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Spitzbarth, Benjamin; Eelkema, Rienk

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Review

Properties and applications of dynamic covalent ureas

Benjamin Spitzbarth¹ and Rienk Eelkema^{1,*}

SUMMARY

Dynamic covalent (DCv) ureas are highly diverse chemical moieties and have become one of the most used motifs in self-healing materials and beyond. This review summarizes the historical development, properties, and applications of DCv ureas in different fields of organic chemistry, materials chemistry, and biomedical applications and provides guidance on the design of different DCv ureas depending on stability and dynamicity requirements.

INTRODUCTION

Dynamic covalent chemistry (DCvC) has taken major strides over the last few decades.¹ The key characteristic of DCv bonds is that they undergo exchange reactions under relatively mild conditions, allowing covalent bonds, which are typically stable, to undergo exchange reactions.^{2–4} This feature leads to interesting applications such as in malleable, recyclable, and self-healing materials, dynamic combinatorial libraries, and more.^{1,5–9} Some of the bonds that are typically utilized in DCvC are Diels-Alder adducts,¹⁰ boronic esters,¹¹ and disulfides.¹² Unlike some species such as Diels-Alder adducts, DCv ureas (Scheme 1) exhibit self-healing under exceptionally mild conditions near room temperature,¹³ offering a valuable addition to the toolkit of DCvC. Apart from exhibiting self-healing near room temperature, the commercial availability of their starting materials, their ease of synthesis, and their chemical nature make them stand out in the field of DCvC, which is why they have received increased attention over the last 10 years, starting with pioneering efforts from the group of J. Cheng.¹³

The aim of this literature review is to offer a comprehensive guide to understand how DCv ureas were developed, where their strengths and challenges lie, and how they are applied today. We will conclude by offering our view on how researchers can use DCv ureas' properties for future directions of research into this emerging field of DCvC. For a more specific overview over how DCvC based on isocyanates can be used in a material context, the reader shall be directed to reviews by N. Zhao et al.¹⁴ and Z. Wang and H. Xia et al.¹⁵

HISTORICAL CONTEXT

The history of urea dates to the founding fathers of organic chemistry, Friedrich Wöhler and Justus von Liebig. They had already discovered feasible, albeit harsh, routes of how urea can degrade, under the influence of nitrous acid, in the early 19th century.¹⁶ In 1893, it was found that aromatic ureas release their corresponding isocyanates upon heating above their melting point.¹⁷ The first tangible findings, however, which indicate that ureas, as well as thioureas, are in equilibrium with their corresponding isocyanates (or isothiocyanates, respectively) and amines upon heating, were shown in 1922.¹⁸ This was demonstrated by heating crude urea and aniline,

¹Department of Chemical Engineering, Delft University of Technology, Van der Maasweg 9, Delft 2629 HZ, the Netherlands

*Correspondence: r.eelkema@tudelft.nl
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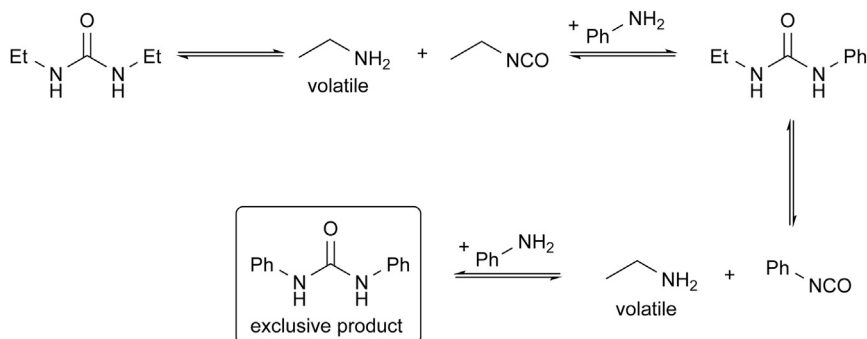
Scheme 1. General equilibrium of a DCv urea species with its corresponding isocyanate and primary or secondary amine

Where the equilibrium lies depends majorly on the nature of substituents, solvent, and conditions.

