Morphology Transformation

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Reversible Morphological Transformation between Polymer Nanocapsules and Thin Films through Dynamic Covalent Self-Assembly**

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Abstract: *A facile method has been developed for synthesizing polymer nanocapsules and thin films using multiple in-plane stitching of monomers by the formation of reversible disulfide linkages. Owing to the reversibility of the disulfide linkages, the nanostructured materials readily transform their structures in response to environmental changes at room temperature. For example, in reducing environments, the polymer nanocapsules release loaded cargo molecules. Moreover, reversible morphological transformations between these structures can be achieved by simple solvent exchanges. This work is a novel approach for the formation of robust nano/microstructured materials that dynamically respond to environmental stimuli.*

In biological systems, morphological transformations of nano/microstructures in response to environmental stimuli are integral to many of the processes necessary for life, including allosteric conformational changes of enzymes,[1a,b] pseudopodium formation during chemotaxis,[1c,d] and the formation and fusion of various vesicles during a variety of cell growth and signaling events.[1e,f] Synthetic nanostructures that can similarly undergo morphological transitions in response to physical and chemical stimuli have attracted a great deal of attention, particularly for the development of smart functional materials.[2] Labile, reversible, and hence adaptable behaviors of supramolecular assemblies formed by non-covalent interactions/bonds enable us to manipulate the morphology of discrete nanostructured assemblies from one to another utilizing stimuli such as pH,[3a,b] temperature,[3c] light,[3d] small molecules or ions,[3e,f] and enzymes.[3g–i] However, these supramolecular assemblies are typically not robust, making them difficult to isolate and use for further downstream applications. Recent advances in dynamic covalent chemistry, which combine error-correcting and proofreading characteristics of supramolecular chemistry with the robustness of covalent bonding,[4] allow the synthesis of a wide variety of nanostructures, including macrocyclic,[5] capsular,[6] and other topologically non-trivial structures[7] at a more robust level. However, the majority of studies using dynamic covalent chemistry have to date focused on the construction of nanostructures. To the best of our knowledge, reversible morphological transformations of these nanostructures through reversible covalent bond formation/breakage have yet to be demonstrated.

Recently, we reported the direct synthesis of robust nano/microstructures composed of several thousand of molecules or more, including polymer nanocapsules,[8a–d] single-monomer-thick two-dimensional (2D) polymer sheets,[8e] and hollow toroidal microrings,[8f] by irreversible covalent cross-linking of flat building blocks having laterally predisposed reactive groups.[8] By carefully choosing building blocks, linkers, solvents, and temperature, we could control the size, shape, and properties of resulting nano/microstructures. We thus anticipated that reversible covalent cross-linking of such building blocks may result in dynamic versions of similar nano/microstructures, the size and shape of which can be readily tuned in response to environmental changes. We decided to construct these nano/microstructures using reversible disulfide linkages, which play an important role in many biological systems[9] and the construction of complex molecular architectures.[7,10] Herein, we report the synthesis of polymer nanocapsules and 2D polymer sheets formed by multiple in-plane cross-linking of monomers through disulfide formation (Scheme 1). Owing to the reversibility of the disulfide linkages, the nanostructured materials readily change their structures in response to environmental changes at room temperature. Most importantly, reversible morphological transformations between the polymer nanocapsules and 2D polymer films could be achieved by simple solvent exchanges (Scheme 1). To the best of our knowledge, this is the first example of a reversible morphological transformation of nano/microstructures at a macroscopic level through reversible covalent bond formation/breakage.

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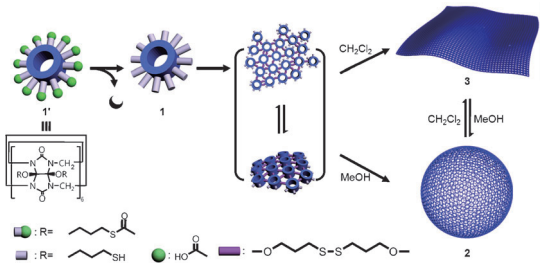

Scheme 1. Formation of 2D polymer film **3** and polymer nanocapsule **2** through reversible disulfide bond formation and reversible morphological transformation between them.

