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Out-of-Equilibrium Assembly Based on Host–Guest Interactions

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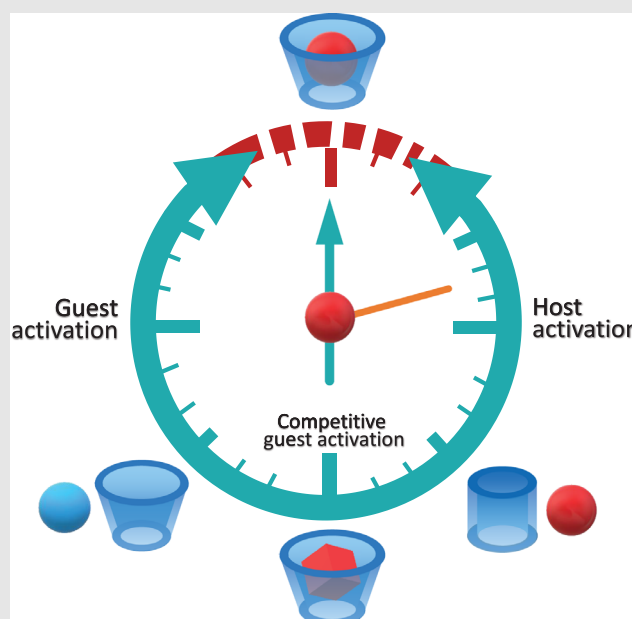
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The field of supramolecular chemistry is rapidly progressing, transitioning from the creation of thermodynamically stable systems found in local or global minima on the free energy landscape to the development of out-of-equilibrium systems that rely on chemical reactions to establish and maintain their structures. Over the past decade, numerous artificial out-of-equilibrium systems have been devised in various domains of supramolecular chemistry, many of which have been extensively reviewed. However, one area that has received limited attention thus far is the use of out-of-equilibrium processes to regulate host–guest interactions. This minireview aims to address this gap by exploring the construction of out-of-equilibrium systems based on host–guest complexation, which likely employs similar strategies to those employed in analogous noncovalent interactions. The review begins with a summary of these shared strategies. Subsequently, it discusses representative publications that exemplify these strategies and classifies them based on which component is being modulated—host, guest, or competitive molecules. Through this examination, our objective is to shed light on the design of out-of-equilibrium systems relying on

host–guest interactions and provide valuable insights into the preparation strategies for various transient materials.



Keywords: out-of-equilibrium, host–guest chemistry, self-assembly, supramolecular materials, chemical fuel

Introduction

Research in supramolecular chemistry often draws inspiration from biological entities such as proteins, lipids, and their multimolecular complexes. Investigating the non-covalent interactions present in these systems is crucial for understanding the biological processes that rely on

these forces for structure and function.¹ Taking cues from living systems, where many assembled structures exist in an out-of-equilibrium state, researchers have started to pay attention to out-of-equilibrium assembly. Since the artificial chemical-fuel-driven system was developed in 2010,² the field has experienced explosive growth in recent years. Unlike self-assembled systems that

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predominantly reside in thermodynamic equilibrium, out-of-equilibrium assembled structures require continuous activation to maintain their state and prevent degradation into their stable chemical elements. This dependence on continuous activation gives out-of-equilibrium supramolecular systems with highly dynamic properties such as self-replication, internal feedback, stimuli-responsiveness, environmental adaptation, self-healing, and signal amplification. The concepts, terminologies, and design principles of out-of-equilibrium systems have been extensively covered in a range of comprehensive tutorial reviews.^{3–12} However, this review will not focus on those aspects. Instead, our emphasis will be on classifying and summarizing the various areas where out-of-equilibrium assembly and host-guest chemistry intersect.

Host-guest complexation is one of the earliest branches of supramolecular chemistry and holds significant value in both biological and chemical systems. Referred to as molecular recognition, this type of interaction is commonly observed in physiological processes, including enzyme-substrate and antigen-antibody interactions. Over the past decades, there has been rapid progress in the development of artificial host-guest systems, expanding the toolkit available to chemists and enhancing our understanding of supramolecular chemistry. Numerous macrocyclic host molecules and their derivatives have been synthesized, including calixarenes (CAs), crown ethers, cyclodextrins (CDs), cyclophanes, cucurbit[n]urils (CBs), pillar[n]arenes (PAs), and others. These host molecules serve as the foundation for creating various materials such as supramolecular polymers, gels, micelles, vesicles, and nanoparticles, exhibiting promising applications in molecular sensing,^{13,14} drug delivery,¹⁵ nanomedicine,¹⁶ fluorescence probes,¹⁷ catalysis,^{18–20} and more.²¹ Currently, there are reports of man-made host-guest pairs that exhibit even higher affinity ($7.2 \times 10^{17} \text{ M}^{-1}$)²² than the strongest known host-guest noncovalent interaction observed in biotin-streptavidin (10^{13} – 10^{15} M^{-1}).²³

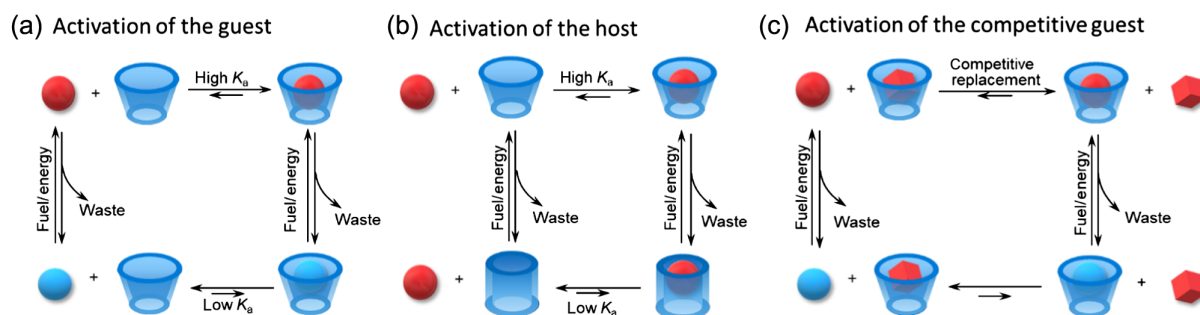
Since 2015, several out-of-equilibrium self-assembly systems based on transient host-guest complexation have been reported. This review aims to comprehensively discuss the significant advancements in this field, providing a summary and analysis of the strategies employed in these studies. The objective is to offer insights into the design of future out-of-equilibrium host-guest systems. Initially, we provide a concise introduction to the general methods used in creating artificial out-of-equilibrium supramolecular systems, with a specific focus on their applicability to host-guest systems. Subsequently, we delve into detailed explanations and discussions of relevant examples from the published literature. Finally, we conclude by examining the possibilities for further improvement and application of these systems in the future, with particular emphasis on developing more life-like features and properties.

General Strategies

In this section, we summarize the strategies of constructing out-of-equilibrium supramolecular systems and implications for application in host-guest assembly.

