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In-situ synthesis of a supramolecular hydrogelator at an oil/water interface for stabilization and stimuli-induced fusion of microdroplets

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Abstract: Supramolecular hydrogels are expected to have applications as novel soft materials in various fields owing to their designable functional properties. Here we developed an *in-situ* synthesis of supramolecular hydrogelators, which can trigger gelation of an aqueous solution without the need for temperature change. This was achieved by mixing two precursors, which induced the synthesis of a supramolecular gelator and its instantaneous self-assembly into nanofibers. We then performed the *in-situ* synthesis of this supramolecular gelator at an oil/water interface to produce nanofibers that covered the surfaces of the oil droplets (nanofiber-stabilized oil droplets). External stimuli induced fusion of the droplets owing to disassembly of the gelator molecules. Finally, we demonstrated that this stimuli-induced droplet fusion triggered a synthetic reaction within the droplets. This means that the confined nanofiber-stabilized droplets can be utilized as stimuli-responsive microreactors.

A supramolecular approach that uses molecular self-assembly has, over the last two decades, emerged as a tool for the preparation of a variety of functional materials and the creation of novel functional properties in the fields of materials engineering, biotechnology and medical science.[1] In particular, the self-assembly of synthetic molecules plays an expanding role in the development of novel functional and intelligent soft materials.[2] Supramolecular hydrogels, especially those composed of low-molecular-weight gelators, have attracted considerable attention as novel functional soft materials as a result of their distinctive characteristics. These hydrogels are thermoreversible, their molecular structures can be designed for a specific purpose and easily fine-tuned, and they are rapidly and selectively responsive to external stimuli. As a result, a considerable number of studies have reported novel supramolecular hydrogels with fascinating functional properties.[3]

One of the representative supramolecular hydrogelators has a surfactant-like structure, composed of both hydrophobic and hydrophilic moieties.[4] Ulijn and coworkers made use of the interfacial activity of such surfactant-like hydrogelators to assemble hydrogelator nanofibers at an oil/water interface and succeeded in the stabilization of oil-in-water (O/W) emulsions.[5] Stupp and coworkers reported the successful preparation of sacs and microcapsules covered with self-assembled peptide amphiphiles through electrostatic interactions between cationic peptide amphiphiles and polyanions.[6] There are also several reports on the interfacial assemblies of supramolecular gelators to stabilize liquid droplets.[7] These studies clearly demonstrate the spatially-controllable self-assembly of gelator molecules.

Emulsions have been widely studied and are used in the fields of food, medicine, cosmetics and organic synthesis for the encapsulation of substances, synthesis and the separation of materials. As reported by Ulijn et al., the self-assembly of gelator molecules has the potential to stabilize emulsions and endow them with stimuli-responsive properties. However, supramolecular gels are often prepared by heating and subsequently cooling a gelator solution. These temperature fluctuations will thermodynamically alter the emulsion conditions and may impair encapsulated thermo-unstable substances. The *in-situ* synthesis of a supramolecular hydrogelator in an emulsion is a rational approach to overcoming this problem and avoiding temperature fluctuation during hydrogel preparation.[8] Additionally, to cover the surfaces of oil droplets in an emulsion with a supramolecular hydrogel, self-assembly of the gelator molecules should occur selectively at the oil/water interface. To this end, we propose the *in-situ* synthesis of a supramolecular hydrogelator in an O/W emulsion. On synthesis of the hydrogelator, its self-assembly is induced immediately at the oil/water interface, and this stabilizes the O/W emulsion. The gelator molecules can be designed to be responsive to external stimuli (pH and heat); this enables the stimuli-responsive fusion of oil microdroplets, which can trigger chemical reactions in the confined microspaces. To our knowledge, this is the first report of an *in-situ* synthesis of a supramolecular gelator at an oil/water interface that can be used to stabilize emulsions and enable stimuli-triggered chemical reactions within the oil microdroplets.

