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On-Demand Release of Secondary Amine Bases for the Activation of Catalysts and Crosslinkers

Benjamin Spitzbarth[a] and Rienk Eelkema*[a]

Abstract: Dynamic covalent (DCv) ureas have been used abundantly to design self-healing materials. We demonstrate that apart from self-healing materials, the species present in the equilibrium of DCv ureas can be employed as responsive organocatalysts. Easily controllable stimuli like heat or addition of water shift the equilibrium towards isocyanate and free base which can function as an in situ released reagent. We demonstrate this application of DCv ureas with two examples. Firstly, we use the liberated base to catalytically activate a latent organocatalyst for acylhydrazone formation. Secondly, this base can be employed in an equimolar manner to trigger the release of nitrile-*N*-oxides from chlorooximes, which react with acrylate-terminated polymers to form an isoxazoline polymer gel.

Introduction

Dynamic Covalent (DCv) ureas have been shown by the group of J. Cheng to be a versatile motif in the development of reversible and self-healing poly(ureaurethanes).[1] Such dynamic motifs have been extensively used for a wide range of applications in materials, imparting polymer networks with desirable properties like self-healing.[2,3]

Generally, amides (and ureas) are considered to be very stable and are frequently employed as protecting groups in organic synthesis due to their inertness under a wide range of conditions.[4] However, substituting the nitrogen in amides with increasingly bulky substituents weakens the C–N bond due to torsion and therefore reduced conjugation.[5]

The concept of reversible amide, urea and urethane bonds has been widely employed in the form of 'blocked isocyanates' as a procedure to access hyperbranched polyurethanes,[6,7] as well as routes to post-polymerization modifications.[8,9]

Besides these material applications however, DCv ureas have found little use, yet they appear to be attractive dormant base release reagents.

The activation of dormant reagents has previously found some application, for instance in mechanocatalytic polymerization,[10] or the time-controlled pH lowering through the hydrolysis of glucono-δ-lactone.[11] Inspired by these works, the findings in this paper focus on the reversible, as well as irreversible, controlled release of the secondary, bulky amine base present in dynamic urea equilibria and demonstration of its application as a triggering reagent in two different reaction cascades. In addition, we show that under the application of heat as a stimulus, the secondary amine can be used directly as a transient, catalytic species and return to its original, dormant urea state upon removal of the stimulus (Figure 1, Scheme 1A). We demonstrate, by means of triggered catalysis as well as triggered gelation (Scheme 1B, C), the versatility of the DCv urea equilibrium as a starting point for a diverse range of reaction cascades. This concept of using species which are present in DCv equilibria to trigger a reaction cascade opens up new possibilities of making use of an on demand change in chemical reactivity upon a change in conditions.

Results and Discussion

We chose two different reactions to showcase the versatility that such an on demand release system of secondary amines can have. First, secondary amine bases are routinely used to

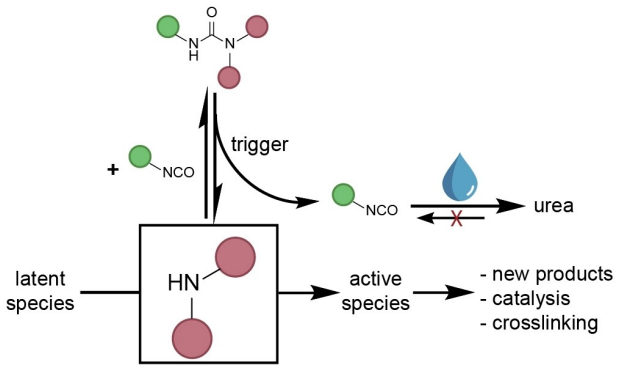

Figure 1. Base present in the equilibrium of DCv ureas can be used to deprotect a blocked organocatalyst. This can happen reversibly under application of heat or irreversibly in the presence of water or alcohols.

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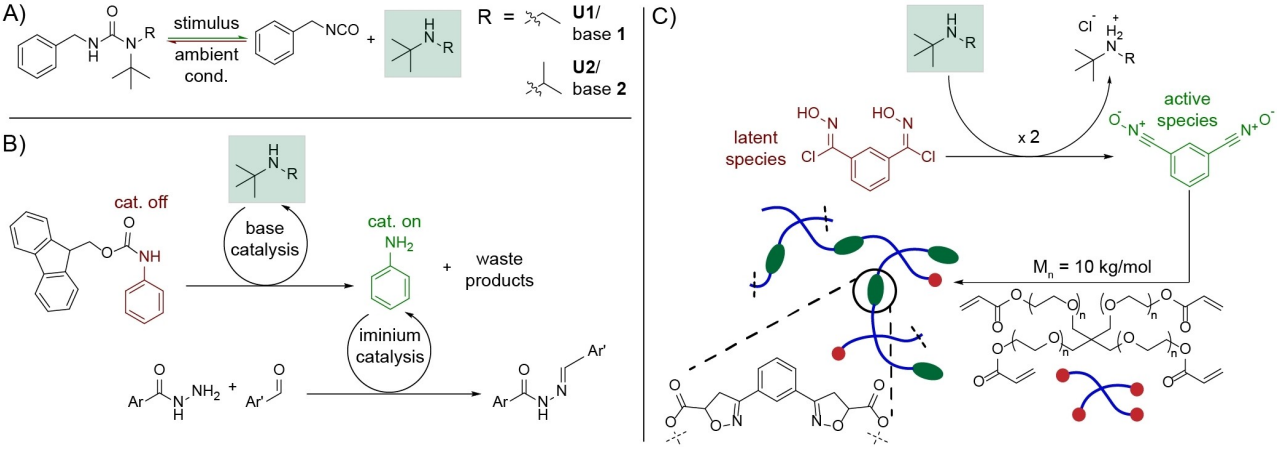


