

REVIEW

View Article Online
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Cite this: *Polym. Chem.*, 2020, **11**, 1410

Received 8th November 2019,
Accepted 24th January 2020

DOI: 10.1039/c9py01694e

rsc.li/polymers

Dynamic covalent bonds in self-healing, shape memory, and controllable stiffness hydrogels

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Emerging technologies are increasingly reliant on materials that deliver multiple functionality. For example, hydrogels using dynamic covalent crosslinks have proven well-suited for the preparation of functional systems with properties including self-healing, shape memory, and stimuli-induced stiffness changes. These covalent bonds are capable of exchanging, dissociating or switching in response to various stimuli. In this review stimuli responsive dynamic covalent hydrogels are discussed on the basis of their chemistry and how the gels are increasingly used in novel applications. Challenges and potential future developments of dynamic covalent hydrogels are also discussed.

Introduction

Hydrogels are three-dimensional networks synthesized by crosslinking hydrophilic (macro)molecules which can absorb and retain a large amount of water.¹ The term 'hydrogel' was first used in scientific literature in the 1890s when it was used to describe a colloidal gel of inorganic salts.² In 1960 Wichterle and Lim were the first to define hydrogels as three dimensional, hydrophilic, crosslinked polymer structures in their article on poly(2-hydroxyethyl methacrylate) (PHEMA)

gels for use as soft contact lenses.³ Hydrogels are now used in many different areas including biomaterials (for drug delivery,^{4,5} cell culture,^{6,7} biomedical implants^{8,9} and regenerative medicine,^{10,11} contact lenses,^{12,13} pharmaceuticals,^{14,15} cosmetics,¹⁶ adhesives,¹⁷ adsorbents,^{18,19} and sensors.^{20,21}

Both synthetic and natural polymers have been used to prepare hydrogels,^{22,23} and the polymer chains can be cross-linked by a variety of chemical bonds or physical interactions.^{24,25} Naturally occurring polymers including polysaccharides, such as hyaluronic acid,²⁶ alginate,²⁷ and heparin,²⁸ and polypeptides, such as gelatin²⁹ and collagen,³⁰ are often used in hydrogels. These hydrogels are typically formed as physical gels. Physical gels are defined as networks held together by molecular entanglements, ionic interactions,

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hydrogen-bonding, hydrophobic interactions, and host-guest interactions.^{31,32} All these interactions are reversible, and can be disrupted by changes in physical properties such as pH, temperature, stress, or addition of a specific chemical stimuli.³³ Synthetic hydrogels use various chemistries to cross-link synthetic hydrophilic molecules,³⁴ and crosslinking results in hydrogels with relatively high mechanical strength.³⁵ The most widely used crosslinking reactions include free radical polymerization, condensation reactions, or orthogonal coupling reactions such as thiol-ene/yne reactions or alkyne-azide reactions.³⁶ Covalently crosslinked hydrogels are called chemical hydrogels, and cannot be dissolved in solvents unless covalent bonds are cleaved.³¹

Some hydrogels are prepared using dynamic bonds that can undergo structural changes in response to a given stimulus by reversibly forming and breaking under one set of conditions and under different conditions acting as permanent covalent bonds.³⁷ These hydrogels are commonly described as “dynamic hydrogels”. For example, hydrogels with disulfide crosslinks can undergo reversible exchange reaction in response to chemical or biological stimuli resulting in changes in matrix stiffness.^{38–40} Hydrazones are stable under neutral and basic conditions but readily hydrolyze under acidic conditions and exchange in the presence of hydrazides, aldehydes or ketones.^{41,42} Imines, the less stable homologs of hydrazones, are obtained from amines and aldehydes or ketones. Boronic esters are less stable, they hydrolyze quite easily and exchange in the presence of vicinal diols and catechols.⁴³ Collectively, these chemistries are attracting increasing attention to prepare dynamic hydrogels and the ability to change the physical properties of these gels have made dynamic hydrogels attractive candidates for a variety of applications.⁴⁴ Dynamic hydrogels including neutral³⁴ and ionic polymers,⁴⁵ degradable polymers,⁴⁶ proteins,⁴⁷ and nanoparticles⁴⁸ have been prepared that are responsive to stimuli such as temperature,⁴⁹ pH,⁵⁰ light,⁵¹ ligands, or biomolecules.⁵² Considering this, we have limited the scope of this review to dynamic hydrogels crosslinked *via* dynamic covalent bonds (Fig. 1).

We discuss how using the exchange reactions of these bonds under different stimuli give rise to properties such as stimuli responsiveness,^{53,54} shape memory,⁵⁵ and self-healing,^{56,57} and how these properties are increasingly used in novel applications.

Self-healing hydrogels

Synthetic materials capable of autonomous healing upon damage, defined as intrinsic and automatic healing,^{58,59} are being developed for potential applications including coatings,⁶⁰ sealants,⁶¹ tissue adhesives,⁶² soft robotics,⁶³ tissue engineering,⁶⁴ and drug delivery.⁶⁵ In the case of hydrogels, the most common types of damage are mechanical damage upon scratching, cracking, puncture, and delamination.⁶⁶ Healing of a damaged site in a hydrogel can be achieved by number of different strategies including reversible dynamic

covalent bonds,^{67,68} non-covalent interactions such as hydrogen bonding,^{69–71} supra-molecular host-guest interactions,^{72–74} electrostatic interactions,^{75,76} metal coordination,^{69,77} π - π stacking,^{78,79} hydrophobic arrangements,^{80–82} and molecular recognition.⁸³ Specific functional groups are required in all these mechanisms to mediate self-healing in the damaged region.⁸⁴

In this section we review hydrogels using dynamic covalent crosslinking chemistry to impart self-healing properties. Boronate complexation,^{85,86} disulfide bonds, Diels-Alder chemistry,^{87–89} oxime bonds,⁹⁰ imine bonds,⁹¹ hydrazone bonds,⁹² and alkoxyamine bonds⁹³ have all been used to prepare self-healing chemical hydrogels with or without various types of external stimuli (*e.g.* light, pH, or temperature).⁹⁴ For example, reversible boronic ester bonds have been used as complexation between boronic acids and 1,2- or 1,3-diols in aqueous solutions results in reversible covalent bonds (Scheme 1). Importantly, the stability of the bond depends on the pH of the solution.^{95,96}

Sumerlin and coworkers⁸⁵ demonstrated this by crosslinking polymer-bound phenylboronic acid (PBA) with either poly(vinyl alcohol) or a catechol-functionalized copolymer (Fig. 2a). The hydrogels demonstrated self-healing at neutral and acidic pH, where the cross-links reconstituted rapidly after removing an applied strain, restoring the moduli of the original hydrogel.

