

Dynamic Covalent Polymers

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ABSTRACT: This Highlight presents an overview of the rapidly growing field of dynamic covalent polymers. This class of polymers combines intrinsic reversibility with the robustness of covalent bonds, thus enabling formation of mechanically stable, polymer-based materials that are responsive to external stimuli. It will be discussed how the inherent dynamic nature of the dynamic covalent bonds on the molecular level can be translated to the macroscopic level of the polymer, giving access to a range of applications, such as stimuli-responsive or self-healing materials. A primary distinction will be made based on the type of dynamic covalent bond employed, while a secondary distinction will be based on the consideration whether the dynamic covalent bond is used in the main chain

of the polymer or whether it is used to allow side chain modification of the polymer. Emphasis will be on the chemistry of the dynamic covalent bonds present in the polymer, in particular in relation to how the specific (dynamic) features of the bond impart functionality to the polymer material, and to the conditions under which this dynamic behavior is manifested. © 2016 The Authors. Journal of Polymer Science Part A: Polymer Chemistry Published by Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2016**, *54*, 3551–3577

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INTRODUCTION Compared to other types of materials, polymer-based materials offer various distinct advantages, such as their low density, processability, and the broad range of monomer building blocks. However, classic polymeric materials, i.e. polymers derived from covalent bonds, typically suffer from unrepairable damage, resulting in a progressive decrease in functionality and/or economic value as the material ages. In addition, such polymers are generally insensitive to their environment. To overcome these limitations, dynamic interactions can be incorporated in polymer materials, thus imparting these materials with dynamic features such as environmental adaptivity, malleability, or self-healing properties. Over the last decades, supramolecular interactions, e.g. hydrogen bonds or aromatic interactions, have been successfully incorporated into polymers as a means to achieve such dynamic material behavior.^{1–4} More recently, however, researchers have also relied on dynamic covalent (DC) bonds^{5–8} to achieve such dynamic behavior, as DC bonds combine the robustness of classic covalent bonds with the reversibility of non-covalent bonds.

More formally, a covalent bond can be considered dynamic if it has the ability to be formed and broken reversibly under

equilibrium control.⁵ To achieve equilibrium conditions, exchange should be sufficiently fast, implying a bond life time on a scale of milliseconds to minutes.⁹ By virtue of their reversibility, DC bonds have been successfully harnessed in the synthesis of dynamic combinatorial libraries^{10,11} or mechanically interlocked species.^{12,13}

In this highlight we will discuss how DC bonds can be used to synthesize robust polymers whose properties are dictated by the inherent dynamic nature of the bonds, which can thus influence the material's relaxation behavior or mechanical response. The dynamic nature on the molecular level is thus translated to the macroscopic level of the polymer, giving access to a range of applications, such as self-healing or stimuli-responsive materials, as reviewed extensively by others.^{14–19} Herein, we primarily discuss the underpinning chemistry that imparts the dynamic behavior or function to the polymer material.

Definition and Scope

The aim of this Highlight is to present an overview of the rapidly growing field of DC polymers.²⁰ We have limited ourselves to a discussion of DC bonds, not including supramolecular interactions. For a recent overview of the

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Fátima García received her PhD in 2013 from the Universidad Complutense de Madrid (ES), for work on supramolecular polymers, performed under the supervision of Luis Sánchez. She then took up a postdoctoral position with Maarten Smulders at the Wageningen University (NL), where her research focussed on the development of multiresponsive coordination polymers utilizing metal-stabilized, dynamic covalent imine bonds. She is currently working at CIQUS (ES) with Diego Peña and her research nowadays concerns the synthesis of nanostructured PAHs for organic electronics.



Maarten Smulders obtained his PhD degree in 2009 from the Eindhoven University of Technology (NL) for research undertaken in the group of Professor Bert Meijer. After postdoctoral positions at the University of Cambridge (UK) and the University of Twente (NL), in 2013 he took up a position as assistant professor in the Laboratory of Organic Chemistry at the Wageningen University (NL). His current research interests lie in the area of supramolecular chemistry, dynamic covalent chemistry, and polymer chemistry.



combination of DC and supramolecular bonds, jointly considered as *constitutional dynamic chemistry*, the reader is referred to excellent reviews by Lehn,²¹ and Zhang and Barboiu.²² While a distinction can be made between DC reactions relying on the formation of new bonds, or on exchange reactions,⁶ herein this distinction will not be explicitly used. This Highlight will primarily distinguish DC polymers based on the type of DC bond employed. We will make a further distinction based on the consideration whether the DC bond is used in the main chain of the polymer (i.e. it is responsible for linking the individual monomers together into the macromolecule), or whether it is used to allow side chain modification of the polymer (which itself is then formed by purely covalent bonds). As explained above, our emphasis will be on the chemistry of the DC bonds present in the polymer, in particular in relation to how the specific (dynamic) features of the bond impart functionality to the polymer material.

DISULFIDE EXCHANGE

The disulfide exchange reaction was one of the earliest recognized DC reactions, in part because it can also be found in biological systems: e.g. in protein folding or in control over the redox state of cells.²³ Disulfide exchange relies on a nucleophilic attack of a thiolate anion on a disulfide, resulting in a release of a thiolate anion from the original disulfide and concomitant formation of a new disulfide species incorporating the attacking thiolate (Scheme 1). As a thiolate anion is required, this exchange reaction is sensitive to pH: (mildly) basic conditions favor the exchange reaction. Exchange can be initiated from a mixture of thiols through oxidation (e.g. by oxygen) in the presence of a base. Alternatively, thiols can be added to pre-existing disulfides, again in the presence of a base. Finally, addition of a catalytic amount of a reducing agent (typically dithiothreitol, DTT) to a mixture of disulfides will also induce exchange.

Apart from the use of disulfide bonds for polymer synthesis, this type of DC bond is also regularly applied within the context of structural supramolecular chemistry.²⁴

Main Chain

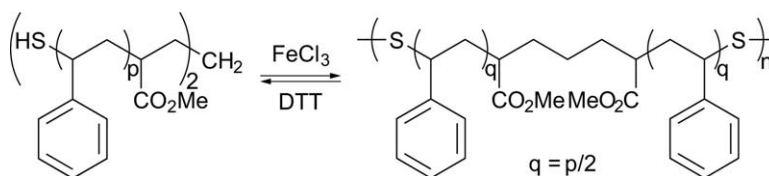
Tsarevsky and Matyjaszewski reported an early example of a DC polymer based on disulfide exchange.²⁵ By performing an atom transfer radical polymerization (ATRP) of styrene using a bifunctional initiator with an internal disulfide bond, it was first of all possible to prepare a polystyrene PS-S-S-PS polymer with an internal disulfide bond. Subsequent treatment with DTT resulted in cleavage of the polymer, yielding the reduced PS-SH fragment, which could be reversible coupled again by oxidation by FeCl₃. In a second set of experiments the authors showed how a α,ω -bromo-functionalized PS polymer could be converted into a mercapto-terminated polymer that could then be reversible polymerized and depolymerized by treatment of FeCl₃ or DTT, respectively (Scheme 2). It was shown by SEC (size exclusion chromatography) that upon oxidation high-molecular weight PS-based polymers (>10⁵ g/mol) had formed.

Yang et al. employed a similar approach relying on redox responsiveness, showing how reversible disulfide bond formation yielded amphiphilic DC diblock copolymers that could reversibly assemble and disassemble into micelles by control over the redox state.²⁶ The desymmetrization of the otherwise symmetrical disulfide bond was elegantly achieved by incorporation of a complementary hydrogen bond motif that favored heterodimerization of the hydrophilic PEG polymer with the hydrophobic PLA polymer. In a recent follow-up publication they employed the same motif to prepare multiblock copolymer micelles.²⁷

Otsuka et al. were the first to report a photoresponsive DC polymer by incorporating disulfide moieties in the main chain of a polyester (Fig. 1).²⁸ Apart from studying low-MW model compounds, to confirm the photoresponsiveness of



SCHEME 1 Disulfide exchange mechanism.



SCHEME 2 Reversible polymerization and depolymerization of mercapto-terminated PS.²⁵

the disulfide-containing polymer (which did not contain any chromophores), a polymer film was fractionated and subsequently irradiated. While no changes in the NMR spectrum could be discerned upon UV irradiation, by SEC a clear widening of the MW distribution and decrease in average MW was observed. The ability to reorganize was further demonstrated by the formation of unimodal MW distribution upon mixing of a low-MW and a high-MW fraction under UV irradiation (Fig. 1).

Finally, disulfide bonds have been employed in the preparation of interlocked macromolecules such as polyrotaxanes.^{29–31} Wang et al. showed that a multistimuli-responsive polyrotaxane, constructed by crown-ether based molecular recognition and disulfide bonds, could be reversible (dis)assembled by control over the redox state (thus addressing the disulfide bonds), over the pH or through competitive binding (both addressing the crown ether binding of an ammonium moiety).³¹ Irreversible disassembly was achieved through UV irradiation, which resulted in cleavage of the disulfide bond.

Side Chain

The disulfide exchange reaction has been employed to reversibly control the crosslinking of various polymer assemblies. Tuten et al. elegantly demonstrated that single-chain nanoparticles, based on poly(norbornene-*exo*-anhydride), could reversible undergo a coil-to-particle transition via the formation or cleavage of intramolecular disulfide bonds.³² These bonds were introduced by postpolymerization modification of a fraction of the anhydride groups with a bifunctional crosslinker containing a pre-made disulfide bond. SEC allowed the authors to monitor the collapse of the polymer nanoparticle through FeCl₃ oxidation and subsequent unfolding by addition of DTT (Scheme 3).

Following a similar approach of redox-controlled crosslinking/decrosslinking, Ryu et al. reported how biocompatible polymer nanoparticles could be used as drug delivery platform.^{33,34} As biologically relevant trigger to disassemble the nanoparticle—with concomitant release of the cargo—glutathione (GSH), which is present in different concentration in the body, was used.

Both Koo et al.³⁵ and Dai et al.³⁶ also relied on GSH-mediated release of a drug from a polymer nanoparticle that was reversibly crosslinked by disulfide bonds. The latter group also relied on a pH-sensitive hydrated polymer core (featuring a tertiary amine that can be protonated), allowing

release not only under reducing conditions but also under acidic conditions. It should be noted that in these last three examples the process is nonreversible in the sense that once the nanoparticles unfold through reduction of the disulfide bonds, the cargo is permanently released from the particle.

Network

Various research groups have prepared self-healing polymer materials by integration of disulfide moieties in covalent polymer networks. For example, Canadell et al. reported a transparent thermoset rubber, prepared from a disulfide-containing epoxy resin and a tetrafunctional thiol (Scheme 4).³⁷ Dynamic mechanical thermal analysis revealed that the material was able to flow at temperatures above 100 °C, indicating disconnection of disulfide linkages. The observation that the rubber could be dissolved in nitrogen-containing solvents was further presented as evidence of scission of the disulfide bonds.

Tensile tests showed that the rubber material heals at 60 °C, as superimposed stress-strain curves were found for

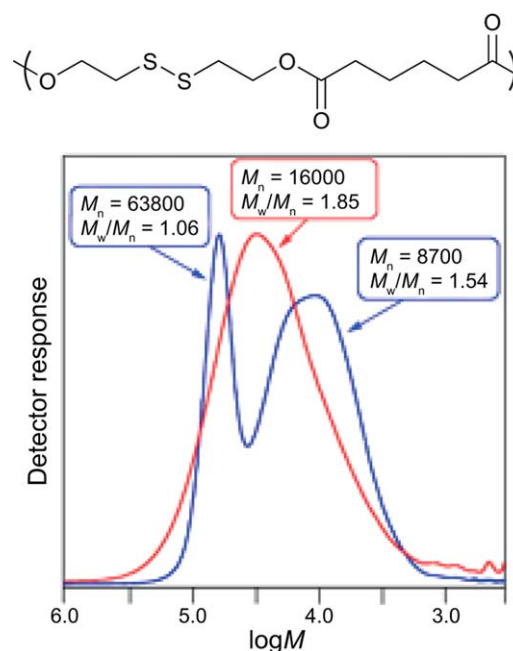
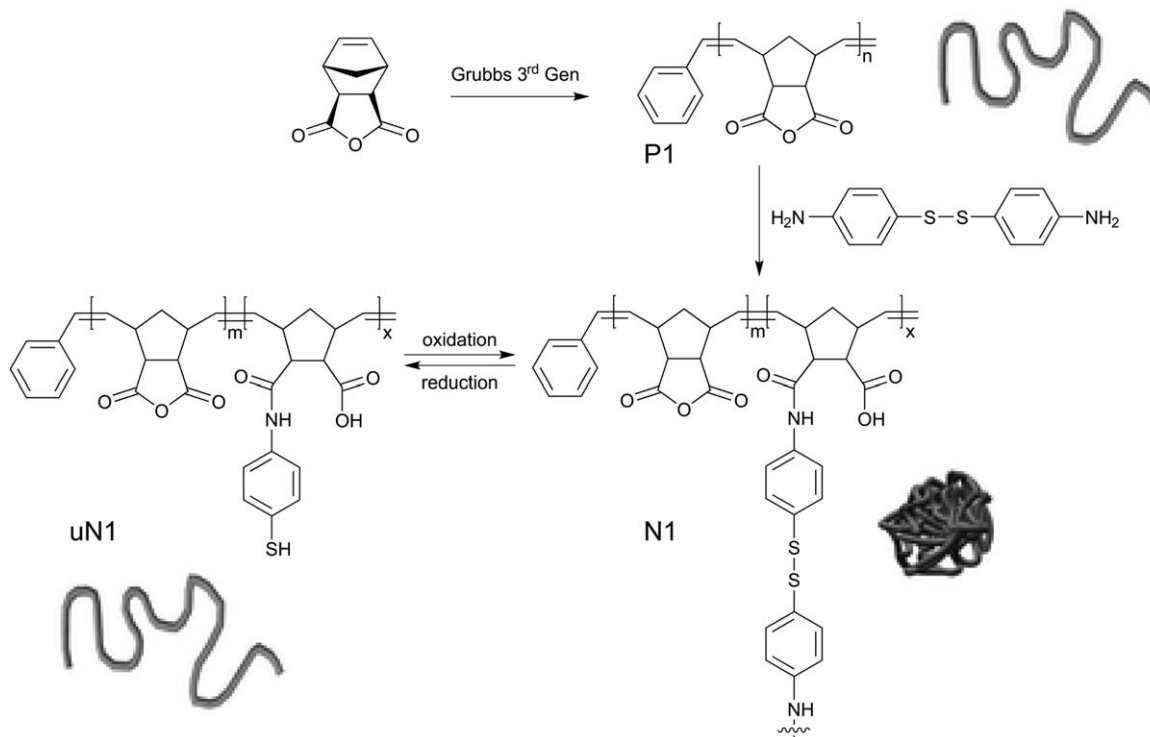


FIGURE 1 Structure of disulfide-containing polyester (top) and SEC traces of a mixture of high-MW and low-MW polymer, before (blue line) and after (red line) photoirradiation (bottom). Reproduced from Ref. 28 with permission from RSC.



SCHEME 3 Reversible single-chain nanoparticle formation via intramolecular disulfide bridges. Reproduced from Ref. 32 with permission from RSC.

samples healed at 60 °C for different times, suggesting that the self-healed material had regained its elastic properties. Moreover the self-healing behavior was maintained through different breaking-healing cycles (Fig. 2).