Scheme 1. A) DCv urea equilibrium to release a bulky base. Studied reaction cascades in which **B)** liberated base from DCv ureas **U1** and **U2** is used for the in situ release of aniline which in turn catalyses acylhydrazone formation and **C)** liberated base is used for the in situ generation of nitrile-*N*-oxides which leads to the formation of an isoxazoline gel in the presence of 4-arm acrylates.

remove protecting groups like the base-labile fluorenyl-methyloxycarbonyl (Fmoc) group.[12] This group can be used to block catalytically active species. The Fmoc group is also well known to be cleaved by catalytic amounts of base and has been applied along those lines, such as for the amplification of organic amines.[13] This sets up Fmoc-blocked catalysts as good candidates for a triggered deprotection by the small amounts of base released in the equilibrium of DCv ureas upon heating or addition of water. Potential candidates for reversible blockage by the Fmoc group include nitrogen-bearing catalysts like amines. Compounds such as anilines and pyrrolidine derivatives like proline or indolines, to name a few, have been extensively studied for their catalytic function in iminium- and enamine-catalysed reactions, such as the formation of acylhydrazones from aldehydes and acylhydrazides.[14–19] Hence, we chose to apply DCv ureas as dormant reagents for a triggered Fmoc deprotection, releasing an amine catalyst on demand, which can then catalyse the formation of acylhydrazones (Scheme 1B).

Second, another reaction in which the basicity of the liberated secondary amine bases can be applied is the elimination of hydrogen chloride from chlorooximes to generate highly reactive nitrile-*N*-oxides in situ.[20] This reaction has found widespread use, for example in the recently developed bioorthogonal isonitrile-chlorooxime ligation,[21] or the synthesis of polyisoxazoles via click polymerisation.[22] The reactivity of nitrile-*N*-oxides towards many species like alkenes and thiols makes them an attractive intermediate in reaction cascades for the formation of new species and materials alike.[23,24] We describe their application for the formation of an isoxazoline polymer gel triggered by the in situ release of secondary amine bases, which generate nitrile-*N*-oxides that proceed to form an organogel by crosslinking with a 4-arm PEG acrylate (Scheme 1C).

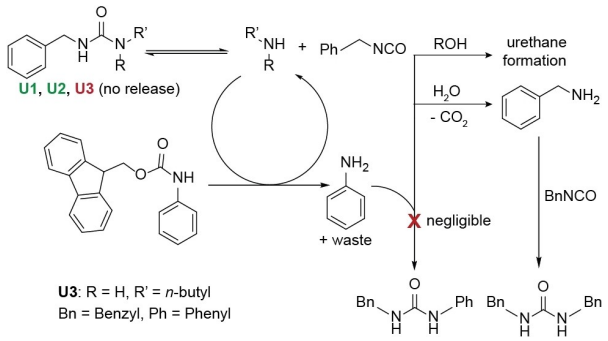
Choice of ureas and triggering conditions

To examine the DCv equilibrium of bulky ureas under varying conditions, small molecule models had to be synthesised and tested. The group of J. Cheng showed that various bulky ureas, for example those based on benzyl isocyanate and two different bulky secondary amine bases, *N*-*tert*-butylethylamine (base **1**) and *N*-*tert*-butylisopropylamine (base **2**), have fast equilibration kinetics (approx. 0.2 h^{-1}, at 37 °C) and a low concentration of free base under ambient conditions (20 °C, $K_{eq} < 10^{-4}$ M^{-1}).[1,25] Furthermore, it was shown that the equilibrium reaction between isocyanate and amine base shows a temperature dependence with Arrhenius-like behaviour,[1] thus making it attractive for a temperature-triggered reversible base release system. The low concentration of free base under ambient conditions is essential to avoid initiating the reaction cascades in the absence of a trigger. One way to irreversibly trigger the release of base is by adding intercepting agents like water or alcohols which react with the generated isocyanate and hence drive the equilibrium towards free base (Scheme 2).

These triggers of applying heat and adding intercepting agents can be combined to tune the time scale and reversibility of the base release.

