ChemComm

ROYAL SOCIETY OF CHEMISTRY

FEATURE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2023, **59**, 14236

Dynamic supramolecular hydrogels mediated by chemical reactions

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Received 2nd September 2023,
Accepted 3rd November 2023

DOI: 10.1039/d3cc04353c

rsc.li/chemcomm

Supramolecular self-assembly in a biological system is usually dominated by sophisticated metabolic processes (chemical reactions) such as catalysis of enzymes and consumption of high energy chemicals, leading to groups of biomolecules with unique dynamics and functions in an aqueous environment. In recent years, increasing efforts have been made to couple chemical reactions to molecular self-assembly, with the aim of creating supramolecular materials with lifelike properties and functions. In this feature article, after summarising the work of chemical reaction mediated supramolecular hydrogels, we first focus on a typical example where dynamic self-assembly of molecular hydrogels is activated by *in situ* formation of a hydrazone bond in water. We discuss how the formation of the hydrazone-based supramolecular hydrogels can be controlled in time and space. After that, we describe transient assembly of supramolecular hydrogels powered by out-of-equilibrium chemical reaction networks regulated by chemical fuels, which show unique properties such as finite lifetime, dynamic structures, and regenerative capabilities. Finally, we provide a perspective on the future investigations that need to be done urgently, which range from fundamental research to real-life applications of dynamic supramolecular hydrogels.

Introduction

The development of supramolecular self-assembly is mainly elevated by the understanding of a biological system where the self-assembled structures are highly dynamic and are usually regulated by complex metabolic processes (chemical reactions).[1–4] Such a chemical reaction mediated supramolecular self-assembly underpins many vital cellular functions.[5,6] For example, the assembly as well as the folding of proteins into bioactive assemblies are typically associated with orchestrated enzymatic reactions.[7,8] Microtubules are dynamically assembled by tubulins with the consumption of high energy guanosine triphosphate (GTP), and the microtubules disassemble into the monomers by catalytic decomposition of GTP, which then support mitosis and intracellular transport of substances.[9] Therefore, coupling a chemical reaction to supramolecular self-assembly in a synthetic scenario may not only further our understanding of the biological phenomena but also unlock new supramolecular products with lifelike functions.[10–13] In a chemical

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reaction-mediated supramolecular self-assembly system, non-assembling precursors are converted into the assembling state by chemical reactions, thus activating the self-assembly into prescribed structures or materials driven by various non-covalent interactions such as hydrogen bonds, hydrophobic interaction, π–π stacking, and electrostatic interaction. It should be noted that the self-assembly is usually driven by multiple non-covalent interactions. Control over supramolecular self-assembly using chemical reactions has received great interest in the past two decades, and this allows for: (1) triggering self-assembly in an aqueous environment immediately without the necessity of heating–cooling or solvent exchange;[14–16] (2) interfering with the self-assembly kinetics, thus leading to kinetically favoured assemblies with spatiotemporally resolved structures and functions;[17–21] (3) giving rise to highly dynamic assemblies at out-of-equilibrium states by taking the energy released by the chemical reaction.[11,22–25] Amongst these developed examples of chemical reaction mediated supramolecular self-assembly, molecular hydrogels have been of particular interest because of their potent applications in biomedicine, and these are the focus of this feature article.

The first occasion of chemical reaction mediated supramolecular hydrogels is associated with formation or cleavage of chemical bonds which regulate the hydrophilic/hydrophobic balance of the hydrogelator precursors, thus activating the self-assembly of the resultant hydrogelators into hydrogels (Fig. 1(a)).[26] For example, Xu and co-workers,[27–29] Ulijn and co-workers,[30–33] and others[34–37] used enzymes to accelerate bond formation or cleavage in peptides, after which the hydrophilic/hydrophobic balance of the resultant peptide-based

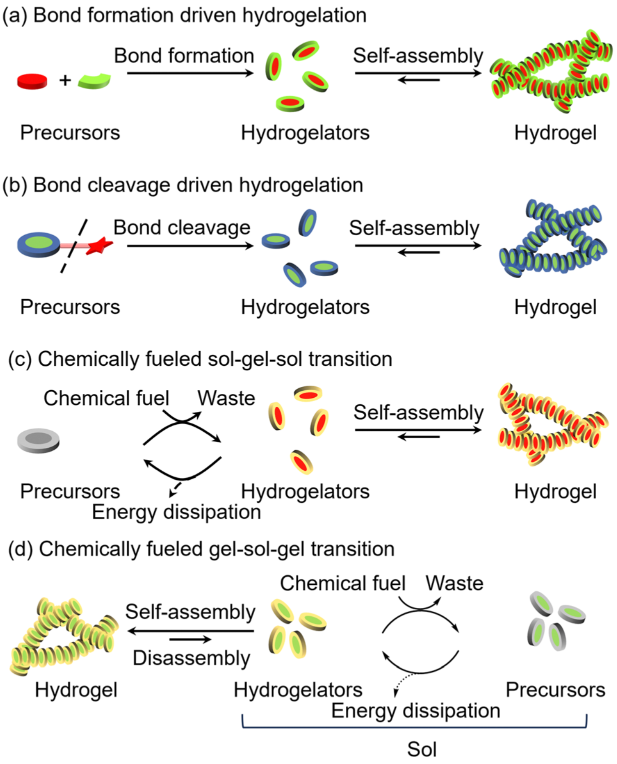

Fig. 1 Scheme of the chemical reaction mediated self-assembly of hydrogelators. (a), (b) Self-assembly of supramolecular hydrogels triggered by (a) formation or (b) cleavage of chemical bonds, (c), (d) transient supramolecular hydrogels, (c) assembly and (d) disassembly of supramolecular hydrogels driven by chemically fuelled out-of-equilibrium chemical reaction networks.

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gelators was changed to favour self-assembly, thus leading to peptide-based supramolecular hydrogels. By coupling the enzymatic hydrogelation with the overexpressed enzymes of cancer cells, such as alkaline phosphatase (ALP), extra/intracellular hydrogelations have been reported, providing a new therapeutic approach for cancers.[34,38,39] Jierry and co-workers immobilised enzymes at specific regions, realising localised hydrogelations at the targeting areas.[40] Some good reviews regarding enzymatic hydrogelation are available,[41,42] and thus they will not be discussed intensively here. These enzymatic self-assembly events have highlighted a new interdisciplinary field called enzymatic noncovalent synthesis (ENS).[4]

In addition to the enzymatic hydrogelation, complete synthetic supramolecular hydrogel systems controlled by organic reactions have also been investigated. For example, catalytic formation of the hydrazone bond[14,43–46] or photo-responsive cleavage of 2-nitrobenzyl ester group[47] have been demonstrated as effective ways to result in hydrogelation. Spatiotemporal control over the self-assembly of hydrogels can be achieved by controlling the spatial distribution of organocatalysts[18,48] or using light.[49,50] It is worth noting that hydrazone-based supramolecular hydrogels which show interesting kinetic effects have been systematically studied in the authors' group together with the group of Eelkema and van Esch, which will be detailed here.