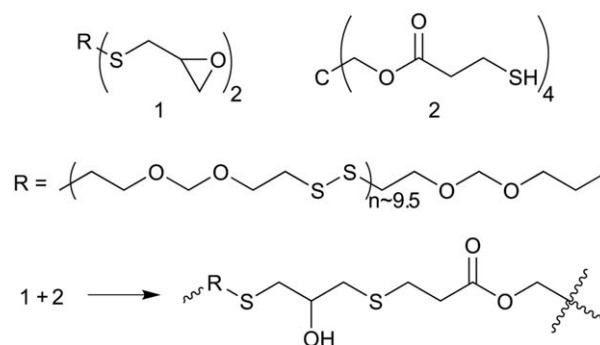
In a more recent contribution, Pepels et al. reported how addition of free a thiol-containing curing agent resulted in a self-healing thermoset through thiol-disulfide exchange and not through disulfide-disulfide exchange reaction.³⁸ Compared to their earlier work, relying exclusively on disulfide-disulfide exchange,³⁷ the possibility of thiol-disulfide exchange greatly enhanced the rate of exchange and self-healing. A drawback of these materials was their oxygen sensitivity: the thiol groups are readily oxidized thus preventing exchange reactions.

To overcome the oxygen sensitivity observed by Pepels et al.,³⁸ Lei et al. introduced tri-*n*-butylphosphine in a polysulfide network.³⁹ Crosslinked epoxidized polysulfides were found to self-heal at room temperature repeatedly, as well as reshaped and reprocessed, only if both the phosphine catalyst and disulfide bonds were present in the material.

Rekondo et al. showed in 2013 how disulfide metathesis allowed formation of a self-healing elastomeric polymer operating catalyst-free at room temperature.⁴⁰ Having established the feasibility of their approach by model compound reactions, they went on to show that a poly(urea-urethane) network built from a mixture of bi- and trifunctional isocyanates and a disulfide-containing diamine could be prepared

by curing in a mould at 60 °C (Scheme 5). The elastomeric material that was thus formed showed remarkable autonomous self-healing behavior at room temperature: a manually cut cylindrical sample could be mended by simply pressing together of the two fragments for a period of time (Fig. 3).

Tensile strength measurements allowed quantification of the self-healing capability, showing up to 97% recovery after 24 h. In contrast, a disulfide-free analogue did not show self-healing behavior; clearly indicating the essential role of the DC disulfide bonds. The authors also noted that inter-chain hydrogen bonds between urea groups, enhances the self-healing capacity of the elastomer.



SCHEME 4 Network forming (curing) reaction of epoxy resin **1** with tetrafunctional thiol **2**, yielding a dynamic self-healing disulfide-containing network.³⁷

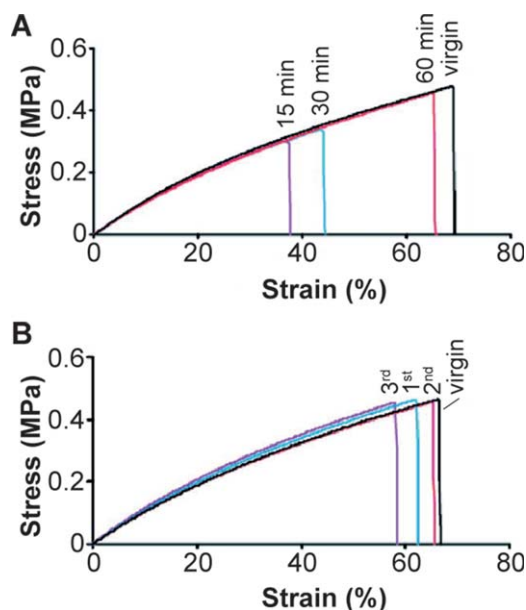


FIGURE 2 Stress–strain curves for different healing times (A) or after repetitive healing (B) for the network polymer shown in Scheme 4. Reproduced from Ref. 37 with permission from ACS.

Tsarevsky and Matyjaszewski have also reported a disulfide-based crosslinked polymer material that could self-heal under solvent-free conditions at room temperature, in air and under visible light illumination.⁴¹ By making use of a thiuram disulfide (N-(C=S)-S-S-(C=S)-N) moiety, also employed as iniferter unit,⁴² the authors could lower the bond dissociation energy of the disulfide and simultaneously enhance the oxygen tolerance, which resulting in the desired dynamic self-healing behavior at room temperature. More specifically, the thiuram disulfide group was incorporated into a low- T_g polyurethane network (Scheme 6), which was then subjected to tensile tests and dynamic mechanical analysis. The essential role of the thiuram disulfide moiety in imparting the self-healing nature on the material was demonstrated by ESR, which revealed the presence of the S-based radical, formed upon illumination. In addition, the corresponding polymer network prepared without the thiuram disulfide group did not display the self-healing behavior. It should be noted that the use of visible light (as opposed to UV light) at room temperature, and the absence of solvent and catalysts, make this type of material interesting for various applications. Gordon et al. later employed the same thiuram disulfide group to create a light-triggered dynamic polymer network that could heal and strengthen on demand.⁴³

Related to the classical disulfide exchange reaction, recently Griebel et al. also showed how inverse vulcanization of elemental sulfur can yield DC polymers.⁴⁴ To this end, elemental sulfur (S_8) was copolymerized with 1,3-diisopropenylbenzene via inverse vulcanization at elevated temperature (185 °C), yielding a copolymer sensitive to heat and

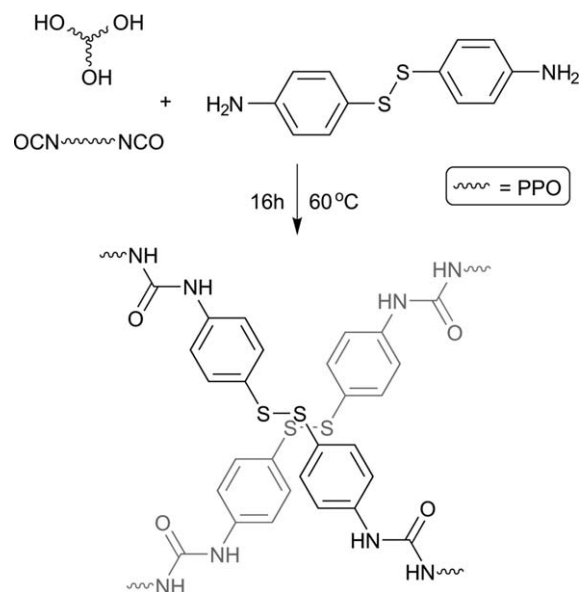
mechanical stress. Control over the feed ratio allowed control over the dynamic properties of the formed polymer, enabling the formation of a self-healing material, as probed by rheological measurements at 130 °C. More recently the authors reported how this thermoresponsive DC copolymer could be used as thermally healable optical polymers for mid-IR thermal imaging applications.⁴⁵

IMINES

Imine bonds are obtained by condensation of a carbonyl compound and an amine derivative (Scheme 7) and have found various uses in organic and supramolecular synthesis.⁴⁶ This reaction was discovered by Schiff,⁴⁷ and thus imines are often referred to as Schiff bases. The reaction involves a nucleophilic attack of the amine on the carbon atom of the carbonyl, followed by dehydration⁴⁸ and their formation can be catalyzed by acid. However, the pH should be chosen such that the amine is not protonated, as this would prevent the initial nucleophilic attack. Because of their reversibility they are normally synthesized by removing the water formed during the reaction, either by distilling it from an azeotropic mixture or by using 4 Å molecular sieves.

Main Chain

The imine bond has been used as linkage to obtain linear polymeric species. Zhao and Moore used two *bis*(imino) end-functionalized oligo(*m*-phenylene ethynylene)s that could exchange via their imine bonds giving rise to a longer oligomer and a small molecule as by-product (Fig. 4).^{49,50} If the equilibration was achieved in an apolar solvent such as chloroform, only small oligomers were obtained. In contrast, when the polarity of the solvent was increased (by increasing the ratio acetonitrile/chloroform) the equilibrium shifted towards the formation of high-MW species, as shown by GPC (Fig. 4). Polar solvents favor the polymerization due to the



SCHEME 5 Synthetic procedure for the disulfide-containing poly(urea-urethane) elastomer.⁴⁰

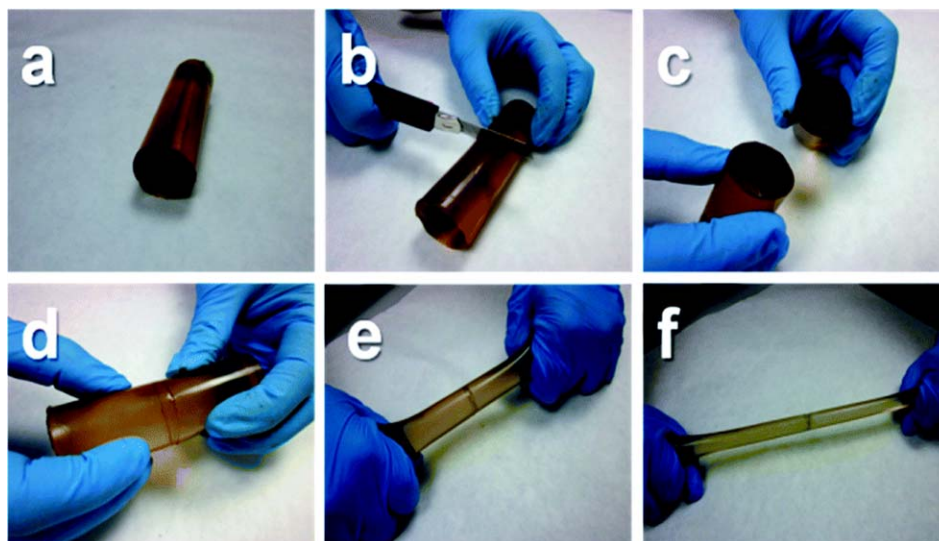


FIGURE 3 Damaging and subsequent self-healing of the elastomeric material (Scheme 5). (A) pristine sample; (B and C) cutting of the sample; (D) self-healing (2 h); (E and F) stretching of the material without rupture. Reproduced from Ref. 40 with permission from RSC.

folding of the oligo(*m*-phenylene ethynylene)s (OPEs) in these conditions, driven by the hydrophobic effect.⁵¹

The folding of hydrophobic polymer segments in DC polymers has also been exploited in an example of the Lehn group, who described a constitutional dynamic library (CDL) based on imine bonds with naphthalenediimide and naphthalene as acceptor (A) and donor (D) moieties, respectively.⁵² Upon imine formation, a polymer comprised of alternating A–D units was obtained. The polyimine folds upon itself when metal salts are added, and the color could thus be tuned depending on the metal ion.

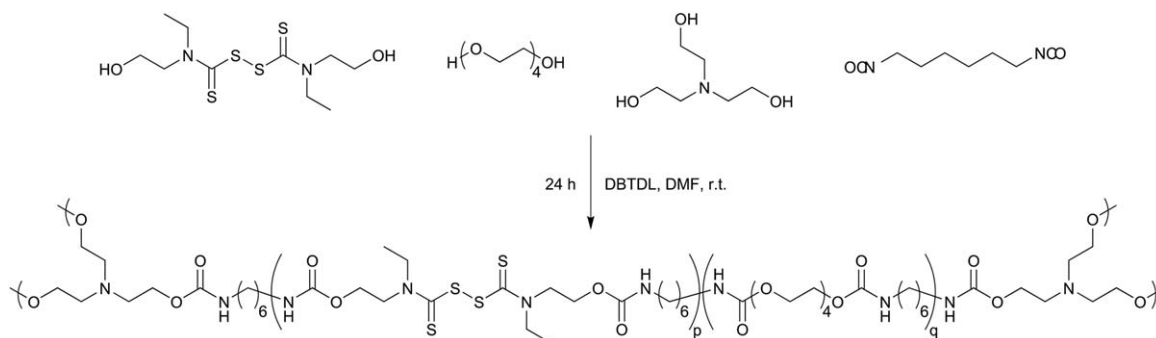
The imine bond has been used in combination with metal–ligand (M–L) interactions, which depending on the nature of the metal and the ligand can lead to dynamic imine bonds.⁵³ Coordination of metal ions to the nitrogen atom of the imine group is well known⁵⁴ and has shown catalytic activity.⁵⁵ Ulrich and Lehn described a polyimine in which the presence of metal ions shifts the equilibrium towards the formation of a metallomacrocyclic in a reversible manner, as shown by DOSY experiments.⁵⁶ The formation of macrocycles is driven by the change in conformation of the polyimine in order to

complex the metal ion. Nasr et al. used M–L interactions to crosslink a polyimine polymer to obtain membranes permeable to gases by a simple procedure.⁵⁷ In another example from Lehn's group, polyimino fluorenones could undergo constitutional recombination in the presence of external additives (H^+ and Zn^{2+}), and thus changed their optical properties when zinc ions were present, as could be inferred from UV-Vis and fluorescence spectroscopic titrations.^{58,59} Moreover, the presence of Zn^{2+} serves as catalyst for the exchange reaction.

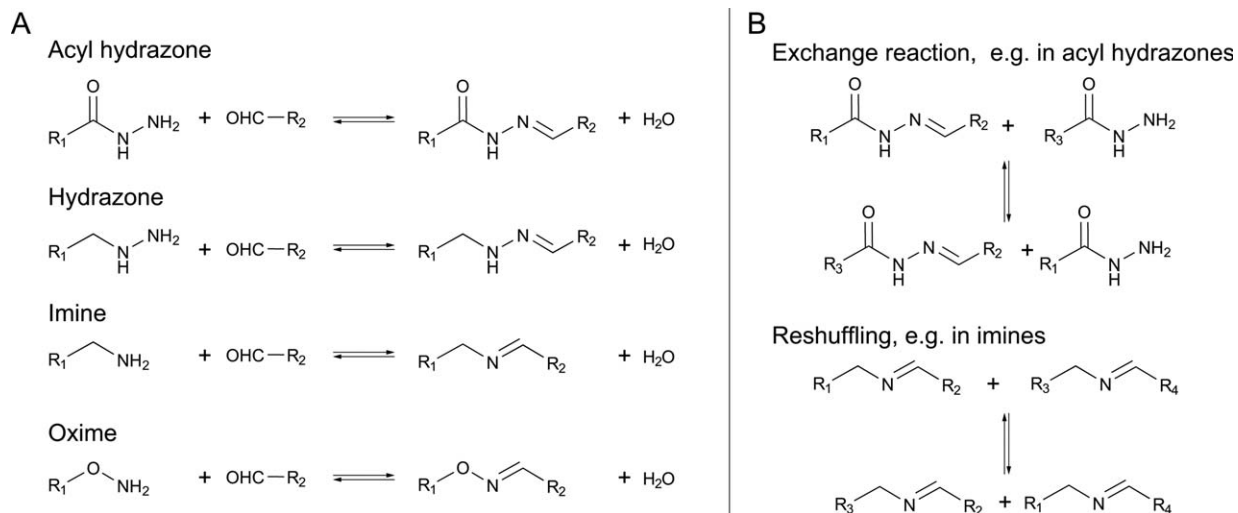
In 2011 de Hatten et al. reported a polyimine system featuring copper ions.⁶⁰ When a solution of this metallopolymer was heated up to 120 °C a gel was obtained, which could reversibly go back to the sol state by cooling down to 20 °C. The authors did not primarily ascribe the gel formation to exchange of the imine bonds but to the formation of copper crosslinking species and concomitant release of a phosphine ligand. This polymer was found also to be electroluminescence.⁶¹

Side Chain

The introduction of amine groups in the side chain of a polymer allows its postfunctionalization with an appropriate



SCHEME 6 Preparation of a thiuram disulfide-containing crosslinked polyurethane.⁴¹



SCHEME 7 (A) Overview of N=C-based dynamic covalent bonds condensation reactions. (B) Exchange and reshuffling reactions on these bonds.

aldehyde via imine bond formation. In this manner, relying on the pH dependence of the imine bond, Gu et al. created micellar structures that could be reversibly PEGylated through an imine bond (Fig. 5).⁶²

Upon subjecting polylysine appended with imine-linked PEG chains to mild acidic conditions, hydrolysis of the imine bond exposed the lysine's ammonium groups, creating a cationic micellar surface.⁶² These micelles became cytotoxic depending on the pH, being thus applicable as delivery systems targeted at tumors, becoming cytotoxic once the pH is slightly lowered. Other authors have also used the imine bond in the side chain for the reversible formation of micelles, by control over the pH.^{63–65}

The Fulton group have used the imine bond to crosslink two copolymers containing either amine or aldehyde side groups, yielding star polymers displaying a MW dependence on the

extent of crosslinking. Large excess of propylamine disrupted the star polymers, inducing a transimination reaction, followed by acid treatment, thus, facilitating the recovery of the initial block copolymers, as shown by GPC. The same group explored this strategy but using an oxime bond,⁶⁸ yielding micelles that could be disrupted upon exchange reactions on the oxime bond with small molecules.