Triggered Fmoc deprotection for catalyst release

To study the catalyst release, we decided to test whether the Fmoc group is also cleavable under our conditions, yet remains untouched by the miniscule amounts of base present at ambient conditions. We synthesised Fmoc-protected aniline as a model compound, probing the release of aniline via ^{1}H NMR. We chose aniline as a substrate due to its easily trackable chemical shift in the ^{1}H NMR spectra, as well as its low basicity and nucleophilicity. The low basicity avoids the Fmoc-depro-



Scheme 2. The isocyanate released in the DCv urea equilibrium of **U1** and **U2** can react with alcohols to form urethanes and with water to form benzylamine, which can further react to *N,N'*-dibenzylurea. The reaction of the isocyanate with aniline is negligible under these conditions (see S.I., Figure S2). Non-DCv **U3** does not release any amine.

tection becoming self-catalysed and allows us to explicitly study the effect that the free base in the DCv urea equilibrium has without the interference of a potential second base, released in the deprotection step. As potential solvent systems DMSO-d_6 and DMSO-d_6/D_2O (4:1) were tested. The solutions of Fmoc-aniline and the ethyl-based DCv urea **U1** were heated to 40 °C. Indeed, in pure DMSO-d_6, an accumulation of aniline could be observed, driven by the catalytic and fully reversible release of base from DCv urea **U1** (Figure 2B). The free base **1** can recombine with the free isocyanate – which is stable in non-aqueous conditions – upon performing the deprotection step and hence does not accumulate over time. In DMSO-d_6/D_2O (4:1), a more pronounced release of aniline could be observed along with an irreversible accumulation of bulky base **1** (Figure 2C). The irreversible release of base over time in the DMSO-d_6/D_2O-system can be attributed to the hydrolysis and subsequent decarboxylation of the free isocyanate to form benzyl amine and *N,N'*-dibenzylurea, accelerating the further reaction (Scheme 2, Figure 2C).[1] We anticipated that free aniline would also be consumed due to reaction with free benzyl isocyanate to form a non-DCv side product. However, no such side reaction was found, likely due to the much higher reactivity of the benzylamine (Scheme 2 and S.I., Figure S2). Hence, choosing a weakly nucleophilic catalyst also aids in preventing side reactions with the free isocyanate.

These results show that by increasing the temperature as well as adding an intercepting agent, in this case water, the DCv urea equilibrium can be manipulated sufficiently to trigger the Fmoc-deprotection. Under ambient conditions, no such release was observed on the same timescale in both solvent systems. To further demonstrate that the release of aniline truly proceeds due to the presence of base released from the DCv urea species, we synthesised a non-bulky non-DCv urea (*N*-Benzyl-*N'*-*n*-butyl urea) and subjected a solution of this urea **U3** with Fmoc-aniline to the same conditions (see S.I., Figure S6). Indeed, we found no release of aniline over 48 h at 40 °C, offering further proof that the DCv properties of ureas **U1** and **U2** are responsible for the observed release of aniline.

To get more clarity about what role the structure of the free base and the solvent play we studied the influence of the base substituents as well as the effect of adding water to the solvent system on the deprotection rates. The results (Table 1) show that adding D_2O to DMSO-d_6 decreases the reaction rate, while less bulky substituents on the amines increase the rate of aniline release. Specifically, 1-butylamine in pure DMSO-d_6 leads to the fastest release, whereas *N-tert*-butylisopropylamine (base **2**) with its two bulky residues and rotational freedom leads to the slowest release of aniline.

Having understood how the base structure and presence of water influence the rate of the deprotection step, we proceeded to study the effect that varying the bulk on the DCv ureas (ethyl-based DCv urea **U1** versus isopropyl-based DCv Urea **U2**) has on the release of base and aniline over time (Figure 2C, D). While in experiment C (DCv urea **U1**), the base is released more slowly than in experiment D (DCv urea **U2**), the release of cargo still occurs on a similar time scale. This effect is caused by two counteracting influences. Firstly, the equilibrium is shifted towards the urea more strongly in the case of less hindered urea **U1**. Thus, less free isocyanate is present at equilibrium which slows down the irreversible isocyanate hydrolysis, hence releasing the base over a longer time span. Secondly, the Fmoc deprotection proceeds faster with less bulky bases, as can be seen from comparing bases **1** and **2** in Table 1, thus releasing aniline faster than in the presence of equal amounts of a bulkier base. These findings suggest that besides temperature and the presence of water, the bulkiness of the DCv ureas (**U1** and **U2**) can also be used to tune the release kinetics of the cargo.

In Figure 2C, D, it can also be seen that the release of aniline proceeds with an 'activation time', during which the rate at which aniline is released is increasing. For Figure 2B, this initial increase in rate cannot be observed. The presence of this inflection could also be explained by reaction of benzyl isocyanate with released aniline (Scheme 2), however this side reaction was not observed (see S.I., Figure S2).

When plotting the first derivative of the conversion graphs over time (see S.I., Figure S5), a characteristic peak, after which the change in rate decreases, can be seen. We used this peak to define an 'activation time' for the system. This simple method of observing the effect that triggered DCv ureas have on a different reaction offers a way to determine the dynamicity of DCv ureas relative to one another. The different values for the two DCv systems show that the more dynamic urea **U2** leads to a significantly shorter activation time. Since this behaviour cannot be observed for the water-free system (Figure 2B), we

Table 1. Rate constants for the Fmoc-deprotection of Fmoc-aniline with varying bases and solvents, determined via ^{1}H NMR. The rate constants were retrieved by assuming pseudo first order kinetics (see S.I., Figure S1). Conditions: 5 mM Fmoc-aniline, 50 mM base, 40 °C.