The design of an out-of-equilibrium system revolves around the incorporation of a chemical reaction involving a reagent (fuel) or light that can elevate non-assembling building blocks to a structure capable of assembly. In 2010, methyl iodide (MeI) was introduced as a chemical fuel to activate the hydrogelator precursor, dibenzoyl-(L)-cystine, resulting in hydrogel formation through esterification.² However, this ester is unstable in water, leading to the hydrogel's collapse after complete consumption of the chemical fuel. The kinetics of activation and deactivation steps can be controlled separately and combined to determine the lifetime and other properties of the out-of-equilibrium state. Also, more recently, temporary pH changes have been used to control transient assembly processes.^{24–27} However, designing a system based on the direct activation of building blocks via chemical reactions requires distinct considerations compared with pH-responsive systems. Therefore, we separate pH changes induced by transient acids/bases as an independent method from other chemical reaction cycles. Alternatively, light can be employed as a driving force for assembly. Light offers complementary advantages to chemical fuels, including diverse activation methods, a wide range of light-sensitive molecules, efficient generation of the activated state, and control over the assembly's lifetime.¹² Other energy sources such as electricity have also been applied to move host-guest systems away from equilibrium.^{28,29} However, we have not included their details in this review, as they are outside the scope of the paper.

Ensuring that the energy-consuming reaction has the capability to modulate host-guest interactions is crucial for the construction of an out-of-equilibrium host-guest assembly. Various factors can influence the affinity between the host and guest, including size and shape, polarity, charge, hydrophobicity, and hydrophilicity. By employing strategies that enable control over these properties using either the guest molecule (Scheme 1a) or host molecule (Scheme 1b), it becomes possible to efficiently switch the state of the host-guest assembly. Additionally, the disassembly of a host-guest complex can be easily accomplished through competitive binding by another guest molecule that exhibits a higher affinity for the host (Scheme 1c).³⁰ Consequently, the structural characteristics of a competitive guest can significantly impact the stability of a host-guest system. In summary, when designing a system, it is essential to consider the three key components: host, guest, and competitive guest, along with their activation/deactivation processes.



Scheme 1 | General reaction cycles of out-of-equilibrium host-guest complexation driven by conversion of energy or fuels. Interaction with the fuel or energy source can change the affinity of the host-guest complex. Depending on the species of guest (a), host (b), or competitive guest (c) interacting with the fuel or energy source, these cycles will have a slightly different layout.

Chemical reaction cycles

As mentioned earlier in the general strategies, the chemical fuel methyl iodide was initially applied in the first synthetic example to drive a supramolecular system far from equilibrium. Subsequently, a more potent methylating agent, dimethylsulfate, was reported to enable faster cycles of the sol-gel-sol transition.³¹ After these pioneering works, more chemical fuels were reported to drive systems far from equilibrium, among which, adenosine triphosphate (ATP)¹⁰ and carbodiimide reagents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)³² are the most widely used. As summarized by Boekhoven and coworkers,¹¹ the minimal requirement of chemical reaction cycles to drive out-of-equilibrium self-assembly is to consist of two chemical reactions, an activation, and a deactivation reaction. The activation reaction has to convert a precursor into a building block, while the deactivation is spontaneous, reverting the product building block to the precursor. The strategies of chemical reaction cycles are also applicable to host-guest systems. So far, ATP³³ and EDC³⁴ have been reported as chemical fuels for driving host-guest assembly far from equilibrium; however, their roles may be quite different compared to those they played in other systems. While chemical fuels can activate either a host or guest directly, they can also activate a competitive guest molecule or even among themselves, act as a transient host, guest, or competitive guest molecule to achieve an out-of-equilibrium assembly.

pH control

Using pH changes to modulate supramolecular forces such as electrostatic attraction/repulsion and hydrophobic interactions through pH-responsive building blocks is a widely employed approach to influence self-assembly. To create an out-of-equilibrium system governed by pH, it is necessary to introduce energy sources capable of

inducing transient pH changes. This can be achieved using various means, including the incorporation of ester derivatives,³⁵ urea/urease,^{36–39} decarboxylating carboxylic acids,²⁶ or a combination of them.^{40,41} Typically, these species are employed in conjunction with another acid/base. Initially, their addition leads to a rapid pH change; subsequently, under specific conditions (e.g., base, enzymes), the decomposition of transient acids/bases gradually reverts the pH to its original value. Alternatively, the use of two temporary species to regulate pH is also feasible, often providing enhanced programmability for the desired pH change.^{40,41} host-guest binding profiles are well known to be modulated by pH as studied in various examples of equilibrium complexation.⁴² In a system with pH mediated by temporary acids/bases, a transient host-guest complex can be achieved when a pH-responsive functional group is incorporated into either the guest or host structures.

Light control

Light, being a clean and widely applied energy source for driving systems operating far from equilibrium, presents several notable advantages. These encompass diminished waste generation when contrasted with chemical fuels, the ability for remote control, convenient operation without externally adding chemicals, and precise control over the lifespan of the system.^{12,43} A requirement for light-driven assembly is the incorporation of a photoswitchable moiety such as azobenzene,^{44,45} spiropyran,^{46,47} dithienylethenes,⁴⁸ viologen, and many others.^{43,49} It is worth noting that, in the case of spiropyran, light has the ability to regulate the environmental pH by releasing a proton during its ring-opening reaction.⁵⁰ This property allows for the modulation of a pH-responsive system using light, as discussed in section “pH Control.” Although photoswitchable molecules are typically used as guest molecules within a photoresponsive host-guest system,⁵¹ they

can also be integrated into macrocyclic structures through deliberate synthesis, resulting in the creation of photo-active host molecules.⁵²

Specific Strategies for Out-of-Equilibrium Host-Guest Systems

This section delves into the detailed discussion of strategies employed to transform host-guest self-assembly into an out-of-equilibrium process, accompanied by relevant examples. These strategies are categorized based on the components by which the fuel-consuming reaction exerts control, namely host molecules, guest molecules, and competitive guest molecules (Scheme 1). This categorization provides an intuitive approach to observing significant changes within a system as it transitions from an equilibrium to a non-equilibrium state. To facilitate a comprehensive understanding of this field, all of these examples are consolidated in Table 1, which is further elaborated upon in the subsequent context.

Control over guest molecules

The structural design of guest molecules offers the most straightforward approach to influencing host-guest binding. This is primarily because a wide range of guest molecules is available, and they typically have more options for chemical modification compared with

macrocycles. Host-guest binding strength can be easily adjusted by activating or deactivating the guest molecules using the methods described in section “General Strategies” (see Scheme 1a).

