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Communication

Active Molecular Gripper as a Macrocycle Synthesizer

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ABSTRACT: A confined space preorganizes substrates, which substantially changes their chemical reactivity and selectivity; however, the performance as a reaction vessel is hampered by insensitivity to environmental changes. Here, we show a dynamic confined space formed by substrate grasping of an amphiphilic host with branched aromatic arms as an active molecular gripper capable of performing substrate grasping, macrocyclization, and product release acting as a macrocycle synthesizer. The confined reaction space is formed by the substrate grasping of the molecular gripper, which is further stabilized by gel formation. Confining a linear substrate in the closed form of the gripper triggers a spontaneous ring-forming reaction to release a macrocycle product by opening. The consecutive open−closed switching enables repetitive tasks to be performed with remarkable working efficiency.

Macrocycle structures with a lack of chain ends exhibit fascinating physical properties including enhanced bioactivity, increased stability, and strengthened intramolecular interactions compared with their linear analogues.[1] The conformational rigidity associated with constraining a linear chain into a macrocyclic topology has a decisive impact on its physical and biological properties.[2] However, their use faces difficulties in the ring closure of linear precursors due to the massive entropic penalty and predominant linear oligomerizations.[3] One strategy to overcome these challenges is the sequestration of a linear precursor into a confined space to hold a folded conformation, while preventing intermolecular oligomerization.[4] Such confined spaces can be formed by self-assembly of rigid aromatic components driven by hydrogen-bonding interactions or metal coordination interactions.[5] These include capsules,[6] cages,[7] and diverse framework structures such as metal−organic frameworks[8] and covalent−organic frameworks.[9] In most cases, the confined structures with internal cavities consist of rigid aromatic building blocks that are essential to support the internal space without collapse.[10] However, their overall performance as a fixed reaction vessel is severely hampered by the insensitivity to substrate changes, diffusion limitations, and product inhibition. Thus, an important goal to address existing challenges in synthetic systems would be the construction of a dynamic reaction space from a single molecular framework that can switch repeatedly between open and closed conformations in response to a substrate conversion.[11] Such a dynamic molecule with conformational switching could bind a substrate by grasping in a closed form through a mutually induced fit that catalyzes a confined reaction to be released by returning to the open conformation. Accordingly, substrate-responsive conformational switching enables the molecule to function as a highly efficient catalytic machine.[12] Although remarkable advances have been made toward molecular machines performing a catalytic action,[13] they are mostly based on open spaces, incapable of constrictive grasping for macrocyclizations. Here, we show a dynamic confined space formed by substrate grasping of a molecular gripper consisting of an amphiphilic aromatic host with conformationally flexible tetrabranched aromatic arms, performing repeated cycles of grasping and ring-forming reactions to release clean macrocycle products, acting as a highly efficient macrocycle synthesizer (Figure 1a).

The construction of synthesizing machines with a confined macrocyclization space requires adaptive molecular grippers that are able to grasp substrates by the formation of a closed container form through conformational switching. Accordingly, we designed and synthesized amphiphilic host molecule **1** as a molecular gripper (Figure 1b), based on branched aromatic arms for grasping molecular objects and hydrophilic oligoether chains for operating in aqueous environments. The pyridine unit embedded inside the aromatic part can function as a base catalyst or provide a potential binding site for metal catalysts for diverse chemical reactions inside the container. The aromatic part features conformationally flexible, tetrabranched arms that enable grasping a hydrophobic substrate through a conformational change into a closed form in aqueous environments, similar to a robotic gripper that manipulates objects in the manufacturing process.[14] The curvature of the aromatic arms imposed by a diazocine unit enables the branched host to form a closed container structure with an internal cavity when they grasp a substrate.[15] Thus, the container structure formed by substrate binding can force a linear substrate to adopt a constrictive folding through mutually induced fit. Macrocyclization can take place under confinement inside of a closed form. The ring closure of the substrate would be followed by substantial reduction in hydrodynamic volume,[16] thereby the loss of stabilizing interactions. Accordingly, the substrate conversion would trigger the closed container form to open

