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CHEMNANOMAT
Focus Review

Self-Assembly

SPECIAL ISSUE

Applications of Dissipative Supramolecular Materials with a Tunable Lifetime

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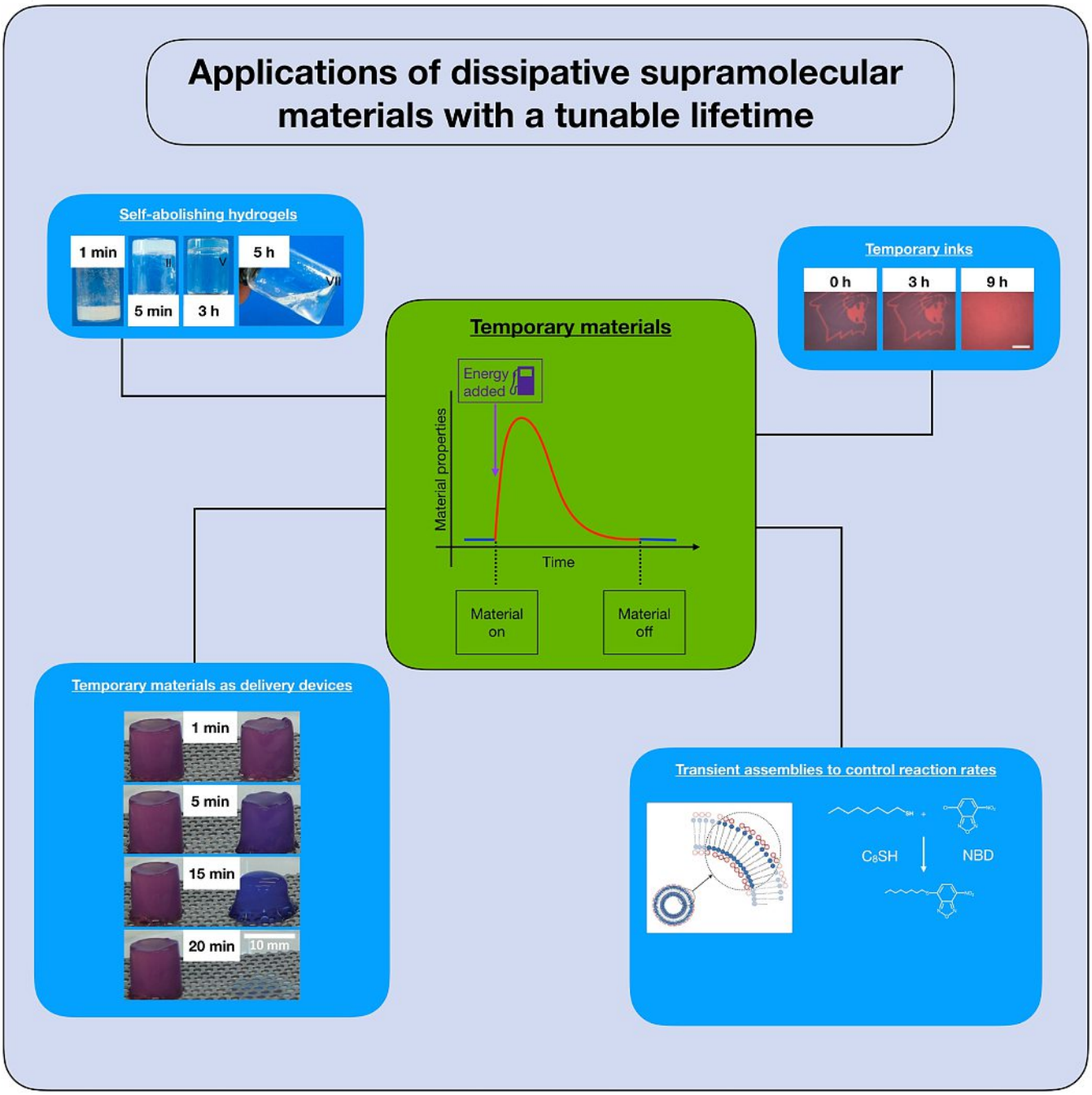

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Abstract: Supramolecular materials are materials in which molecular building blocks are held together by non-covalent interactions. These materials exist in equilibrium with their environment. In contrast, most biological materials exist out of equilibrium. They require constant dissipation of energy and consumption of nutrients to be sustained. As a result of their non-equilibrium nature, biological materials have superior properties compared to their in-equilibrium counterparts. These properties include spatial and temporal control over their presence, the ability to self-heal and even the ability to self-replicate. Inspired by biology, researchers have developed analogs of such dissipative supramolecular materials. This Focus Review introduces the crucial differences between in-equilibrium and dissipative supramolecular materials. We focus on one unique property of the emerging materials: their tunable lifetime. With recent examples, we show the principles involved and how these materials can be applied in the future.

1. Introduction

Supramolecular materials are materials in which molecular building blocks are held together by non-covalent interactions, like hydrogen bonding or π-orbital overlap.[1] Over the past decades, the field of supramolecular materials has seen explosive growth, in part because of design rules[2–8] new synthetic methods and prominent applications.[9–11] Successful examples include block copolymer micelles[12] that can be used to deliver drugs at diseased sites[13,14] or supramolecular polymers[15] that help the body to regenerate lost tissue.[16,17] Despite their success, man-made supramolecular materials remain rather basic compared to supramolecular materials as found in biology. Biological supramolecular materials, like skin, bone or even cells, demonstrate some remarkable features, including self-replication, the ability to make decisions and the ability to self-heal.[18] Although many of these processes in biological supramolecular materials are ill-understood, one concept recurs in all of these materials: supramolecular biological materials almost always exist out of equilibrium with their environment.[18] That means that biological materials can only exist by constant dissipation of energy taken from their surrounding.[19,20] Irreversible (photo-)chemical reactions deliver the source of energy. A prime example is the dissipative self-assembly of microtubules driven by GTP.[21] Due to their energy-dissipating nature, these materials have several unique properties that we do not observe in in-equilibrium materials.

