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Thermo-switchable surfactant gel†

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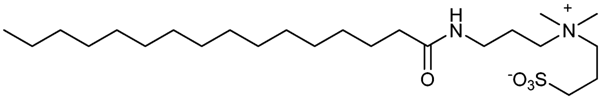
A thermo-switchable surfactant gel with the property of gelation on heating was developed for the first time based on palmitylamidosulfobetaine. Micellar growth from globular aggregates to entangled worms upon heating is responsible for the thermal gelation.

Recently, there has been a growing research focus on selectively tailored supramolecular assemblies,[1] particularly those with switchability.[2] These smart systems, which respond dramatically to environmental stimuli,[1–3] could be used to change wettability,[2c] regulate transportation of ions or molecules[2a,3b] and convert electrical,[2a,c] optical,[3c] thermal[3d] or pH[2b,3d] signals into chemical or biochemical ones and *vice versa*. Thus, they are playing an increasingly important role in a wide range of areas,[1a] such as drug delivery,[4] diagnostics, biosensors,[3b] tissue engineering[5] and smart optical systems.[6] Thermally responsive hydrogels[5a,c] that are triggered by the ambient temperature represent one of the successful examples of these smart systems. Among these intelligent gels,[5a,c,7] those that undergo a thermally reversible transition between a poorly viscous solution and a rigid hydrogel are of particular interest.[7] The thermally-triggered hydrogelation can be achieved in two distinct ways: cooling or heating.[7a] The mechanism responsible for gelation upon cooling is the formation of physical cross-links that denature at higher temperatures.[7a,b,8] Conversely, systems that experience heating-induced hydrogelation take advantage of the weakening ability of water to solubilize the hydrophobic moieties of amphiphiles at elevated temperatures,[7a,9] which means heating decreases the solubility of the hydrophobes and thus results in the formation of network gels.[7a] These switchable gels are normally prepared from polymers[5a,c,7–9] or peptides.[5c,7a]

Surfactants have recently been proved to be a new generation of gelators.[10] To the best of our knowledge, the surfactant gels reported so far are normally formed at lower temperatures and gelation upon cooling is their common characteristic.[10a–c] Here, we developed a brand new strategy based on palmitylamidosulfobetaine (PDAS, Scheme 1) to prepare a thermo-switchable hydrogel with the property of gelation upon heating.

This work was inspired by our experience of observing the dramatic change in the flow behavior of a concentrated PDAS solution in the presence of 0.5 M NaCl (named "PDAS/NaCl" below) upon heating. The initial PDAS/NaCl solution at 30 °C is a poorly viscous fluid and flows freely under a slight shear stress (Fig. 1a). When gently heated to 40 °C, a marked variation occurs—the poorly viscous sample becomes a strongly viscoelastic gel with the appearance of soft glass, and it does not flow from top to bottom in a glass vial with a high-density magnetic bar (Fig. 1b). When cooled back to 30 °C, the sample regresses to the initial state and the suspended magnetic bar moves to the bottom (Fig. 1c).

The transition of the solution upon heating can be elucidated by rheological measurements. As shown in Fig. 2a, the shear viscosity η of the sample at 30 °C maintains only 0.05 Pa·s regardless of the shear rate, which corresponds to typical Newtonian flow behavior. The micellar structures of the surfactant solution can be attributed to globular micelles or unentangled, short, rod-like micelles.[11] However, upon increasing the temperature to 40 °C, the surfactant solution shows shear-thinning behavior as gels,[12] which is normally regarded as the evidence of worm-like micelles that undergo structural changes regarding the alignments of long worms at high shear rates.[2b,13] Dynamic rheological experiments (Fig. 2b) indicate that the rheological response of the sample at 30 °C is viscous, with G'' being much higher than G' within all shear frequencies, whereas it is elastic with G' exceeding G'' over the entire frequency range when the external temperature is increased to 40 °C. G' at 30 °C is so small that it is negligible. However, it increases by several orders of magnitude with heating to 40 °C. The strong elasticity of the heated solution is attributed to the formation of entangled worms.[2b,13] In short, the sample is a poorly viscous solution at 30 °C, but it is a strongly elastic gel at 40 °C. It is worth mentioning that the PDAS gel, similarly to those reported previously,[10d,12,14] is a "viscoelastic gel" (*i.e.*, gel-like), since G' and G'' may cross over with each other in an experimentally inaccessible range and a finite relaxation time is usually observed rather than an infinite one.[10d] Therefore, G' and G'' do not exhibit a real plateau but a slight increase with ω.