The synthesis of hollow polymer nanocapsule **2** was achieved by the formation of reversible disulfide bonds between mercaptopropylcucurbit[6]uril (**1**), a disk-shaped macrocycle with twelve mercaptopropyl groups laterally predisposed around the rigid cucurbit[6]uril (CB[6]) core,[11] without any templates or pre-organization of the monomers (Scheme 1). In a typical experiment, in situ generation of **1** by the hydrolysis of thioacetate-functionalized CB[6] (**1′**) in methanol at room temperature by addition of aqueous sodium hydroxide solution, and stirring the solution for 3 h followed by dialysis produced polymer nanocapsule **2** in 78% yield of isolated product (Supporting Information, Figure S1). A combination of scanning electron microscopy (SEM), transmission electron microscopy (TEM), and light-scattering studies confirmed the formation of hollow nanospheres with an average diameter of 150 ± 50 nm and average shell thickness of 1.3 ± 0.2 nm (Figure 1; Supporting Information, Figure S2). Considering the height (ca. 1 nm) of a CB[6] molecule, the nanocapsule shell is almost single-monomer-thick.

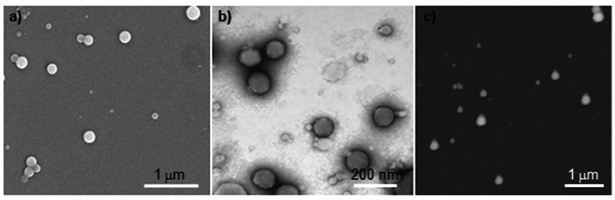

Figure 1. Microscopic images of hollow nanocapsules **2**. a) SEM image, b) TEM image, c) AFM image.

The shell of polymer nanocapsule **2** was composed of a 2D polymer network formed by multiple in-plane cross-linking of monomer **1** through intermolecular disulfide bonds between its mercaptopropyl moieties (Scheme 1). X-ray photoelectron spectroscopy (XPS) studies showed two major peaks with a ratio of approximately 3:1 at 165.4 eV and 164.2 eV corresponding to S–S bonds and free thiol groups, respectively (Supporting Information, Figure S3),[12] which confirms the formation of disulfide linkages between the monomers, and that about five of the twelve mercaptopropyl moieties of **1** do not participate in the formation of disulfide linkages and remain as free thiol. The presence of disulfide bonds is also evident from the disassembly of **2** upon treatment with tris(2-carboxyethyl)phosphine hydrochloride (TCEP), a thiol-free reducing agent for cleaving disulfide bonds,[13a,b] which could be confirmed by dynamic light-scattering (DLS) and SEM (Supporting Information, Figure S4).

To understand the formation mechanism of the polymer nanocapsule, we monitored the self-assembly process by DLS studies, which revealed that after an induction period (80 min), the average size of the product suddenly increased and quickly reached 150 nm in 3 h and remained essentially the same afterward (Supporting Information, Figure S5). The overall reaction profile is similar to that of the polymer nanocapsule produced by irreversible covalent bond formation,[8a–d] suggesting that the present polymer nanocapsule **2** is also formed by a similar mechanism: **1** generated by slow hydrolysis of its precursor **1′**, reacts with each other to form 2D oligomeric patches by multiple in-plane stitching of the monomer through disulfide bond formation; the 2D patches with a certain size become curved and further react each other to form a hollow sphere (see Figure 4 of Ref. [8b]).

Large guest molecules can be entrapped inside the hollow polymer nanocapsules by performing the nanocapsule formation reaction in the presence of the guest molecules. For example, in situ generation of **1** in methanol in the presence of carboxyfluorescein (CF) molecules and incubation of the mixture with stirring for 3 h followed by dialysis produced a polymer nanocapsule encapsulating CF (CF@**2**) with an average diameter of 240 ± 50 nm, as evidenced by DLS, SEM, and confocal laser scanning microscopy studies (Supporting Information, Figure S6). The encapsulated CF molecule was released by treating CF@**2** with dithiothreitol,[13c] a common reducing agent used for the cleavage of disulfide bonds (Supporting Information, Figure S7), which suggests that the hollow polymer nanocapsule **2** may be useful as a stimuli-responsive delivery vehicle.

