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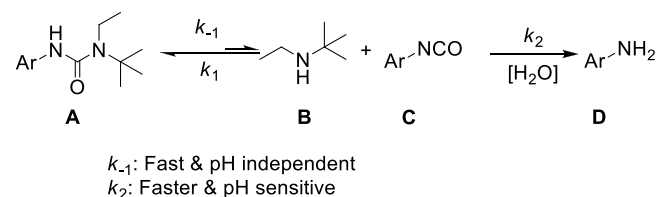# Dynamic Ureas with Fast and pH-independent Hydrolytic Kinetics

Kaimin Cai, Hanze Ying, and Jianjun Cheng*

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 developed so far have pH-dependent hydrolytic kinetics. Here, we report 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 hydrolysis half-life of 10 minutes in solution. More importantly, these fast degradable hindered aromatic polyureas can be easily prepared by addition polymerization from commercially available monomers and 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 is unprecedented in polyurea material, which will have remarkable implications in materials design and applications such as sacrificial coatings and biomaterials.

Hydrolysble 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 materials 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

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         Supporting information for this article is given via a link at the end of the document.

demonstrated to degrade to half the molecular weight within ten minutes at room temperature in solution while 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 isocyanates 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 a faster hydrolytic kinetics, we designed to replace the previous aliphatic isocyanate with aryl isocyanate. Aryl amines, as the degradation product of aromatic hindered ureas, have much lower nucleophilicity than aliphatic amines and generate undesired non-dynamic urea side product[13] that is not well soluble in common solvents.

k_{-1}: Fast & pH independent
k_2: Faster & pH sensitive

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.

We first designed a set of aryl ureas with distinguished electronic effect on the conjugated phenyl ring (Table 1) and studied the corresponding K_{eq} by ^{1}H NMR through exchanging of the urea with a set of bulky amines in *d*-chloroform (Figure S1-S12). 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). All of the three *t*-butyl-ethylureas (tBEU) showed high K_{eq} (> 2×10^4) 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-*t*-butyl amine or *t*-butyl amine (Figure S13-S18) and calculated through linear regression of $\ln\left(\frac{[c_{tBEU}]}{[c_{tBEU}]_0} - A\right)$ -*t*.[12] Remarkably, the amine exchange of the tBEU could reach equilibrium within one hour at room temperature in *d*-chloroform (Figure 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 M^{-1}·h^{-1} indicating that the urea formation can complete within seconds upon mixing. The substituent on the arene can remotely affect the HUB through

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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.

Table 1. Equilibrium constants and dissociation rates of different N-t-butyl-N-ethyl ureas (tBEU) in d-chloroform at room temperature. k_1 is calculated as $K_{eq} \times k_{-1}$. The constant of aliphatic HUB (**4**) was adapted from reference[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(M$^{-1} \cdot$h^{-1})	3.1×10^5	2.7×10^5	1.5×10^7	3.3×10^4

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 ^{1}H 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).
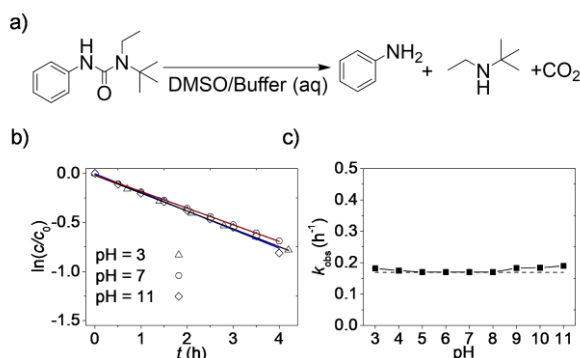

Figure 1. Hydrolysis of phenyl-tBEU in 1:1 DMSO-aqueous buffer with various pH at room temperature analyzed by HPLC. (a) Chemical structure of Ph-tBEU and hydrolysis product. (b) Selected plot of ln ([urea]/[urea]$_0$)-t in buffer solution at different pH and linear fittings. (c) Pseudo first order hydrolytic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

The hydrolysis of aryl tBEU at different pH was then studied in 1:1 DMSO-aqueous buffer solution at room temperature (23 °C). An aqueous buffer cocktail with 0.1 M Na$_2$HPO$_4$, (NH$_4$)$_2$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. As being analyzed by HPLC, the degradation of phenyl-tBEU showed remarkably fast degradation throughout all the pH tested (Figure 1c) and the observed hydrolysis constant k_{obs} was independent of pH ranging from 3-11 (Figure 1c). Fitting of the ln([urea]/[urea]$_0$)-t revealed a linear relationship ($R^2 > 0.99$), which indicated a first-order reaction kinetics (Figure 1b). More importantly, the apparent hydrolysis constant ($k_{obs} = 0.17$ 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 is

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

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

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 well matched 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 diisocyanate (MDI) and N,N'-di-t-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 and 2c) while the less bulky N,N-diethyl urea showed negligible M_w change under the same condition (Figure S24). On the other hand, MDI-tBEU polymer was extremely stable under ambient storage condition. We stored the MDI-tBEU powder in capped scintillation vial at room temperature. No hydrolytic arylamine product was detected according to ^{1}H NMR analysis over 2 months. (Figure S25).
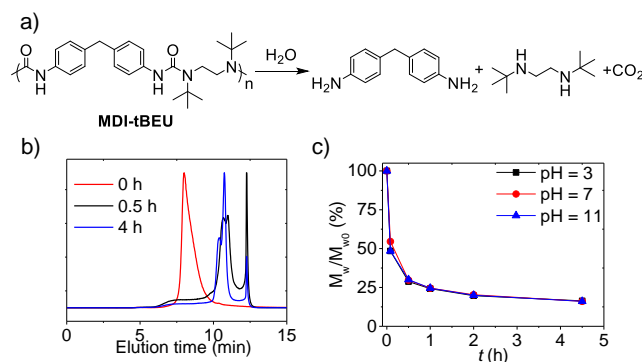

Figure 2. pH independent hydrolysis of polymeric HAU at different pH. (a) Chemical structure of degradable linear MDI-tBEU and corresponding degradation product. (b) Representative GPC trace of MDI-tBEU before and after water degradation in THF (5% v/v water content) at room temperature. The spike peak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

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 order of magnitudes faster ($k_{-1} > 1$ 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 remain stable in powder form under ambient condition 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 is

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unprecedented in such a simple material, which has remarkable implications in materials design and applications such as sacrificial coatings, biomaterials, and surface erosion materials

Conflict of interest

The authors declare no conflict of interest.

Keywords: Dynamic hindered urea • dynamic covalent chemistry • degradable material • pH independency

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A hydrolysable material derived from dynamic hindered urea can hydrolyze rapidly in a pH-independent profile.

Dynamic hindered ureas can hydrolyze consistently fast over a wide range of pH.
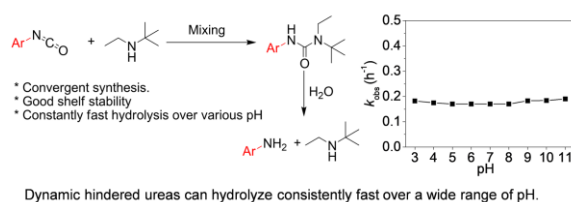
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