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Multivalent H-bonds for self-healing hydrogels†

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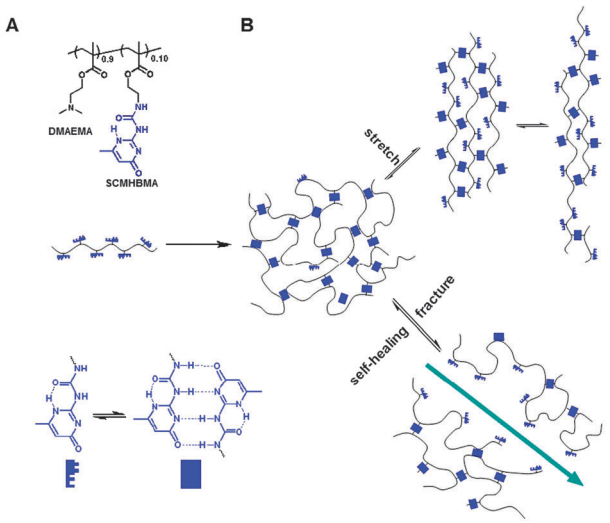
UPy is used as a reversible and dynamic crosslinker to prepare hydrogels that are injectable and undergo rapid self-healing in response to damage.

Self-healing materials possess the ability to repair themselves in response to damage leading to a new route towards safer, longer-lasting products.[1] Self-healing mechanisms in bulk polymer materials are either based on the release of repair agents upon damage,[1] or on the inclusion of latent molecular functionalities in the polymer structure that trigger repair *via* thermally reversible reactions, hydrogen bonding, ionomeric arrangements, or molecular diffusion and entanglement.[2] Recently self-healing properties have been extended to hydrogels. Different reversible molecular interactions have been exploited for this purpose: electrostatic interactions between polyelectrolytes,[3] molecular-recognition (protein–protein[4] and host–guest[5] interactions), metal coordination,[6] hydrophobic[7] or π–π stacking[8] association, dynamic chemical bonds[9] or molecular diffusion and entanglement.[10]

Surprisingly, hydrogen bonds, being one of the common mechanisms used in bulk self-healing materials and ubiquitous in living systems,[11] have rarely been exploited as a repairing mechanism for hydrogels. Very recently a branched covalent crosslinked hydrogel containing amide and carboxylic groups in the branches has shown self-healing properties based on the H-bonds between these groups.[13] The self-healing properties of poly(ethyleneglycol) based hydrogels containing 2-ureido-4-pyrimidone (UPy) as end groups have also been recently mentioned, though only poor experimental verification has been reported.[12] 2-Ureido-4-pyrimidone (UPy) can dimerize *via* quadruple H-bonding ($>10^6$ M in $CHCl_3$)[14] and is one of the most commonly used units to build up supramolecular (co)polymers[11] and reversible networks.[15] In this article we exploit the associated multivalent H-bonds of the UPy unit to form stable crosslinked hydrogels by copolymerization of a UPy-functionalized building block with different water soluble monomers. The resulting materials gelify without the need of covalent bonds by dimerization of self-complementary UPy units. This property facilitates processability of the materials, making them stretchable and injectable. By incorporating UPy units into different backbones multiresponsive self-healing hydrogels were obtained.



Scheme 1 Chemical structure of the copolymer containing DMAEMA and SCMHBMA (A) and the schematic model of self-healing and stretching of the hydrogel formed by the copolymer (B).

Scheme 1A presents the chemical structure of the copolymer containing two different components: 2-(dimethylamino)-ethyl methacrylate (DMAEMA) and 2-(3-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)ureido)ethyl methacrylate (SCMHBMA). DMAEMA is the main component of the chain and confers water solubility and temperature response.[16] The SCMHBMA monomer contains UPy units in the side chain, able to form dimers by self-complementary H-bonding. The expected self-repair and stretching ability of the system as a consequence of the presence of UPy unit are depicted in Scheme 1. Dynamic assembly and disassembly of UPys should enable *in situ* recovery in response to damage and chain reorientation along the stretching direction.

The SCMHBMA monomer was obtained by reaction of 6-methylisocytosine and 2-isocyanatoethyl methacrylate (Scheme S1 in ESI†).[17] Its ^{1}H-NMR spectrum in $CDCl_3$ showed NH proton signals at 13.0, 12.0, 10.5 ppm, indicative of extensive hydrogen bonding (Fig. S1 in ESI†).[14] Copolymerization of DMAEMA–SCMHBMA was carried out in 1,4-dioxane at 70 °C with azodiisobutyronitrile (AIBN) as an initiator. A copolymer with an average molecular weight $M_n = 3.8 \times 10^4$ Da was obtained with high yield (90%). The feed molar ratio of DMAEMA–SCMHBMA used for polymerization was