Our previous studies on self-assembly through irreversible covalent bond formation demonstrated that either polymer nanocapsules or free-standing 2D polymer films can be exclusively synthesized by carefully choosing the reaction medium: in general, poor solvents drive the system towards polymer nanocapsule formation, whereas good solvents promote the formation of 2D films.[8] In the present work, similarly, use of good solvents for self-assembly such as dichloromethane and chloroform led to the formation of thin films **3** in 75% yield of isolated product, which was confirmed by various microscopic techniques (Figure 2; Supporting Information, Figure S8). SEM and TEM analysis revealed the formation of thin films **3** with lateral dimensions ranging

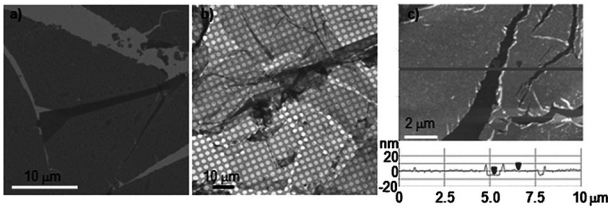

Figure 2. Microscopic images of polymer thin film **3**. a) SEM image, b) TEM image, and c) AFM image and height profile of **3** along the line in (c).

from submicrometer to several tens of micrometers. Section analysis of the AFM image of **3** revealed that its thickness is around 4 nm. Similar to the case of hollow nanocapsule **2**, the presence of reversible disulfide linkages and free thiols in **3** was confirmed by XPS analysis (Supporting Information, Figure S3) as well as disassembly of **3** upon treatment with TCEP, which was monitored by DLS and SEM (Supporting Information, Figure S9).

As described above, the reaction medium or solvent is one of the most important shape-determining factors in our self-assembly systems.[8] We thus reasoned that a simple exchange of solvent from one to another might induce a reversible shape transformation between the hollow nanocapsule **2** and thin film **3**. To test this idea, we dialyzed **2** dispersed in methanol against dichloromethane using a dialysis membrane having a molecular weight cut-off (MWCO) of 1000. The simple solvent exchange resulted in dramatic morphological evolution from a nanosphere to thin film. DLS studies showed that the hollow nanocapsules with an average diameter of 150 nm completely disappeared, and at the same time several tens of micrometer-sized objects newly appeared (Supporting Information, Figure S10), which were revealed to be thin films by SEM and TEM studies (Figure 3).

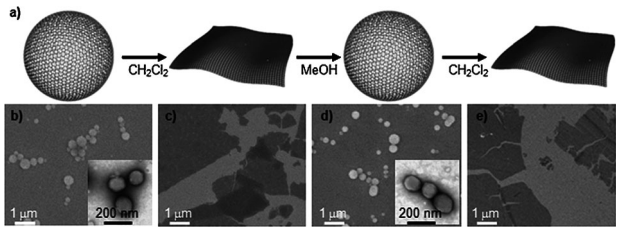

Figure 3. a) Representation of reversible morphological transformation between polymer nanocapsules and thin films by solvent exchanges. b) SEM images of as-synthesized polymer nanocapsules, c) thin films after first solvent exchange to dichloromethane, d) polymer nanocapsules after second solvent exchange to methanol, and e) thin films after third solvent exchange to dichloromethane. Insets: TEM images of polymer nanocapsules showing the hollow interior of them.

The opposite morphological transformation from thin film to nanosphere was also demonstrated in a similar way. DLS, SEM, and TEM studies confirmed the complete disappearance of the thin film and concurrent formation of nanosphere when the thin film dispersed in dichloromethane was dialyzed against methanol (Figure 3). Furthermore, the reversible morphological transformation between the nanocapsule and thin film can be repeated for at least four cycles in a series of dialyses alternately using methanol and dichloromethane, although the size of the resulting nanosphere and thin film changed slightly after each cycle. To the best of our knowledge, this is the first example of a reversible morphological transformation between one discrete nanostructure to another achieved through the reversible formation and breakage of disulfide bonds.

