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Transient self-assembly of molecular nanostructures driven by chemical fuels

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Over the past decades, chemists have mastered the art of assembling small molecules into complex nanostructures using non-covalent interactions. The driving force for self-assembly is thermodynamics: the self-assembled structure is more stable than the separate components. However, biological self-assembly processes are often energetically uphill and require the consumption of chemical energy. This allows nature to control the activation and duration of chemical functions associated to the assembled state. Synthetic chemical systems that operate in the same way are essential for creating the next generation of intelligent, adaptive materials, nanomachines and delivery systems. This review focuses on synthetic molecular nanostructures which assemble under dissipative conditions. The chemical function associated to the transient assemblies is operational as long as chemical fuel is present.

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Introduction

Over the past decades self-assembly has emerged as the most powerful strategy for the formation of molecular nanostructures. It has permitted the development of innovative systems for diagnostics and catalysis and has enabled enormous advances in the fields of materials chemistry and nanotechnology [1]. Although inspired by nature, there is a strong current awareness that nature is only mimicked to a certain extent [2•]. While many biological self-assembly processes are driven by thermodynamics [3], just as in synthetic self-assembly, there are also situations in which self-assembly is associated with an energy consumption process, referred to as dissipative self-assembly [4,5]. Nature exploits dissipative self-assembly as a way to obtain temporal control over the chemical functions associated with the assembled state [6–10]. There is currently a strong drive to implement the same principle also in synthetic systems, with the ultimate aim of creating intelligent materials and devices able to perform different functions based on the stimuli provided in the form of energy [11,12,13•,14–20]. In the last years this has led to the development of various chemical systems that require energy to self-assemble into functional structures. Most frequently, energy is provided in the form of physical stimuli, mainly as light [16,21–27], but also as ultrasound [28], electrical current [29], osmotic pressure [30] or, alternatively, by (transiently) changing the pH [31,32]. This is highly attractive, because this energy can be delivered in a clean manner to the system and is consumed without the creation of waste. However, nature predominantly exploits chemical energy as a trigger for the selective activation of function. The design of synthetic systems that rely on chemical fuels for self-assembly is challenging and has mainly focused on the development of hybrid structures in which natural dissipative systems, such as microtubules, are conjugated with synthetic elements such as nanoparticles [33–38]. Another successful approach relies on the coupling of a self-assembly process to a chemical oscillator, such as the Belousov–Zhabotinsky (BZ) reaction, which operates intrinsically out-of-equilibrium [39–43]. However, although functional, these systems do not provide much flexibility since the energy dissipation process is extremely well-defined and difficult to modulate [44•]. The scope of this short review is to highlight recent advances made in the design of synthetic molecular assemblies that require chemical fuels to be functional. It will be shown that such systems maintain the assembled state only as long as chemical fuel is present. The result is that the chemical functions exerted by the assemblies have a transient character.

Soft materials

The first step towards artificial systems able to mimic the transient nature of microtubule-formation was reported by Van Esch *et al.* [45••] Their approach was based on dibenzoyl-L-cystine (DBC), which is a pH-responsive gelator (Figure 1a). Above the pK_a-value of the carboxylic acids (around 4.5) gel formation does not occur, because of electrostatic repulsion between the carboxylate groups. Protonation of the carboxylic groups at pH-values below

