# Interconversion of Planar Networks and Vesicles Triggered by Temperature[a]

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Dumbbell-shaped amphiphiles based on an elongated rod segment can self-assemble into planar networks with in-plane hexagonally ordered pores in aqueous solution. On increasing temperature, the 2D networks change into hollow capsules passing through the closed sheets as an intermediate structure due to a LCST behavior of the oligoether dendritic exterior. The primary driving force for this interesting feature seems to originate from a consequence of the energy balance between hydrophobic interactions of anisotropic rod segments and alkyl chains, and repulsive interactions between dissimilar blocks. This dynamic structural variation triggered by external stimuli in a self-assembling system can provide a useful strategy to create smart supramolecular materials and biomimetic systems.
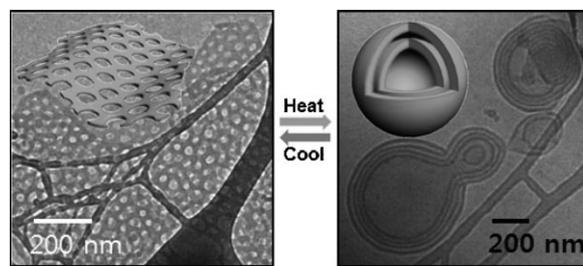
Introduction

Manipulation of supramolecular nanostructures with well-defined shape and size has been one of the major research focuses in the field of chemical biology and materials science.[1] Elaborately designed rigid rod-flexible coil block molecules that mimic lipid amphiphilicity have been promising scaffolds for self-organization into nanoscopic objects with desired functions and properties.[2] Contrary to the conventional coil–coil block molecules, rod–coil amphiphilic molecules can form well-ordered structures, even at low molecular weights because the stiff and anisotropic rod block has a strong tendency to impart orientational organization. Depending on the molecular structure of the respective blocks, it has been possible to construct various nanoarchitectures including spheres, cylinders, toroids, networks, tubes, and hollow capsules in solution.[3]

Among these nanostructures formed by self-assembly of rod amphiphilic molecules, a vesicular structure has proved to be particularly interesting for potential applications such as delivery vehicles and nanoreactors that can be able to effectively encapsulate guest molecules into their cavity.[4] To enhance their expediency for application, many efforts have been devoted to the precise control of the self-assembling behavior at the supramolecular level for the formation of the vesicles.[5] In particular, one of the most attractive issues regarding the strategy for the preparation of hollow capsules is the capability to respond to external stimuli such as pH, temperature, solvent polarity, and guest molecules.[6] For example, helical nanofibers are formed by self-association of symmetric dumbbell-shaped amphiphilic molecules consisting of an aromatic rod and chiral aliphatic oligoether dendrons, and subsequent transformed into hollow capsules on addition of aromatic guest molecules.[7]
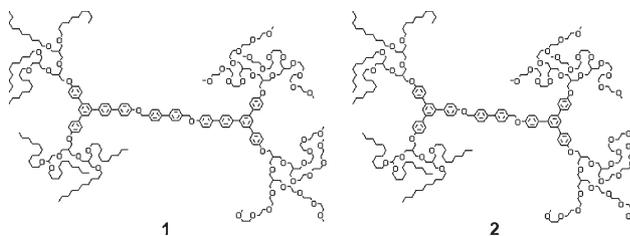
Recently, we have reported that asymmetric dumbbell-shaped rod amphiphilies containing hydrophilic dendrons at one end and hydrophobic ones at the other end can generate nanorings, two-dimensional (2D) networks and vesicles depending on the hydrophobic chain length.[8] This

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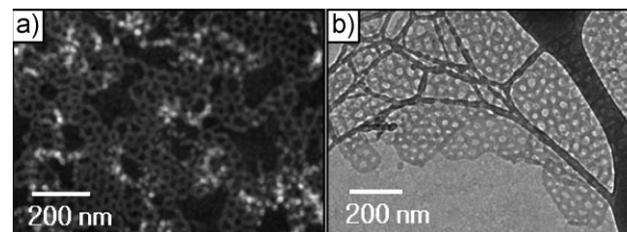**Scheme 1.** Chemical structures of asymmetric dumbbell-shaped rod amphiphiles **1**, **2**.

$-CH_2CH_3$); Anal. Calcd for $C_{258}H_{422}O_{54}$: C 70.62, H 9.69; Found C 70.58, H 9.67; Calcd MALDI-TOF-MS m/z 4 410.08 ($[M + Na]^+$), Found 4 408.88.