To understand the mechanism of the solvent-triggered morphological transformation between the nanocapsule and thin film, we decided to monitor the reversible shape transformation processes by DLS, SEM, and AFM. However, the size and shape of the polymers changed so quickly under the solvent exchange conditions described above that it was extremely difficult to trace any intermediates and hence the detailed mechanism of the shape evolution. To slow down the process, the solvent exchange was performed by dialysis against a mixture of methanol and dichloromethane. We first dialyzed polymer nanocapsule **2** (dispersed in methanol) against a 6:4 (*v*/*v*) mixture of methanol and dichloromethane and monitored the size change of the polymer by DLS, which revealed that the average size of the polymer gradually increased and eventually reached almost 10 μm after 3 h. Similarly, slow conversion of thin film **3** into nanocapsule **2** was achieved by dialyzing **3** (dispersed in dichloromethane) against a 7:3 (*v*/*v*) mixture of methanol and dichloromethane for 5 h. The process was monitored by DLS, which showed that the average size of the polymer gradually decreased and finally became approximately 150 nm (Figure 4), which is almost comparable to that of the original polymer nanocapsule **2** directly synthesized from **1** in methanol.

Furthermore, SEM studies (Figure 4) also showed that during dialysis of polymer nanocapsule **2** against a 6:4 mixture of methanol and dichloromethane, the nanospheres first formed aggregates (30 min) and subsequently transformed themselves into films with an uneven surface, which finally turned into smooth thin films. Likewise, when thin film **3** was dialyzed against a 7:3 mixture of methanol and dichloromethane, the smooth thin films become rough (60 min), and then disassembled into aggregated particles that eventually turned into separate spherical particles (Figure 4). Similar morphological changes were also observed by AFM studies (Supporting Information, Figures S11 and S12).

Interestingly, we found that the morphological transformation from nanocapsule to thin film could be prevented under slightly acidic conditions, which is known to slow down the thiol–disulfide exchange (Supporting Information, Figure S13).[14] This result suggests that the thiol–disulfide exchange plays a crucial role in the morphological transformation. Furthermore, we found that although the spherical morphology was established by solvent exchange of **3** in the presence of CF only after 2 h, a significant amount of the CF inside the resulting nanocapsule leached out. However, the release of the encapsulated CF became negligible when the solvent exchange was extended to a total of 4 h or more (Supporting Information, Figure S14). These results suggest that although the spherical morphology can be established within 2 h, some imperfect sites exist, through which the encapsulated CF can leach out. These sites are eventually sealed off, presumably through the reorganization of the monomers incorporated in the nanocapsule by dynamic thiol–disulfide exchange reactions.

As our system involves a huge number of monomers each having twelve reactive sites, it is not an easy task to elucidate the molecular level mechanism of the reversible morphological transformation. Nevertheless, on the basis of the above observations and general features of the thiol–disulfide exchange,[14] we propose a plausible mechanism for the morphological transformation. Upon the hydrolysis of thioacetate groups of **1′**, the monomers **1** start to polymerize through the formation of intermolecular disulfide bonds, and