Kloxin, Sumerlin, and coworkers⁵⁷ similarly introduced self-healing properties into hydrogels under physiological conditions by crosslinking statistical copolymers of *N,N*-dimethylacrylamide and a pinacol protected ester of 2-acrylamidophenylboronic acid with poly(vinyl alcohol) (Fig. 2b). The self-healing property of these gels were demonstrated in relevant cell culture media and could be used in dynamic co-cultures of breast cancer cells and lung fibroblasts. Hydrogel ‘blocks’ loaded with the different cell types were self-healed to prepare the co-culture hydrogels. These co-culture hydrogels will enable study of cellular processes such as migration, mechanotransduction, and cell-cell signaling. Similarly, Cooper-White and coworkers⁹⁷ demonstrated the preparation of a cytocompatible and viscoelastic hydrogel with reversible boronate ester cross-links to probe timescale dependent mechanotransduction of fibroblasts. The viscoelastic properties (storage and loss moduli) of the gels were tuned using the equilibrium kinetics of the dynamic covalent crosslinks.

Imine bonds (Schiff bases)⁹⁸ undergo reversible imine-amine exchange and this reaction (Scheme 2a) can result in self-healing properties in imine crosslinked hydrogels.

For example, Maynard and coworkers⁴³ developed imine-crosslinked poly(ethylene glycol) (PEG) self-healing hydrogels that demonstrated self-healing in less than 10 min. The hydrogels also demonstrated degradability when treated with pH 5.6 cell culture media because of the pH sensitivity of the imine crosslinks, and were used to encapsulate murine mesenchymal stromal cells (mMSCs) cells to evaluate the controlled release of cells. Similarly, naturally-sourced chitosan has been used in preparing dynamic self-healing hydrogels using imine bonds

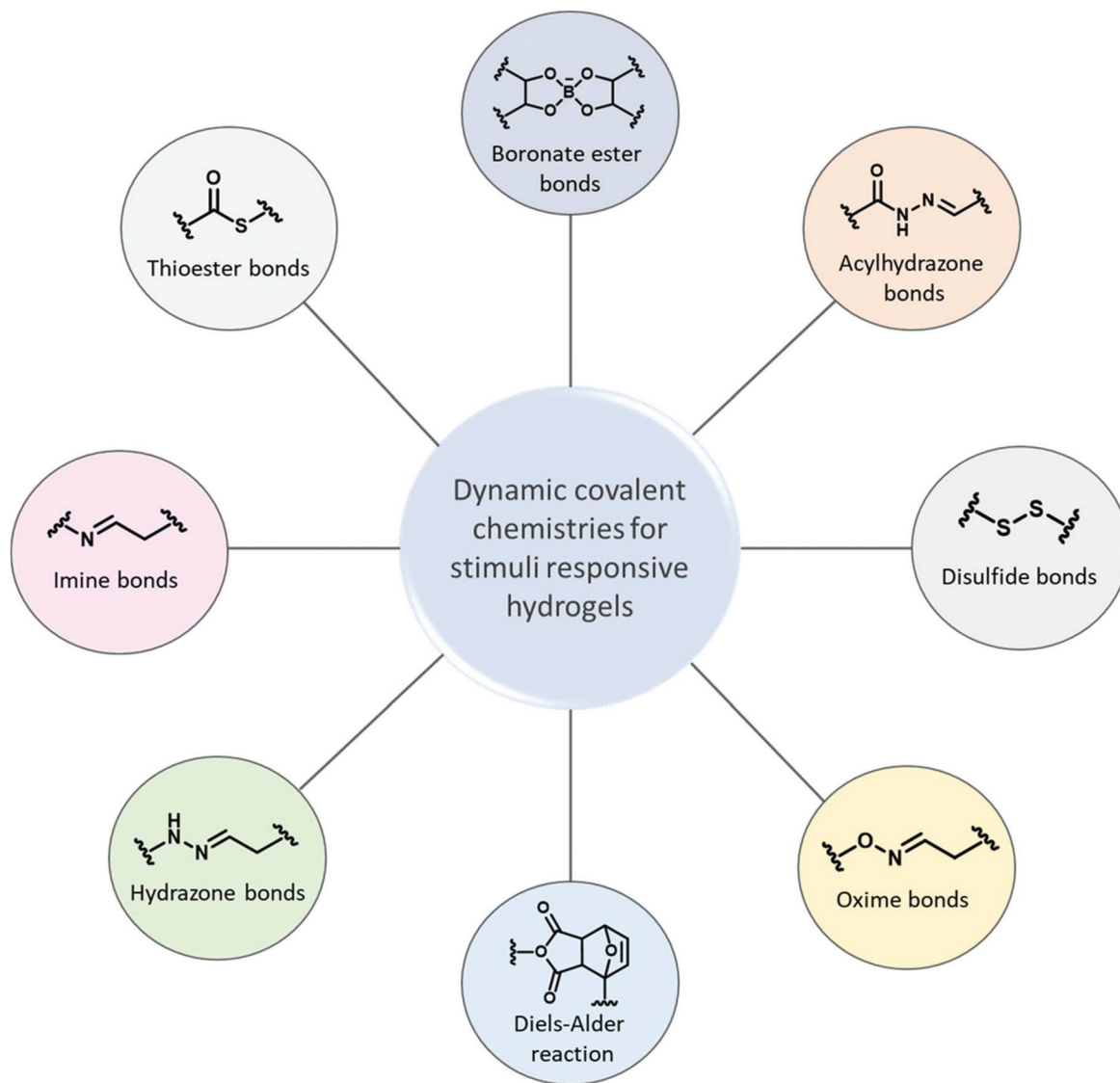
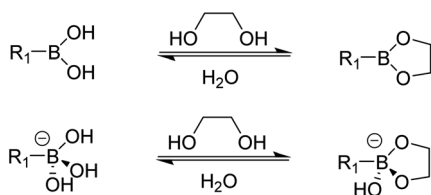


Fig. 1 Dynamic covalent bonds used for preparation of stimuli responsive hydrogels.



