Supramolecular polymer materials based on ureidopyrimidinone quadruple hydrogen bonding units

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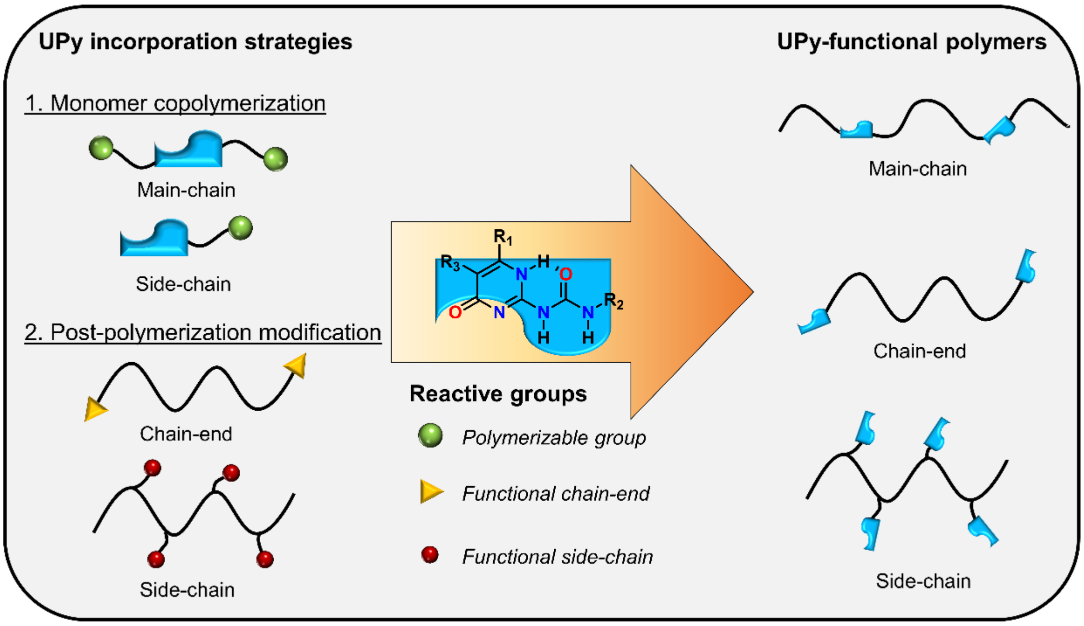
Abstract

Supramolecular polymer materials are polymeric structures which are physically crosslinked by non-covalent interactions such as ionic interactions, host-guest complexation and hydrogen bonding. The resulting materials generally display stimuli-responsive behavior and/or healable properties, which makes them excellent candidates for the design of dynamic materials. Inspired by its omnipresence in natural systems, hydrogen bonding has proven to be useful for the development of synthetic materials with dynamic properties. Inspired by the base-pairing in the DNA double helix, Meijer *et al.* developed the self-complementary quadruple hydrogen bonding unit ureidopyimidinone (UPy), which has a strong dimerization constant ($K_{dim} > 10^7$ M^{-1}). The incorporation of UPy motifs in polymeric precursors led to a plethora of hydrogen bonded materials with applications ranging from artificial arteries to reversible adhesives. This review will focus on design strategies to synthesize these UPy-containing polymermaterials, which can be split into three main categories based on the location of the UPy arrays: UPy in the main-chain, UPy in the side-chains or UPy at the chain-ends. In addition to the synthetic routes, the material properties of the resulting supramolecular materials will be discussed.



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List of abbreviations

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^{4}PCL-U	UPy-telechelic four-arm star-shaped poly(ε-caprolactone)
AA	Acrylic acid
ADMET	Acyclic diene metathesis
ARGET	Activator regeneration by electron transfer
ATRP	Atom transfer radical polymerization
IC-OH	Isocytosine with alcohol on R_1 position
CDI	1,1'-carbonyldiimidazole
DMSO	Dimethyl sulfoxide
DOPA	Dopamine hydrochloride
HDI	Hexamethylene diisocyanate
HMDI	Dicyclohexylmethylmethane-4,4'-diisocyanate
IPDI	Isophorone diisocyanate
PB	1,2-polybutadiene
PBA	Poly(*n*-butyl acrylate)
PCL	Poly(ε-caprolactone)

PDMS	Poly(dimethylsiloxane)
P(DMS-*co*-HMS)	Poly(dimethylsiloxane-*co*-methylhydrosiloxane)
PE	Polyethylene
PEG	Poly(ethylene glycol)
PMMA	Poly(methyl methacrylate)
PP	Polypropylene
PPG	Poly(propylene glycol)
PPM	Post-polymerization modification
PPO	Poly(propylene oxide)
PSeD	Poly(sebacoyl diglyceride)
PTMEG	Poly(tetramethylene ether glycol)
PTMEG-U	UPy-telechelic poly(tetramethylene ether)glycol
PTMC	Poly(trimethylene carbonate)
PTMG	Poly(tetramethylene glycol)
PU	Polyurethane
ROMP	Ring-opening methathesis polymerization
SA	Stearyl acrylate
SET-LRP	Single electron transfer living electron polymerization
SPM	Supramolecular polymer materials
TEG	Tetraethyleneglycol
T_g	Glass transition temperature
TMS	Trimethylsilyl
TPE	Thermoplastic elastomer
UPy	2-Ureido-4-pyrimidinone
$(UP)_3T$	UPy-terminated three-arm siloxane oligomers
UPy-MA	UPy-methacrylate

1 Introduction

The advances in polymer chemistry have unlocked the potential of designing all sorts of polymeric architectures next to the conventional linear polymers, including star polymers,[1,2] polymer bottlebrushes,[3,4] dendrimers[5,6] and polymer networks. By replacing the covalent bonds with reversible non-covalent counterparts, the same architectures can be translated towards supramolecular materials.[7–9] Supramolecular networks are formed when multitopic monomer units are used. Towards this end, Leibler *et al.* designed a supramolecular rubber based on oligomeric chains that are physically crosslinked by hydrogen bonding between amide and urea moieties.[10] Although the material is build up from oligomers, it behaves like a rubber due to the high concentration of hydrogen bonding groups. Additionally, rapid self-healing was achieved by putting fractured surfaces back together by contact pressure at room temperature, which is caused by a fast reshuffling of the hydrogen bonds at the surfaces. Another beautiful example of a hydrogen bonded supramolecular network was developed by the group of Weder where a trifunctional 2-ureido-4-pyrimidinone (UPy) compound formed a glassy material showing thermo- and UV-responsive properties.[11] The high dimerization constant of UPy results in strong supramolecular crosslinks, which in combination with the relatively short linker between the UPy motifs are responsible for the glassy appearance at room temperature. Nonetheless, by heating or irradiating the material, the hydrogen bonds become more dynamic, transforming the network in a viscoelastic material. These characteristics made the supramolecular network suitable for healable coatings.

When the concepts of supramolecular chemistry are translated to macromolecular systems, supramolecular polymer materials can be formed, providing access to new, dynamic properties compared to their covalent equivalents. A wide range of non-covalent interactions have successfully been incorporated into polymer materials, including host-guest complexation,[12–14] π-π stacking,[15,16] metal-ligand complexation,[17–19] electrostatic interactions[20–22] and hydrogen bonding.[23–25] The reversibility of these supramolecular interactions allowed the development of many dynamic materials, displaying self-healing and stimuli-responsive behavior.[26]

Hydrogen bonding, in particular, is a valuable type of supramolecular interaction for the controlled assembly of supramolecular structures because of the highly directional nature of hydrogen bonds, the bond selectivity and the tunable strength, and has been applied in supramolecular materials for many years. Weak hydrogen bonded materials exhibit fast exchange dynamics, leading to fast equilibration with their surroundings, which introduces stimuli-responsiveness. Strong hydrogen bonding slows down the exchange dynamics and results in more solid-like characteristics. Additionally, the inherent temperature responsiveness of hydrogen bonds allows viscoelastic materials to transform from solid elastomers to low-viscosity melts, enabling dynamic properties such as self-healing, shape-memory and energy dissipation, besides the ability of low temperature processing.[27]

The direct attachment of hydrogen bonding groups to polymer chains is currently a popular strategy to design hydrogen bonded polymer networks and mostly involves multiple hydrogen bonding arrays, where triple,[28–31] quadruple[32–35] and sextuple[36–38] hydrogen bonding motifs are the most common. The quadruple hydrogen bonding array UPy in particular has been an invaluable tool in the development of hydrogen bonded polymer networks due to its high binding strength, self-complementarity, easy synthetic availability and customizability.[39,40] Meijer and coworkers investigated the conformational structure of UPy in solution, and two main structures were identified: 2-ureido-4[1H]-pyrimidinone where hydrogen bonding donor (D) and acceptor (A) groups are arranged in AADD configuration, and 2-ureido-4-pyrimidinol with DADA conformation as a result of keto-enol tautomerism (**Fig. 1**). It was observed that the substituents on the R_1 and R_2 positions influenced the ratio of the AADD and DADA tautomers, where electron withdrawing groups push the equilibrium towards the DADA tautomer. In case of a CF_3 group, only the DADA tautomer was observed, and with *n*-alkyl substituents on both R_1 and R_2 positions, exclusively the AADD was present. These two structures are both self-complementary, which means they can form homodimers. Interestingly, the dimerization constant of the DADA array ($K_{dim,Y}$) was significantly higher than expected based on the primary and secondary interactions between the H-bonding groups ($K_{dim,theo}$ = 310 M^{-1} vs. $K_{dim,exp}$ >10^5 M^{-1}), which can be ascribed to the preorganization induced by the intramolecular H-bond [39] The AADD tautomer showed strong H-bonding with a dimerization constant ($K_{dim,X}$) of 5.7 x 10^7 M^{-1}.[41]

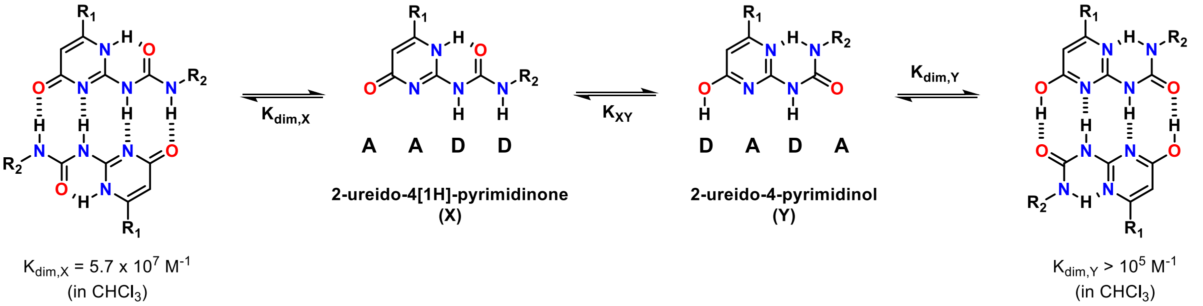

Fig. 1. Tautomeric and association equilibria of UPy in solution; with $K_{dim,X}$ = the dimerization constant of tautomer X, K_{XY} = the tautomeric equilibrium, and $K_{dim,Y}$ = the dimerization constant of tautomer Y.