Yan et al. showed how side chain functionalization via a DC bond allows tuning of the material properties.⁶⁹ For polylysine it was found that depending on the degree of imine bond formation with a hydrophilic aldehyde bearing side group, the phase transition temperature (from dissolved to aggregated state) of the polymer could be tuned.

Our research group has described a multi-responsive DC metallopolymer.⁷⁰ Macromonomers equipped with a 2,6-diiminopyridine pincer motif at both chain ends could assembly

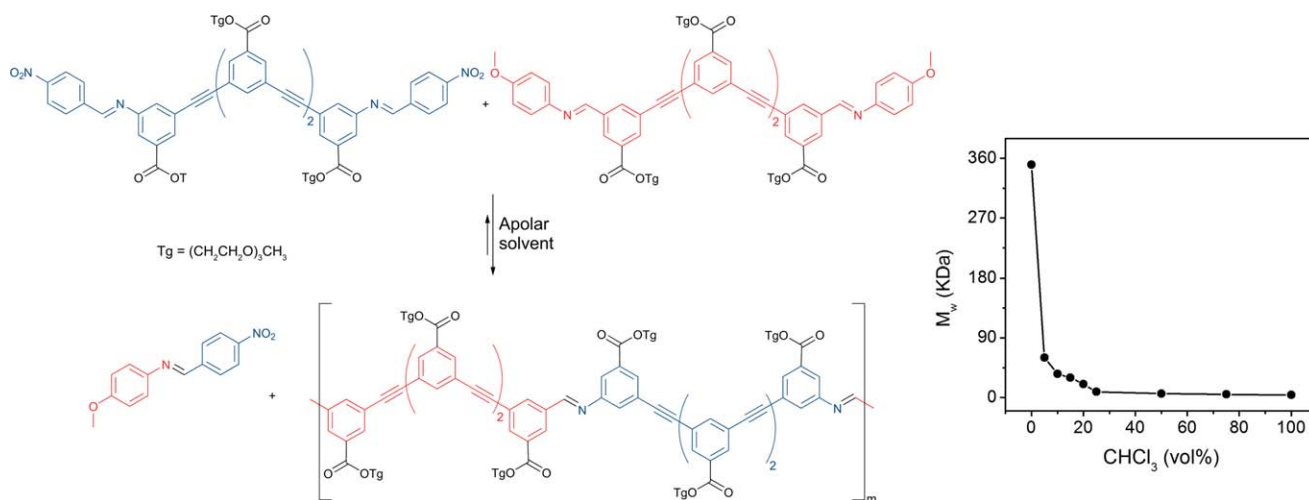


FIGURE 4 Chemical structure and formation of OPE-based polyimines (left) and molecular weight of the polymers obtained from GPC experiments as a function of the polarity of the solvent (right). Reproduced from Ref. 49 with permission from ACS.

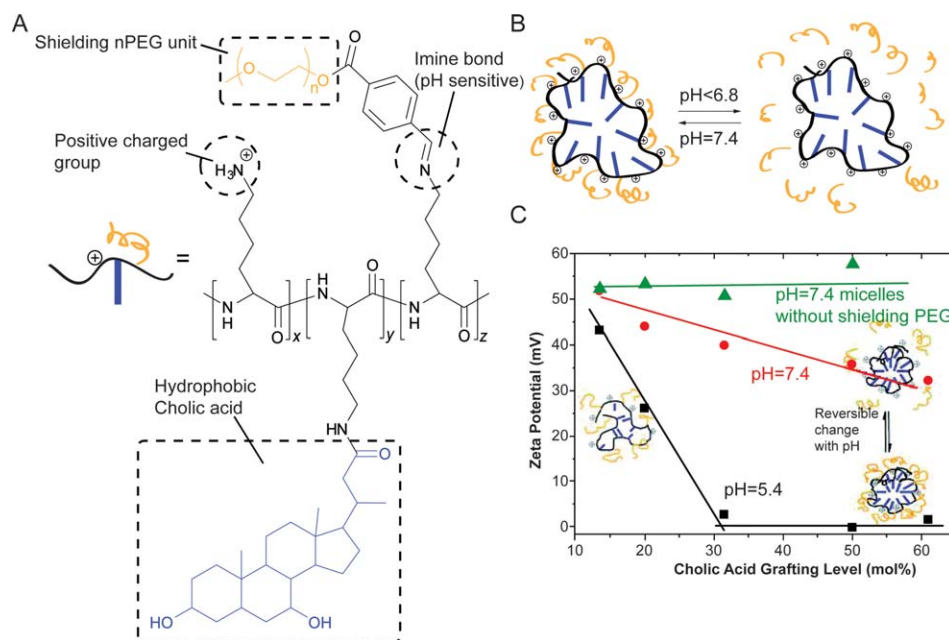


FIGURE 5 (A) Chemical structure of the polylysine PEGylated via imine bonds. (B) Schematic representation of the pH dependence of the imine bonds in the polycationic micelles. (C) Zeta potential dependence on the cholic acid coverage of the micelles. Reproduced from Ref. 62 with permission from ACS.

into larger coordination polymers upon addition of metal ions, as inferred from ¹H NMR, DOSY, and viscometry measurements. These DC metallopolymers were sensitive to pH and exchange reactions with amines of different nucleophilicity. Moreover, transimination reactions with a more nucleophilic, bifunctional, amine enabled reversible control over the degree of crosslinking between different polymer chains, ultimately yielding gels at a high degree of crosslinking (Fig. 6).

Sanchez-Sanchez et al. relied on a DC enamine moiety, which is structurally related to imines, to reversibly crosslink polymer nanoparticles.⁷¹

Network

Taynton et al. elegantly demonstrated that synthesis of adaptive materials based on DC polymers can be straightforward.⁷² They prepared a crosslinked polyimine network from commercially available monomers: terephthalaldehyde, ethylene triamine, and triethylene tetraamine (Scheme 8).

Mixing these components in the correct stoichiometry in a mixture of organic solvents (1:1:8, CH₂Cl₂/EtOAc/EtOH), followed by air drying, yielded a hard and glassy polyimine film. IR spectroscopy confirmed the disappearance of the aldehyde end groups together with the appearance of the imine groups. This hard polymer becomes malleable when heated at 80 °C allowing fast exchange of the imine bonds [Fig. 7(a–e)]. The reversibility of the imine bonds enabled the recycling of this material without any decrease in the mechanical strength over multiple generations, as inferred

from the stress–strain curves (Fig. 7). Moreover, this polyimine could also be reshaped by simply wetting the polymer in water at room temperature.

In a more recent example, Zhang and Barboiu used 1,3,5-tri-benzaldehyde and different hydrophilic and hydrophobic diamines.⁷³ When these components were cast onto a template, phase segregation between the hydrophilic and the hydrophobic segments occurred, allowing the formation of asymmetric membranes, able to transport water only in one direction.

The dynamic nature of the imine bond was nicely explored by Zhang et al. in 2011.⁷⁴ In their contribution, chitosan bearing amine groups and an α,ω -aldehyde-terminated PEG were used. The crosslinking via imine bonds of these two polymers took place very fast at room temperature, forming an hydrogel that could be reversibly disrupted by varying the pH. In addition, transimination reactions with amine-containing biomolecules such as amino acids, enzymes and vitamin B6 derivatives, could transform the hydrogel back to the sol state. Rheology measurements performed on the hydrogels confirmed their self-healing ability.

Denissen et al. have used enamines (referred to by the authors as vinylogous amide bonds) to create a crosslinked network that can undergo transamination exchange reactions at elevated temperatures.⁷⁵ This vitrimeric polymer material showed viscoelastic liquid behavior (becoming processable at elevated temperatures) together with recyclability without any loss on the mechanical properties.

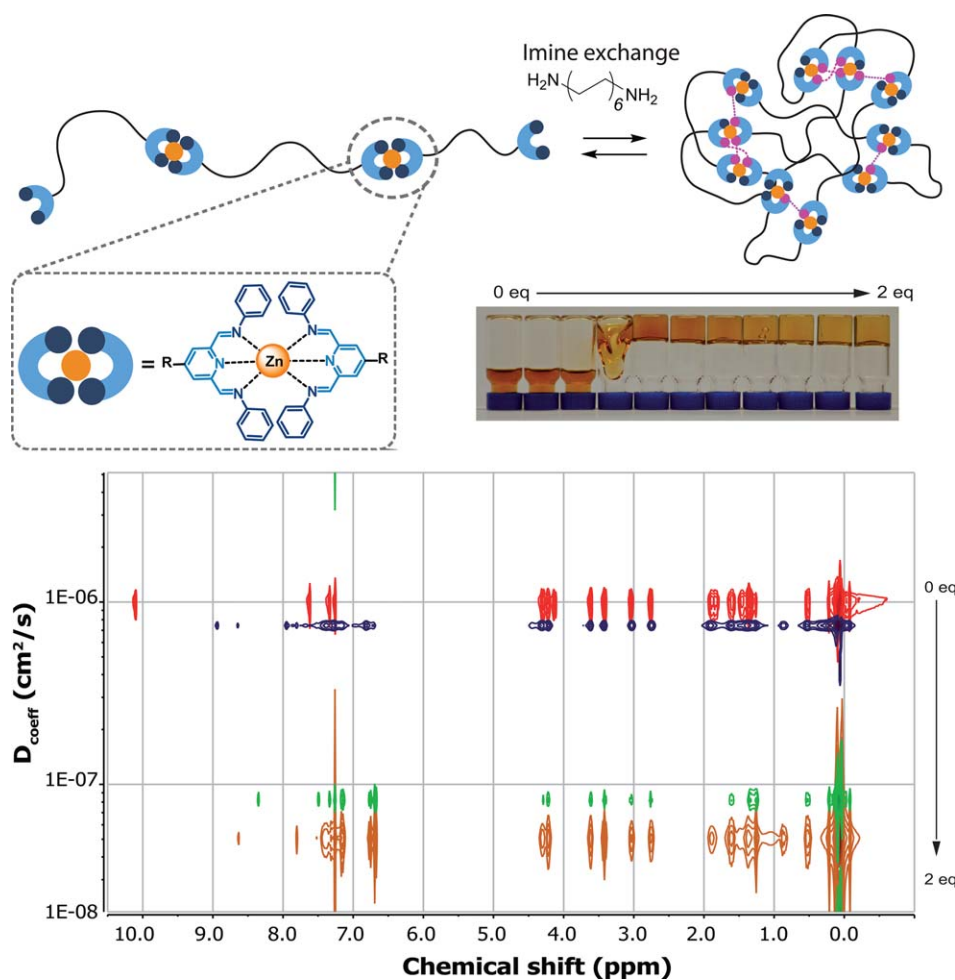


FIGURE 6 Top, cartoon representation of multi-responsive metallopolymers and the transimination reaction with a diamine yielding a network gel at high exchange ratio. Bottom, DOSY NMR overlaid spectra of different samples with different ratio of cross-linking showing the formation of higher MW polymers.⁷⁰

ACYL HYDRAZONES

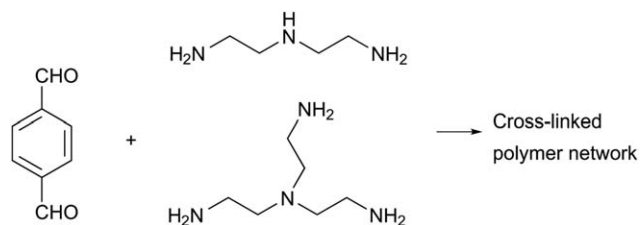
Hydrazones and acyl hydrazones are formed upon condensation between a carbonyl compound and an hydrazine or hydrazide, respectively (Scheme 7). The lone pair of electrons in the electronegative atom adjacent to the C=N bond makes acyl hydrazones (and oximes) more stable than imines and therefore, they can be stable even in the presence of water. Their formation is catalyzed in the presence of acid, which makes this bond responsive to pH: in acidic environment, its formation is favored, while it is retarded upon increasing the pH. It is dynamic under mild conditions, which facilitates a reshuffling of hydrazones when multiple hydrazones are present or their exchange with different hydrazines (Scheme 7). Beyond the scope of polymer synthesis reviewed here, acyl hydrazones have been more generally used in the synthesis of functional materials.⁷⁶

Main Chain

The group of Lehn has extensively used the acyl hydrazone bond as the linking motif to access DC polymers by direct

reaction between bifunctional acyl hydrazones and dialdehydes.^{77–79} Interestingly, the amide group present in acyl hydrazones makes them susceptible to hydrogen bonding (blue box in Fig. 8), which due to its non-covalent nature also imparts dynamic character, giving rise to so-called double dynamers, increasing thus the overall responsivity of the polymers.^{77,79}

These alternating copolymers are able, through monomer exchange, to access different polymer compositions and



SCHEME 8 Structures used by Taynton et al. to create a polyimine crosslinked network.⁷²

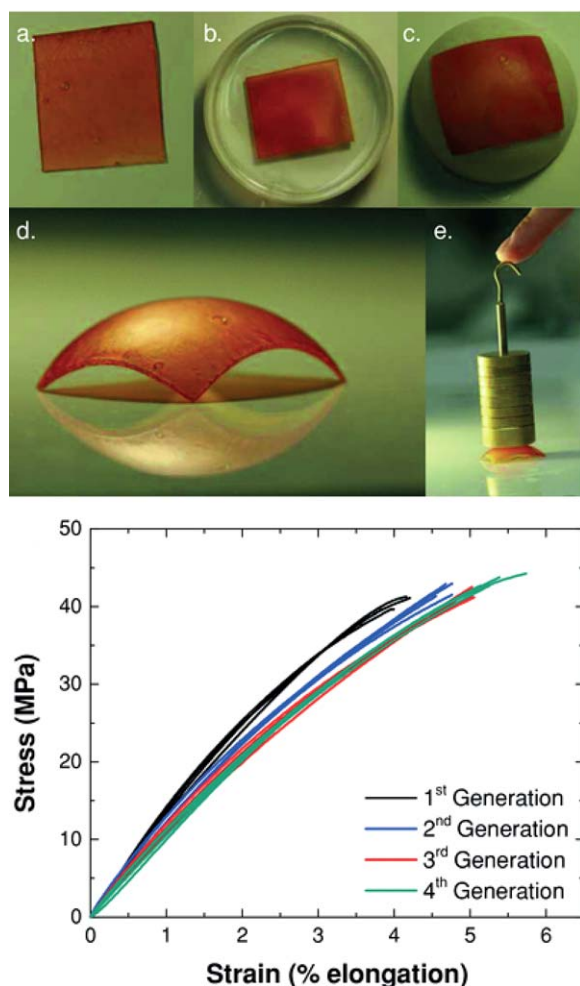


FIGURE 7 Top, water-induced malleability experiments. (a) Initial solid polyimine film (Scheme 8); (b) film after soaking in tap water for 3 h; (c) wet film is stretched over a round mould; (d) film after following 24 h drying; (e) evidence that film can withstand pressure. Bottom, stress–strain curves for the cross-linked polyimine showing the little difference in mechanical properties upon recycling it for four generations. Reproduced from Ref. 72 with permission from Wiley.

functionalities. Lehn's group has used this strategy to obtain polymers with tuneable mechanical properties.^{80,81} When two monomers containing flexible siloxane-derived spacer units as *soft* component were combined (**M1** and **M3** in Fig. 8), a homopolymer was obtained as a very soft and stretchy film (Fig. 8). In contrast, if the spacer was composed of rigid units as *hard* components, a hard and fragile film was formed. The exchange reaction between monomers bearing hard components (**M2** or **M4**) within the *soft* polyacylhydrazone was achieved by dissolving them in the presence of catalytic amount of acid and heating, in order to accelerate the exchange reaction (although it was shown that exchange also takes place in the neat polymers). Depending on the exchange rate and the nature of the exchanging monomers,

polyacylhydrazone copolymers with different T_g and viscoelasticity values could be obtained.