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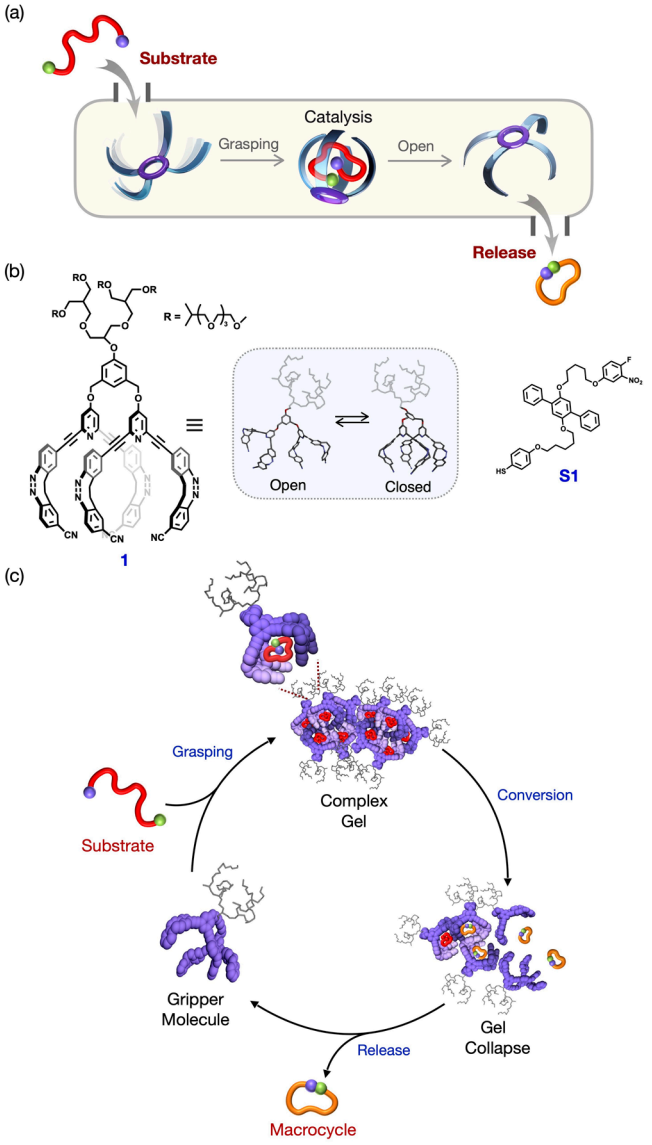

Figure 1. (a) Schematic representation of a molecular gripper performing substrate trapping, catalyzing, and macrocycle product release through open−closed conformational switching. (b) Chemical structure of amphiphilic host **1** and substrate **S1**. (c) Schematic illustration of a repetitive cycle.