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0.92/0.08 and resulted in a copolymer composition of 90 mol% DMAEMA and 10 mol% SCMHBMA as calculated by ^{1}H NMR spectroscopy (Fig. S2 in ESI†). A low content of SCMHBMA unit was necessary in order to retain water solubility of the copolymer at room temperature, since the lower critical solution temperature (LCST) of PDMEAMA decreases with the addition of hydrophobic components.[18] The resulting copolymer maintained the temperature response of PDMAEMA and showed a LCST of 40 °C at pH 8 (determined by a turbidity experiment in a 20 mg mL^{-1} solution), lower than the LCST of the PDMAEMA homopolymer at the same pH (50 °C).[16]

The DMAEMA–SCMHBMA copolymer was soluble in water at acidic pH and rendered viscous solutions at a concentration of 0.2 g mL^{-1}. Addition of aqueous NaOH to increase the pH to >8 induced gelation of the solution, suggesting dimerization of the UPy units in water and formation of a 3D network. In order to demonstrate that the UPy units were responsible for hydrogel formation, we evaluated the binding ability of the copolymer to a UPy-modified surface *via* quartz crystal microbalance (QCM) measurements. This technique can monitor the gravimetric and viscoelastic changes at the surface by the shifts in the frequency (Δf) and dissipation (ΔD). A UPy-based silane coupling agent (Fig. 1A) was used for functionalisation of a silica surface (Scheme S2 in ESI†). In this molecule the photocleavable group *o*-nitrobenzyl is attached to the carbonyl group of the UPy ring (caged UPy) and inhibits the self-coupling ability.[19] Light exposure removes the cage and generates a UPy functionalized surface able to bind to the copolymer. Fig. 1B presents the Δf and ΔD of the crystal modified with caged UPy during incubation with a solution of DMAEMA–SCMHBMA in chloroform or buffer (10 mM Tris·HCl at pH of 8.0) and washing. No changes in Δf and ΔD were observed after washing, indicating that the copolymer chains could not form H bonds with the caged UPy at the surface. However, incubation of the copolymer solution with the light-exposed UPy modified QCM crystal caused a clear decrease in the frequency that was maintained after rinsing with the solvent (Fig. 1C). This corresponds to a mass increase at the surface due to the fixation of the copolymer *via* H-bonding interactions between the UPy units. This result also agrees with the increase in energy dissipation observed in the *D*-factor, characteristic of the growth of a soft surface layer.[20] A 25 Hz frequency change was observed in chloroform, while 14 Hz was observed in aqueous buffer. This result indicates that UPy dimers with slightly higher stability formed in chloroform solution.

The presence of H-bonds as reversible crosslinks in the hydrogel was also confirmed during mechanical stretching and deformation of the hydrogel. Hydrogel samples at pH 8 and temperature 20 °C were stretched by pulling with tweezers. Fiber formation was clearly observed (Fig. 2b) as a consequence of the reversible and dynamic nature of the H-bonding that allows and reinforces reorientation and flow of the polymer chains.[21] It is important to note that this property is relevant for injectable materials for applications in drug delivery and tissue engineering.[4] This strategy represents an alternative to physical thermogelling hydrogels currently used for these applications.

Fig. 2a demonstrates the self-healing ability of the DMAEMA–SCMHBMA hydrogel. A hydrogel sample was prepared at pH