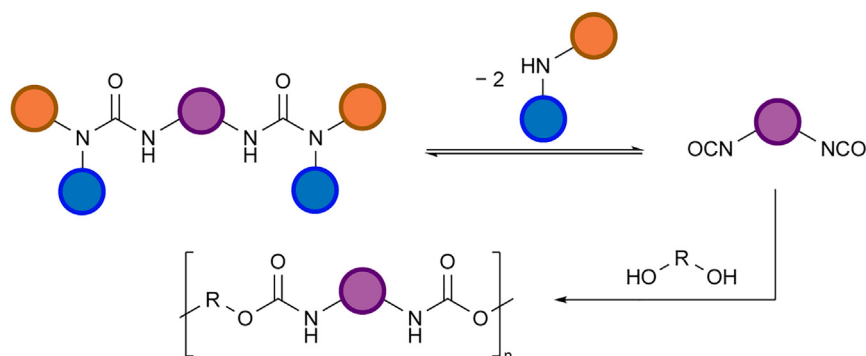
yielding phenylurea at 160°C. It was concluded that this transformation is possible due to the reaction of aniline with isocyanic acid present in urea's dissociative equilibrium. Further studies revealed that these transformations also take place in boiling water, yielding phenylurea and *sym*-diphenylurea from urea and aniline hydrochloride while expelling ammonia from the solution.¹⁹ Asymmetrically substituted *N,N'*-alkyl-aryl ureas were found to dissociate exclusively into isocyanic acid and secondary amines, and the presence of an excess of amines did not yield tetrasubstituted ureas, corroborating the hypothesis that free isocyanates are part of the transformation. Importantly, it was found that the product formation can be controlled via the volatility of the released species. Heating diethylurea with aniline will progressively yield *N,N'*-ethylphenylurea and *sym*-diphenylurea, respectively.¹⁹ While *N,N'*-ethylphenylurea can, in principle, dissociate via two pathways, the exclusive formation of *sym*-diphenylurea was observed due to the higher volatility of ethyl amine, escaping the solution (Scheme 2).

Further studies to investigate the lability of ureas with varying substitution degrees, substituent properties, and solvent properties to elucidate the kinetics of the involved dissociation processes were undertaken in the 1950s by T. Mukaiyama and co-workers.^{20–25} While previous examples demonstrated the dissociation of non-hindered ureas under harsh conditions, these studies began to show that hindered ureas dissociate into their isocyanates and amines under relatively mild conditions, with a strong dependence on the bulkiness of the substituents. Further studies in the 1970s corroborated these discoveries with findings that ureas²⁶ and semicarbazides²⁷ with hindered substituents dissociate appreciably into isocyanates and the corresponding amines or hydrazines, respectively, even at room temperature. Stowell and Padegimas generalized these findings in 1974 to derive a method of estimating sterical hindrance of secondary amines by observing the dissociation equilibria of the corresponding ureas formed with 2,6-dimethylphenylisocyanate.²⁸

The first industrial applicability for ureas' dissociation properties came with the advent of "blocked isocyanates." Isocyanates are extremely versatile reagents and



Scheme 2. When *sym*-diethylurea is heated with aniline, *sym*-diphenylurea will form exclusively due to the dynamic nature of all species involved and the higher volatility of ethylamine



Scheme 3. The use of blocked isocyanates as pioneered by A. Sultan Nasar and colleagues

A DCv urea made from secondary aromatic amines and a bis-functional aromatic isocyanate can release the isocyanate upon heating, leading to a curing reaction with a diol, forming polyurethanes without the direct need for isocyanates.³²

are widely used in academia and industry.^{29,30} However, due to their high reactivity and long list of health concerns,³¹ it is generally desirable to work with reagents that can release isocyanates on demand. While blocked isocyanates have been reviewed elsewhere in depth,²⁹ ureas, which may in this context be referred to as “amine-blocked isocyanates,” comprise a notable subclass of these compounds. The introduction of ureas as a further group of compounds that are labile enough to release isocyanates widened the accessible conditions for polymerization reactions involving blocked isocyanates. Among the first examples of studies investigating the feasibility of DCv ureas for their application in curing reactions of polyurethanes are the works by A. Sultan Nasar and co-workers in 1999 and the years thereafter (Scheme 3).^{32–34}

More recently, the group of J. Cheng pioneered the detailed investigation of hindered ureas in a different context, going beyond their usage as a synthetical or polymerization starting point and exploiting their reversibility for material/self-healing applications.¹³ This quest for the application of the desirable properties of DCv (hindered) ureas in a material context has sparked research into and the development of a whole range of interesting materials and other uses in recent years, which will be discussed in detail.