Entry	Base, solvent	Rate constant [min^{-1}]
1	1-butylamine, DMSO-d_6	0.81 ± 0.01
2	Base **1**, DMSO-d_6	0.15 ± 0.01
3	2,2,6,6-Tetramethylpiperidine, DMSO-d_6	0.0508 ± 0.0008
4	Base **2**, DMSO-d_6	0.034 ± 0.003
5	Base **1**, DMSO-d_6/D_2O (4/1)	0.062 ± 0.006

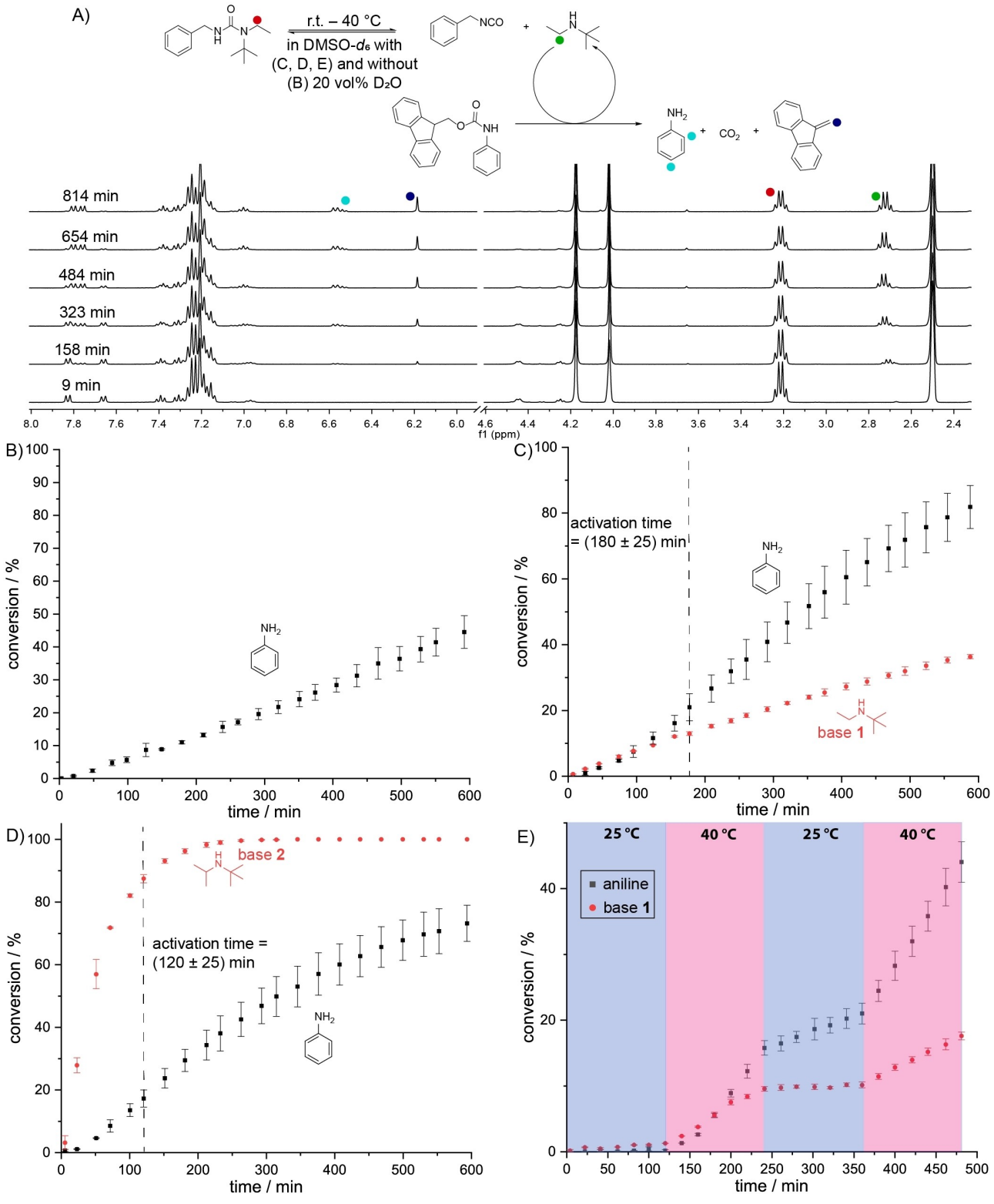


Figure 2. A) Reaction cascade (Scheme 1 B) studied via ^{1}H NMR with application of temperature and water as triggers. **B)** Conversion of Fmoc-aniline (5 mM) to aniline in DMSO-d_6 at 40 °C in the presence of ethyl-based DCv urea **U1** (50 mM). No base release could be observed. **C)** conversion of Fmoc-aniline (5 mM) to aniline and irreversible release of *N-tert*-butylethylamine from ethyl-based DCv urea **U1** (50 mM) in DMSO-d_6/D_2O (4 : 1) at 40 °C. **D)** conversion of Fmoc-aniline (5 mM) to aniline and irreversible release of *N-tert*-butylisopropylamine from isopropyl-based DCv urea **U2** (50 mM) in DMSO-d_6/D_2O (4 : 1) at 40 °C. The dashed line marks the activation time of the DCv systems in C) and D) (see S.I., Figure S5). **E)** conversion of Fmoc-aniline (5 mM) to aniline and irreversible release of *N-tert*-butylethylamine from ethyl-based DCv urea **U1** (50 mM) in DMSO-d_6/D_2O (4 : 1) at varying temperature over time.

hypothesise that the reason for this activation time is the delayed accumulation of base over time. In the water-free environment, only the equilibration between DCv urea and free base, which happens on a relatively fast time scale,[1] is required for the deprotection step to proceed.

