exhibit interesting dynamic properties^{1–3}. The dynamic features of reversible polymers have been employed in the design of self-healing, shape-memory and environmentally adaptive materials^{4–6}. Non-covalent interactions are relatively weak with only a few exceptions such as quadruple hydrogen bonding^{7,8}, high-valence metal chelation^{9,10} and host-guest interaction^{11,12}. Dynamic covalent bonds, on the contrary, usually have higher strength and more controllable reversibility. Well-known dynamic covalent bonds or structures include hydrazone¹³, substituted cyclohexenes capable of retro-Diels-Alder reaction¹⁴ and thiol radical species amenable to radical association-dissociation^{15–17}. These dynamic chemistries have been used in preparing polymers with unique properties and functions. For instance, self-healing materials, emerging functional

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Author contributions

H. Y. and J.C. planned the project and designed experiments. Y.Z. contributed to the project design. H. Y. carried out the experiments and collected data. H. Y. and J.C. analysed the experimental data, prepared figures and wrote the manuscript.

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materials that can heal the cut or crack with recovered mechanical property¹⁸, can be achieved not only through the release of the encapsulated or embedded healing reagents/catalysts^{19,20}, but also through reversible exchange of non-covalent interaction^{21–28} or dynamic covalent bonding^{29–34} at the cut or crack interface. Recently, there has been growing interest in the design of dynamic covalent chemistry that can be incorporated with conventional polymers for self-healing application. Along this direction, Guan et al. developed a method to make dynamic poly(butadiene) by activating double bonds with the Grubb's catalyst^{35,36}. Leibler et al. synthesized dynamic polyesters with metal catalysts to accelerate high temperature esterification^{37,38}. A few catalyst-free, low-temperature dynamic covalent chemistries have also been reported for the synthesis of reversible polymers^{32,33}.

The amide bond forms the basic structure of numerous biological and commodity polymers (e.g., nylon, polypeptide, etc.) and, as such, is one of the most important organic functional groups. It has remarkable stability due to conjugation effects between the lone electron pair on the nitrogen atom and the π -electrons on the carbonyl *p*-orbital. Reversing the amide bond (amidolysis) usually requires extreme conditions (e.g., highly basic or acidic solutions and/or high temperature) or the presence of special reagents (e.g., enzymes)³⁹. Introducing bulky substituents to an amide nitrogen atom has been reported to weaken the amide bond which results in amidolysis under mild conditions. The addition of a bulky group is believed to disturb the orbital co-planarity of the amide bond, which diminishes the conjugation effect and thus weakens the carbonyl–amine interaction (Fig. 1a)⁴⁰. However, the dissociated intermediate from amidolysis (ketene), if formed, would be too reactive to show dynamic reversible formation of the amide bond. To make carbonyl-amine structures reversible, it is required that the dissociated carbonyl structure is stable under ambient conditions but still highly reactive with amines. One such functional group that satisfies these requirements is isocyanate. Isocyanate is reasonably stable under ambient conditions and can react with amines rapidly to form a urea bond, a reaction that has been broadly utilized in the synthesis of polyurea and poly(urethane-urea). Similar to the bulky amide bonds described above, urea bonds bearing a bulky group on the nitrogen atom can reversibly dissociate into isocyanate and amine, the reverse process of typical urea bond formation (Fig. 1b)^{41,42}.

Here we report the design of dynamic hindered urea bonds (HUBs) and their application in the design and synthesis of polyureas and poly(urethanes-urea), some of the widely used materials in the coating, fibre, adhesive and plastics industries, that are capable of catalyst-free dynamic property change and autonomous repairing at low temperature.

Results

Design of HUBs and evaluation of their binding constants

Reversible chemistry does not necessarily lead to polymers with dynamic properties. To render reversible chemistry dynamic and practical for the synthesis of polymers with bulk properties, two criteria must be met. First, both the forward and the reverse reactions should be fast (large k_1 and k_{-1} , Fig. 1c). Second, the equilibrium must favour the formation of the polymer (large $K_{eq} = k_1/k_{-1}$)⁴³. In the design of dynamic polyurea, it is therefore crucial to

identify a HUB with a properly selected substituent on the amine group so that the corresponding HUB can meet these two requirements.

We first performed equilibrium studies using 2-isocyanatoethyl methacrylate (**1**) and amines with different steric hindrance to identify such HUBs (Fig. 1c and Table 1). 2,2,6,6-Tetramethylpiperidine (**2a**), a bulky amine containing two *tert*-butyl equivalent groups, was selected and mixed with **1** in CDCl₃ in attempts to synthesize **3a** bearing a HUB moiety—2,2,6,6-tetramethylpiperidinylcarboxamide (TMPCA) (Fig. 1c). As expected, TMPCA is reversible and the coexistence of **1**, **2a** and **3a** was observed in CDCl₃ based on ¹H NMR analysis (Supplementary Fig. 1). Interestingly, the three compounds were in thermodynamic equilibrium with a binding constant K_{eq} of 88 M⁻¹ at room temperature, independent of the concentration of **1** and **2a** (Supplementary Figs 1–2). By reducing the substituent bulkiness on the amine by using *N*-isopropyl-2-methylpropan-2-amine (**2b**) to replace **2a**, a larger binding constant was observed ($K_{eq} = 5.6 \times 10^3$ M⁻¹, Supplementary Fig. 3 and Supplementary Note 1). While the reversibility of 1-(*tert*-butyl)-1-isopropylurea (TBIPU), the corresponding HUB, is reduced compared to TMPCA and the reaction is more prone toward the formation of the urea bond, the K_{eq} is still too small to be of practical use. If HUBs with such small K_{eq} values were used in the design of polymers via condensation reactions, the resulting polymer would have a low degree of polymerization (DP) and limited bulk mechanical property⁴³. Thus, although **3a** and **3b** are both reversible HUBs, they are clearly not the ideal dynamic bonds to be used in the preparation of dynamic polyureas with applicable bulk properties.

To obtain a larger K_{eq} , we further reduced the bulkiness of the *N*-substituents on the amine and used *tert*-butyl-ethylamine (**2c**), diisopropyl amine (**2d**) and diethylamine (**2e**) to react with **1** to prepare **3c–3e** containing the corresponding HUBs: 1-(*tert*-butyl)-1-ethylurea (TBEU), 1,1-diisopropylurea (DIPU) and 1,1-diethylurea (DEU), respectively (Fig. 1c). These HUBs showed much larger binding constants than **3a** and **3b** ($K_{eq} = 7.9 \times 10^5$ for TBEU, $K_{eq} > 10^7$ M⁻¹ for DIPU and DEU, Supplementary Fig. 4 and Supplementary Note 1). We went on to determine their dissociation constants (k_{-1}) through intermediate trapping experiments (Supplementary Figs 5–7). As expected, **3c** has the largest k_{-1} among these three HUBs (0.042 h⁻¹ at room temperature, Table 1 and Supplementary Fig 5), while **3d** and **3e** have much smaller k_{-1} even at elevated temperature (Table 1). Because TBEU has both large K_{eq} (k_1) and k_{-1} , we next designed experiments to study whether it could serve to control bond exchange and re-formation under mild conditions in TBEU-containing small molecules and polymers.