Nowadays, a plethora of polymer materials have been synthesized in which physical crosslinking by UPy dimerization resulted in improved material properties such as mechanical strength, toughness and extensibility.[23,32–35,42–76] In addition, Dankers and coworkers recently confirmed the in-vitro biocompatibility of UPy-based materials and their degradation products, which is an important step towards the implementation of UPy-containing materials in biomedical applications.[77]

It should be noted that (macro)molecules with two or more UPy moieties can be subjected to ring-chain equilibria, where ring conformations are generally favored in dilute conditions, while increasing the concentration of the UPy-containing molecules will eventually cause a transition to the thermodynamically more favorable chain conformation.[78] Although this phenomenon is mainly associated with dissolved UPy-telechelic polymers or small molecules, it is important to keep in mind as it can also have an impact on the processing of supramolecular materials based on H-bonding.[79]

In this review, the emphasis will be placed on the synthetic strategies leading to polymers crosslinked by UPy dimerization where a subdivision will be made based on the location of incorporation of the UPy units: in the main-chain, on the side-chains or at the chain-ends. As illustrated in **Fig. 2**, the reported synthetic strategies will be discussed within each subcategory, followed by a discussion of the properties of the obtained materials. Before going into more detail into such UPy-based supramolecular polymer materials, a short overview of the available synthetic routes to obtain functional UPy units, as required for coupling to polymers, will be provided.

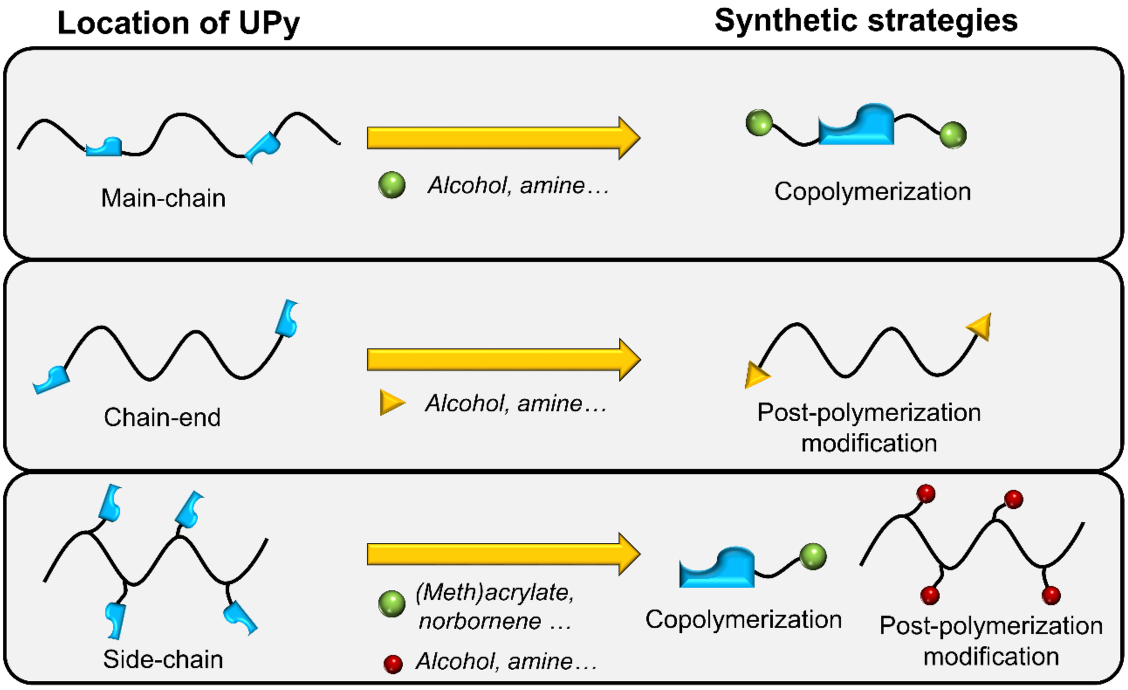

Fig. 2. Overview of synthetic strategies for UPy-based supramolecular polymer materials.

2 Synthesis of functional UPy units

As illustrated in the bottom part of **Fig. 3**, the synthesis of UPy units generally starts from an isocytosine core. In the following step, there are two options to form the urea group that is required to obtain the self-complementary quadruple hydrogen bonding motif. In the first and most popular route, the isocytosine is directly coupled to an isocyanate. However, due to the low nucleophilicity of the primary amine group on the isocytosine, an excess of the isocyanate is often needed, in combination with a catalyst, to achieve a sufficiently high reaction yield. This route is more attractive for commercially available isocyanates as they are generally cheaper. The second route involves a two-step procedure and was developed by Meijer and coworkers to provide an alternative for the isocyanate route.[40] In the first step, the primary amine group on the isocytosine is activated with 1,1'-carbonyldiimidazole (CDI) with the formation of an imidazolide, followed by the addition of a primary amine containing compound to obtain the desired UPy unit. This route is generally preferred if there is no commercial isocyanate available as it can be employed with any primary amine.

When looking at the molecular structure of UPy, three positions can be identified to introduce functional groups, as can be seen in **Fig. 3**. The R_1 and R_2 groups can be customized in the synthesis of the isocytosine precursor, which is depicted in the upper part of **Fig. 3**. The isocytosine core is generally synthesized by ring-closure of a β-keto ester (mostly with an ethyl ester) with guanidinium carbonate, where R_3 is most commonly a hydrogen, and R_1 consists of the desired side-chain at the 6 position. Although commercially available β-keto esters are available in some cases (*e.g.* with R_1 = trifluoromethyl, para-nitrophenyl or *n*-hexyl, and R_3 = H for the three compounds), synthetic routes for preparation of custom β-keto esters are relatively straightforward.[80,81] In the most common route, a condensation of an acid chloride (with the desired R_1 functionality) with ethyl potassium malonate catalyzed by magnesium chloride and trimethylamine is used.[55,81,82] Alternatively, another route was reported for the synthesis of an isocytosine with an undecanyl group at R_1, where a condensation of 2-tridecanone with diethyl carbonate was used to obtain the corresponding β-keto ethyl ester.[81]

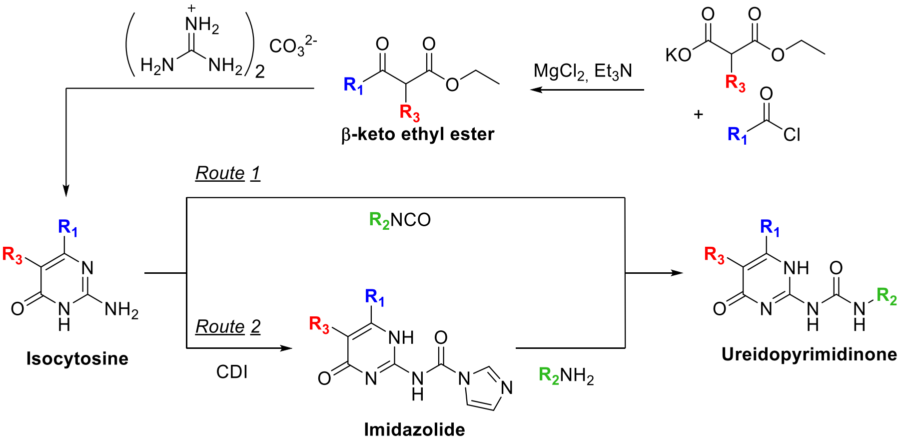

Fig. 3. Synthetic scheme of the synthesis of the isocytosine (top), and the two main routes for the synthesis of UPy molecules (bottom).

3 Polymer materials with UPy in the polymer main chain

3.1 Synthesis of polymers with UPy in the main chain

To incorporate the UPy moieties in the backbone of a polymer, two functional handles are required which can react with a complementary (macro)monomer. This can be achieved by modifying R_1 or R_2 in the synthesis of the isocytosine core as shown in **Fig. 3**, which is mostly done by condensation of commercially available guanidine carbonate and α-acetylbutyrolactone, resulting in an isocytosine with an alcohol at the R_1 position (IC-OH) (**Fig. 4**a).[43,83] In the next step, the alcohol and amine groups can be reacted with an excess of diisocyanate, resulting in Macromonomer 1. The final supramolecular polymer material can be obtained as a reversibly crosslinked polyurethane after polycondensation of Macromonomer 1 with a polymeric diol precursor (Pre-polymer 2), which is commonly a low molecular weight polymer. By choosing a diisocyanate with an appropriate spacer, the molecular weight of the UPy segment can be tuned accordingly.

Inspired by the biological protein titin, Guan and coworkers developed another route to incorporate UPy into the polymer backbone through biomimetic design.[84] Here, the functional handles are introduced at the R_1 and R_2 positions on the UPy units, as shown in **Fig. 4**b. The monomer synthesis went through a *p*-nitrobenzyl protected UPy to prevent dimerization, thereby facilitating the purification. The final UPy unit was functionalized with two alcohol groups, which were coupled to a ditopic isocyanate pre-polymer resulting in a supramolecular crosslinked polyurethane (**Fig. 4**b). The *p*-nitrobenzyl protected intermediate served as a chain extender for the synthesis of a control polymer, which is deprived of hydrogen bonding crosslinks by disrupting the dimerization of UPy motifs. However, this procedure requires 7 steps towards the final UPy compound (5 steps without the nitrobenzyl protection and deprotection), which is a less feasible route compared to the previous strategy. For a detailed description of the synthetic pathways, the reader is directed to ref. [84].