In 2017, Yan et al.⁵³ observed periodic and self-adaptive pulsating motion in a polymer micellar system controlled by ATP (Figure 1a). They synthesized an amphiphilic block-copolymer composed of a poly(ethylene oxide) (PEO) block and functionalized CD as the host receptor for ATP. This PEO-b-PCD copolymer formed small micellar nanoparticles (16 ± 3 nm). When ATP was added, CD in the micelle core bound with ATP, resulting in increased micellar hydrophobic domains and micellar expansion (55 ± 9 nm). Simultaneously, the phosphatase potato apyrase decomposed the ATP to phosphate (Pi) and adenosine monophosphate (AMP). The formed AMP did not associate with the receptors in the copolymer due to a significantly lower affinity of AMP with the positively charged CD compared with ATP ($K_B = 7.52 \times 10^7 \text{ M}^{-1}$ vs $K_B < 10^2 \text{ M}^{-1}$).⁵⁴ Consequently, the swollen micelles transitioned into a spontaneous shrinking stage, returning to their original state (18 ± 4 nm). This process could be performed iteratively through the continuous supply of ATP for up to five cycles. The frequency and magnitude of pulsation within the micelles could be adjusted by varying the concentration of ATP and the potato apyrase enzyme. Furthermore, this system successfully achieved controlled and periodic release of doxorubicin (Dox).

Table 1 | Summary of Out-of-Equilibrium System Based on Host-Guest Interaction

Strategies	Macrocyclic Host	Effect	Application	Note	References
Guest control	β -CD ^a	Periodic pulsating	Controlled release of Dox		53
	β -CD	Gel-sol-gel	D-glucose sensor		55
	α -CD	Fluorescent changes		pH control	56
	CB[7] ^a	Sol-gel-sol			57
	CB[8]	Sol-gel-sol	Antibacterial agent	Light- driven	58,59
	CB[8]	Morphological and fluorescent changes	Cell imaging	Light- driven	60
Host control	Analogues of crown ethers	Uptake-release			34
	Calix[6]arene	Release-reuptake		pH control	66
	γ -CD	Color and fluorescent changes	Self-erasable writing		17
	α -CD	Sol-gel-sol			63
	γ -CD	Gel-sol-gel	Adaptive adhesive patch		64
Competitive guest control	β -CD ^a	Gel-sol-gel, swelling of microgels			33
	CB[7]	Fluorescent changes	Catalytic control		67
Other	CB[8]	Reversible formation of microcrystals		pH control	68

^a Macrocyclic host molecules are incorporated in polymers.

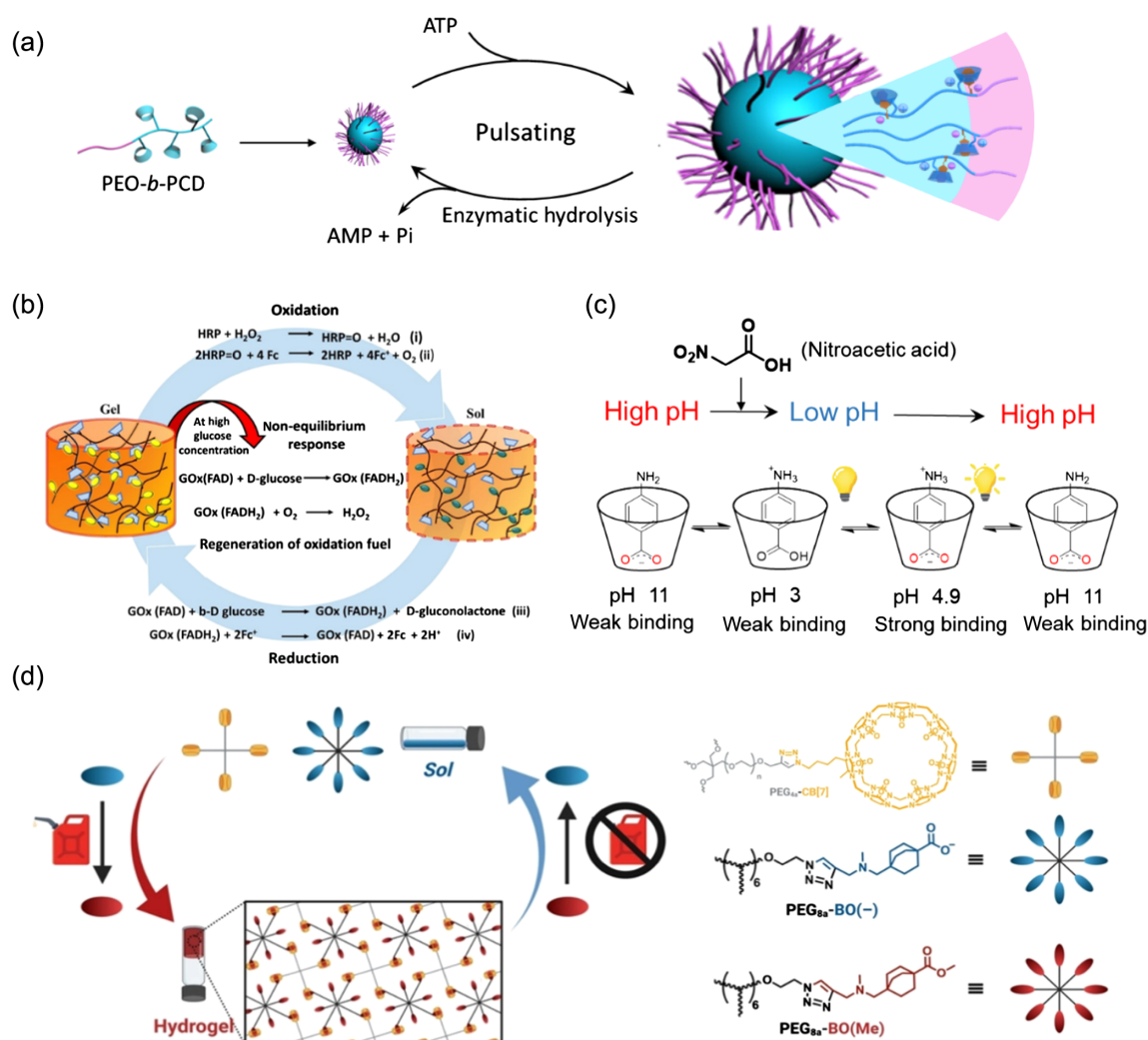


Figure 1 | Examples of transient host-guest complexes by guest control. (a) Illustration of the pulsating polymer micelle in the dissipative self-assembly process. Adapted with permission from ref 53. Copyright 2017 ACS Publications. (b) Fuel-driven and enzyme-regulated redox-responsive supramolecular hydrogels. Adapted with permission from ref 55. Copyright 2021 John Wiley & Sons, Inc. (c) Time-programmable pH by decarboxylation of nitroacetic acid allows time-controlled complexation. Reproduced with permission from ref 56. Copyright 2021 Royal Society of Chemistry. (d) Transient and dissipative host-guest hydrogel driven by the direct reaction of chemical fuel. Adapted with permission from ref 57. Copyright 2023 John Wiley & Sons, Inc.

Essentially, the use of ATP as a guest molecule was incorporated directly into the building blocks, enabling the stabilization of expanded micellar nanoparticles through host-guest interactions.

