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Catalytic control over the formation of supramolecular materials

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In this Perspective, we will discuss how the rate of formation of supramolecular materials can be drastically enhanced by catalytically controlling the rate of formation of their molecular building blocks, resulting in the formation of out-of-equilibrium soft materials with enhanced mechanical properties. Also, the use of surface confined, patterned catalysts allows spatial control over self-assembly, which can be applied to the formation of regular, micrometer sized hydrogel patterns. Catalysis has been applied for decades as an indispensable tool in the synthesis of both simple and highly complex molecules and polymers, ranging from milligram lab-scale to multi-ton industrial processes. However, despite being widespread in nature, until recently the use of catalysis to control the formation of supramolecular materials has remained limited. We will demonstrate the large potential of using catalysis as a tool in the construction of soft materials, illustrated by recent developments.

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Catalysis is an indispensable tool in the synthesis of both simple and highly complex molecules and polymers, ranging from milligram lab-scale to multi-ton industrial processes. In nature, catalysis is often used to control localised formation of molecules and supramolecular structures, to control their stability and response, in feedback loops and for

achieving homeostasis, for motility, and for signalling processes.¹ In artificial systems catalysis is used nearly exclusively as a means to achieve formation of molecular solutions as homogeneous systems. Nevertheless, building on the two quintessential properties of catalysts: the capability to accelerate chemical reactions, and to do a reaction several times with a single catalyst (multiple turnovers), it should be possible to control the structure and properties of supramolecular materials, as well as their distribution in time and space, by controlling the rates of material formation using catalysis.

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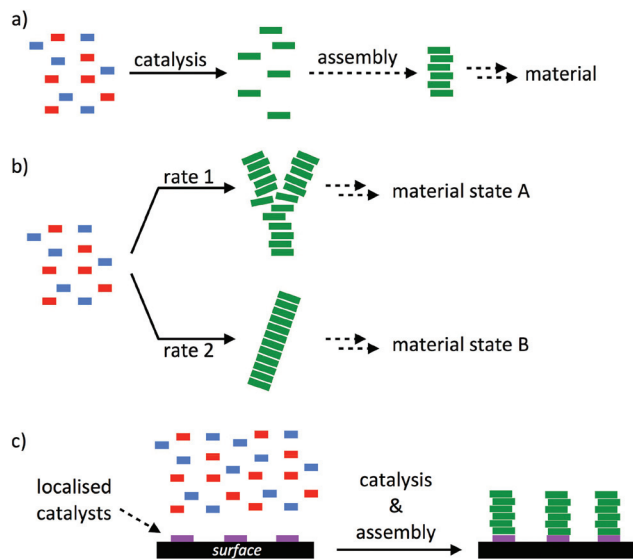


Fig. 1 General concept of using catalysis to control self-assembly processes. (a) Two precursor molecules (red and blue) react for a building block capable of self assembly (green). Subsequent assembly leads to the formation of larger structures and, ultimately, a material. (b) Control over the rate of building block formation can provide access to different material states. (c) Control over the distribution of self-assembled materials in space can be achieved using localised catalysts.

The past decades have seen pronounced advances in the design and synthesis of advanced materials. Great strides have been made in generating structured materials either using top-down techniques (e.g., lithography, microcontact printing), or bottom-up, by physical processes programmed into the molecular components (e.g., phase separation of block copoly-

