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Heat-Induced Morphological Transformation of Supramolecular Nanostructures by Retro-Diels–Alder Reaction

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Abstract: Controlling the morphology of supramolecular nanostructures in response to external stimuli is an important challenge in the development of functional soft materials. Here we show that a morphological transformation from 2D nanosheets to a network of 1D nanofibers is triggered by heating, which induces molecular conversion of a bolaamphiphile to a hydrogelator by means of a retro-Diels–Alder reaction, thereby producing a new heat-set supramolecular hydrogel. We anticipate that our design will be a starting point for more sophisticated supramolecular systems that integrate the thermodynamics of molecular assembly and the kinetics of chemical reactions to create complex supramolecular nanostructures.

Keywords: amphiphiles · gels · nanostructures · self-assembly · supamolecular chemistry

Introduction

Supramolecular chemistry based on molecular assembly is a powerful approach to fabricate well-defined nanostructures from small molecules.[1–3] To date, thermodynamically stable supramolecular nanostructures of various shapes and sizes have been constructed by using multiple weak noncovalent interactions, such as hydrogen bonding, electrostatic interactions, and van der Waals forces.[4] Recently, supramolecular nanostructures that respond to stimuli in aqueous media by changing their morphology and function have attracted much attention in the development of intelligent soft materials for myriad bioapplications.[5,6] To install stimuli-responsive structures and functions in supramolecular assemblies, modulation of the noncovalent interactions between the component molecules has been predominantly employed.[7,8] Rearrangement of covalent bonds (their cleavage and formation) has rarely been used to control morphological transformation of supramolecular assemblies, whereas it was well studied in the fields of cleavable surfactants.[9] We believe that the rational coupling of a change in molecular formula driven by chemical reactions with noncovalent interactions is a promising strategy to control supramolecular nanostructures and functions in response to unique stimuli. Indeed, there are several examples of photochemical reactions that involve photoresponsive supramolecular assemblies that undergo a photoinduced change in molecular formula.[10] It has also been demonstrated that enzyme-coupled chemical bond formation or cleavage can trigger nanofiber assembly.[11] As an example using dynamic combinatorial chemistry, supramolecular assemblies constructed by in situ amphiphile formation that are responsive to external conditions have been reported recently.[12] Very recently, we successfully developed stimuli-responsive nanofiber assemblies from a simple dipeptide scaffold, which can be selectively degraded in response to redox or photo stimuli with simultaneous cleavage of a carbamate bond in the component molecules.[13]

In this report, we show that the "retro-Diels–Alder" (retro-DA) reaction can be used to trigger morphological transformation of supramolecular nanostructures.[14] As illustrated in Figure 1, a self-assembled 2D nanostructure that consists of a heat-sensitive bolaamphiphile is converted into a 1D nanostructure in response to heat stimuli by means of a retro-DA reaction-based bond cleavage. This morphological transformation was probed by transmission electron microscopy (TEM) and atomic force microscopy (AFM) obser-

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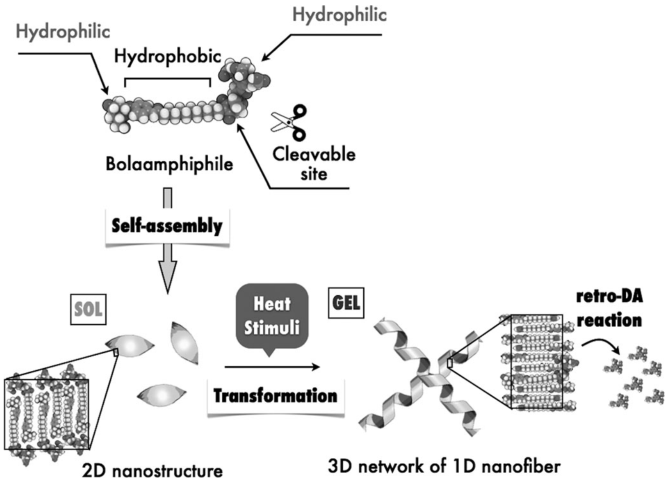