2, ^{1}H NMR (250 MHz, CDCl$_3$): δ(ppm) = 7.75–7.58 (m, 26Ar–H), 7.12–6.99 (m, 12Ar–H, o to ArO), 5.16 (s, 4H, –phenylCH_2OAr), 4.07 (m, 8Ar–H, Ar–OCH_2), 3.63–3.38 (m, 200H, –OCH_2), 2.34–2.17 (m, 12H, –CH(OCH$_2$)$_2$), 1.58–1.25 (m, 128H, –CH_2), 0.85 (t, 24H, –CH$_2$CH_3); Anal. Calcd for $C_{246}H_{414}O_{54}$: C 69.75, H 9.85; Found C 69.79, H 9.88; Calcd MALDI-TOF-MS m/z 4 257.89 ($[M + Na]^+$), Found 4 256.48.

Results and Discussion

The dumbbell-shaped molecules can self-assemble into an aggregate structure in an aqueous solution because of their amphiphilic characteristics. Aggregation behavior of the molecules was subsequently studied in aqueous solution, a solvent suitable for oligoether dendrons. Transmission electron microscopy (TEM) and cryogenic-TEM (cryo-TEM) investigations revealed that molecules of **1** (from a 0.01 wt.-% solution) self-assemble into planar sheets consisting of in-plane nanopores (Figure 1), consistent with the result reported previously.[8]

The formation of porous sheets with hydrophilic oligoether dendritic exterior suggests that they may lead to temperature dependent assembling behavior in aqueous solution due to low critical solution temperature (LCST) behavior of oligoether chains. Indeed, the solution of **1** exhibits a thermoreversible transition at 45 °C (Figure 2a). The transition temperature was determined by turbidity measurements by using UV–Vis transmittance. To corroborate the structural change of the aggregates at the LCST, fluorescence microscopy experiments were performed on aqueous solution of **1**. In contrast to the image taken at room temperature,[8] the image at high temperature above the LCST shows the presence of spherical aggregates against dark background (Figure 2b). For direct visualization of spherical objects formed in aqueous solution, cryo-TEM experiments were performed with a 0.01 wt.-% aqueous solution. Remarkably, as shown in Figure 2c, the image shows multi-lamellar hollow capsules with overall diameters ranging from a few hundred nanometers to a few

Experimental Part

Synthesis

A general outline of the synthetic procedures is shown in Scheme S1.

Synthesis of Rod Amphiphiles **1** and **2**

Compounds **1** and **2** were synthesized using the same procedure. A representative example is described for compound **1**. Compounds **4a** (350 mg, 0.14 mmol), **5a** (370 mg, 0.18 mmol), and excess K$_2$CO$_3$ were dissolved in 100 mL of acetone. The mixture was heated at reflux for 24 h and then cooled to room temperature. The solvent was removed in a rotary evaporator, and the resulting mixture was poured into water and extracted with dichloromethane. The dichloromethane solution was washed with water, dried over anhydrous magnesium sulfate, and filtered. After the solvent was removed in a rotary evaporator, the crude products were purified by column chromatography (silica gel) using ethyl acetate/methanol = 10:1 as an eluent, and the product was further purified by recycling preparative HPLC to yield 346 mg (56%) of a colorless waxy solid.

1, ^{1}H NMR (250 MHz, CDCl$_3$): δ(ppm) = 7.77–7.57 (m, 34Ar–H), 7.13–6.99 (m, 12Ar–H, o to ArO), 5.18 (s, 4H, –phenylCH_2OAr), 4.07 (m, 8Ar–H, Ar–OCH_2), 3.64–3.38 (m, 200H, –OCH_2), 2.34–2.15 (m, 12H, –CH(OCH$_2$)$_2$), 1.56–1.25 (m, 128H, –CH_2), 0.87 (t, 24H,
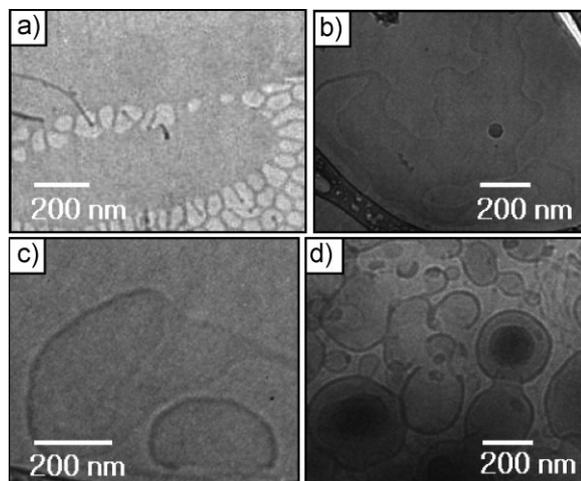