PROPERTIES OF DCv UREAS

Stability trends and reactivity

In general, amides and ureas are known to be highly stable functional groups, and degradation is usually achieved only under prolonged heating in strongly acidic or basic conditions.^{28,35} However, both can be envisioned to dissociate into ketenes and amines or isocyanates and amines, respectively.¹³ These unfavorable reaction pathways require structural manipulations to make them more feasible. One of the key factors leading to the high stability of amides and ureas is the conjugation of the nitrogen lone pairs with the carbonyl centers. Partly breaking this conjugation under loss of coplanarity and endowing the carbonyl center with more ketone-like properties enable a fast and efficient degradation. For urea itself, such a dissociation requires harsh conditions,¹⁶ while for tetrasubstituted ureas, this dissociative pathway is not possible due to the absence of a proton that can be transferred during the dissociation step. Alkyl-substituted species are still highly stable species, which require harsh conditions to dissociate, while aryl-substituted ureas dissociate more easily into the resonance-stabilized isocyanates and amines.^{17,19} The species

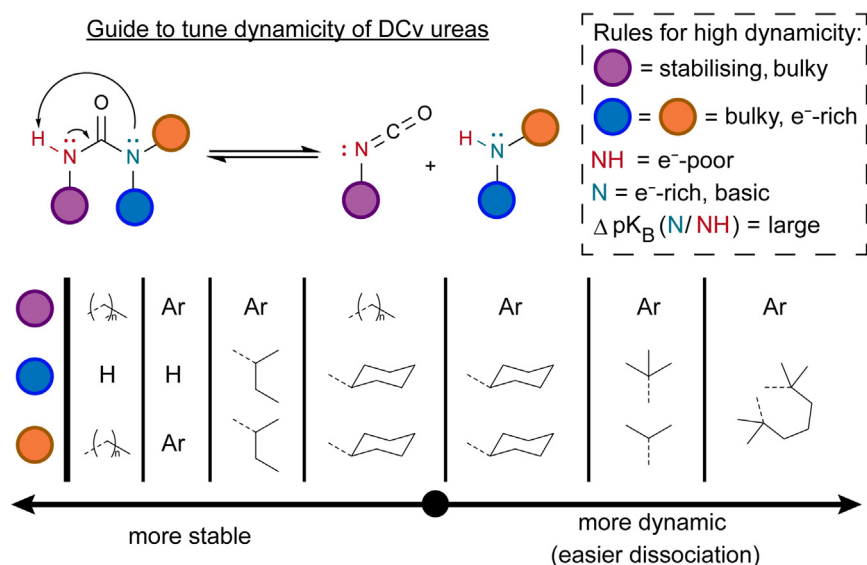


Figure 1. Stability of urea derivatives with different substitution patterns and general guidelines to design a DCv urea with high lability (i.e., easy dissociation)

With decreasing stability from left to right in the table, the ease of the DCv urea's dissociation and the basicity of the free base increase. While for non-hindered ureas (first 2 entries, left to right), resonance stabilization of the species plays a big role, for hindered ureas, the bulkiness, and hence torsion, of the C–N bond plays a more important role.

that dissociate most easily into isocyanates and amines are trisubstituted ureas with sterically highly demanding substituents (Figure 1).