On the basis of our previous study,[9] we designed a supramolecular gelator based on water-soluble NH_2-lauroyl-GGGH (precursor A, Fig. 1a). This precursor can form a Schiff base on reaction with hydrophobic 1,4-phthalaldehyde (precursor B). Precursor A was synthesized using standard Fmoc solid-phase synthesis. We then simply mixed precursors A and B (the molar ratio of A/B was 2 and the sum of the concentrations of A and B was 1 wt%) in a homogeneous aqueous solution of phosphate buffer (50 mM, pH 7.4) to produce supramolecular gelator ABA *in-situ* (Fig. 1a). After 15 min, the solution changed to a transparent hydrogel, the hydrogel turned slightly opaque and it became cloudy after 2 h (Fig. 1b). To confirm the synthesis of the supramolecular gelator, we analyzed the obtained hydrogel using matrix-assisted laser

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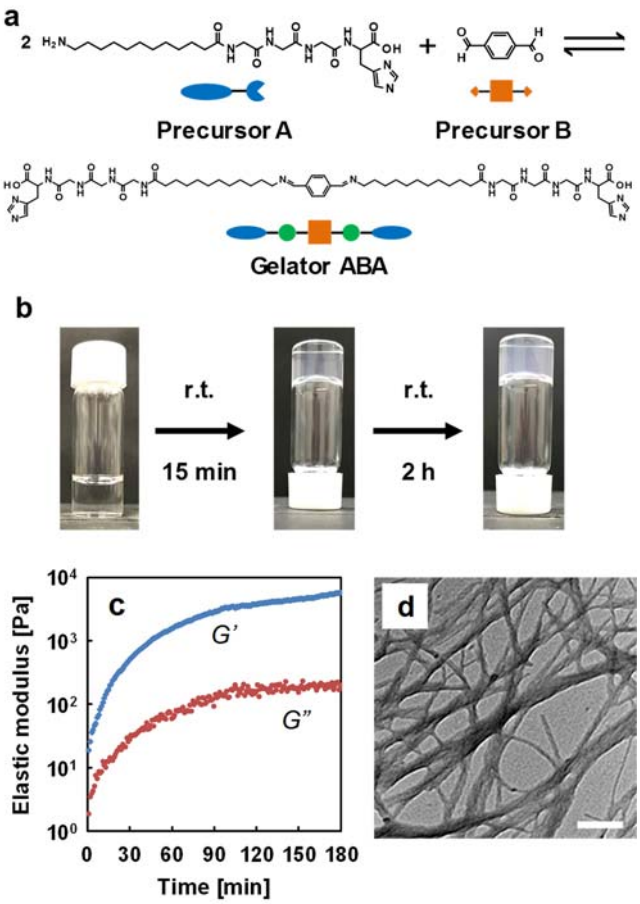


Figure 1. (a) Reaction scheme for the *in-situ* synthesis of a supramolecular hydrogelator using precursors A and B. (b) Photographs of a mixture containing precursors A and B (left), and the corresponding hydrogel formed 15 min after mixing (middle) and 2 h after mixing (right). (c) Dynamic time sweep measurements for the rheological properties of an aqueous solution containing precursors A and B. The sum of the initial concentrations of A and B was 1 wt%. The molar ratio of precursors A/B was 2. (d) Transmission electron microscopy image of the obtained hydrogel. The scale bar represents 200 nm.