Scheme 1 Formation of boronic esters from boronic acid and a 1,2-diol (top) and formation of anionic boronate monoester from boronate anion and 1,2-diol (bottom).

derived from amino-groups along the polymer backbone.^{99,100} In work from Zhang and coworkers,¹⁰¹ the amine groups in chitosan were cross-linked with benzaldehyde terminated PEG to form a hydrogel with imine crosslinks. The mechanical properties of a self-healed hydrogel were similar to those of the original gel, and a crack on the hydrogel surface completely

disappeared after 2 h indicating high self-healing efficiency (Fig. 3). These gels were used for encapsulation and controlled release of proteins such as lysozyme. Other biomacromolecules such as gelatin and collagen which contain amine groups have also been used to develop imine crosslinked self-healing hydrogels.^{102,103}

Baker and coworkers¹⁰⁴ demonstrated the reversible self-healing ability of oxidized alginate-based hydrogels cross-linked by imine-type dynamic covalent chemistries (oxime, semicarbazone, and hydrazone). The different crosslinks in the hydrogel contributed properties including self-healing, shear thinning, injectability, and printability. Interestingly, only hydrazone and semi carboazone gels could undergo self-healing, whereas all three crosslink types enabled gels to be printable and injectable (shear thinning). These hydrogels may be used to prepare bio-inks for printing extra cellular matrix (ECM) mimicking biomaterials.

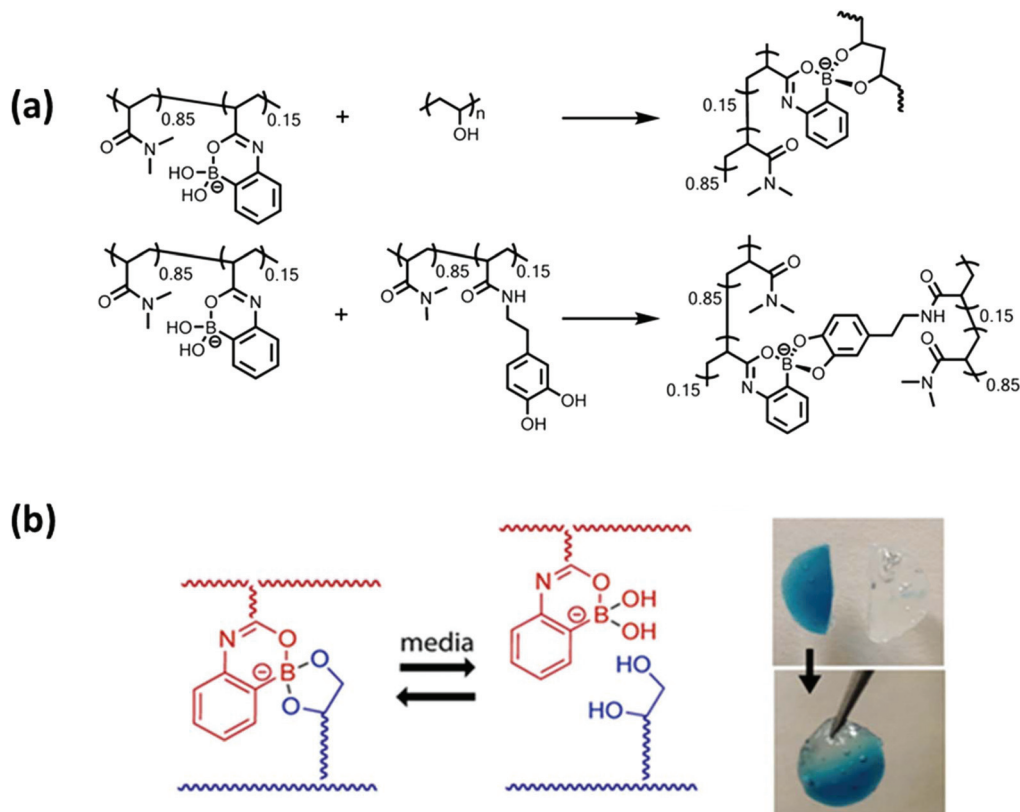
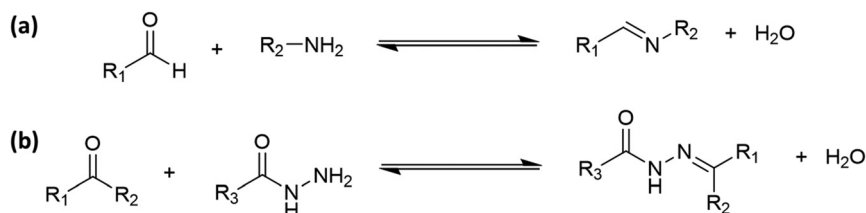


Fig. 2 (a) Synthesis of self-healing hydrogel using crosslinking polymer-bound phenylboronic acid (PBA) with either poly(vinyl alcohol) or a catechol-functionalized copolymer. Reprinted with permission from ref. 73. Copyright 2015, American Chemical Society. (b) Self-healing mechanism and macroscopic self-healing of hydrogels prepared by Kloxin and coworkers. Reprinted with permission from ref. 52. Copyright 2018, American Chemical Society.