Dynamic exchange of HUBs in small molecules and polymers

We first studied the dynamic exchange of TBEU by mixing **3c** with *t*-butylmethyl amine (**2f**), a compound with very similar *N*-substituent steric bulkiness as **2c**. We monitored the ratio change of each compound in CDCl₃ through ¹H NMR. Although the concentration of **1**, the isocyanate intermediate, was too low to be observed, *t*-butylmethyl urea (**3f**) and *t*-butylethyl amine (**2c**) were produced and detected by NMR. This observation verified the exchange reaction through the isocyanate intermediate **1** (Fig. 2a). As shown in Fig. 2b, the concentration of compound **3f** and **2c** increased over time while the concentration of

compound **3c** and **2f** decreased until equilibrium was reached. Linear regression of the reaction kinetics proved the reversible exchange mechanism of these species (Supplementary Note 2 and Supplementary Fig. 8). The time needed to reach complete equilibrium was about 20 h at 37 °C and the dissociation rate was determined to be 0.21 h^{-1} ($t_{1/2} = 3.3 \text{ h}$) (Fig. 2c and Table 1). Thus, these experiments clearly demonstrated dynamic urea bond exchange in small molecules containing the TBEU moiety.

We next tested the dynamic behaviour of TBEU in polymers by mixing 1,3-bis(isocyanatomethyl)cyclohexane (**4a**) and *N,N'*-di-*tert*-butylethylenediamine (**5c**, a bisfunctional analogue of **2c**) at 1:1 stoichiometry and $[\mathbf{4a}]_0$ (or $[\mathbf{5c}]_0$) concentration of 1.0 M in DMF (Fig. 2d). We used the β -branched diisocyanate **4a** instead of a linear diisocyanate in order to increase the solubility of the corresponding polymers. Several HUBs formed with cyclohexanemethyl isocyanate (**1''**), a monofunctional analogue of **4a**, have similar dynamic properties (especially nearly identical k_{-1}) as those prepared from **1**, indicating that β -substitution/branching of isocyanate has limited effect on dynamic property of HUBs (Supplementary Table 1). Poly(**4a/5c**) was formed with an M_n of $1.7 \times 10^4 \text{ g/mol}$ as analysed by gel permeation chromatography (GPC) (see the mono-modal light scattering peak in the upper curve, Fig. 2e). The addition of another equivalent of **5c** resulted in degradation of the polymer to very low molecular weight (MW) molecules after 12 h incubation at 37 °C (middle curve, Fig. 2e). Interestingly, when one equivalent **4a** was added to the reaction solution to restore the **4a:5c** ratio back to 1:1 (DMF was also added to keep $[\mathbf{4a}]_0$ (or $[\mathbf{5c}]_0$) at 1.0 M), the low MW light scattering peaks completely disappeared and a new, higher MW, monomodal GPC curve which overlays nearly perfectly with the original poly(**4a/5c**) GPC curve was observed (lower curve, Fig. 2e). In a separate experiment, we mixed two poly(**4a/5c**) samples with distinctly different MWs ($M_{n1} = 13.0 \times 10^3 \text{ g/mol}$ and $M_{n2} = 2.8 \times 10^3 \text{ g/mol}$) in DMF solutions. After stirring the solution for 12 h at 37 °C, the two original GPC light scattering peaks disappeared and a new monomodal light scattering peak corresponding to an M_n of $4.8 \times 10^3 \text{ g/mol}$ was observed (Supplementary Fig. 9). These experiments demonstrate that the TBEU bonds are in fast dynamic exchange in both TBEU-containing small molecules and polymers. In several control experiments, we studied the condensation polymerization of **4a** with bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate (**5a**, a more bulky amine compared to **5c** and a bisfunctional analogue of **2a**) and *N,N'*-di-*iso*-propylethylenediamine (**5d**, a less bulky amine compared to **5c** and a bisfunctional analogue of **2d**). As expected, the mixture of **4a** and **5a** at 1:1 ratio in DMF only yielded very low MW polymer because of its low K_{eq} (Supplementary Fig. 10). The mixture of **4a** and **5d** at 1:1 ratio in DMF yielded high MW polyurea (poly(**4a/5d**)) with very stable urea bond. No detectable dynamic bond exchange was observed when the formed poly(**4a/5d**) was treated with **5d** at 37°C for 12 h (Supplementary Fig. 11). Thus, the dynamic change of HUBs can be controlled by tuning the steric bulkiness of the substituent attached to the urea bonds.

Synthesis and study of self-healing HUB-containing polymers

After demonstrating the dynamic property and bond exchange features of HUBs, we next attempted to use HUBs in the design of catalyst-free, low-temperature self-healing materials (as illustrated in Fig. 3a). Specifically, we designed cross-linked poly(urethane-ureas)

containing HUBs and tested their self-healing property (Fig. 3b). Triethanolamine (TEA) was used as the cross-linker and tetra(ethylene glycol) (TEG) was used as the chain extender. Hindered diamines **5a**, **5c** and **5e** were used to form the corresponding HUB motifs (TBEU, TMPCA and DEU) in the desired network polymers **6a**, **6c** and **6e**, respectively. TEA, TEG and diamine were allowed to react with hexamethylene diisocyanate (**4b**) in DMF with dibutyltin diacetate (DBTDA) as the catalyst to yield cross-linked poly(urethane-urea)¹⁷. The molar ratio of TEA:**4b**:TEG:**5** was set at 1:12:6.8:4 for the synthesis of the self-healing material. The cross-linking density (determined by the amount of TEA), dynamic moiety concentration (determined by the amount of **5**) and polymer flexibility (determined by the amount of TEG) were optimized to ensure efficient self-healing with the optimal mechanical stiffness¹⁷. The hydroxyl and amine groups were included in excess of the isocyanate groups to improve the material stability against hydrolysis by increasing the free amine concentration (Supplementary Note 3 and Supplementary Figs 12–14).

