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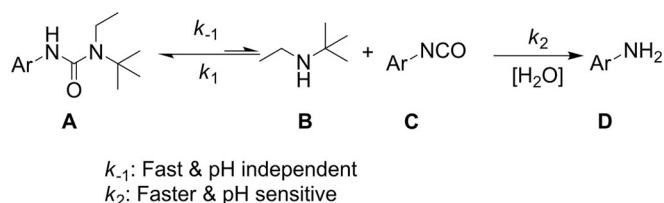
Dynamic Ureas with Fast and pH-Independent Hydrolytic Kinetics

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Abstract: Low cost, high performance hydrolysable polymers are of great importance in biomedical applications and materials industries. While many applications require materials to have a degradation profile insensitive to external pH to achieve consistent release profiles under varying conditions, hydrolysable chemistry techniques developed so far have pH-dependent hydrolytic kinetics. This work reports the design and synthesis of a new type of hydrolysable polymer that has identical hydrolysis kinetics from pH 3 to 11. The unprecedented pH independent hydrolytic kinetics of the aryl ureas were shown to be related to the dynamic bond dissociation controlled hydrolysis mechanism; the resulting hindered poly(aryl urea) can be degraded with a hydrolysis half-life of 10 min in solution. More importantly, these fast degradable hindered aromatic polyureas can be easily prepared by addition polymerization from commercially available monomers and are resistant to hydrolysis in solid form for months under ambient storage conditions. The combined features of good stability in solid state and fast hydrolysis at various pH values is unprecedented in polyurea material, and will have implications for materials design and applications, such as sacrificial coatings and biomaterials.

Hydrolysable materials have been widely used in a variety of fields including biomedical applications^[1] and environmental science.^[2] Engineered materials that release encapsulated cargo consistently independent of surrounding environment, especially pH, have found tremendous significance in industries of encapsulation and drug delivery.^[3] Orally delivered drugs, for example, often have varied in vivo bioavailability and thus uncontrolled therapeutic efficacy due to the variation of drug release kinetics in response to the change of gastrointestinal pH. The hydrolysis of conventional degradable polymers including esters,^[4] anhydrides,^[5] orthoesters,^[6] carbonate,^[7] acetal,^[8] phosphoesters,^[9] are generally logarithmically pH dependent. So far, only complex formulations can achieve pH-independent cargo release^[10] due to the lack of simple chemistries that can degrade consistently irrespective of pH change over a wide range.^[11] Here, we report a pH-independent, hydrolysable material based on hindered aromatic ureas (HAU). Degradation profiles of the HAU were shown to be correlated with urea bond dissociation irrespective of the solution pH. Polymeric HAU was demonstrated to degrade to half the molecular weight within ten minutes at room temperature in solution, whereas ambient storage of the solid powder showed negligible hydrolysis over two months. The transient feature of the HAU and its facile preparation will have remarkable implications in materials design and applications such as sacrificial coatings and biomaterials.

Our previous studies have shown that, by incorporating a secondary hindered substituent onto the nitrogen atom, the resulting hindered urea bond (HUB) was shown to be dynamic and can reversibly dissociate into secondary amine and isocyanate.^[12] The isocyanate can be hydrolyzed to a primary amine, which leads to the breakdown of HUB by water.^[13] Although isocyanate hydrolysis is highly pH dependent,^[14] we hypothesized that, by incorporating a pH-insensitive urea dissociation as the rate-limiting step, the hydrolysis of this type of "pro-isocyanate" bond can be pH independent (Scheme 1). To further achieve faster hydrolytic kinetics, we designed to replace the previous aliphatic isocyanate with aryl isocyanate. Aryl amines,



Scheme 1. Fast and pH-independent hydrolysis of hindered aromatic ureas (HAU). The hydrolytic kinetics is limited by the urea bond dissociation rate k_{-1} , which is independent of solution pH.

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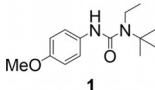
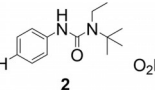
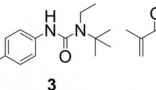
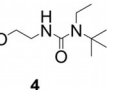
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as the degradation product of aromatic hindered ureas, have much lower nucleophilicity than aliphatic amines and generate less undesired non-dynamic urea side product,^[13] which is poorly soluble in common solvents.

We first designed a set of aryl ureas with favorable electronic effect on the conjugated phenyl ring (Table 1) and studied the corresponding K_{eq} by ¹H NMR through exchange of the urea with a set of bulky amines in *d*-chloroform (Figures S1–S12 in

Table 1. Equilibrium constants and dissociation rates of different *N*-*tert*-butyl-*N*-ethyl ureas (tBEU) in *d*-chloroform at room temperature. k_1 is calculated as $K_{\text{eq}} \times k_{-1}$. The constant of aliphatic HUB (4) was adapted from Ref. [12] for comparison.