For the first two non-hindered urea derivatives in Figure 1, resonance stabilization of the fragments plays an important role. Aromatic amines and isocyanates are more stable, and hence the corresponding ureas dissociate more readily than aliphatic ones. For hindered ureas, steric bulk is one of the key factors that influence urea stability. An especially noteworthy observation is the large difference in stability between bis-secondary (e.g., N,N-ethyl-iso-propyl) ureas and secondary-tertiary (e.g., N,N-ethyl-tert-butyl) ureas.^{13,28} Introducing tertiary alkyl groups has a large impact on the stability of the hindered urea. Furthermore, the basicity of the urea nitrogen atoms is important in estimating stability. Generally, a more basic secondary amine—assuming similar steric hindrance—will form less stable ureas, as the more basic nitrogen will facilitate the proton transfer required for the dissociation process to take place. Similarly, the difference of basicity between the two nitrogen atoms plays a role as well, as a less basic NH moiety will further facilitate proton transfer to a highly basic NR₂ unit.²³ The general rules, in order of decreasing influence, to design a highly dynamic urea would hence be as follows.

- (1) Choose trisubstituted ureas over mono- and disubstituted species (tetrasubstituted ureas are not dynamic).
- (2) Use a highly basic, sterically demanding secondary amine with at least one tertiary substituent.
- (3) Pick a resonance-stabilized, electron-deficient isocyanate (ideally hindered, e.g., 2,6-dimethylphenylisocyanate²⁸).

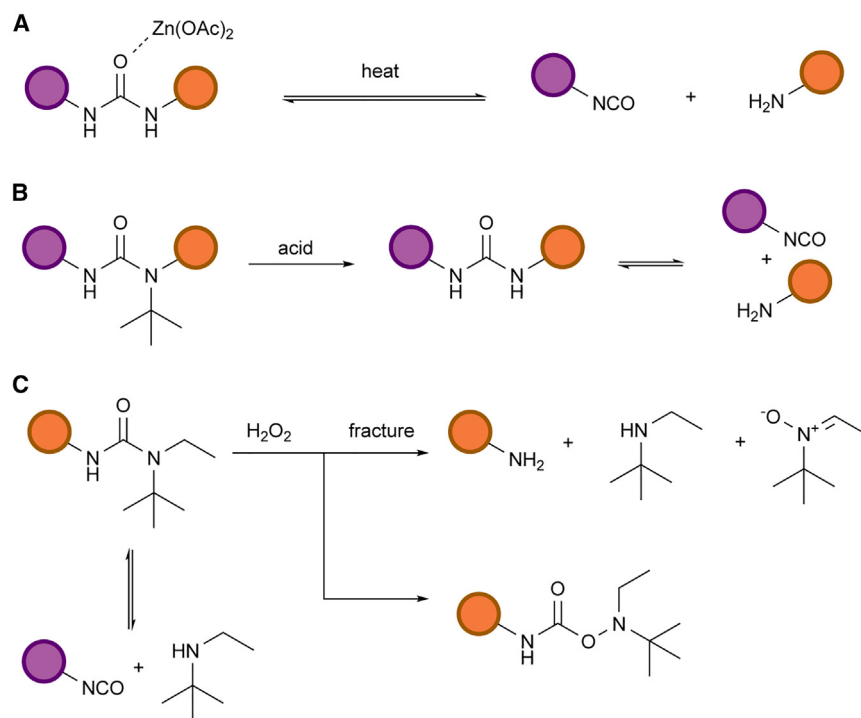
These general guidelines (Figure 1, top right) enable researchers to design urea structures meeting a wide range of stability and dynamicity demands.

However, as basicity and steric hindrance of an amine do not always go hand in hand, there are some exceptions to the generally expected stability trends. Padegimas and Stowell used the E_s values (steric substituent constants) of the Taft equation to define the expected trends of urea stability. They found that, in line with E_s values, amines with the sterically more demanding 3-pentyl group form ureas with 2,6-dimethylphenylisocyanate more slowly than amines with a cyclohexyl residue. On the contrary, their dissociation follows the inverse trend, showing a slower dissociation for the 3-pentyl-substituted urea than for the cyclohexyl substituted urea.²⁸