In 2021, Jain and Ravoo⁵⁵ conducted a study that integrated chemical reaction networks (CRNs) regulated by enzymes and host-guest molecular recognition using β -CD and ferrocene (Fc) as a model system (see Figure 1b). In an aqueous solution, CD exhibited a high affinity for Fc, with a binding constant of $\sim 4800 \text{ M}^{-1}$, while the oxidized form of Fc, ferrocenium ion (Fc⁺), showed no affinity for CD. In the presence of horseradish peroxidase (HRP) and H₂O₂, Fc was oxidized to Fc⁺. Interestingly, in this work, a re-oxidation of Fc was

observed without the addition of further H₂O₂, where only D-glucose additions were required for four additional cycles. The autonomous re-oxidation mechanism involved the regeneration of H₂O₂ from O₂ and GOx[FADH₂], an intermediate product resulting from the reaction between glucose oxidase (GOx) and D-glucose. After studying the redox properties of Fc in the presence of these enzyme couples, the researchers utilized them to prepare responsive supramolecular hydrogels through the host-guest interaction between CD-functionalized polyacrylic acid (pAA) and Fc. The pAA-CD/pAA-Fc hydrogel could be disassembled into a sol by the addition of the oxidation catalyst HRP and H₂O₂ and subsequently reassembled into a gel by the reduction catalyst GOx and

fuel D-glucose. However, the reformed gels were unstable and reverted to a sol state without any additional oxidant. The gel-sol transformation was confirmed by the detection of H_2O_2 reformation from O_2 and GOx[FADH₂] using 2,2'-azino-bis(3-ethylbenzothiazoline)-6-sulfonic acid (ABTS). This work incorporated enzymatic reaction networks to build an out-of-equilibrium system with self-regulating properties. While demonstrated in a host-guest crosslinked hydrogel here, the concept of combining fuel-driven and enzyme-regulated strategy shows great promise for an extension to other synthetic soft materials.

In 2021, Di Stefano et al.⁵⁶ conducted a study on transient pH changes in guest molecules to create an out-of-equilibrium system (see Figure 1c). A time-programmable sequence of pH variations [pH1(high)-pH2(low)-pH3(high)] was achieved by utilizing nitroacetic acid and a basic aqueous solution (NaOH) as a starting point. The addition of nitroacetic acid to the NaOH solution (0.01 M) resulted in rapid pH changes from basic to acidic, followed by decomposition reactions of nitroacetic acid that elevated the pH back to a basic value. The pH jump [pH1(high)-pH2(low)] and the duration for the pH to rise from acidic to basic values [pH2(low)-pH3(high)] could be precisely controlled by adjusting the concentrations of the base and acid. As a proof of concept, this pH-programmable system was applied successfully to a pH-dependent host-guest complex involving α -CD and p-aminobenzoic acid. The extent of host-guest binding was monitored through fluorescence, with higher fluorescence emission indicating stronger binding. Initially, at pH 11, the solution exhibited very low fluorescence emission ($\lambda_{\text{exc}} = 282 \text{ nm}$, $\lambda_{\text{em}} = 338 \text{ nm}$). However, upon the addition of nitroacetic acid, the pH dropped to 3.0, resulting in an immediate and significant enhancement of fluorescence emission. Subsequently, as the acid underwent decarboxylation, the pH started to rise, but the fluorescence emission continued to increase until it reached pH 4.9. At this point, the predominant zwitterionic form of the guest molecule was strongly bound to CD. As the pH continued to rise beyond 4.9, the guest molecule gradually transformed into a negatively charged form, resulting in weaker binding to CD. Consequently, the fluorescence emission started to decrease once again.

In a recent study, Webber and colleagues⁵⁷ reported on host-guest hydrogels regulated by the consumption of chemical fuels using the methylation method introduced in section "Chemical Reaction Cycles" (see Figure 1d). The guest molecule, bicyclo[2.2.2]octane (BO), exhibited a high affinity for the cucurbit[7]uril (CB[7]) macrocycle. However, when a carboxylate group was introduced, its anionic form BO(−) showed poor binding to CB[7]. By tuning the pH to protonate the carboxylate or transiently converting it to its methyl ester through a reaction with chemical fuel, the high affinity of BO for CB[7] was

restored. To construct the host-guest hydrogels, BO(−) units and CB[7] were connected to multi-arm polyethylene glycol (PEG) macromers through click reactions. Under pH 11 conditions, the mixed macromers bearing these host and guest motifs were in a sol state. However, by adjusting the pH to 7, a mechanically robust hydrogel could be formed. The transition from sol to gel state was also achieved by esterifying BO(−) to BO(Me) using dimethyl sulfate (DMS) as a chemical fuel. Then over the course of days, the gel spontaneously returned to its original sol form due to the slow hydrolysis of the ester. Two experimental parameters, fuel dose, and pH, influenced the rate and lifetime of gelation. The dose of DMS fuel primarily controlled gelation through the forward methylation reaction, while the pH level primarily governed the back reaction of ester hydrolysis, leading to gel dissipation once the fuel was consumed. Furthermore, the presence of CB[7] enhanced the stability of BO(Me), slowing down its hydrolysis and prolonging the lifetime of the hydrogel. This work demonstrated the successful application of an existing chemical fuelling system to create a host-guest hydrogel with out-of-equilibrium properties.

In 2019, Zhang and co-workers⁵⁸ reported on out-of-equilibrium host-guest assembly driven by light (Figure 2a). They described the design and behavior of a bifunctional monomer called VDV, containing viologen moieties and a 1,4-diazabi-cyclo[2.2.2]octane (DABCO) linker. In the presence of CB[8] in an aqueous solution, the viologen moieties formed a 1:1 host-guest complex with CB[8], preventing the formation of supramolecular polymers. However, when the VDV-CB[8] system was irradiated with light at 254 nm, a photoinduced electron transfer (PET) occurred, converting the viologens into viologen radical cations ($\text{V}^{+\bullet}$). These radical cations then formed a stable dimer within the CB[8] cavity, converting the 1:1 complexation to a 2:1 complex. This process allowed for the formation of out-of-equilibrium supramolecular polymers. Once the light source was removed, the system returned to equilibrium in the presence of air and a dark environment. The viologen radicals were unstable in the air and get oxidized back to viologen cations by oxygen, which reverted the complexation to 1:1, leading to the disassembly of the supramolecular polymer and the recovery of its original state. This light-powered strategy was not limited to linear supramolecular polymerization but could also be extended to dissipative cross-linked supramolecular polymerization by incorporating methyl viologens into sodium carboxymethylcellulose. Under UV irradiation, this modified polymer could form transient hydrogels through supramolecular cross-links in a far-from-equilibrium state. After the removal of the light source, the hydrogel gradually returned to a solution state in $\sim 9 \text{ h}$. This sol-gel-sol transition could occur at least three times, indicating good reversibility of the dissipative cross-linked supramolecular