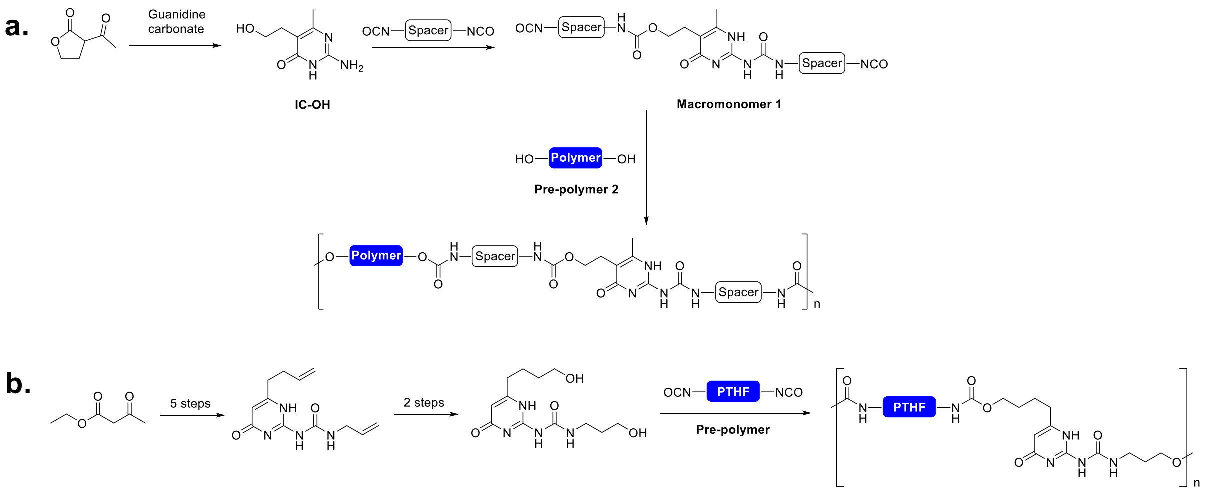

Fig. 4. a) Schematic illustration of the synthesis of supramolecular polymer networks with UPy in the backbone; b) Synthetic route towards the biomimetic polymer of Guan and coworkers.

Nevertheless, further development of this strategy lead to a second generation material where the introduction of terminal alkenes on positions R_1 and R_2 were used to covalently connect a UPy dimer pair *via* ring-closing metathesis (**Fig. 5**).[85] Subsequent deprotection of the alcohols at position R_1 allowed the coupling of isocyanate-functional methacrylate groups, resulting in a bis-methacrylate crosslinker with a cyclic UPy dimer that can be used in (controlled) radical polymerization techniques. An important difference with the previously mentioned supramolecular polymer networks with UPy moieties in the backbone is that in this case, the UPy units in the dimer cannot completely dissociate as they are covalently attached to each other, meaning that the resulting polymers are essentially chemically crosslinked, whereby the disruption of UPy dimers provides energy dissipation capability.

In a third generation material, Guan *et al.* synthesized an alternative to the bis-methacrylate crosslinker where a decenyl group with terminal alkene was attached to the alcohol units on the R_1 positions (**Fig. 6**).[86] The bifunctional alkene was then polymerized by acyclic diene metathesis (ADMET) to form a linear modular polymer, which was close to the natural protein titin, the biological inspiration for this approach. In addition, a blocked hydrogen-bonding monomer was synthesized by coupling an *o*-nitrobenzyl protecting group onto the UPys and subsequently polymerized as a reference polymer to compare the influence of hydrogen bonding on the mechanical properties, which will be discussed in the next section.

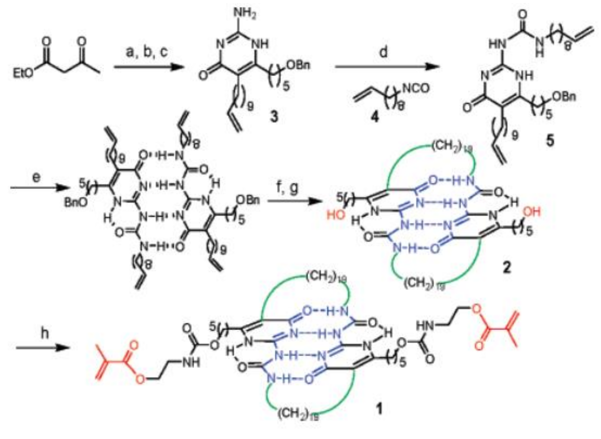

Fig. 5. Synthetic route towards the biomimetic cyclic UPy crosslinker. [85], Copyright 2007. Adapted with permission from American Chemical Society.

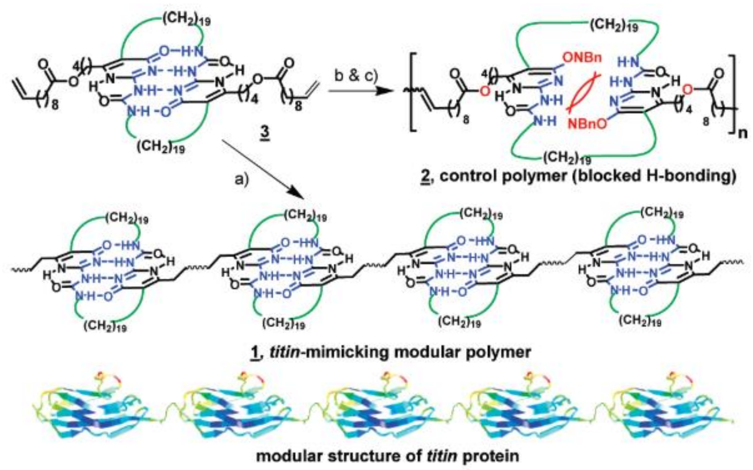

Fig. 6. Synthesis of the third generation biomimetic linear modular polymer by Guan *et al.* [86], Copyright 2009. Adapted with permission from American Chemical Society.

3.2 Material properties of polymers with UPy in the main-chain

By combining the UPy hard segments with different pre-polymers, the properties of the obtained polyurethane materials can be tuned, either as bulk materials or hydrogels.

One of the first materials following the synthetic template as illustrated in **Error! Reference source not found.** was reported by Baaijens and coworkers.[43] Here, two macromonomers were prepared by reacting IC-OH with hexamethylene diisocyanate (HDI) and isophorone diisocyanate (IPDI), respectively, which were subsequently converted to their corresponding supramolecular thermoplastic elastomer (TPE) by addition of poly(propylene adipate). Interestingly, the HDI polymer revealed both rubbery and plastic behavior under deformation, while the IPDI polymer responded like a classic rubbery material. Indeed, the increased steric bulk originating from the IPDI segments allowed more chain mobility, resulting in a more dynamic material, while the HDI polymer formed phase separated stacks of dimerized UPy units, yielding additional mechanical strength to the supramolecular elastomers.

Following a similar synthetic route, Weng *et al.* developed a tough stress sensing polyurethane by incorporating a mechanoresponsive spiropyran and UPy units in a modular fashion.[50] The resulting polymers displayed a Young's modulus of 8.4 MPa, an ultimate tensile strength of 23.7 MPa, a material toughness of 111.2 MPa and an elongation at break of 970%, which were all significantly larger than the control sample without UPy units, indicating the positive influence of the inter-chain hydrogen bonding on the mechanical properties.

By incorporation of a hydrophilic poly(ethylene glycol) (PEG) chain in the soft segment and incorporation of additional hydrophobic spacers in the hard UPy-containing segment, Meijer *et al.* created a strong semicrystalline polymer that was capable of forming a tough supramolecular hydrogel when soaked in water (**Fig. 7**).[52] In the hydrogel state, the material exhibited an almost complete strength recovery at deformations over 300%, which was partially attributed to the hydrophobically shielded UPy dimers in the hydrated PEG segments. The high strength and flexibility combined with the biocompatible nature of the high PEG content enabled biomedical applications such as adaptive sutures and tissue engineering.[67,87,88]

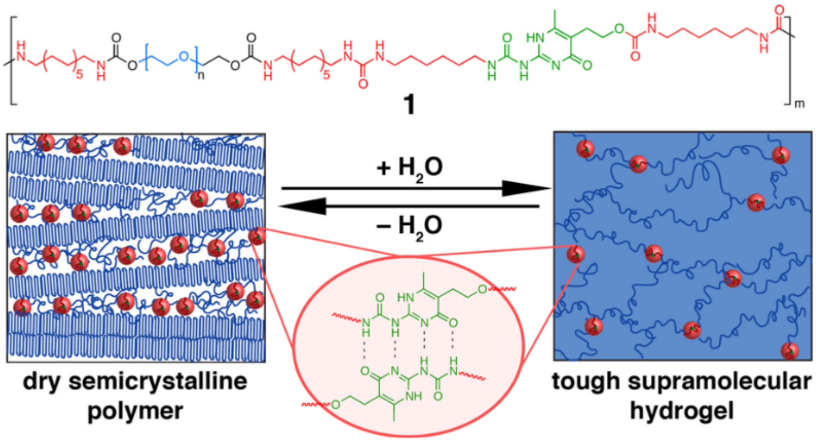

Fig. 7. Schematic illustration of PEG-based UPy-chain extended polyurethane for tough supramolecular hydrogels. [52], Copyright 2014. Reproduced with permission from American Chemical Society.

Recently, Bao *et al.* reported highly stretchable supramolecular polymer materials (SPMs) as stretchable electrodes by incorporating UPy in the polymer backbone in different ratios, ranging from 0 to 30% (**Fig. 8**).[63] The soft segment was mainly composed of poly(tetramethylene glycol) (PTMG) to introduce flexibility, while the bulky groups from IPDI next to the UPy units and tetraethylene glycol (TEG) moieties avoid stacking of the UPy dimers. The significant influence of the UPy content on the mechanical properties of the SPMs is nicely illustrated in the tensile curves shown in the bottom left of **Fig. 8**. SPM-0 with 0% UPy has weak mechanical strength and behaves like a viscous liquid. With a UPy content of 10%, the SPM-1 already displays a considerable increase in tensile stress and elongation, which is even more prominent in SPM-2 with a further increased crosslink density of 20% UPy motifs resulting in a maximum tensile stress and elongation of 0.91 MPa and 17 000%, respectively (**Fig. 8**, bottom right). In SPM-3 with 30% UPy units, a maximum tensile stress of 3.74 MPa was reached, while the stretchability decreased to 3100% due to the higher supramolecular crosslink density.

Further development of the aforementioned UPy-based SPMs yielded a supramolecular lithium ion conductor that enabled the fabrication of stretchable lithium ion batteries and impact protective SPMs.[89,90]

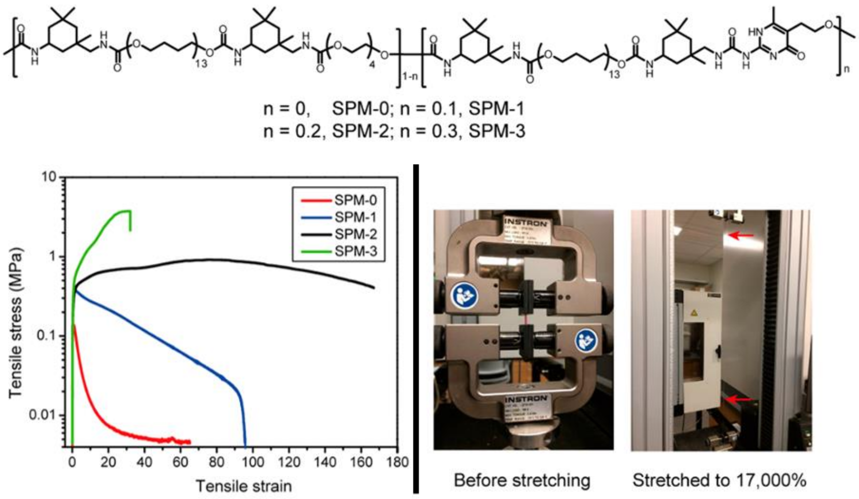

Fig. 8. Top: molecular structure of the supramolecular polymer materials (SPM); bottom left: stress-strain curves of the SPMs; bottom right: picture of SPM-2 on the tensile testing machine before elongation and at a strain of 17000%. [63], Copyright 2018. Adapted with permission from American Chemical Society.