Another emerging type of control over supramolecular hydrogels using chemical reactions is to couple the self-assembly of hydrogelators with out-of-equilibrium chemical reaction networks regulated by high-energy chemicals (chemical fuels).[22,51,52] In the chemically fuelled supramolecular hydrogel systems (Fig. 1(c)), the non-assembling precursors are converted into self-assembling hydrogelators by their reaction with the chemical fuels immediately or by incorporating a signal, for example pH, released by the chemical fuel governed reactions.[53–56] As a consequence, the activated hydrogelators are allowed to self-assemble into hydrogels with the consumption of chemical energy. However, the hydrogelators are unstable and will transform backwards to the non-assembling state when the chemical fuels are depleted. These out-of-equilibrium hydrogels are highly dynamic, and their structures and properties are maintained at an out-of-equilibrium state with the continuous consumption of chemical fuels. The group of van Eelkema and van Esch pioneered the development of out-of-equilibrium supramolecular hydrogels using methylation reagents as the fuels.[22,53] After that, various beautiful examples of out-of-equilibrium supramolecular assemblies powered by different chemical fuels, including carbodiimide,[57–62] ATP,[55,63–69] pH regulators,[70–75] enzymatic reactions,[15,66,76–78] carbon dioxide,[79,80] and others,[81–84] have been carefully developed. The resultant supramolecular hydrogels show high dynamics, tunable lifetime and stiffness, and a regenerative capability.[11,61,85–87] In addition to the chemically fuelled sol–gel–sol transition, the reversed case, *i.e.*, a chemically fuelled gel–sol–gel transition, has been reported as well (Fig. 1(d)).[87–89] In this case, the hydrogels are in the equilibrium state. The chemical fuel additive will drive the hydrogels' transformation into a solution, and then the transformation will reverse to the assembly state once the fuels are depleted. We also developed a series of out-of-equilibrium hydrogels powered by carbodiimide,[90,91] sugar[88] and reaction–diffusion mediated fuels,[92] which will be discussed later in this feature article.

From the previous discussion, it is clear that dynamic supramolecular hydrogels resulting from chemical reaction mediated self-assembly has been an active area of research and discussion in the field of supramolecular chemistry and soft matter. This feature article mainly focuses on the examples investigated by the authors, including supramolecular hydrogels based on *in situ* formation of hydrazone bonds from the hydrazide and aldehyde precursors, and transient supramolecular hydrogels driven by chemically fuelled out-of-equilibrium chemical reaction networks. By introducing these detailed examples, we will show why using chemical reactions to control the self-assembly of supramolecular hydrogels deserves attention, what the state-of-the-art is and what future studies should be focusing on.

Dynamic supramolecular hydrogels based on hydrazone formation

Hydrazone-based supramolecular hydrogelation system

Typically, the formation of supramolecular hydrogels is associated with solvent exchange or heating–cooling reactions,[93–96] by which the self-assembly process is usually hard to control. In contrast, the supramolecular self-assembly in biological systems occurs under very mild conditions, that are thought to be controlled by complex metabolic processes (chemical reactions). As an inspiration, chemists also started to focus on supramolecular hydrogelation by coupling hydrogelator self-assembly to chemical reactions. During the chemical reactions, the non-assembling precursors are converted into hydrogelators by *in situ* bond formation or cleavage, eventually leading to direct hydrogelation in water. The group of Eelkema and van Esch developed a chemical reaction mediated supramolecular self-assembly system based on the *in situ* formation of a hydrazone-based hydrogelator **3** from its non-assembling precursors, hydrazide **1** and aldehyde **2** (Fig. 2(a)).[14] Interestingly, the subsequent formation of the self-assembly kinetics of **3** can be dramatically accelerated by using nucleophile catalysts such as an acid or aniline (Fig. 2(b)). Denser hydrogel networks and stiffer hydrogels are formed with the addition of a catalyst because of the branched growth of the hydrogel fibres at a higher assembly rate (Fig. 2(c) and (d)). On the basis of the catalyst-responsive self-assembly behaviour, they further achieved spatial control over the growth of the hydrogels by triggering the localised formation and self-assembly of **3** using a light-switchable catalyst[49] and a surface-confined catalyst.[18]

Spatiotemporal control over hydrogelation

In living systems, supramolecular self-assembly is ubiquitous and is well controlled in time and space.[9,97] The hydrazone-based hydrogelator system provides a versatile synthetic

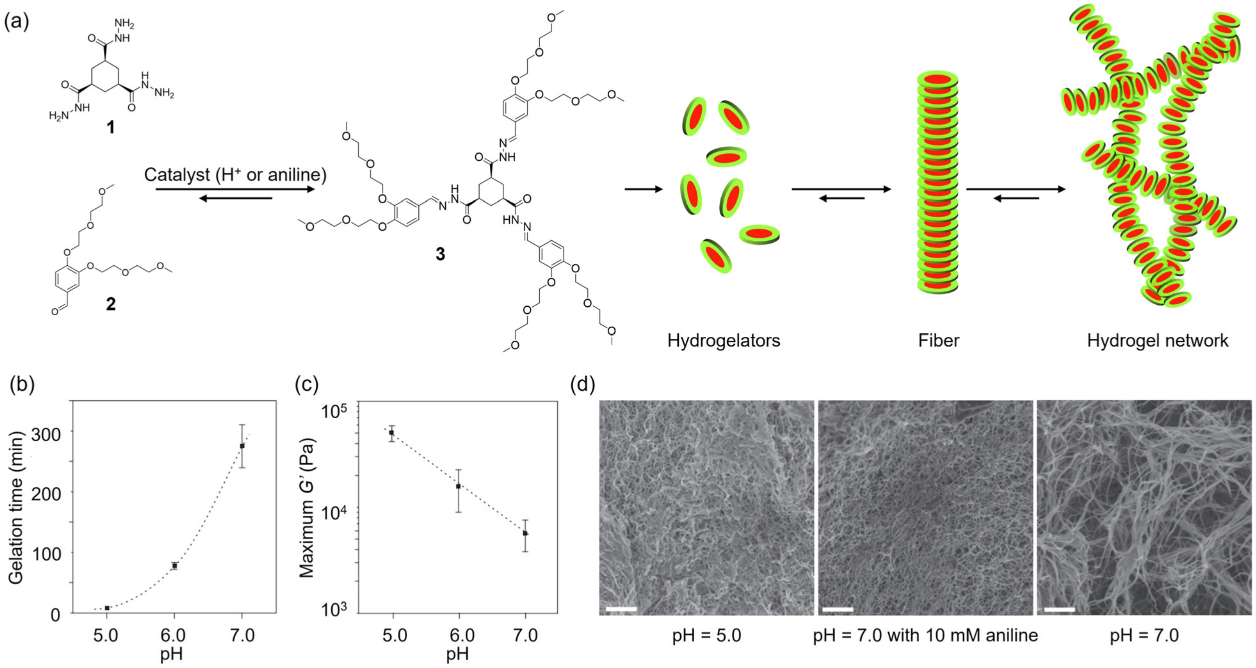

Fig. 2 Hydrazone-based supramolecular hydrogel system. (a) Catalytic formation of hydrazone-based hydrogelator **3** from the water-soluble precursors of **1** and **2** leading to self-assembly of fibres which thereby entangle to form supramolecular hydrogel; effects of pH on (b) gelation time; (c) stiffness; and (d) network morphologies of the hydrazone-based hydrogels. Copyright 2013, Springer Nature Limited.[14]

platform for the investigation of biomimetic self-assembly, because many vital *in vivo* self-assembly processes are associated with the catalysis of enzymes, giving rise to groups with spatiotemporally resolved structures and properties. Relying on this catalyst-responsive hydrazone-based hydrogelator system, we grafted a negatively charged polymer poly(acrylic acid) (PAA) onto the surface of a cover glass with defined shapes using a microcontact printing technique.[98] The densely grafted PAA chains were found to be able to capture protons attracted by the brush surface, which can effectively catalyse the rapid formation and self-assembly of **3**, leading to hydrogel micropatterns with well-controlled resolution (Fig. 3(a) and (b)). Furthermore, by controlling the grafting density of the PAA, the thickness of the hydrogels can be regulated as well (Fig. 3(c)). Such an approach enabling localised control over the growth of three-dimensional supramolecular hydrogel objects is very useful for many high-tech applications. For example, it can be used to create supramolecular hydrogel structures for a tissue scaffold or to trigger self-assembly of gelators at the surface of cancer cells, and this may provide an alternative way to kill cancer cells.