In a very nice contribution by the same group it was reported how a folding-driven sequence selection, can develop DC polymers with well-defined secondary structures.⁸² To this end, they developed ditopic dialdehydes and dihydrazide monomers bearing an hydrophobic core functionalized with an hydrophilic hexaglyme, as shown in Figure 9. This design yielded a DC polyacylhydrazone, presenting a nonpolar main chain from which hydrophilic moieties emanate at regular intervals. This folding-driven sequence gave rise to a nuclear-growth polymerization mechanism, yielding well-defined rod-like structures as evidenced by TEM and SANS data (Fig. 9). It also yielded a high degree of polymerization as evidenced by NMR spectroscopy, thus facilitating the incorporation of new monomers into the polymer chain. One of the reported polyacylhydrazones was found also to display lower critical solution (LCS) behavior.⁸³

When heating this polymer above the LCS temperature in acidic environment, a huge increase in the molecular weight of the polymer was observed by SEC, which was in contrast to what was observed when this was accomplished under basic conditions where the hydrazone bonds were stable. This responsive behavior was fully reversible and rather remarkable because typically reversible polymerizations result upon heating in lower MW species. This folding driven by hydrophobic interactions was also used to obtain globular structures, although reversibility was not reported.⁷⁸

The group of Lehn described another example of self-healing behavior for a polyacylhydrazone featuring a polysiloxane unit, although the healing mechanism was not discussed in detail, it was demonstrated to be completed in just a few hours without the need of any heating.⁸⁴

The same group has shown that these exchange reactions between acylhydrazones are not limited to the solution state, but that they could also take place in the solid state.⁸⁵ In this example, two conjugated polymer films based on polyhydrazones, **P1** and **P2**, upon heating in their interface, exchanged hydrazone bonds, which gave rise to a more conjugated polymer (**P3**) which exhibited different optical properties as shown in Figure 10. Although this exchange was not demonstrated to be reversible, this methodology allowed the preparation of optical patterns (Fig. 10). Also, Hayden et al. reported a polyhydrazone-based polymer with nonlinear optical properties, although its dynamic character was not explicitly addressed.⁸⁶

Hydrazone polymers could also be exploited in biological applications. In that direction, the Lehn group has reported oligosaccharide-based DC polymers.^{87–89} The main advantage of these glycodynamers in comparison with conventional covalent glycopolymers is that the acylhydrazone bond confers an adaptive character to the presence of a chemical template. In this example, the templated used was lectin and these glycodynamers displayed improved affinity for it, in

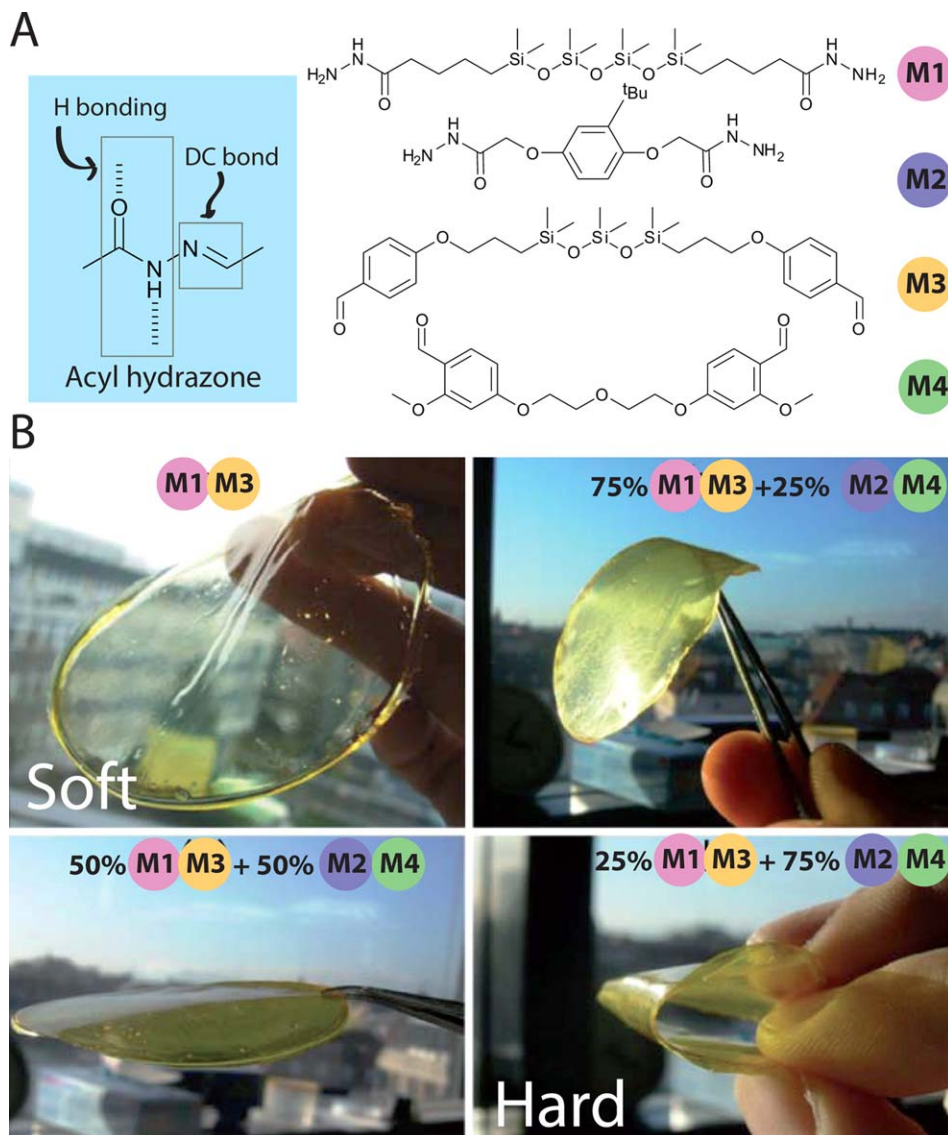


FIGURE 8 Structure of acyl hydrazones (blue box in (A)) and chemical structures of the monomers used for obtaining polymer films with different mechanical properties as shown in (B). Reproduced from Ref. 80 with permission from RSC.

comparison with the monosaccharides, due to the multivalency effect. The exchange between the glycodynamers was evidenced by a change in the fluorescence properties. More recently, Bouillon et al. have taken advantage of the pH responsiveness of the hydrazone bond to obtain polyacylhydrazones that complex to double-stranded DNA in biological media and that degrade at acidic pH.⁹⁰

The acylhydrazone bond has also been employed to obtain block copolymers. Rao and Khan described a diblock polymer based on polystyrene (PS) and polyethyleneglycol (PEG) linked through an hydrazone bond.⁹¹ This copolymer assembled into a nanostructured cylindrical morphology in thin films by phase separation of both units. Due to the dynamic character, the PEG block could be cleaved (demonstrated by ¹H NMR and IR) from the film by stirring in methanol:water

(1:2) at acidic pH to give rise to porous nano-channels as evidenced by AFM, TEM and SEM. The nano-channels could undergo postfunctionalization in the gas phase by reacting with small molecules bearing amine groups.

Another PS-PEG block copolymer described by Jin et al. was found to be able to encapsulate a small molecule (methyl porphyrin), whose release could be tuned by control over pH, as monitored by UV-Vis spectroscopy.⁹² Later, they used a similar approach to yield triblock polymers that also formed micelles, but with an oxime DC bond instead of the acyl hydrazone.⁹³ These micelles encapsulated the drug doxorubicin, which could be taken up by living cells through endocytosis. The release of the drug could be tuned with pH: while at physiological conditions release was very slow, at pH 5 it increased due to the instability of the oxime bonds.

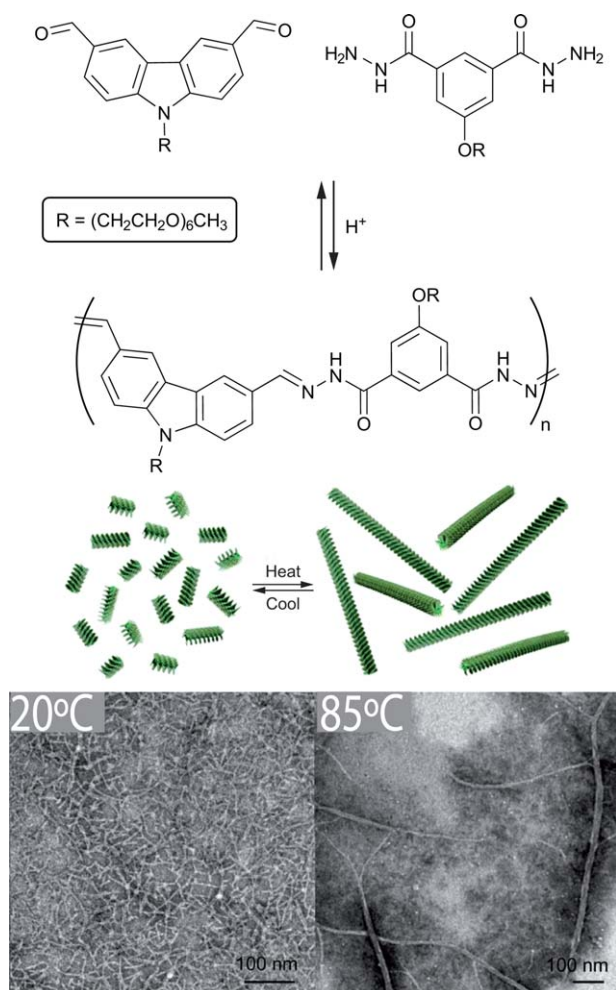


FIGURE 9 Chemical structures (top) of the pH and thermoresponsive polyacylhydrazone, their schematic temperature-dependent assembly (middle) and TEM images showing the well-defined temperature dependent rod structures (bottom). Reproduced from Ref. 83 with permission from ACS.

As also discussed above, this system would thus be a suitable *in vivo* drug delivery vehicle, showing cytotoxicity when in contact with endosomes and lysosomes of cells, with a more acidic environment than blood.

Side Chain

In 2008, Fulton described a preformed polystyrene grafted with aldehyde functional groups, able to further react with acylhydrazides of different length to form hydrazone bonds in the presence of a catalytic amount of TFA.⁹⁴ After 2 h the reaction was completed, as confirmed by GPC and IR. Using the same polyvinylbenzaldehyde polymer they were able to crosslink the polymer chains by reacting the aldehydes present in the polymer chain with a small amount of *bishydrazides*, resulting in the polymer's collapse into single chain nanoparticles (SCNPs) as shown in Figure 11.⁹⁵ More recently, they showed that heating a solution of similar SCNPs at

pH 4.5 resulted in the formation of an hydrogel.⁹⁶ These conditions favored intermolecular exchange reactions, instead of intramolecular exchange (Fig. 11).

In another example, Chen et al. described a microgel based on a PNIPAM polymer that also incorporates a fraction of pendant hydrazides groups in its polymer backbone.⁹⁷ Upon reaction of the hydrazide functional pendant groups with aldehydes of different hydrophilicity, the temperature at which the microgel reversible turns into colloids could be tailored.

Network

Deng et al. used a *bis*(acylhydrazine) PEG macromonomer and a *tris*[(4-formylphenoxy)methyl]ethane bearing three aldehyde groups to obtain a polyacylhydrazone network (Fig. 12).⁹⁸ Viscometry measurements showed a sharp increase in the viscosity of the mixture upon mixing both components in the presence of catalytic amount of acid; ending with the formation of a gel in various solvents, which IR confirmed to be due to hydrazone bond formation. These gels were found to be responsive to pH: lowering the pH below pH 4 resulted in breakdown of the gel in favor for the sol state, while subsequently increasing the pH again restored the gel. Moreover, rheological studies showed that a cut gel was able to completely recover its original properties after self-healing for 24 h under ambient conditions. The gel's self-healing process was accelerated to 8 h, when coated with acetic acid which catalyzed the hydrazone formation (Fig. 12).⁹⁹

DIELS-ALDER AND *RETRO*-DIELS-ALDER REACTION

The Diels-Alder reaction is a [4 + 2] cycloaddition reaction between a conjugated diene and a double bond-containing dienophile, forming a six-membered cyclohexene ring.¹⁰⁰ After discovery of the (forward) Diels-Alder reaction, also the backward *retro*-Diels-Alder reaction was described.¹⁰¹ A beneficial feature of the Diels-Alder reaction is that it is a self-contained reaction, preserving all atoms and it does not require a catalyst. Diels-Alder reactions can be facilitated by making one of the reactants electron-rich (the diene) and the other electron-poor (dienophile). The net effect of the Diels-Alder reaction is the conversion of two π bonds into σ bonds, rendering the reaction exothermic. As a consequence, the *retro*-Diels-Alder is endothermic, thus generally elevated temperatures are required to proceed.¹⁰¹ Recent efforts have focussed on lowering the temperature required to favor the *retro*-Diels-Alder reaction (*vide infra*).

To date most of the DC polymers based on Diels-Alder chemistry are network polymers. Before discussing this large class of polymers, the examples describing polymers relying on reversible main and side chain crosslinking by Diels-Alder reactions will be discussed.