mers²). Supramolecular chemistry has seen an evolution from molecular complexation to the design and application of molecular materials, ranging from dynamic and non-equilibrium structures,³ to supramolecular polymers,⁴ and multicomponent architectures,⁵ amongst many others. Incorporation of molecular switches,⁶ molecular complexation (e.g., protonation), or stimulus-induced phase transitions has led to a range of responsive materials.⁷ Still, control over the rate of material formation, and over their distribution in time and space, is generally difficult to achieve. At the origin of this lack of control lies the fact that, as the formation of the weak non-covalent bonds holding together these supramolecular (soft) materials is typically (nearly) barrierless, control over their kinetics can be difficult to achieve, and has subsequently received little attention so far. In contrast, the formation of stronger covalent bonds generally carries an activation energy, which implies that the rates of their formation can be controlled through catalysis. Incorporation of such catalysis-susceptible covalent bonds in key locations in supramolecular materials will thereby provide control over the rate of structure formation. Moreover, catalysis can then be used to control when and where structures are formed, as long as catalytic activity can be controlled in time and space (Fig. 1). These systems require reagents that by themselves, when dissolved in an appropriate solvent, do absolutely nothing. However, once they react with one another to form a covalent bond, they form a molecule that shows a tendency to self assemble due to a particular arrangement of interaction sites in the molecular structure (e.g., hydrogen bonding sites, hydrophobic surfaces). Self-assembly can then lead to the formation of larger structures and eventually a material (Fig. 1). So far, covalent bond formation between non-assembling building blocks has been

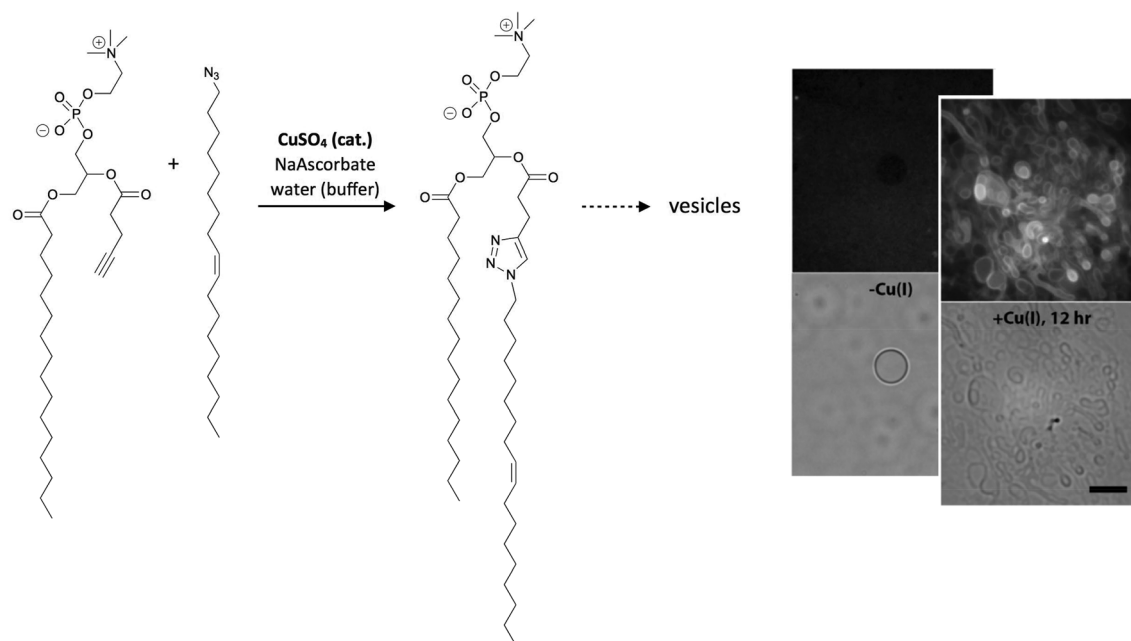


Fig. 2 Copper-catalysed formation of phospholipids leads to vesicle and bilayer assembly. (Reprinted (adapted) with permission from *J. Am. Chem. Soc.*, 2012, **134**, 751–753. Copyright 2012 American Chemical Society.)