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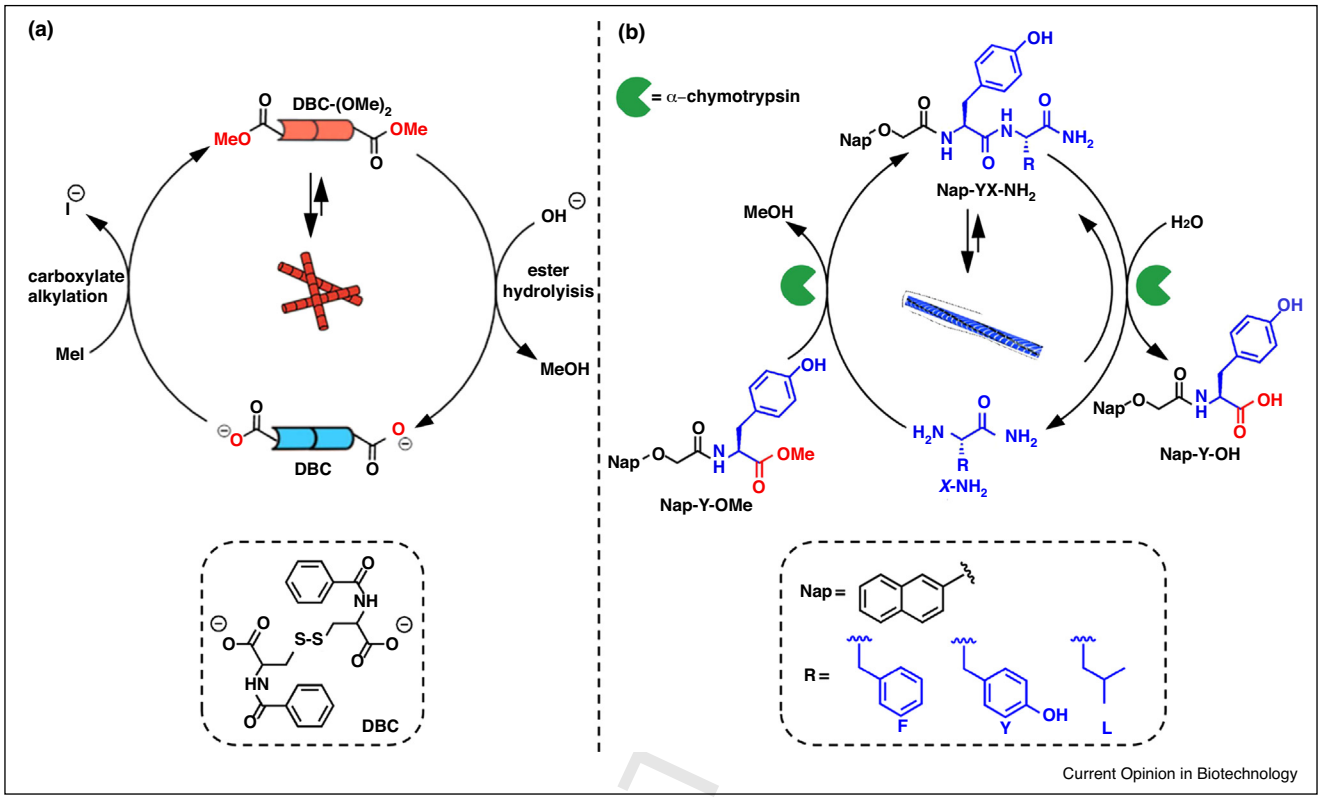
Figure 1



Transient gel formation relying on **(a)** the rapid esterification of the pro-gelator DBC or **(b)** the rapid formation of a dipeptide hydrogelators under hydrolytic conditions.

the pK_a results in neutralization and consequent self-assembly of the molecule in long fibers, stabilized by intermolecular hydrogen-bonding. On the other hand, the corresponding DBC-diester (DBC-$(OMe)_2$) assembles at all pH-values, even above the pK_a. The properties of these molecules were used to design a dissipative cycle in which methyl-iodide (MeI) was used to methylate DBC under ambient conditions (35°C). Under these conditions a spontaneous hydrolysis of the formed esters also took place leading to a return to the starting compound, which crucially was at a rate that is lower than that of ester formation. This implies that the addition of MeI leads to the transient presence of the gelator DBC-$(OMe)_2$ in the system, with a lifetime that depends on the amount of fuel added. Transient gel formation was confirmed by light scattering studies and scanning electron microscopy (SEM). Confirmation that the system returned to the original state was demonstrated by the observation that the addition of a new batch of MeI induced a second cycle of transient gel formation. This first system suffered from relatively long response times with life-cycles in the order of days. In a follow-up study, the life times could be reduced to hours by changing the chemical fuel and optimizing the pH level [46]. However, the importance of this study lays in the demonstration that the mechanical properties of the gel could be controlled by the initial level of the chemical fuel. The addition of low concentrations of MeI resulted in short-lived weak gels, whereas long-lived stiff gels were obtained at high concentrations of fuel. Furthermore, it was also shown that these materials had a much higher capacity for self-regeneration after destruction when high fuel levels were present.