Motivated by the access to localised self-assembly of **3** at the microscale, a more challenging investigation, *i.e.*, spatial control over the self-assembly of **3** at the nanoscale, was performed.[99] Therefore, the catalytic PAA chains were grafted onto the surface of polystyrene (PS) nanoparticles as the catalyst (Fig. 3(d)). It was found that the condensed H^+ in the vicinity of the nanoparticles can dramatically accelerate the formation and self-assembly of **3** (Fig. 3(e)). Use of Cryo-TEM further demonstrated that dense hydrogel fibres were specifically formed around the catalytic nanoparticles, in stark contrast to the control sample that used noncatalytic nanoparticles. Access to spatial control over the formation of hydrogel fibres at the nanoscale may open a new way for therapy. For example, localised formation of hydrogel fibres at the surface of nanoscale viruses may effectively induce their aggregation, thus decreasing their infection capability.

Kinetically favoured metastable hydrogels

Self-assembly kinetics has been demonstrated to show a significant effect on the self-assembly results.[100,101] By controlling the self-assembly kinetics, self-assembly can be controlled to proceed along different pathways, leading to various supramolecular products which occupied different metastable or kinetically trapped states on the thermodynamic energy landscape. Each of the assemblies shows very different structures and material properties even when they share the same molecular composition. Meijer *et al.* first revealed the pathway complexity in supramolecular self-assembly in 2012, after which the dependence of supramolecular self-assembly on kinetics emerged as a focus in the field of supramolecular chemistry.[101] The previously discussed hydrazone-based supramolecular hydrogelator system provides an important platform to study effects of self-assembly kinetics by using catalysts. In fact, control over the supramolecular self-assembly by interfering with the self-assembly kinetics is also widely observed in nature.[6,102–104] However, in contrast to the synthetic system, the self-assembly in living systems is associated with multicomponent biological discrete that is much more complex than manmade systems. Therefore, the study of kinetic effects on the

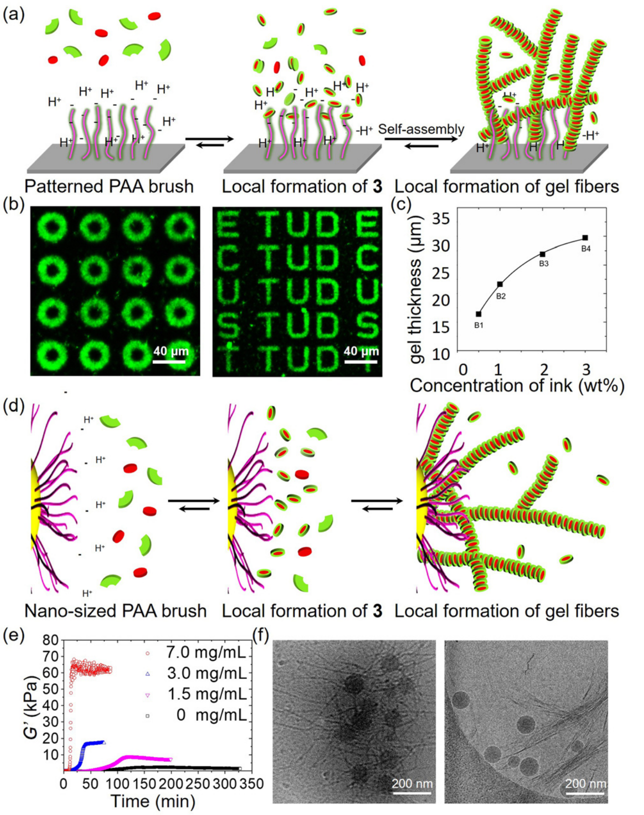

Fig. 3 Spatiotemporal control over hydrogelation. (a) Scheme showing localized formation and self-assembly of **3** at the surfaces grafted with catalytic PAA brush; (b) micropatterns of hydrogels formed from the surfaces of PAA brushes; (c) thickness of the hydrogels as a function of grafting density of PAA; (d) localized formation and self-assembly of **3** at surface of nano-sized PAA brush; (e) hydrogelation with the addition of catalytic/non-catalytic nanoparticles; and (f) Cryo-TEM images showing the localized self-assembly of hydrogel fibres at the surface of the nano-sized PAA brush. (a)–(c) Copyright 2019, Wiley-VCH.[103] (d)–(f) Copyright 2018, Wiley-VCH.[104]

system shifting from monocomponent to multicomponent self-assembly would be beneficial for the development of more advanced supramolecular assemblies with new functionalities.

The previously mentioned hydrazone-based supramolecular hydrogelator system has a useful modular feature and by simply changing the aldehyde building block, offers an opportunity to study multicomponent self-assembly in water. In a previous study, we obtained a series of hierarchically compartmentalised supramolecular hydrogels by introducing a simple negatively charged aldehyde building block **4** (Fig. 4(a) and (b)).[105] The results of rheological tests and fluorescence characterisation suggested that there was a multilevel self-sorting mechanism that underpins the hydrogel formation (Fig. 4(c)). In the first stage, the neutral hydrogelator **3** and the negatively charged hydrogelator **5** were formed at a comparable rate (Fig. 4(d)). Because of the electrostatic repulsion, the self-assembly of **5** significantly lagged behind **3**, leading to the earlier formation of neutral fibres (**NFs**). In the second stage, the continuous formation and accumulation of **5** led to a supersaturation state that eventually activated the self-assembly of **5** or its co-assembly with **3** into negatively charged fibres (**CFs**). After these two stages, the resultant hydrogel gelators **3** and **5** underwent molecular level self-sorting driven by the different self-assembly kinetics, giving rise to the differently charged fibres. Typically, molecular self-sorting mainly depends on very different molecular structures. Such a kinetically controlled self-sorting demonstrated a new way that could lead to molecular self-sorting. Interestingly, the **NFs** and **CFs** formed could further self-sort at the fibrous length scale, ultimately resulting in the hierarchically compartmentalised supramolecular hydrogels, reminiscent of the complex supramolecular structures in living cells.[106] Although the self-sorting at the fibrous length scale remains unclear, such a multilevel self-sorting system observed in the hydrazone-based supramolecular hydrogel system demonstrated access to biomimetic hierarchical supramolecular structures on the basis of pure synthetic molecules.

