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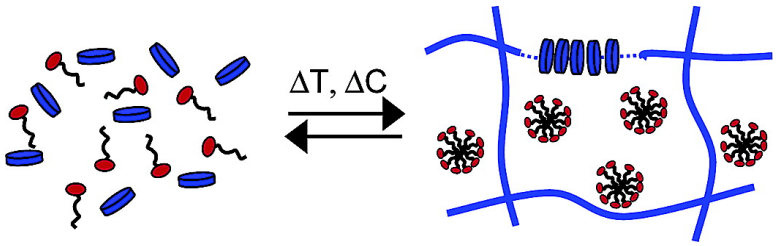

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Orthogonal Self-Assembly of Low Molecular Weight Hydrogelators and Surfactants

André Heeres,[†] Cornelia van der Pol,[†] Marc Stuart,[‡] Arianna Friggeri,[†] Ben L. Feringa,*[,‡] and Jan van Esch*[,‡]

BioMaDe Technology Foundation, Nijenborgh 4, 9747 AG Groningen, The Netherlands, and Laboratory of Organic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

Received June 28, 2003; E-mail: esch@chem.rug.nl

The self-assembly of partially incompatible molecular components leading to (micro-) phase separation comprises a powerful approach toward the fabrication of complex nanoarchitectures and new materials and plays an essential role in nature, for example, in protein folding and the formation of biological membranes.[1−3] Phase-separated systems are so far usually based on the immiscibility of block-copolymer segments[4] or fluorinated compounds with hydrocarbons,[5] and this toolbox has only very recently been extended by low molecular weight organogels in liquid crystalline phases.[2b] Here, we report on the concurrent self-assembly of new low molecular weight hydrogelators[6,7] and various surfactants in water, leading to self-assembled fibrillar networks with encapsulated micelles. This prototype system presents an example of orthogonal self-assembly, that is, the independent formation of two different supramolecular structures, each with their own characteristics that coexist within a single system.

Recent progress in the design of low molecular weight gelators has emphasized the importance of self-complementary and highly anisotropic interactions for the gelation ability.[6b,8−10] In the present work, we employed the 1,3,5-trisamide cyclohexane[11] moiety because it can self-assemble into 1D arrays stabilized by six hydrogen bonds. We have extended this moiety with hydrophobic amino acids to shield the amide groups from competitive interactions with water and have thereby enforced the anisotropic self-assembly of the gelator molecules in water due to the concurrent action of hydrogen bonding and hydrophobic effects. A similar combination of interactions stabilizes secondary protein structures, which are stable in the presence of weakly interacting surfactants and lipids.[3]

Compounds **1**−**3** are examples of gelators[12] (Chart 1) that fulfill these requirements and are easily prepared by coupling of the corresponding (C-derivatized) amino acids with 1,3,5-tris(carbamoyl chloride)cyclohexane. Compounds **1**−**3** all form thermoreversible gels in water at very low concentrations.[13,14] The very low critical gelation concentrations (cgc) and the high gel−sol phase transition temperatures (T_{GS}) of the gels clearly indicate that self-assembly of **1**−**3** is driven by strong intermolecular interactions. FTIR spectroscopy of xerogels and of hydrogels of **1** showed amide I vibrations typical for hydrogen-bonded amides at almost the same position of 1639 and 1635 cm^{-1}, respectively.[15] This indicates that the amide moieties participate in a similar hydrogen-bonded network in hydrogels and their corresponding xerogels. Hydrogels of **1**−**3** tolerate NaCl concentrations up to at least 100 mM and are stable for at least 3 months. Transmission electron microscopy (TEM and cryo-TEM) of the gels in water revealed that **1**−**3** self-assemble into elongated fibers (diameters for **1**, 20−150 nm; **2**, 10−50 nm; **3**, 10−200 nm), which in turn form an entangled fibrillar network, thereby immobilizing the solvent.

Chart 1

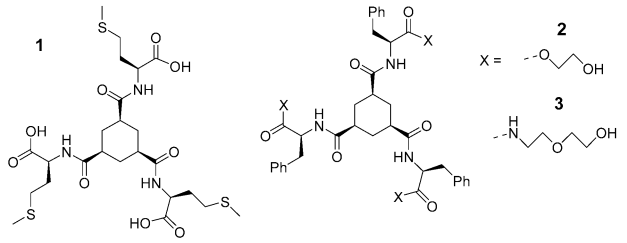

Table 1. Gelation of Water by **1**−**3** in the Presence of Surfactants[a]

	anionic (SDS)		cationic (CTAB)		nonionic (OG)	
gelator[b]	<cmc (4.6)[c]	>cmc (13.6)[c]	<cmc (0.5)[c]	>cmc (2.2)[c]	<cmc (6.8)[c]	>cmc (34)[c]
1	G	G	p	p	G	G
2	G	G	G	G	G	G
3	G	G	G	G	G	G

[a] SDS, sodium dodecyl sulfate (cmc = 8.1 mM); CTAB, cetyltrimethylammonium bromide (cmc = 0.9 mM); OG, *n*-octyl-*β*-D-glucopyranoside (cmc = 25 mM); G, gel; p, precipitation. [b] [**1**] = 16 mM, [**2**] = 13 mM, [**3**] = 11 mM. [c] Concentration of surfactant in mM.