All three samples behaved as elastic gels with good mechanical stiffness (with Young's modulus around 1 MPa, see Fig. 4a and Table 2) and thermal stability (Supplementary Fig. 15). They all have subambient glass transition temperatures (T_g , Supplementary Fig. 16), which provides sufficient chain mobility for bond exchange. Swelling experiments demonstrated that these polymers were cross-linked network. Both **6a** and **6c** could be dissolved in DMF containing **2f**, substantiating the dynamic bond exchange property of the built-in HUBs (Supplementary Fig. 17). Next, we examined the creep-recovery behaviours to further understand the elastomeric property of these three samples (Fig. 4b)^{23,27}. As expected, **6a** showed completely different behaviour from **6c** and **6e**. When a stress of 0.08 MPa was applied to **6a** and held for 60 min, the strain increased from 50% to ~350% (strain increase of 6.3% per min). After the stress was released, the gel could not return to its original length and had a residual strain as high as ~150% (blue trace, Fig. 4b). This phenomena can be explained by the weak strength of TMPCA bonds in **6a**, thereby making the material behave like a physically cross-linked rubber that yields upon stretching. For **6e** under the same condition, very slow strain increase was observed. After stress was released, the material recovered its original dimension with negligible residual strain (red trace, Fig. 4b). This experiment demonstrated that the DEU bonds in **6e** are strong with very poor dynamic exchange property. Compared to **6e**, **6c** showed a slightly elevated strain increase (0.09% per minute) and residual strain (6%) (black trace, Fig. 4b), both of which were much smaller than those of **6a**. This experiment showed that even with chain exchange, **6c** is still strong enough to maintain satisfactory dimensional stability under externally applied stress.

We next tested the self-healing behaviour of these three poly(urea-urethane) materials containing HUB moieties. We cured the polymers in a dog-bone shaped mould and cut the polymer as illustrated in Fig. 3a with a razor blade. We then gently brought the two pieces back in contact for 1 min and let the materials cure without external force and protection with inert gas. TMPCA-based **6a** showed fast self-healing because of the highly reversible urea bond. After the two cut pieces were brought in contact for just 5 min at room temperature and stress was then immediately applied to the healed materials without further curing, strong reconnection of these two pieces and good recovery of mechanical strength

were observed. However, complete recovery of the breaking strain in the self-repaired **6a** can never be achieved. Because of the low binding constant (88 M^{-1} , Table 1) and fast dynamicity of the TMPCA bonds, there should be substantial amount of free isocyanate groups in **6a** without being used to form the TMPCA bonds. These free isocyanate groups are susceptible to hydrolysis, in particular for those at the surfaces of the cut pieces that are more exposed to the moisture in air, and irreversibly transform to amine groups after decarboxylation that can react with free isocyanate groups to form irreversible non-dynamic urea bonds. As such, **6a** is expected to gradually lose self-healing property and prolonged healing is expected to lead to reduced instead of increased breaking strain, which was exactly what we have observed (Supplementary Fig. 18). We also noticed that the gel **6a** was transparent initially but became turbid after several hours under ambient conditions, suggesting substantial material property change presumably due to the hydrolysis of the isocyanate groups.

Compared to **6a**, **6e** showed much slower healing as a result of its reduced dynamicity of the urea bonds (DEU, Fig. 3b). After a dog-bone shaped **6e** was cut, the two pieces were brought back in contact and the polymer was allowed to heal for 24 h at 37°C , approximately 30% of the original breaking strain was recovered (Fig. 4c). Extended curing did not improve healing (red vs. blue trace, Fig. 4c). Stretching of the cured **6e** resulted in fracture at the cut site.

Self-healing experiments with TBEU-based **6c** revealed that this HUB has an advantageous balance of dynamicity (much large k_1 than that of DEU of **6e**) and urea bond strength (much higher binding constant than that of TMPCA of **6a**, Table 1). The self-healing experiment of **6c** was similarly performed as **6a** and **6e**. The cut of **6c** could self-heal at room temperature with moderately high recovery breaking strain ($\sim 50\%$ after 12 h curing, dotted trace, Fig. 4d). At elevated temperature (37°C), the materials showed much faster and better self-healing property. A breaking strain of 50% was recovered after putting the two cut pieces back in touch for 1 min and curing the materials for just 1 h. Longer curing time led to improved self-repairing and increased breaking strains (Fig. 4d). After 12 h of curing at 37°C , the extensibility of the cured **6c** had recovered 87% of its initial strain (Fig. 4d) and did not always fracture at the cut position (Supplementary Movie 1).

Discussion

Integrating dynamic moieties to polymers, especially those capable of dynamic covalent bonding in widely-used conventional polymers are of tremendous interest. In one particular application, for example, materials bearing such dynamic moieties may theoretically self-heal for unlimited times if the healing is directed by the reversible exchange of dynamic covalent bonds. However, bringing dynamic properties to conventional polymers often involves special dynamic moieties^{13–17} that may require tedious synthesis and/or use of external stimuli such as catalyst^{35,36} or high temperature^{37,38} for dynamic property activation and control. In this study we report the design of dynamic polyureas and poly(urethane-urea)s by attaching bulky substituents to the urea nitrogen to create the so-called hindered urea bonds (HUBs, Fig. 1). As HUBs are synthesized through the reaction of isocyanate and amine, conventional polyureas and poly(urea-urethane)s with stable bulky

properties can thus be readily made dynamic by replacing regular amine with bulky amines (amines containing bulky substituents). By screening five HUBs with different substituent bulkiness, we identified *N*-tertbutyl-*N*-ethylurea (TBEU) as a promising HUB and successfully demonstrated its application in making dynamic polymers (Fig. 2e) and self-healing materials (Fig. 4d). Polymer chain reshuffling was observed for a linear polyurea based on TBEU (Fig. 2e). We incorporated TBEU moieties into a cross-linked poly(urethane-urea) to obtain catalyst-free self-healing materials under mild condition with good mechanical strength, dimensional rigidity and chemical stability. TBEU has a large K_{eq} for retaining strong bonding and a reasonably large k_{-1} for efficient dynamic bond exchange under mild conditions (Table 1). Very bulky *N*-substituent in HUBs may result in faster dynamic bond exchange, as shown in the case of TMPCA, but its weak bond strength (smaller K_{eq} , Table 1) makes it less favoured for self-healing applications (Supplementary Fig. 18). HUBs present a number of desirable properties for the synthesis of dynamic and self-healing polymers. They can be easily synthesized through the reaction of an isocyanate and a hindered amine, both of which are widely available and inexpensive. The dynamic properties of HUBs can be well controlled by adjusting bulkiness of the substituents. HUBs possess a hydrogen-bonding motif via its urea bond that can increase the mechanical strength of polymers, a property that most of other dynamic covalent chemistries lack. We anticipate that HUB structure and chemistry can be readily integrated in the design of a wide range of materials, bringing modular and tuneable dynamic properties to conventional polyureas and urea-containing polymers.