Scheme 2 (a) Reaction between aldehyde and amines to form imine bonds and (b) reaction between a ketone or aldehyde and hydrazine to form acylhydrazone bond.

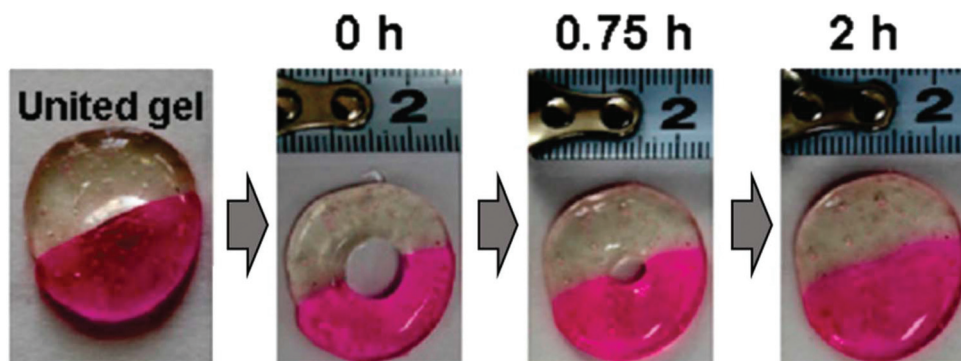
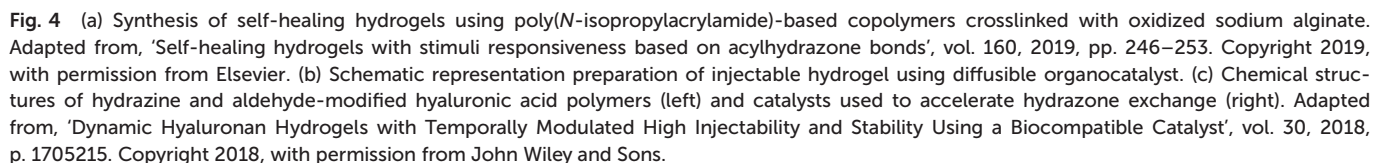
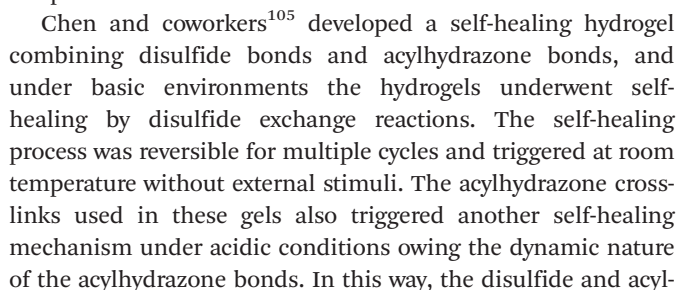
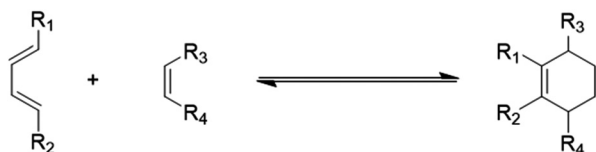


Fig. 3 Self-healing with time of two imine-containing hydrogels dyed with different colors. Reprinted with permission from ref. 87. Copyright 2011, American Chemical Society.



Disulfide bonds are dynamic covalent bonds resulting from oxidation of thiols (Scheme 3).¹⁰⁸ The self-healing of disulfide bonds can either be through an exchange reaction or a metathesis reaction, although the former is used in hydrogels





Scheme 4 Bond formation resulting from the Diels–Alder reaction and retro-Diels–Alder reaction.

hydrazone bonds enabled reversible sol–gel transitions in the gels in response to both pH and chemicals such as dithioerythritol or hydrogen peroxide. The authors of this study suggested that the self-healing hydrogels are potential candidates for organ repair or stimuli responsive drug delivery.

The Diels–Alder [4 + 2] cycloaddition between a diene and a dienophile is subjected to kinetic and thermodynamic control. The forward reaction (Scheme 4) occurs when $\Delta H > T\Delta S$ and the retro reaction occurs when $\Delta H < T\Delta S$.^{109,110} This reversibility has been used to make self-healing hydrogels.^{88,111,112}

In work by Yang and coworkers,¹¹³ furyl-modified carbon nanotubes were crosslinked with maleimide end-functionalized PEG using a Diels–Alder reaction to prepare self-healing nanocomposite hydrogels. The self-healing hydrogels were able to heal when incubated at 90 °C. The mechanical properties of the self-healed nanocomposite hydrogels were assessed by tensile testing, and the stress where the hydrogel failed was up to 78% of that experienced by the original gels (Fig. 5a and b).

Dextran self-healing hydrogels using a Diels–Alder reaction between fulvene-modified dextran and dichloromaleic acid-modified poly(ethylene glycol) were reported to be cytocompatible by Chen and coworkers.⁸⁸ The hydrogels demonstrated excellent self-healing at physiological conditions (pH 7.4 and 37 °C) within 7 h (Fig. 6). The amount of healing in the hydrogels was defined as the ratio of the depth of the scratch after different times to the depth of the scratch initially, and values

of close to 100% healing were reported. The authors suggest these gels can potentially be used in biomedical applications including cell encapsulation.