				
	1	2	3	4
K_{eq} (M^{-1})	2.8×10^4	3.0×10^4	2.6×10^6	7.9×10^5
k_{-1} (h^{-1})	11.2	8.9	5.7	0.042
k_1 ($\text{M}^{-1} \text{h}^{-1}$)	3.1×10^5	2.7×10^5	1.5×10^7	3.3×10^4

the Supporting Information). Similar to our previous findings,^[12] the equilibrium constant of the aryl urea bond increases as the bulkiness of the substitution on amine decreases (Table S1 in the Supporting Information). All of the three *tert*-butyl-ethylureas (tBEU) showed high K_{eq} ($> 2 \times 10^4$) and the K_{eq} increases as the phenyl ring becomes more electron deficient (Table 1). The dissociation constant k_{-1} was measured by exchange study of the ureas with *N*-methyl-*tert*-butyl amine or *tert*-butyl amine (Figures S13–S18) and calculated through linear regression of $\ln\left(\frac{[C_{\text{tBEU}}]}{[C_{\text{tBEU}}]_0} - A\right) - t$.^[12] Remarkably, the amine exchange of the tBEU could reach equilibrium within one hour at room temperature in *d*-chloroform (Figures S13–S15). The k_{-1} of tBEU with aryl substitution is two orders of magnitudes larger than the reported aliphatic urea (Table 1) and among the fastest dynamic chemistries reported so far.^[15] In addition, the calculated k_1 is larger than $10^5 \text{ M}^{-1} \text{ h}^{-1}$ indicating that the urea formation can complete within seconds upon mixing. The substituent on the arene can remotely affect the HUB through electronic effect, thus offering an extra tunability on the K_{eq} and k_{-1} of the bond, which is unprecedented in hindered urea chemistry. The large value of K_{eq} also makes it possible to prepare high molecular weight polymeric aromatic hindered urea materials.

We next studied the hydrolytic product of the aryl tBEU in water-containing solvent. The degradation of the aryl tBEU in *d*⁶-DMSO were analyzed by ¹H NMR. All of the three ureas showed fast degradation kinetics with hydrolysis half-life less than 1.5 hours at 37 °C in 5% water (*v/v*) containing *d*⁶-DMSO (Figure S19), which is 10 times faster than aliphatic HUB under the same condition.^[13] Furthermore, the lowered reactivity of the aryl amines greatly suppresses the formation of stable urea (Figure S20–S22) as the arylamine and secondary amine were the exclusive degradation products observed when the conjugated arene structure is electron deficient (Figure S22).

The hydrolysis of aryl tBEU at different pH values was then studied in 1:1 DMSO-aqueous buffer solution at room temperature (23 °C). An aqueous buffer cocktail with 0.1 M Na_2HPO_4 , $(\text{NH}_4)_2\text{CO}_3$, citric acid, and HCl/NaOH was used to ensure a buffering capacity ranging from pH 3 to 11 and eliminate the potential salt effect on the urea degradation. From HPLC analysis, the degradation of phenyl-tBEU showed remarkably fast degradation throughout all the pH values tested (Figure 1 c) and the

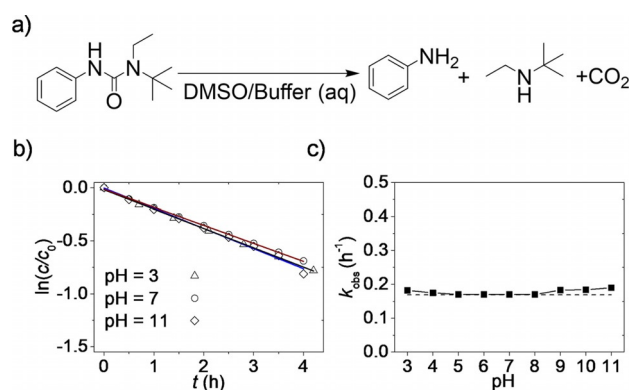


Figure 1. Hydrolysis of phenyl-tBEU in 1:1 DMSO-aqueous buffer at various pH values at room temperature analyzed by HPLC. (a) Chemical structure of Ph-tBEU and hydrolysis product. (b) Selected plot of $\ln([urea]/[urea]_0) - t$ in buffer solution at different pH and linear fittings. (c) Pseudo first-order hydrolytic constant (k_{obs}) of Ph-tBEU. The dotted line marked the measured k_{-1} of the Ph-tBEU through exchange with 20 equivalent *tert*-butyl amine at neutral pH.