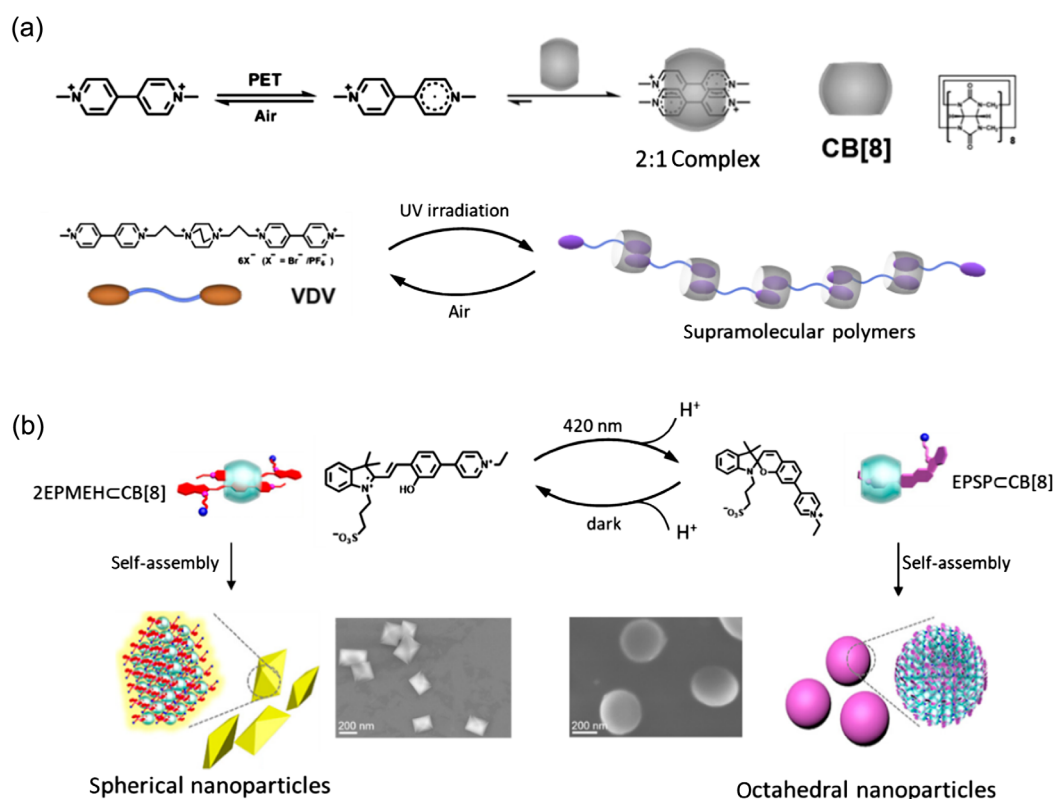


Figure 2 | Examples of out-of-equilibrium host-guest assembly based on guest design driven by light. (a) Dissipative supramolecular polymerization powered by light. Adapted with permission from ref 58. Copyright 2019 Chinese Chemical Society. (b) Light-controlled pseudorotaxane assembly with tuneable fluorescence and deformable nanoparticles. Adapted with permission from ref 60. Copyright 2023 ACS Publications.

polymerization. Furthermore, the system's capabilities were extended to anaerobic bacteria reduction-powered in situ supramolecular polymerization. Additionally, the activated polymer exhibited good near-infrared photo-thermal anti-bacterial properties, showing high bactericidal efficiency (>99.9%) specifically against *Escherichia coli* when subjected to 1064 nm light.⁵⁹

Very recently, Li and co-workers⁶⁰ reported an aqueous light-activated dissipative molecular machine based on a cationic pyridinium-conjugated spiropyran derivative (EPMEH) and CB[8] (Figure 2b). EPMEH was encapsulated inside the CB[8] cavity forming a host-guest complex in a 2:1 stoichiometry. When irradiated with light at a wavelength of 420 nm, 2EPMEH encapsulated by CB[8] (2EPMEH $\subset$ CB[8]) underwent a conversion into a different complex called EPSP $\subset$ CB[8] in a 1:1 stoichiometry. Both EPMEH and its host-guest complexes exhibited luminescence properties. Upon irradiation at 420 nm, the fluorescence intensity of either 2EPMEH or 2EPMEH $\subset$ CB[8] decreased significantly. However, when kept in the dark, the fluorescence spontaneously recovered to its original intensity. This reversible behavior could be repeated for up to 10 cycles, indicating a high degree of reversibility. Furthermore, the 2EPMEH $\subset$ CB[8] complex formed regular octahedral nanoparticles

under irradiation at 420 nm. However, as the complex was converted into EPSP $\subset$ CB[8], the nanoparticles transformed into larger spherical nanoparticles. The morphologies of these nanoparticles also exhibited a high degree of reversibility, as the spherical nanoparticles gradually transformed back into faceted octahedral shapes when kept in the dark. It is worth noting that in the absence of CB[8], neither EPMEH nor EPSP could form large particles. The time-dependent fluorescent host-guest complexation between 2EPMEH and CB[8] has applications in imaging the Golgi apparatus, a cellular organelle. This technique shows promise as an organelle-targeted cell imaging method, utilizing the reversible fluorescence properties of the host-guest complexes.

Control over host molecules

Macrocyclic molecules such as crown ethers, CAs, CBs, PAs, and CDs are generally known for their stability. However, there are methods to synthesize transient host molecules by introducing hydrolyzable groups that can undergo enzymatic reactions or pH-responsive groups into the host structure (Scheme 1b).

In 2017, Kariyawasam and Hartley³⁴ reported the transient formation of host molecules driven by reaction with