In this review, we will explain the difference between equilibrium and dissipative supramolecular materials. We will highlight the unique properties of the dissipative materials, and we will focus on one of their specific features: the ability to be controlled over time. We will review strategies to manage the lifetimes of these materials, their possible applications and we close with an outlook.

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This manuscript is part of a Special Issue on Supramolecular Nanostructures. Click here to see the Table of Contents of the special issue.

2. Chemical Reactions to form Unique Materials Supramolecular Materials

2.1 Chemical Reaction Networks to Induce Dissipative Self-assembly

In dissipative supramolecular materials, materials are formed by the self-assembly of molecules. Crucially, the formation of these assemblies is coupled to a chemical reaction network of at least two chemical reactions.[22–26] In the activation reaction, a non-assembling molecule (precursor) reacts with a sacrificial high-energy molecule (fuel) or with light (photon) to form a metastable product (Figure 1a). It is essential that this activation reaction is irreversible and that the fuel is thus irreversibly "burned." The second reaction brings the product back to the precursor. Also for this deactivation reaction, it is crucial that the reaction is irreversible and the reaction has to occur spontaneously. Under these set of conditions, a product is formed by the dissipation of energy (fuel or photon), and it remains transiently present. In its limited lifetime, the product can act as a building block to form assemblies which constitute the supramolecular material.

We clarify the above definition with a recently introduced chemical reaction network by our group.[27] The precursors are derivatives of aspartic acid (Figure 1b). The two carboxylates of aspartic acid render the molecule well soluble in aqueous buffer. In the activation reaction, the two carboxylates react with a carbodiimide fuel to irreversible transforms it into an cyclic anhydride (product). The product, in the aqueous environment, is metastable and hydrolyzes to its original precursor state. The half-life of the anhydride is in the range of several minutes to several seconds at pH 6, depending on its nature. Hartley and coworkers described that the chemical reaction network could also be applied to larger macrocycles.[28] In essence, the chemical reaction networks entail the transient anhydride formation driven by carbodiimide hydrolysis.

The conversion of the precursor's two anionic carboxylates into non-charged anhydride makes the product more hydrophobic than its precursor. The hydrophobization can be used to induce self-assembly into a supramolecular material, which we will discuss in detail in the sections below. In contrast to equilibrium materials, the properties of the emerging supramolecular material are determined by the governing

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reaction rates and lifetimes of the product, which is the focus of this review.

2.2 Unique Properties of Dissipative Supramolecular Materials

Because of their non-equilibrium nature, dissipative supramolecular materials have unique properties compared to their in-equilibrium counterparts.[19] Due to the dynamic product activation and deactivation, the emerging materials can be intrinsically self-healing. To that end, researchers have shown that supramolecular hydrogels that are typically not self-healing, can regenerate after damage when formed via dissipative self-assembly.[29] Another unique property of dissipative assemblies is that patterns of the assemblies can emerge on much greater length-scales than the molecules or assemblies themselves. This phenomenon, referred to as self-organization, has so far only been demonstrated for biological dissipative assemblies, like microtubules[21] that form asters and vortexes on millimeter length scales.[30,31] Other properties of dissipative assemblies include the ability to self-replicate and the ability to be controlled over space and time. The temporal control has been the most studied unique property of dissipative materials and is the focus of this review.

3. Supramolecular Materials with a Tunable Lifetime

In this section, we will discuss examples of dissipative supramolecular materials, in which the researchers focused on controlling the lifetime of the emerging materials.[32] The general strategy in these studies involves the application of a finite amount of energy to the chemical reaction network (Figure 2). The energy in these examples is added in the form of a chemical fuel or by irradiation with light. In response, the chemical reaction network activates some of its precursors to their product state. The product can then self-assemble into the supramolecular material. With the formation of the product, deactivation commences. As the reaction network is running out of fuel, the rate of deactivation will be higher than the activation rate, and, consequently, the supramolecular material starts to decay. Equilibrium is reinstated when all fuel has been consumed, and the material has entirely decayed. We demonstrate the success of dissipative supramolecular materials with self-erasing inks, self-abolishing hydrogels, assemblies that release molecules after a predetermined time, and materials that can enhance or inhibit reactions for specific times.

3.1 Self-erasing Inks

In dissipative supramolecular inks, the self-assembly of building blocks results in a change in color or turbidity of the material. In these systems, a polymeric matrix traps the precursors and their solvent such that energy can be applied locally. Thus, a pattern, image or message appears only where the energy is applied. During the reinstatement of equilibrium, the message self-erases after which the material can be reused. As such, dissipative supramolecular inks, offer an exciting platform for the development of a reusable paper.

To that end, Grzybowski and coworkers introduced a first self-erasing ink based on the dissipative self-assembly of gold- or silver-nanoparticles driven by UV-light (Figure 3).[33] They functionalized nanoparticles with a trans-azobenzene derivative which served as the precursor in the chemical reaction network (Figure 3a). The precursor can isomerize to cis-azobenzene in response to UV-light as the energy source (Figure 3b). Importantly, the isomerized cis-azobenzene state was not the thermodynamically favored state but reverted to the trans-state spontaneously. The UV-induced isomerization caused a change in the dipole moment of the azobenzene-functionalized particles. That dipole moment-shift was sufficient to induce the self-assembly of the nanoparticles into large clusters (Figure 3c). As the cis-azobenzene groups spontaneously isomerized back to their thermodynamically more favored trans-state, the cluster started disassembling over time, when the energy source (UV-light) was taken away. Taken together, UV-light can convert precursor into an activated product state that can self-assemble, but the thermal energy spontaneously brings the activated state back to the disassembled precursor.