Debnath *et al.* developed an alternative hybrid biosynthetic system for transient gel formation which relied on the gelating properties of naphthalene-dipeptides and the ability of enzymes to form and cleave peptide bonds (Figure 1b) [47•]. Starting point was the α-chymotrypsin catalyzed transacylation of a series of hydrophobic amino acids *X*-NH_2 (with *X* = Y, F or L) using Nap-Y-OMe as an acyl-donor which rapidly yielded the dipeptide hydrogelator Nap-Y*X*-NH_2. However, in time α-chymotrypsin caused the installment of an equilibrium between the hydrogelator Nap-Y*X*-NH_2 and the hydrolysis products Nap-Y-OH and the original amino acid *X*-NH_2 leading to a constant equilibrium concentration of the gelator. When F-NH_2 was used, the final concentration of Nap-YF-NH_2 was above the critical gelation concentration (CGC) leading to the formation of a stable gel. On the other hand,

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transient gel formation was observed when amino acids Y-NH_2 and L-NH_2 were used, as the concentration of the dipeptide in these systems remained only for a limited time above the CGC. The lifetime of these gels could be tuned by changing the pH. It was shown that the system could be refueled up to three times by adding additional equivalents of Nap-Y-OMe. After three cycles the system was no longer able to reach the dipeptide-concentrations required to reach the CGC, presumably because of interference with the accumulating amounts of the waste product Nap-Y-OH in the system.

This approach was then extended to a system of tripeptide-gelators in which structurally diverse amino acids were ligated in an analogous manner to aspartame, a DF-dipeptide methylester [48]. Only for F-NH_2 and Y-NH_2 transient gel formation was observed; in the presence of amino acids W, L, V, S and T, no gelation was observed. For the latter amino acids, rapid formation of the end product DF-OH was seen. Hardly any formation of the tripeptide was observed, despite the fact that some of these amino acids (L, V, S) were used as effective nucleophiles in previous studies. The observation of gel formation for F and Y suggests that these transient nanofibers are less prone to enzymatic hydrolysis and thus permit conditions for transient structure formation ($rate_{formation} > rate_{destruction}$). Interestingly, while the DFF-NH_2 peptide turned out to be thermodynamically more stable compared to DFY-NH_2, direct competition experiments revealed that the selection in this system relied on kinetic control, yielding DFY-NH_2 as the major product.

An alternative biocatalytic approach towards transient hydrogel formation relied on the sucrose-fueled production of CO_2 by yeast [49]. Acidification of an aqueous solution upon the dissolution of CO_2 resulted in the protonation of a peptide-based surfactant causing the formation of a gel. Gradual elimination of CO_2 from the system upon evaporation resulted in spontaneous return to the original state.

A different approach towards transient polymer self-assembly was developed by Kumar *et al.* and relies on the exploitation of naphthalenediimide chromophores appended with Zn(II)-complexes [50]. Whereas the building block by itself showed no signs of aggregation, the addition of adenosine phosphates (A*X*P with *X* = M, D, or T) resulted in the formation of helical stacks with the anionic A*X*Ps lined up against the outward-pointing cationic side-groups [51]. Interestingly, it was observed that the handedness of the supramolecular polymer depended on the nature of the adenosine phosphate. This provided an important tool to follow the spontaneous transition of the structures across the supramolecular energy landscape upon the enzyme-catalysed hydrolysis of ATP → ADP → AMP → P_i. The system is in principle amenable to repetitive cycles by displacing P_i with the high-affinity binder ATP under dissipative conditions.

Nanostructures

Surfactant-based systems

The self-assembly of surfactants into large structures, such as micelles and vesicles, has always attracted great interest because of the similarity of these structures to cells and also for their numerous practical applications [52]. The functional properties of these systems mainly originate from the presence of an internal compartment that is separated from the bulk and from the presence of an apolar phase in aqueous media. Methodology to control the formation of these systems through the addition of chemical fuel under dissipative conditions would give temporal control over their associated functions. As illustration, Wang *et al.* coupled the formation of supra-amphiphiles to the chemical oscillator IO_3^--NH_3OH^+-OH^- which periodically generates iodine [53]. Reaction of iodine with the PEG segment of a hydrophilic block copolymer increased the hydrophobicity of that domain and induced its self-assembly into supra-amphiphiles. The oscillating concentration of iodine caused spontaneous transitions between assembled and dissociated states as a function over time. Although not surfactant-based, the system nicely illustrates the possibility to regulate the self-assembly process in time using a chemical fuel. The following examples illustrate how this can be used to control the chemical functions associated with the assembled state.