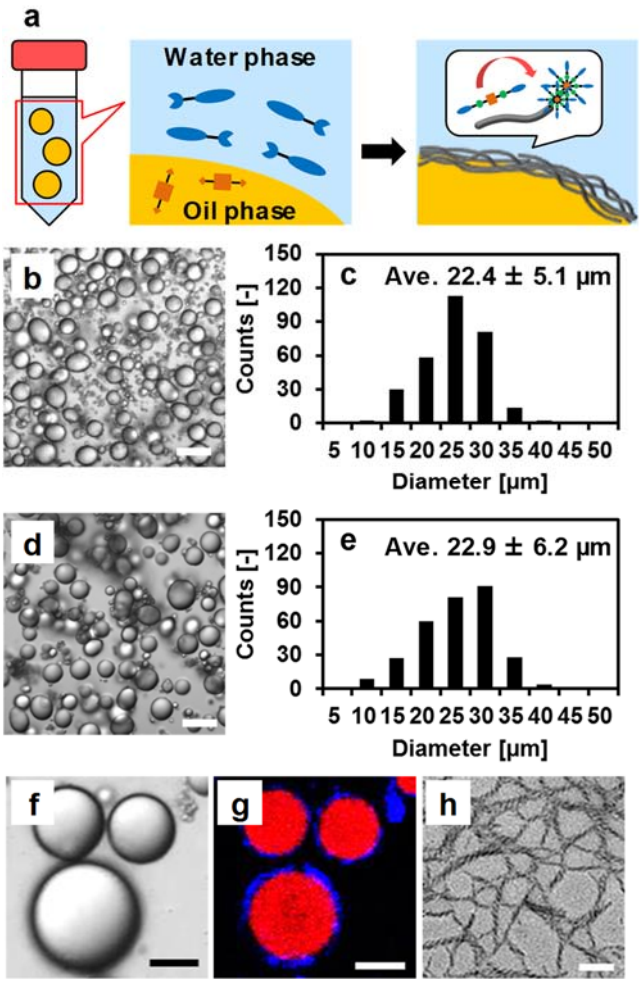


Figure 2. (a) Schematic illustration of the *in-situ* synthesis of a supramolecular hydrogelator at an oil/water interface. (b, d) Optical microscope images and (c, e) size distributions of nanofiber-stabilized oil droplets; (b, c) as prepared, (d, e) after 1 day. Scale bars represent 50 μm. (f, g) Optical and confocal laser scanning microscopy images of 8-anilino-1-naphthalenesulfonic acid (ANS)-stained nanofiber-stabilized droplets. The oil phase was stained with Nile red. Scale bars represent 25 μm. (h) Transmission electron microscopy image of dried nanofiber-stabilized emulsions. The scale bar represents 200 nm.

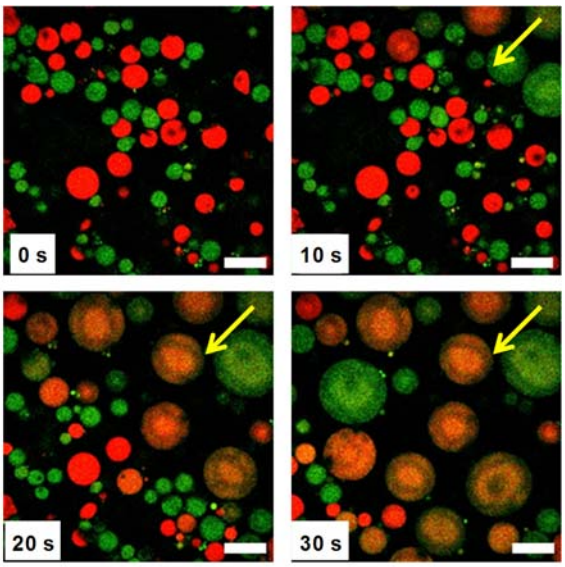
desorption ionization time-of-flight mass spectrometry (MALDI-TOF/MS). Peaks corresponding to gelators ABA and AB were observed, which indicated that the reaction between precursors A and B successfully yielded the supramolecular gelator (see Fig. S3 in the Supporting Information (SI)). Gas chromatography (GC) analysis suggested that about 20% of precursor B was transformed after 24 h (Fig. S4). This suggests that the gelator concentration reached approximately 0.1–0.2 wt% in the hydrogel, which is reasonable for hydrogelation according to our previous report.[9] Investigation of the rheological properties of the obtained hydrogel using dynamic time sweep measurements revealed that, 3 min after mixing the precursors, the value of the storage modulus (G') was 10 times larger than that of the loss modulus (G''), and that G'' reached a plateau in 2 h (Fig. 1c). After 2 h, G' was more than 20 times higher than G'' over the full range of angular frequencies (Fig. S7a) and was still increasing slowly. These results indicate that self-assembly of the gelator molecules occurred immediately after starting the synthetic reaction and that hydrogelation occurred in a short time (less than 1h). The morphology of the obtained hydrogel was characterized by transmission electron microscopy (TEM). The TEM image of the xerogel revealed an entangled fibrous network composed of nanofibers approximately 30–100 nm in width (Fig. 1d). The self-assembly of the synthesized gelator molecules would formed nanofibers and they seemed to assemble to form thick bundles. Differential scanning calorimetry showed that a gel–sol transition occurred at about 75 °C (Fig. S8). The present hydrogel also exhibited a reversible gel–sol transition in response to pH stimulus (at low and high pH, Fig. S9), probably as a result of protonation or hydrolysis of the Schiff base.[10] These investigations demonstrate that simple mixing of precursors A and B at room temperature produced supramolecular gelators ABA (and AB), which self-assemble to form nanofibers, and thus a hydrogel, without the need for temperature change. The resulting hydrogel showed thermoreversible and pH-responsive gel–sol transitions.

We next investigated the *in-situ* synthesis of the supramolecular gelators at an oil/water interface with the aim of stabilizing O/W emulsion droplets with the nanofibers formed in the self-assembly of the hydrogelators (Fig. 2a). Because precursor A was designed to be water-soluble and precursor B was hydrophobic, we used a phosphate buffer solution (pH 7.4) containing 20-mM precursor A and a toluene solution containing 10-mM precursor B (volume ratio of aqueous/oil phases = 4:1), and formed the emulsion by homogenization for 1 min in an ice bath. Optical microscope images showed that oil droplets with an average diameter of 22.4 μm were obtained and that there was no distinct change in their size distribution after 1 day (Fig. 2b–e), which indicated stabilization of the emulsion.[11] In the absence of the gelator precursors, the emulsion demulsified and separated into two phases rapidly (Fig. S10). We also examined several volume ratios of aqueous/oil phases and found that the present ratio resulted in the stable emulsion, which might be related with the precursors ratios.