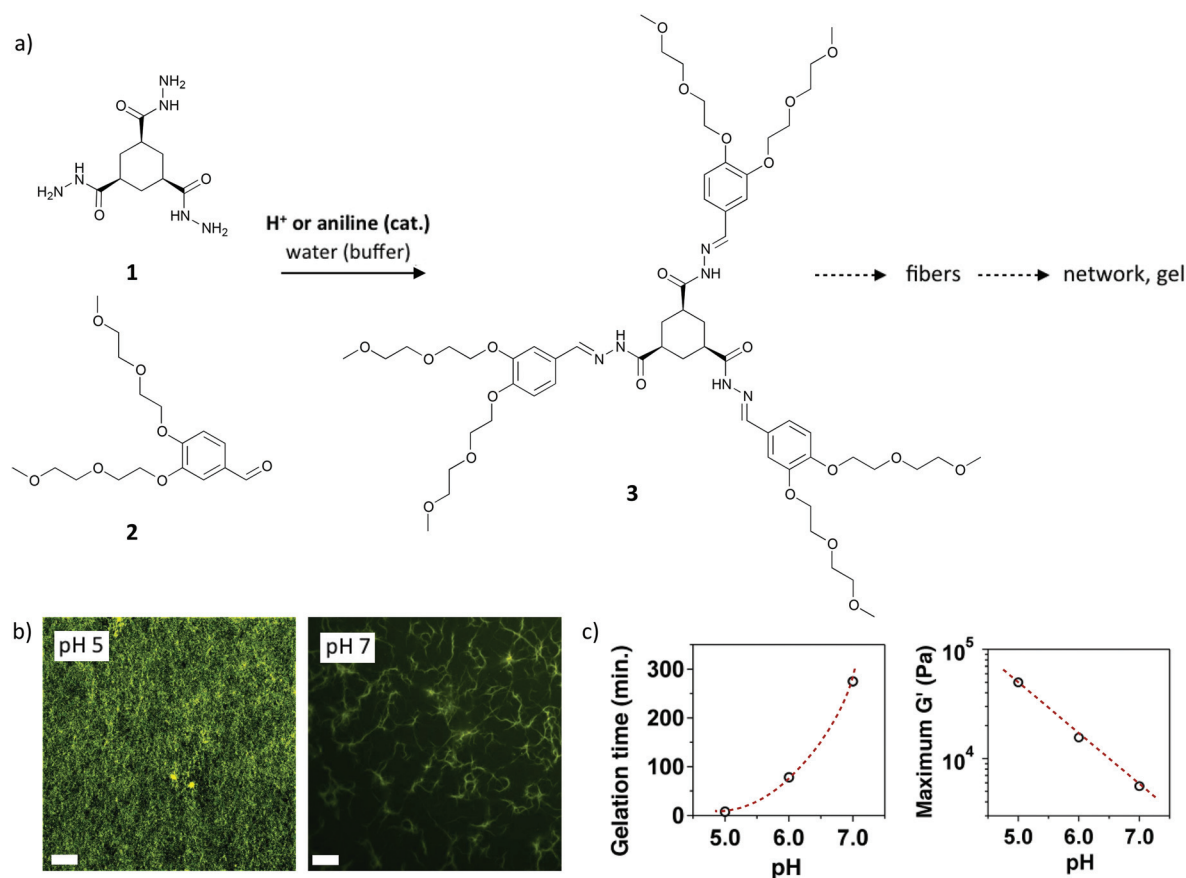


Fig. 3 Catalytic control over hydrogelator formation. (a) Hydrazone-based gelator **3** is formed by condensation of hydrazide **1** with 3 molecules of aldehyde **2**, a reaction that can be catalysed using either acid or aniline. Subsequent self-assembly of **3** gives fibres which eventually crosslink, gelling the solvent. (b) Gel network morphology obtained at different pH, visualised using confocal laser scanning microscopy. (c) Both gel formation times and gel stiffness (G') depend heavily on catalyst content, in this case the pH. (Reprinted with permission from ref. 15. Copyright 2013 Nature Publishing Group.)

used for material formation through dynamic covalent chemistry, using reversible covalent bonds.⁸ There, however, the main focus has been on thermodynamically controlled building block selection, and less on controlling the kinetics of structure formation. The structure and properties of self-assembled materials can depend heavily on the rate of the self assembly process, giving rise to the formation of various kinetically trapped states ('meta stable states').⁹ When the rate of self assembly is closely coupled to the rate of building block formation, catalysis can provide access to these states by controlling this rate (Fig. 1).