The dissipative assembly of these nanoparticles induced a color-shift of the sample from red to blue. The researchers embedded the chemical reaction network in a polymer gel and

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Job Boekhoven is a Rudolf Mößbauer assistant professor at the Department of Chemistry of the Technical University of Munich. He received his M.Sc. degree in Chemistry in 2008 from the University of Groningen. In 2012, he got his Ph.D. for his work in the group of Prof. Jan van Esch and Prof. Rienk Eelkema at Delft University of Technology. He pursued his academic career as a Rubicon postdoctoral fellow in the group of Prof. Sam Stupp at Northwestern University from 2012 to 2015. Boekhoven's current work focusses on the development of supramolecular materials via non-equilibrium self-assembly.



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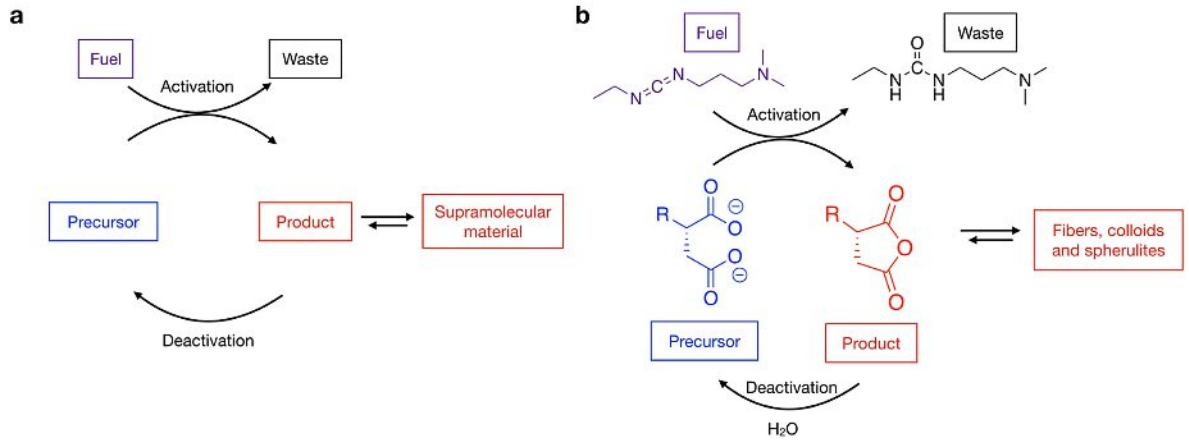

Figure 1. a) General chemical reaction network for dissipative self-assembly. A precursor (blue) reacts irreversibly with a fuel (purple) to form a product (red) in the activation reaction. The metastable product reverts spontaneously to the original precursor in the deactivation reaction. In its limited lifetime, the product can self-assemble into a supramolecular material. **b**) In the depicted chemical reaction network, a dicarboxylate precursor converts into a metastable anhydride driven by the hydrolysis of carbodiimides.

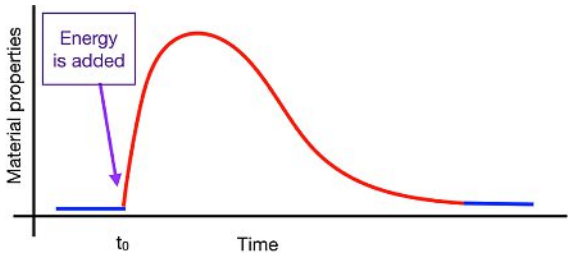

Figure 2. Generalized profile of material properties against time for dissipative supramolecular materials. At t_0, a finite amount of energy is added. Consequently, the supramolecular material (red line) emerges. When the system runs out of energy, equilibrium (blue line) is reinstated. The lifetime of the material can be controlled by parameters like the amount of fuel applied or the concentration of precursor.

irradiated the gel with UV-light through a photomask. Upon irradiation, the color of the gel changed from red to blue for the gold nanoparticles. For the silver nanoparticles, the color-shift was from yellow to blue (Figure 3d). The researchers showed that a UV-laser pen could also be used induce the color–shift. Moreover, they were able to write messages on the material. Crucially, all the patterns and messages erased over time as soon as the researchers removed the source of UV-light. The self-erasure time could be tuned from seconds to hours.

Our group recently demonstrated that self-erasing inks could also be based on chemical fuels, as opposed to UV-light, to deliver the required energy. The chemical reaction network is similar to the one described in Figure 1b. The precursor in this reaction network consisted of fluorenylmethyloxycarbonyl protected aspartic acid (Fmoc-D, Figure 4a). The precursor converted into its corresponding anhydride by addition of carbodiimide condensing agent as a fuel (Figure 4b). Upon conversion from precursor to product, the molecule lost two of its negatively charged carboxylates which made it less soluble. As a consequence, the anhydride product self-assembled into spherulites which transformed an initially clear solution into a turbid one (Figure 4c). Because of the anhydride's transient nature, the spherulites were temporary present, and the turbid solution reverted to a clear one when the system ran out of fuel. A solution of the precursor was trapped in a polyacrylamide hydrogel, and the fuel was applied onto the gel, either with a paint-brush or using a spray-coating setup. As a result, the turbidity of the gel increased where fuel was applied, and messages could be written (Figure 4d). Due to their non-equilibrium nature, the hydrogels lost their increased turbidity over the course of hours. Moreover, the self-erasure time could be tuned from one to several hours by the concentration of the applied fuel solution.

3.2 Self-abolishing Hydrogels

In supramolecular hydrogels, molecules assemble into fibers that subsequently form a network that traps its solvent.[34–36] Consequently, the self-assembly of molecules can convert an aqueous buffer into a material with solid-like properties.[37] For biomedical purposes, hydrogels have proven extremely powerful, ranging from applications as scaffolds for cells[38–41] to reservoirs that control the release of drugs.[42–45] Coupling these useful features of hydrogels to the unique properties dissipative self-assembly can thus result in self-abolishing hydrogels with a finite lifetime which is the focus of this section.