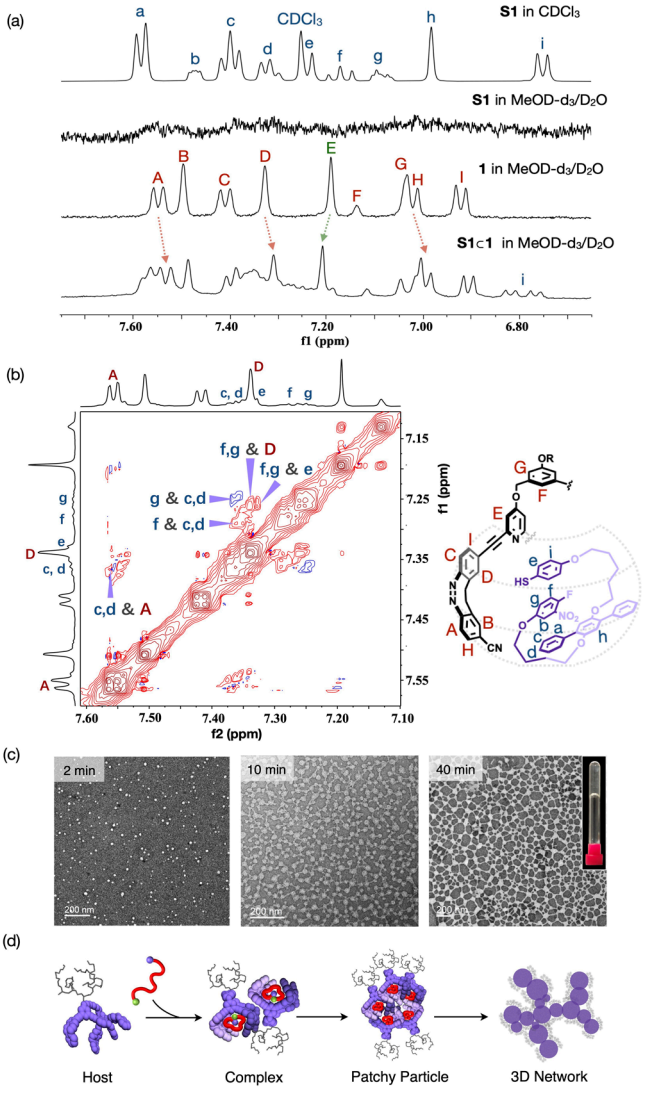

Figure 2. (a) ^{1}H NMR spectra of **S1** in $CDCl_3$, **S1** (2 mM), **1** (2 mM), and **S1⊂1** (2 mM) in a solution of 350 μL of MeOD-d_3 and 150 μL of D_2O. (b) Partial 2-D NOESY spectrum of **S1⊂1**. Chemical structure of the **S1** folded conformation in the cavity of **1** (right). (c) Negative-stain TEM images of **S1⊂1** at different aging times. The inset shows gel formation at 500 μM. (d) Schematic representation of the substrate-induced 3-D network formation.

again with the product release. Thus, reversible open−closed switching of the molecular gripper triggered by a substrate conversion enables the branched host molecule to act as a molecular machine performing repetitive macrocyclizations and release (Figure 1c).

To induce a closed container structure by binding a substrate, we selected **S1** as a linear substrate because its estimated size in a constrictive conformation is compatible with the estimated internal cavity according to molecular models (Figure 1b). **1** shows sufficient solubility for trapping hydrophobic substrates in water containing 30% MeOH in which the substrate is not soluble. Thus, we selected a 30% MeOH aqueous solution as suitable for all of our investigations. When it binds **S1**, the aromatic protons associated with the host appear upfield shifted in ^{1}H NMR spectra (Figure 2a), indicative of the close proximity of the substrate to the aromatic parts of the host.[17] Trapping the substrate in the aromatic cavity of **1** was further confirmed by 2-D NOESY NMR measurements, which show both intermolecular couplings between **1** and **S1** and intramolecular couplings associated with a folded conformation of **S1** (Figure 2b). Indeed, titration experiments using ^{1}H NMR showed a saturation point at 1:1 mol ratio of **1** and **S1** when adding insoluble substrate **S1** into a solution of **1** at a concentration of 2 mM (Figure S15), indicative of a close fit of the substrate with constrictive folding into an internal cavity of **1**. These observations demonstrate the formation of a host−substrate complex through a conformational change of the branched host to a closed container form by surrounding a folded conformation of the linear substrate through aromatic interactions. Subsequently, the amphiphilic container form trapping the substrate undergoes gelation to fix its conformation. The formation of a 3-D network structure upon grasping the substrate was investigated using TEM, which showed small spherical micelles with a diameter of ∼9 nm, corresponding to approximately twice the molecular length of **1** at the initial stage

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(Figure 2c), which was additionally confirmed by dynamic light scattering (DLS) experiments (Figure S18). Subsequently, the substrate-induced micelles grow into larger micelles that form a 3-D network gel. This result indicates that the closed form of the amphiphilic molecular gripper self-assembles into discrete spherical aggregates, which are not fully surrounded by hydrophilic chains (Figure 2d). Subsequently, the spherical micelles with partially exposed hydrophobic surfaces self-assemble to form 3-D network structures, similar to cross-linked colloidal patchy particles.[18] These results demonstrate that the closed form of the molecular gripper trapping a substrate is stabilized by subsequent self-assembly into 3-D network structures, enabling the linear substrate to adopt constrictive folding in each compartmentalized space.