Our group developed a strategy for the transient stabilization of vesicular aggregates (Figure 2a) [54••] based on a previous study aimed at transient signal generation by a nanoparticle-based system [55]. A surfactant containing a cationic 1,4,7-triazacyclononane (TACN)·Zn(II) head group was found to form micellar aggregates with a critical micelle concentration (CMC) of around 100 μM. However, the presence of ATP resulted in the formation of vesicular aggregates at much lower concentrations. This is attributed to the stabilizing interactions between ATP and the oppositely charged head groups, which also causes a repositioning of the surfactants. Importantly, previous studies using monolayer protected gold nanoparticles containing identical head groups had demonstrated a strong dependence between the number of negative charges present in a series of adenosine phosphates (A*X*P with *X* = M, D, or T) and the affinity for the multivalent surface [55]. The incapacity of AMP to stabilize aggregates below the cmc was then exploited for the transient self-assembly of vesicular aggregates. ATP was added to surfactants at concentrations below the cmc in the presence of potato apyrase, which is an enzyme that hydrolyses ATP into AMP + 2P_i. Since the rate of aggregate formation induced by ATP is more rapid than the decay rate of

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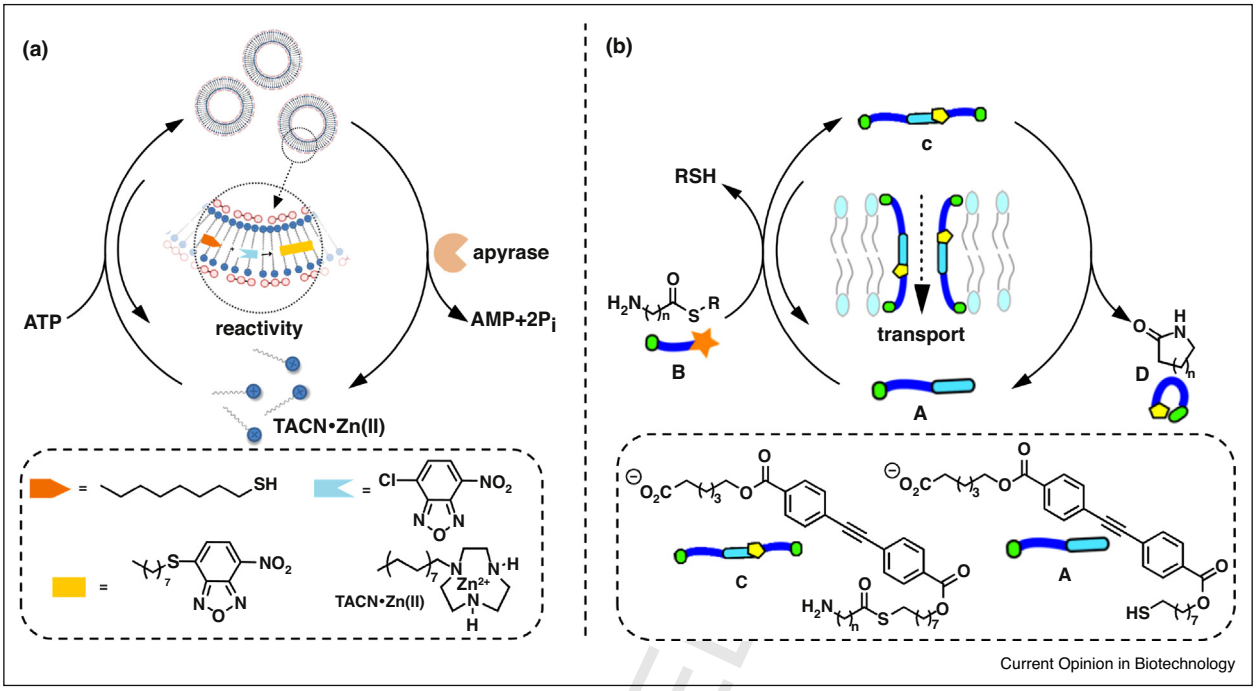
Figure 2



(a) The transient formation of vesicles driven by ATP and **(b)** the transient formation of membrane channels driven by the activation of precursor **A**.