The self-healing ability of hydrogels prepared using Diels–Alder crosslinks has also been studied by Heilshorn and co-workers.⁸⁹ Hydrogels prepared using a Diels–Alder reaction between fulvenes and maleimides demonstrated improved gelation kinetics and hydrolytic stability compared to other commonly used DA reaction pairs such as furan–maleimide gels that can take hours to cross-link under physiological conditions.¹¹⁴

Self-healing multifunctional hydrogels are a promising class of hydrogels prepared using dynamic covalent chemistries.¹¹⁵ These hydrogels demonstrate self-healing properties along with another function, such as electrical conductivity, magnetism, or luminescence, in a single gel. For example, hydrogels used in artificial skin applications,^{116–118} soft actuators,^{119,120} or for artificial muscles^{120,121} have been reported. However, many self-healing hydrogels possess poor mechanical properties. Several efforts to develop mechanically tough self-healing hydrogels have been reported, for example preparing composite hydrogels with materials such as graphene oxide¹²² or using hydrophobic interactions⁸⁰ to enhance the mechanical properties (toughness) of the hydrogels. High strength networks have been obtained by preparing double network hydrogels,^{123,124} topological hydrogels¹²⁵ and tough and stretchable hydrogels.^{126,127} Despite these methods, there is still often a gap between the mechanical properties of self-healing gels and tough gels that can sustain MPa stress and exhibit fracture energy of the order of 1000 J m^{-2} .⁸⁴

Shape memory hydrogels

Shape memory hydrogels can be made to change shape under a specific set of conditions, such as temperature and stress,

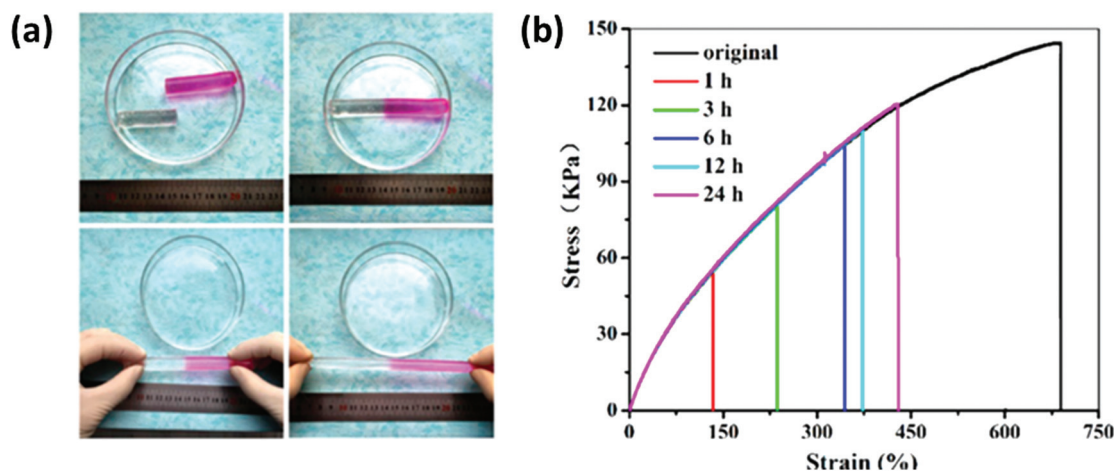


Fig. 5 (a) Macroscopic self-healing of carbon nanotube-containing hydrogels cut in half and then re-cured at 90 °C. (b) Stress–strain curves of the original and self-healed hydrogel after various healing times. Reprinted (adapted) with permission from ref. 95. Copyright 2017, American Chemical Society.

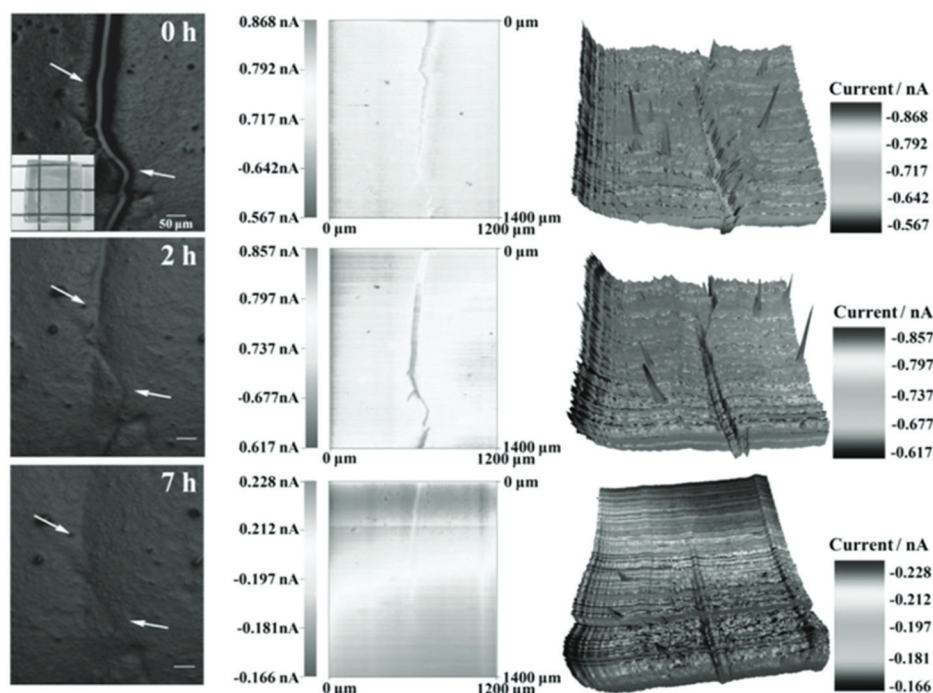


Fig. 6 Optical microscopy images (left) and corresponding scanning electron microscopy (middle and right) images of self-healing of a scratch on the surface of a fulvene-modified dextran and dichloromaleic acid-modified poly(ethylene glycol) hydrogel after different times. Reprinted with permission from ref. 76. Copyright 2013, John Wiley and Sons.

into a “fixed” temporary shape and then later relax to the original macroscopic shape under new stimuli.^{128,129} Physical interactions such as host–guest interactions,^{130–132} metal ion co-ordination,^{133,134} and hydrogen-bonding^{135,136} are often used with shape memory hydrogels. Dynamic covalent bonds can also be used for incorporating shape recovery properties into hydrogels, for example with phenylboronic acid–diol exchange reactions,¹³⁷ or imine chemistry.¹³⁸

In a representative example, Chen and coworkers¹³⁷ developed a pH- and sugar-responsive shape memory hydrogel prepared by crosslinking phenylboronic acid modified sodium alginate (Alg-PBA) and polyvinyl alcohol (PVA). Phenyl boronic acid–diol ester bonds acted as dynamic crosslinks, while Ca^{2+} -alginate ionic bonds behaved as permanent crosslinks in the hydrogels. The permanent shape could be recovered in a slightly acidic solution (pH = 6), or in a 0.2 M glucose solution as glucose breaks the original PBA–diol interactions (Fig. 7).