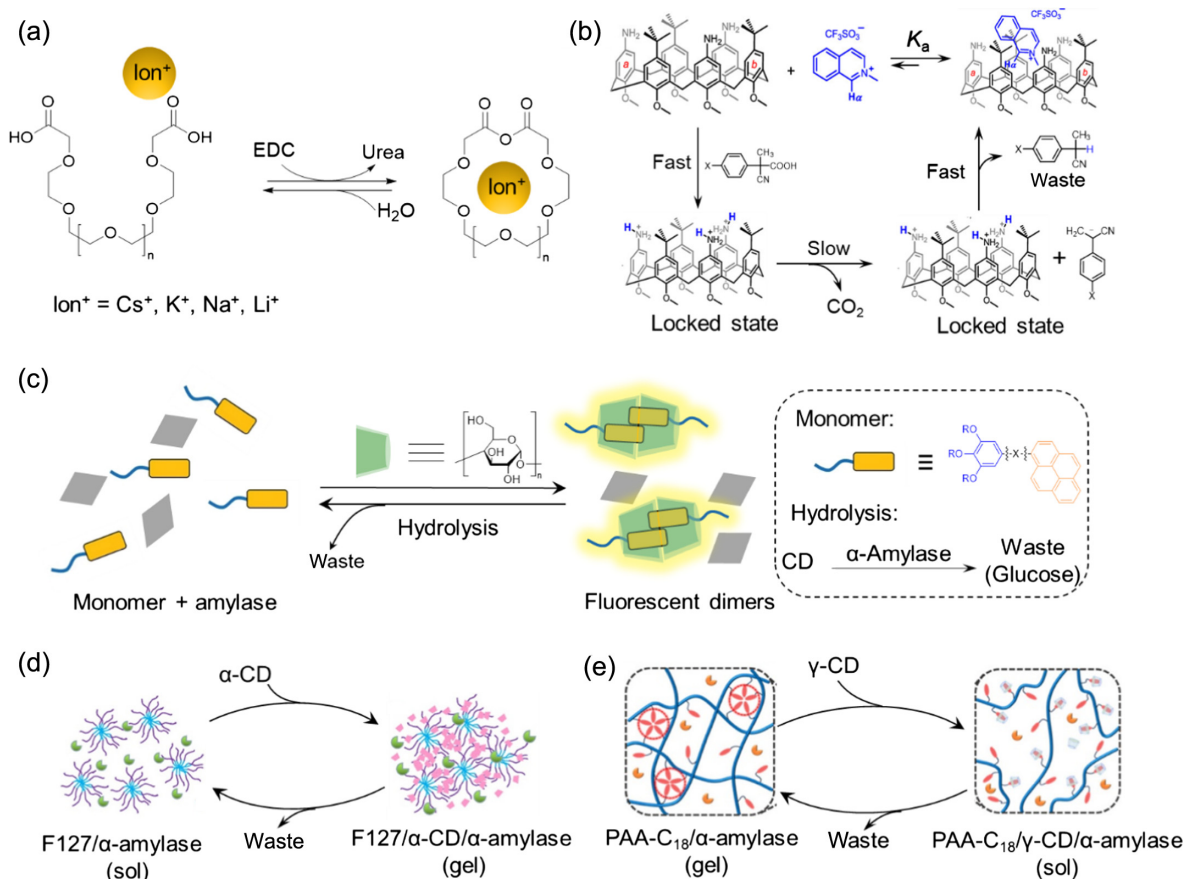


Figure 3 | Examples of transient host-guest complex by control on the host. (a) Formation of macrocyclic anhydrides treated with EDC. Adapted with permission from ref 34. Copyright 2017 ACS Publications. (b) Schematic representing the release-reuptake controlled by programmable pH. Adapted with permission from ref 66. Copyright 2022 ACS Publications. (c) Schematic representation of the transient assembly cycle of color-tunable fluorescence system controlled by γ -CDs. Adapted with permission from ref 17. Copyright 2020 Springer Nature Limited. (d) Schematic representation of transient supramolecular hydrogels-based host-guest interaction with hydrolyzable α -CD. Adapted with permission from ref 63. Copyright 2022 John Wiley & Sons, Inc. (e) Schematic representation of transient gel-sol-gel transition-based host-guest interaction with hydrolyzable γ -CD. Adapted with permission from ref 64. Copyright 2023 ACS Publications.

EDC (Figure 3a). When oligo(ethylene glycol) diacids were subjected to treatment with EDC, this resulted in the formation of hydrolytically unstable cyclic anhydrides. These cyclic anhydrides bore a resemblance to crown ethers like 18-crown-6 or 21-crown-7. When exposed to ions such as Li⁺, Na⁺, K⁺, and Cs⁺, the hydrolysis rate of these cyclic anhydrides decreased, indicating a host-guest binding effect. Interestingly, the presence of ions had an impact on the net yield of anhydride formation in the order of Li⁺ > Na⁺ > Cs⁺ > K⁺. This order is contrary to the well-known cation affinities exhibited by crown ethers. The authors of the study termed this phenomenon “negative templation,” wherein the matched cations hinder the formation of anhydrides. However, the specific molecular-level mechanism underlying this process remains unclear. In another related publication, temporary macrocyclic molecules were also synthesized

through the use of EDC. However, limited exploration of the host-guest interactions associated with these transiently formed macrocycles. Further investigation and research are necessary to gain a deeper understanding of the behavior and mechanisms governing these temporary macrocyclic systems and their host-guest interactions.^{61,62}

Using the hydrolyzable host molecule γ -CD in the presence of α -amylase, in 2020, Tian et al.¹⁷ reported an out-of-equilibrium host-guest assembling system (Figure 3c), resulting in multicolor switchable and transient fluorescence. The system started with pyrene units in an aqueous solution, which acted as guest molecules exhibiting blue fluorescence. Upon the addition of γ -CD, 2:2 host-guest complexes were formed, leading to a redshift in fluorescence and the observation of yellow emission. To hydrolyze γ -CD, the enzyme α -amylase was

introduced, resulting in the disassembly of host-guest complexes and a return to blue fluorescence. This out-of-equilibrium system could be cycled through three iterations. Additionally, using this control over multicolor fluorescence, a self-erasable message was written in a fluorescent gel, allowing for a write-erase process that could be repeated four times. This work took advantage of host-guest assembly to exert control over molecular fluorescence emission and pioneered the use of hydrolyzable host molecules to create out-of-equilibrium systems based on host-guest interactions.

Very similarly, in a recent publication, Wang and co-workers⁶³ presented a work using hydrolyzable host molecules to drive the system to a non-equilibrium state (Figure 3d). In their work, α -CD was used as the host molecule which is hydrolyzable in the presence of α -amylase. In their system, a triblock copolymer Pluronic F127 (PEO₁₀₀PPO₁₀₀PEO₁₀₀) was used as the guest, where the PEO chain can penetrate the cavity of α -CD, forming a host-guest polymeric gel. In the presence of α -amylase, α -CD underwent hydrolysis leading to the collapse of the hydrogel network, with maltose formed as waste. In optimized conditions, the addition of α -CD (80 mg/mL) to F127 (100 mg/mL) containing α -amylase (50 mg/mL) led to the formation of opaque hydrogels in 20 min, which slowly transferred to liquid in 390 min. The process could sustain multiple cycles but with a prolonged gelation lifetime and reduced maximum G' in the latter cycles. Other Pluronic polymers are also able to achieve this gel-sol transition, where higher PEO content leads to longer gel lifetimes.

Using the same strategy, Li et al.⁶⁴ reported a system capable of gel-sol-gel transition behavior (Figure 3e). They applied poly(acrylic acid) grafted with octadecyl chains (PAA-C18) to form a supramolecular hydrogel driven by hydrophobic interactions. With the addition of γ -CD the hydrogel gradually converted to a sol state, through host-guest inclusion. The resulting sol then spontaneously returned to the initial gel state due to the enzymatic hydrolysis of γ -CD catalyzed by α -amylase. The lifetime of the transition cycle could be easily tuned by changing the concentration of γ -CD and α -amylase. Unlike some of the previously reported chemical fuelling systems, the hydrogels in this work exhibited good biocompatibility. Building upon this, a detachable and adaptive adhesive patch was developed. PAA-C18 hydrogels containing α -amylase were converted to solution by adding γ -CD and then coated on the surface of porcine skin. Within ~20 min, the hydrolysis of γ -CD led to a spontaneous sol-gel transition, generating adhesivity that allowed the gauze patch to adhere to porcine skin. Upon adding 1.0 equiv of γ -CD onto the adhesion area, the attached gauze patch could be gently removed within ~2 min. This repeatable adhesive behavior allowed the patch to be reused in a different area if erroneously placed. Although its real-life application in vivo remains

a challenge, this work achieved the adjustment of adhesive properties and extended the applications of out-of-equilibrium materials.