Van Esch and Eelkema introduced the first example of chemically driven dissipative self-assembly of fibers.[46,29] The chemical reaction network involved a well-soluble precursor, *N,N'*-dibenzoyl-L-cystine, that has two carboxylates (Figure 5a). When a methylating agent like methyl iodide or dimethyl sulfate was added, it reacted with the precursor to form the corresponding methyl ester (Figure 5b). Under the employed conditions, the methyl-ester product deactivated to the original precursor via hydrolysis. The reaction network thus formed metastable methyl-esters at the expense of methylating agent. The methyl ester, due to its loss of anionic carboxylates, was less soluble and self-assembled into fibers. The ensemble was

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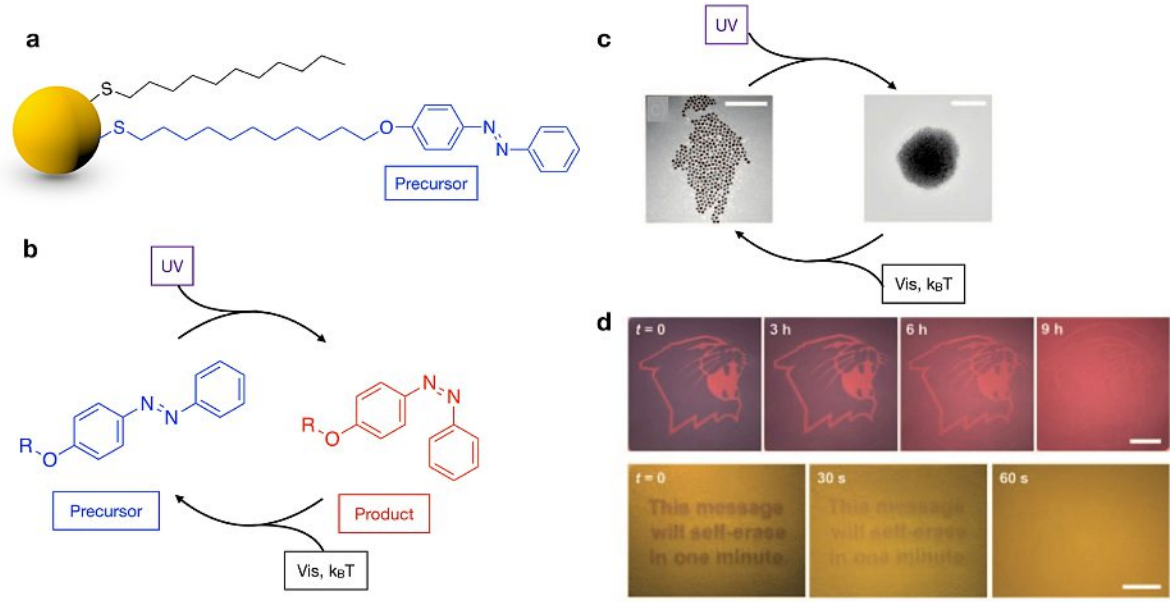

Figure 3. a) Schematic depiction of the precursor used in the study. **b**) In the depicted chemical reaction network, the azobenzene precursor (blue) absorbs a UV-photon (fuel, purple) and is isomerized to the metastable product (red). The product reverts spontaneously to the original precursor. **c**) TEM images of the precursor in solution (left) and the aggregates (right). The scale bar measures 100 nm. **d)** Photographs of self-erasing images or text using gold nanoparticles (first row) and silver nanoparticles (second row). The scale bars measure 1 cm. Reproduced with permission from Ref. 32. Copyright **2009** Wiley-VCH.