Methods

General

2-Isocyanatoethyl methacrylate was purchased from TCI America (Portland, OR, USA) and used as received. Anhydrous dimethylformamide (DMF) was dried by a column packed with 4Å molecular sieves. Tetrahydrofuran (THF) was dried by a column packed with alumina. All other chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received unless otherwise specified. NMR spectra were recorded on a Varian U400 (400 MHz), a U500 (500 MHz) a VXR-500 (500 MHz), a UI500NB (500 MHz), or a UI600 (600 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 HELEOS was set at 658 nm. Separations were performed using serially connected size exclusion columns (100 Å, 500 Å, 10³ Å and 10⁴ Å Phenogel columns, 5 µm, 300 × 7.8 mm, Phenomenex, Torrance, CA, USA) at 60 °C using DMF containing 0.1 M LiBr as the mobile phase. Creep-recovery experiments were performed on DMA Q800 (TA instruments, New Castle, DE, USA). Stress-strain experiments were performed on a custom built bi-directional screw driven rail table assembled by IMAC Motion Control Group (Elgin, IL, USA) with translation stage from Lintech (Monrovia, CA, USA), motor from Kollmorgen (Radford, VA, USA), load cell from Honeywell Sensotech (Columbus, OH, USA). Glass transition

temperatures were tested by differential scanning calorimetry (Model 821e, Mettler Toledo, Columbus, OH, USA)

Synthesis of model hindered ureas **3b~3f**

Urea compounds **3b~3f** were synthesized by mixing **1** (1.0 mmol) with equal molar **2b~2f** (1.0 mmol) in DCM (5 mL) at room temperature. After 1 h, the crude compound was purified by flash column with EtOAc as the eluent. Compounds **3b~3f** were obtained quantitatively. Note: Because of the low binding constant, we could not get pure **3a** under ambient condition.

2-(3-(tert-Butyl)-3-isopropylureido)ethyl methacrylate (3b)—¹H NMR (500 MHz, CDCl₃): δ 6.11 (dq, *J* = 1.6, 1.0 Hz, 1H, COC(CH₃)=CH₂), 5.57 (dq, *J* = 1.6, 1.6 Hz, 1H, COC(Me)=CH₂), 4.80 (t, *J* = 5.1 Hz, 1H, NH), 4.26 (t, *J* = 5.1 Hz, 2H, O-CH₂), 3.65 (h, *J* = 6.9 Hz, 1H, CH(CH₃)₂), 3.52 (q, *J* = 5.1 Hz, 2H, NH-CH₂), 1.94 (dd, *J* = 1.0, 1.6 Hz, 3H, COC(CH₃)=CH₂), 1.32 (s, 9H, -C(CH₃)₃), 1.25 (d, *J* = 6.9 Hz, 6H, -CH(CH₃)₂). ¹³C NMR (125 MHz, CDCl₃): δ 167.4, 160.1, 136.2, 126.0, 64.2, 56.3, 45.7, 39.5, 29.1, 23.4, 18.5. ESI-MS (low resolution, positive mode): calculated for C₁₄H₂₆N₂O₃, *m/z*, 271.2 [M + H]⁺; found 271.2 [M + H]⁺.

2-(3-(tert-Butyl)-3-ethylureido)ethyl methacrylate (3c)—¹H NMR (500 MHz, CDCl₃): δ 6.11 (dq, *J* = 1.6, 0.9 Hz, 1H, COC(CH₃)=CH₂), 5.58 (dq, *J* = 1.6, 1.6 Hz, 1H, COC(CH₃)=CH₂), 4.74 (t, *J* = 5.4 Hz, 1H, NH), 4.27 (t, *J* = 5.4 Hz, 2H, O-CH₂), 3.51 (q, *J* = 5.4 Hz, 2H, NH-CH₂), 3.23 (q, *J* = 7.1 Hz, 2H, -CH₂CH₃), 1.94 (dd, *J* = 0.9, 1.6 Hz, 3H, COC(CH₃)=CH₂), 1.41 (s, 9H, -C(CH₃)₃), 1.15 (t, *J* = 7.1 Hz, 3H, -CH₂CH₃). ¹³C NMR (125 MHz, CDCl₃): δ 167.8, 158.3, 136.3, 126.0, 64.4, 56.2, 40.2, 39.2, 29.7, 18.5, 16.6. ESI-MS (low resolution, positive mode): calculated for C₁₃H₂₄N₂O₃, *m/z*, 257.2 [M + H]⁺; found 257.2 [M + H]⁺.

2-(3,3-Diisopropylureido)ethyl methacrylate (3d)—¹H NMR (500 MHz, CDCl₃): δ 6.11 (dq, *J* = 1.7, 0.9 Hz, 1H, COC(CH₃)=CH₂), 5.58 (dq, *J* = 1.7, 1.7 Hz, 1H, COC(CH₃)=CH₂), 4.57 (t, *J* = 5.3 Hz, 1H, NH), 4.27 (t, *J* = 5.3 Hz, 2H, O-CH₂), 3.89 (h, *J* = 6.9 Hz, 2H, CH(CH₃)₂), 3.55 (q, *J* = 5.3 Hz, 2H, N-CH₂), 1.94 (dd, *J* = 0.9, 1.7 Hz, 3H, COC(CH₃)=CH₂), 1.22 (d, *J* = 6.9 Hz, 12H, CH(CH₃)₂). ¹³C NMR (125 MHz, CDCl₃): δ 167.6, 157.1, 136.2, 126.0, 64.4, 45.1, 40.1, 21.5, 18.5. ESI-MS (low resolution, positive mode): calculated for C₁₃H₂₄N₂O₃, *m/z*, 257.2 [M + H]⁺; found 257.2 [M + H]⁺.

2-(3,3-Diethylureido)ethyl methacrylate (3e)—¹H NMR (500 MHz, CDCl₃): δ 6.09 (dq, *J* = 1.6, 0.9 Hz, 1H, COC(CH₃)=CH₂), 5.56 (dq, *J* = 1.6, 1.6 Hz, 1H, COC(CH₃)=CH₂), 4.74 (t, *J* = 5.3 Hz, 1H, NH), 4.25 (t, *J* = 5.4 Hz, 2H, O-CH₂), 3.51 (q, *J* = 5.4 Hz, 2H, N-CH₂), 3.22 (q, *J* = 7.1 Hz, 4H, -CH₂CH₃), 1.92 (dd, *J* = 1.6, 0.9 Hz, 3H, COC(CH₃)=CH₂), 1.10 (t, *J* = 7.1 Hz, 6H, -CH₂CH₃). ¹³C NMR (125 MHz, CDCl₃): δ 167.7, 157.1, 136.2, 126.0, 64.3, 41.3, 40.4, 18.4, 13.9. ESI-MS (low resolution, positive mode): calculated for C₁₁H₂₀N₂O₃, *m/z*, 229.2 [M + H]⁺; found 229.2 [M + H]⁺.