A pH control strategy was also applied to modulate the host molecule structure and build a transient host-guest complex with temporal pH sources. In 2022, Di Stefano et al.⁶⁵ extended their previously developed “locked/unlocked” method on a macrocyclic calix[4]arene scaffold to achieve transient host-guest interactions. Using 2-cyano-2-phenylpropanoic acid as a transient acid to protonate two amino groups on the upper rim of calix[4]arene, a closed pinched cone conformation or “locked” state for calix[4]arene was obtained. Subsequent decarboxylation of the transient acid resulted in deprotonation of the calix[4]arene amino groups and regeneration of the native “unlocked” state. Specifically, in this work (Figure 3b),⁶⁶ guest molecule *N*-methylisoquinolinium with a binding constant K_{ass} of $500 \pm 30 \text{ M}^{-1}$ with calix[6]arene was applied, while the protonated calix[6]arene had no affinity to the positively charged *N*-methylisoquinolinium. By introducing a transient acid to temporally change the pH, release-reuptake of the guest was achieved as indicated by chemical shifts in ¹H NMR. Moreover, the amount of the released guest and the duration of the unloaded state could be controlled by modulation of the quantity of transient acid added.

Control over competitive guest molecules

Host-guest complexes can exhibit selective yet highly dynamic binding interactions. This feature creates an opportunity to introduce a competitive guest molecule that possesses a stronger affinity than the original guest with the host, replacing the initial guest and forming a new host-guest complex. Activating a competitive guest precursor thus enables the formation of out-of-equilibrium host-guest complexes (Scheme 1c).

In 2022, Yan et al. developed an approach for temporal control over the host-guest process, based on their previous work on gel swelling⁵³ induced by ATP (Figure 4a).³³ In this study, macrogels were obtained by combining β -CD (host) and adamantane (guest) functionalized polymers, which were cross-linked through host-guest interactions. The introduction of ATP, which has a higher affinity for β -CD compared to adamantane, acted as a competitive guest and disrupted the supramolecular crosslinks. When ATP was added to the hydrogel preloaded with potato apyrase (an enzyme that catalyzes the hydrolysis of ATP to weakly binding AMP), a gel-sol-gel transition was observed. This cycle could be repeated more than 10 times, indicating minimal impact on the cycle from waste accumulation. Additionally, the researchers extended this approach to fabricate chemo-mechanochromic microgels using spiropyran as a force-responsive crosslink in the polymer. In this case, the addition of ATP caused temporary swelling of the

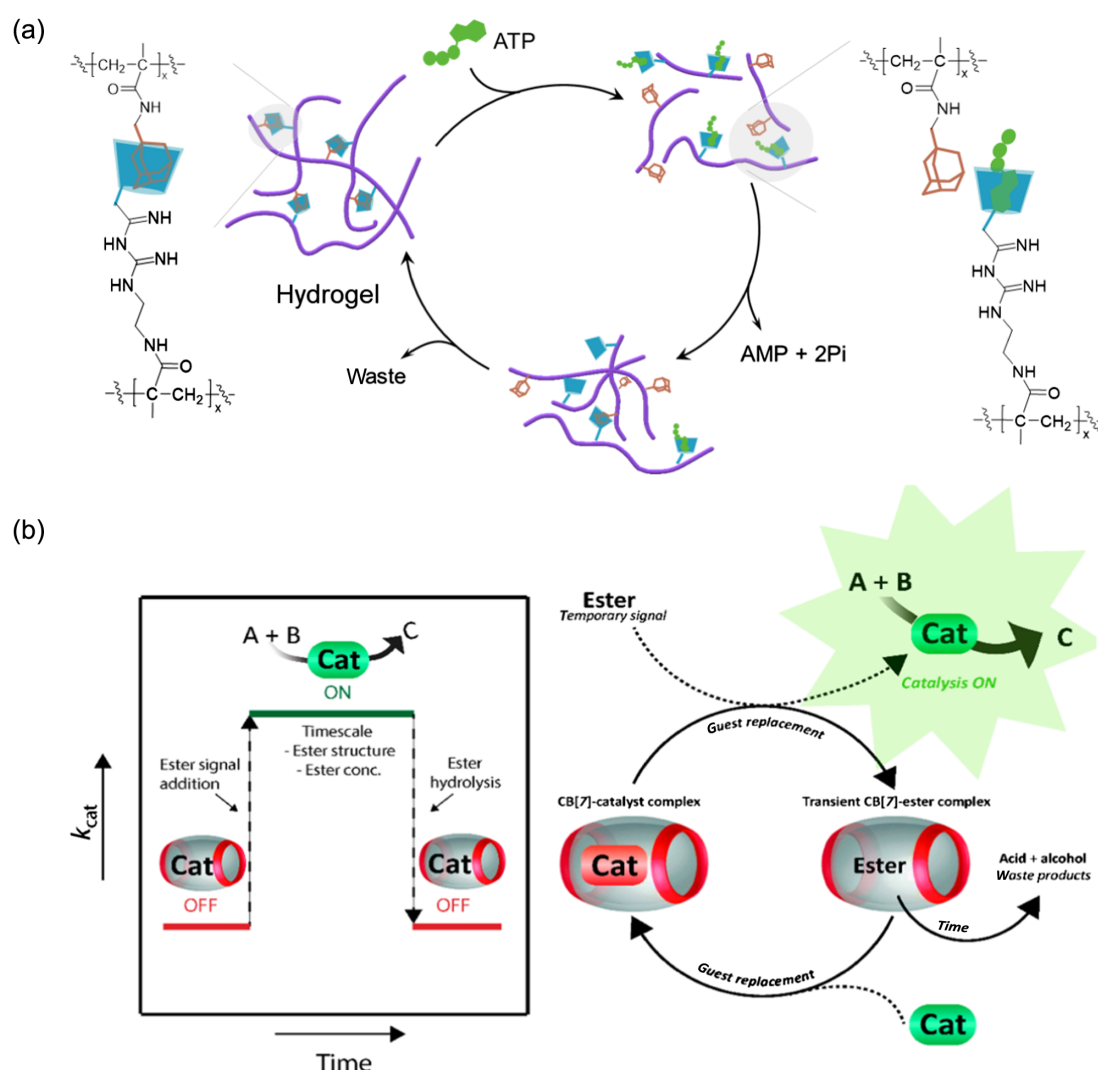


Figure 4 | Examples of transient host-guest complexation by competitive guest control. (a) Schematic representation of dynamic macro/microgels driven by ATP-induced competitive host-guest interaction. Adapted with permission from ref 33. Copyright 2021 Chinese Chemical Society. (b) Transient host-guest complexation to control catalytic activity by temporary signals of hydrolytically unstable esters. Adapted with permission from ref 67. Copyright 2022 ACS Publications.

microgels, exerting strain on the force-responsive cross-links, which triggered a color change due to the force-induced spiropyran-to-merocyanine transition. This work underlines the potential of controlling competitive guest molecules as a means to regulate the properties of host-guest materials under out-of-equilibrium conditions.