Considering that the end parts of the substrate are functionalized for an S_NAr coupling reaction, confining the substrate inside the internal cavity bearing pyridine units would catalyze confined macrocyclization due to close proximity between pyridine, thiol, and the other chain end, fluorophenyl groups.[19] In ^1H NMR spectra (Figure 2a), indeed, a proton signal associated with the host pyridine (proton E) shows a downfield shift due to hydrogen-bonding interactions between the thiol group of **S1** and the internal pyridine.[20] Notably, the trapped substrate spontaneously undergoes a clean macrocyclization at ambient temperature without using any additional catalysts. Over time at room temperature, an additional peak corresponding to the reaction product was identified in analytical HPLC of which the intensity increases gradually over 6 h at the expense of **S1** (Figure 3a), demonstrating that pure confinement catalyzes a macrocyclization. The macrocyclization under confinement is completed over 6 h with a conversion of ~98%. Indeed, calculations show that confinement significantly stabilizes a Meisenheimer complex, an intermediate formed during the course of an S_NAr reaction,[21] which explains the remarkable catalytic activity of the gripper molecule in a closed form (Figure 3b).

Remarkably, the complex gel gradually collapses as the reaction proceeds spontaneously, accompanied by the release of a macrocycle product (Figure 4a). The gel collapse was confirmed by TEM experiments that showed gradual network scission with time and then complete collapse to restore the molecularly dissolved host solution over 6 h (Figure 4b). After the gel is completely disintegrated, analytical HPLC measurements with the supernatant solution and the precipitate showed only pure host **1** and a macrocycle product, respectively (Figure 4c), indicative of clean product separation by precipitation out of the solution. This result indicates that the substrate conversion leads to gel collapse to restore the open form to release the product to precipitate, which was further confirmed by an increase in fluorescence intensity of **1** with conversion (Figure 4d). Upon addition of the substrate to the host solution, the fluorescence quenching of **1** occurs rapidly at 406 nm.

As the reaction proceeds, the fluorescence is gradually recovered, illustrative of product release from the host by conformational switching into an open form. Consistent with this, an increase in fluorescence intensity correlates well with conversion (Figure 4e), suggesting that the macrocycle product binds to the surrounding wall of the gripper molecule with an affinity much lower than that of the linear substrate. Indeed, calculations show that a structural change of a linear substrate into a cyclic geometry is followed by a decrease in size due to restriction in its conformational flexibility. This leads to an obvious difference in the calculated binding energy between the

