# Ultrastable Steroidal Nanotube Formed in Organic Solvents

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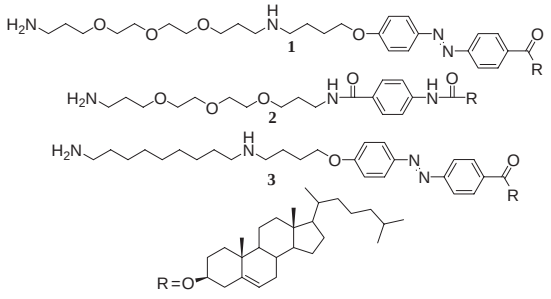
Cholesterol-based amphiphile not only formed the tubular structure in organic solvents such as acetonitrile as well as acetone, but also maintained the tubular structure until 72 °C.

The design and fabrication of nanometer-sized functional materials have become a widely studied field in nanotechnology because of their potential use as building blocks in nanodevices.[1] Smart nanotubes, which can recognize specific complementary molecules, have become increasingly important to design nanodevices for electronics, optics, and sensor applications.[2]

The study in formation of tubular structural amphiphiles in aqueous solution has been attracted considerable interest for its application in the bottom-up construction of engineered materials.[3] In spite of these lines of importance, there have been reported a few amphiphiles which can form the tubular structure by self-assembly in organic solvents.[4] In addition, any systematic studies have never been attempted on the influence of solvophilic and solvophobic groups.

With these objects in mind, we designed cholesterol-based amphiphile **1**, which has azobenzene and cholesterol skeletons as a aggregate-forming sites or a solvophobic group and a 1,13-diamino-4,7,10-trioxatridecanyl unit as a solvophilic head group. Also, compounds **2** and **3** were synthesized as reference compounds. For examples, the azobenzene unit of **1** was changed into the phenyl group of **2**. Also, compound **3** was introduced 1,13-diaminodecanyl moiety as a solvophilic head group instead of a 1,13-diamino-4,7,10-trioxatridecanyl group of **1**. We have found that **1** not only forms the tubular structure in organic solvents, but also maintains the tubular structure until about 72 °C.




Compounds **1**–**3** were synthesized according to a similar method reported previously.[5] They were dissolved in boiling acetonitrile or acetone to give a clear solution, and were slowly cooled to room temperature. Fine fibrous structures were obtained within 30 min under ambient conditions. The fibrous structures were confirmed by various methods, including light microscopy and energy-filtration transition electron microscopy (EF-TEM). In addition, the thermal stability of the self-assembled **1** prepared from acetonitrile was measured by circular dichroism (CD), light microscope equipped with a hotstage and differential scanning calorimetry (DSC).

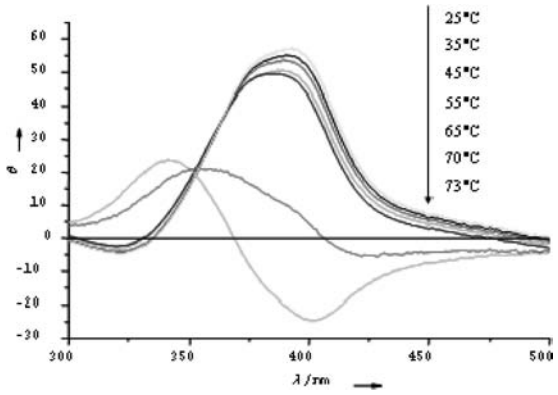



**Figure 1.** CD spectra of the self-assembled **1** in acetonotile by change of temperature.

To characterize the aggregation mode in the self-assembled superstructure of **1**, we observed the CD spectrum of self-assembled **1**. We found that the $\lambda_{\theta=0}$ value appears at 335 nm, which is consistent with the absorption maximum at $\lambda_{max} = 335$ nm. One can thus assign the CD spectrum to the exciton-coupling band, although it is somewhat asymmetrical (Figure 1a). It is known that azobenzene-appended cholesterol derivatives with a natural (*S*) C-3 configuration tend to give a positive sign for the first Cotton effect, indicating that the dipole moments of azobenzene chromophores tend to orient into the clockwise direction.[5c] The CD intensity of the self-assembled **1** was scarcely changed until 65 °C, which exhibited the positive sign for the first Cotton effect of the self-assembled **1**. Very interestingly, on the other hand, the strong positive sign for the CD spectrum of the self-assembled **1** changed into a negative sign at about 70 °C, then continuously exhibited the negative sign for the first Cotton effect at about 73 °C. These results indicate that, basically, the self-assembly **1** with (*S*)-chirality is more stable than that with (*R*)-chirality. The self-assembled **1** with (*R*)-chirality is a metastable phase formed by heating. This result is quite similar to that obtained from cholesterol derivative previously.[5d,5e] Also, this finding strongly supports the view that the helical motif in the molecular packing of the tubular structure is somewhat different from the vesicular structure of cholesterol derivative. However, it is still not clear how the helicity is converted by heating.