Having demonstrated that the self-sorting of **3** and **5** was driven by their different self-assembly rates, a catalyst, aniline, was further introduced into the previously mentioned multicomponent hydrogelation system, effectively influencing the self-assembly pathways (Fig. 5(a)).[107] The addition of aniline was found to dramatically accelerate the formation and therefore the rapid supersaturation of both **3** and **5**. As a result, the delayed self-assembly rates between **3** and **5** were remarkably reduced, leading to the co-assembly of **3** and **5** into **CFs** which ultimately form a uniform hydrogel network (Fig. 5(b)). Interestingly, the uniform hydrogels were found to occupy a metastable state, which could cause their networks to evolve into the previously observed compartmentalised state over time (Fig. 5(c)). On the basis of these results, a pathway-dependent self-assembly mechanism was proposed, as shown in Fig. 5(d). Typically, the differently formed, charged **3** and **5** self-assembled into **NFs** and **CFs** by kinetically controlled molecular self-sorting, whereas the **NFs** and **CFs** formed could further self-sort at the fibrous length scale, giving rise to thermodynamically stable compartmentalised hydrogels. However, the addition of aniline reduced the difference of self-assembly rates between **3** and **5**, and accelerated their co-assembly instead of self-sorting into **CFs** along a kinetically favoured pathway. More interestingly, the resultant **CF** hydrogel network occupied a metastable state, which spontaneously converted into the thermodynamically stable compartmentalised hydrogel network over time. In addition to the use of the catalyst, we also found that reducing the self-assembly rate difference between **3** and **5** by accelerating their nucleation process using seeds could also force the self-assembly of **3** and **5** along a similar kinetically favoured pathway, giving rise to metastable hydrogels comprising of **CFs**.[108,109] These studies strongly suggest that interfering with the self-assembly kinetics may force the self-assembly of hydrogelators along different pathways, therefore resulting in various kinetically favoured hydrogels that may show distinctly different structures and material properties even with the same hydrogelator compositions.

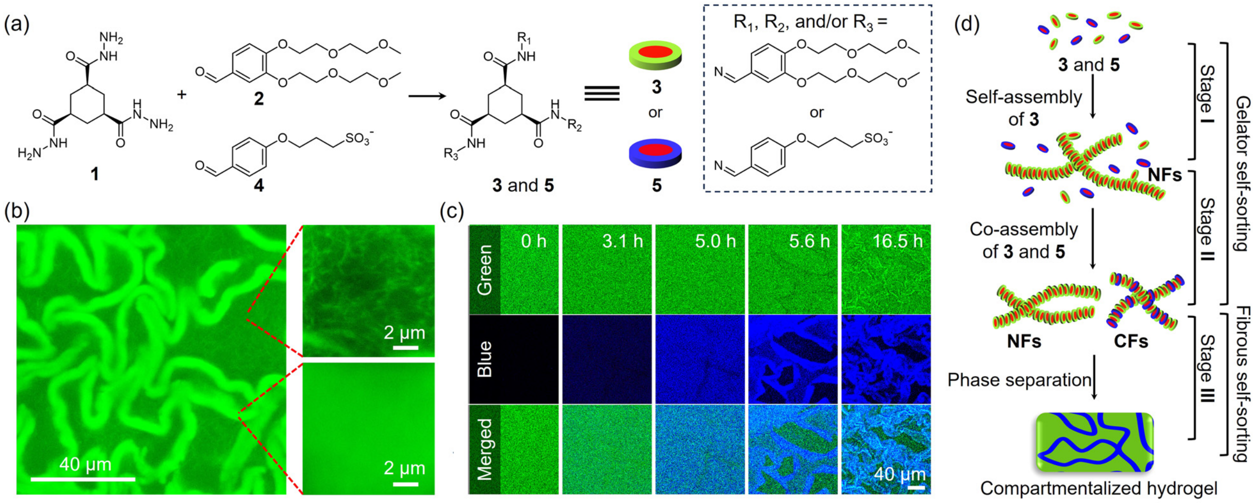

Fig. 4 Compartmentalized supramolecular hydrogels through multilevel self-sorting. (a) Multicomponent hydrazone-based hydrogelators (**3** and **5**) bearing different charges formed from **1**, **2** and **4**; (b) morphology of the compartmentalized supramolecular hydrogel networks with differently charged regions; (c) the dynamic formation process of the compartmentalized supramolecular hydrogels; and (d) the proposed multilevel self-sorting mechanism underpinning the hydrogel formation. Copyright 2019, American Chemical Society.[110]

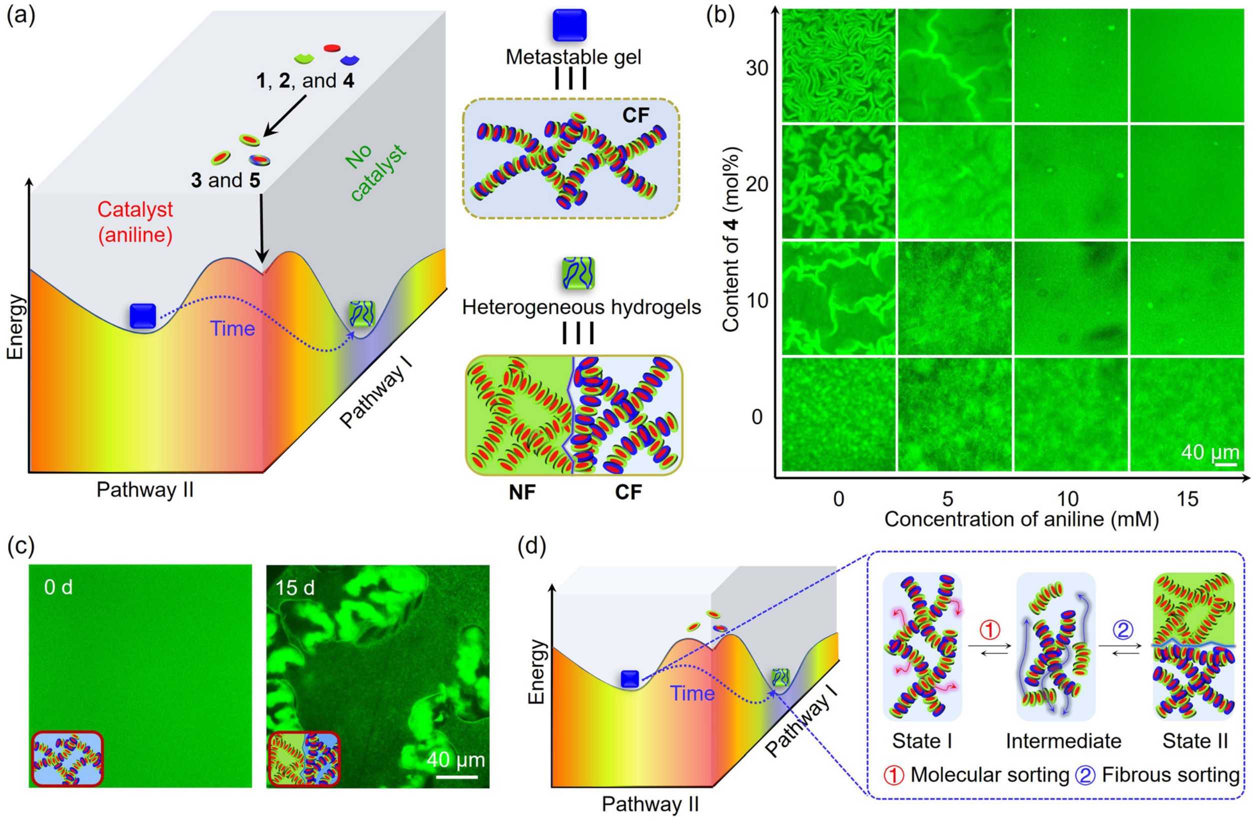

Fig. 5 Access to kinetically favored supramolecular hydrogels through catalytic self-assembly of multicomponent hydrogelators. (a) The presence of catalyst leads to kinetically favored hydrogels composed of **CFs** that are formed by rapid coassembly of **3** and **5**, the hydrogels are metastable and convert to the thermodynamically stable state over time; (b) the hydrogel network morphologies with the addition of different contents of aniline; and (c) conversion of the kinetically favored metastable hydrogels into thermodynamically stable hydrogels; and (d) illustration of the energy landscape of the hydrogel formation through different pathways. The samples were prepared in 0.1 M, pH 7.0 phosphate buffer. Copyright 2020, Royal Society of Chemistry.[112]