A hydrogel with triple shape memory properties combining Schiff-base bonding with metal coordination interactions was prepared by free radical polymerization of polyacrylamide with chitosan and oxidized dextran.¹³⁸ Conventional shape memory hydrogels can only memorize one temporary shape in each shape memory cycle. Triple shape memory refers to the ability of a shape memory hydrogel to memorize two temporary shapes in a single shape memory cycle.¹³⁹ Reversible Schiff base bonds formed between the amino groups of chitosan and aldehyde groups on oxidized dextran enabled shape memory behavior. In alkaline media the temporary shape was fixed within 5 min due to the rapid formation of Schiff base bonds.

Subsequently, the imine bonds were broken when exposed to a buffer solution at pH = 3, and the hydrogel recovered the original shape (Fig. 8). The shape recovery ratios in these hydrogels reached almost 100%, and these types of triple shape memory hydrogels have the potential to be applied in new research areas such as actuators, defect recoverable coatings, and smart adhesives.

Hydrogels with stimuli-induced stiffness changes

Hydrogels with material properties that can undergo temporal changes (*i.e.* changes with time) are gaining increasing attention in regenerative medicine^{140,141} and drug delivery.¹⁴² Bond formation or bond breaking in response to external stimuli changes the crosslink density in dynamic hydrogels, and hence the stiffness of the gel changes.^{143,144} Different strategies have been proposed to prepare temporally dynamic gels, including forming crosslinks through host–guest interactions,¹⁴⁵ ionic interactions,¹⁴⁶ *cis/trans* azobenzene isomerization,¹⁴⁷ and reversible covalent bonds.¹⁴⁸ Free radical polymerization,^{149,150} photocleavage of crosslinks,^{144,151} supramolecular guest–host interactions,¹⁵² ionic interactions,¹⁵³ and metal ion co-ordination¹⁵⁴ have also been used to cause temporal changes in hydrogel properties, however their discussion falls outside the scope of our review.

Disulfide exchange reactions have been used in dynamic hydrogels.^{155,156} As we described for self-healing hydrogels, di-

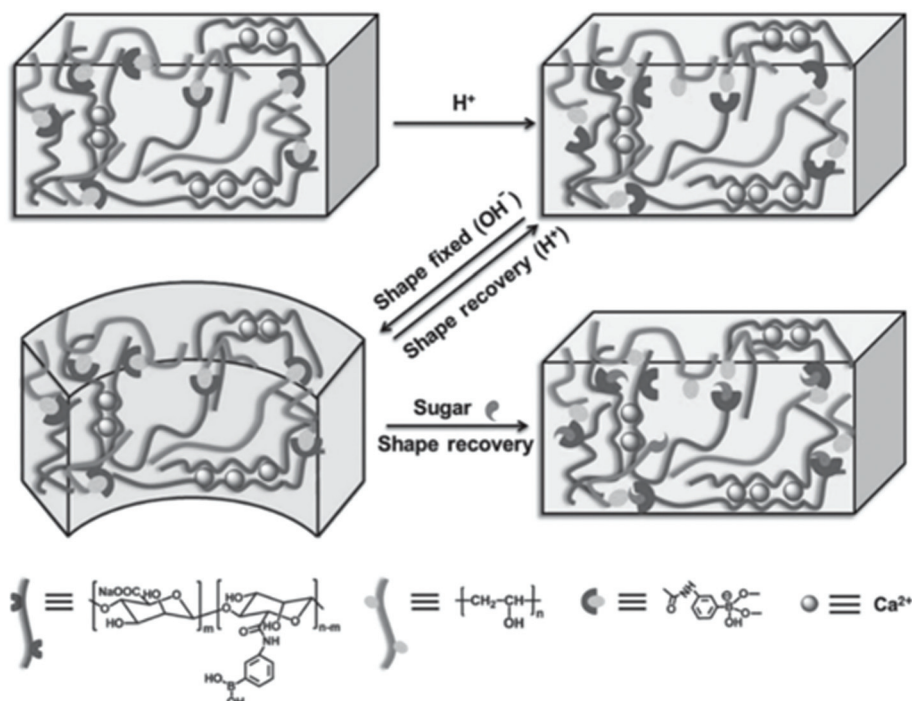


Fig. 7 Description of pH and sugar-induced shape memory effects in a reversible phenylboronic acid–diol ester hydrogel. Reprinted with permission from ref. 115. Copyright 2015, John Wiley and Sons.

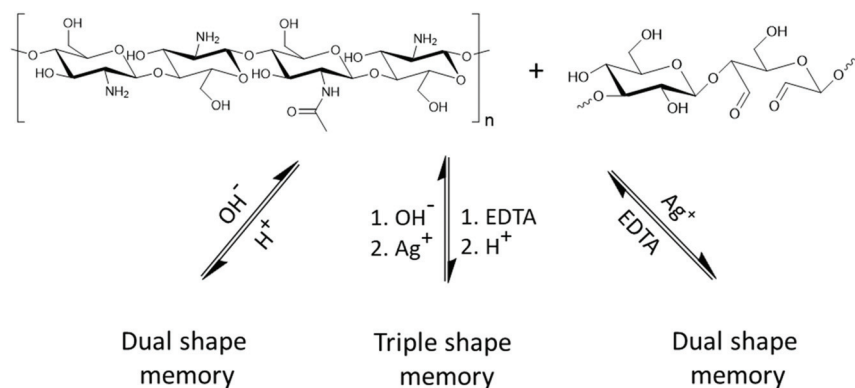


Fig. 8 Schiff base bonds in the triple shape memory gel hydrogel reported by Chen and co-workers respond to pH and Ag^+ ions.¹³⁸