In addition, we subjected the aniline release system with DCv urea **U1** to a temperature ramp programme where we varied the temperature between 25 °C and 40 °C (Figure 2E). In an aqueous environment, the accumulation of base is negligible under ambient conditions but leads to an irreversible accumulation at 40 °C. This leads to a great degree of control over the release of precise amounts of base even through a relatively small change in temperature. Furthermore, the release of aniline is also significantly retarded initially. During the first heating cycle, the release of aniline can be observed. However, even after the first heating cycle, the release of aniline continues slowly even under ambient conditions due to the irreversible release of base, which continues to react with Fmoc-aniline to produce aniline.

Triggered acylhydrazone formation

The aniline release system was then applied to the formation of acylhydrazones as a triggered catalysis system (Scheme 1B).[26–28] Specifically, we chose to study the formation of the acylhydrazone formed from benzhydrazide and 4-nitrobenzaldehyde, which has been studied in our group and shown to proceed significantly faster in the presence of aniline.[29] We studied the formation in the absence of catalysts (i.e. background reaction), the direct influence of 100 mol% catalyst (i.e. aniline), the influence of 5 equiv. DCv hindered urea in combination with 100 mol% blocked catalyst (i.e. Fmoc-aniline), the influence of 5 equiv. DCv hindered urea without addition of any (pre-)catalyst and the influence of 100 mol% benzylamine waste product. The results of these studies (Figure 3, Figure S9) show that the addition of aniline as a catalyst significantly speeds up the formation of acylhydrazone over the background reaction, as expected. However, even the DCv hindered urea **U1** by itself speeds up the reaction and a combination of **U1** with pre-catalyst Fmoc-aniline as a triggered release system leads to the largest increase in reaction rate. This surprising result suggests that another catalytically active species must be present or produced in the early stages of the release reactions. While the catalytic action of the aniline that is released from Fmoc-aniline is well understood,[19] we decided to test whether the bulky base **1** released from DCv urea **U1** as well as a simple non-dynamic urea moiety **U3** (i.e. H-bonding catalyst) can also catalyse the acylhydrazone formation. While the non-dynamic urea **U3** showed no formation above background levels (see S.I., Figure S8), the free bulky base **1** showed a catalytic effect on the acylhydrazone formation (Figure 3). This observation explains why the reaction catalysed by a combination of Fmoc-aniline and DCv urea **U1** shows a higher maximum rate than the aniline-catalysed reaction alone.

Furthermore, we found the same phenomenon as the previously defined 'activation time' in the triggered systems

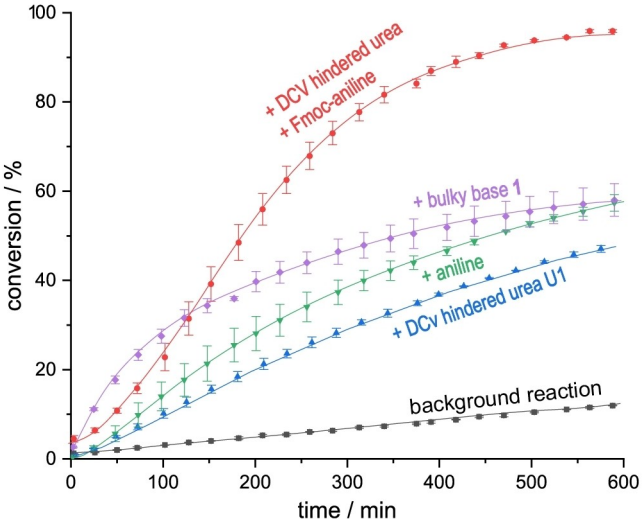


Figure 3. Formation of acylhydrazone from benzhydrazide and 4-nitrobenzaldehyde over time in 4:1 DMSO-d_6/D_2O at 40 °C. Black squares: background reaction between benzhydrazide (10 mM) and 4-nitrobenzaldehyde (10 mM). Green inverted triangles: addition of 100 mol% aniline. Red circles: addition of 5 mM Fmoc-aniline and 50 mM DCv urea **U1**. Blue triangles: addition of 50 mM DCv urea **U1**. Violet squares: addition of 50 mM bulky base **1**. The data points are connected to guide the eye.