Properties of the kinetically favoured hydrogels

In a supramolecular hydrogelation system, self-assembly kinetics influences the structures and material properties of hydrogels by changing the stacking mode of the hydrogelators or the entanglement of the hydrogel fibres. In principle, control over the self-assembly of hydrogelators deviating along different pathways is capable of creating very different hydrogel products.[110–114] For example, in the study discussed previously, we have found that the addition of the catalyst, aniline, can effectively change the optical properties of the hydrogels. In the presence of **4**, increasing the amount of aniline can lead to hydrogels with increased transparency (Fig. 6(a)).[107] This is because the co-assembly of **3** and **5** is favoured in the presence of aniline, leading to formation of more **CFs** rather than **NFs**. The **CFs** effectively prevent the formation of large fibrous bundles (Fig. 6(b) and (c)), generating a hydrogel network composed of nano-sized **CFs** which show high transparency when compared with the sample obtained without the addition of aniline.

Besides the different transparencies of the kinetically favoured hydrogels with the addition of aniline, the hydrogels were found to show a very unique strain-stiffening behaviour that is widely observed in biological tissues (Fig. 6(d)).[115] In stark contrast, the hydrogels obtained by standard self-assembly without the addition of aniline exhibited a normal strain-softening mechanical property.[14,105] This was explained by the formation of kinetically favoured **CFs** in the presence of aniline. The **CFs** featured semi-flexible properties whose bending modulus of the assemblies was comparable to the thermal agitation energy, k_BT.[116] Before the breakage of the hydrogel network, the semi-flexible fibres will reach the stiffening regime, thus showing strain-stiffening behaviour. The bending of the semi-flexible filaments causes the stiffening with a factor of 1.0 which is comparable to that of many biological filaments,[117,118] demonstrating a rare observation of strain-stiffening behaviour in synthetic materials. By incorporating liposomes in the hydrogels using orthogonal self-assembly of the hydrazone hydrogelators and lipids, an artificial supramolecular complex material bearing strain-stiffening behaviour that closely mimics biological tissues was created (Fig. 6(e)). The strain-stiffening biomimetic supramolecular system developed may be able to serve as a synthetic platform for many fundamental studies, for example, studying the effects of the strain-stiffening fibrous network on the behaviour of living cells.

Transient supramolecular hydrogels controlled by chemical reaction networks

Chemically fuelled transient hydrogelation

Inspired by the enzymatic supramolecular self-assembly in living systems, we have shown that our access to spatiotemporal control

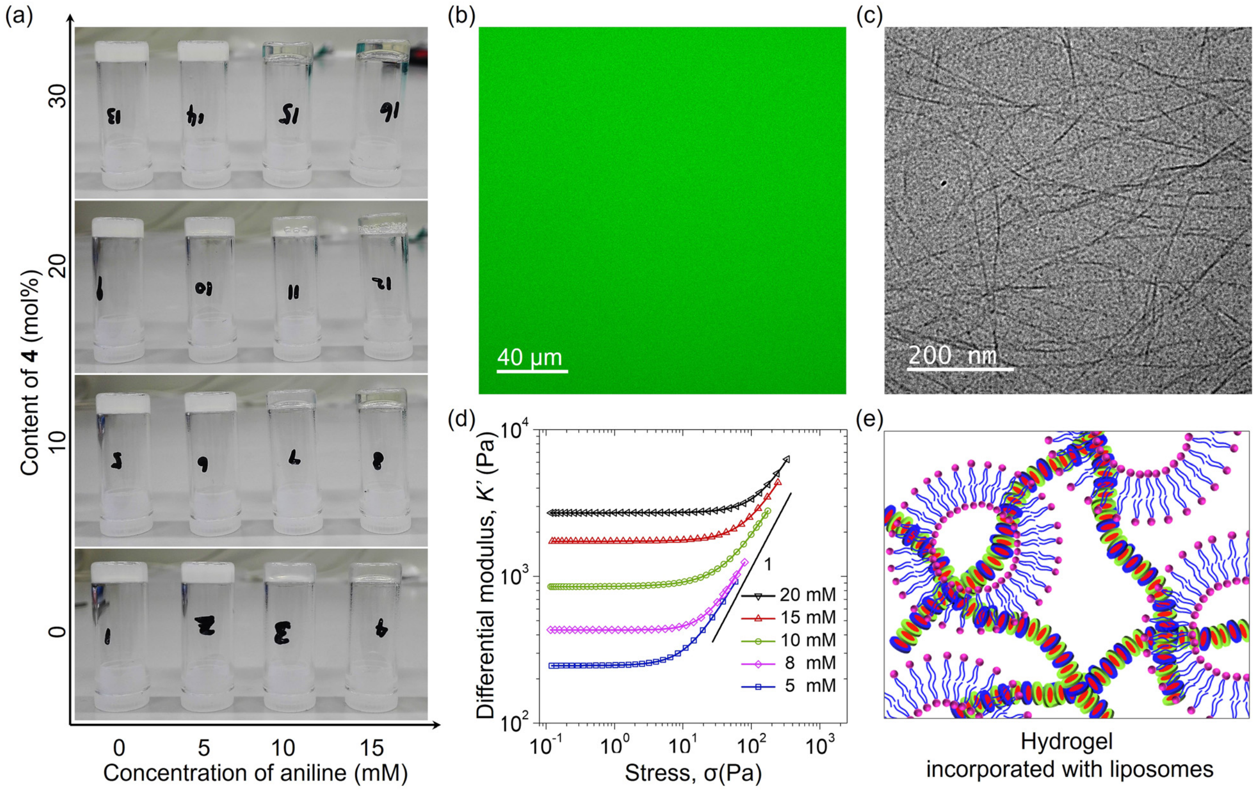

Fig. 6 Properties of kinetically favored hydrazone-based supramolecular hydrogels. The hydrazone-based supramolecular hydrogels formed by rapid co-assembly of **3** and **5** showing (a) high transparency; (b) uniform hydrogel network composed of (c) single nanofibers; (d) unique strain-stiffening behavior of the kinetically favored hydrazone-based supramolecular hydrogels; and (e) strain-stiffening complex supramolecular structures formed through the orthogonal self-assembly of the hydrazone-based hydrogelators and lipids closely mimicking biological tissues. The samples were prepared in 0.1 M, pH 7.0 phosphate buffer. (a) Copyright 2020, Royal Society of Chemistry.[112] (b)–(e) Copyright 2020, Wiley-VCH.[120]

during the self-assembly of supramolecular hydrogels can control the self-assembly kinetics by using a catalyst to give a catalyst-responsive hydrogelator system. In addition to the kinetically controlled self-assembly, living organisms also use high-energy chemicals (chemical fuels), such as ATP and GTP, to power out-of-equilibrium self-assembly, producing various out-of-equilibrium supramolecular structures bearing highly dynamic features.[5,7,8,119] For example, microtubules are formed by the self-assembly of tubulin driven by GTP, but they disassemble backwards to tubulin with the depletion of GTP.[9] Such a chemically fuelled out-of-equilibrium self-assembly is typically realised by coupling molecular self-assembly with chemical reaction networks.[76,120] With the consumption of a chemical fuel, the chemical reaction has the power to proceed along the direction that accelerates the molecular self-assembly into certain supramolecular structures. However, when the chemical fuel is depleted, the self-assembling building blocks spontaneously convert to the original state by another reaction pathway (Fig. 1(c) and (d)), leading to the collapse of the supramolecular structures. Reproducing such chemically fuelled out-of-equilibrium self-assembly in synthetic scenarios may not only further our understanding of the out-of-equilibrium phenomena in living systems but also provide a biomimetic approach to unlock new supramolecular materials bearing lifelike functionalities.