There seems to be enormous potential for using catalysis in controlling structure formation and behaviour in soft self assembled materials. Nevertheless, this concept is only very recently starting to receive attention, and only a few specific examples of catalytic control over supramolecular materials exist. This Perspective aims at discussing recent developments in this field, focussing on recent papers by our group regarding the catalytically controlled formation of supramolecular hydrogel materials.

The first examples of catalytic control over material formation were published around 2005,¹⁰ and were thereon

largely concerned with using enzymes to control the formation of peptidic and glycosidic gels and surfactants.¹¹ Similar concepts have been used for the enzymatically catalysed disassembly of peptide based gelators and dendrimer-based amphiphilic nanocontainers.¹² Non-enzymatic catalysis offers an extremely large diversity in reactivity, reactants, chemical bonds and solvents as a toolbox for the catalytically controlled formation of molecular materials. Nevertheless, reports on the use of non-enzymatic catalysis are scarce. Recently, Devaraj and Budin have described a system where phospholipid surfactant formation is catalysed by a homogeneous copper catalyst, in attaching one of the hydrophobic tails through triazole formation (sometimes referred to as "click-chemistry").¹³ Without catalyst the azide and alkyne building blocks are entirely unreactive towards one another. Here, a naturally occurring structure can be formed using a non-natural catalyst, which may be a first step en route towards the formation of synthetic cells (Fig. 2). Besides this, there are some reports on the use of non-enzymatic (auto)catalysis to control the assembly and disassembly of surfactants in bilayers.¹⁴

To test the concepts put forth in Fig. 1, we have recently developed a low molecular weight hydrogelator system that is



made *in situ* by formation of hydrazone bonds between otherwise non-assembling molecules.¹⁵ The formation of the hydrazone bond is susceptible to acid and aniline catalysis, and can be performed in aqueous solvents at ambient temperatures.¹⁶ We based the molecular design on a class of hydrogelators previously developed in our group.¹⁷ In the current system, water soluble, non-assembling trishydrazide **1** and aldehyde **2** are dissolved and mixed in the presence of a catalytic amount of aniline, or at acidic pH (pH 4–6). *In situ* formation of C_3 -symmetric gelator **3** will, above a typically millimolar threshold concentration, lead to the formation of fibers through self assembly, driven by hydrogen bonding and hydrophobic interactions. Once these fibers crosslink to form a network, they gel the surrounding solvent, forming a soft material (Fig. 3).

The rate of material formation, the appearance and the mechanical properties of the formed gel materials depend hugely on the absence or presence of a catalyst during the formation process. Without a catalyst (at pH 7), the system forms a precipitate at lower starting concentrations of **1** and **2**, whereas at higher concentrations, relatively weak, highly turbid gels are formed. Using either acid or aniline as a catalyst leads to the formation of strong, opalescent gels in a matter of minutes, where it can take up to six hours without a catalyst. Using acid as a catalyst, the storage modulus (G') of the obtained gels increases by an order of magnitude going from a neutral (pH 7.0, $G' = 5$ kPa) to a slightly acidic reaction medium (pH 5.0, $G' = 50$ kPa). The critical gelation concentration (the CGC, the minimal gelator concentration needed to form a stable gel) also depends heavily on the pH, with the lower CGCs observed at higher catalyst content.¹⁸ Analysing the conversion to gelator **3** revealed that in all cases (independent of pH or aniline content) >95% **3** formed over night. This essentially means that, apart from the presence of the catalyst, these samples have identical chemical composition, despite having very different appearance and mechanical properties. This implies that by controlling the kinetics of the reaction using a catalyst, it is possible to address various kinetically trapped out-of-equilibrium self assembled states of the system (Fig. 1b). Analysis of the morphology of the obtained fibre networks confirmed this hypothesis. In the absence of catalyst (pH 7), thick bundles of fibres formed a poorly connected network, whereas using either aniline or acid, thin, heavily branched fibres form a well-connected, dense, homogeneous network throughout the solvent. These observations also corroborate the observed differences in stiffness between these materials. As such, this system serves as an example where a higher rate of formation leads to less order in the assembled structures. In contrast, Ulijn and coworkers have published an enzymatically catalysed fibre forming system where catalysis leads to a higher degree of ordering in the fibres.^{11a}