Figure 1. (a) Transmission electron microscopy (TEM) and (b) cryo-TEM images of a planar network structure of **1** at room temperature (in a 0.01 wt.-% aqueous solution).

a)

b)

c)
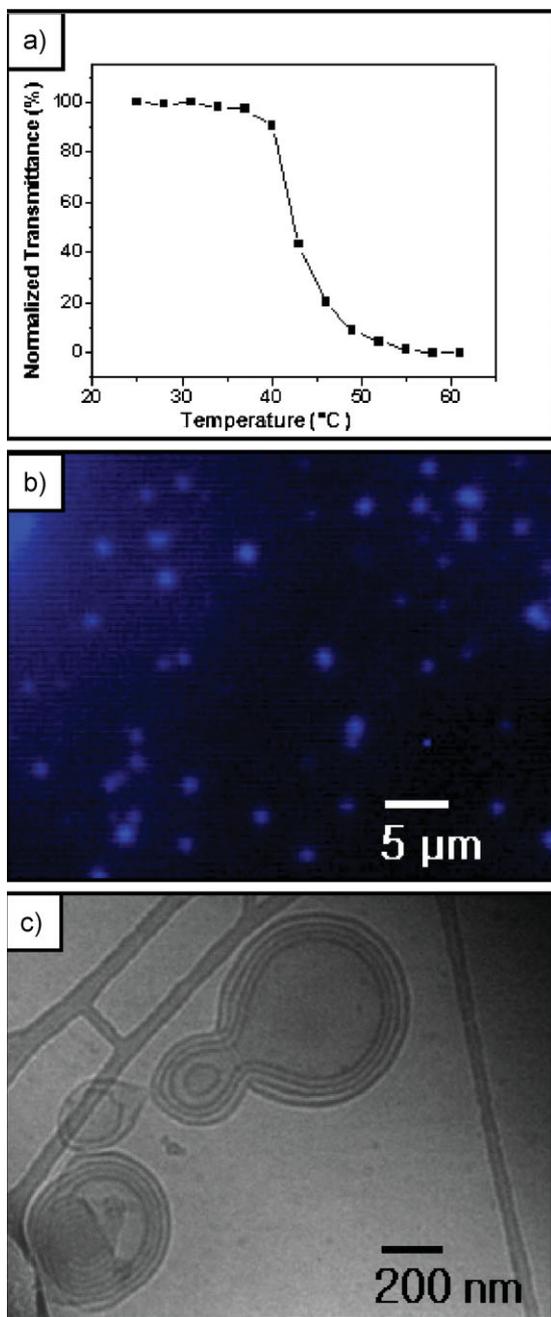
Figure 2. (a) Change of optical transmittance of aqueous solution of **1** upon heating at various temperatures. (b) Fluorescence micrograph and (c) a cryo-TEM image of multi-walled vesicles formed from aqueous solution of **1** after heating to 60 °C.

Figure 3. Structural changes on heating of **1** in aqueous solution (0.01 wt.-%). Cryo-TEM images (a–c) at 35 °C and (d) at 45 °C.

microns against the vitrified solution background, in which there is uniform spacing between the walls. The wall thickness is ≈12 nm and the spacing between the walls is ≈22 nm. The hydrophobic cores appeared to be dark, whereas the solvated oligoether dendrons were not directly visible. Therefore, the dimension of the wall is in reasonable agreement with twice the length of the hydrophobic

segment including the aromatic segments and alkyl chains (ca. 6.2 nm by CPK modeling), thus indicating bilayer packing. This morphology is similar to reported aggregates, the so-called concentric vesicles.[9]
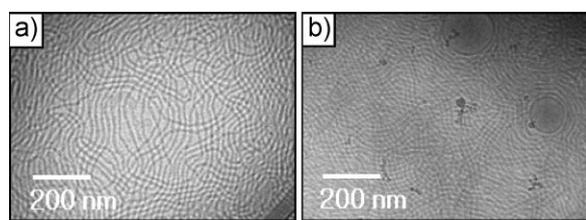
To understand the formation mechanism of the hollow capsules, cryo-TEM experiments were carried out at different temperatures. Upon heating to 35 °C, the micrographs of solution show closed sheet-like structures (Figure 3a and b). In some cases, planar sheets can be seen to fold into semi-vesicle (Figure 3c). On further heating to 45 °C, we observed that the aggregated spherical vesicles fuse with each other (Figure 3d). The small vesicles are merged into bigger vesicles. After annealing at 60 °C, they finally formed hollow capsules with multi-walls (Figure 2c and Figure S1). When the temperature cooled to room temperature, the planar sheets are regenerated (Figure S2).