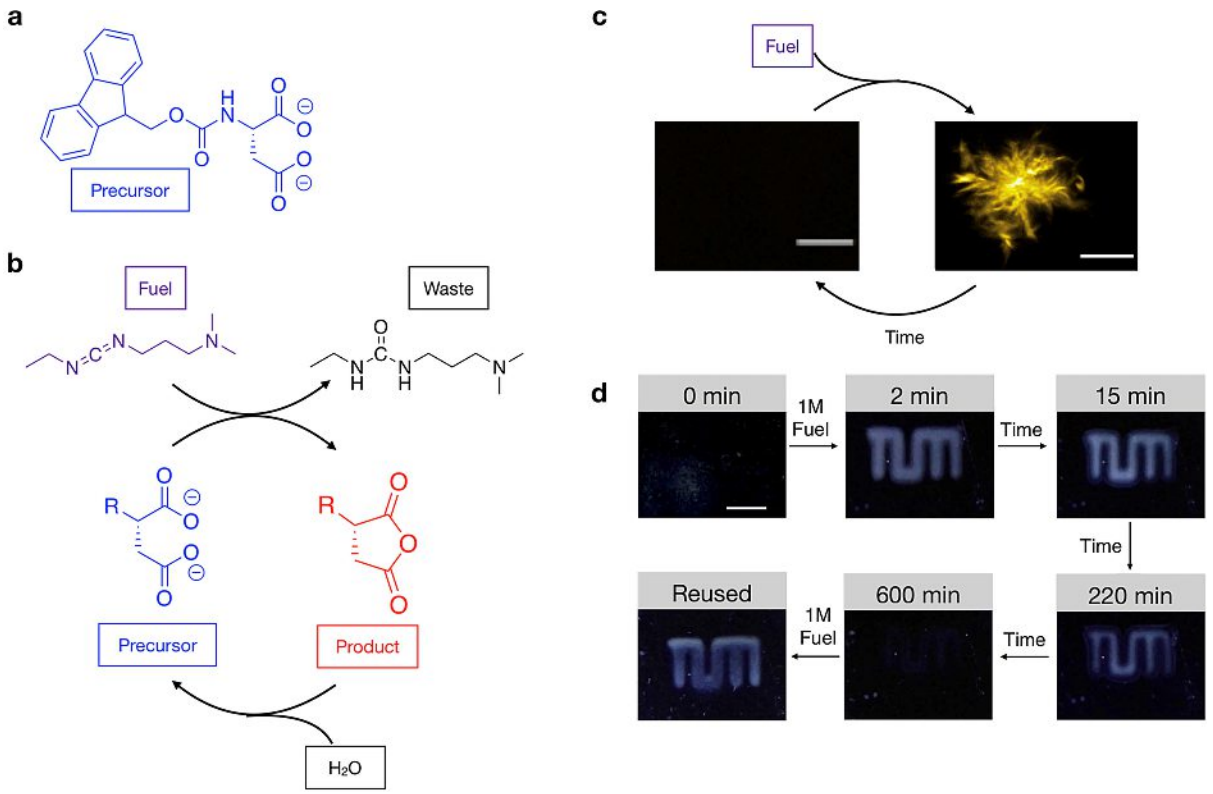

Figure 4. a) Chemical structure of the precursor Fmoc-D. **b**) In the depicted chemical reaction network, the dicarboxylate precursor (blue) reacts irreversibly with a carbodiimide fuel (purple) to form a metastable anhydride product (red). Hydrolysis deactivates the anhydride to the precursor. **c**) Confocal micrograph of the transiently arising spherulites of Fmoc-D in response to carbodiimide as fuel. The scale bar measures 10 μm. **d**) Photographs of the self-erasing inks at different times during the cycles. The scale bar measures 1 cm. Reproduced with permission from Ref. 26. Copyright **2017** Nature Publishing Group.

thus able to transform a solution of the precursor into a temporary hydrogel at the expense of methylating agent as fuel (Figure 5c). The lifetime of the hydrogels could be tuned from several hours to days by the pH of the solution or the

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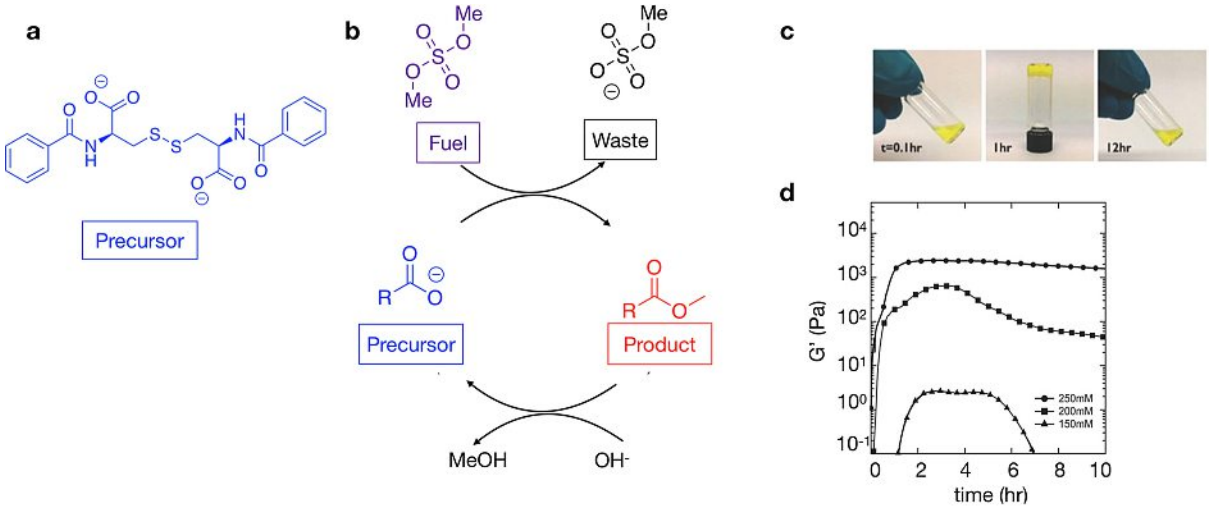

Figure 5. a) The molecular structure of the N,N-dibenzoyl cystine precursor. **b**) The depicted chemical reaction network converts the precursor into its corresponding methyl ester product at the expense of dimethylsulfate as fuel. The methyl ester hydrolyzes back to the precursor over time. **c**) Photographs of the transient hydrogel at different times after addition of fuel. **d**) The viscoelastic response against time of the samples as measured by plate-plate rheology in response to various amounts of fuel. When more fuel was added, gels were stronger and persisted for longer times. Reproduced with permission from Ref. 28. Copyright **2015** American Association for the Advancement of Science.

amount and nature of the methylating agent as fuel added (Figure 5d).

Work by Ulijn and coworkers showed that the formation of dissipative hydrogels was not limited to methylating agents, but could also be induced by enzymes.[48,49] The study described a tyrosine-based precursor (Figure 6a). The precursor that was activated by reaction with a second amino acid as fuel, specifically the methyl ester of tyrosine with its N-terminus