By locally changing the rate of building block formation using a catalyst, it should be possible to obtain spatial control over material formation and distribution.^{8a} We first chose to approach this challenge by localising a catalyst for the hydrazone gelator formation reaction on a surface, to see if this would lead to localised hydrogel growth. For this purpose, we

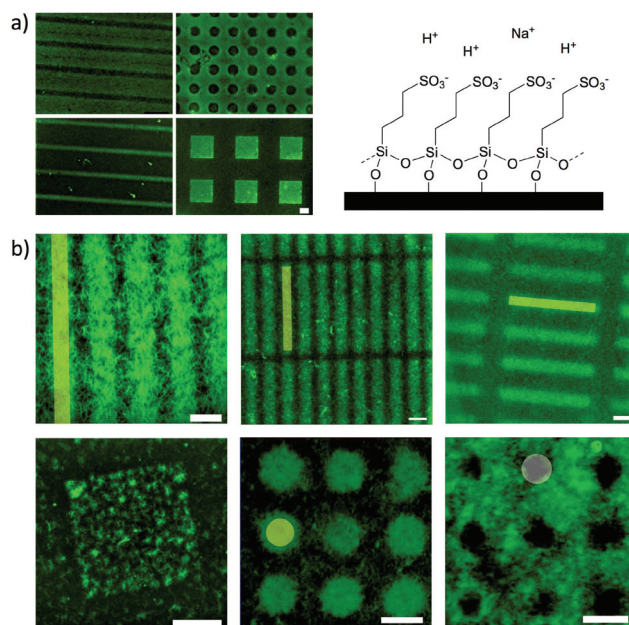


Fig. 4 Spatial control over hydrogel formation using patterned surface confined catalysts. (a) Catalyst patterns applied by microcontact printing on glass slides (left, imaged by confocal microscopy and visible in green) and structure of the printed catalyst (right). (b) Confocal microscopy images of hydrogel fibers of **3** (green) grown over patterned catalyst surfaces. The solid figures in the pictures indicate the shape and dimensions of the catalyst patterns. Scale bars are 20 μm . (Reprinted with permission from ref. 19. Copyright 2014 Wiley Interscience.)

developed glass slides functionalised with micrometer-sized patterns of sulfonic acid functional groups, applied by microcontact printing. When immersed in buffer, protons accumulate near the negatively charged sulfonate groups on the surface because of electrostatic interactions, leading to a local decrease in the pH in the few nanometers directly over the catalysts. This slight drop in local pH (typically 1–1.5 points, depending on ionic strength) was enough to induce preferential material formation near the surface by locally increasing the reaction rate. When immersed in a buffered solution containing hydrazide **1** and aldehyde **2**, we observed preferential growth of hydrogel fibres directly over the printed catalysts on the surface (Fig. 4).¹⁹ Over time, hydrogel patterns grew from the surface, following the shape of the catalyst patterns. As such, locally changing reaction rates using localised catalysts can be used to control spatial distribution of molecular materials.

Outlook

Using hydrogelator formation as an example, we have shown how catalytic control over the rate of assembler building block formation can be used to change the mechanical properties, the rate of formation, and the spatial distribution of self-assembled molecular materials. In the future, catalysis will



play a major role in achieving control over the behaviour of soft materials. We will see the emergence of a class of materials where both material dynamics and response, and distribution in time and space, can be controlled using switchable catalysts and the introduction of catalytically controlled feedback loops. Also, catalysis will be used to bias pathways in the reaction networks that control the behaviour of dynamic, out-of-equilibrium materials ('systems chemistry').²⁰

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