sulfide crosslinks can be cleaved or formed *via* physiologically relevant reduction/oxidation reactions or thiol–disulfide exchange reactions.^{157,158} A recent example of thiol–disulfide exchange reactions to form and subsequently dissolve a hydrogel used a zwitterionic carboxybetaine disulfide crosslinker (Fig. 9).¹⁵⁸ Hydrogels using the zwitterionic carboxybetaine disulfide crosslinker underwent mass loss in less than 10 min, this is a stark contrast to the hydrolytically-degraded bonds typically used, such as esters and carbonates, which exhibit degradation kinetics from days to months.^{159,160} The disulfide crosslinker could be split upon exposure to redox stimuli such as dithiothreitol, and the hydrogels were used to encapsulate fluorescein isothiocyanate-labeled bovine serum albumin and

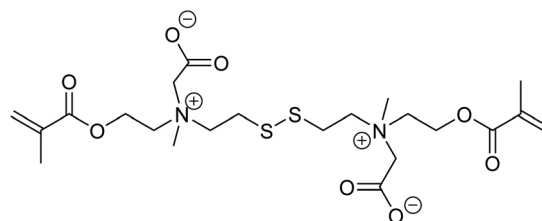


Fig. 9 Chemical structure of the carboxybetaine disulfide cross-linker used by Jiang and co-workers.¹⁵⁸

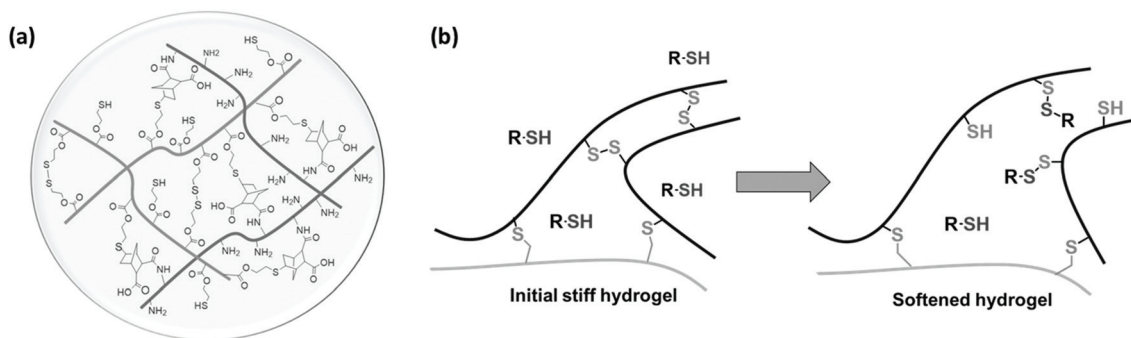


Fig. 10 (a) Structures of crosslinks in the thiol norbornene hydrogels. (b) Softening of the hydrogels via thiol–disulfide exchange reactions.

then release the protein in a controlled manner using different concentrations of dithiothreitol.

Disulfide crosslinks have also been used in combination with static crosslinks to soften hydrogels without dissolving the gel. An example of this was described in work from our lab,¹⁵⁷ where gelatin-based hydrogels were prepared using both alkyl sulfide and disulfide crosslinks. Norbornene modified gelatin was crosslinked with a thiol containing crosslinking polymer maintaining an excess concentration of thiols to enable disulfide formation (Fig. 10a). The thiol–disulfide exchange reactions were performed using 2-mercaptoethanol to soften the hydrogels by 15–25% of their original mechanical properties (Fig. 10b).

Conversely, Peyton and coworkers¹⁶¹ demonstrated that disulfide bonding could stiffen hydrogels under shear by using disulfide reduction and formation chemistry in PEG-based hydrogels using a “latent crosslinking” approach with a disulfide containing monomer. Interestingly, these gels could be cycled through several oxidation/reduction cycles with the thiols, leading to reversible changes in the moduli of the gels.

Thiol–thioester bonds undergo reversible exchange reactions in aqueous solution (Scheme 5).^{162–164} In the thiol–thioester exchange reaction, a thiolate anion reacts with a thioester to form new thiolate and thioester products. Hupe and Jencks experimentally showed that the rate of the thioester exchange is a function of the pK_a of the conjugate acid of the incoming thiol and the leaving thiolate anion.¹⁶⁵

In work by Grinstaff and coworkers,¹⁶⁶ thioester exchange was used to induce degradation in hydrogel wound sealants in the presence of L-cysteine methyl ester. The hydrogels consisted of lysine-based dendrons and thioester-containing crosslinkers (Fig. 11). The crosslinker was end capped with N-hydroxy succinimide ester, which reacted with the amines in the dendron to form the network. The thioester containing hydrogels dissolved upon exposure to L-cysteine methyl ester

within 30 min, but no changes in stiffness were observed when lysine methyl ester was used, or if L-cysteine methyl ester was used on a hydrogel without thioester linkages.

Anseth and coworkers¹⁶⁷ have prepared adaptable tissue engineering scaffolds for regenerative biology using this thiol–thioester exchange chemistry. In their study, hydrogels containing an 8-arm thiolated polyethylene glycol were crosslinked with a thioester-containing divinyl crosslinker using a photo-initiated thiol–ene reaction (Fig. 12).