To offer some more concrete data to the reader on the stability range of DCv ureas showcased in Figure 1, some equilibrium constant (K_{eq}) values from the pioneering work of Cheng and colleagues will be given.¹² In their initial work, they studied the exchange of bases in different DCv ureas via nuclear magnetic resonance (NMR) spectroscopy. Species with the highly bulky 2,2,6,6-tetramethylpiperidinyll base show very low stabilities with a K_{eq} of 88 M^{-1} . These highly dynamic DCv ureas were found to be too labile for use in the materials. Of special note, the stability of *tert*-butyl-*iso*-propyl-based DCv ureas ($5,600 \text{ M}^{-1}$) was found to increase by over two orders of magnitude by the removal of a single methyl group to yield *tert*-butyl-ethyl-based DCv ureas with a K_{eq} of $79,000 \text{ M}^{-1}$. Even more significantly, the isomeric di-*iso*-propyl-based DCv urea shows a K_{eq} of $>10^7 \text{ M}^{-1}$, demonstrating the importance of the *tert*-butyl group in destabilizing the urea bond.¹² The isocyanate unit, on the other hand, seems to offer less control over the K_{eq} of DCv ureas than the base moiety does. These values, combined with the general rules given above, can be used by the reader to get a rough idea of the stability range that DCv ureas can offer. While most recent publications involve highly hindered DCv ureas due to their significant dissociation under ambient or near-ambient conditions and the interesting properties that come with this dynamicity, there are some notable examples of non-hindered DCv ureas. Aromatically trisubstituted ureas have been extensively employed as amine-blocked isocyanates for polymerizations.^{32,33} Typically, these DCv ureas can cure in polymerization reactions with de-blocking temperatures of roughly 120°C – 150°C .

Recently, the group of Hesheng Xia explored different ways of making non-hindered ureas more dynamic. They found that disubstituted aliphatic ureas, which are highly stable under ambient conditions, can undergo exchange reactions via a dissociative pathway in the presence of zinc acetate at elevated temperatures (70°C – 90°C).³⁶ The formation of an O-bound zinc complex accelerates the dissociation of these urea species by several orders of magnitude (Scheme 4A). This is a significant finding, as it widens the scope of urea motifs that can be used for applications in which fast exchange kinetics are required. In another recent work, the group discovered that near-infrared (NIR) irradiation of urea-based networks can enable self-healing of these polymers.³⁷ It is hypothesized that the high, localized heat generation from the NIR radiation as well as entropy changes in the polymer system favor the dissociation of the stable urea bonds, leading to a temporary depolymerization of the network.

On the contrary, Cheng and colleagues have recently introduced a strategy to “switch off” the dynamic behavior of DCv ureas carrying a *tert*-butyl group on one of the nitrogens.³⁸ By adding acid, the *tert*-butyl group of the dynamic urea can be removed, forming a non-dynamic urea moiety (Scheme 4B). This on-demand off switch for the dynamicity of different DCv ureas could dramatically widen their applications by increasing the stability of the material when needed.



Scheme 4. Reactivity of DCv urea units under different conditions

(A) Despite not showing dynamic behavior under standard conditions, aliphatic ureas can undergo dissociative exchange in the presence of zinc catalysts.³⁶

(B) Dynamic ureas carrying a *tert*-butyl group can be turned into non-DCv ureas via de-*tert*-butylation in the presence of acid.³⁸

(C) DCv ureas show different reactions in the presence of hydrogen peroxide, leading to both non-reversible fracture as well as permanent fixation of the bond.³⁹

Another interesting feature of DCv ureas is their reactivity toward hydrogen peroxide. While perhydrolysis of the free isocyanate in the urea's equilibrium leads to bond fracture, oxidation of the amine can lead to formation of a urethane-like product, which does not show dynamic behavior (Scheme 4C).³⁹ It was, however, not possible to achieve control over which pathway dominates.