In 2010, the group of Eelkema and van Esch reported the first example of a chemically fuelled out-of-equilibrium supramolecular system.[53] In following work, they employed a highly efficient methylation reagent, dimethyl sulfate (DMS), as a chemical fuel, which vividly showed the transient assembly of supramolecular hydrogels.[22] The hydrogelator precursors bearing dissociated carboxyl groups were dissolved in basic aqueous solution that could not self-assemble because of the intermolecular electrostatic repulsion. With the addition of DMS, the carboxyl groups were converted into esters, thus activating the self-assembly of the newly formed molecules into hydrogels. However, with the depletion of DMS, the hydrogelators containing the ester bonds were unstable in basic conditions and spontaneously hydrolysed into the initial non-assembling state, thus leading to the disassembly of the hydrogels (Fig. 7(a) and (b)). Relying on the *in situ* observation of the growth of the hydrogel fibres, they further found that the formation and degradation of the fibres showed nonlinear dynamics, reminiscent of the dynamic assembly of microtubules (Fig. 7(c)).

In the past decades, a number of out-of-equilibrium supramolecular hydrogel systems were designed and created by orchestrating inverse chemical reaction networks such as enzymatic reactions,[77–79] pH feedback loops,[70,73,121–124] redox reactions,[124] oscillatory reactions,[125] and transient chemical signals dictated by reaction-diffusion.[92,126,127] Amongst them, a pH-dependent reversible condensation/hydrolysis reaction of boric acid and diols has been reported by Liu and coworkers.[128] The added chemical fuels (KOH and lactone) resulted in transient pH variation, leading to the transient assembly of guanosine and 5-fluorobenzoxaborole into hydrogels dictated by the dynamic formation of a boronic ester bond.

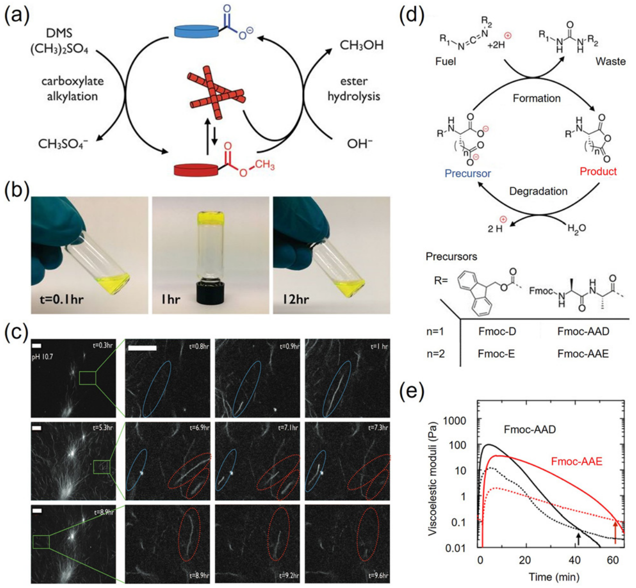

Fig. 7 Transient assembly of supramolecular hydrogels driven by chemical reactions. (a) Transient assembly of supramolecular hydrogels regulated by the temporary removal of negative charge from the gelator precursors through methylation of carboxyl followed by spontaneous hydrolysis of the resultant ester; (b) transient sol–gel–sol transition with the addition and consumption of fuel (DMS); (c) time-lPAAe confocal images showing the high dynamics of the hydrogel fibres; (d) transient hydrogelation regulated by carbodiimides powered transient formation of anhydride; and (e) rheological behaviors of the fueled self-assembly samples over time. (a)–(c) Copyright 2015, American Association for the Advancement of Science.[27] (d) and (e) Copyright 2017 Springer Nature Limited.[66]

In addition, reversible anhydridisation/hydrolysis reactions powered by carbodiimide, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), have also received intensive attention in recent years.[58,61] The charges of the non-assembling precursors decorated with carboxyl groups were removed by the formation of anhydride powered by EDC, activating the self-assembly of the resultant hydrogelators into hydrogels (Fig. 7d).[61] However, with the depletion of EDC, the anhydride-based hydrogelators spontaneously hydrolysed into the charged state, thus leading to the collapse of the hydrogels (Fig. 7e). By tuning the contents of the added EDC, the material properties, such as lifetime and stiffness, can be regulated simply. We recently also extended EDC driven transient formation of anhydride to polymer hydrogels, creating various dynamic polymer hydrogels crosslinked by an anhydride. On the basis of the unique transient behaviour, these dynamic hydrogels were employed to control the formation and free release of pharmaceutical crystals.[90] Using the contraction of a muscle powered by ATP as an inspiration, we further developed autonomous soft actuators composed of a polymer network containing carboxyl groups.[91] The addition of EDC converted the hydrophilic carboxyl groups into hydrophobic anhydride, leading to the shrinkage of the hydrogels. With the depletion of EDC, the hydrophilicity of the hydrogels recovered with the spontaneous hydrolysis of the anhydride, thus leading to swelling of the hydrogels. Relying on the EDC powered dynamic shrinking-swelling behaviour, the hydrogel actuators with an autonomous actuation capability have been created, and were analogous to the chemically fuelled soft motions observed in nature.

Chemically fuelled transient gel–sol–gel transition

Chemically fuelled supramolecular hydrogels have been of great interest because of their highly dynamic properties. However, most of the cases focused on the chemically fuelled hydrogelation, and the chemical fuels involved were usually toxic and this was unfavourable for their use in real-life applications.[78] Very recently, we have developed a biocompatible out-of-equilibrium hydrogel system where cyclic sugar cyclodextrin (CD) was used as the chemical fuel (Fig. 8(a)).[88] In this system, PAA grafted with octadecyl (PAA-C_{18}) was dissolved in water and a stable supramolecular hydrogel was formed due to the formation of hydrophobic C_{18} aggregates. With the addition of the chemical fuel, CD, the hydrophobic C_{18} aggregates disintegrated because of the formation of a host–guest complexation of CD and C_{18}, resulting in a gel–sol transition. However, the fuel, CD, can be hydrolysed by the already added enzyme, α-amylase, over time, and the sol is allowed to spontaneously convert into gel due to the recovery of the C_{18} aggregation. As a consequence, transient gel–sol–gel transition was achieved based on CD powered dynamic formation of the host–guest complexation (Fig. 8(b)). By tuning the amount of CD used, the transition lifetime could be easily controlled (Fig. 8(c)). It is worth noting that this chemically fuelled supramolecular hydrogel system was demonstrated to be biocompatible (Fig. 8(d)), which is greatly expected for biomedical applications. Such a dynamic gel–sol–gel property was further used as proof-of-concept bioadhesives that show adaptive adhesion capability under the regulation of the chemical fuel (Fig. 8(e)). In contrast to previously developed chemically fuelled supramolecular hydrogels, the hydrogel state in this work is the stable state, which is beneficial for its stable functioning. More information regarding transient supramolecular hydrogels based on host–guest interactions can be found in a good review paper written by Eelkema and co-workers.[129]