Scheme 1 The chemical structure of palmitylamidosulfobetaine (PDAS).

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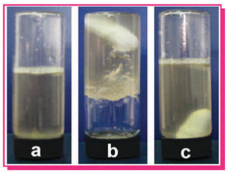

Fig. 1 Photographs of the PDAS/NaCl solution at 30 °C (a), 40 °C (b) and 30 °C again (c).

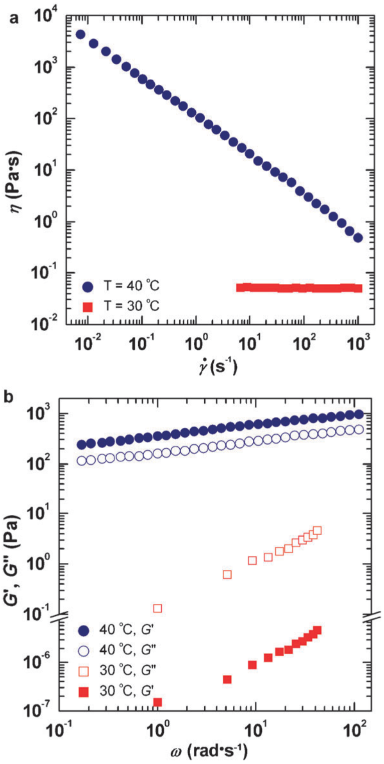

Fig. 2 The thermal stimuli response of the PDAS/NaCl solution: (a) shear viscosity η as a function of shear rate $\dot{\gamma}$ and (b) elastic (G') and viscous (G'') modulus as a function of oscillatory shear frequency ω.

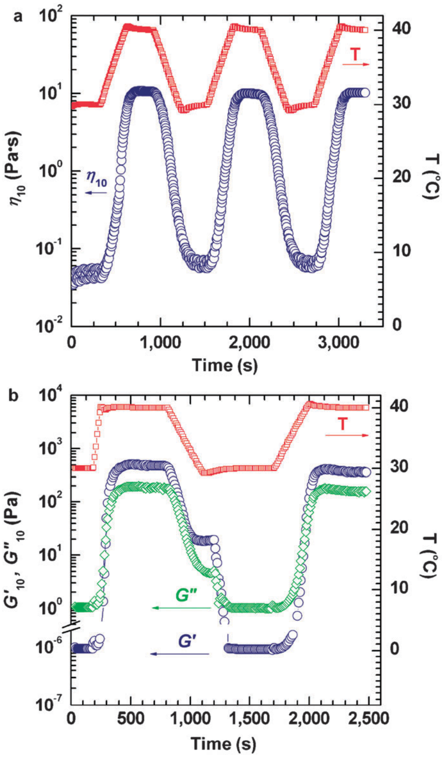

Fig. 3 The thermoreversible rheological response of the PDAS/NaCl solution. The temperature was controlled *via* a preset procedure and the resulting apparent viscosity was at a shear rate of 10 s^{-1}, η_{10} (a) and the apparent moduli at 10 rad s^{-1} G'_{10} and G''_{10} (b) were recorded as a function of time.

In addition to the stimuli responses discussed above, the PDAS gel can also be de-gelled by cooling (Fig. 3), which enables one to control the rheological behavior easily by adjusting the ambient temperature *via* a preset procedure. The initial solution was kept at 30 °C, so the apparent viscosity at a shear rate of 10 s^{-1} (η_{10}) is maintained at 0.05 Pa·s (Fig. 3a). When the temperature is increased from 30 °C to 40 °C, η_{10} grows gradually because of the thermal stimulus and the equilibrium values of η_{10} at 40 °C are about two hundred times that at 30 °C. During cooling back to 30 °C, η_{10} regresses and after several heating/cooling cycles η_{10} can still regress back to the original state. G' and G'' can also be controlled by adjusting the external temperature. The sample is poorly viscous ($G' < G''$) at 30 °C and elastic ($G' > G''$) at 40 °C; and a clear gelling and de-gelling process occurs with the corresponding increases and decreases in temperature (Fig. 3b). In brief, one can freely switch the PDAS gel between its "on" (strongly elastic) and "off" (poorly viscous) state; thus, it is a smart reversible thermogel because of its response to thermal stimuli and switchability.