The compatibility of hydrogel formation by **1**−**3** with various types of surfactants was investigated by dissolving **1**−**3** in surfactant solutions below and above the critical micelle concentration (cmc)[16] at $T > T_{GS}$ and by subsequently examining the samples for gelation after they had been cooled to room temperature (Table 1). Gels of **1** are formed in combination with nonionic (OG) or anionic (SDS) surfactants either by temperature-induced gelation or by the lowering of the pH from 7 to 3.5,[13] but with cationic CTAB immediate precipitation occurred, due to salt formation. Most interestingly, cryo-TEM showed no significant differences between hydrogels of **1** alone and in the presence of OG (Figure 1), and furthermore the melting temperatures of hydrogels of **1** are not changed by the presence of OG up to concentrations well above the cmc (35 mM). The gelation behavior of the nonionic gelators **2** and **3** is even more tolerant toward the presence of surfactants, and transparent gels are obtained in the presence of SDS, CTAB, or OG below and well above the cmc of the surfactants. These results clearly indicate that the self-assembly of **1**−**3** leading to the gelation of water is not markedly affected by the presence of surfactants or surfactant assemblies, except when strong interactions between surfactant and gelator are possible, like electrostatic interactions between acidic gelator **1** and the cationic surfactant CTAB.

[†] BioMaDe Technology Foundation.
[‡] University of Groningen.

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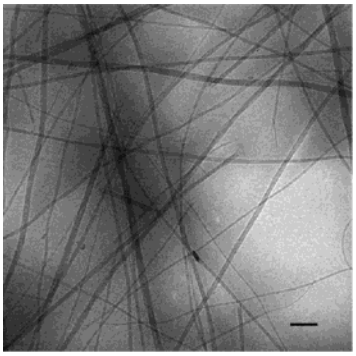

Figure 1. Cryo-TEM of a hydrogel of **1** (3.3 mM) in the presence of 33 mM of OG, that is, well above the cmc of OG. For a cryo-TEM of a gel of **1** without surfactant, see the Supporting Information. The scale bar is 300 nm.

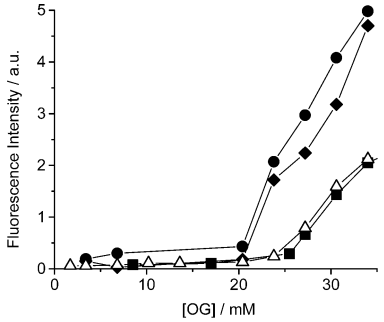

Figure 2. Fluorescence intensity of ANS (2×10^{-5} mmol L^{-1}) as a function of the OG concentration without gelator (△), and in the presence of **1** below the cgc (0.66 mM, ■), and above the cgc (2.46 mM, ◆; 4.92 mM, ●). λ_{ex}, 370 nm; λ_{em}, 490 nm; $T = 25$ °C, in 50 mM NaCl. The pH has been adjusted with HCl to a value of ~3.5.

It is an intriguing question whether the presence of a gel network or free gelator molecules interferes with the formation of micelles by the surfactants. To study micelle formation by the surfactants in the presence of a fibrous gel network, we employed the well-known fluorescence probe 8-anilino-1-naphthalenesulfonic acid (ANS).[16a] ANS itself shows only a weak fluorescence in water, and addition of gelator **1** below and above its cgc has no effect on the fluorescence properties of ANS. Upon addition of OG above the cmc, micelles are formed and ANS becomes incorporated in the less polar micellar environment, resulting in a red-shift of the emission wavelength to 490 nm and a strong increase of the quantum yield (Figure 2). The fluorescent intensity shows an abrupt increase at higher surfactant concentrations which marks the formation of micelles, and the cmc value of 24 mM (graphically determined from the intercept of the tangents) is in excellent agreement with the reported cmc for OG.[16c] The cmc of OG does not change by addition of gelator **1** below its cgc, and the cmc of OG decreases only slightly to a value of 20−22 mM above the cgc of **1** when the solutions have turned into hydrogels. The slight decrease is most likely due to some association of the surfactant molecules with the gel fibers, but the cmc of OG does not decrease any further if the gelator concentration is increased, which makes extensive association of OG with the gelator network highly unlikely. It is therefore concluded that OG self-assembles into micelles in the presence of a gel network formed by self-assembly of gelator molecules of **1**!

The results presented here show that self-assembly of **1** and of OG are orthogonal processes, leading to the independent formation of a fibrillar network with encapsulated micelles, and the comparable gelation behavior and molecular architecture with **1** form a clear indication that **2** and **3** with surfactants behave similarly. We speculate that the orthogonal self-assembly of our hydrogelators and surfactants is due to their different molecular architectures as well as the in part different driving forces for self-assembly, that is, hydrogen bonding and hydrophobic effects versus hydrophobic effects alone, respectively. The straightforward design of 1,3,5-trisamide-cyclohexane-based gelators and the thermoreversibility and pH-sensitivity[13] of the hydrogels make them ideal model systems to investigate the factors controlling self-assembly and phase separation in gelator−surfactant systems and employ them as cytoskeleton mimics in liposomes.

Supporting Information Available: Experimental details on the preparation and characterization of **1**−**3**, and cryo-TEM (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A full report on the synthesis and gelation properties of 1,3,5-trisamide-cyclohexane gelators is in preparation.

(13) Interestingly, reversible gelation and dissolution of water by **1** is observed by changing the pH from 7 to 3.5 and back.

(14) Cgc at 25 °C for **1**, 1.7 mM; **2**, <3 mM; and **3**, 1.3 mM; and T_{GS} of gels of **1**, 73 °C (6.4 mM); **2**, 104 °C (3.5 mM); and **3**, 118 °C (1.7 mM).

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