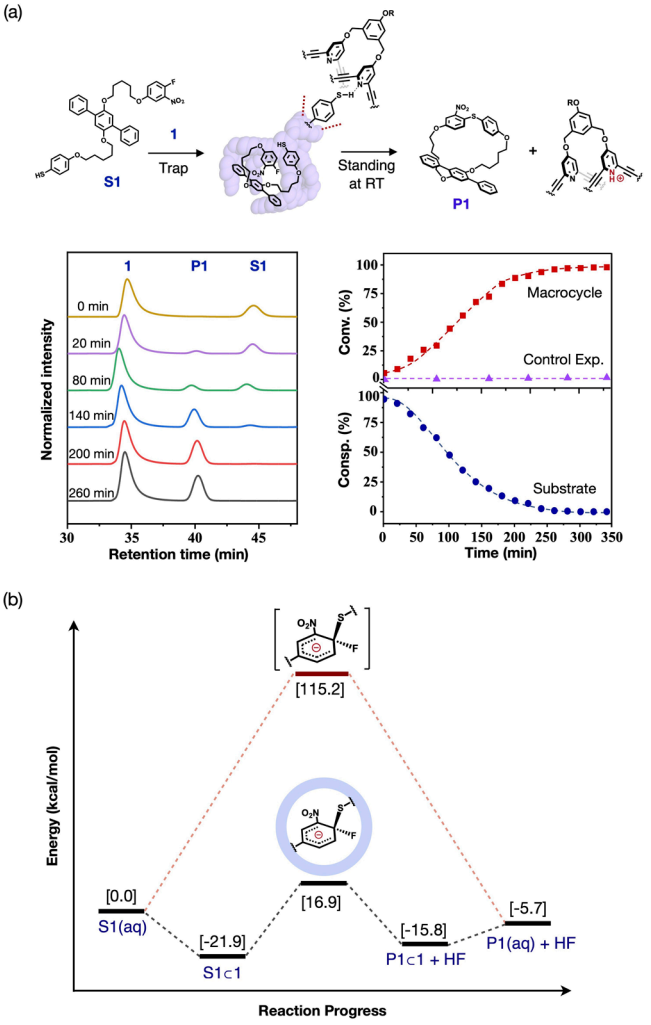

Figure 3. (a) Macrocyclization of **S1** proceeds spontaneously to generate **P1** at ambient conditions, as traced by time-dependent reverse phase HPLC (left). The conversion (red square) and consumption (blue cycle) of **S1** in a confined state in a H_2O−MeOH solution (7:3 v/v) and control experiment in a dissolved state of **1** in acetonitrile (purple triangle) as a function of reaction time (right). (b) Calculated energy profile for the macrocyclization of **S1** with and without **1**.

substrate and the cyclized product in the closed container form (Figure 4f). As a result, the substrate conversion forces the closed form to be open due to an affinity change to spontaneously release the product. In the presence of a nonreactive substrate (**S2**) in this condition (SI Section 2.3), the gel remains stable over at least 1 month, supporting that the confined space is maintained transiently only as long as the substrate is present without chemical conversion. When Suzuki coupling reaction of **S2** occurs by addition of Pd catalysts, the **S2⊂1** network structure is also collapsed with product release (Figures S26−S31).

The regenerated open conformation of the host after neutralization of the protonated host pyridine using K_2CO_3 can carry out a new cycle of grasping a substrate to convert into a macrocycle in a closed state and then release it as a precipitate by switching to an open state (Figure 5a). Indeed, upon subsequent addition of **S1** into the supernatant solution after removal of the precipitated product by decanting, a new cycle of the substrate conversion takes place without compromising the performance in conversion efficiency (Figure 5b and 5c). The subsequent

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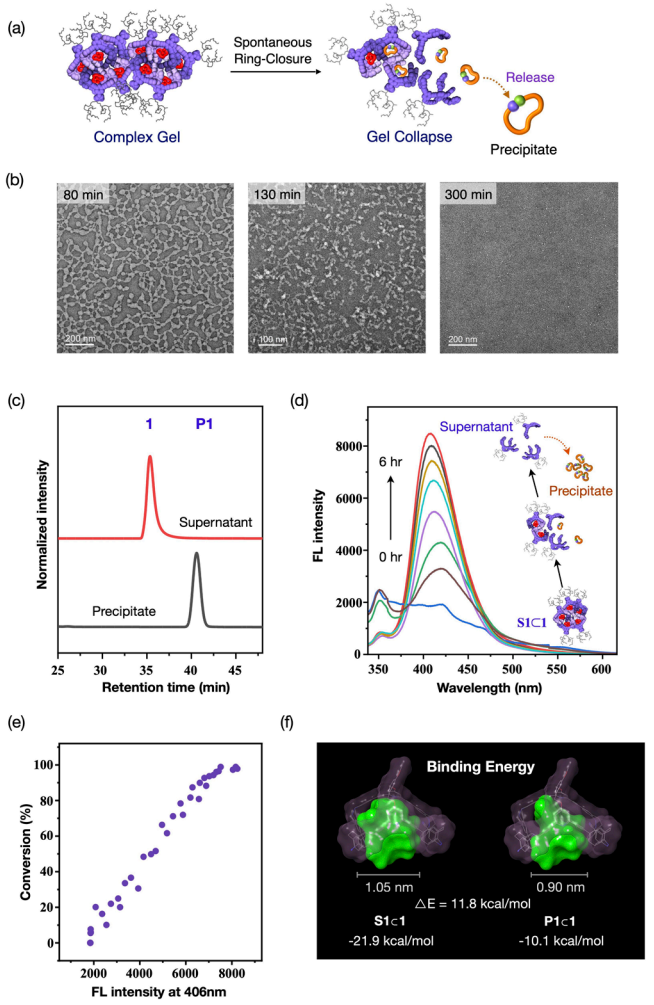