where the acylhydrazone formation was tracked. For the system with the addition of the DCv hindered urea **U1** (Figure 3, blue triangles), we observed an activation time of 100 ± 25 min, whereas for the system with the addition of DCv hindered urea **U1** and Fmoc-aniline (Figure 3, red squares), we observed an activation time of 130 ± 25 min, which can be attributed to the delayed release of free bulky base **1** and aniline, respectively. For the aniline-catalysed reaction we observed a relatively short activation time of 50 ± 25 min, attributed to the initial reaction between aniline and 4-nitrobenzaldehyde to form the corresponding imine as a catalytic intermediate. Additionally, we decided to compare the maximum rates of the triggered and non-triggered systems to quantify the differences (Table 2). It can be seen that the triggered aniline-release system shows a roughly two-fold increase in maximum rate of product formation compared to the traditional aniline-catalysed system, whereas it is roughly 12.5-times faster than the background reaction. These findings show that DCv ureas can not only be

Table 2. Maximum rates and activation times of formation of acylhydrazone from benzhydrazide (10 mM) and 4-nitrobenzaldehyde (10 mM) in the presence of different catalytically active species as well as without catalysts (background reaction) in 4/1 DMSO-d_6/D_2O, derived from the conversion graphs in Figure 3. For systems where no initial increase in reaction rate is observed, an activation time is not applicable (N/A).

System	Maximum rate [mM/min]	Activation time [min]
DCv urea **U1** + Fmoc aniline	0.033 ± 0.001	130 ± 25
Bulky base **1**	0.036 ± 0.001	N/A
Aniline	0.017 ± 0.003	50 ± 25
DCv urea **U1**	0.0116 ± 0.0003	100 ± 25
Background reaction	0.00264 ± 0.00003	N/A

used for the triggered release of catalysts protected with the Fmoc-group, but can also enhance traditional catalysis by releasing a second, catalytically active species and increase reaction rates above the rate observed for each individual catalyst alone.

Triggered elimination for the release of nitrile-N-oxides

Next, we use an example in soft material formation to demonstrate the broad application area of DCv ureas as dormant base release reagents. Here, the base eliminates hydrogen chloride from bis-chlorooximes to release nitrile-*N*-oxides in situ. These highly reactive nitrile-*N*-oxides can react with acrylates to form isoxazolines, which we apply as a crosslinking reaction in the formation of a polymer gel (Scheme 1C). To demonstrate this concept, we probed the formation of isoxazolines via ^{1}H NMR spectroscopy in a small molecule test at elevated temperature. The result can be seen in Figure 4A. As base **1** is released from DCv urea **U1**, the formation of nitrile-*N*-oxide starts and leads to the cycloaddition with methyl acrylate, resulting in the formation of the bis-cycloaddition product (orange squares, Figure 4A, in good agreement with literature data for aromatic isoxazolines[30]) over time. The hydrochloride salt of bulky base **1** is among the waste species formed.

To put the concept of the in situ formation of nitrile-*N*-oxides to use, we decided to test the heat-triggered gelation of the generated bisfunctional nitrile-*N*-oxides with tetrafunctional 4-arm PEG acrylates ($M_n = 10$ kg/mol). Tests were performed