Figure 1. Schematic representation showing heat-induced morphological transformation (heat-set supramolecular hydrogel) of supramolecular nanostructures that consist of a bolaamphiphilic self-assembly unit bearing a site that can be cleaved by retro-Diels–Alder (retro-DA) reaction.

vations, as well as dynamic light scattering (DLS) and small-angle X-ray scattering (SAXS) experiments. This study provides novel insights into the remaining challenges in controlling the morphology of supramolecular nanostructures through a combination of thermodynamics of molecular assembly and kinetics of chemical reactions.[15]

Results and Discussion

Rational molecular design of a self-assembling precursor: Bolaamphiphiles that consist of two polar head groups bridged by a hydrophobic unit can form a variety of water-soluble nanostructures such as rods, disks, and hollow spheres and tubes.[16] We thus sought to use a bolaamphiphile as a self-assembling precursor of a hydrogelator. We also reasoned that a thermoreversible DA reaction would be suitable to construct a heat-sensitive precursor from a hydrogelator that bears a dienophile and a water-soluble diene, as shown in Figure 2. It was anticipated that heating would facilitate molecular conversion from the bolaamphiphile to the hydrogelator by means of a retro-DA reaction, which causes a drastic morphological transformation from a bolaamphiphile with a soluble nanostructure to the 1D nanofibers of the hydrogelator, and a consequent hydrogel that consists of a 3D network. Three carboxylate groups were attached to the water-soluble diene unit as a polar head group to suppress extensive self-assembly of the bolaamphiphile by electrostatic repulsion. According to this design principle, we simply needed to develop a hydrogelator that bore a maleimide to develop a new heat-set supramolecular hydrogel.

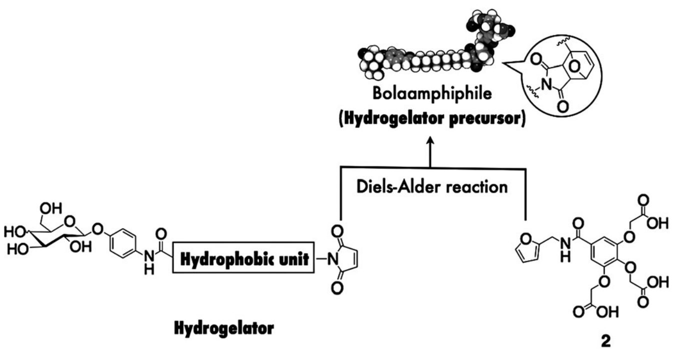

Figure 2. Molecular design of a bolaamphiphile constructed from a hydrogelator bearing a dienophile and a water-soluble diene (**2**) by means of Diels–Alder reaction.

Preparation of a bolaamphiphile by Diels–Alder reaction: Hydrogelators that bear a maleimide group were determined by screening sugar-appended amphiphiles as shown in Figure 3.[17] Two derivatives formed thermally reversible hydrogels by conventional heating/cooling treatment. In particular, compound **1** that bears D-glucose as a sugar head and a C11 methylene linker exhibited the lowest critical gel concentration (*CGC*) of 0.2 wt% (3.6 mM) in 200 mM HEPES (pH 7.2), and its gel-to-sol phase transition temperature (T_{gel}) exceeded 80 °C even at 0.2 wt% (see Figure S3 in the Supporting Information for concentration dependence), above the temperature of which a typical maleimide–furan pair can undergo retro-DA reaction (see below).[14] Therefore, **1** was used as part of the bolaamphiphile.