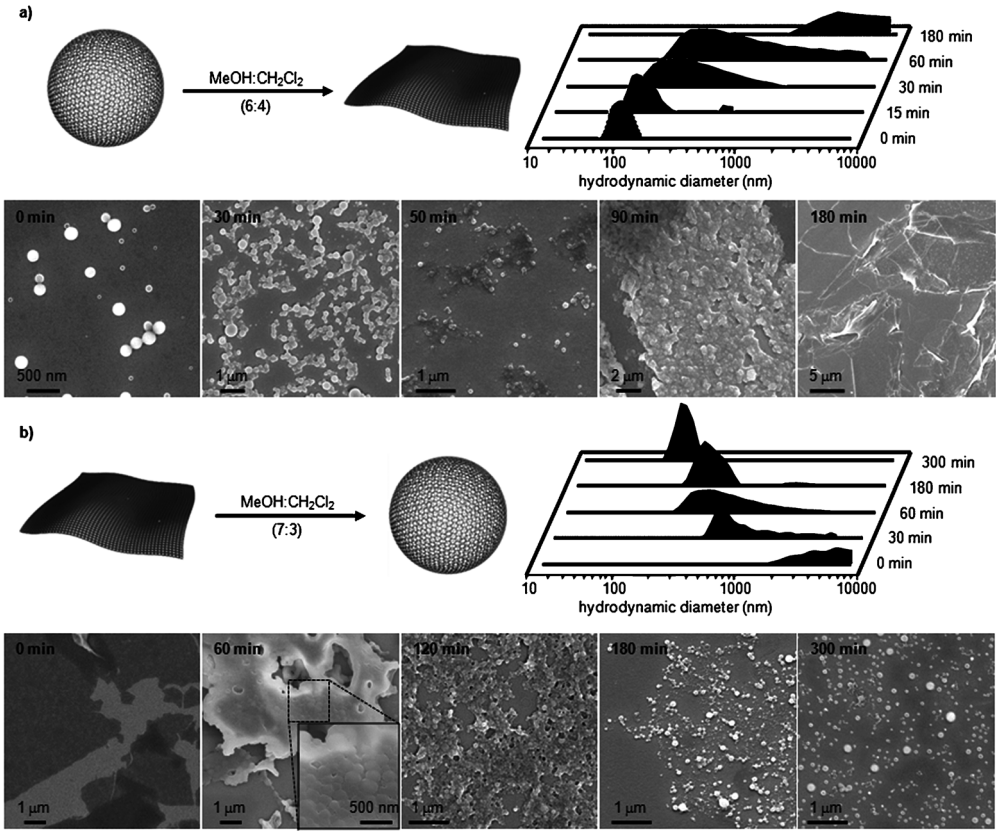

Figure 4. Monitoring the morphological transformation between polymer nanocapsules and thin films by DLS and SEM studies.

eventually grow into the hollow nanocapsules **2** in methanol or 2D films **3** in dichloromethane, which is presumably due to different chain conformations and surface curvatures of the polymers in different solvents.[8,15] During the formation of **2** or **3**, the remaining free thiols of **1** can react with the nearest disulfide linkage through thiol–disulfide exchange, which may cause perturbations in the local arrangement of the monomers involved therein, and subsequently induce the subtle reorganization of the entire monomers incorporated in the polymer. In a given solvent, this reorganization of the monomers caused by the thiol–disulfide exchange may drive the polymer towards a specific morphology with fewer defect sites. When the solvent is replaced with another, the interfacial tension between the surface of the polymer and surrounding solvent may change, which presumably alters the surface curvature of the polymer and subsequently induces structural deformation of the polymer (Supporting Information, Figure S15). The reorganization of the monomers now may allow the system to alter its morphology into a new one that is more preferred in the new solvent allowing the system to adapt to environmental changes.

In summary, we have successfully demonstrated the facile synthesis of hollow polymer nanocapsules and thin films by multiple in-plane cross-linking of monomers through disulfide bonds. Moreover, we demonstrate reversible morphological transformations between these structures using simple solvent exchanges. This novel property combined with the unique host–guest chemistry of CB[6] may be useful for the design of stimuli-responsive smart materials with applications in many diverse areas such as biomedical engineering, sensing, and separation. In particular, we note that the reversible nature of disulfide linkages enables us to release cargo molecules from the polymer nanocapsules by treating with a reducing agent. Given that aberrant changes in cellular redox potentials is associated with a variety of diseases,[16] such polymer nanocapsules may be useful as a stimuli-responsive drug delivery vehicle. Furthermore, our work provides a simple model system for studying fundamental principles underlying morphological transformations of nanostructures which could inform how more complex transitions such as those observed in biological systems could be implemented in synthetic complex adaptive systems.

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