The previous examples focused exclusively on the reactivity of DCv ureas in a dissociative fashion, forming a free isocyanate and amine in the reaction. However, a far less common associative pathway is also possible. In 1992, it was found that aryl-substituted ureas undergo a second-order nucleophilic substitution at the carbonyl center of the urea via the attack of primary or secondary amines and subsequent displacement.⁴⁰ This method works especially well with monosubstituted ureas, as the steric hindrance for the nucleophilic attack is minimal and the released ammonia can easily be expelled from the solution due to its high volatility. While this work technically does not fall into the realm of DCvC due to the non-reversibility of the process, it is worth mentioning, as it provides an easy synthetic route to substituted ureas and proceeds via an associative pathway, which will be discussed more in depth at a later point.

Challenges and limitations

While DCv ureas are applicable under a wide range of conditions and in a wide range of solvents, there are some factors that do need to be considered when working with these compounds. One of the downsides is the use of isocyanates in the synthesis of

DCv ureas. They are highly toxic compounds, leading to many chronic health issues.³¹ While their use during synthesis can be handled safely, the presence of free isocyanates in the equilibrium of DCv ureas may limit their area of applications. The high reactivity of isocyanates presents another, more practical challenge. DCv ureas have been shown to be labile toward solvolysis, for example in water or alcohols, due to the degradation of isocyanates.^{41–43} This feature can, however, also be a desirable behavior, leading to new applications such as solvent-triggered release systems (see below). Another potential limitation is the relatively high oxidative lability of the secondary amines present in the DCv urea equilibrium. We have observed in our laboratory the discoloration of highly dynamic ureas upon prolonged storage, due to the degradation of both amine and isocyanate, as observed in ¹H-NMR spectroscopy.

DCv urea network properties and requirements

The properties of DCv urea networks mostly reflect their molecular properties. As previously indicated, the exchange mechanism of DCv urea is typically dissociative in nature.¹³ There is, however, a limited number of examples of associative DCv urea networks.^{44,45} This expands the application scope of DCv ureas further, as it allows access to dissociative as well as vitrimer networks (i.e., networks with a constant crosslinking density throughout the whole self-healing process). Apart from the small number of vitrimer-like DCv urea networks, typical requirements for dissociative DCv urea networks with good stability, reprocessability, self-healing, and malleability are a large K_{eq} , as well as fast kinetics of both the dissociation and association processes.¹³ This means that the exchange process must be fast, and the equilibrium of the dissociation process must be mostly on the side of the urea, not the isocyanate and amine, to construct a useable material. As discussed above, the dynamicity can be regulated relatively easily by changing the sterical demand of the amine in the DCv equilibrium.^{13,46} It was found that sterically more demanding amines lead to a decrease in flow temperature of the networks, as well as a lower degree of connectivity and hence improved self-healing in the order of ethyl-, *iso*-propyl-, *tert*-butyl-, and tetramethylpiperidinyl-based substituents.⁴⁶ Another important factor that can influence the properties of DCv urea networks is the concentration of DCv urea bonds in the network. It was found that, typically, >50% of DCv urea bonds (in urea-urethane networks, i.e., as a fraction of urea bonds compared to all functional groups) is needed to allow for good self-healing, whereas <50% of DCv urea bonds leads to suboptimal reprocessability.⁴⁷

APPLICATIONS

Materials

Due to their dynamic exchange reactions, the most widespread application of DCv ureas is in self-healing materials. When damage, such as scratches, cuts, or generally any mechanical failure, is inflicted upon the material, the DCv urea moieties near the interfaces at the site of damage can exchange between those interfaces, leading to a healed material (Figure 2).

Since the introduction into this field in 2014 by the group of J. Cheng, many works exploring the scope of these materials have been published. Typically, a large part of recent research focuses on improving the mechanical characteristics such as malleability, as well as the recyclability of these materials.^{48–50} These findings have significantly improved the diversity and properties of DCv urea materials and expanded their accessibility by exploring different, commercially available monomers. A common example of where DCv urea materials can find applications is in self-healing clear coats. In one example, a self-healing clear coat, containing DCv