The UPy-based biomimetic modular polymer material (polymer 1) displayed in **Fig. 6** showed the large impact of hydrogen bonding on the mechanical properties when compared to a control polymer containing blocked UPy units (polymer 2).[86] The structural design of polymer 1 led to a relatively high elastic modulus of 200 MPa and a strain at break of > 100% representing a stiff and flexible material, while the control polymer 2 shows brittle behavior with a low strain at break and limited toughness (**Fig. 9**). In addition, polymer 1 also showed shape-memory behavior, which was explained by the cyclic UPy dimers that are originally in their homo dimerized state and unfold when stress is applied to the material, resulting in inter-chain crosslinking. With heating or time, the inter-chain crosslinks can unfold again and return to the homo dimer state.

Very recently, Sun *et al.* reported a bioinspired polyurethane combining various physical interactions to attain a high-performance reprocessable material with self-healing properties.[71] The polymer was constructed in multi-functional block modules, as illustrated in **Fig. 10**. The semi-crystalline polycaprolactone (PCL) segments introduced strain-hardening behavior, whereby the urethane bonds mimic the amide hydrogen bonding in proteins, the UPy motifs in the polymer backbone increase the hydrogen bond density and provide physical inter-chain crosslinking, and pendant catechol groups originating from dopamine hydrochloride (DOPA) were incorporated to achieve additional physical crosslinking by metal-ligand coordination after addition of Fe^{3+} ions. The combination of the semi-crystallinity with the hydrogen bonding and metal-coordination interactions resulted in a material featuring both a good stiffness and toughness as can be seen in the bottom left of **Fig. 10**, displaying the stress-strain curves of the bioinspired material (PU-UPy-DOPA-Fe), together with reference materials lacking one or more crosslinking modules. The reprocessability of PU-UPy-DOPA-Fe was tested by grinding the pristine sample followed by hot compression molding into new test specimens, after which a tensile test revealed a recovery of 89.6% and 72.0% of the elongation and stress at break, respectively (**Fig. 10**, bottom right).

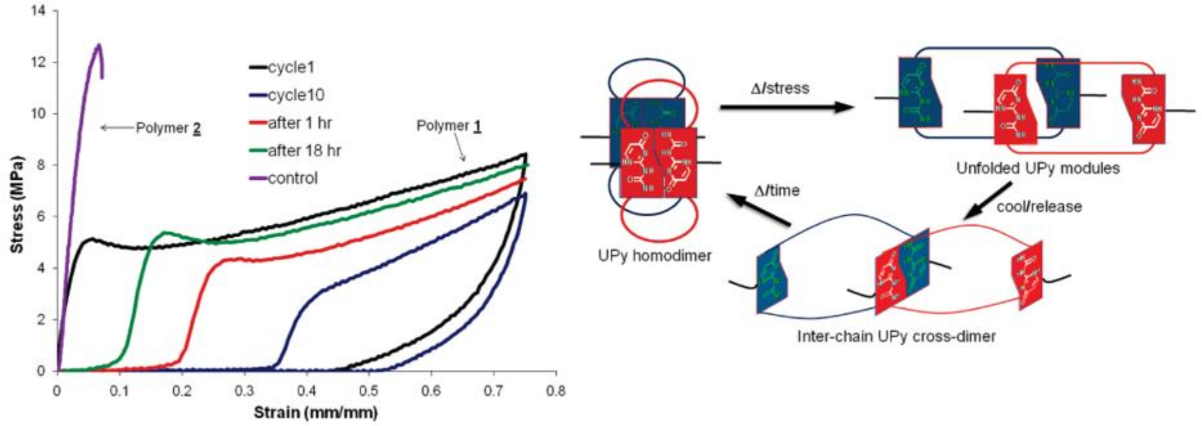

Fig. 9. Left: stress-strain curves of The UPy-based biomimetic modular polymer 1 and the control polymer with blocked UPy motifs; right: the proposed molecular mechanism. [86] Copyright 2009. Adapted with permission from American Chemical Society.

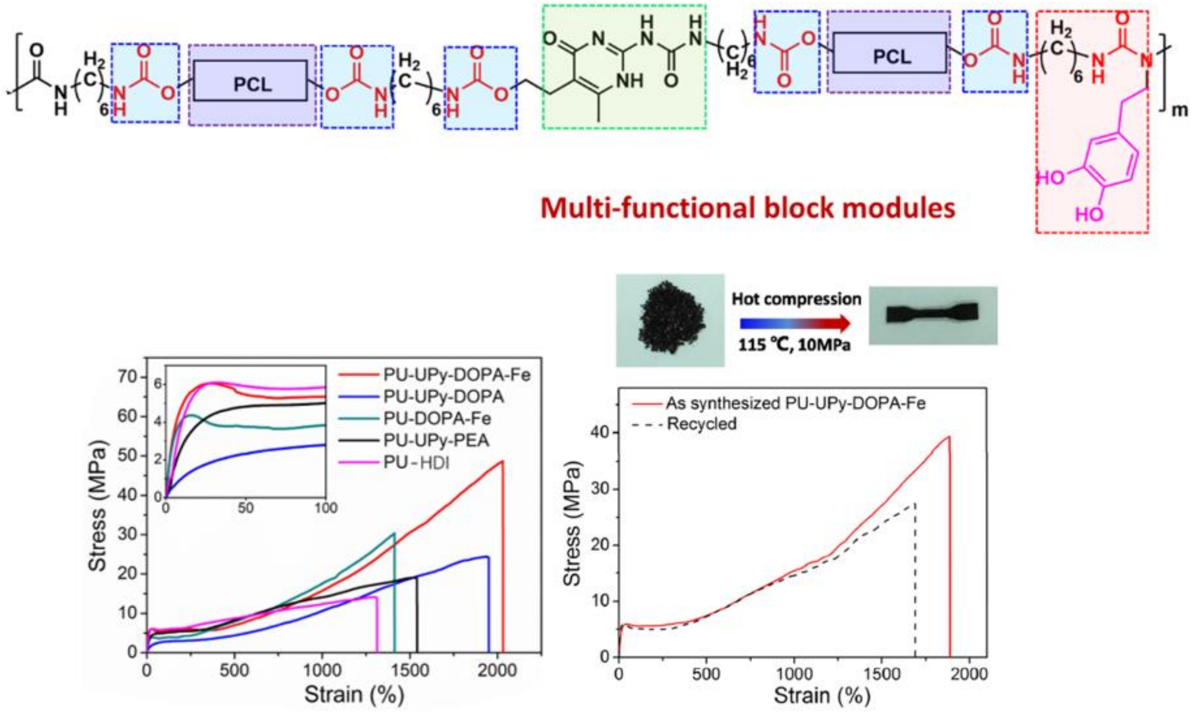

Fig. 10. Top: molecular structure of bio-spired polyurethane; bottom left: stress-strain curves of pristine and reprocessed PU-UPy-DOPA-Fe; bottom right: stress-strain curves of PU-UPy-DOPA-Fe and reference materials PU-UPy-DOPA (lacking metal-coordination crosslinks), PU-DOPA-Fe (lacking UPy crosslinking), PU-UPy-PEA (lacking the DOPA modules) and PU-HDI (lacking both UPy and DOPA modules). [71], Copyright 2021. Adapted with permission from American Chemical Society.

4 Polymer materials with UPy at the polymer chain-ends

4.1 Synthesis of polymers with UPy at the polymer chain ends

Many reports were published in which UPy motifs were attached to polymer chain-ends. This approach can either result in supramolecularly chain-extended polymer in case of linear polymers or in supramolecular polymer networks when star-shaped polymers are used.[23,72,91] Functionalization of the chain-ends requires the presence of functional groups at the heads and tails of the polymer chains, which is a common feature in the synthesis of functional polymers.[92–95] These chain-end functionalities can be achieved through the polymerization mechanism by selecting the appropriate initiator and/or terminator, and through post-polymerization modification.[96] Additionally, many commercial polymers are available that already contain functional end groups.

Presumably the most frequently applied polymer functionalization method to introduce UPy units to the chain-ends is to combine polymers with alcohol or amine end-groups with isocyanate-bearing UPy motifs (**Fig. 11**).[32,42,44,45,51,56,60,65,74,75,82,91,97–114] Alternatively, the isocyanate can be added to the polymer chain-ends, followed by the formation of the UPy motifs by adding the isocytosine core.[115] In addition, an amine- or hydroxy-functional UPy could also be used for UPy-attachment to the polymer.[70]

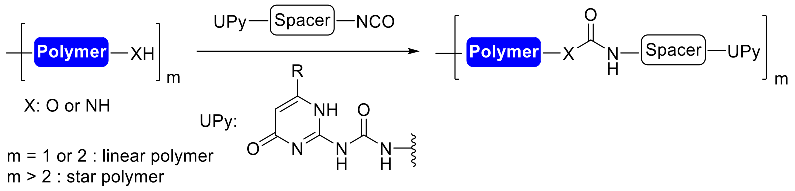

Fig. 11. Schematic overview of the synthesis of telechelic UPy supramolecular polymer materials by isocyanate-bearing UPy motifs.

As mentioned in section 2 for the synthesis of functional UPy motifs, CDI can also be used as an alternative to the isocyanate route to functionalize telechelic polymers. Here, the CDI activated imidazolide is added to a multitopic amine-functional polymer, *in situ* generating UPy units at the polymer chain-ends.[116] Aside from these UPy-specific methods, general post-polymerization modification (PPM) reactions such as azide-alkyne reactions,[117] activated esters[118] and cycloaddition reactions[119] have also been used to attach UPy to the polymer chain-ends.