2-(3-(*tert*-Butyl)-3-methylureido)ethyl methacrylate (3f)— ^1H NMR (500 MHz, CDCl_3): δ 6.10 (dq, $J = 1.6, 0.9$ Hz, 1H, $\text{COC}(\text{CH}_3)=\text{CH}_2$), 5.56 (dq, $J = 1.6, 1.6$ Hz, 1H, $\text{COC}(\text{CH}_3)=\text{CH}_2$), 4.67 (t, $J = 5.4$ Hz, 1H, NH), 4.23 (t, $J = 5.4$ Hz, 2H, O- CH_2), 3.48 (q, $J = 5.4$ Hz, 2H, N- CH_2), 2.79 (s, 3H, - CH_3), 1.92 (dd, $J = 0.9, 1.6$ Hz, 3H, $\text{COC}(\text{CH}_3)=\text{CH}_2$), 1.37 (s, 9H, $\text{C}(\text{CH}_3)_3$). ^{13}C NMR (125 MHz, CDCl_3): δ 167.7, 159.0, 136.2, 126.0, 64.4, 55.7, 40.1, 31.7, 29.1, 18.4. ESI-MS (low resolution, positive mode): calculated for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_3$, m/z , 243.2 $[\text{M} + \text{H}]^+$; found 243.2 $[\text{M} + \text{H}]^+$.

Determination of equilibrium constants

Equilibrium constants at different initial ratios of amine and isocyanate—1 and 2a were dissolved in CDCl_3 (0.5 mL) with three different ratios and added to the NMR tubes (see Supplementary Fig. 1 for details of the concentrations). ^1H NMR spectra were collected 30 min after **1** and **2a** were mixed at room temperature when equilibrium was reached (Supplementary Fig. 1). Concentration of each species was calculated based on the integral ratios of the ^1H NMR signals and the initial concentrations of **1** and **2a**. The equilibrium constants were calculated as:

$$K_{\text{eq}} = [\mathbf{3a}]_{\text{eq}} / ([\mathbf{1}]_{\text{eq}} \bullet [\mathbf{2a}]_{\text{eq}}) \quad (1)$$

Equilibrium constants at different temperatures—1 (8.5 mg, 0.055 mmol) and 2a (7.5 mg, 0.054 mmol) were dissolved in CDCl_3 (0.5 mL) for NMR analysis. ^1H NMR spectra were collected at different temperatures (Supplementary Fig. 2). Concentration of each species was calculated according to the integral ratios of ^1H NMR signals and the initial concentrations of **1** and **2a**. The equilibrium constants were calculated as equation 1.

Dissociation kinetics of TBEU, DIPU and DEU

Determination of dissociation rates of TBEU, DIPU and DEU—Butyl isocyanate (compound **1'**) was added to **3c**, **3d** or **3e** and the consumption rates of **3c**, **3d** or **3e** were monitored by ^1H NMR at room or higher temperature. The dissociation rates were calculated based on those data (Supplementary Figs 5–7).

Study of TBEU bond exchange with an amine—Urea **3c** (11.3 mg, 0.044 mmol) that has a TBEU moiety and *tert*-butylmethylamine **2f** (8.8 mg, 0.102 mmol) were mixed in CDCl_3 (0.5 mL), quickly transferred to a NMR tube, and heated to 37°C . ^1H NMR spectra were collected at selected time intervals until chemical equilibrium was reached.

Dynamic property of TBEU-based polymers

TBEU-based poly(4a/5c)—Equal molar 1,3-bis(isocyanatomethyl)cyclohexane (**4a**, 437 mg, 2.25 mmol) and *N,N'*-di-*tert*-butylethylene-diamine (**5c**, 387 mg, 2.25 mmol) were dissolved in DMF (2.0 mL). The mixture was stirred at 37°C for 2 h vigorously and analysed by GPC to check if poly(**4a/5c**) was formed. Next, another equiv **5c** (378 mg, 2.20 mmol) in DMF (0.90 mL) was added. The reaction was allowed to proceed for an additional 20 h. The solution was analysed by GPC to check if poly(**4a/5c**) was depolymerized to form oligomers at the $[\mathbf{4a}]_0:[\mathbf{5c}]_0$ ratio of 1:2. Finally, one equiv **4a** (427 mg, 2.20 mmol) in DMF

(1.05 mL) were added to the reaction solution to bring the [4a]₀: [5c]₀ ratio back to 1:1. Two hours later, the solution was analysed by GPC to check if higher molecular weight poly(4a/5c) was re-formed (Fig. 2e).

In another experiment, two batches of poly(4a/5c) were prepared. One polymer (poly(4a/5c)-1) was prepared by mixing 4a (338 mg, 1.74 mmol) and 5c (299 mg, 1.74 mmol) in DMF (1.5 mL) and the other polymer (poly(4a/5c)-2) was prepared by mixing 4a (338 mg, 1.74 mmol) and 5c (337 mg, 1.96 mmol) in DMF (1.5 mL). They were analysed by GPC with M_n of 13.0×10^3 g/mol and 2.8×10^3 g/mol, respectively. Next, equal volume (500 μ L) of the solution of poly(4a/5c)-1 and poly(4a/5c)-2 were mixed and stirred vigorously at 37 °C for 12 h. The mixture was analysed by GPC to verify if the polymer chain reshuffling happened which would result in a polymer with intermediate MW (lower than that of poly(4a/5c)-1 and higher than that of poly(4a/5c)-2) and monomodal GPC distribution (Supplementary Fig. 9).

TMPCA-based poly(4a/5a)—Equal molar of 1,3-bis(isocyanatomethyl)cyclohexane (4a, 152 mg, 0.78 mmol) and bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate (5a, 376 mg, 0.78 mmol) were dissolved in DMF (1.0 mL). The mixture was stirred at 37 °C for 2 h vigorously and analysed by GPC (Supplementary Fig. 10).

DIPU-based poly(4a/5d)—Equal molar 1,3-bis(isocyanatomethyl)cyclohexane (4a, 203 mg, 1.05 mmol) and *N,N'*-di-*iso*-propylethylene-diamine (5d, 151 mg, 1.05 mmol) were dissolved in DMF (1.0 mL). The mixture was stirred at 37 °C vigorously for 2 h. The sample was analysed by GPC for the formation of poly(4a/5d). To the mixture was then added another equivalent 5d (153 mg, 1.06 mmol) with DMF (0.43 mL) to make the [4a]₀: [5d]₀ ratio 1:2. The reaction solution was stirred for 20 h and analysed by GPC (Supplementary Fig. 11).