Main Chain

The Lehn group reported linear polymers that are dynamic at room temperature,¹⁰² relying on earlier work on the Diels-Alder reaction between a fulvene derivative and diethylidicyanofumarate, which was found to be reversible at

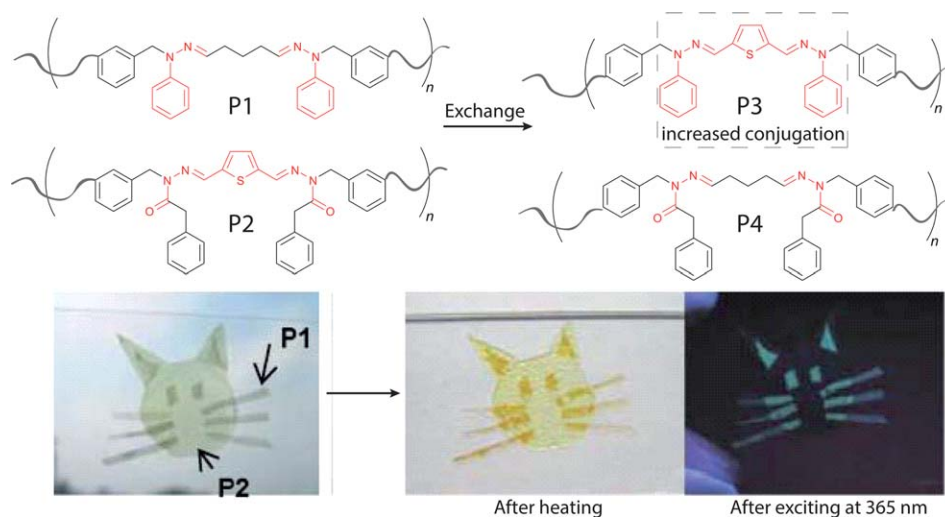


FIGURE 10 Polyhydrazones that upon exchange reaction in their interface yield different absorption and fluorescence properties. Reproduced from Ref. 85 with permission from RSC.

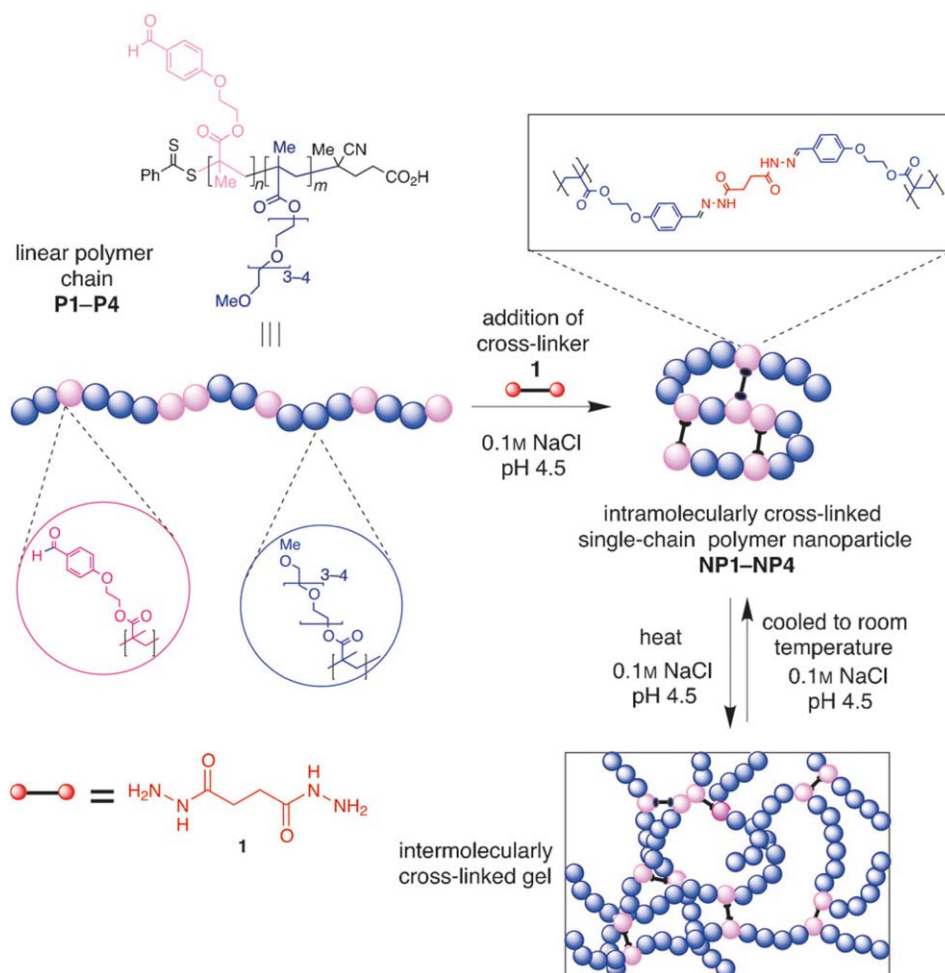


FIGURE 11 Chemical structure of the polymer functionalized with aldehyde side chains and schematic representation of the cross-linked structures obtained by acyl hydrazone formation. Reproduced from Ref. 96 with permission from Wiley.

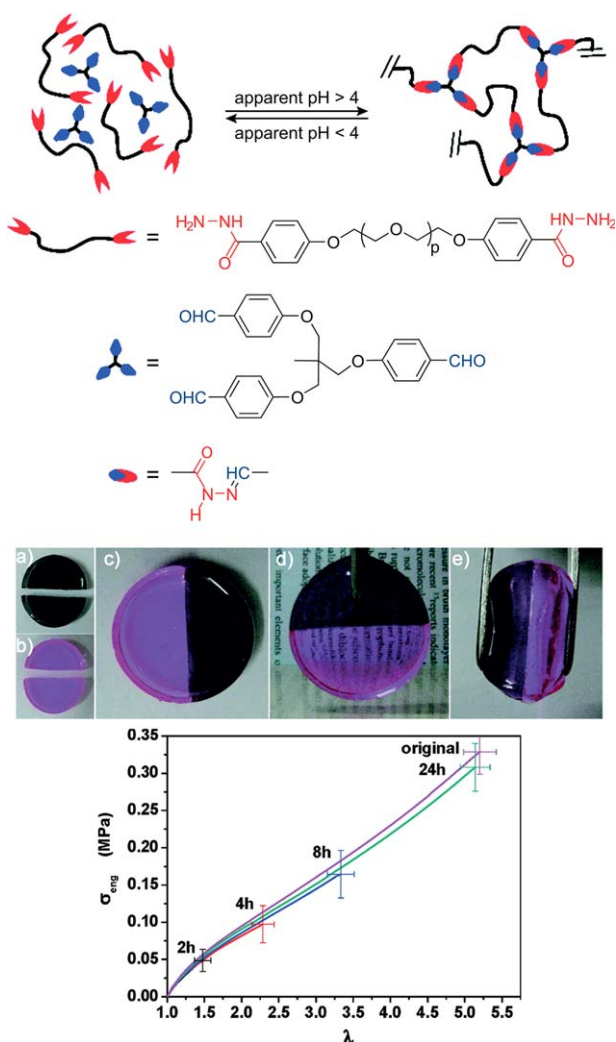


FIGURE 12 Chemical structure of the bishydrazide and trialdehyde units and the formation of the hydrazone network (top). Gels obtained from the system shown above and its macroscopic self-healing ability doped with different dyes to facilitate the visualization (middle). Engineering stress (σ_{eng}) against extension ratio (λ) for the gel self-healed for different times (bottom). Reproduced from Refs. 98 and 99 with permission from ACS.

ambient conditions.¹⁰³ Reaction of a *bis*(fulvene) and a *bis*(tricyanoethylene-carboxylate) or *bis*(dicyanofumarate) resulted in a rapid equilibration of the mixture and concomitant polymer formation (Scheme 9), as monitored by DOSY and SANS.

The polymer film properties could be modulated by addition of a tetrafunctional fulvene crosslinker. Finally, for the dynamic polymer prepared from the *bis*(fulvene) and the *bis*(dicyanofumarate), it was found that simply pressing two freshly cut polymer film fragments for 10 s at room temperature was sufficient to heal the film (Fig. 13).

Instead of a [4 + 2] cycloaddition, Xu et al. relied on the reversible photo [4 + 4] cycloaddition of anthracene, which

in combination with reversible host-guest interactions between pillar[5]arene and imidazole, yielded a doubly dynamic polymer.¹⁰⁴ Chen and Chen reported a reversible photocleavable polyurethane by incorporation of a coumarin dimer, formed by a photo [2 + 2] cycloaddition.¹⁰⁵

Side Chain

To date, most of the reported DC polymers that are based on the Diels-Alder reaction, rely on furan as the diene.^{106–109} Both the groups of Bapat et al.¹⁰⁶ and Barthel et al.¹⁰⁷ relied on a thermoreversible Diels-Alder reaction to control the crosslinking of micelles. The former group prepared alternating block copolymers of maleic anhydride and styrene by RAFT, which in a second step were reacted with furfurylamine to append furan moieties from the polymer backbone by a ring-opening reaction with the anhydride (Fig. 14).¹⁰⁶

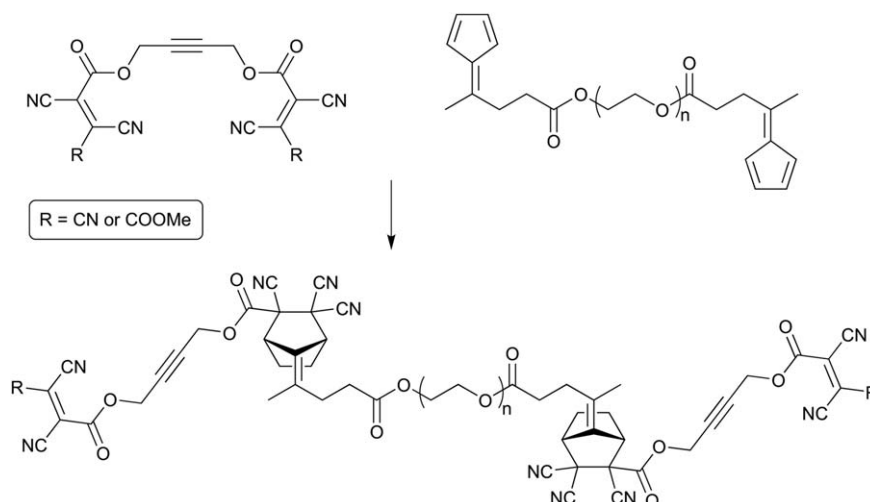
Addition of a *bismaleimide* at 50 °C resulted in the formation of core-crosslinked micelles, as observed by SEC, light scattering, TEM, and AFM. Upon heating the micelles at 120 °C for 30 min, SEC and DLS showed near-completed dissociation to unimers. The process of assembly/disassembly was found to be reversible over at least four cycles (Fig. 14). A similar thermoreversible control over micelle formation was achieved for a PEG-PFGE (poly(furfuryl glycidylether) diblock copolymer (prepared by living anionic ring opening polymerization), which was allowed to react with a *bismaleimide* crosslinker.¹⁰⁷

The Wang group used the Diels-Alder reaction between furfurylamine and *N*-aminoethylmaleimide to create a diamino crosslinker with an internal Diels-Alder adduct.¹⁰⁸ This thermoresponsive crosslinker was reacted with a *bis*epoxy monomer, resulting in a crosslinked epoxy monomer, whose crosslinks are thermoreversible. The thus formed polymer combines thermoplastic and thermoset features, imparting self-healing properties to the material. At ambient conditions it behaved like a classic thermoset, but at elevated temperature (75 °C) the polymer could be reprocessed and remoulded.

Kang et al. recently reported the formation of thermoreversible block copolymers containing pendant triphenylamine (A) and furan (B) by anionic polymerization, resulting in an A-B-A block copolymer.¹⁰⁹ Upon addition of a *bismaleimide* crosslinker at 50 °C a crosslinked polymer was formed, as evidenced by DSC, which showed a large increase in T_g due to reduction in chain mobility. DSC also confirmed the reversible nature of the crosslinks: in the heating curve at 149 °C an intense endothermic peak was found, while in the cooling curve a broad exothermic peak at 112 to 163 °C was observed, indicating occurrence of the *retro*-Diels-Alder reaction and Diels-Alder reaction, respectively.

Network

Pioneering work on Diels-Alder-based DC polymer networks that are thermoresponsive was performed by the Wudl group.¹¹⁰ In their 2002 *Science* paper they reported how the Diels-Alder reaction between a tetrafunctional furan



SCHEME 9 Preparation of a self-healing Diels-Alder-based polymer.¹⁰²

monomer and a trifunctional maleimide monomer yielded a crosslinked polymer material after dropcasting (Scheme 10).

The mechanical properties of the polymer were found to be comparable to commercial crosslinked epoxy resins and unsaturated polyesters. However, in contrast to these materials, the reversibility of the Diels-Alder reaction, allowed partial disruption of the network upon heating: approximately 25% of the Diels-Alder adducts disconnected at 150 °C, as probed by UV-Vis spectroscopy. Subsequent quenching and reheating to 80 °C restored practically all connections. DSC and solid state ¹³C NMR spectroscopy provided further evidence for the thermoreversible nature of the Diels-Alder bonds. As a consequence, a fractured specimen could heal by pressing the two fractured pieces together at a temperature of 120 to 150 °C (under nitrogen for 2 h) (Fig. 15). Fracture tests revealed a remarkable healing efficiency: 57% recovery with respect to the original fracture load. In a follow-up

paper the group also showed that these materials could be further improved in the sense that they could also be prepared solvent-free as a colorless, transparent material.¹¹¹

Later, more research groups have incorporated the furan-maleimide Diels-Alder chemistry in crosslinked polymer materials to achieve self-healing behavior.^{112–116} Extending earlier work from their group,¹¹⁷ Pratama et al. showed how this type of chemistry can be integrated in an epoxy-amine thermoset to yield autonomic self-healing by encapsulation of a polymaleimide healing agent.¹¹³ Zhang et al. combined the furan-maleimide Diels-Alder chemistry with a noncovalent fourfold hydrogen bonding motif in a polymer network.¹¹⁴ They selected the latter moiety for its highly dynamic exchange behavior at room temperature, while the former moiety requires elevated temperatures. As a consequence the material showed only partial healing at room temperature, but could fully heal upon long exposure at 90 °C. A beneficial effect of the slow Diels-

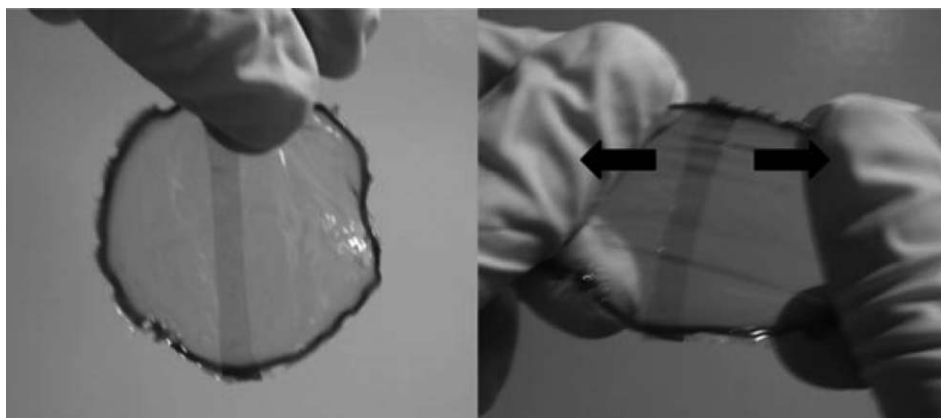


FIGURE 13 A self-healed thin film of a Diels-Alder-based polymer (Scheme 9) after self-healing (left) capable of elongation (right). The darker rectangular region in the centre is the area where the two pieces were superposed and the self-healing took place. Reproduced from Ref. 102 with permission from Wiley.