The variation in rheological behavior is normally attributable to the micellar structural changes. The microstructural morphology of the 30 °C and 40 °C PDAS solutions were investigated *via* Cryo-TEM observations. There were globular and short rod-like micelles in the 30 °C solution (Fig. 4a), which can perfectly explain the poorly viscous Newtonian flow behavior. However, in the case of the 40 °C solution, networks of entangled worm-like micelles form, which are responsible for the strongly elastic gel behavior (Fig. 4b).

The thermal stimulus response of the PDAS/NaCl solution may be ascribed to the decrease of the solubility of the hydrophobes upon heating, as occurs for polymer gels with the property of gelation upon heating.[7a,9] Note that an inorganic salt, NaCl, with a concentration of 0.5 M exists in the solution, so the thermo-response may have a certain correlation with the "salting out" effect of the hydrophobic moieties of the amphiphiles. A possible mechanism of the switchable gelation is schematically illustrated in Fig. 5. At 30 °C, the "salting out" effect of the amphiphilic PDAS caused by NaCl is weaker, and thus more PDAS molecules are dispersed as surfactant monomers, but it is stronger at 40 °C and thus the solubility of the hydrophobic moieties of the PDAS tail is lower, resulting in the loss of the monomers (*i.e.*, the decrease in the solubility of the PDAS). These molecules then join to create the smaller self-assemblies, which promotes the growth of the micelles from short rods into entangled long worms. This micellar transition results in the gelation of the PDAS/NaCl solution. When the temperature is decreased to

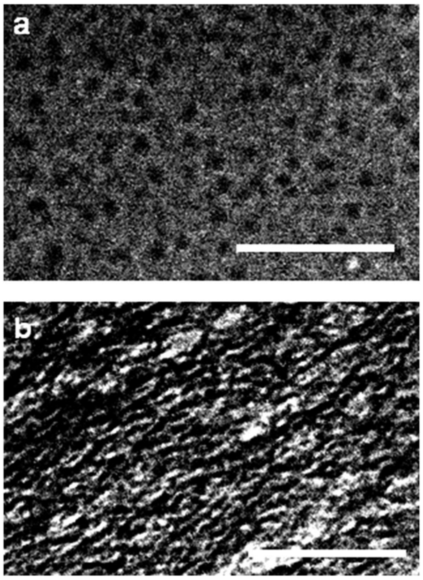

Fig. 4 Cryo-TEM observations of the 30 °C (a) and 40 °C (b) PDAS/NaCl solutions. Bars are 100 nm.

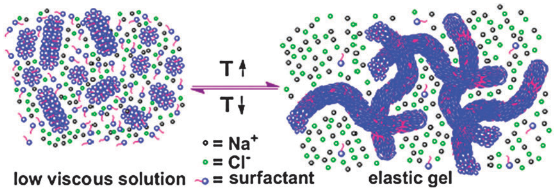

Fig. 5 A schematic illustration of the switchable gelation mechanism.

the initial value, the long worms decompose because of the loss of amphiphiles, and the micellar structures, as well as the rheological properties, regress to the initial state. If this mechanism is correct, thermogelation will not be observed for a PDAS solution without NaCl. This presumption can be demonstrated by rheological comparison of two solutions of 1.0 M PDAS in the presence and absence of NaCl upon heating (Fig. 6). With increasing temperature, thermogelling occurs in the former solution but no change could be detected for the latter one.

PDAS is a betaine surfactant, which normally show good biocompatibility.[10a,13c,15] The gelling temperature of the PDAS thermogel is approximately equal to that of human body, making it promising for potential applications in tissue engineering. One can easily prepare a mixed solution of cells and surfactant at room temperature and inject it into the desired site, which will consequently result in a solid cell/gel construct because of heating of the surfactant by the body.[5a]

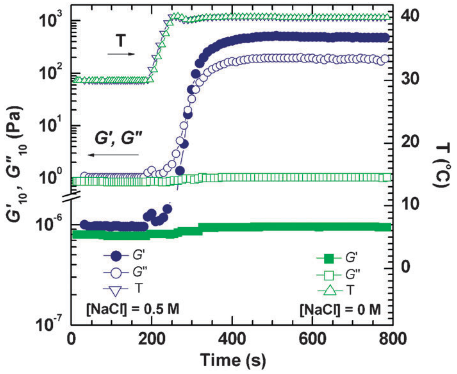

Fig. 6 A rheological comparison of the two solutions, 1.0 M PDAS in the presence of 0.5 M NaCl and absence of NaCl, upon heating.

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