Synthesis and study of self-healing HUB-containing polymers

Synthesis of 6a—In a typical experiment, hexamethylene diisocyanate (1.280 g, 7.6 mmol) and DMF (0.380 g, 15% weight ratio) were charged in a glass vial and cooled to 4 °C. Diamine 5a (1.220 g, 2.54 mmol) was slowly added to form oligo-urea. After the solution was brought to room temperature, TEA (0.094 g, 0.63 mmol) and TEG (0.829 g, 4.27 mmol) were added and the solution was vigorously homogenized. Then the pre-polymer was charged to a dog-bone shaped mould (dimension shown in Supplementary Fig. 19) followed by addition of dibutyl tin diacetate (DBTDA, 1 drop, ~10 mg). The polymer was allowed to cure at room temperature for 24 h under N₂.

Synthesis of 6c—In a typical experiment, hexamethylene diisocyanate (1.380 g, 8.2 mmol) and DMF (0.317 g, 15% weight ratio) were charged in a glass vial and cooled to 4 °C. Diamine 5c (0.471 g, 2.74 mmol) was slowly added to form oligo-urea accompanied with significant heat release. After cooling the mixture to room temperature, TEA (0.102 g, 0.69 mmol) and TEG (0.897 g, 4.62 mmol) were added and the solution was vigorously homogenized. Then the pre-polymer was charged to a dog-bone shaped mould followed by

addition of DBTDA (1 drop, ~10 mg). The polymer was allowed to cure at room temperature for 12 h and then at 60 °C for another 12 h under the protection of inert gas.

Synthesis of 6e—In a typical experiment, hexamethylene diisocyanate (1.450 g, 8.6 mmol) and DMF (0.707 g, 30% weight ratio) were charged in a glass vial and cooled to 4 °C. Diamine **5e** (0.330 g, 2.84 mmol) was slowly added to form oligo-urea. After the solution was cooled to room temperature, TEA (0.107 g, 0.72 mmol) and TEG (0.939 g, 4.84 mmol) were added and the solution was vigorously homogenized. Then the pre-polymer was charged to a dog-bone shaped mould followed by addition of DBTDA (1 drop, ~10 mg). The polymer was allowed to cure at room temperature for 12 h and then at 60 °C for another 12 h under the protection of inert gas.

Swelling and amine-induced degradation of 6c—**6c** was immersed in DMF with or without the addition of amine **2f** (2 equiv relative to TBEU bond in **6c**), and then incubated at 37°C for 24 h.

Stress-strain experiments—Stress-strain experiments were performed on a custom-built bidirectional screw driven rail table that allows tensile testing of samples with both grips translating simultaneously and in opposite directions, keeping the centre of mass of the sample stationary. The samples were extended at the speed of 2 mm s⁻¹. Load was measured via a 22 N capacity load cell.

Creep-recovery experiments—The samples were fixed by the grips, pulled to a certain strain (~50%) and held for 60 min. After that, the stress was released and the samples were allowed to relax for another 60 min.

Self-healing experiments—The samples were cut by a blade and then the cut pieces were gently pressed in touch for 1 min, left to heal at 37 °C for selected healing times without the protection of inert gas, and then subject to stress-strain experiments to test the recovery of their breaking strains.

Statistical analysis—Data are given as mean ± s.e.m.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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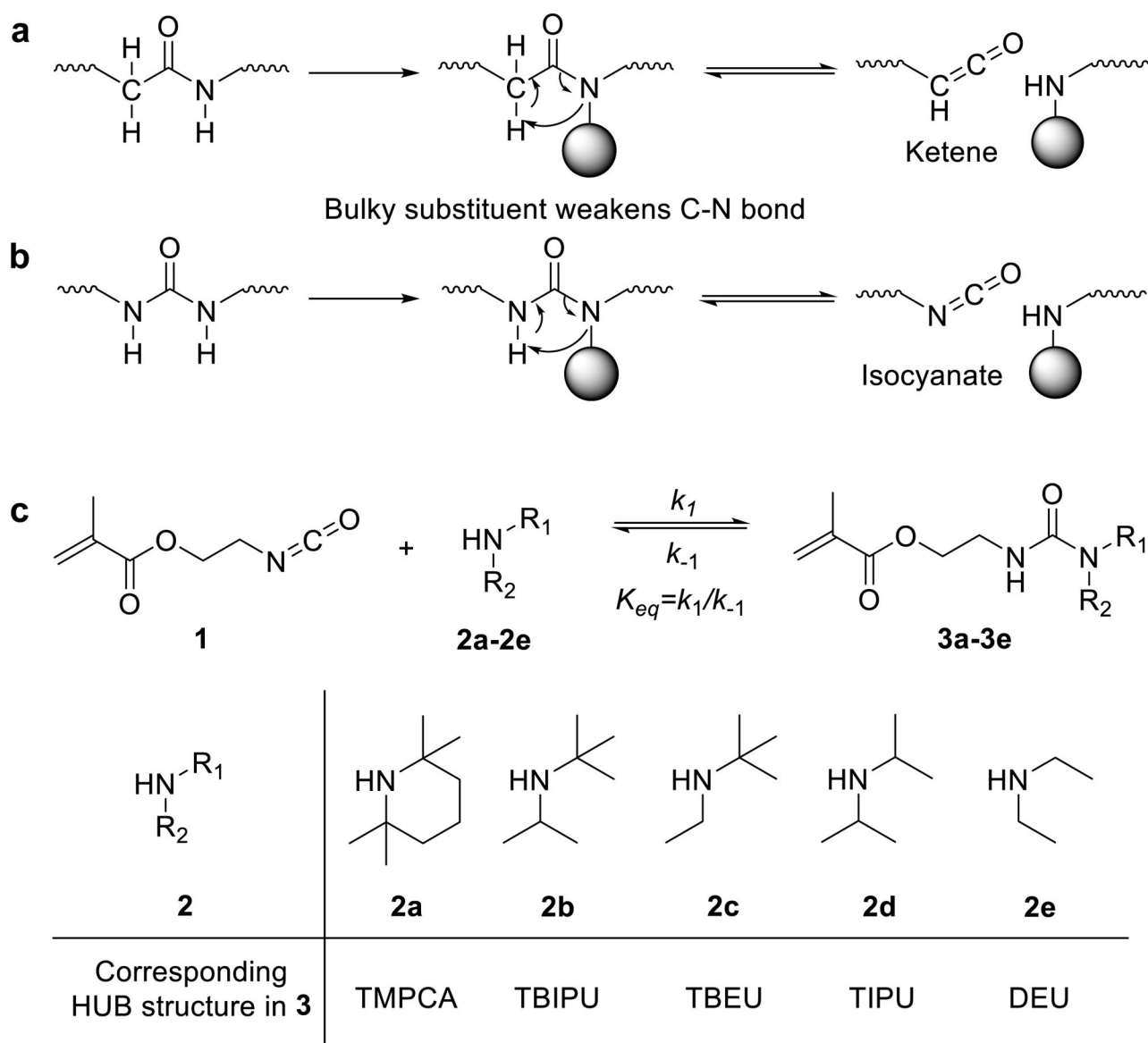