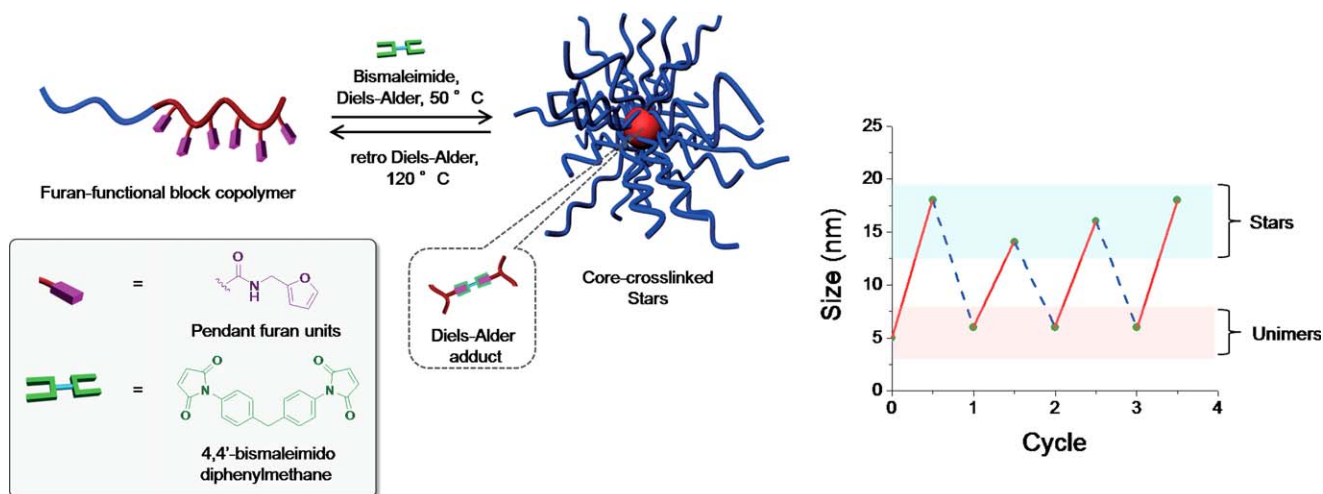


FIGURE 14 Schematic overview of the assembly and disassembly of DC star polymers based on Diels-Alder chemistry (left). By SEC the cyclic switching between assembled (stars) and disassembled (unimers) state could be monitored (right). Reproduced from Ref. 106 with permission from RSC.

Alder exchange kinetics was the corresponding limited extent of creep and full recovery after release of the stress.

In order to prepare DC polymers, Inglis et al. used a hetero Diels-Alder reaction between a (trifunctional) dithioester and an α,ω -cyclopentadiene-functionalized PMMA polymer, which undergo a rapid [4 + 2] cycloaddition under ambient conditions.¹¹⁸ Heating at 80 °C for a short period of time (less than 5 min) resulted in the cleavage of the Diels-Alder bonds as observed by SEC and UV-Vis spectroscopy. Solvent-mediated rebonding was achieved at room temperature, yielding—remarkably—a crosslinked polymer with smaller PDI (2.14) than the original material (PDI = 2.57).

Following earlier work on the more classical furan-maleimide Diels-Alder chemistry to prepare thermo-remendable shape memory thermosets,¹¹⁹ The Du Prez group published in 2014 a new type of DC polymer based on the Diels-Alder reaction of 1,2,4-triazoline-3,5-dione (TAD) derivatives with indole groups (Fig. 16).¹²⁰ Initially, the authors showed how the TAD moiety—irrespective of whether it is linked to a polymer fragment or not—could be efficiently introduced on indole-containing polymer substrates, in a click-like reaction, and how the adduct could be subsequently “transclicked” by reaction of a (polymer-linked) diene.

This approach does not only allow for dynamic block copolymers, which could be disrupted at 120 °C, but also for dynamic polyurethane-based networks. The resulting material was able to heal a scratched surface by 1 h heating at 120 °C. Moreover, a fragmented polymer film could be remoulded at 120 °C under moderate pressures (Fig. 17).

The Constanzo group demonstrated that a soybean-based resin could be functionalized with thermally responsive Diels-Alder linkages. The resulting resin was incorporated into polyurethane two-component automotive formulations, yielding thermally responsive coatings.¹¹⁶

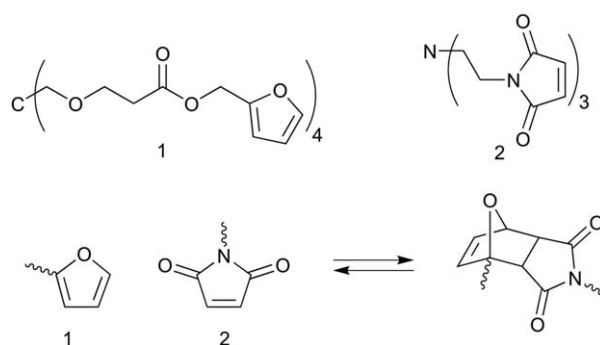
BORONATE ESTER

The condensation of a boronic acid and a diol leads to the formation of a stable, yet reversible boronate ester.¹²¹ Often a 1,2-diol or a 1,3-diol is employed in the condensation reaction, as these will lead to formation of a stable five- or six-membered ring, respectively; the former being the most stable of the two (Scheme 11).

As no catalyst is required, and since reversibility can be achieved also in aqueous medium, at room temperature, this type of DC bond has received a significant amount of attention,^{122,123} in particular in the formation of responsive hydrogels,¹²⁴ as further discussed below. While often sugars are used to react with boronic acids, it should be noted that because of the availability of multiple (i.e. more than two) hydroxyl groups per sugar molecule, crosslinking can occur.

Main Chain

First to report a linear boronic acid-derived condensation polymer were Mikami and Shinkai, who reported in 1995



SCHEME 10 Tetrafunctional furan-based monomer and trifunctional maleimide-based monomer that can reversibly form a self-healing network polymer via Diels-Alder chemistry.¹¹⁰

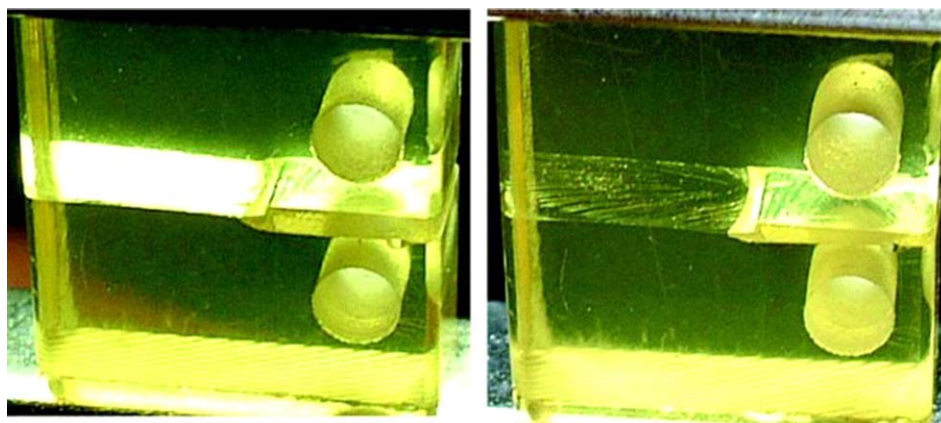


FIGURE 15 Damaged (left) and thermally healed (right) Diels-Alder-based polymer (Scheme 10). Reproduced from Ref. 110 with permission from AAAS.

how the reaction between bifunctional aromatic boronic acids and saccharides yielded polymers, as evidenced by circular dichroism (CD) spectroscopy.¹²⁵ In their work the boronic acid reacts both with the 1,2-diol and the 3,4- or 4,6-diol, i.e. crosslinking is not possible. Instead of a single saccharide, Nakazawa et al. used a bifunctional disaccharide to condense with a diboronic acid to create linear DC polymers, as probed by ¹¹B NMR spectroscopy and multiangle laser light scattering (MALLS).¹²⁶ By control over pD the polymer could be reversibly switched between associated (at pD = 10.8) and dissociated (at pD = 3). To avoid crosslinking that is typically observed for saccharide-derived DC polymers, Niu et al. selected pentaerythritol as *bis*diol to react with diboronic acid (Fig. 18).¹²⁷

Interestingly, the length of the formed linear polymer could not only be controlled by control over the monomer ratio, but also by postpolymerization processing: under reduced pressure longer polymers were formed. In contrast, by hydrolysis in wet chloroform a reduction in length was observed. This degraded material could be repaired by simply storing it under reduced pressure, which illustrates a self-healing mechanism operating for this DC polymer.

Hydrogels

Tarus et al. reported dynamic hydrogels derived from polysaccharides appended with either phenyl boronic acids groups or maltose groups.¹²⁸ The formation of a dynamic network resulting from the boronic ester crosslinks was confirmed by rheology. This network could be disrupted by either lowering the pH or addition of glucose, thus demonstrating the dynamic nature of the DC polymer network. Finally, also recovery of mechanical properties following application of stress to the materials underlines the dynamic nature of the material. Relying on a 1,2-benzoxaborole instead of a boronic acid, Kotsuchibashi et al., prepared dynamic hydrogels by appending this group on a methacrylate-based monomer, which was subsequently copolymerized with *N*-isopropylacrylamide (NIPAAm).¹²⁹ This polymer could reversibly form a hydrogel network when it was mixed with glycopolymers (poly(3-

gluconamidopropyl methacrylamide), PGAPMA or poly(2-lactobionamidoethyl methacrylamide), PLAEMA), and was sensitive to temperature, pH, and the presence of free glucose (Fig. 19).

Lin et al. later utilized the same benzoxaborole to prepare dynamic hydrogels with properties depending on the exact stereoconfiguration of the sugar.¹³⁰ Methacrylate-based polymers with either pendant mannose, galactose or glucose groups were found to form progressively worse gels, when mixed with a benzoxaborole-containing polymer. While all

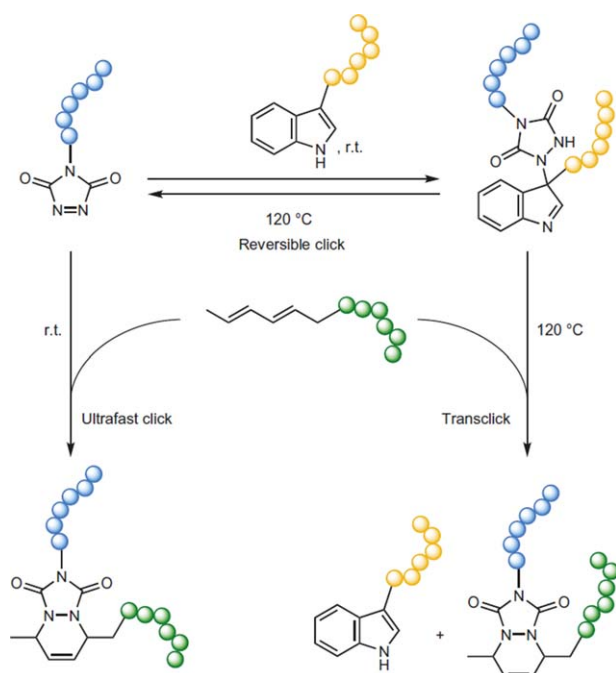


FIGURE 16 Schematic overview of TAD-based polymers, capable of reversible ligation through Diels-Alder reaction with indole derivatives, as well as of irreversible coupling. Reproduced from Ref. 120 with permission from NPG.

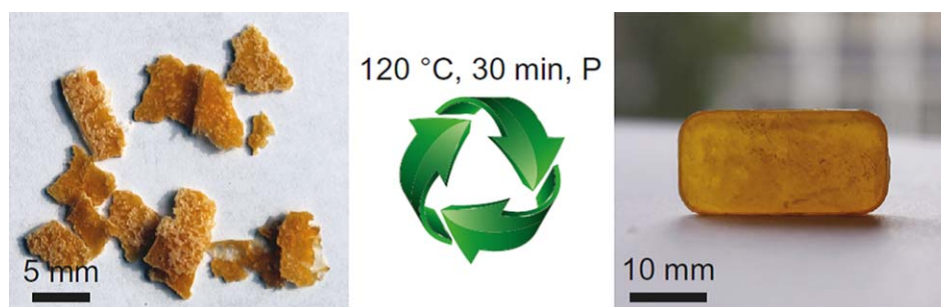


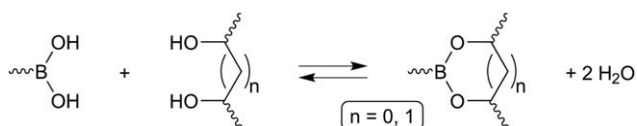
FIGURE 17 Image of a crosslinked TAD-based polyurethane sample that was broken into smaller pieces (left) and the same sample after being put into a mould under pressure at elevated temperature. Reproduced from Ref. 120 with permission from NPG.

hydrogels showed pH responsiveness, only the galactose- and glucose-based gels could be disassembled by addition of free glucose.

Cash et al.¹³¹ and Deng et al.¹³² have recently reported boronic acid-based self-healing hydrogels, extending earlier work from the same group on the self-assembly of boronic acid-terminated polymers¹³³ and on the boronic ester-based, reversible switching between a linear polymer and a polymer micelle.¹³⁴ The authors synthesized a boronic ester diene, which was subsequently reacted with a dithiol and tetrathiol via a photoinitiated thiol-ene reaction (Fig. 20).¹³¹ The thus formed polymer was found to be stable in water, suggesting that the relative hydrophobicity of the network was sufficient to retard water infiltration and concomitant material degradation by boronic ester hydrolysis. However, when water was applied to the exposed interface of a cut disc-like sample, self-healing occurred within minutes, leading ultimately full recovery after 4 days (Fig. 20). Tensile testing at 85% humidity quantitatively confirmed the self-healing properties of the network through multiple cycles, while also showing a dependence on the relative amount of dithiol.

The same group demonstrated that instead of a boronic acid, a modified intramolecularly coordinating boronic acid monomer, 2-acrylamidophenylboronic acid could be used for boronate ester-based self-healing hydrogels.¹³² The internal coordination helped to stabilize the crosslinks at acidic and neutral pH, thus extending the use of boronate esters in DC polymer (networks) beyond the typically required basic conditions.

Roberts et al. showed that instead of a diol moiety also a salicylhydroxamic acid can be used to form phenylboronate-salicylhydroxamate-based hydrogels.¹³⁵ In contrast to more classical borate-polyol hydrogels that typically require basic conditions for exchange, this alternative chemistry allows



SCHEME 11 Reversible reaction between a boronic acid and a diol, yielding a boronate ester.

reversibility under physiological conditions, rendering the gel an interesting vehicle for drug delivery, cell encapsulation, or biomedical implants.