4.2 Material properties of polymer with UPy at the chain-ends

In case of linear UPy end-functionalized telechelic polymers, the UPy dimerization results in non-covalent chain extension and a subsequent increase of the virtual molecular weight of the polymer, accompanied with an elevated viscosity of the materials. When low molecular weight polymer precursors are used, materials with a low melt viscosity can be designed displaying an improved processability at relatively low temperatures. Meijer and coworkers reported such UPy-based supramolecular polymer materials synthesized from low molecular weight polymer precursors.[72] An apparent change in mechanical properties could be observed for the functionalization of low molecular weight poly(ethylene-*co*-butylene) before and after UPy-functionalization of the OH end groups. The material with OH end groups was liquid at room temperature, while a solid material was obtained after coupling of UPy units to the chain-ends, which increase the virtual molecular weight by chain extension caused by intermolecular UPy dimerization (**Fig. 12** left and right, respectively). Similarly, other polymers such as polysiloxanes,[42] polyethers[45] and polyesters[99,113] exhibited improved mechanical properties after modification with telechelic UPy moieties. The addition of secondary hydrogen bonding moieties such as urethane and urea bonds, which supplement the UPy interactions, was found to have an influence on the formation of lateral aggregates of UPy dimers and further improvement of the material properties.[42,75] This nanofiber formation by stacking of the UPy dimers could be prevented by introducing a sterically hindered substituent on the six-position of the UPy unit.[82,112]

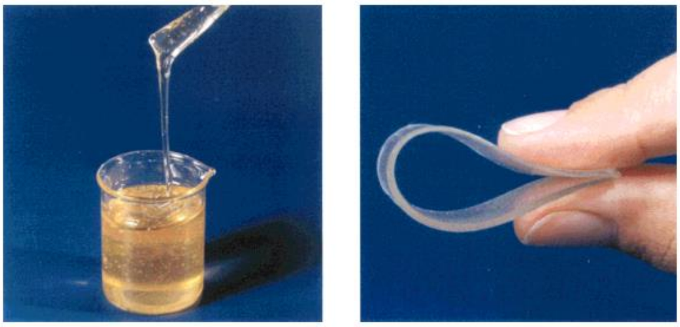

Fig. 12. Pictures of low molecular weight poly(ethylene-*co*-butylene) end-capped with OH groups (left) and UPy units (right). [72], Copyright 2000. Reproduced with permission from John Wiley & Sons Inc.

For star-shaped polymers on the other hand, UPy-functionalization of the three or more functional chain-ends enables the formation of polymer networks. Long *et al.* reported the synthesis and mechanical analysis of linear telechelic and trifunctional UPy star-shaped poly(ethylene-*co*-propylene)s and observed an improvement of the tensile properties in the case of the star polymer.[115] The triple UPy functionality in the star polymer enabled network formation and was translated to a higher elastic modulus compared to the linear telechelic equivalent (1.65 and 0.92 MPa, respectively), but also decreased the elongation at break from 330% to 139%.

Similarly, Meijer and coworkers reported linear and star-shaped poly(trimethylene carbonate) (PTMC) end-capped with UPy molecules, targeting biomedical applications.[76] Short bifunctional and trifunctional hydroxy-terminated TMC polymers with different chain lengths were prepared and subsequently functionalized with UPy units. Chain extension by inter-chain UPy dimerization transformed the original TMC polymers from viscous liquids to strong, flexible films. The material properties were tunable by variation of the chain length of the TMC part, which also affected the UPy content in the material. Furthermore, mixing of bifunctional and trifunctional UPy-TMC polymers allowed further tuning of the mechanical properties of these UPy-based supramolecular materials.

The combination of bifunctional and multifunctional UPy-containing polymers was further investigated by Yang *et al*. in the development of triple shape memory and self-healing materials.[56] Here, UPy-telechelic poly(tetramethylene ether glycol) (PTMEG-U) was blended with a UPy-telechelic four-arm star-shaped poly(ε-caprolactone) (^{4}PCL-U) in different ratios. Gradual increase of the ^{4}PCL-U fraction improved the tensile strength of the materials, but also decreased the extensibility due to the strong hydrogen bonding network originating from the high UPy concentration. By decreasing the ^{4}PCL-U content, the decrease in crosslink density enabled more efficient healing of damaged materials. The triple shape memory behavior was achieved by thermally reversible crystallization of the PTMEG and ^{4}PCL polymer segments around 25 °C and 45 °C, respectively, and the reversible aggregation of UPy stacks around 65 °C. The hydrogen bonding crosslinks served as crosslinking points, whereas the crystalline polymer phases could be triggered at lower temperatures to manipulate the material into temporary forms.

More recently, the concept of a crystalline PCL phase combined with physical crosslinking by UPy-dimerization and stacking was utilized by Pan and coworkers to design a shape-memory material based on trifunctional UPy-telechelic star-shaped PCL.[120] Similar results regarding shape-memory and mechanical properties were achieved as compared to the blended polymer system described above.

Another example of a UPy-telechelic polymer material solely employing trifunctional star polymers was reported by Yao *et al*. (**Fig. 13**).[121] The UPy-terminated three-arm siloxane oligomers ($(UP)_3T$) formed a strong hydrogen bonded network with a high Young's modulus of 47.39 MPa, originating from the semi-crystalline nature resulting from microphase-separation of UPy stacks in the apolar polydimethylsiloxane (PDMS) matrix. Interestingly, the material could be swollen in water and featured water-enhanced healing. The low water permeability of the PDMS matrix enabled free movement of water molecules through the material to interact with the UPy motifs, consequently weakening the crosslinking points and increasing chain mobility, allowing the reorganization of the UPy hydrogen bonds when damaged surfaces are pushed together. The $(UP)_3T$ films showed good recovery of the mechanical performance after 5 healing cycles in water at 70 °C, which can be attributed to the high crosslink density and semi-crystallinity of the supramolecular polymer networks. Potential applications of the healable supramolecular siloxane material include flexible electronics, smart coatings and biomedical applications.

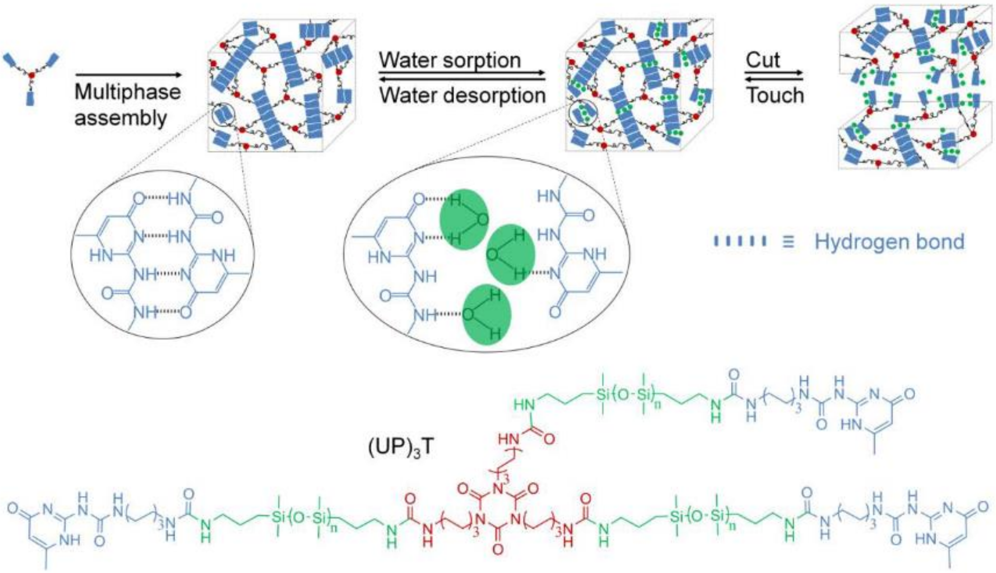

Fig. 13. Multiphase design (top) and molecular structure (bottom) healable UPy-telechelic siloxane oligomer $(UP)_3T$. [121], Copyright 2018. Reproduced with permission from John Wiley & Sons Inc.

Generally, low molecular weight UPy-terminated trifunctional star-shaped polymer networks generate brittle, glassy materials due to the strong physical crosslinking from the high UPy content.[11] Recently, Weder *et al.* developed a strategy to toughen these supramolecular glassy materials by integrating a rubbery phase.[64] This was achieved by blending two supramolecular macromonomers based on a trifunctional poly(propylene oxide) (PPO) core with a low and high number-average molecular weight (M_n, 440 and 3000 g/mol, respectively) (**Fig. 14** top). The low molecular weight trifunctional star polymer (M1) formed a britle, glassy material, while the higher molecular weight variant (M2) produced flexible films. Subsequent blending of M1 and M2 allowed tuning of the mechanical properties by variation of the M1:M2 ratio, as shown in the bottom of **Fig. 14**, with Young's moduli of 35-345 MPa and strain at break from 1.8% to 7.7%. By increasing the M2 content in the polymer blends, a significant increase of the material toughness could be achieved. However, extended heating caused the blends to irreversibly phase-separate, indicating that the blends are essentially kinetically trapped assemblies and that repeated melt-processing would be detrimental for the material properties.