General principle of self-healing DCv-urea-based materials

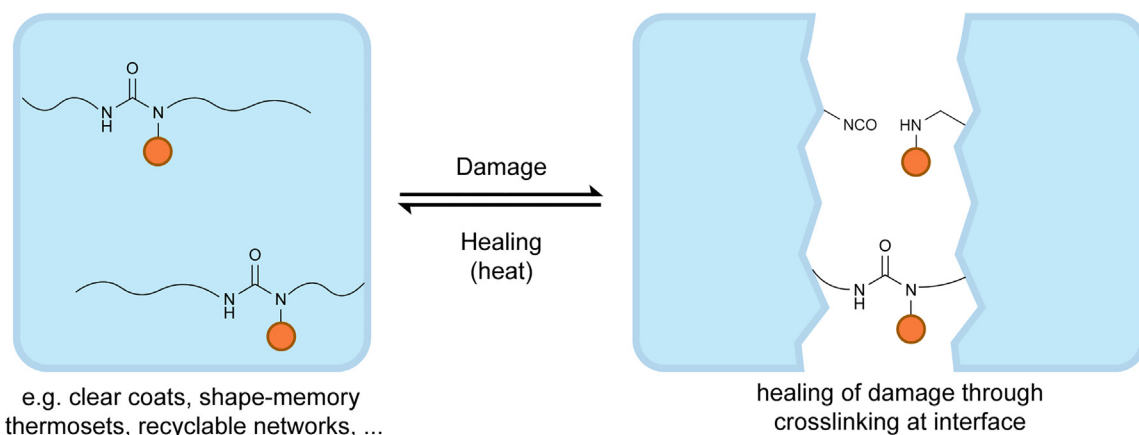


Figure 2. General principle of self-healing materials based on DCv ureas

Exchange reaction between interfaces lead to the material growing back together and recovering its initial mechanical properties.

ureas and a polysiloxane, was fabricated.⁵¹ While the DCv urea moieties endowed the clear coat with its self-healing properties, the polysiloxane offered self-cleaning properties such as repellence of water, oil, and ink. In addition, the clear coat showed excellent optical and mechanical properties. In other examples, DCv ureas were incorporated into polycarbonates and polyurethanes to make clear coats with applications such as automotive coatings.^{52,53}

Further, in one instance, silver nanowires were incorporated into a self-healing DCv urea network, which allowed for healable and stretchable electrodes.⁵⁴ Upon cutting the electrode in half, the team demonstrated that it can be reused within 30 min of healing at 60°C.

In another work, hindered urea bonds were incorporated into shape-memory thermosets, based on poly(urea-urethane) polymers.⁵⁵ Not only did this endow the original shape-memory thermoset with self-healing properties, but it also endowed the material with triple-shape-memory performance under very mild conditions without the need for conventional curing in a mold. The DCv urea units play a crucial role in the shape-memory process, as they can fix the polyurethane network in a different topological shape at an elevated temperature by rebonding and then revert to the original shape by reheating the sample, leading to full relaxation of the strained DCv urea bonds.

Despite their degradability in aqueous conditions, advances were also made in applying DCv urea polymers as self-healing tubes for flowing water.⁵⁶ It was shown, while flowing water with a temperature of 37°C, that tubes that were scratched showed self-healing behavior upon wetting the scratched area. The group explained this behavior with the formation of free isocyanate units that can hydrolyze and react with further free isocyanate to form non-DCv ureas, thus making the tubes water adaptive.

Encapsulation and delivery of biological cargo

Besides these more material-focused works, further advances were made in the fields of drug as well as stem cell delivery. Here, the hydrolysis of the isocyanate from the DCv urea's equilibrium plays a crucial in controlling the degradation

kinetics of the encapsulation matrix. In one instance, a hindered urea-based polymer was pegylated on both chain ends to form micelles, which could incorporate the chemotherapy drug paclitaxel.⁵⁷ The group demonstrated the entry of these drug-loaded micelles into breast cancer cells in mice and subsequent inhibition of tumor growth. The tuneable release kinetics of these micelles by variation of the DCv urea structure may present further interesting applications in the field of controlled drug release. In another example, crosslinked hydrogels containing hindered urea bonds were prepared and loaded with stem cells. The networks were found to be biocompatible, and the hydrolytic release of these cells could be tuned over 5 days by changing the structure of the DCv ureas.⁵⁸