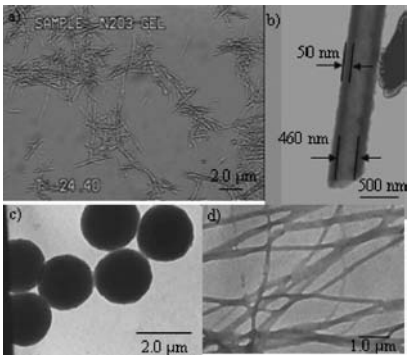



**Figure 2.** (a) A light microscopic and (b) TEM images of the self-assembled **1**, (c) **2**, and (d) **3** prepared from acetonitrile.

The phase-transition temperature will be explained later in more detail.

In order to obtain visual insights into the aggregation mode, we observed the self-assembled **1** by light microscopy and EF-TEM. Figure 2 shows light microscopic and EF-TEM images of the self-assembled **1** formed in acetonitrile. The light microscopic image reveals that they extend in length to several hundred micrometers. The EF-TEM image of unstained samples in acetonitrile shows the tubular structure with uniform external diameter of ca. 560 nm, and wall thicknesses of 50 nm. The tubes are open-ended, with uniform shape and internal diameter. The reports on the tubes formed in organic solvents are still very limited even though there are several tens of the tubes formed in aqueous solution. Therefore, this is one example for formation of tubular structure by self-assembly in organic solvents. The structure of **1** is quite different from sugar-based and peptide-based amphiphiles previously reported.[3a–b] These amphiphiles were transformed from the vesicle to the helical ribbon structure and to the tubular structure in aqueous solution by ultrasonication, whereas **1** forms only the tubular structure with ca. 510 nm of inner diameter even in organic solvents without sonication. The formation of the helical ribbon structure in the preliminary stage is not ruled out. However, the growth of the tubular structure was too fast to observe it in organic solvents.

The cholesterol tubes were examined using differential scanning calorimetry (DSC), revealing a phase transition temperature at 73.5 °C for the self-assembled **1**. This value is almost consistent with that obtained from the CD observation. In addition, confirmation of the value using a light microscope equipped with a hot stage revealed that the tubes formed from **1** can exist until 72 °C. It is interesting to note that the tubes completely disappeared at above 74 °C, which is close to the boiling point of acetonitrile. These results indicate that the phase-transition temperature of the cholesterol-based tube formed in acetonitrile is much higher than that formed in aqueous solution. However, the vesicular structure of the self-assembled **1** at above 72 °C could not be detected because of the limitation for magnification of the light microscope.

On the other hand, the self-assembled **2**, which has a phenyl group instead of the azobenzene group of **1**, formed the spherical structure with outer diameter of ca. 2 μm in acetonitrile (Figure 2c). This result indicates that the azobenzene moiety in **1** plays an important role to form the tubular structure by self-assembly with mainly $\pi$–$\pi$ stacking and van der Waals interaction between azobenzene and azobenzene groups as well as cholesterol and cholesterol groups. In addition, **3** which has a amine group as a polar head group instead of the diaminoethylene glycol moiety of **1**, induced the fibrous structure with outer diameter of 200–300 nm (Figure 2d). These results support the view again that probably the solvophilic and solvophobic groups are dependent to morphological formation by self-assembling in organic solvent.

In conclusion, we have demonstrated that morphologies of the self-assembled cholesterol-based derivatives are controlled by the solvophilic and solvophobic group in organic solvents. The stabilization of the self-assembled cholesterol-based tubes is achieved more efficiently in organic solvents than in water.

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