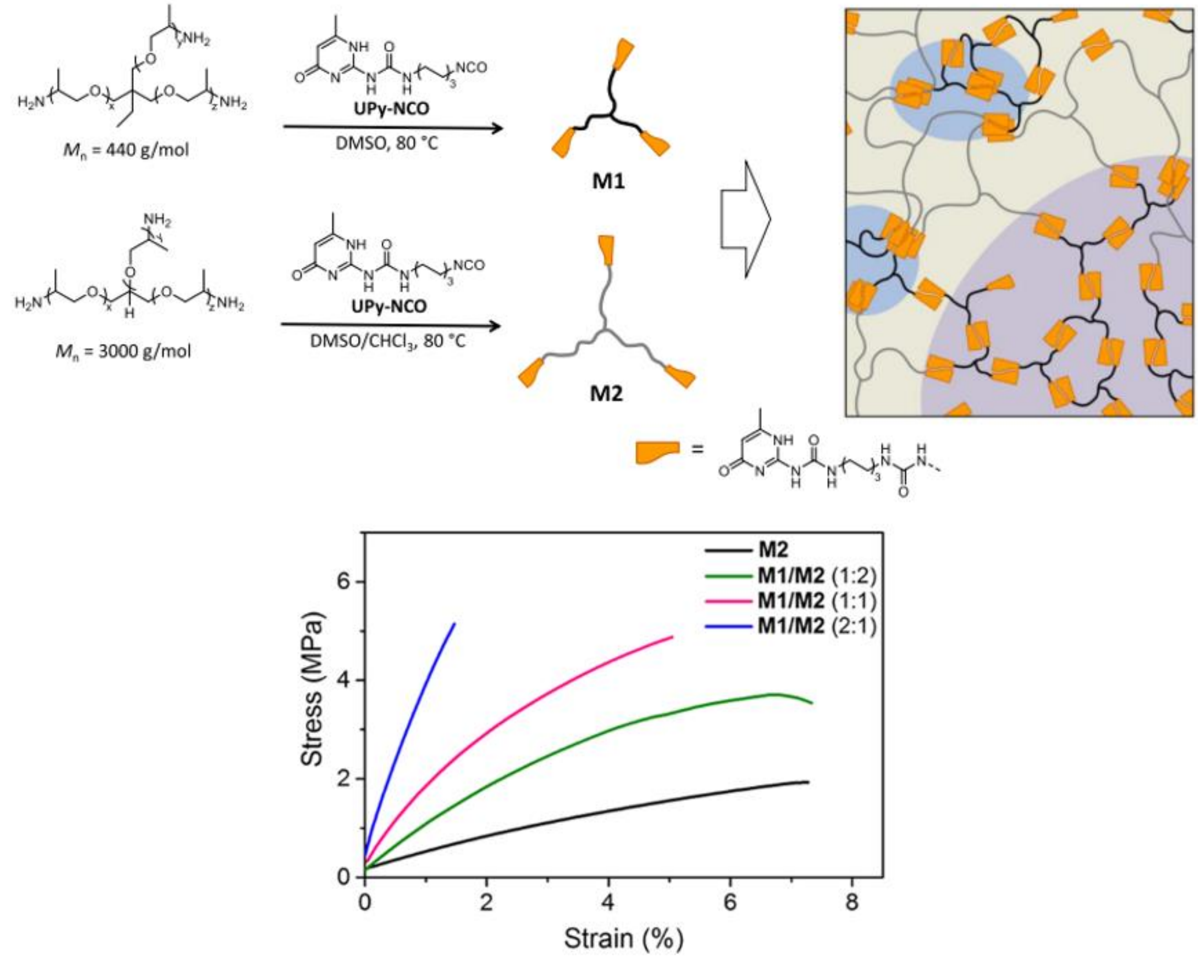

Fig. 14. Schematic illustration of the synthesis and network formation of a UPy-functionalized supramolecular monomers M1 and M2 (top); Stress-strain curves of melt-processed films of M2 and M1/M2 blends (bottom). [64], Copyright 2019. Adapted with permission from American Chemical Society.

5 Polymer materials with UPy in the side-chains

5.1 Synthesis of polymers with UPy in the side-chains

Next to the polymer main chain and the chain-ends, UPy motifs can be attached to the monomer side chains. The introduction of UPy units in the polymer side chains can be achieved *via* two strategies: firstly, there is the possibility to copolymerize a monomer containing the UPy moiety, and secondly the UPy can be introduced *via* post-polymerization modification. Both methods will be discussed in more detail below.

5.1.1 UPy monomer

For the incorporation of UPy units at the polymer side chains, the direct copolymerization of UPy-functional monomers is a frequently used method. Combined with controlled radical polymerization techniques, the polymer composition and UPy content can be controlled.

Due to their synthetic availability and established polymerization conditions, (meth)acrylates have been the main choice as a platform to develop UPy monomers, where methacrylates[33,49,55,73,122–132] were generally more common than acrylates.[54,133] The most common UPy-containing (meth)acrylate monomers are summarized in **Fig. 15**a. These monomers commonly feature a UPy motif with a methyl side-chain resulting from the commercial availability of 6-methylisocytosine precursor, but can theoretically be extrapolated to a larger variety of UPy units with custom side chains when the corresponding isocytosine is synthesized, such as 6-adamantylisocytosine.[55]

However, the aforementioned UPy-containing monomers have a limited solubility in most organic solvents and require the use of dimethyl sulfoxide (DMSO) for polymerization. In addition, they also show limited miscibility with most common (meth)acrylic monomers, which prevents copolymerization in bulk. Weder *et al.* reported a methacrylamide monomer with an oligo(propylene oxide) spacer between the UPy urea bond and the methacrylamide unit, which is a liquid and displays good miscibility with various conventional methacrylates.[131] The monomer is synthesized in three steps from an amine-terminated oligo(propylene oxide). The primary amine at one chain-end is reacted with an imidazolide to form the UPy moiety, and the other amine is converted to a polymerizable methacrylamide by addition of methacrylic anhydride. The liquid state of the UPy-monomer and its good miscibility with other methacrylate monomers allowed its solvent-free photoinitiated copolymerization with alkyl- or aryl methacrylates to yield UPy-functionalized polymers.

A UPy-containing olefin monomer was reported by Coates and coworkers.[134] In contrast to the previously mentioned monomers, the polymerizable functionality was incorporated in the side-chain of the isocytosine (R_1 group), which was converted to the corresponding UPy monomer by addition of *n*-butylisocyanate. Subsequent coordination polymerization with 1-hexene yielded physically crosslinked poly(1-hexene) copolymers. Meijer *et al.* synthesized an *o*-nitrobenzyl protected UPy monomer with a terminal norbornene unit, which was copolymerized with norbornene *via* ring-opening methathesis polymerization (ROMP).[135] The *o*-nitrobenzyl protection prevented UPy dimerization and preliminary polymer precipitation. After UV irradiation, the protecting group was cleaved and the polymers collapsed in nanoparticles due to UPy dimerization. Two variants of the UPy-norbornene monomer were synthesized that varied in the way that the UPy was linked to norbornene, as depicted in **Fig. 15**b. In the first monomer, the UPy motif was coupled to a hydroxy-functional norbornene *via* a urethane bond, while the second monomer featured a urea bond to connect the UPy to the norbornene. Following up on the polynorbornene nanoparticles, Meijer and coworkers applied the same methodology for the development of folded poly(methyl methacrylate) (PMMA) nanoparticles for which an *o*-nitrobenzyl-protected UPy-methacrylate monomer was copolymerized with methyl methacrylate *via* atom transfer radical polymerization (ATRP).[136] Since traditional ATRP reaction conditions failed to copolymerize the protected UPy monomer with ethyl methacrylate, activator regeneration by electron transfer (ARGET) ATRP was used as a more active alternative to regular ATRP. However, the obtained molar masses were lower than targeted, presumably due to interactions of the UPy monomer with the copper catalyst. Therefore, a more efficient route was developed based on post-polymerization modification, which is highlighted in section 5.1.2.

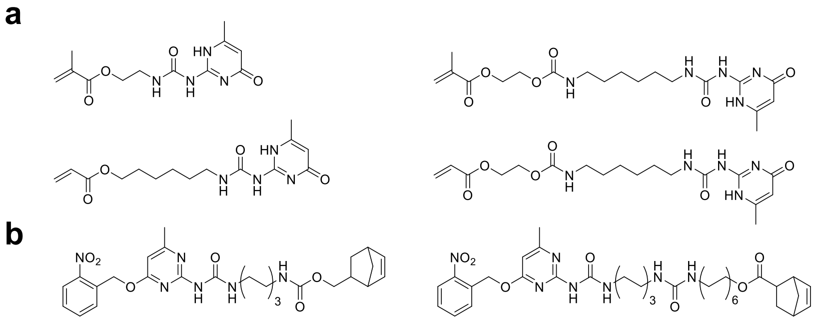

Fig. 15. a) Schematic overview of the most common (meth)acrylate UPy monomers. b).*o*-Nitrobenzyl protected UPy-containing norbornene monomers with additional urethane (left) and urea (right) groups as used for the synthesis of physically crosslinked poly(norbornene) nanoparticles.

Next to radical mediated polymerizations, UPy units can also be implemented *via* polyaddition reactions.[35,137] In a recent publication by Li and coworkers, a physically crosslinked polyurethane was reported where the UPy motifs were incorporated as a side-chain of the diol chain extender (**Fig. 16**).[35] Different soft and hard segments were used to tune the material properties. For the soft segment, PTMEG or poly(propylene glycol) (PPG) were chosen, where the latter introduced more steric hindrance through the extra methyl group. The hard segment consisted of dicyclohexylmethylmethane-4,4'-diisocyanate (HMDI) or isophorone diisocyanate (IPDI). The UPy chain extender was synthesized by coupling of an isocyanate-containing UPy motif with the amine group of 2-amino-2-methyl-1.3-propanediol introduced in different amounts to tune the mechanical properties and self-healing of the resulting polymer materials.

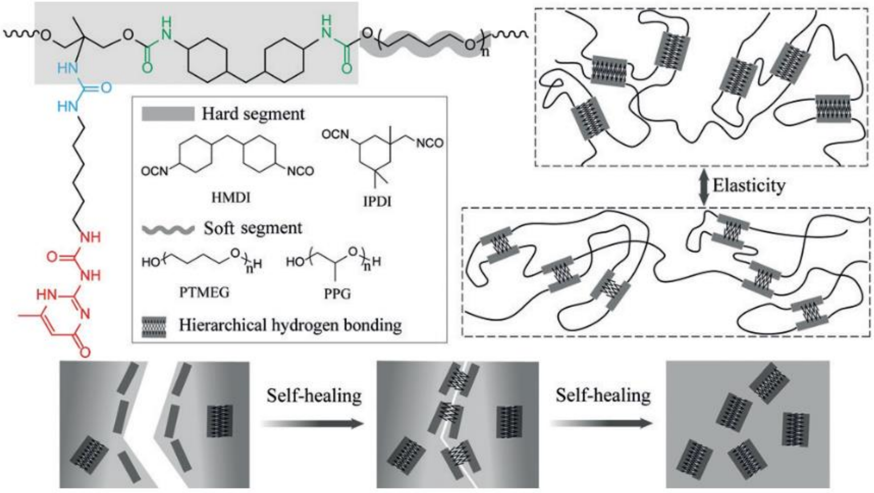

Fig. 16. Schematic illustration of the synthesis and self-healing process of physically crosslinked polyurethane with pendant UPy groups. [35] Copyright 2018. Reproduced with permission from John Wiley & Sons Inc.

5.1.2 Post-polymerization modification

Next to integration during polymerization, post-polymerization modification is another frequently used method to introduce UPy motifs to polymer side-chains and is closely related to the previously discussed chain-end functionalization in section 4.1.

Like chain-end functionalization, the coupling of UPys with a terminal isocyanate to polymers with alcohol[57,61,69,138–141] or -amine[62,66] side-chains is the most frequently applied strategy to functionalize polymer side-chains *via* post-polymerization modification. Alternatively, polymers with Boc-protected amine side-chains were functionalized with CDI-activated isocytosines after deprotection of the amine with trifluoroacetic acid.[142,143] Recently, Dalcanale and coworkers reported the synthesis of UPy-functional polyethylene (PE) *via* reactive extrusion.[141] Here, PE copolymers with hydroxyl-functional side-chains were synthesized, which were subsequently coupled with isocyanate-containing UPy units. For reactive extrusion, a UPy motif with isopropyl side-chain was chosen because of its lower melting point compared to the UPy with methyl side-chain, and significantly shorter reaction times were achieved as compared to solution grafting.

As an alternative to the monomer-based strategy to synthesize PMMA nanoparticles at the end of section 5.1.1, Meijer *et al.* developed an additional synthesis route by applying azide-alkyne click chemistry to link an azide-functional *o*-nitrobenzyl-protected UPy motif to PMMA that contained propargylic esters in the side-chain.[136] The alkyne-containing PMMA was obtained by copolymerization of methyl methacrylate with trimethylsilyl (TMS)-protected propargyl methacrylate *via* single electron transfer living electron polymerization (SET-LRP). After “clicking” the protected UPy units to the polymers, the nanoparticles were generated by deprotecting the polymer-bound UPy motifs under UV irradiation induced by the collapse of the polymers by UPy dimerization.