Figure 4. (a) Schematic representation of gel collapse with conversion, followed by spontaneous release of the macrocycle product. (b) Negative-stain TEM images of the reaction solution with time. (c) HPLC traces of the supernatant (red curve) and precipitate (gray curve) from the solution in 6 h after centrifuging. (d) Fluorescence spectra of the reaction solution from 0 to 6 h (time interval: 1 h; excitation wavelength: 318 nm). (e) Plot of substrate conversion and fluorescence intensity of **1** at 406 nm as the reaction proceeds under confinement. (f) DFT-computed binding energy difference between **S1⊂1** and **P1⊂1**.

cycles showed that the gripper molecule repeatedly performs nearly full conversion and complete release without noticeable fatigue over at least 5 cycles. These experiments demonstrate that the branched aromatic arms as a molecular gripper undergo open−closed switching consecutively to produce a macrocycle product as a precipitate by consuming a linear substrate without the help of any additional energy sources.

In summary, the combination of dynamic open−closed switching and robust confinement, as illustrated here, enables the gripper molecule to act as a highly efficient macrocycle synthesizer, performing repetitive cycles of substrate conversion by grasping and macrocycle product release by opening. The open−closed switching of the molecular gripper operated by substrate conversion allows a repetitive task without recourse to additional energy sources. We anticipate that our approach can provide access to a future catalytic robot performing the synthesis of highly complex macrocycles with precise stereo-

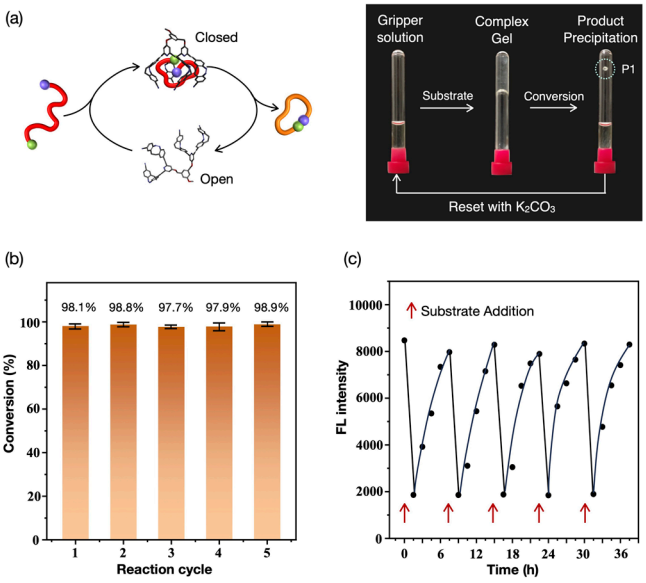

Figure 5. (a) Schematic representation of open−closed conformational switching of **1** triggered by substrate conversion (left). Upon substrate binding, **1** self-assembles into a gel structure, which facilitates macrocyclization and releases the product as a precipitate (right). (b) Conversions of ∼98% over five reaction cycles. (c) Time-dependent fluorescence intensity of **1** at 406 nm with five repetitive additions of substrate **S1** with a mole ratio of 1:1 (excitation wavelength: 318 nm).

control in applications ranging from synthetic chemistry to nanotechnology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c10029.

Experimental procedures, synthesis of molecules, NMR data, ESI-TOF MS data, TEM images, and spectroscopy data (PDF)

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Notes

The authors declare no competing financial interest.

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