The thioester-containing hydrogels could be completely dissolved by L-cysteine at physiological pH, as the pK_a of the conjugate base of L-cysteine is lower than that of the thioester formed after the exchange reaction. The breakdown of the hydrogel was solely due to the presence of thioester linkages in the network, this was confirmed by a control experiment where a similar hydrogel was prepared using a poly(ethylene glycol) diene crosslinker instead of TEDVE (Fig. 12) resulting in permanent covalent crosslinks. The hydrogels were prepared so that they possessed similar initial material properties regardless of the type of crosslinker used. While the biological relevance and high efficiency of the exchange reaction is useful for biomedical applications, the reaction efficiency in organic solvents and compatibility with a wide pH range also makes this chemistry suitable for non-biological applications.^{168,169}

Summary

Hydrogels have become far more complex than a network of hydrophilic polymers with a large volume of imbibed water and are increasingly being used in a variety of application areas. In this review we have highlighted the main dynamic covalent chemistries used to prepare functional hydrogels with dynamic covalent bonds. While the function can change, *e.g.* self-healing, temporal responsiveness, *etc.* it is clear that a “toolbox”



Scheme 5 Generic reaction scheme of thiol–thioester exchange reaction.

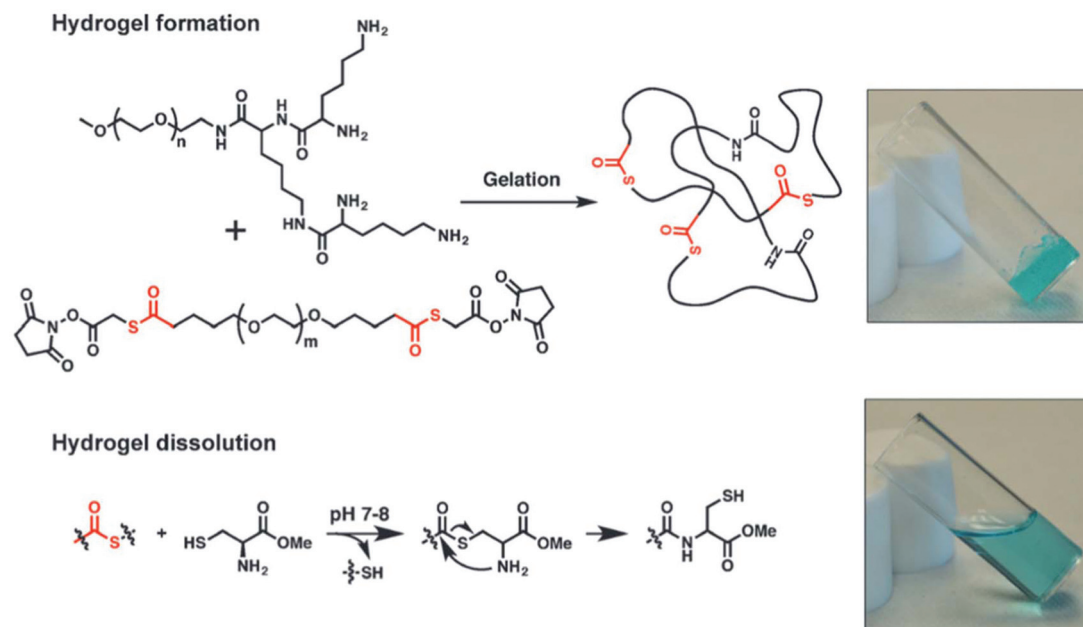


Fig. 11 Reaction between an amine-functionalized dendron and a thioether containing crosslinker forms hydrogels with “on-demand” hydrogel degradation using thiol–thioester exchange reaction with an L-cysteine methyl ester solution. Reprinted with permission from ref. 144. Copyright 2016, John Wiley and Sons.

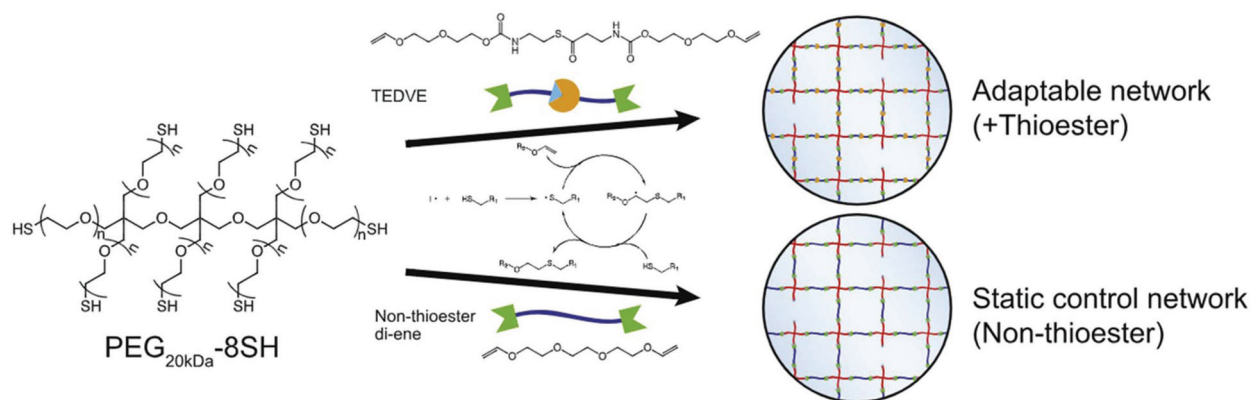


Fig. 12 Star-PEG macromonomers that are end-functionalized with thiols were crosslinked using thioether di(vinyl ether) (TEDVE) with and without thioesters to prepare adaptable and static hydrogels respectively. Reprinted with permission from ref. 145. Copyright 2018, John Wiley and Sons.

of dynamic covalent bonding is typically used. It is not surprising that these dynamic bonds are compatible with different functional groups and tolerant to different reaction conditions, making them ideal for materials development. Through this mini-review we have also touched on some persistent challenges for dynamic hydrogels, for example a lack of toughness, and highlighted some emerging and creative approaches to mitigating these challenges such as double networks and composite gels. As this field continues to evolve it will be interesting to see how dynamic bonding will be combined with existing and other nascent strategies, for example tyrosine dimers,¹⁷⁰ to give value added properties in advanced applications, including drug delivery, biomaterials, and non-biomedical applications

such as sensing,^{171–173} chemical separation,¹⁷⁴ physical and chemical absorption agents¹⁷⁵ and adhesive agents.¹⁷⁶

Conflicts of interest

There are no conflicts of interest to declare.

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