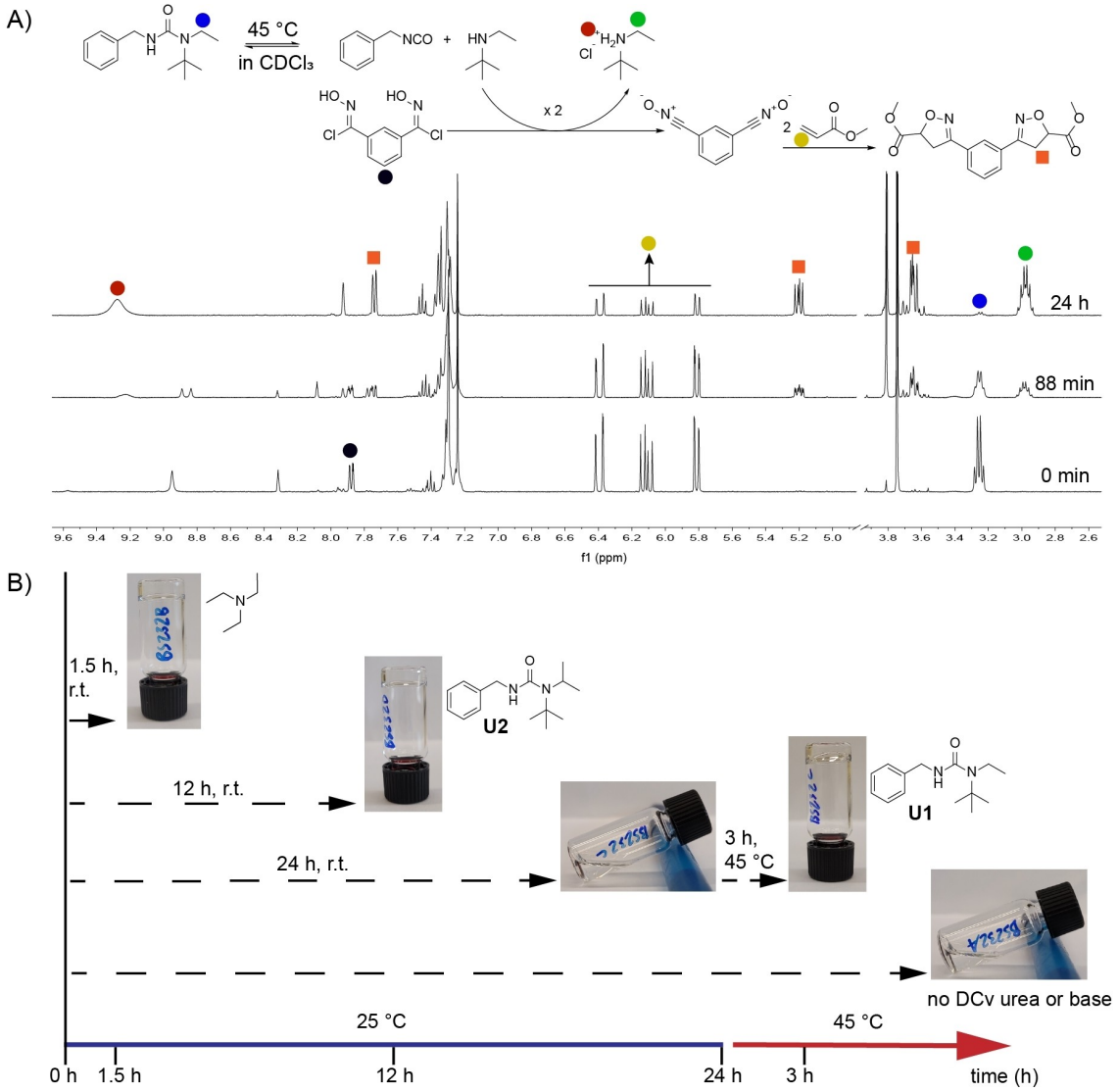


Figure 4. Temperature-dependent gelation of a 5 % w/v solution of bis-chlorooxime (2.0 equiv.) and 4-arm PEG acrylate (1.0 equiv.) in chloroform with the addition of 5 equiv. (1.25 equiv. relative to acrylate and chlorooxime groups) of DCv ureas with different substituents. **A)** Reaction with a small molecule acrylate tracked via ^{1}H NMR, 45 °C, in $CDCl_3$. **B)** Time- and temperature-dependent gelation upon addition of a free base and DCv ureas **U1** and **U2** to bis-chlorooxime.

with the ethyl-based **U1** and *iso*-propyl-based **U2** DCv ureas. The 5% w/v solutions in 9/1 $CHCl_3$/DMSO were kept at room temperature for 24 h and heated to 45 °C thereafter.

Figure 4B shows that the ethyl-based DCv urea **U1** is a good candidate to enable a temperature-triggered gelation via isoxazoline formation. All experiments start with a clear solution of bischlorooxime, additive and 4-arm PEG acrylate. In the case of the *iso*-propyl based DCv urea **U2**, a colourless transparent gel is formed within 12 h at room temperature, whereas in the experiment with the ethyl-based DCv urea **U1**, the solution does not gel under the same conditions even after 24 h. Upon heating the latter sample to 45 °C for 3 h, a transparent gel ultimately forms as well. These findings can be attributed to the different equilibrium constants of the DCv ureas. For DCv urea **U2**, where the equilibrium is more on the side of the free base than for DCv urea **U1**, gelation can occur faster. The reference sample without additives on the other hand remained a colourless solution over weeks. We performed a control by adding triethylamine as a free base to the solution. In this case, we observed gelation within 90 minutes under ambient conditions to form a transparent gel, suggesting that the gelation times can be tuned over a wide range, depending on whether a free base or DCv ureas with varying bulkiness are added to the solution of bischlorooxime and 4-arm PEG acrylate.

Conclusion

We demonstrated that the species present in the equilibrium of DCv ureas can be used in reaction cascades and as organocatalysts on demand. We show that the base released in the urea equilibrium can be applied to 1) catalytically cleave the base-labile Fmoc protecting group, releasing active organocatalysts which in turn catalyse the formation of acylhydrazones above levels found for the free catalyst alone and 2) form highly reactive nitrile-*N*-oxides in situ which can lead to the gelation with acrylates present in solution, forming an isoxazoline polymer gel.

Further, we demonstrated that the temperature- and bulk-dependence of the urea equilibrium as well as the reactivity of the released isocyanate species towards nucleophiles can be employed to tune the urea equilibrium, reversibly and irreversibly, in a way that allows great control over the release of Fmoc-blocked aniline and nitrile-N-oxides on demand.

We envisage that these findings have great potential in the design of responsive materials which possess useful functionalities on demand. Especially the sensitivity of the urea equilibrium at or near body temperature sets these triggered release-systems up for potential uses in biomedical materials.

Our group is currently working on applying these equilibria in crosslinked materials to design triggered, self-healing networks.

Experimental Section

Triggered hydrazone formation: Benzhydrazide (10 mM) and 4-nitrobenzaldehyde (10 mM) were dissolved in 4/1 DMSO-d_6/D_2O. The corresponding catalyst or DCv urea was added and the solution was heated to 40 °C in a water bath and ^{1}H NMR spectra were recorded over time with the probe head heated to 40 °C.