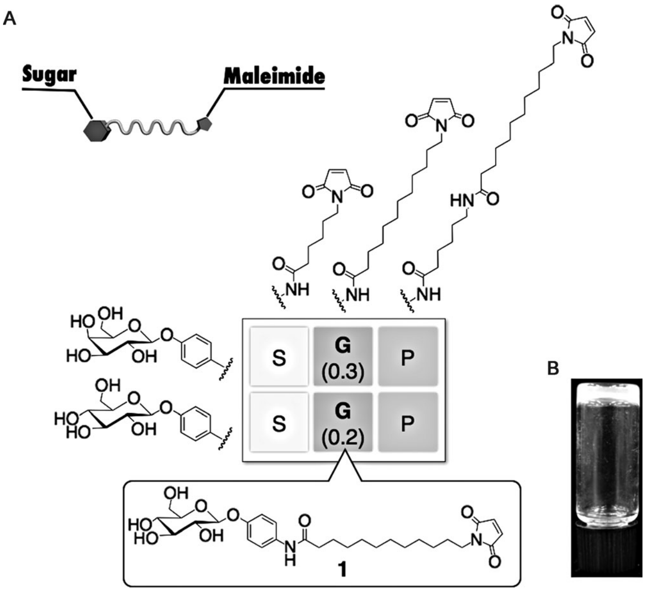

Figure 3. Screening hydrogel formation by amphiphilic maleimide derivatives. A) Gelation test of sugar lipids. G, S, and P denote gel, sol, and precipitate, respectively. *CGC* [wt%] of gels is given in parentheses. B) Photograph of hydrogel **1** ([**1**] = 0.4 wt% (7.2 mM), 200 mM HEPES (pH 7.2))

DA reaction between **1** and water-soluble furan **2** (typical diene) successfully generated bolaamphiphile **1·2**. Interestingly, we found that the *endo* isomer of **1·2** (namely, **1·2**-*endo, endo*/*exo* = 92:8 determined by analytical reverse-