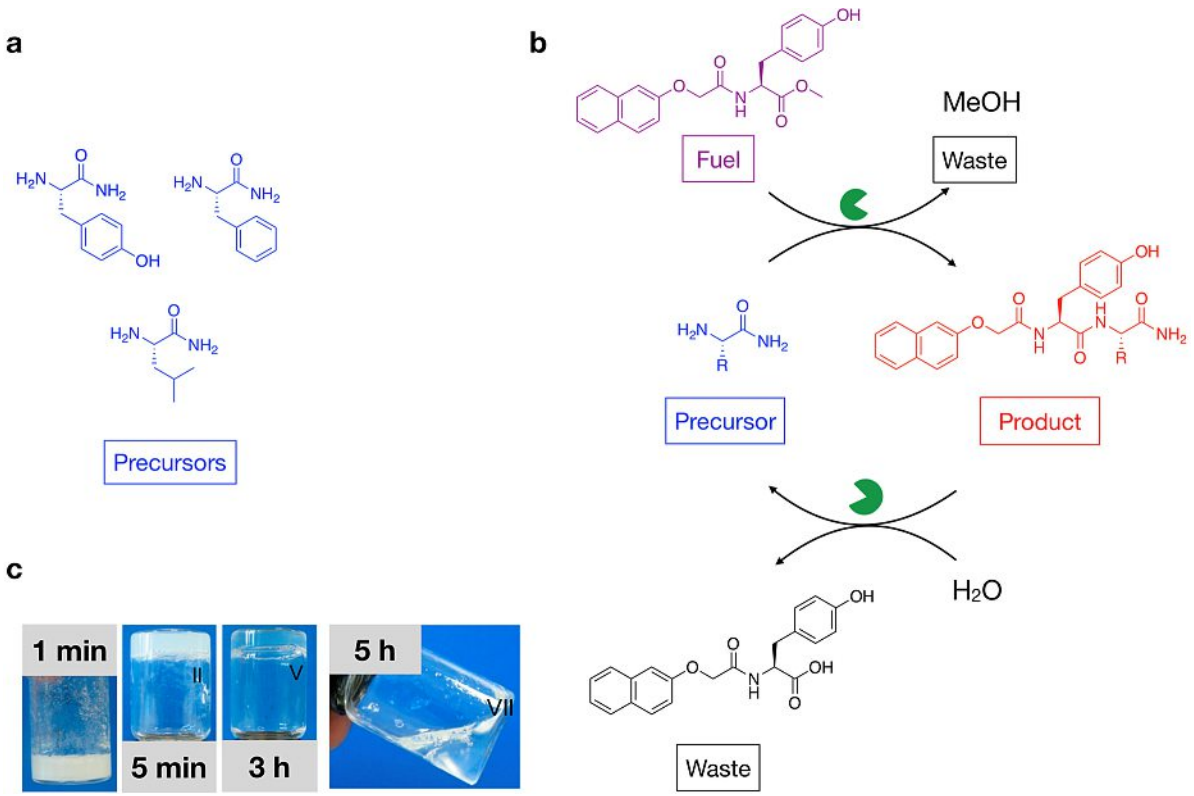

Figure 6. a) The molecular structures of the tyrosine-based precursors. **b**) The depicted chemical reaction network converts the precursor into a dipeptide product at the expense of the tyrosine methyl ester as fuel. The network requires chymotrypsin (green) for both the activation and deactivation reaction. **c**) Photographs of the transient hydrogel taken at different times after addition of fuel. Reproduced with permission from Ref. 47. Copyright **2015** Wiley-VCH.

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protected by a naphthoxyacetyl group (Figure 6b). The activation reaction did not occur spontaneously, but the enzyme α-chymotrypsin was used to catalyze it. Crucially, the same enzyme catalyzed the hydrolysis of the dipeptide product to the precursor, which rendered the dipeptide metastable. The dipeptide was designed to assemble into a hydrogel-forming fiber network (Figure 6c). With the enzyme concentration and the nature of the precursor, the authors could tune the lifetime of the hydrogel from minutes to several hours.

The self-abolishing hydrogels and supramolecular polymers we highlighted above, as well as work by others,[50–57] are an exciting development for the field of biomaterials. Specifically, in regenerative medicine, the creation of a hydrogel with embedded cells that changes its function over time has been a long-standing challenge.[58]

3.3 Temporary Materials as Delivery Devices

Another promising biomedical application for materials with a tunable lifetime is as a delivery vehicle for drugs. To that end, Walther and coworkers demonstrated the burst release of a product from a dissipative hydrogel.[59] The chemical reaction network was described in earlier work and based on the addition of the enzyme urease and citric acid as fuel (Figure 7a).[60] The acid addition induced a decrease in the pH. In parallel, the urease hydrolyzed urea to form ammonia as a product. The released ammonia raised the pH back to alkaline. As a result, the pH was only temporary brought to acidic values and reverted to the starting pH.

The unique approach allowed the researchers to couple pH-responsive assemblies to the chemical reaction network. Indeed, when the chemical reaction cycle was carried out in the presence of a pH-responsive hydrogelator, the decrease in pH resulted in the formation of a transient gel (Figure 7b). The researchers demonstrated that the lifetime of the hydrogel could be tuned from minutes to hours by the amount of urease in the system (Figure 7c). Moreover, it was also demonstrated that their temporary hydrogels could release hydrophilic dye after a preprogrammed time (Figure 7d). Because of the generality of the principle, several other assemblies have been formed via this principle including DNA i-motifs[61] and photonic devices.[62]

To demonstrate the use of dissipative materials as delivery vehicles, we recently described the release of hydrophobic dyes from a dissipative supramolecular material. We used Fmoc-protected glutamic acid (Fmoc-E, Figure 8a) as a precursor in the carbodiimide-fueled chemical reaction network described in Figure 3a. The activated building block self-assembled into colloids driven by hydrophobic collapse. Due to the transient nature of the activated anhydride building block, the colloids had a finite lifetime that could be tuned from 30 to 120 minutes by the amount of fuel added to the system (Figure 8b). We found that hydrophobic dyes could be incorporated into these colloids. Moreover, the time point in the cycle when the dye was added determined where it was incorporated. For example, when Nile Red was added from the beginning of the cycle, i.e., with the fuel, it was incorporated in the core of the colloid (Figure 8c). When pyrene was added 10 minutes after initiating the cycle, it was built into the outer layers of the colloids. The inhomogeneous distribution of the dyes could be used to