Transient and macroscopically structured supramolecular hydrogels mediated by reaction–diffusion

Life is full of beautiful dynamic supramolecular assemblies with well-defined hierarchical structures and high dynamics which are thought to be the result of a reaction–diffusion-mediated supramolecular self-assembly.[130,131] The previously discussed chemically fuelled supramolecular hydrogels feature many lifelike properties such as high dynamics with tunable lifetime and stiffness, autonomous structure evolution, and regenerative capabilities, but they mainly function under homogenous conditions, without control of their macroscopic structures.[74,78,132] In a recent work, we proposed a concept of shaped chemical fuelling self-assembly, and achieved the dynamic growth of macroscopic hydrogel structures (Fig. 9).[92] The chemical fuels (urea and H^+) were shaped in the gel matrix substrates and were allowed to diffuse into the solution. When this shaped chemical fuel was integrated with a container containing an aqueous solution of urease, the H^+ diffused out rapidly to trigger the self-assembly of dibenzoyl-L-cystine (DBC) (Fig. 9(a)–(c)). However, over time, with the diffusion and enzymatic decomposition of urea, and a sufficient amount of base, NH_3 was created, which leads to the collapse of the H^+

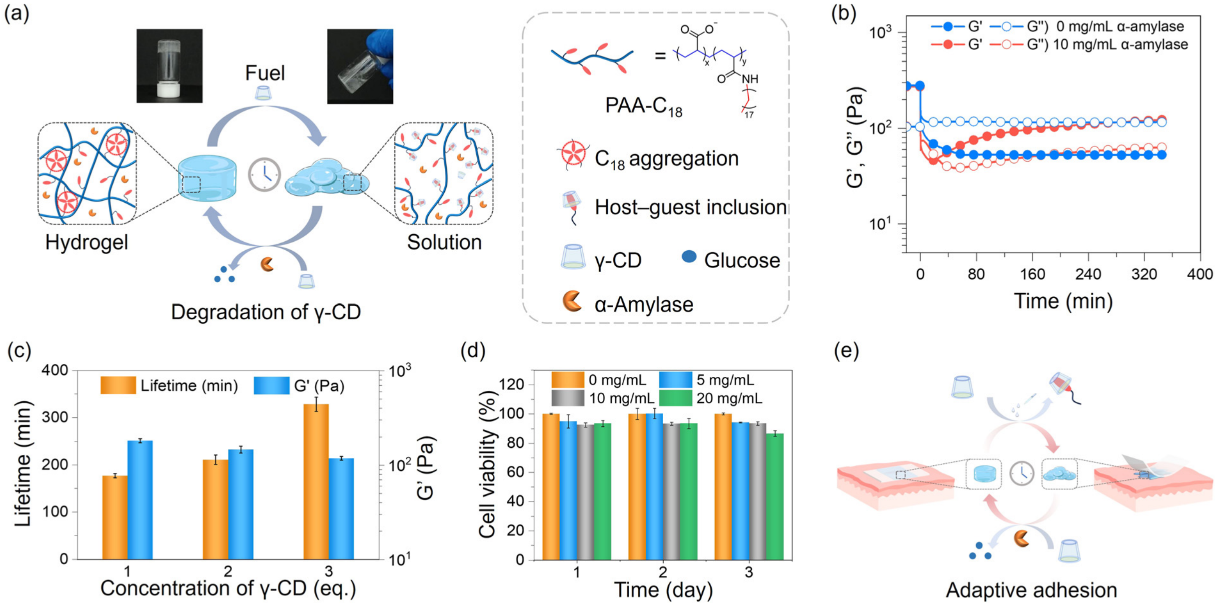

Fig. 8 Transient gel–sol–gel transition. (a) Transient gel–sol–gel transition of PAA-C18 dictated by enzymatic transient host–guest inclusion; (b) rheological measurements of the transient gel–sol–gel transition; (c) lifetime of the transient transition process; (d) cytotoxicity of the fueled PAA-C18 hydrogels; and (e) proof-of-concept application of the transient hydrogels for adaptive adhesion. Copyright 2023, the American Chemical Society.[93]

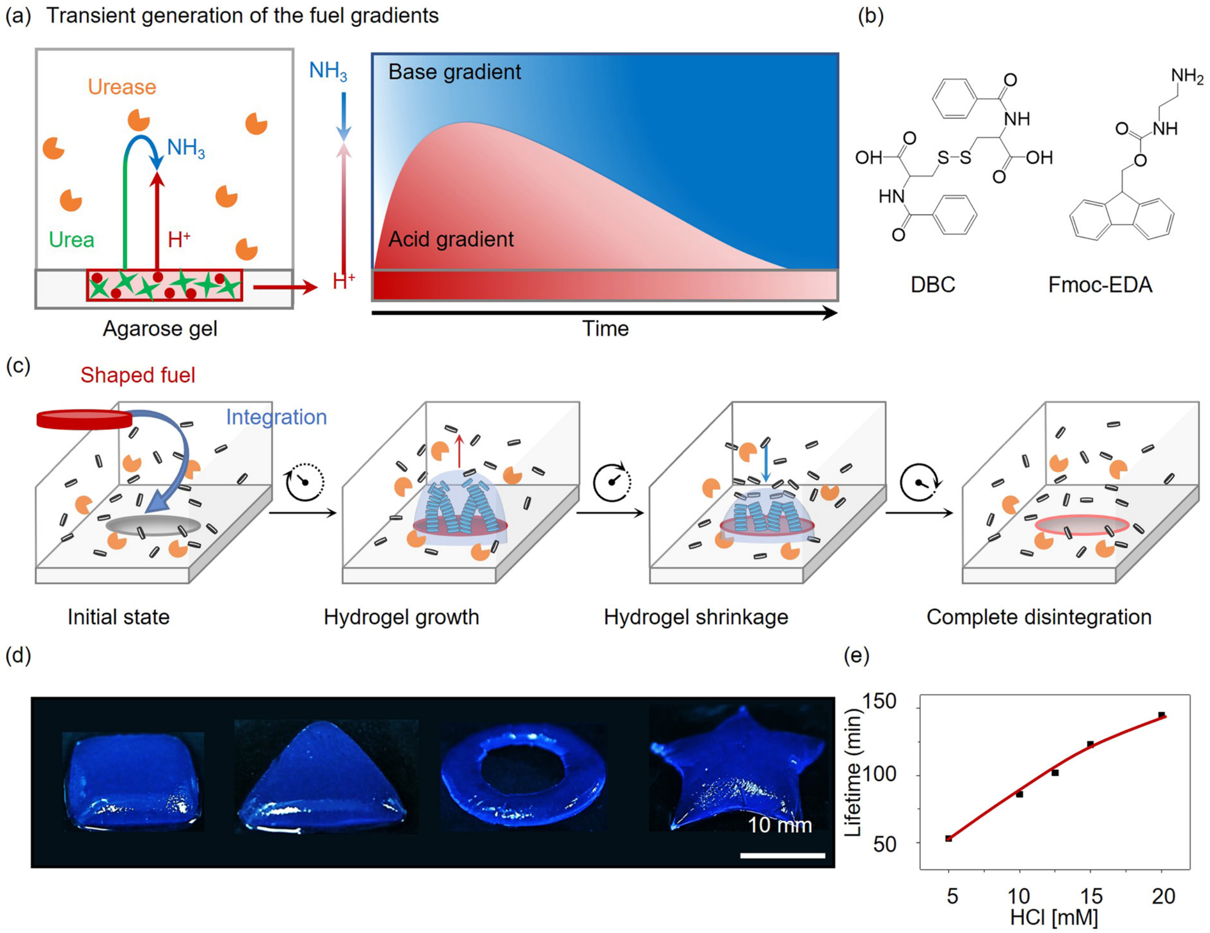

Fig. 9 Transient assembly of macroscopically structured supramolecular hydrogels powered by shaped chemical fuels. (a) Transient propagation of pH signal from shaped substrates; (b) molecular structures of hydrogelators DBC and Fmoc-EDA; (c) transient assembly of the supramolecular hydrogels; (d) the resultant hydrogels with varying shapes; (e) lifetime of the hydrogels against the contents of HCl. Copyright 2023, the American Chemical Society.[97]