In 2022, our group⁶⁷ presented a work based on a previously reported strategy of catalytic control through host-guest chemistry²⁰ (Figure 4b). We incorporated hydrolytically unstable competitive guests to temporarily activate an organocatalyst. Glycine betaine esters bearing a quaternary ammonium moiety strongly bind with CB[7] to form a transient host-guest complex, replacing the originally bound aniline as the catalyst. Upon release, the aniline restores properties such as

fluorescent emission and catalytic activity. These esters, acting as competitive guest molecules, are unstable and undergo hydrolysis in basic conditions (pH 7.5), which leads to guest reuptake. This concept was initially demonstrated in the temporary release and reuptake of a dye and was further applied to modulate the reaction rate of aniline-catalyzed hydrazone formation. The signals from the esters were effectively utilized for in situ catalyst activation and allowed for at least three consecutive cycles of signal-controlled transient catalysis, as demonstrated by multiple signal additions. Furthermore, the experimental data were supported by a kinetic model. This work demonstrates a promising application of catalysis control by constructing an out-of-equilibrium CRN.

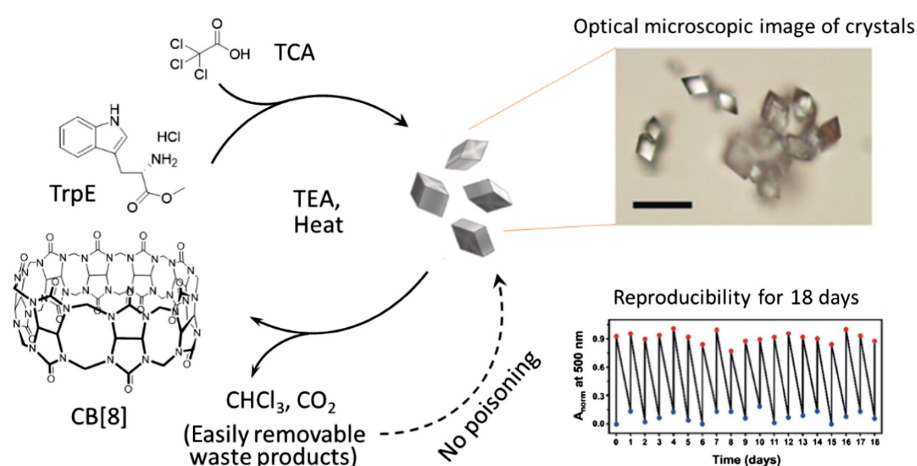


Figure 5 | TCA-driven transient crystallization of TrpE@CB[8] without the accumulation of wastes. Adapted with permission from ref 68. Copyright 2019 John Wiley & Sons, Inc.

Other

Although most of the reported examples can be assigned to one of the three categories, there is one example that falls outside the categories defined above.

In 2019, a transient crystallization of CB[8]-based host-guest complex was reported (Figure 5). Upon addition of trichloroacetic acid (TCA), L-tryptophan methyl ester (TrpE) formed rhombohedral-shaped crystals with CB[8] (TrpE@CB[8]) as indicated from single-crystal X-ray diffraction.⁶⁸ Unlike conventional pH-controlled protonation/deprotonation on specific molecular structures, here the authors found that the extensive hydrogen-bonding network between complexes by the addition of TCA facilitated the formation of TrpE@CB[8] crystals. After that, thermal decarboxylation of TCA by trimethylamine (TEA) and heating at 75 °C for a day resulted in the dissolution of microcrystals. By re-feeding TCA, microcrystals were quickly formed again. In addition, the lifetime of the microcrystals can be tuned by varying the temperature for the decarboxylation or by changing the amount of TCA. They then built an out-of-equilibrium system by adding TCA to a solution of TrpE@CB[8] and TEA under continuous heating to maintain the solution temperature at 75 °C. The durability of the transient crystallization process was tested by consecutive feeding of TCA every 24 h for 18 days. The turbidity of the mixture solution was monitored for these processes, revealing a good reproducibility of the transient crystallization for 18 cycles without significant damping. The remarkable durability comes from the bare accumulation of wastes, since the generated volatile chemical wastes (CO₂ and CHCl₃) are spontaneously removed from the solution.

Conclusion and Outlook

In summary, we have examined representative examples of out-of-equilibrium supramolecular systems based on

host-guest interactions. We discussed general strategies and considerations, along with specific examples in the categories of control over host, guest, and competitive guest molecules. Out-of-equilibrium host-guest systems offer complementary properties to other supramolecular systems, allowing for easy achievement of temporal control over fluorescent emission and catalytic activities. As demonstrated by a variety of examples, designing an out-of-equilibrium system entails selecting appropriate activation/deactivation pathways in relation to the strength of the non-covalent interaction.^{4,11} Moreover, there are some specific features of host-guest chemistry that should be highlighted: (1) careful inspection of all structures involved is necessary to avoid unnecessary binding, which can lead to poor reversibility and system durability, especially when dealing with waste products; (2) bio-catalytic reactions involving enzymes provide unique regulation capabilities, including negative feedback responses, and enable a wider range of possibilities, such as the use of hydrolyzable host molecules; and (3) competitive guest control offers an efficient way to switch between equilibrium and nonequilibrium states, often proving more convenient since it does not require direct chemical conversion of the initial building blocks.

Despite the impressive examples discussed above, it is evident that the field of out-of-equilibrium host-guest assemblies is still in its early stages compared to biological systems. As efforts continue to explore spatio-temporal control of supramolecular structures, several optimizations are necessary to further advance this field. These optimizations include reducing the amount of fuel required while maintaining efficient activation, minimizing the negative impact of accumulative wastes, and developing additional methods to regulate assembly lifetime beyond fuel concentration. One potential approach is to make use of elegant thermodynamic equilibrium self-assembly systems that have already been

developed. For instance, Meijer's group⁶⁹ achieved a photoactivated gel-sol transformation using only 0.6 wt % of a photoresponsive comonomer. Furthermore, there is also a need to expand to real-life applications besides the currently reported functions.⁷⁰ Additional appealing and promising applications could be in energy storage,^{71,72} drug delivery,⁷³ tissue engineering,⁷⁴ and many others which were well-established in conventional supramolecular materials. Additionally, considering the involvement of enzymes, ATP, and other biological species in constructing artificial out-of-equilibrium systems, an exciting direction could be the formation of transient materials in vivo for disease treatment, followed by their spontaneous and programmed degradation. Further efforts in both in- and out-of-equilibrium supramolecular systems are necessary to create artificial life-like materials with sophisticated functions.

Conflict of Interest

There is no conflict of interest to report.

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