Triggered gelation: 200 μL of a 9/1 $CHCl_3$/DMSO 5% w/v solution of 4-arm PEG acrylate (M_n = 10 kg/mol, 1.0 μmol, 10 mg) and bischlorooxime (2.0 equiv., 2.0 μmol, 0.47 mg) was prepared. 5.0 equiv. triethylamine or DCv urea were added and the solutions were kept at room temperature. Gelation was probed via inverted vial test. After 24 h, the samples were heated in a water bath to 45 °C. A reference sample without base additive was prepared.

Further experimental details, analysis and spectra can be found in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: dynamic covalent chemistry · dynamic covalent urea · latent catalyst · organocatalysis · organogel

[1] H. Ying, Y. Zhang, J. Cheng, *Nat. Commun.* **2014**, *5*, 1–7.
[2] Y. Jin, C. Yu, R. J. Denman, W. Zhang, *Chem. Soc. Rev.* **2013**, *42*, 6634–6654.
[3] J. M. Winne, L. Leibler, F. E. Du Prez, *Polym. Chem.* **2019**, *10*, 6091–6108.
[4] P. G. M. Wuts, T. M. Greene, *Greene's Protective Groups in Organic Synthesis* **2006**.
[5] M. Hutchby, C. E. Houlden, M. F. Haddow, S. N. G. Tyler, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2012**, *51*, 548–551; *Angew. Chem.* **2012**, *124*, 563–566.
[6] T. Shanmugam, A. S. Nasar, *Macromol. Chem. Phys.* **2008**, *209*, 651–665.
[7] R. Spindler, J. M. J. Fréchet, *Macromolecules* **1993**, *26*, 4809–4813.
[8] K. A. Günay, P. Theato, H. A. Klok, *J. Polym. Sci. Part A* **2013**, *51*, 1–28.
[9] M. S. Rolph, A. L. J. Markowska, C. N. Warriner, R. K. O'Reilly, *Polym. Chem.* **2016**, *7*, 7351–7364.
[10] R. T. M. Jakobs, S. Ma, R. P. Sijbesma, *ACS Macro Lett.* **2013**, *2*, 613–616.
[11] D. J. Adams, M. F. Butler, W. J. Frith, M. Kirkland, L. Mullen, P. Sanderson, *Soft Matter* **2009**, *5*, 1856–1862.
[12] L. A. Carpino, G. Y. Han, *J. Org. Chem.* **1972**, *37*, 3404–3409.
[13] K. Arimitsu, M. Miyamoto, K. Ichimura, *Angew. Chem. Int. Ed.* **2000**, *39*, 3425–3428; *Angew. Chem.* **2000**, *112*, 3567–3570.
[14] P. M. Pihko, I. Majander, A. Erkkilä, *Top. Curr. Chem.* **2009**, *291*, 29–75.
[15] A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470.
[16] Y. Zhou, I. Piergentili, J. Hong, M. P. van der Helm, M. Macchione, Y. Li, R. Eelkema, S. Luo, *Org. Lett.* **2020**, *22*, 6035–6040.

[17] F. Trausel, C. Maity, J. M. Poolman, D. S. J. Kouwenberg, F. Versluis, J. H. Van Esch, R. Eelkema, *Nat. Commun.* **2017**, *8*, 1–7.
[18] M. P. van der Helm, B. Klemm, R. Eelkema, *Nat. Chem. Rev.* **2019**, *3*, 491–508.
[19] D. K. Kölmel, E. T. Kool, *Chem. Rev.* **2017**, *117*, 10358–10376.
[20] D. Cerniauskaite, J. Rousseau, A. Sackus, P. Rollin, A. Tatibouët, *Eur. J. Org. Chem.* **2011**, 2293–2300.
[21] R. Schaefer, M. R. Monaco, M. Li, A. Tirla, P. Rivera-Fuentes, H. Wennemers, *J. Am. Chem. Soc.* **2019**, *141*, 18644–18648.
[22] T. Matsumura, Y. Koyama, S. Uchida, M. Yonekawa, T. Yui, O. Ishitani, T. Takata, *Polym. J.* **2014**, *46*, 609–616.
[23] M. H. Benn, *Can. J. Chem.* **1964**, *42*, 2393–2397.
[24] Y. G. Lee, Y. Koyama, M. Yonekawa, T. Takata, *Macromolecules* **2009**, *42*, 7709–7717.
[25] H. Ying, J. Cheng, *J. Am. Chem. Soc.* **2014**, *136*, 16974–16977.
[26] C. Maity, F. Trausel, R. Eelkema, *Chem. Sci.* **2018**, *9*, 5999–6005.
[27] W. Xi, M. Krieger, C. J. Kloxin, C. N. Bowman, *Chem. Commun.* **2013**, *49*, 4504–4506.
[28] G. Li, F. Trausel, M. van der Helm, B. Klemm, T. Breve, S. van Rossum, M. Hartono, H. Gerlings, M. Lovrak, J. van Esch, R. Eelkema, *Angew. Chem. Int. Ed.* **2021**, *60*, 2–10; *Angew. Chem.* **2021**, *133*, 2–2.
[29] F. Trausel, B. Fan, S. A. P. van Rossum, J. H. van Esch, R. Eelkema, *Adv. Synth. Catal.* **2018**, *360*, 2571–2576.
[30] Y. Iwakura, S. Shiraishi, M. Akiyama, M. Yuyama, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1648–1653.

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