Figure 1. Dissociation of carboxylate/amine bonds bearing bulky *N*-substituent
(a) Hindered amide bond dissociates to unstable ketene intermediate. **(b)** Hindered urea bond (HUB) dissociates to isocyanate, which is stable at low temperature but reactive to amine to reform the HUB bond, making HUB a dynamic covalent bond; **(c)** Equilibrium between isocyanate **1**, bulky amines (**2a–e**) and corresponding ureas (**3a–e**), the chemical structures of bulky amines (**2a–e**), and the urea **3a–e** bearing the corresponding HUB: 2,2,6,6-tetramethylpiperidinylcarboxamide (TMPCA), *N*-tertbutyl-*N*-isopropylurea (TBIPU), *N*-tertbutyl-*N*-ethylurea (TBEU), *N,N*-diisopropylurea (DIPU) and *N,N*-diethylurea (DEU).

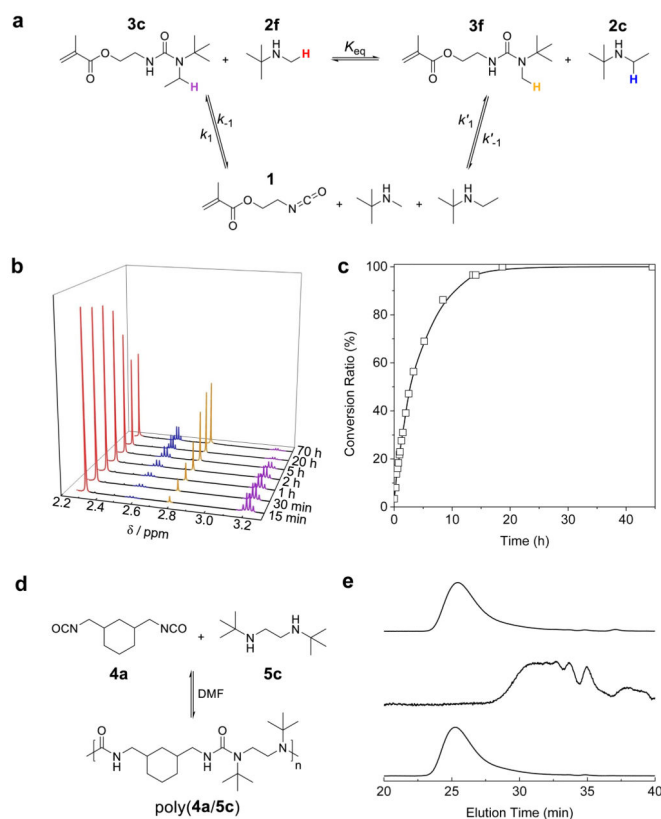


Figure 2. Dynamic exchange reactions in TBEU-bearing small molecule or polymer
(a) Exchange reaction between **3c** and **2f** produces **3f** and **2c** with isocyanate **1** as the intermediate. **(b)** ^1H NMR spectra after mixing **3c** and **2f** for different durations at 37°C . The proton peak intensities of **3c** and **2f** gradually decreased over time, along with the gradual increase of proton peak intensities of **3f** and **2c** until an equilibrium of the exchange reaction was reached at approximate 20 h. The protons subject to analysis from these four compounds were labelled with different colours in Fig. 2a, which correspond to the colours of peaks in Fig. 2b. **(c)** Conversion of **3c** toward reaching equilibrium (Conversion ratio = $([\mathbf{3c}]_0 - [\mathbf{3c}]_t)/([\mathbf{3c}]_0 - [\mathbf{3c}]_{eq})$, $[\mathbf{3c}]_0$ = initial concentration of **3c**, $[\mathbf{3c}]_t$ = concentration of **3c** at time t, $[\mathbf{3c}]_{eq}$ = equilibrium concentration of **3c**). **(d)** Poly(**4a/5c**), TBEU-bearing dynamic polymers, prepared via the polycondensation of **4a** and **5c**. **(e)** Dynamic tuning of poly(**4a/5c**) shown by GPC analysis (signal from light scattering detector). Firstly, polymer solution was prepared by mixing **4a** and **5c** with $[\mathbf{4a}]_0:[\mathbf{5c}]_0=1:1$ ($[\mathbf{4a}]_0$ (or $[\mathbf{5c}]_0$) at 1.0 M in DMF), and the GPC experiment was performed after 2 h incubation at 37°C (upper curve). One additional equiv **5c** was then added to tune the $[\mathbf{4a}]_0:[\mathbf{5c}]_0$ ratio to 1:2 and the GPC experiment was performed after 12 h incubation of the mixture at 37°C (middle curve). Finally, one additional equiv **4a** was added to restore the $[\mathbf{4a}]_0:[\mathbf{5c}]_0$ ratio back to 1:1. DMF was also added to keep $[\mathbf{4a}]_0$ (or $[\mathbf{5c}]_0$) at 1.0 M. GPC experiment was performed after 2 h incubation of the mixture at 37°C (lower curve).