Next to the various reports on hydrogels, there is a limited number of publications on organogels based on boronate esters. Dai et al. reported dynamic gels based on reversible phenylboronic acid-diol esters, prepared by crosslinking of *N,N*-dimethylacrylamide-4-((4-vinylbenzyloxy)-carbonyl)phenylboronic acid copolymer, poly(VPB-*co*-DMA), and poly(2,2-bis(hydroxymethyl)butyl acrylate) (PHBA) in several organic solvents at ambient temperature.¹³⁶ Gels prepared in DMF were found to be able to repeatedly self-heal. In a follow-up contribution the same group showed how this kind of organogels could be used to create dynamic hybrid gels containing single-walled carbon nanotubes.¹³⁷

ALKOXYAMINES

Alkoxyamines can yield stable radical species involving the breakage of the C–ON bond, especially if the nitrogen atom

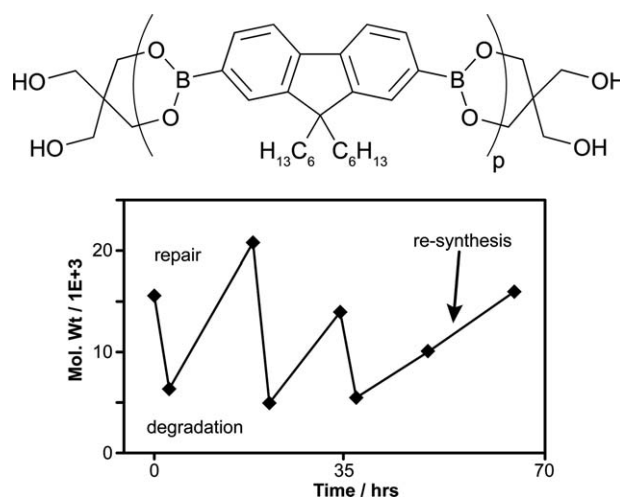


FIGURE 18 Chemical structure of the boronate ester-based self-healing polymer (top) and its cycling between hydrolytic degradation and repair under reduced pressure, as evidenced by its MW (from GPC). Reproduced from Ref. 127 with permission from RSC.

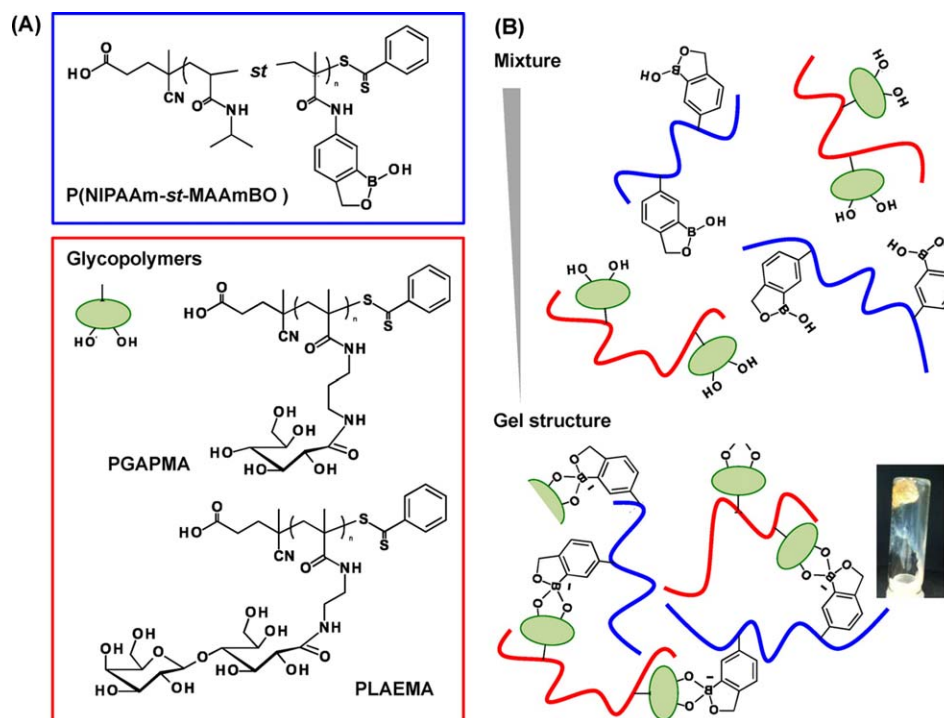


FIGURE 19 (A) Chemical structure of benzoxaborole-containing PNIPAAm polymer and the poly(3-gluconamidopropyl methacrylamide) (PGAPMA), and poly(2-lactobionamidoethyl methacrylamide) (PLAEMA). (B) Schematic overview of their reversible gel formation via boronic-diol interactions. Reproduced from Ref. 129 with permission from ACS.

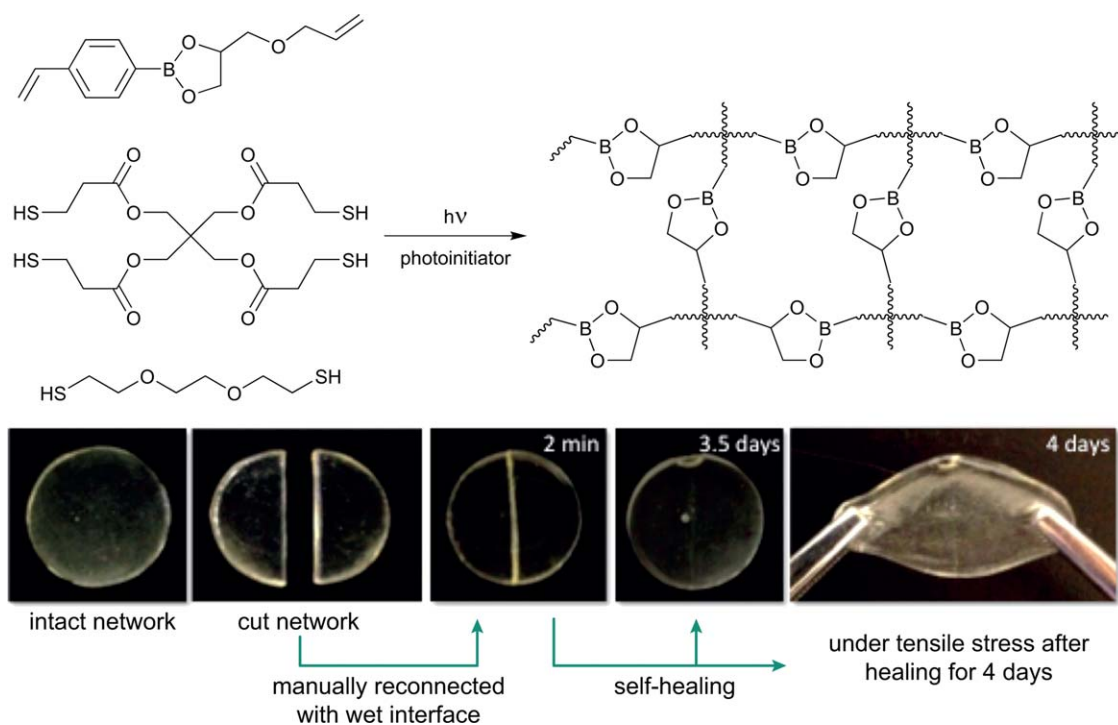
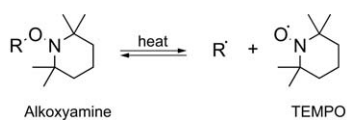
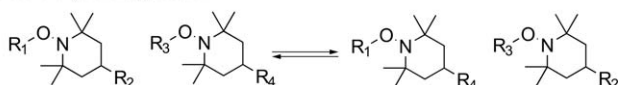


FIGURE 20 Chemical synthesis of the DC boronic ester polymer network (top) and its self-healing behavior over a period of 4 days. Reproduced from Ref. 131 with permission from ACS.



Cross-over (exchange) reaction:



SCHEME 12 Formation of radical TEMPO (top) and cross-over reaction between alkoxyamines (bottom).

bears two bulky substituents which stabilize the nitroxide free radical formed when subjected to high temperatures (Scheme 12). Nitroxides have been widely used since the 1990s as initiators in nitroxide-mediated polymerization (NMP),^{138–140} which is a type of living polymerization in which this DC group, mostly incorporated as a 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) unit, is responsible for the narrow polydispersities typical for this method even at elevated conversions. In this process the key step is the formation of the stable free radical TEMPO which can react with the short time radical from the growing chain in a reversible manner, thus protecting it from termination reactions.

It was soon after the discovery of this polymerization method when Hawker et al. described exchange reactions (also considered radical crossover reactions) for this DC bond.¹⁴¹ In order to confirm the exchange reactions during polymerization, they used mixtures of different alkoxyamines as initiators for the polymerization of PS. The chemical structure of the initiators was carefully chosen so that by HPLC analysis was possible to differentiate between chains containing each unit of the alkoxyamine. After different reaction times, HPLC chromatograms revealed the crossover reactions by comparison with the polymerization reactions in which only one initiator was used. Turro et al. used the crossover reaction between alkoxyamines to synthesize monodisperse polymers end-functionalized with photoactive groups.¹⁴² This was achieved by adding the appropriate alkoxyamine bearing the photoactive group in excess at the end of the polymerization under equilibrium conditions (125 °C).

Main Chain

The use of alkoxyamines as the driving force to yield polymers and not only to postfunctionalize—or to initiate polymerizations—was extensively used by Otsuka¹⁴³ to obtain a large variety of polymer architectures. In an early work¹⁴⁴ the group found that above 60 °C the crossover reaction between small TEMPO-containing alkoxyamines takes place, and the higher the temperature was, the faster the reaction reached the equilibrium (e.g. 12 h for 100 °C). When two different chain length alkoxyamine-based polyesters ($M_n = 12,000$ and 4300) were mixed and subsequently heated, a new polymer with a M_n of 5600 was obtained, due to the crossover reaction between the DC bonds as evidenced by comparison of the GPC profiles before and after heating.¹⁴⁴ This approach was used to tune the MW of the final

polymers, although this could only be achieved at the expense of increasing PDI values.¹⁴⁵ For this polymer the equilibrium shift between macrocyclic and polymeric species was also shown, which was facilitated by intermolecular crossover reactions, as evidenced by GPC and fast atom bombardment (FAB) MS measurements.¹⁴⁶ These results are indirect evidence for the dynamic nature of the polymer.

A similar approach reported by the same group was utilized but mixing different polymers, a polyester and a polyurethane, bearing also alkoxyamines as depicted in Figure 21, yielding scrambling of the polymer monomers

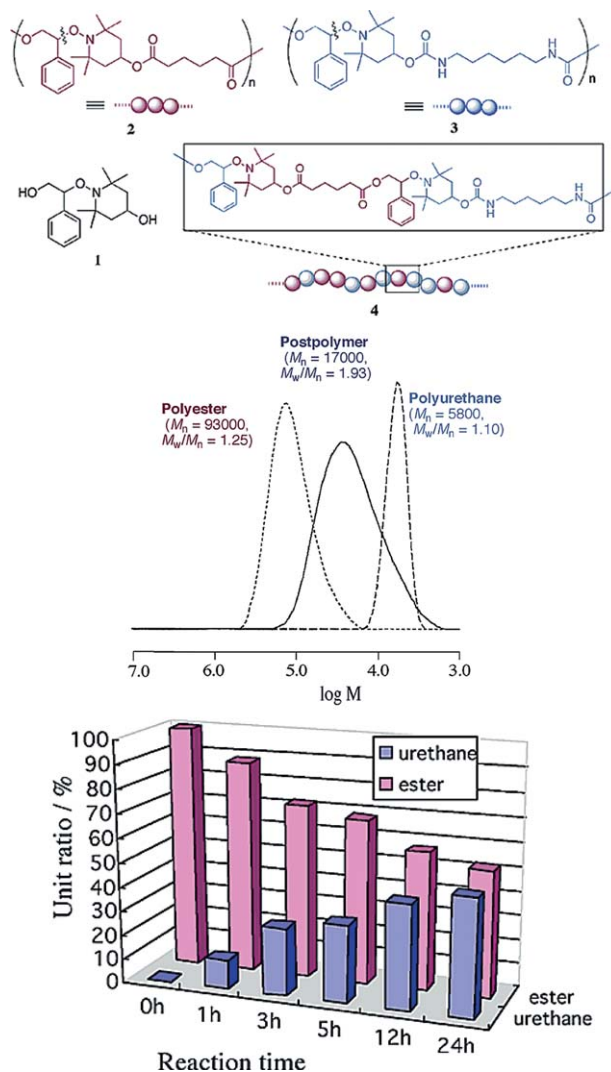


FIGURE 21 Chemical structure of the two different alkoxyamine-based polymers used to show its dynamic character (top). GPC profiles showing the change in MW distribution before and after the exchange reaction (middle). Unit molar ratios of the ester and urethane moieties after the exchange reaction of polyester and polyurethane (bottom). Reproduced from Ref. 147 with permission from ACS.

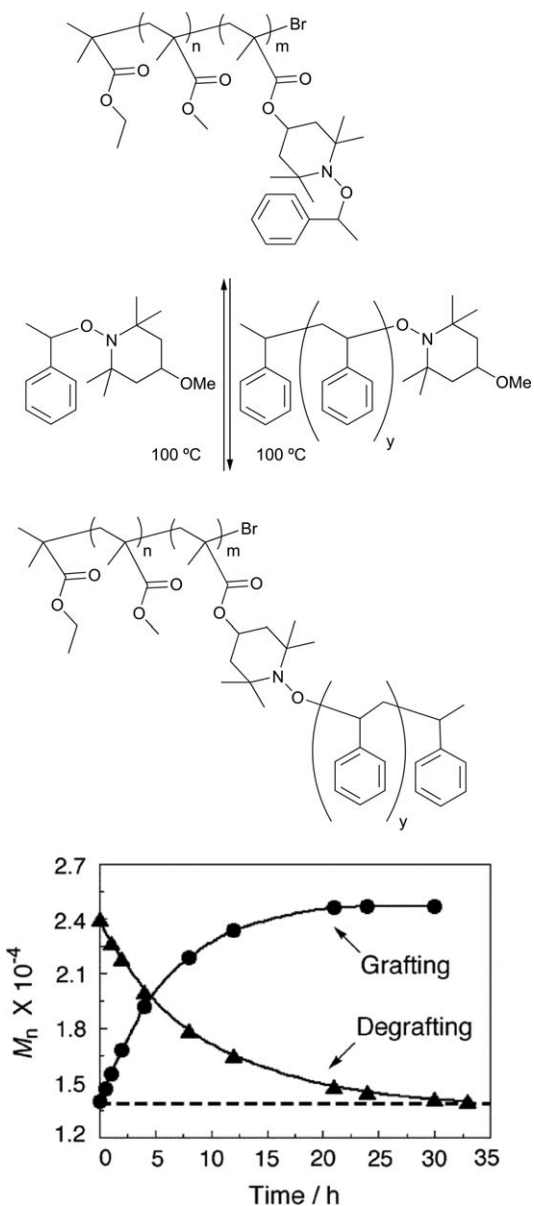


FIGURE 22 Chemical structures of the reaction to obtain the grafted polymer by alkoxyamine exchange and the degrafting process (top). Change in the MW with time upon heating at 100 °C in anisole in presence of the grafting polymer (circles) and with 50 eq. of small molecule of alkoxyamine (triangles) (bottom). Reproduced from Ref. 148 with permission from ACS.

already after 1 h, as evidenced by HPLC, GPC, and ^1H NMR experiments.¹⁴⁷

Side Chain

Dynamic exchange of the alkoxyamine bond is rather tolerant with a variety of functional groups, provided that they withstand 100 °C. Introducing an alkoxyamine in a polymerizable monomer can lead to grafted copolymers by simple addition of an end-functionalized alkoxyamine polymer. Higaki et al. used this approach,¹⁴⁸ synthesizing a methacrylate

copolymer bearing alkoxyamines in the side chain, as shown in Figure 22. After the reaction with an alkoxyamine-terminated polystyrene, a grafted polymer was obtained. The formation of the grafted polymer could be reversed by the addition of excess (8.3 eq.) of a small alkoxyamine molecule and heating up to 100 °C, as shown by GPC (Fig. 22).