To visualize the nanofibers formed by self-assembly of the supramolecular gelators at the oil/water interface, we stained the nanofibers with 8-anilino-1-naphthalenesulfonic acid (ANS)[12] and the oil phase with Nile red. Confocal laser scanning microscopy (CLSM) images confirmed that the toluene phase was a dispersion phase and revealed the blue fluorescence of ANS around the oil droplets (Fig. 2f–g). It should be noted that the blue fluorescence was not observed when only one of precursor A or precursor B was used to prepare the emulsions (Fig. S11). The CLSM image indicated that the thickness of the gel surrounding an oil droplet was 1-4 μm. We also conducted TEM of the dried emulsions, and observed entangled nanofibers with widths of approximately 30–40 nm (Fig. 2h), which were thinner than those prepare in a bulk phase (Fig. 1d). Since the precursors were present in different phases separately in the beginning, the synthesis of the gelator mainly occurred at interfaces and formed entangled nanofibers at interfaces, which might affect the diffusion of the substrates and inhibit the growth of a gel phase. MALDI-TOF/MS analysis of the emulsions also indicated the formation of gelators ABA and AB. HPLC analysis revealed that the conversion of precursor A was 14% after 24 h and GC analysis revealed that the conversion of precursor B was 66% after 24 h, indicating that the molar ratio of ABA/ AB was approx. 2.3. Unreacted precursor B was supposed to be in oil droplets and in nanofibers because of its hydrophobicity. The emulsion remained fluid after 2 h, meaning that the aqueous phase was not hardened. This was unlike the homogeneous aqueous solution described above, which formed a bulk hydrogel. These results indicate that the *in-situ* synthesis of gelator ABA (and AB) successfully occurred at the oil/water interface and the resultant gelator molecules instantaneously self-assembled to form nanofibers at the interface, which stabilized the oil droplets. We term these stabilized droplets “nanofiber-stabilized droplets”.

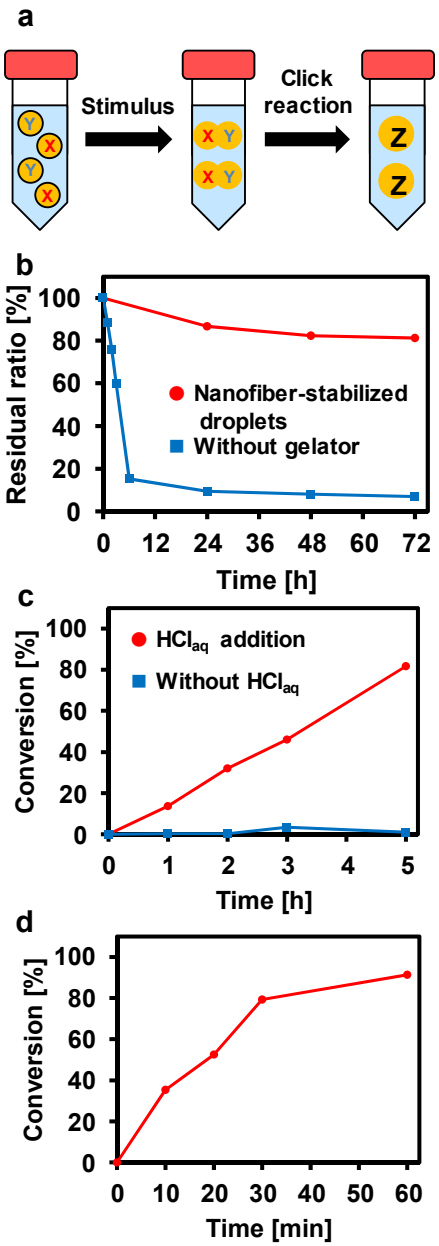
Because the bulk hydrogel composed of the present gelators exhibited a stimuli-responsive gel–sol transition, we next studied the external stimuli-induced fusion of the nanofiber-stabilized droplets. We confirmed that the addition of an aqueous HCl solution and heating (80 °C) demulsified the nanofiber-stabilized emulsions (Fig. S12). To visualize this fusion process, we prepared two types of nanofiber-stabilized droplets with oil phases stained with red (Nile-red) and green (NBD-C12) fluorophores. These droplets were mixed at a volume ratio of 1:1, and then aqueous HCl (0.1 M) was added and time-lapse CLSM observations were performed. The fluorescent red and green oil droplets were present individually at 0 s (Fig. 3), which indicated that simple mixing of the two oil droplets did not induce their fusion. However, when aqueous HCl was added, the droplets became larger through fusion and orange fluorescence appeared in the fused droplets (Fig. 3 and supplementary movie in the SI). Oil droplets with diameters of more than 100 μm were observed after 30 s. These results show that an acid stimulus induced the fusion of the oil droplets and that this resulted in mixing of the encapsulated fluorophores inside the fused droplets.