ATP, a transient period exists in which aggregates are formed. Upon depletion of ATP, the system spontaneously reverted to the non-aggregated state, which was confirmed by a series of techniques which included DLS, UV–vis, fluorescence and confocal microscopy. The process of transient aggregate formation could be repeated multiple times upon the addition of new batches of ATP. Next, this process was coupled to a chemical reaction that was strongly favored by the apolar bilayer of the aggregates. It was shown that the lifetime of the vesicles determined the amount of reaction product formed by the system. Thus this system provides a new means to indirectly control the outcome of a chemical reaction through the exploitation of a transient phenomenon driven by a chemical fuel.

The group of Fyles described the transient formation of channels in a membrane system driven by a chemical fuel (Figure 2b) [56•]. The project was based on the knowledge that compounds analogous to **C** are able to span a bilayer membrane and create a hydrophilic pore able to translocate ions across the membrane. The key novel feature of molecule **C** is the presence of a labile thioester-bond. In the absence of the acyl part (such as in **A**), channel activity was not observed and this represents the inactive resting state. Upon the addition of thioester **B** as a chemical fuel, thiol-thioester exchange occurs spontaneously leading to the *in situ* formation of the channel-forming compound **C**. Channel activity was measured using the voltage-clamp technique which measures changes in conductivity upon the transport of ions across the membrane [57]. Importantly, compound **C** is terminated with a nucleophilic amine, which is able to intramolecularly attack the thioester bond leading to the spontaneous re-formation of the resting compound **A** and the cyclic waste product **D**. The rate of the intramolecular reaction can be tuned by changing the spacer length separating the amine and the carbonyl-group of the thioester-bond. Transient accumulation of the pore-forming compound **C** occurs if the intramolecular cyclization-rate is slower than the transthioesterification reaction. Time-dependent conductance measurements confirmed the spontaneous decrease in pore-activity, which could be regenerated upon the addition of a fresh batch of fuel. It is noted that this system is intrinsically dissipative in the sense that formation of the active compound automatically installs a mechanism of self-destruction because of the presence of the nucleophile. This makes it different from most other systems discussed here, that rely on the creation of dissipative conditions by external elements (such as enzymes or bases). The ability to tune the efficacy of the intramolecular reaction and thus control the dissipative process illustrates the advantages and potential of synthetic systems.

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Molecular cages

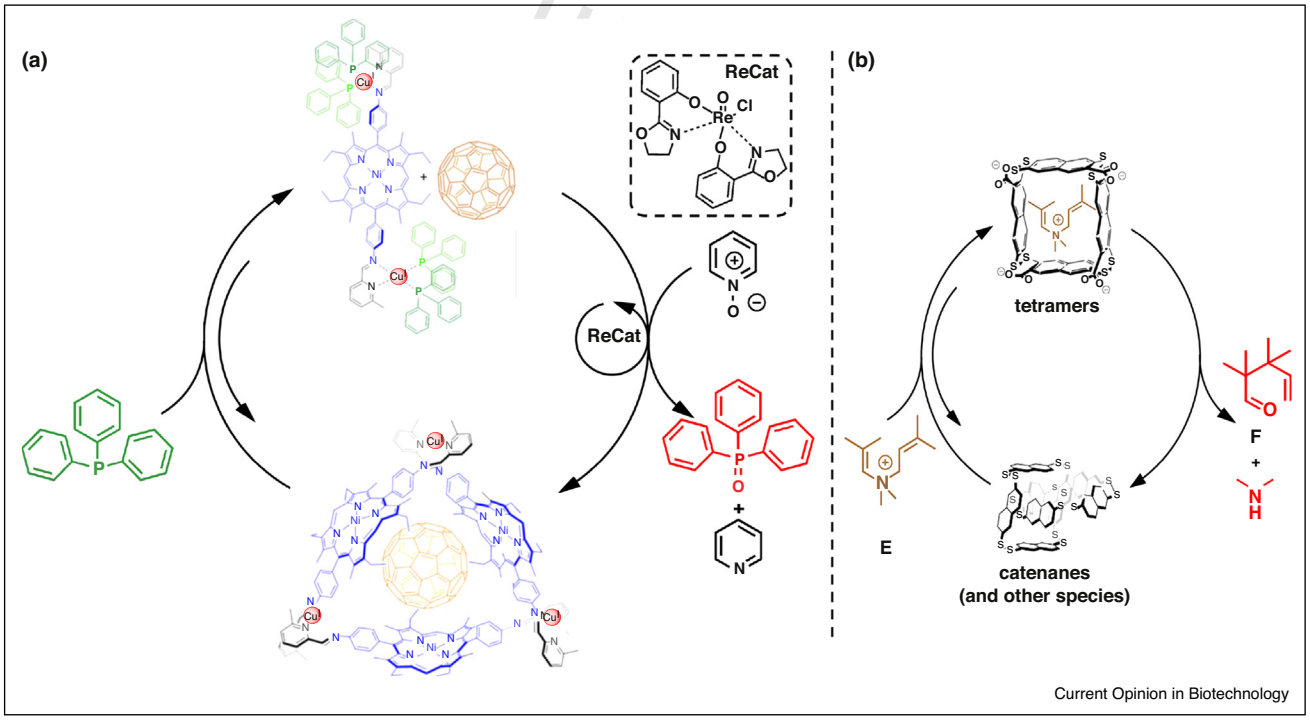
The first examples are appearing in which the self-assembly of molecularly well-defined structures is governed by the transient action of chemical fuels. Wood *et al.* reported a self-assembled cage composed of porphyrin building blocks and Cu(I)-metal ions that dissociate upon the addition of triphenylphosphine (PPh_3) [58•]. This is because of the preferential formation of heteroleptic N, P-complexes with Cu(I) (Figure 3a). However, when PPh_3 is added under oxidative conditions (because of the presence of pyridine *N*-oxide as an oxidant and the *oxo*-transfer catalyst ReCat as an accelerator), it is slowly converted to triphenylphospine oxide which no longer coordinates Cu(I). Consequently, the system reverts back to the assembled state. A new cycle can be initiated by adding a new batch of PPh_3. Transient dissociation of the cage occurs because the oxidation rate is much lower compared to rate of the ligand exchange. A hint of a possible application as delivery agent was provided by demonstrating the transient release of an encapsulated C_{60}-guest upon the addition of fuel.