Catalysis

In our group, we recently showed that DCv ureas can also be applied as latent catalysts and reagents. The concentration of the free base present in the equilibrium of hindered ureas can be raised by increasing the temperature to 45°C or adding water to induce isocyanate hydrolysis. This effectively creates a temperature- and solvent-triggered base release system. We show that this base can be used catalytically to release Fluorenylmethoxycarbonyl-protected aniline, which can in turn catalyze the formation of acylhydrazones. The action of aniline as well as bulky base in response to heat or solvent greatly enhance the formation of acylhydrazones over the background reaction. Further, we showed that DCv ureas can be used to release highly reactive nitrile-*N*-oxides from chlorooximes via the elimination of hydrogen chloride. These nitrile-*N*-oxides can undergo cycloadditions with tetrafunctional acrylates to form organogels in response to a thermal stimulus. In addition, the bulkiness of the DCv urea can be used to tune the gelation kinetics.⁵⁹

Synthesis

DCv ureas have also been used as precursors in several synthesis procedures. Recently, the group of J. Cheng has demonstrated the first high-yielding synthesis of macrocycles with high reaction concentrations, utilizing *tert*-butyl-substituted hindered ureas as the template.⁶⁰ Further, unsymmetrical ureas can be synthesized by reacting primary or secondary amines with phenylurea, displacing ammonia in the process.⁶¹ The solvolysis of DCv ureas, discussed as one of the downsides above, can also be utilized as a synthetic procedure. Alcohols can be carbamoylated efficiently in the presence of DCv ureas under mild conditions without the need for free isocyanates.⁴³ Lastly, low-boiling isocyanates can be generated via distillative removal from the equilibrium of DCv ureas under heating.^{62,63}

Urea-derived DCv bonds

The increased attention that DCv ureas have received over the last years has also led to the development of other, urea-derived DCv bonds. Among these are pyrazole-blocked isocyanates,^{64,65} imidazole-blocked isocyanates,³⁴ polyacylsemicarbazides,^{66,67} DCv thioureas,^{68,69} and isoureas used for their ability to generate radicals during their bond cleavage.⁷⁰ These bonds enable the expansion of the stability range of traditional DCv ureas, as shown in Figure 1, even further and allow for fine-tuning of dynamic behavior over a wide temperature range.

CONCLUSION AND OUTLOOK

The field of DCvC has made large strides over the last few decades and continues to gain importance with the rising need for more sustainable materials that show properties such as reprocessability and recyclability. DCv ureas are an important addition to the field of DCvC because of their widely tuneable dynamicity, making them applicable over a large range of conditions. Despite some downsides such as

solvolytic lability and the presence of toxic isocyanates in their equilibrium, they have found widespread use in different fields such as drug and stem cell delivery systems, self-healing electrodes, clear coats, recyclable and malleable networks, triple-shape-memory networks, triggered catalysis, and synthesis. With the knowledge gathered about the properties of DCv ureas, the future will see further developments utilizing these moieties. Their ability to release isocyanates *in situ* makes them interesting candidates for further applications, replacing the direct need for isocyanates. Furthermore, the wide range of self-healing polymers with different properties and the easy tuneability of their stability presupposes DCv ureas for more applications in materials science, such as coatings, or sensors for detecting mechanical stress. The wide stability range of DCv ureas and their derivatives may be enhanced even further by further tuning the substituents on the nitrogen atom, for example by introducing photoswitchable moieties near the carbonyl center to tune the bulkiness *in situ* without the need for any chemical modifications. Their more recent development in the release of biological cargo also offers further options in the field of drug delivery. Another area that may see advances due to the development in the field of DCv urea is 3D printing. The presence of self-healing moieties may help bonding in the z direction of 3D-printed parts between layers. Lastly, the extremely wide chemical versatility of the amine species present in DCv ureas' equilibria offers many possible applications in reactions where amines participate as substrates or catalysts, as recently shown with their applications as heat-triggered catalysts and reagents. As such, hindered ureas offer a general method to replace amines with a heat- or solvent-triggered alternative that can release amines on demand.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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