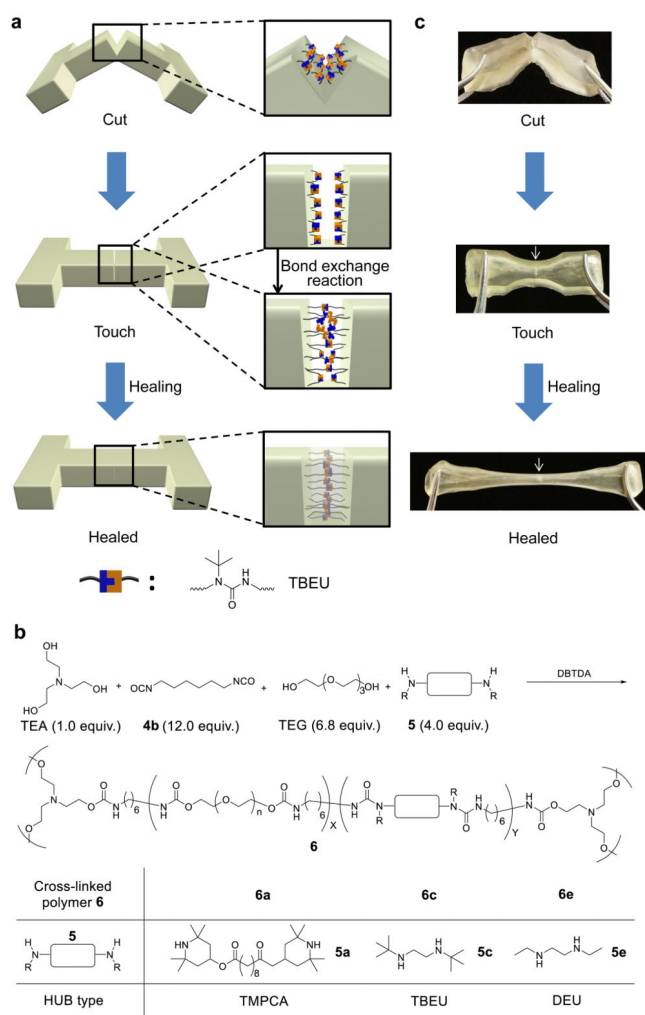


Figure 3. Design of HUB-based self-healing materials

(a) Illustration of the self-healing process of TBEU(*N*-tertbutyl-*N*-ethylurea)-based poly(urethane-urea). (b) Chemical structures and ratios of components used for the synthesis of HUB-based cross-linked poly(urethane-urea). (c) Selected snapshots during the course of the self-healing experiment of TBEU-based poly(urethane-urea) **6c**. The cut pieces was gently pressed together and left to heal for 12 h at 37°C. The gel was then stretched. No fracture at the cut region was observed, showing efficient recovery of mechanical properties at the cut interface. The arrow indicates the position being cut.

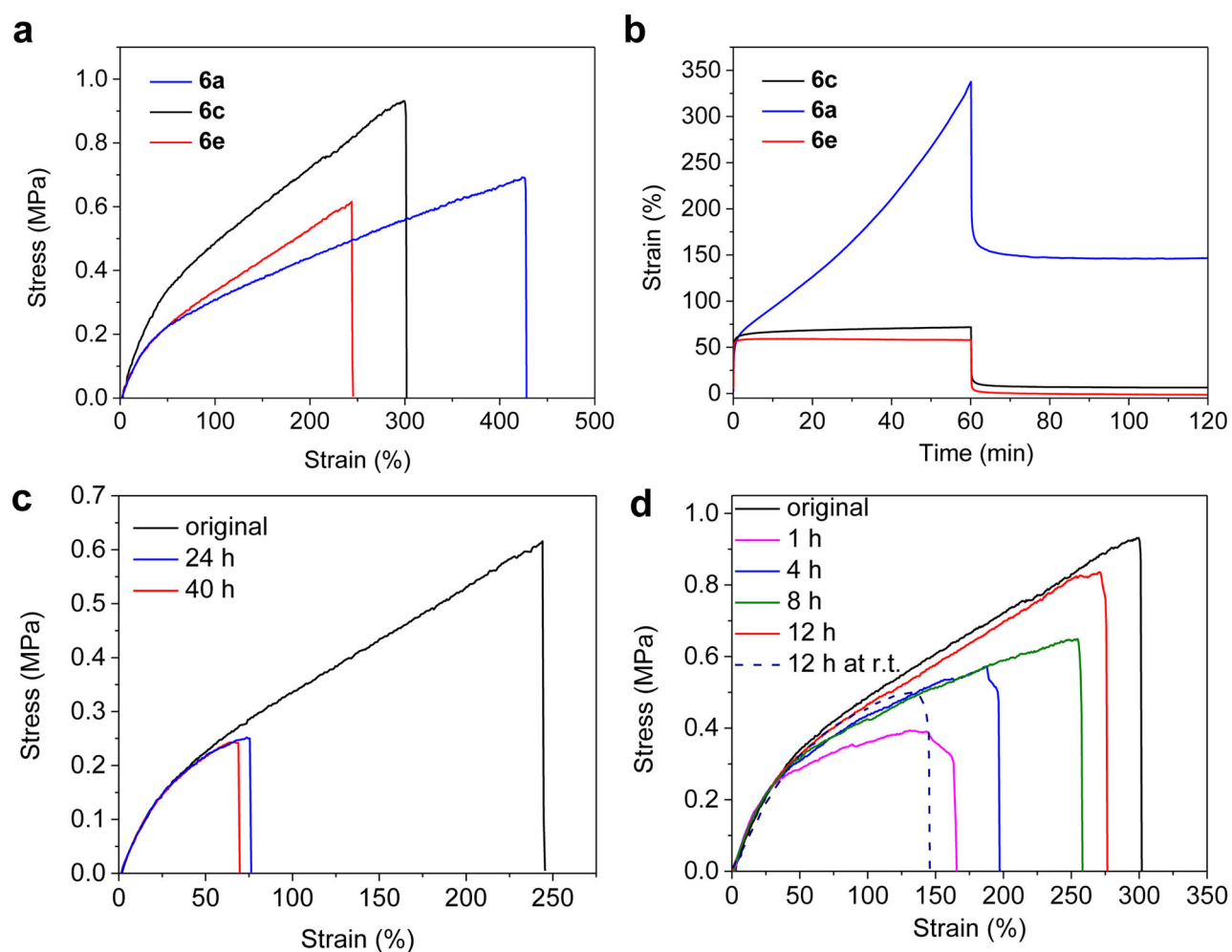


Figure 4. Mechanical characterization of HUB-based cross-linked poly(urethane-urea)
(a) Stress-strain curves of **6a**, **6c** and **6e**. **(b)** Creep-recovery of **6a**, **6c** and **6e** with initial strain of 50%. **(c)** Inefficient recovery of the breaking strain of **6e** after long period of healing. **(d)** Recovery of breaking strain of sample **6c** under various healing conditions. The breaking strain of the cut and healed **6c** was efficiently and largely restored after 12 h self-healing (87%) at 37°C. The healing at room temperature is less efficient (dotted line).

Table 1

Equilibrium constant and dissociation rate of HUBs.

HUB structure in 3	TMPCA (3a)	TBIPU (3b)	TBEU (3c)	DIPU (3d)	DEU (3e)
K_{eq} (M^{-1})	88	5.6×10^3	7.9×10^5	$>10^7$	$>10^7$
k_{-1} (h^{-1})	-	-	$0.042(0.21^a)$	0.0015^a	0.0011^a

^aExperiments performed at 37°C

Table 2

Physical properties of cross-linked poly(urethane-urea) with different HUBs.

T_g (°C)	Young's modulus (MPa)	Before cutting			After cutting and healing			Breaking strain recovery (%)
		Breaking stress (MPa)	Breaking strain (%)	Breaking stress (MPa)	Breaking stress (MPa)	Breaking strain (%)		
6a	0.87±0.04	0.69±0.05	426±20	/	/	/	/	
6c	1.22±0.12	0.93±0.06	301±12	0.71±0.05	268±13	87±4	87±4	
6e	0.87±0.20	0.62±0.02	243±21	0.32±0.08	68±4	29±2	29±2	