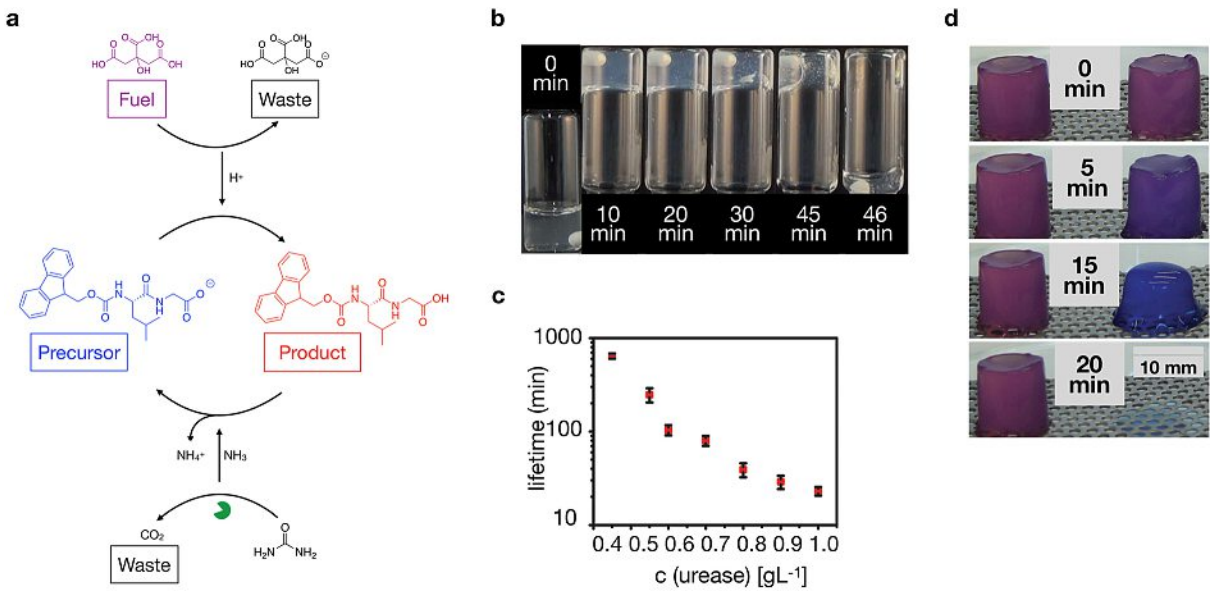

Figure 7. a) In the depicted chemical reaction network, citric acid is used as a fuel to release protons. The decrease in pH-activated the enzyme urease which releases ammonia and resets the pH to the original value. If the cycle was carried out in the presence of a dipeptide as a precursor, it was temporarily protonated and self-assembled into fibers. **b**) Photographs of the gel at different time points. **c**) A plot of the lifetime against concentration urease. The amount of enzyme can tune the lifetime of the hydrogel. **d**) Photographs of a static (left) and a transient (right) hydrogel at different times. The transient hydrogel decayed after a preprogrammed time and released the encapsulated dye Resazurin. The scale bar measures 1 cm. Reproduced with permission from Ref. 58. Copyright **2015** Wiley-VCH.

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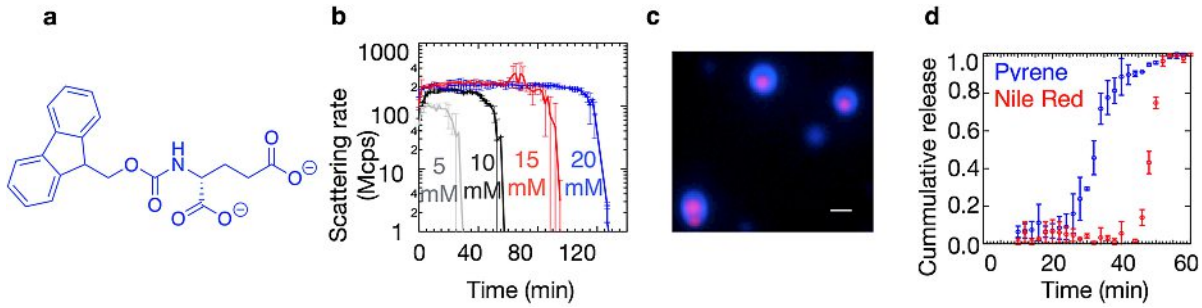

Figure 8. a) Chemical structure of Fmoc-E used as a precursor molecule for the dissipative chemical reaction network based on carbodiimide hydrolysis. **b**) DLS measurement of the dissipative network against time showed the transient nature of the assemblies. **c)** Confocal images of colloids coded with Nile red and pyrene. The scale bar measures 1 μm. **d**) Release profile obtained from the collapse of the colloids. Reproduced with permission from Ref. 26. Copyright **2017** Nature Publishing Group.

control the order of the release of the hydrophobic molecules from the colloids. Because the colloids were deactivated from their outer shells, the blue pyrene was released first (Figure 8d). Near the end of the lifetime of the colloids, also the Nile Red in the core was released. Consequently, the sequence of release of hydrophobic dyes could be controlled by order of incorporation of the dyes during the preparation of the colloids. Moreover, the amount of fuel could be used to tune the point at which the molecules were released.

The examples described above demonstrate the ability to release both hydrophobic and hydrophilic dyes from dissipative assemblies. Moreover, both the time when the material is released as well as the sequence of the released dyes can be predetermined by the users. These studies, as well as other from the field,[63] show the exciting possibilities of dissipative supramolecular materials as drug delivery vehicles or other biomaterials in the future.

3.4 Transient Assemblies to Control Reaction Rates

Besides the application of dissipative assemblies as delivery devices, researchers have used dissipative supramolecular materials to control reaction rates. A recent study of Prins and coworkers explored that principle. In their work, a cationic surfactant, $C_{16}TACN{\cdot}Zn^{2+}$ (Figure 9a), served as a precursor.[64] The precursor was electrostatically complexed by the anionic fuel ATP (Figure 9b). The complexation screened the charges of the surfactant and induced its assembly into vesicles (Figure 9c) as evidenced by confocal and electron microscopy (Figure 9d). However, under the employed conditions, the ATP was unstable and hydrolyzed to AMP. As a consequence, the surfactant disassociated from the AMP which induced the disassembly of the vesicles. Addition of the enzyme potato apyrase increased the hydrolysis rate, which allowed the researchers to control the lifetime of the transient vesicles.

The researchers hypothesized that the bilayer of the vesicles could serve as a hydrophobic container that hosts reactants. Following that idea, they were able to tune the kinetics of an aromatic nucleophilic substitution reaction between two hydrophobic compounds (Figure 9e). The amount of ATP added to the system increase the number of vesicles in the solution and, consequently, it increased the yield of the aromatic nucleophilic substitution (Figure 9f).