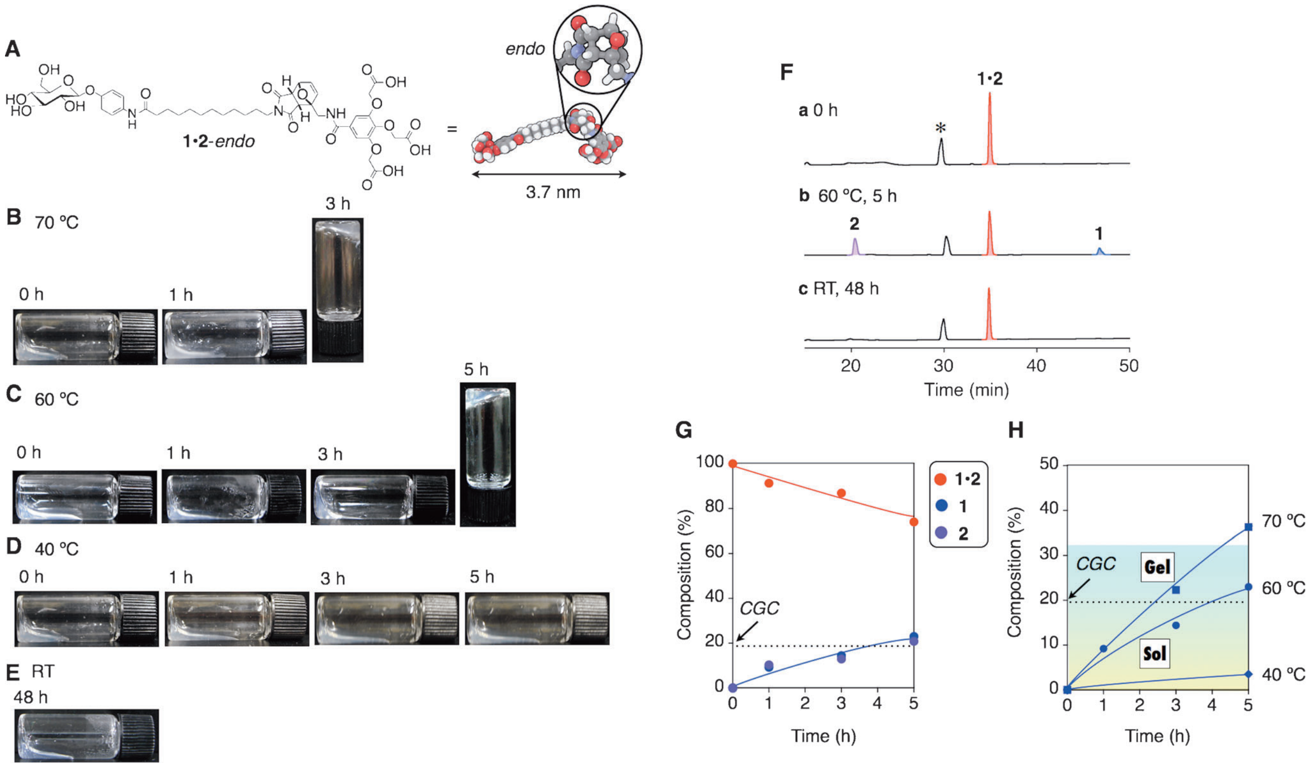

Figure 4. A) Molecular structure of **1·2**-*endo* and photographs of aqueous dispersions of **1·2**-*endo* (18 mM, 200 mM HEPES (pH 7.2)) before and after heating at B) 70 °C, C) 60 °C, and D) 40 °C for 1, 3, and 5 h, and E) after incubation at ambient temperature for 48 h. The sample vial was tilted in an oil bath during heating to confirm that hydrogels formed without cooling. F) HPLC traces monitoring the change in composition during heat-induced hydrogelation of **1·2**-*endo* (18 mM, 200 mM HEPES (pH 7.2)). HPLC conditions: acetonitrile/phosphate buffer (10 mM, pH 7.4) = 0:100 to 5:95 (10 min) to 80:20 (60 min). G) Time-dependent change in the composition of each component estimated from HPLC traces during heat-set hydrogelation of **1·2**-*endo* at 60 °C. H) Time-dependent change in the composition of **1** estimated from HPLC traces at three different reaction temperatures (40, 60, and 70 °C).

phase (RP)-HPLC; see Figure 4A for the molecular structure of **1·2**-*endo*) disperses well in aqueous media even at 5 times the *CGC* of **1** (5×3.6 mM), whereas **1·2**-*exo* does not. This difference in the dispersibility could be because the intermolecular electrostatic repulsions between carboxylate groups in the bent conformation of **1·2**-*endo* are stronger than those in the extended conformation of **1·2**-*exo*. In addition, **1·2**-*endo* is a kinetically favorable product, and therefore is expected to dissociate by means of a retro-DA reaction more rapidly than **1·2**-*exo*. We thus investigated the properties of the bolaamphiphile **1·2**-*endo* in the following studies.

Heat-set hydrogel formation of bolaamphiphile 1·2-*endo*: As expected, an aqueous dispersion of bolaamphiphile **1·2**-*endo* (18 mM (5×*CGC*(**1**))) gradually became viscous and formed a stable hydrogel (heat-set hydrogel) when the solution was heated continuously in an oil bath at 60 °C (Figure 4C). This strongly indicated that heating induced the generation of a 3D network of nanostructures. HPLC/ESI-MS analysis revealed that **1·2**-*endo* gradually dissociated into hydrogelator **1** and **2** and the conversion reached 23 % after 5 h (Figure 4F, G). In contrast, the aqueous dispersion of **1·2**-*endo* maintained its fluid state when left at room temperature for 2 days (Figure 4E).[18] The rate of heat-set gelation increased when the temperature was raised from 60 to 70 °C (gelation time decreased from 5 to 3 h).[19] In contrast, gel formation was not observed even after 5 h of heating at 40 °C (Figure 4B, D). Figure 4H shows plots of the concentration of **1** generated over time at each temperature, clearly revealing that gelation only occurred above the *CGC* of **1**.