Finally, a very intriguing example was reported by Fanlo-Virgos *et al.* which described the transient adaptation of a dynamic molecular network to the addition of a guest (Figure 3b) [59••]. A library of very diverse molecular structures including catenanes and tetramers was spontaneously formed upon the partial oxidation of a building block containing two thiol moieties. The reversibility of the disulfide bond permitted interconversion between the library members and imparted adaptability to the network. A remarkable spontaneous shift in the library composition towards the tetrameric species was observed upon the addition of compound **E** ascribed to the installment of favorable interactions between the tetramers and compound **E**. In the absence of other events this would just have been an example of guest-induced templated synthesis, but in this particular case it was observed that in time the system spontaneously returned to the original composition. It turned out that the tetramers catalyze the conversion of compound **E** into product **F** and dimethylamine through an *aza*-Cope rearrangement. The fact that a second addition of guest induces a new transient shift in library composition confirms the reversibility of the process and demonstrates the capacity of the system to spontaneously dissipate the energy provided by the guest. Like the transmembrane pore-formation discussed above, also this system is intrinsically dissipative. The exciting prospect offered by these results is the development of dynamic networks that are able to transiently evolve into different directions depending on the input of chemical information.

Outlook

Compared to traditional self-assembly processes which rely on the installment of a functional thermodynamically

Figure 3



(a) Transient displacement of fullerene from a molecular cage driven by triphenylphosphine and **(b)** transient adaptation of a molecular network to a substrate.

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stable state, the key novelty introduced by performing self-assembly under dissipative conditions is that control can be gained over the lifetime of the chemical function associated with the assembled state. Energy can also be delivered using a variety of physical means, but the use of chemical fuels brings us one step closer to mimicking biological networks that mostly rely on fluxes of energy stored in molecules. The examples presented here are still rather primitive and in most cases dissipative conditions are artificially created by the addition of an external component (catalyst, enzyme, reagent) to the system that dissipates the energy stored in the fuel. Yet, some of the systems discussed are intrinsically dissipative, implying that it is the self-assembled structure itself that causes energy dissipation. One further step up the ladder is the design of structures that assemble as a result of energy dissipation. The ability to use time as a regulatory element in designing chemical systems offers new and exciting possibilities for the design of reaction networks, functional materials and delivery systems.

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