Figure 3. Acid-induced fusion of nanofiber-stabilized toluene droplets. The time of 0 s represents the addition of aqueous HCl (0.1 M, 50 μL). The yellow arrow shows the direction of the aqueous HCl flow. Scale bars represent 100 μm.



Finally, we aimed to establish a novel microreactor system using the nanofiber-stabilized droplets, in which the mixing of reaction substrates, and thus a chemical reaction, could be induced by an external stimulus (Fig. 4a). We adopted the Cu-free click reaction[13] as a model reaction for this system, and chose azide X and alkyne Y as hydrophobic substrates (Fig. S13). Before performing the stimuli-induced reaction in the nanofiber-stabilized droplets, we investigated the stability of encapsulated azide X in droplets with and without nanofibers. Nanofiber-stabilized droplets containing azide X and those containing alkyne Y were mixed and left for 3 days at room temperature. The residual ratio of azide X was then measured by GC, which showed that less than 19% of azide X was reacted in the nanofiber-stabilized droplets after 3 days. In contrast, the amount of azide X decreased by 85% in 6 h in the absence of the nanofibers (Fig. 4b). These results confirm that the nanofibers formed by the self-assembly of supramolecular

Figure 4. (a) Schematic illustration of the stimuli-induced fusion of nanofiber-stabilized toluene droplets and a chemical reaction within the fused droplets. (b) Residual ratio of azide X encapsulated in toluene droplets after mixing droplets containing azide X with those containing alkyne Y. (c) Conversion of azide X after adding 1-M aqueous HCl to a mixture of nanofiber-stabilized microdroplets containing azide X and alkyne Y. (d) Conversion of azide X after heating a mixture of nanofiber-stabilized microdroplets containing azide X and alkyne Y at 70 °C.



gelators at the oil/water interface stabilize the oil droplets and prevent their fusion.

We then performed the Cu-free click reaction in the nanofiber-stabilized droplets by adding an external acid stimulus. Aqueous HCl (1 M) was added to a mixture of nanofiber-stabilized droplets that contained azide X and, separately, alkyne Y. The conversion of azide X increased over time and reached 81% after 5 h, whereas the amount of azide X did not change when no acid was added (Fig. 4c). MALDI-TOF/MS analysis showed that product Z was produced (see "Click reaction of azide X and alkyne Y in nanofiber-stabilized droplets" in the SI). Because the self-assembly of the present supramolecular gelators is thermoreversible (the gel–sol transition temperature of the nanofiber-stabilized droplets is 68.5 °C (Fig. S14)), a thermal stimulus was also investigated to induce the reaction in the nanofiber-stabilized droplets. When the mixture of nanofiber-stabilized droplets containing azide X and alkyne Y was heated at 70 °C, the conversion of azide X also increased with time and reached 88% after 1 h (Fig. 4d). These results demonstrate that chemical reactions within the confined droplets can be induced by the stimuli-triggered disassembly of the supramolecular gelators.

In conclusion, we have demonstrated the *in-situ* synthesis of supramolecular gelators at an oil/water interface and their self-assembly into nanofibers for the stabilization of emulsion droplets. We have also shown that the stabilized emulsion droplets can be utilized as microreactors for a synthetic Cu-free click reaction, in which external stimuli act as the initiators. The *in-situ* synthesis and hydrogelation of the supramolecular gelators does not require heating and enables their spatially controlled hydrogelation, which is of great advantage for thermodynamically unstable substances and systems. Spatiotemporal control of self-assembly is a powerful strategy used to form micro- and nano-structured architectures in artificial and living systems,[3d, 3e, 3h, 14] and the *in-situ* synthesis of self-assembling monomers. Their spontaneous spatially controlled self-assembly is likely to greatly extend the potential of this strategy in artificial and living systems.

Experimental Section

Methods are in Supporting Information.

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Keywords: interfacial synthesis • gels • low-molecular-mass gelator • nanofibers • self-assembly

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