observed hydrolysis constant k_{obs} was independent of pH ranging from 3–11 (Figure 1 c). Fitting of the $\ln([urea]/[urea]_0) - t$ revealed a linear relationship ($R^2 > 0.99$), which indicated first-order reaction kinetics (Figure 1 b). More importantly, the apparent hydrolysis constant ($k_{\text{obs}} = 0.17 \text{ h}^{-1}$) turned out to be equal to the k_{-1} of the urea in the same solvent condition (Figure S23), which clearly suggested that the hydrolysis rate of the urea is exclusively determined by the dissociation of HUB instead of the isocyanate hydrolysis. Kinetic analysis of the hydrolytic kinetics (Supporting Information page S5) confirmed that the overall urea degradation rate is determined by the urea dissociation and can be expressed as Equation (1):

$$r(\text{hydrolysis}) = -\frac{d[A]}{dt} = k_{-1} [A] \quad (1)$$

The above equation indicates that the hydrolysis is a first-order reaction and the apparent hydrolysis rate k_{obs} equals to the HAU bond dissociation constant k_{-1} , which matched well with the experimental results.

Polymeric HAU (pHAU) were then prepared to characterize the hydrolytic feature of HAU in polymeric materials. Considering the wide availability of aryl isocyanates and bulky amines, a gigantic library of pHAU structures can be potentially generated by combination of the two components. As a proof of concept, we chose to adopt a simple alternating polymer structure by addition polymerization of methylene diphenyl

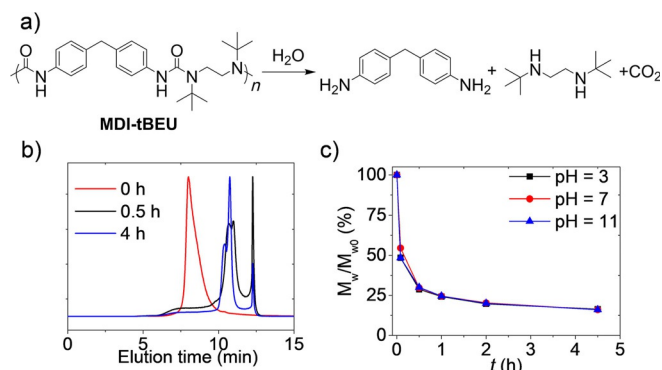


Figure 2. pH-independent hydrolysis of polymeric HAU at different pH values. (a) Chemical structure of degradable linear MDI-tBEU and corresponding degradation product. (b) Representative GPC trace of MDI-tBEU before and after water degradation in THF (5% v/v water content) at room temperature. The spike peak at 12.5 min signals the aqueous content. (c) Relative molecular weight change of MDI-tBEU in 5% buffer-THF solution at room temperature.

diisocyanate (MDI) and *N,N'*-di-*tert*-butyl-ethylenediamine at 1:1 molar ratio (Figure 2a). The polymer was then analyzed by gel permeation chromatography (GPC). Based on the calibration of polystyrene standards, the M_w of the MDI-tBEU polymer was calculated to be 4.5 kDa. In the presence of 5% water (v/v) in THF at room temperature (23 °C), the polymer degraded into less than 50% of the original M_w within 10 minutes (Figure 2b,c), whereas the less bulky *N,N*-diethyl urea showed negligible M_w change under similar conditions (Figure S24). On the other hand, MDI-tBEU polymer was extremely stable under ambient storage condition. We stored the MDI-tBEU powder in a capped scintillation vial at room temperature. No hydrolytic arylamine product was detected according to ^1H NMR analysis over 2 months. (Figure S25).

In summary, we report a class of dynamic hindered aromatic ureas (HAU) as the first example of hydrolysable polymers with pH-independent hydrolytic kinetics. The urea bond dissociation of HAU is two orders of magnitude faster ($k_{-1} > 1 \text{ h}^{-1}$) than the reported aliphatic hindered ureas in organic solvent^[12] and among the fastest dynamic chemistries ever reported. The ureas can be easily prepared within minutes by simple mixing of commercial available aryl isocyanate with bulky secondary amine and they remain stable in powder form under ambient conditions for months while they can be quickly degraded within tens of minutes in solution at pH 3 to 11. The combined features of good stability in solid state and fast hydrolysis at various pH values is unprecedented in such a simple material, which has remarkable implications in materials design and applications such as sacrificial coatings, biomaterials, and surface erosion materials.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: degradable material · dynamic covalent chemistry · dynamic hindered urea · pH independency

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