This structural transition can be explained by the LCST behavior of the oligoether chains located at the planar porous sheet surface.[4d,8,10] Above the LCST, the oligoether dendrons are dehydrated and can adopt a molecular globule, which lead to a decrease in the effective hydrophilic volume. The evidence of dehydration of the oligoether dendron at the surface was confirmed by ^{1}H NMR measurements. Upon heating above the LCST, the resonances associated with the ethylene oxide chains are noticeably broadened together with a decrease in intensity (Figure S3), demonstrating the loss of hydrogen bonding interactions between ether oxygens and water molecules.[11] Consequently, the anisotropic rod segments are packed more closely in a parallel fashion within the core owing to shrinkage of the oligoether dendritic chains caused by dehydration, again resulting in the exposure of the hydrophobic side faces of porous sheets to water. To reduce this unfavorable contact, the 2D nets with in-plane nanopores transform into closed 2D structures through side

by side hydrophobic interactions. However, the closed sheets could be metastable due to hydrophobic edge parts and subsequent fold into a hollow vesicular structure to avoid energetically unfavorable contact between the hydrophobic edge and water.[12] The formation of the vesicles from the sheets seems to originated from the balance between the low bending elasticity of anisotropic rod arrangement and high surface tension between the dissimilar blocks.[13] Subsequently, the uni-lamellar vesicles aggregate together driven by increasingly hydrophobic interactions because of the continuous dehydration of oligoether dendrons during the LCST transition. The overlapped and encapsulated small vesicles progressively self-organize inside the large vesicles into a multi-walled vesicle. Therefore, the formation of multi-layer vesicles at the equilibrium state arises from the fusion of the overcrowded vesicles with single walls.

Although dynamic structural variation has been reported in synthetic self-assembling systems including block copolymers and surfactant molecules,[14,15] only a few examples of the structural change from sheets to vesicles has been reported. Furthermore, the transformation of 2D sheets into vesicles triggered by external stimuli is a still challenging field of research because of its potential as drug delivery vehicles and nanoreactors. Thus, a remarkable feature of the rod amphiphiles investigated here is their ability to form planar networks which fold into hollow capsules by passing through 2D closed sheets as an intermediate structure, triggered by temperature. The strong propensity of the elongated rod segments to be aligned in a parallel fashion seems to be the primary driving forces in this structural progression.

To gain insight into the role of the elongated rod segments for this transformation, we have prepared the amphiphilic molecular dumbbell (**2**) with a decrease in both hydrophobicity and rigidity of a rod segment through a decrease in rod length. In contrast to amphiphile **1**, molecule **2** showed to form cylindrical fibers with a uniform diameter of 11 nm and lengths of at least several micrometers in aqueous solution (Figure 4a). Upon heating above the LCST, morphological change of solution of **2** did not occur completely, while the only small amounts of vesicles are formed (Figure 4b). It is well known that cylindrical fibers directly transform into vesicles in coil–coil block copolymer and surfactant solutions.[15] Therefore, this result suggests that the length of rod segments plays a critical role in the interconversion of planar networks and hollow vesicles.

Conclusion

In summary, the results described here demonstrate that dumbbell-shaped amphiphiles based on an elongated rod segment self-assemble into aggregate structures that differ significantly as a function of temperature. On increasing temperature, the supramolecular structure changed from planar networks, 2D closed sheets to hollow capsules. This remarkable feature in response to temperature is attributed to the molecular reorganization, a consequence of effective volume change of the oligoether dendrons caused by LCST behavior. These results represent a significant example of dynamic structural variation triggered by external stimuli in a self-assembling system, thus providing a useful strategy to create smart supramolecular materials and biomimetic systems.

Figure 4. Cryogenic-TEM (cryo-TEM) images of aqueous solution of **2** (a) at room temperature and (b) at 60 °C.

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