Recently, supramolecular crosslinked poly(dimethylsiloxane) (PDMS) networks were reported by Palmans and coworkers based on three hydrogen bonding motifs, including UPy, each with a different binding strength.[144] Commercial poly(dimethylsiloxane-*co*-methylhydrosiloxane) (P(DMS-*co*-HMS)) was post-functionalized by direct hydrosilylation of terminal alkenes on the hydrogen bonding units with the Si-H groups from the polymer using Karstedt's catalyst, resulting in hydrogen bonded polymer networks with varying material properties.

Hoogenboom and coworkers very recently synthesized UPy-functional polybutadiene by coupling thiol-containing UPy molecules to the vinyl side-chains of 1,2-polybutadiene *via* thiol-ene reactions.[145] Unlike most UPy-containing materials, the UPy motif was synthesized with a branched alkyl side-chain instead of a methyl substituent, which resulted in a significantly improved solubility in organic solvents and a better compatibility with the apolar polymer matrix. In addition, the bulky alkyl group could also prevent potential stacking of UPy dimers.

5.2 Material properties of polymers with UPy in the side-chain

Like described for UPy-telechelic star-shaped polymers, UPy incorporation in polymer side-chains enables the introduction of multiple UPy motifs on the polymer and therefore the formation of supramolecular polymer networks.

The apolar character of polyolefins makes them an attractive platform for the development of hydrogen bonded polymer networks, as the hydrogen bonds are reinforced in the aliphatic polymer matrix. Coates *et al.* reported a poly(1-hexene) copolymer with UPy side-chains, which significantly increased the elongation at break and tensile strength relative to the homopolymer with similar molecular weight.[134] However, crystalline polyolefins tend to produce less dynamic materials as the crystalline regions inhibit free movement of the UPy units through the polymer matrix and require elevated temperatures to enable UPy dimerization. This was observed for polypropylene (PP) polymers with UPy side-chains by Bosman and coworkers, where temperatures above 100 °C were needed to melt the crystalline regions in the PP matrix.[57]

Dalcanale *et al.* functionalized polyethylene (PE) with UPy side-chains *via* reactive extrusion, which reduced the reaction time significantly compared to solution grafting.[141] The authors opted for a lower melting UPy unit with isopropyl side-chain to allow processing of the material in the extruder. However, the extruded PE-UPy materials were found to be unstable when processed above 150 °C. The UPy-functional PE displayed greatly improved elongation at break, toughness and maximum tensile strength compared to the non-functionalized PE.

Similar as polyolefins, apolar elastomers like polybutadiene are attractive polymers to review the impact of hydrogen bonding on the material properties. Very recently, Hoogenboom *et al.* developed a low molar mass 1,2-polybutadiene (PB) with UPy units attached to the side-chains.[145] The UPy content was varied by alternation of a thiol-functional UPy motif in the feed, which was coupled to the polymeric vinyl side-chain by a photo-initiated thiol-ene reaction. The resulting supramolecular polymer materials showed a large range in T_g, going from -29 °C for unfunctionalized PB to 44 °C for the material with 13% UPy relative to the vinyl side-chains. Using the strategy of o-nitrobenzyl protected monomers to avoid preliminary crosslinking of the UPy units, Meijer and coworkers synthesized poly(norbornene) nanoparticles with improved processability of the resulting supramolecular films. [79] After copolymerization of the UPy-functional norbornene monomer with the *n*-alkyl-containing alternative, the UPy motifs were deprotected using UV irradiation, resulting in the formation of nanoparticles due to intramolecular H-bonding of the UPy units within the same polymer chain. By collapsing the polymer chains, there are significantly less entanglements between the polymer chains, which improves processability. After applying the dissolved nanoparticles as a film, the substrate was heated to break the UPy dimers. Subsequent cooling induced intermolecular H-bonding of the UPy side-chains, forming a stable supramolecular polymer network.

Poly(alkyl (meth)acrylates) are an interesting polymer platform as it allows convenient tuning of the polymer properties by variation of the ester substituent. Especially low-glass transition temperature (T_g) polymers such as poly(*n*-butyl acrylate) (PBA) are frequently considered to investigate the formation of supramolecular polymer networks.[54,73,122,142,146] After the introduction of UPy units in the side-chains, an increasing UPy content led to a linear increase in T_g of the resulting polymer networks (attributed to inter-chain hydrogen bonds and comonomer structure), but also a decreased thermal degradation temperature inherently linked to the lower thermal stability of the UPy moieties.[73]

Further research by Zeng *et al.* on UPy-containing PBA copolymers highlighted significantly improved adhesion and self-healing properties ascribed to the physical crosslinking by inter-chain UPy dimerization.[54] Jangizehi and coworkers explored the dynamics of PBA-UPy networks with high molecular weight PBA precursors (M_n = 142 kg/mol) and observed the formation of high-order associations when the UPy content in the material exceeded 4 mol%, which was caused by stacking of UPy dimers [140]

Recently, Weder and coworkers synthesized UPy-functional poly(*n*-hexyl methacrylate) (poly(UPy-HMDI-HEMA-*co*-hexyl-MA) and poly(*n*-butyl methacrylate) (poly(UPy-HMDI-HEMA-*co*-butyl-MA) by copolymerizing the UPy-methacrylate polymer with hexyl methacrylate or butyl methacrylate respectively.[130] By increasing the UPy fraction in the resulting polymers, the Young's modulus and tensile strength increased while decreasing the elongation at break (**Fig. 17**), which is consistent with other UPy polymer networks. It was found that the presence of the supramolecular crosslinks significantly improved adhesion in the rubbery state and good adhesion was achieved over a large temperature range with comparable performance to commercial hot-melt adhesives. In addition, the UPy crosslinks allowed bonding and de-bonding on demand by using either heat or light.

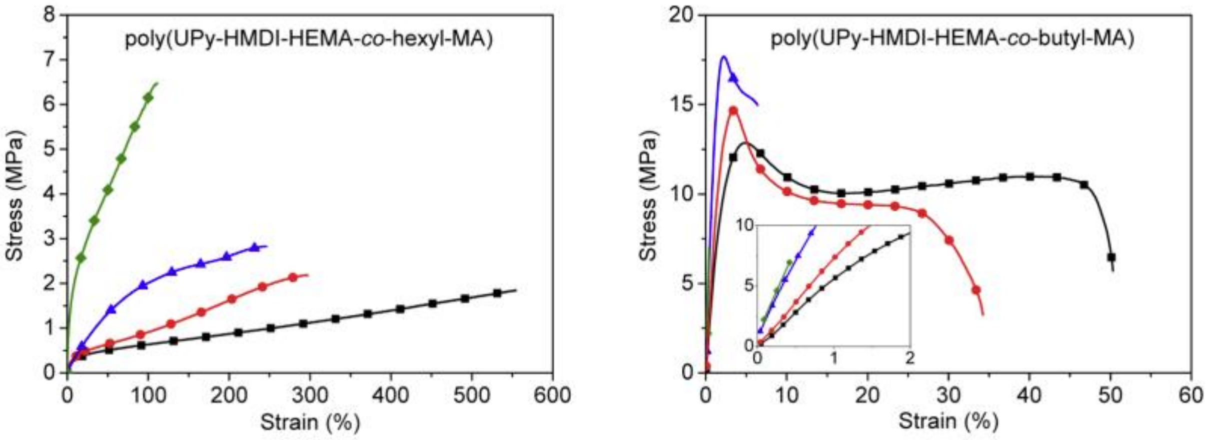

Fig. 17. Stress-strain curves of poly(UPy-HMDI-HEMA-*co*-hexyl-MA) (left) and poly(UPy-HMDI-HEMA-*co*-butyl-MA) (right) with a UPy content of 0 mol % (black squares), 2.5 mol % (red circles), 5 mol % (blue triangles) and 10 mol % (green diamonds). [130], Copyright 2015. Reproduced with permission from American Chemical Society.

When UPy-methacrylate (UPy-MA) is copolymerized with hydroxyethyl methacrylate (HEMA), swelling of the resulting copolymers in water resulted in the formation of physical hydrogels.[49] It was observed that the swelling rate decreased with increasing UPy content, which the authors attributed to osmotic stresses caused by the reversible network. Rheological analysis revealed that the shear activation energy scaled linearly with UPy-content and confirmed that UPy-dimerization was still present in the hydrated state, which opens possibilities for the use of these materials as injectable hydrogel in biomedical applications.

Another example of a supramolecular hydrogel with UPy side-chains was recently reported by Pan *et al.*[147] Here, copolymerization of UPy-MA, stearyl acrylate (SA) and acrylic acid (AA) was employed to design a dual-crosslinked polymer (P(UPyMA-*co*-SA-*co*-AA), where the crosslinking was organized by hydrogen bonding of the self-complementary UPy units and hydrophobic association of the alkyl chains of SA (**Fig. 18**). After equilibrium swelling in water, the obtained hydrogels with a water content of 40-80 wt% showed good mechanical performance with a tensile strength up to 4.6 MPa and maximum elongation of up to 680%. These properties were explained by the synergy between the hydrophobic association and hydrogen bonding. Furthermore, the AA groups introduced pH-responsiveness and could be targeted for crosslinking by metal-coordination after addition of metal salts, which enabled shape-memory behavior.

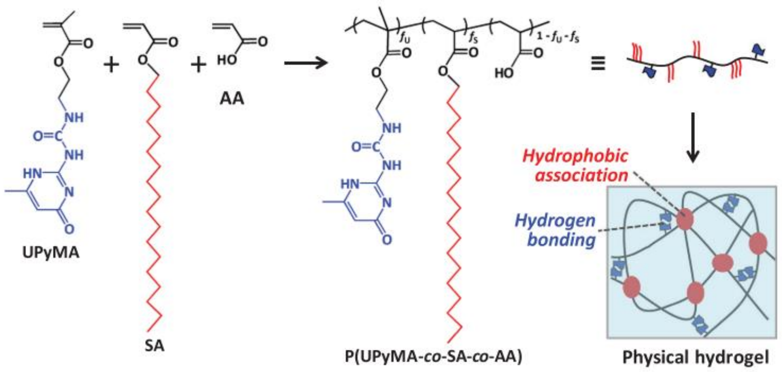

Fig. 18. Schematic illustration of the synthesis of dual-crosslinked P(UPyMA-*co*-SA-*co*-AA) hydrogel. [147], Copyright 2018. Reproduced with permission from John Wiley & Sons Inc.