gradient. As a result, the alreadyformed hydrogels were spontaneously degraded over time (Fig. 9(c)). Upon using the shaped fuels of varying shapes, various free-standing supramolecular hydrogels with controlled macroscopic structures can be captured by removing the aqueous solutions during the growing process (Fig. 9(d)). The lifetime of the hydrogel was tuneable by altering the fuel contents (Fig. 9(e)). Such a versatile shaped chemical fuelling concept can easily be adapted to other chemical fuels, enabling the growth of macroscopic hydrogel structures with different hydrogelators and high-energy chemicals, and thus unlocking new high-tech applications.

In another example of a reaction–diffusion-mediated dynamic supramolecular self-assembly, dynamic poly(acrylic acid) (PAA)/amorphous calcium carbonate (ACC) hydrogels were formed in an agarose gel by performing the diffusion of $PAA/CaCl_2$ and $Na_2CO_3/NaCl$ from opposite sides. These two hydrogel precursors diffused and met in a defined area, resulting in formation of ACC nanoparticles which can crosslink PAA into hydrogels by an electrostatic interaction. However, over time, the concentration of NaCl at the hydrogel area gradually increased to a level that could screen the electrostatic interaction between the PAA and the ACC nanoparticles, thus leading to the collapse of the already formed supramolecular PAA/ACC hydrogels. The macroscopic structures as well as the lifetime of the PAA/ACC hydrogels can be easily controlled by defining the positions of the precursors and the initial concentration of the NaCl.

Conclusions and perspectives

The work discussed in this feature article illustrates that the chemical reaction provides a powerful approach to controlling the self-assembly of supramolecular hydrogels in time and space. In the past few years, we have developed various dynamic supramolecular hydrogels controlled by chemical reactions, including supramolecular hydrogels mediated by hydrazone formation, and those powered by chemical fuels. On the basis of the previous studies of the chemical reaction mediated supramolecular hydrogelation, it has been demonstrated that control over the *in situ* formation of hydrogelators from their water-soluble precursors enables the direct self-assembly of supramolecular hydrogels in an aqueous environment without necessarily needing heating–cooling or solvent exchange. Incorporating catalysts to change the subsequent formation of the self-assembly kinetics of hydrogelators allows the interruption of the self-assembly pathways, giving rise to kinetically favoured supramolecular hydrogels with distinctly different structures and material properties, and even sharing the same hydrogelator compositions. These supramolecular hydrogels are either kinetically trapped at a local energy minimum state or they occupied a metastable state and they are capable of evolving their structures and properties over time to approach a thermodynamic stable state. The assembly of supramolecular hydrogels can also be coupled to out-of-equilibrium chemical reaction networks regulated by chemical fuels. The fuels are irreversibly consumed to convert the hydrogelator precursor into the self-assembling state, thus triggering the assembly of the supramolecular hydrogels. However, with the depletion of the fuel, the hydrogelators spontaneously reverse to the non-assembling state along another reaction pathway. As a consequence, transient supramolecular hydrogels bearing various unique properties such as highly dynamic structures, a finite lifetime, and a regeneration capability are obtained.

Thus, it is clear that the chemical reaction mediated hydrogelation offers a powerful approach to control the fabrication of supramolecular hydrogels in an aqueous environment, and this may unlock new high-tech applications especially in biomedicine. Here we envision some issues that may further the advances in this emerging field. The current focus is mainly limited to the design of chemical reaction mediated supramolecular hydrogelation, subsequently giving rise to various dynamic hydrogel products. However, the self-assembly mechanism of the hydrogelators in aqueous media remains unclear, although nucleation and elongation has been regarded as a reasonable explanation.[133–135] Very recently, Yan and coworkers have reported a new finding that the self-assembly of gelators triggered by solvent exchange undergoes a unique liquid–liquid phase separation process, further insight into the self-assembly mechanism of the hydrogelators.[136–139] However, the self-assembly of hydrogelators in a pure aqueous environment remains unexplored, and by addressing this we should be able to not only control the hydrogelation in a more logical way, but also further our understanding of the biological self-assembly process that occurs in the pure aqueous environment. In the chemically fuelled supramolecular hydrogel systems, although we have obtained various dynamic supramolecular hydrogels by coupling the self-assembly of hydrogelators with out-of-equilibrium chemical reaction networks, the out-of-equilibrium self-assembling structures are rarely observed because of their extreme instability.[140] Freezing the structures using covalent chemistry may provide a route to study the out-of-equilibrium structures. Furthermore, the fuelled self-assembly process features high dynamics, but the self-assembly pathway complexity has not been studied much so far, except for the rare examples reported by the groups of Boekhoven[141,143] and Deng and Walther.[142] Being able to address these fundamental issues may further new advances in the field of chemical reaction mediated supramolecular hydrogels.

Another issue in this field is how to find applications for these dynamic supramolecular hydrogels. To achieve the applications, new hydrogelators that are easy to synthesise and are inexpensive and biocompatible should be considered. An emerging application is to design a new hydrogelator system that can respond to metabolic processes in the living system, thus providing a synthetic approach to regulate the fate of the living system. We are currently making efforts to design new hydrogelators whose self-assembly can be triggered by the metabolic processes, resulting in the assembly of supramolecular hydrogel (fibres) structures in the peri/intercellular environments which may lead to new therapeutic approaches. This is important, because new chemical reactions that can trigger dynamic molecular self-assembly are required for the development of new dynamic supramolecular hydrogels as well as their high-tech applications. We envision that further work may contribute to the coupling of oscillatory reactions with molecular self-assembly, creating living hydrogels with the capability of autonomously evolving their structures and functions.[125] In addition, new chemical reactions that are mild, non-toxic, highly efficient and biorthogonal, such as the 'click' reaction and the Diels–Alder reaction,[144,145] are highly desired for triggering the assembly of dynamic supramolecular hydrogels, which may find real-life applications in biomedicine.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We acknowledge the financial support of the Shanghai Pilot Program for Basic Research (grant no. 22TQ1400100-9), the ''Chenguang Program'' supported by the Shanghai Education Development Foundation and Shanghai Municipal Education Commission (grant no. 20CG36), the Natural Science Foundation of Shanghai (grant no. 22ZR1417700), the National Key Research and Development Program of China (grant no. 2022YFD70050101), the Open Project of State Key Laboratory of Chemical Engineering (grant no. SKL-ChE23C01), and the Fundamental Research Funds for the Central Universities.

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