Heat-triggered morphological transformation of supramolecular nanostructures: To obtain further insight into the morphological transformation of nanostructures during heat-set hydrogel formation of **1·2**-*endo*, dynamic light scattering (DLS) experiments, and TEM and AFM observations were carried out. DLS measurements of an aqueous dispersion of **1·2**-*endo* (18 mM) before heating showed an intensity distribution with a broad peak that corresponded to an average hydrodynamic diameter of 88 nm, thus indicating that **1·2**-*endo* self-assembled into a water-soluble nanoaggregate (Figure S5A in the Supporting Information). When 8-anilino-1-naphthalene sulfonate (ANS), a typical environmentally sensitive fluorescent dye, was added to the aqueous dispersion of **1·2**-*endo*, a substantial increase of fluorescence intensity was observed (Figure S5B in the Supporting Information). This revealed that the nanoaggregates of **1·2**-*endo* contained hydrophobic domains. From a plot of fluorescence intensity against the concentration of **1·2**-*endo*, the critical association constant was found to be about 6 mM, which is a typical value for bolaamphiphiles (Figure S5C in the Supporting Information).[16] In good agreement with DLS data, a TEM image of **1**·**2**-*endo* before heating showed 2D nanostructures with a size of 100–200 nm (Figure 5A). AFM showed that the 2D nanostructures possessed a thickness of approximately 4 nm, thereby suggesting that the aggregates are a unilamellar structure of **1**·**2**-*endo* (approximately 4 nm in length) (Figure 5E), which is also characteristic of bolaamphiphiles.[16]

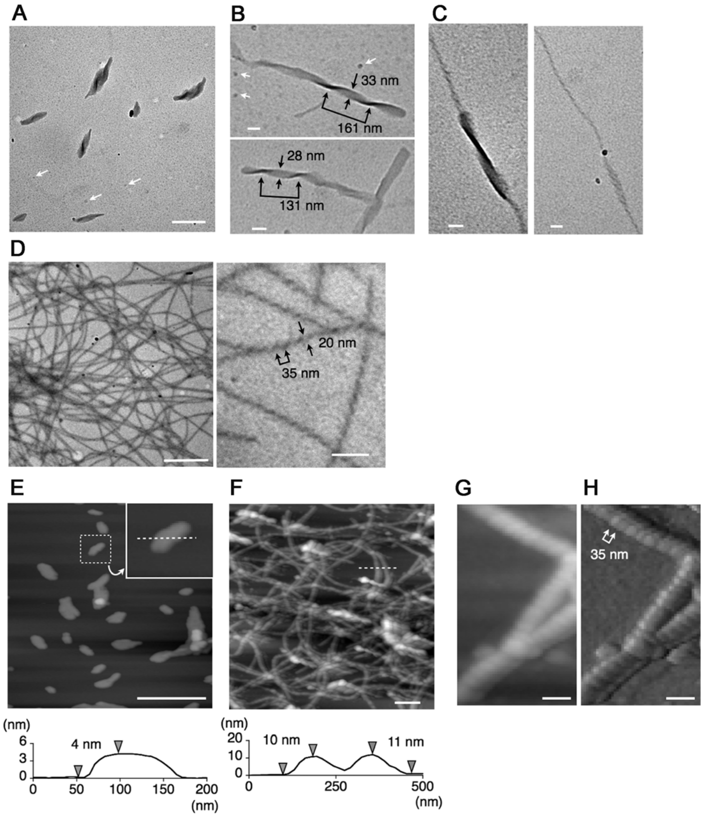

Figure 5. Microscopic observations during heat-induced hydrogelation of **1**·**2**-*endo* (18 mM, 200 mM HEPES (pH 7.2)). TEM images A) before and B, C) after 1 and D) 5 h at 60 °C; E–G) AFM height and H) amplitude images E) before and F–H) after 5 h at 60 °C. Scale bar [nm]: A) 200, B, C) 50, D) 500 (left), 100 (right), E, F) 500, and G, H) 100.