Li and coworkers presented a super-tough healable polyurethane material with pendant UPy groups (**Fig. 16**).[35] The UPy side chains were added as a diol chain extender in a conventional polycondensation reaction, and variation of the hard and soft segments allowed tuning of the material properties. All mechanical properties (tensile strength, Young's modulus and toughness) increased with increasing UPy content, with a tensile strength of 44 MPa combined with a toughness of 345 MJ/m^3 after self-healing for the elastomer containing 20% UPy and the authors proposed potential applications in the field of stretchable electronics.

You *et al.* reported a UPy-functional bioelastomer based on poly(sebacoyl diglyceride) (PSeD), which is a refined version of the commercially available poly(glycerol sebacate) (**Fig. 19**, left).[61] The pendant OH-groups on the polymer were utilized to couple the isocyanate-containing UPy units to realize the physically crosslinked PSeD network (PSeD-U). The PSeD starting material is a crystalline polymer with a limited elongation at break of 12%. The attachment of pendant UPy motifs inhibited crystallization and produced completely amorphous materials with significantly improved elongation and toughness, as seen in the stress-strain curves of PSeD-U materials with 23.4% and 32.7% UPy content relative to the theoretical amount of OH groups on PSeD (PSeD-U20 and PSeD-U30, respectively) displayed in the right of **Fig. 19**. Furthermore, the dynamic UPy crosslinks allowed self-healing under mild conditions and reprocessing at higher temperatures, and the authors demonstrated that the PSeD-U materials were biocompatible and biodegradable, which enables potential use in biomedical applications.

In a follow-up publication in the context of bio-integrated electronics, the PSeD-U material was covalently crosslinked by inter-chain esterification of the residual pendant OH groups on the polymer.[148] The covalent crosslinking was achieved by thermal curing of the PSeD-U polymers at different curing times to vary the crosslink density. When comparing the tensile properties of materials with variable UPy content cured under the same conditions, depicted in the left of **Fig. 20**, a significant increase in toughness and maximum elongation was observed. However, the Young's modulus was similar for all UPy concentrations, indicating that the UPy crosslinks did not contribute to the material stiffness. The curing time of 12 hours was preferred because it produced materials with a modulus closest to that of skin (0.64 MPa and 0.42-0.75 MPa, respectively) (**Fig. 20**, right).

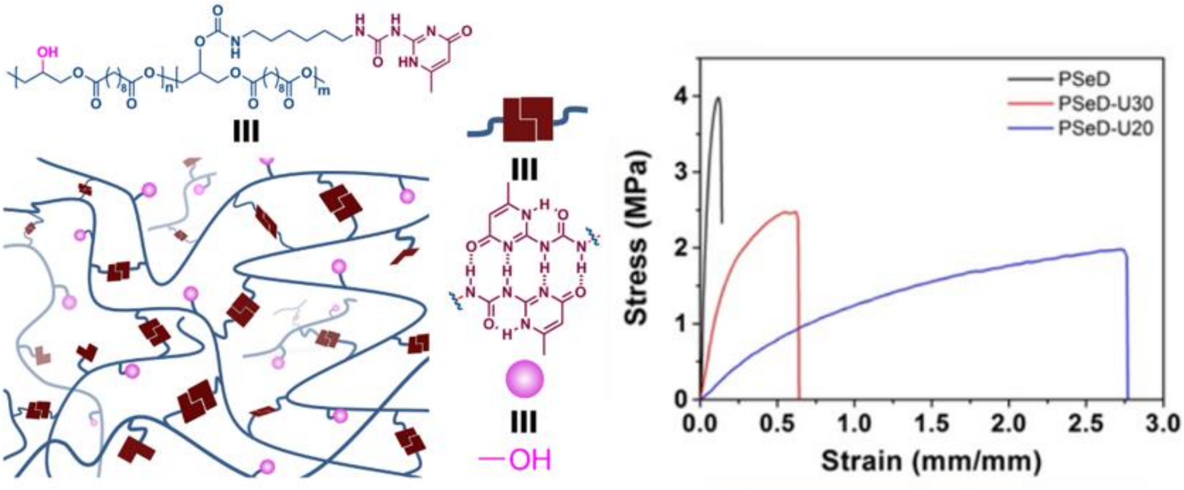

Fig. 19. Schematic illustration of the molecular structure of bioelastomer PSeD-U (left) and stress-strain curves of PSeD-U with 23.4% and 32.7% UPy (PSeD-U20 and PSeD-U-30, respectively) compared to the crystalline PSeD starting polymer. [61], Copyright 2016. Adapted with permission from American Chemical Society.

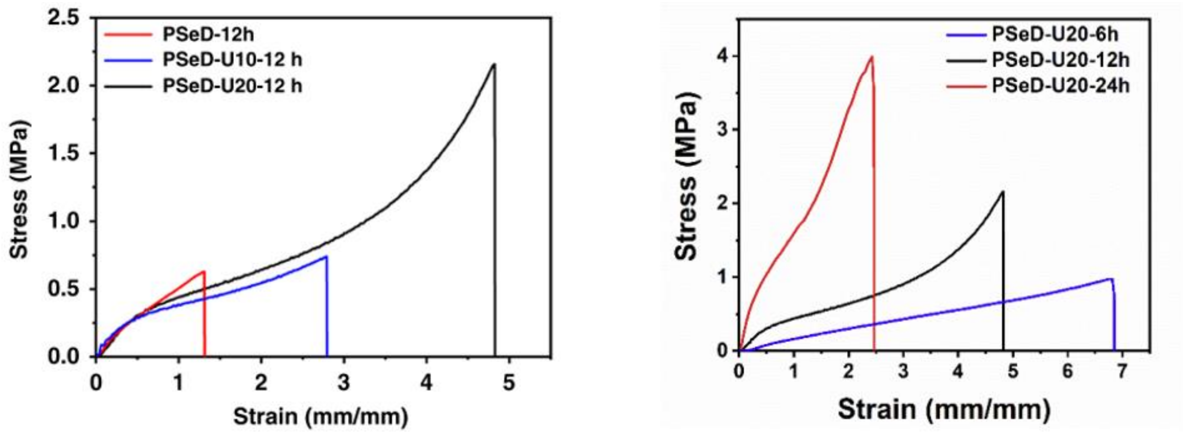

Fig. 20. Stress-strain curves of thermally cured PSeD-U materials with varying UPy content (left) and varying curing time. [148], Copyright 2020. Reproduced with permission from Nature Publishing Group.

6 Conclusions and outlook

By incorporation of UPy motifs in polymeric structures, a plethora of supramolecular polymer materials have been designed with enhanced mechanical properties. These materials can be subdivided according to the location where the UPy units are attached on the polymer precursors, namely into the main chain, at the chain-ends or at the side-chains.

Introduction of UPy units into the polymer backbone requires a specific synthetic strategy for the preparation of UPy units with two functional groups and is mainly focused on polyurethanes. Functionalization of the polymer chain-ends is generally done by post-polymerization modification and requires the presence of functional handles at the polymer chain-ends. Most frequently, these chain-ends are hydroxyl groups or amines and are coupled with isocyanate-containing UPy molecules to synthesize the desired materials. For bifunctional UPy-telechelic polymers, the chain-end interactions increase the virtual molecular weight, enabling chain entanglements, but a low-melt viscosity was maintained at elevated temperatures when low molecular weight polymer precursors are used. To design supramolecular polymer networks, UPy end-functionalized star polymers can be used. When a urethane or urea group is added next to the UPy motifs, formation of microfibers by formation of UPy stacks is possible. A drawback of UPy-telechelic polymers is the limited tunability of the UPy content, *i.e.* UPy units can only be coupled at the chain-ends. However, variation of the chain length enables adjustment of the overall UPy content. Supramolecular polymer materials with UPy motifs at the side-chains are synthesized in two ways: a UPy-functional monomer can be copolymerized with the desired monomers, or the UPy units can be introduced to a polymer-precursor with functional handles on the monomer side-chains *via* PPM. The synthetic protocols for the PPM are closely related to the chain-end functionalization. Compared to UPy-telechelic polymers, a better tunability of the UPy content can be achieved. Furthermore, higher UPy contents are possible for side-chain-functional polymers, although care should be taken in case of high UPy densities. When too many UPy crosslinks are present, the materials can quickly become rigid due to the decreased chain mobility. Therefore, low T_g polymers are generally preferred when high UPy contents are pursued. Another strategy to increase the mobility of UPy units in the side-chains is to increase the spacer length, which also enables the potential formation of UPy stacks. Recently, a new method was developed for the synthesis of polymers with UPy in the side-chain, where polymerization of *o*-nitrobenzyl protected UPy units were collapsed into nanoparticles. This was achieved by deprotecting the UPy units in dilute conditions, resulting in intramolecular H-bonding. These nanoparticles allowed more convenient processing of the materials, and could eventually be converted to the intermolecular H-bonded supramolecular polymer network in a reversible manner.

In summary, this review provides an overview of various UPy-functional materials and the synthetic strategies to obtain them. The material properties can be tuned by using polymers with different chemical compositions and/or topologies, and by the location where the UPy units are incorporated. This tunability enables the synthesis of a wide range of materials with applications such as reversible adhesives,[130] polymeric nanoparticles,[136] stretchable electronics,[63,117,148] binder materials for batteries,[69,124,133] vascular grafts[67] and heart valves,[149] as well as printable electrolytes.[150] However, the limited thermal stability of the UPy compound largely exclude applications that require elevated temperatures. Another drawback of UPy-based materials is the need for a low-T_g polymer platform, which is needed to enable sufficient mobility for the polymer chains to allow dynamic behavior. Moreover, the dissociative nature of physically crosslinked networks is often accompanied with a lack of creep resistance. This can be solved by combining the dynamic behavior of intermolecular UPy dimerization with covalent crosslinks, where the covalent crosslinks maintain the network integrity and the H-bonds act as sacrificial bonds which increase the toughness of the materials. These covalent crosslinks can either be irreversible[58,148,151,152] or reversible.[153–157] In case of the latter, the network gains complete reversibility, which can be an interesting property for self-healing and responsive materials. Recent work involving these hybrid networks combining UPy dimerization with reversible covalent bonds apply boronic esters,[153,156,157] mechanoresponsive compounds[154] and thiol-Michael bonding[155] to establish the dynamic covalent network junctions.

Despite the large amount of research regarding UPy-containing polymers, there is still a lot to learn concerning the dynamics of the UPy hydrogen bonding in polymer materials, as stacking of the UPy dimers can also occur. In this regard, interactions among the UPy moieties can potentially be isolated by the incorporation of bulky groups on or near the UPy units to avoid the formation of secondary structures, hence simplifying the system. Nonetheless, the dynamics of the UPy-based supramolecular polymer networks needs to be studied in more detail, where rheological experiments combined with modelling can provide more insight into this complex matter.

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