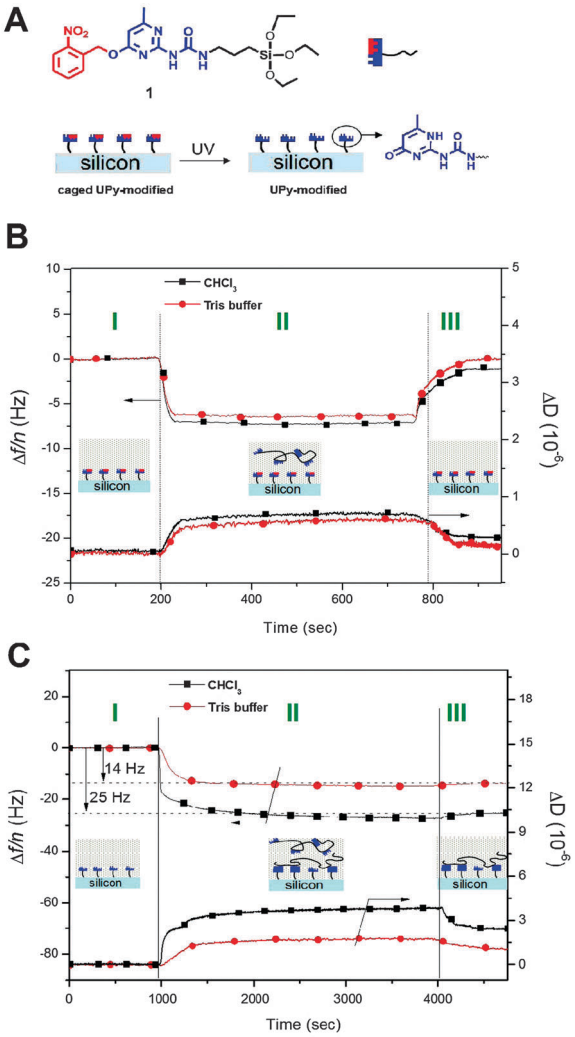

Fig. 1 (A) The UPy-based silane coupling agent 1 and the scheme of caged and light-exposed UPy modified surfaces. (B) Evolution of the Δf and ΔD of the third overtone of a caged UPy modified QCM crystal (I) during incubation with a solution of 2 mg mL^{-1} DMAEMA–SCMHBMA copolymer in $CHCl_3$ or buffer (10 mM Tris·HCl, pH 8) (II) and posterior washing (III). (C) Evolution of the Δf and ΔD of the third overtone of a UPy modified QCM crystal (I) during incubation with a solution of 2 mg mL^{-1} DMAEMA–SCMHBMA copolymer in $CHCl_3$ or buffer (10 mM Tris·HCl, pH 8) (II) and posterior washing (III).

between 7 and 8 and room temperature and cut into two pieces (Fig. 2a). Self-healing occurred in 5 min within this pH range. This property was not observed in the PDMAEMA homopolymer and is attributed to the presence of reversible H-bonding between SCMHBMA units (Scheme 1B). Self-healing did not occur if the sample was kept above the LCST, indicating that dimerization could be switched on and off by changing the temperature. Fig. 2c–g show an incision in a hydrogel film performed at 50 °C (Fig. 2c) that did not heal after 30 min (Fig. 2d and e). When the temperature was cooled to 20 °C and the sample was kept in a humid environment, the incision disappeared within 2 min (Fig. 2f and g). These results indicate that diffusion of the chains is restricted in the collapsed state and the H bonds cannot be restored. The combination of the temperature responsive DMAEMA chain

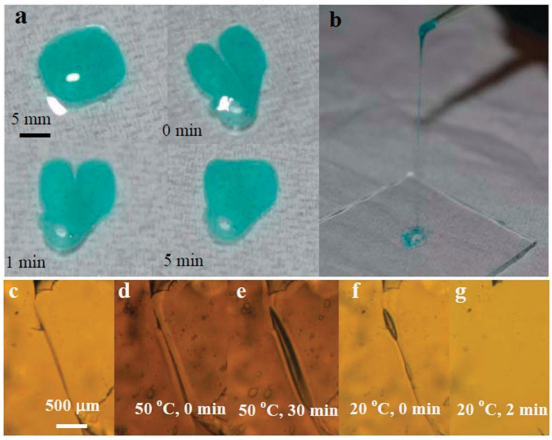

Fig. 2 Demonstration of the self-healing (a, c, d, e, f, g) and the stretching (b) properties of the DMAEMA–SCMHBMA hydrogel at pH 8. The gel in (a) and (b) was coloured with methyl blue for better imaging. Optical microscopy images (c–g) were obtained from a hydrogel film with an incision (c) after annealing at 50 °C (d, e) and subsequent cooling to 20 °C (f, g).

with the self-complementary UPy side groups allows a temperature regulated self-healing mechanism.

The self-healing ability was also tested in covalently cross-linked DMAEMA–SCMHBMA gels prepared by copolymerization with *N*,*N*′-methylene bisacrylamide. In this case two hydrogel samples were prepared independently and brought into contact. As they touched each other, self-healing occurred immediately (movie in ESI†). The "glued" hydrogel withstood stretching, shaking and overload stretching without visible damage to the contact region. Similar experiments were performed using different monomers for hydrogel formation, in order to prove if the SCMHBMA unit was able to confer self-healing properties to other materials. Copolymers of SCMHBMA with 2-hydroxyethyl methacrylate (HEMA), 2-(2-methoxyethoxy)ethyl methacrylate (MEO2MA), *N*-isopropylacrylamide (NIPAm), and *N*,*N*′-dimethylacrylamide (DMAA) were prepared. The copolymers with HEMA, MEO2MA and NIPAm presented similar self-healing behaviour, demonstrating that the recovering ability of UPy multivalent H-bonds can be applied to different materials. The DMAA–SCMHBMA hydrogel was brittle and did not self-heal. Additional work will be done to clarify the limitations of the system.

In conclusion, UPy-based monomers can form self-complementary H-bonds in an aqueous environment and be used as a reversible and dynamic cross-linker to obtain supramolecular hydrogels that rapidly self-heal. The self-healing properties conferred by the Upy unit can be coupled to the thermal response of the polymer matrix to generate hydrogels with thermo-regulated self-healing behaviour. This strategy could be further extended to different commercially available monomers, demonstrating that it is a flexible route towards self-healing hydrogels with various functions. This is the first reported example of multivalent H-bonds cross-linked hydrogel materials with thermo-gated recovery ability. In addition, the physical hydrogel flows and stretches under mechanical strain, representing an alternative to physical thermogelling hydrogels for injectable materials for biomedical applications.

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