Upon heating the aqueous dispersion of **1**·**2**-*endo*, the correlation function of the scattered intensity (correlation coefficient: $g(2)(t)-1$) in DLS experiments translated to a longer decay time, thus indicating an increase in the size of the aggregates (Figure S6 in the Supporting Information). The resultant distribution was too polydisperse to obtain size information from DLS measurements after heating at 60 °C for just 1 h. TEM images obtained after heating for 1 h at 60 °C (Figure 5B) showed short ribbons with a left-handed twist, an average diameter of 30 nm, and length of several hundred nanometers, which is dramatically different from the 2D structures observed before heating. More interestingly, we successfully observed a transient structure that contained both short twisted ribbons and 1D long helical ribbon in one construct, as shown in Figure 5C. This strongly suggests the gelation mechanism of **1**·**2**-*endo*, that is, association of the twisted nanosheets gave twisted short ribbons, followed by the transformation from the twisted to long helical ribbons. Both the twisted and helical ribbons are left-handed, indicative of a chiral arrangement of component molecules in the fibrous aggregates, which could arise from the D form of the sugar moiety. Further heating (60 °C, 5 h) produced an entangled 3D network of long, left-handed helical ribbons with a diameter of about 20 nm and helical pitch of about 35 nm, as shown in Figure 5D. AFM observations consistently supported this structural transition, as shown in Figure 5F–H, which is attributed to hydrogel formation. We also confirmed that hydrogel **1** prepared by conventional heating/cooling treatment formed similar 1D left-handed helical ribbons (Figure S7A in the Supporting Information). This further supports our view that the molecular conversion of **1**·**2**-*endo* to **1** by retro-DA reaction facilitates a morphological transformation from 2D twisted nanosheets to 1D helical supramolecular nanostructures.[20,21]

Further evidence of this morphological transformation during heat-set hydrogel formation of **1**·**2**-*endo* in solution and the hydrogel state was obtained by X-ray solution scattering (SAXS). Figure 6A shows SAXS patterns obtained before and after heating an aqueous solution of **1**·**2**-*endo*; the heat-induced change of the slope from −2 to −1 in the low q region suggests the structural transition from a 2D to

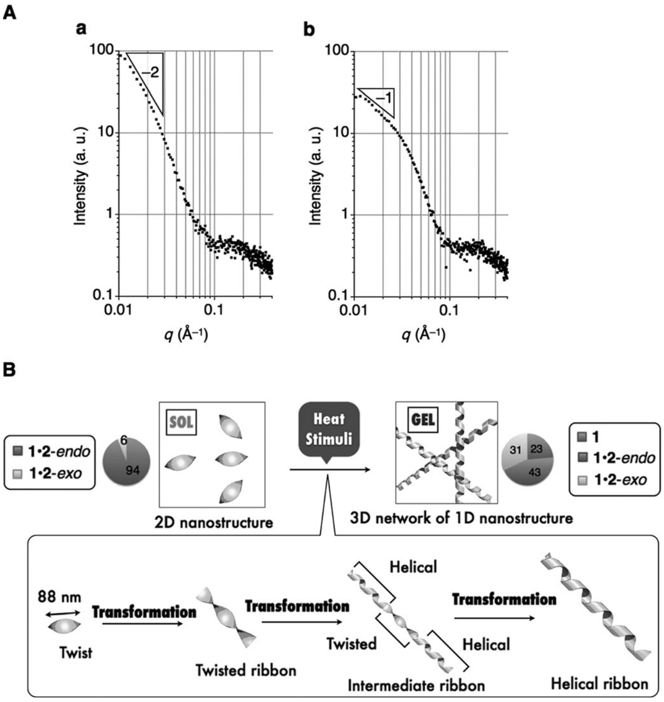

Figure 6. A) SAXS patterns of **1**·**2**-*endo* in aqueous solution a) before and b) after 5 h at 60 °C. ([**1**·**2**-*endo*] = 18 mM, 200 mM HEPES (pH 7.2)). B) Morphological transformation during heat-set supramolecular hydrogel formation of **1**·**2**-*endo*. Pie charts show compositions before and after heating at 60 °C for 5 h.