Examples of the dissipative assembly of nanoparticles have also been reported. The systems make use of nanoparticles but with different roles. In a first example, the surface of the nanoparticles acted as a catalyst, and their transient assembly thus decreased the reaction rate.[65] Klajn *et al.* described a system in which the assembly helped concentrating the reactants, thus serving as a temporary "nano flask."[66] As a result, reaction rates accelerated upon assembly.

4. Conclusions

In this Focus Review, we described recent examples of dissipative self-assembly that researchers developed with the intention to tune the lifetime of the emerging materials. In these dissipative supramolecular materials, energy-dissipating chemical reaction networks are coupled directly or indirectly to the self-assembly of molecules into supramolecular materials. The emerging materials have properties that are determined by the kinetics of the chemical reaction networks. In this Focus Review, we chose to focus on the finite lifetime of the material. A facile way to tune the lifetime is by the initial amount of fuel added. Other methods include adjusting the precursor concentration or the concentration of reactants that are involved in the deactivation.

Preliminary studies have shown that the emerging dissipative supramolecular materials can be used as self-erasing inks or as a reusable paper. Another application includes self-abolishing hydrogels. Such gels could find application as a biomaterial that aids the body to regenerate lost tissue, and, after its function has been carried out, self-abolish. Alternatively, these materials can be used to deliver pharmaceuticals at a predetermined time or following a specific sequence. A final application of dissipative supramolecular materials we discussed is as a material that can control reaction rates over time.

In biological dissipative materials, we can find, besides a finite lifetime also other exciting, unique properties, which include the ability to self-heal, self-replicate and to sponta-

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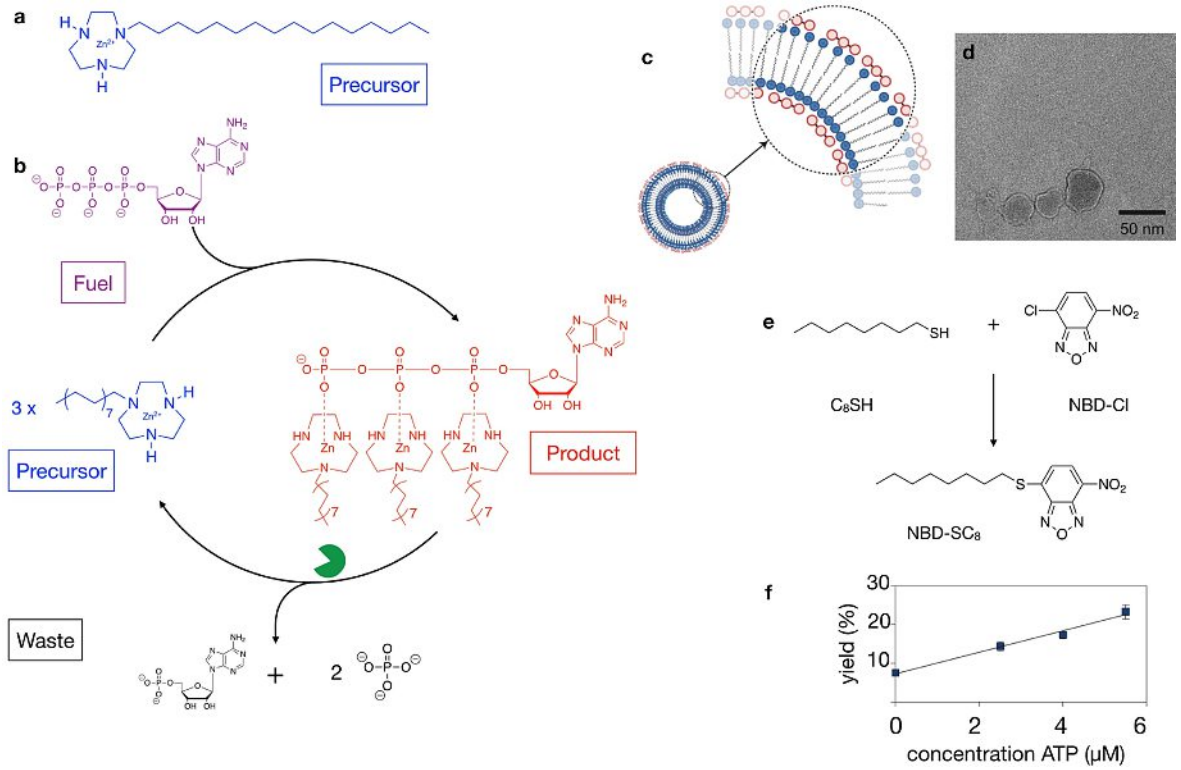

Figure 9. a) Molecular structure of the amphiphilic C_{16}TACN·Zn^{2+} precursor. **b**) Chemical reaction network that forms vesicles under ATP usage by coordinating the precursor. The enzyme potato apyrase (green) hydrolyzes ATP to AMP and two-times P_i. **c**) Schematic representation of the vesicle bilayer. **d**) Cryo-TEM of the dissipative vesicle. The scale bar measures 50 nm. **e**) Scheme of the aromatic nucleophilic substitution reaction carried out in the vesicular system. **f**) The yield of NBD-C_8 as a function of ATP concentration after a reaction time of 30 minutes. Reproduced with permission from Ref. 63. Copyright **2016** Nature Publishing Group.

neously form patterns. Engineering such behavior in artificial supramolecular materials is one of the primary goals for the field of supramolecular chemistry. A step towards that objective is implementing feedback of the assemblies on their chemical reaction network. For example, the assembly of microtubules catalyzes its building block deactivation, which is a crucial element of the complex behavior of the emerging structures.[21] Very recent work by our group has shown that feedback of the assemblies on their network can indeed initiate new behavior that includes self-selection[67] or an increased robustness of the assemblies.[68] However, true complex behavior of the resulting materials, like self-replication or pattern formation is still missing. With these unique properties, we foresee a significant role of dissipative self-assembly in the materials of the future.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: dissipative self-assembly · lifetime · self-assembly · supramolecular materials · temporary material

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