DC chemistry can also be a powerful tool for the functionalization of surfaces in a reversible manner. Sato et al. have also explored the alkoxyamine for this purpose and have shown by XPS the growth of a polymer brush with alkoxyamine units on its side chains on silicon.¹⁴⁹ The alkoxyamines were able to undergo exchange reaction with an alkoxyamine terminated poly(2,3,4,5,6-pentafluorostyrene) (PPFS) upon heating at 100 °C in anisole yielding a PPFS-grafted polymer brush as inferred from the increase in the fluorine 1s peak in XPS. Although the grafting was only successful in the outer surface, due to the difficult diffusion of the long polymer into the reactive brush, it was shown to be reversible by heating with excess of small-molecule alkoxyamine. A similar strategy was used later on to graft an hydrophilic polymer and turned out to be a successful tool to tune the hydrophilicity of the silicon surface.¹⁵⁰ More recently, it was used to tune the dispersibility of silicon nanoparticles, depending on the nature of the grafted polymer.¹⁵¹

Network

Sato et al. have also used the alkoxyamine units for the synthesis of polymer networks. Two different copolymers containing complementary reactive alkoxyamines in their side chain, (in such a way that the two different alkoxyamines can crossover) led to the formation of crosslinked polymers, as shown by the gel formation (Fig. 23).¹⁵² The gel state could be disrupted back to the solution by adding an excess amount of a small molecule alkoxyamine and heating at 100 °C for 48 h, which shifted the equilibrium to the de-crosslinked state as shown by the GPC profiles, which corresponded to the mixture of the initial polymers. Reversible hydrogel formation was also described for water-soluble polymers functionalized with alkoxyamine side chains.¹⁵³

In a follow-up contribution,¹⁵⁴ the same group combined two alkoxyamine features (DC bond and initiator for NMP), by reporting a polymer network obtained by alkoxyamine crosslinking, which could also insert styrene units at the crosslinking points. The insertion of styrene was performed by swelling the polymer network in a mixture of styrene and anisole.

By increasing the rational design on these DC polymers, more sophisticated polymer structures could be constructed: when alkoxyamines were selectively introduced in one block of a diblock polymer, instead of crosslinking the whole polymer, selective crosslinking across the block containing the alkoxyamines took place and star nanogels could thus be obtained.^{155–157} The equilibrium was reached after 24 h and monitored by GPC, together with HPLC for the release of alkoxyamine. The star-shaped polymers were directly

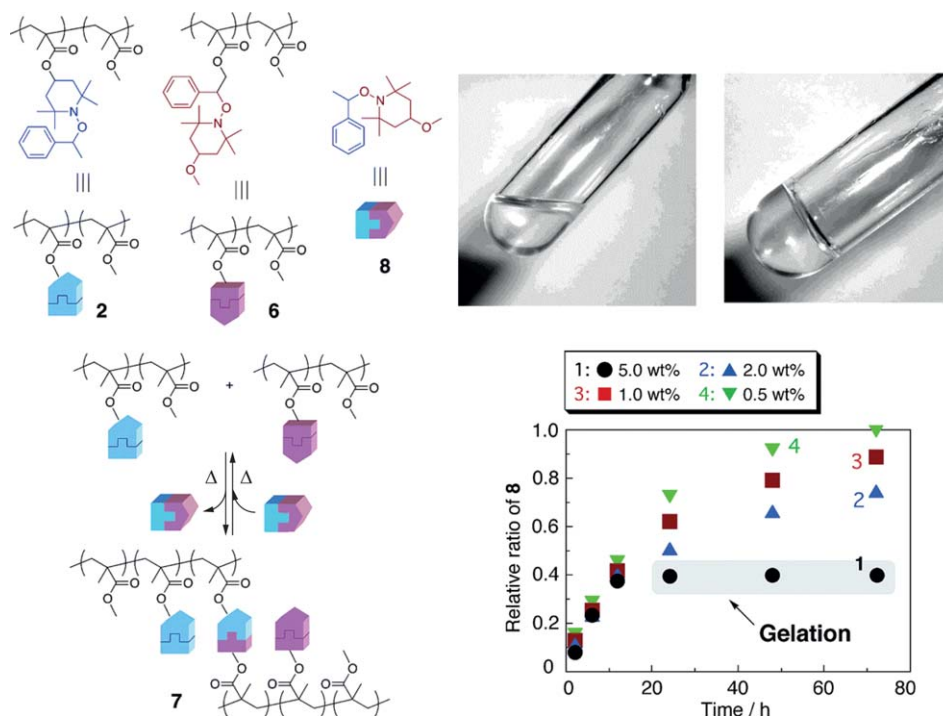


FIGURE 23 Representation of the crosslinking process by exchange of the alkoxyamine groups (left). Pictures before and after heating in anisole (100 °C, 24 h, 10 wt %) a mixture of both polymers (right, top). Dependence of the relative ratio of small alkoxyamine on reaction time for the crosslinking reaction at different concentrations in anisole at 100 °C (Right, bottom). Reproduced from Ref. 152 with permission from ACS.

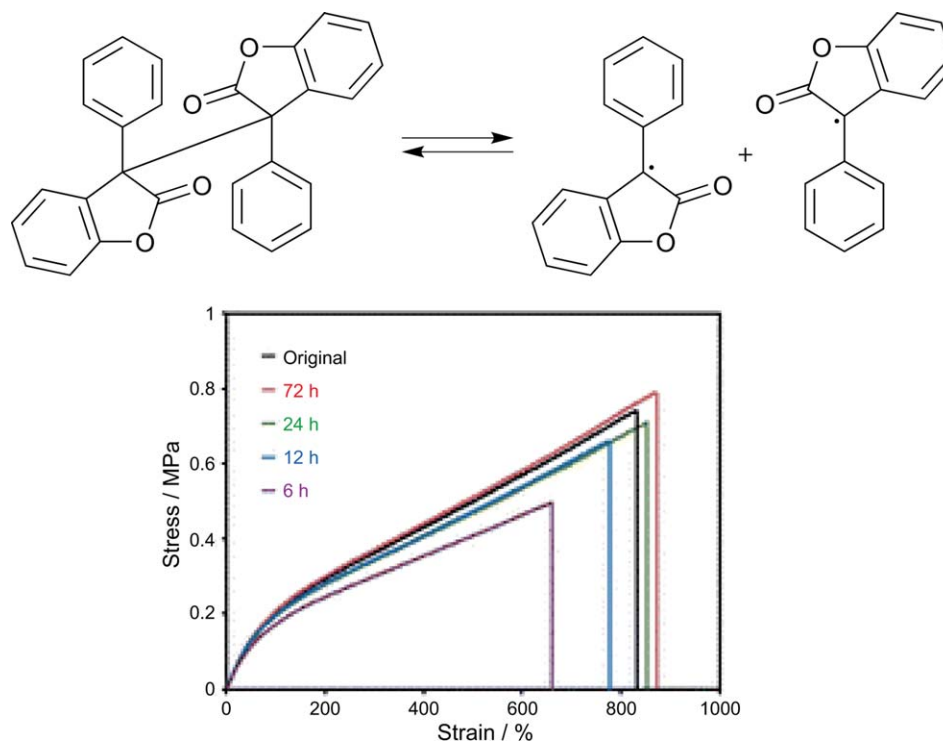


FIGURE 24 Reversible dissociation of a diarylbibenzofuranone into two carbon-centered radicals (top) and typical stress-strain curves for the diarylbibenzofuranone-based polymer before and after healing for different times at 50 °C (bottom). Reproduced from Ref. 167 with permission from ACS.

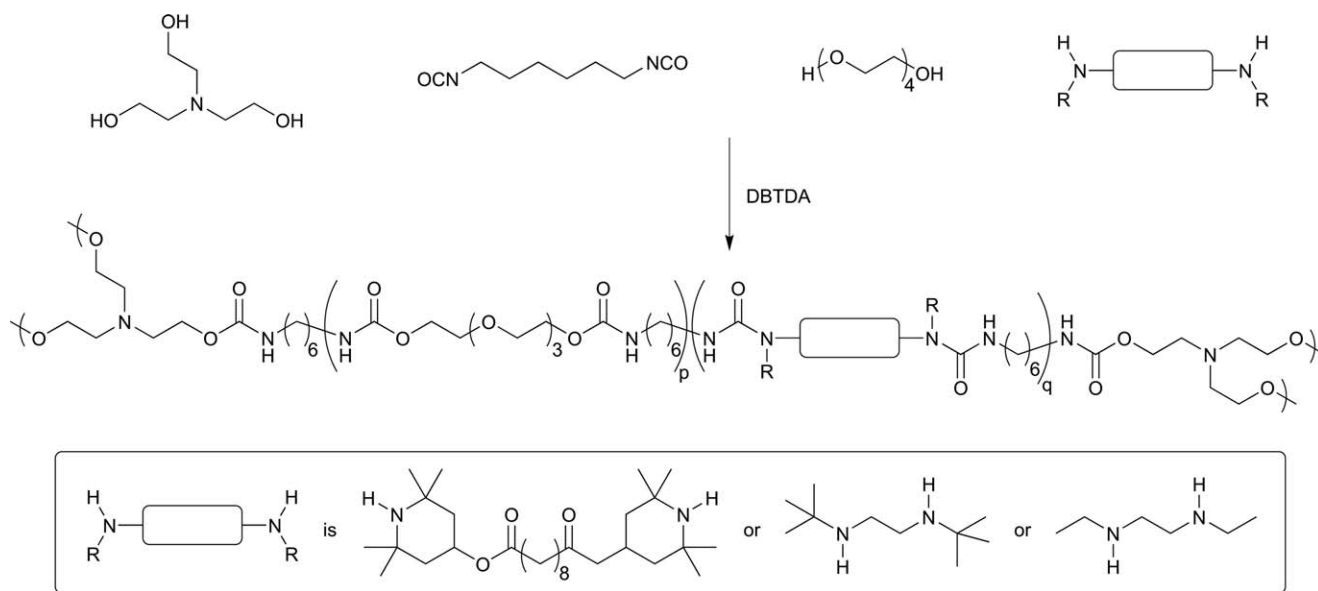


FIGURE 25 Synthesis and structure of the DC polymer featuring hindered ureas.¹⁶⁹

visualized by scanning force microscopy. Moreover, this switch between block copolymers and star-nanogels was shown to be reversible when subjected to heating and addition of excess (40 eq.) of a capping alkoxyamine. Increasing the complexity of the final polymer architectures was achieved by using two different block copolymers with complementary alkoxyamine blocks. This combination yielded star-like nanogels with different arm lengths.^{158,159}

OTHERS

We conclude our discussion of DC chemistries used in polymer synthesis with an overview of chemistries that cannot be classified in the above categories.

Based on early work on dynamic polymers derived from spiroorthoesters^{160–162} or bicyclo orthoesters,^{163,164} the Endo group have shown that also six-membered cyclic carbonates can undergo reversible ring opening polymerization (ROP). Equipping the cyclic carbonate with a styrene monomer resulted, after ROP, in a linear polymer with pendant styrene groups. Radical crosslinking of the linear polymer was achieved via the styrene groups, while in a second step de-crosslinking was possible through anionic depolymerization.

Thermally responsive dynamic polymers based on the reversible dimerization of carbene were reported by Kamplain and Bielawski.¹⁶⁵ Temperature- and concentration-dependent ¹H NMR experiments on polymerized bifunctional carbenes confirmed the dynamic nature of the polymerization, reminiscent of a classical step-growth polymerization. The dynamic nature of the polymer also allowed introduction of a chain transfer agent to control polymerization or end group functionalization. Imato et al. demonstrated that the reversible dissociation of a diarylbibenzo-furanone into two carbon-centered radicals can be used to create polyurethane networks that can undergo exchange at ambient

temperature.^{166,167} The self-healing behavior was evaluated on the macroscopic level by mechanical testing (Fig. 24) and on the microscopic level by EPR.

Scott et al. reported a covalently crosslinked network capable of undergoing photomediated reversible cleavage of its backbone by relying on addition-fragmentation chain transfer between an thiyl radical and a carbon-carbon double bond.¹⁶⁸ A key feature of the network is that while the topology of the network changes, the polymer chemistry and network connectivity are unaltered. The resulting material thus allowed for photoinduced plasticity, actuation and equilibrium shape changes without residual stress in the polymer.

By cleverly designed hindered ureas, Ying et al. showed that the urea's C–N bond can be weakened to such an extent that they can be considered a DC bond.¹⁶⁹ Incorporation of these hindered ureas in poly(urethane-urea) networks yielded a dynamic material (Fig. 25), capable of autonomous self-healing at low temperatures, without the need of a catalyst. Recovery rates up to 87% could be achieved. By control over the size of the substituent the rate of exchange could be varied, with concomitant effect on the mechanical properties of the corresponding polymer material.

CONCLUSION

While relatively late to arrive at the scene compared to supramolecular polymers (based on noncovalent interactions), dynamic covalent polymers have gained a lot of attention in recent years in the area of *smart* polymer materials. In this Highlight we have demonstrated how the inherent dynamic nature of various dynamic covalent bonds constituting these polymers can impart features such as adaptivity and responsiveness to the materials.

OUTLOOK

In the near future we foresee the further development of DC chemistries in polymers, in particular by the incorporation of multiple dynamic interactions. Recent efforts into this direction have already demonstrated that it can lead to a more fine-tuned control over the material properties as it becomes sensitive to more than one stimulus. For example, the combination of DC imine and disulfides bonds,¹⁷⁰ the combination of DC imines and boronic esters¹⁷¹ and the dual use of host-guest chemistry and DC bonds¹⁰⁴ have all been successfully employed to create multistimuli-responsive materials.

The combination of multiple DC chemistries can also facilitate a more systematic design of structurally dynamic polymer materials. Rowan and co-workers coined the term *systems materials* to emphasize this development of “new structurally dynamic systems that use a multitude of components designed to work synergistically and lead to the evolution of new, increasingly complex materials behavior and responses.”¹⁷² In line with such a systems materials approach, Cromwell et al. demonstrated how the use of tuneable rates of boronic ester transesterification allowed tuning of the malleability and self-healing efficiencies of bulk materials.¹⁷³

Within the context of *systems materials* the synthesis and functioning of DC polymers under nonequilibrium conditions is foreseen to gain more attention. While traditionally the formation of DC polymers is achieved under thermodynamic control, in the future researchers will more and more focus on out-of-equilibrium states to achieve new material function and behavior; with increased complexity, more on a par with the complexity found in (dissipative) living systems.¹⁷⁴

Another avenue that will undoubtedly be further explored in the future is related to the development of autonomously behaving DC polymer materials, i.e. materials in which they achieve their responsive/adaptive behavior without the need of an externally applied stimulus. For example, self-healing coatings and materials that can spontaneously heal when damaged without the need for heat, light or another stimulus.

Finally, to fully harness the potential of DC polymer materials, their use should be extended beyond the academic realm into the industrial environment. As reviewed in this Highlight, the development of DC polymer materials has seen a rapid development, but this has led so far to very few commercial applications of these materials. To this end, polymer chemists, material scientists and process engineers will have to work together to be able to convert academically interesting findings into polymer materials with commercial value.

As highlighted above, the design and synthesis of dynamic covalent polymers is a research area in which there has been much recent innovation that undoubtedly will continue to advance, thus remaining a fertile ground for the development of novel *smart* polymer materials with advanced functionality.

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