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Triggered Self-Assembly of Simple Dynamic Covalent Surfactants

Christophe B. Minkenberg, Louw Florusse, Rienk Eelkema, Ger J. M. Koper, and Jan H. van Esch*

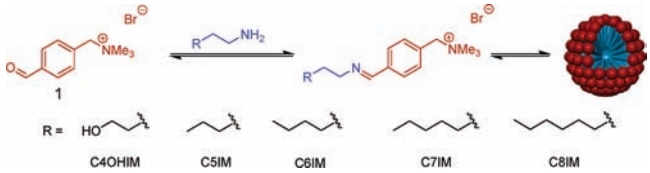
Delft University of Technology, DelftChemTech, Julianalaan 136, 2628 BL Delft, The Netherlands

Received April 16, 2009; E-mail: j.h.vanesch@tudelft.nl

Surfactants continue to attract widespread industrial and scientific attention, ranging from applications in detergent formulation to self-assembly of protocells and controlled drug delivery. Control of surfactant self-assembly using environmental stimuli is critical in many of these applications and could provide a breakthrough in the construction of artificial biomimetic architectures. Several surfactant systems in which a change in aggregate morphology is triggered by external stimuli have been reported.[1−6] However, systems in which the on/off assembly and disassembly of amphiphiles can be triggered remain largely unexplored. Dynamic combinatorial chemistry (DCC)[7−9] is a powerful tool for the construction of supramolecular architectures because of its reversible molecular recognition properties and has already led to the controlled formation and amplification of macrocycles,[10,11] gels,[12,13] and polymers.[14−16] Recently, it has been shown that the formation and dissociation of dynamic covalent surfactants[17] based on insoluble precursors lead to autocatalytic micelle formation[18] and transformation into vesicles and oil droplets,[19] respectively.

Here we report a prototype surfactant system that can be switched between an aggregated, amphiphilic state and a nonaggregated, nonamphiphilic state by a change in pH or temperature. This switchable surfactant system is formed from simple nonamphiphilic, water-soluble precursors through the formation of a dynamic covalent bond. The reversible character of this bond allows control over the surfactant concentration, which can be used to trigger self-assembly, simply by displacing the equilibrium away from the water-soluble nonamphiphilic precursors by changing the pH and temperature. To this end, we mixed a polar aldehyde-functionalized headgroup fragment[20] and an apolar primary-amine-functionalized chain extender, forming amphiphiles in situ through the formation of covalent imine bonds (Scheme 1). The advantage of using imine chemistry is that both the aldehyde and amine building blocks have only one active functionality for directional dynamic bond formation, which prevents the formation of nonamphiphilic compounds.[7] We chose to combine an aromatic aldehyde with several aliphatic amines (Scheme 1)[20] because in general the equilibrium constant for imine formation is largest using this combination.[21]

Scheme 1. Dynamic Formation of Imine Amphiphiles[a]



[a] In pH 11.8 phosphate buffer at 25 °C.

Imine formation was observed by ^{1}H NMR spectroscopy, even at millimolar concentrations, after mixing equimolar amounts of both building blocks in an aqueous buffer solution (pH 11.8) at 25 °C. The observation of separate peaks for the aldehyde and imine indicates that the imine formation equilibrium is slow on the NMR time scale. However, at higher concentrations the imine peak gradually shifts upfield, indicating that association into micellar structures involves an equilibrium that is fast on NMR time scale. The concentration from which the imine signals significantly shift upfield ($\Delta\delta > 0.05$ ppm) was taken as the critical micelle concentration (CMC) (see Table 1, Figure 1B, and Figure S3 in the Supporting Information). This phenomenon was investigated in more detail by drop-volume surface tension and dynamic light scattering (DLS) measurements. The surface tension studies clearly showed that the formed imines are surface-active, with surface tensions of 37 mN/m at surfactant concentrations above the CMC (Figure S6).

The CMC values determined with surface tension match nicely with the ^{1}H NMR results and, as expected, decrease with increasing chain length of the surfactant (see Table 1 and Table S1). The hydrodynamic diameters measured by DLS were ∼5 nm, which is a typical size for micelles formed from single-chain surfactants (see Table 1 and Table S2).

Table 1. CMCs and Hydrodynamic Diameters for Micelles of **1**[a]

surfactant system	CMC_{ald} (mM)[b]	CMC_{im} (mM)[c]	D_h (nm)[d]
C4OHIM	–	–	–
C5IM	22.7	10.7	3.8 ± 0.8
C6IM	13.5	6.7	4.4 ± 1.2
C7IM	5.5	3.8	5.5 ± 1.1
C8IM	1.8	0.9	6.0 ± 1.6

[a] All measurements were performed in pH 11.8 phosphate buffer at 25 °C. [b] Determined using ^{1}H NMR, expressed in terms of the initial aldehyde concentration. [c] Determined using ^{1}H NMR, expressed in terms of the equilibrium imine concentration. [d] Determined using DLS.