a 1D object, which is consistent with the TEM and AFM observations described above. In addition, curve fitting of the SAXS profile for the gel sample obtained after heating with a polydisperse core–shell cylinder model yielded an average fiber diameter of 35 nm (Figure S9 in the Supporting Information), which is comparable to the values estimated from TEM and AFM images. Taken together, it is clear that the morphological transformation of supramolecular nanostructures from 2D unilamellar nanosheets to 1D left-handed helical ribbons and their 3D entangled network is required for heat-set hydrogel formation of bolaamphiphile **1·2**-*endo* (Figure 6B).

Conclusion

In conclusion, we demonstrated that a bolaamphiphile that contaisns a heat-triggered cleavage site exhibits thermally induced morphological transformation from 2D nanosheets to a 3D network of 1D nanofibers. The well-defined morphological transformation of supramolecular architectures was observed not only by means of TEM and AFM, but also by means of SAXS techniques. The present study provides a rational molecular design toward heat-induced supramolecular hydrogel formation, which has been an important challenge to overcome.[7] In addition, this simple but versatile molecular design that couples covalent bond rearrangement with a subsequent change of noncovalent interactions might extend morphological transformation to other structural motifs such as vesicles and nanotubes. Unfortunately, the heat stimuli required in the present system that uses a maleimide–furan pair is too harsh for bioapplications including proteins and live cells. However, this system is potentially applicable to various molecular structures that have a diene–dienophile pair. Further research along these lines is under progress with a view toward producing smart supramolecular nanomaterials for various applications.

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[19] Continuous heating at 70 °C for 5 h weakened the gel, which suggested that the gel state is kinetically stable but not thermodynamically stable. Upon careful elucidation of the heat-induced hydrogel formation process by HPLC, we noticed that the concentration of **1·2**-*exo* increased constantly (Figure S4 in the Supporting Information). This indicates that DA reaction between released **2** and **1** took place again. We speculate that the newly generated **1·2**-*exo* collapses the network of supramolecular nanofibers required for hydrogelation.

[20] To evaluate the distribution of each component (**1**, **2**, **1·2**-*endo*, **1·2**-*exo*) in the soluble and insoluble parts, the hydrogel obtained after 5 h at 60 °C was subjected to centrifugation (5000 g, 5 min). We found that **1** and **1·2**-*exo* were mainly recovered from the insoluble part (probably mostly nanofibers), whereas **2** and **1·2**-*endo* were mainly recovered from the soluble one. This suggests that **1·2**-*exo* is incorporated into self-assembled nanostructures of **1** and/or the DA reaction proceeded between self-assembled **1** and **2** (Figure S8 in the Supporting Information). The detailed influence of **1·2**-*exo* on the morphology of the nanostructures is not yet fully understood.

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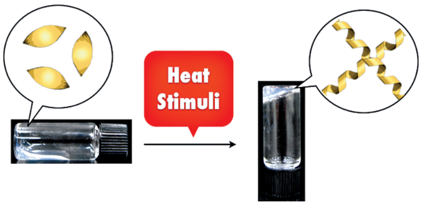
The heat is on: We show that a morphological transformation from 2D nanosheets to a network of 1D nanofibers is triggered by heating (see figure), which induces molecular conversion of a bolaamphiphile to a hydrogelator by means of a retro-Diels–Alder reaction, thereby producing a new heat-set supramolecular hydrogel.



Supramolecular Chemistry

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Heat-Induced Morphological Transformation of Supramolecular Nanostructures by Retro-Diels–Alder Reaction