Neither the aldehyde nor the amine building blocks are surface-active under the mentioned conditions. Additionally, the control system C4OHIM, which was composed of **1** and the polar chain extender 4-amino-1-butanol, did not show amphiphilic behavior or micelle formation either (Figure 1B and Figures S3 and S6).

From a constitutional point of view, it is anticipated that micelle formation should lead to imine stabilization.[18] We investigated this by measuring imine conversion curves for C4OHIM and micelle-forming C5IM, C6IM, C7IM, and C8IM at thermodynamic equilibrium[20] and observed that above their CMCs, C7IM and C8IM clearly deviate from the other investigated systems. The slopes of the sigmoidal C7IM and C8IM curves are significantly steeper than those for the C4OHIM, C5IM and C6IM systems. The situation below the CMC was described by fitting the C4OHIM data with a simple one-binding-site model; this gave an equilibrium constant for imine formation of 1050 ± 35 M^{-1}, which is of the same order of magnitude as those reported for similar systems (see Figure 1A and Figure S2).[21] We can conclude from these results that in contrast to C4OHIM, C5IM, and C6IM, micelle association for C7IM and C8IM is more cooperative, resulting in additional imine stabilization. These NMR studies point out that the imine self-assembly equilibrium, which is fast on the NMR time scale, is

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coupled to the imine formation equilibrium, which is slow on NMR time scale. In contrast with similar systems,[18,19] the precursors are not surface-active and remain soluble at low surfactant concentrations, which makes this system fully reversible. These properties make these systems ideal smart-surfactant assemblies, in which a displacement of the imine equilibrium by, for example, pH or temperature can be used to trigger self-assembly.

The pH-triggered demicellization of a C7IM solution was examined using fluorescence emission spectroscopy, with Nile Red as a hydrophobic probe.[22] Nile Red emission was observed at 654 nm in buffer, but addition of C7IM at concentrations above its CMC_{im} was accompanied by a blue shift of the Nile Red emission to 645 ± 2 nm, indicating the incorporation of the Nile Red probe molecules into the hydrophobic microenvironment of the C7IM micelles. The imine micelles dissociated upon titration of a concentrated C7IM micelle solution with acid, and this was accompanied by a red shift in the emission due to the release of Nile Red from the hydrophobic micelle core (Figure 2A).

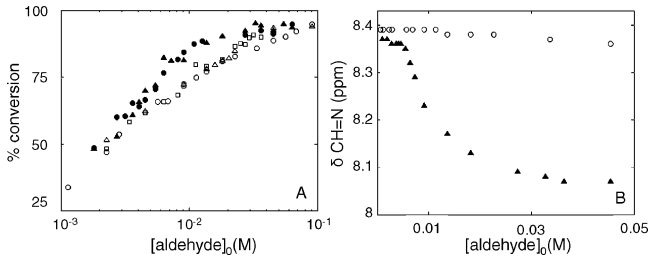

Figure 1. (A) Imine conversion curves for C4OHIM (○), C5IM (△), C6IM (□), C7IM (▲), and C8IM (●) as functions of initial aldehyde concentration. (B) Imine CH═N chemical shifts of C7IM (▲) and C4OHIM (○) as functions of initial aldehyde concentration, obtained from ^{1}H NMR measurements in pH 11.8 phosphate buffer at 25 °C.

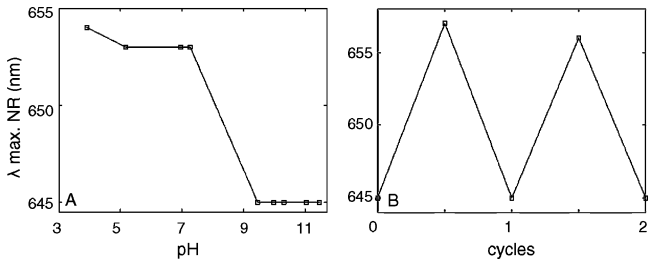

Figure 2. (A) Nile Red maximum emission wavelength as a function of pH, starting with a 12.5 mM C7IM micelle solution at 25 °C and pH 11.8. Nile Red was excited at 550 nm and used in probe concentrations of 5 μM. (B) Nile Red encapsulation is pH reversible, going from pH > 10.5 (cycles 0, 1, and 2) to pH < 7.2 (cycles 0.5 and 1.5).

At pH 7.2, an emission maximum of 654 ± 2 nm was observed, corresponding to Nile Red emission in pure buffer. ^{1}H NMR experiments showed that at this pH the imine surfactants had completely dissociated into their aldehyde and amine precursors (see Figure S8). The demicellization process was entirely reversible, which was observed by a blue shift from 654 ± 2 to 645 nm when the pH of the acidic solution was changed back to its original alkaline state and vice versa (Figure 2B).

Secondly, we were interested in seeing whether dynamic covalent micelles can be switched between assembly and disassembly by changes in temperature. We studied this effect using ^{1}H NMR spectroscopy by measuring the aggregation behavior of a pH 11.8 surfactant solution of C7IM (**I**) well above ($[imine]_{total}$ = 7.2 mM ≈ 2 × CMC_{im}) and (**II**) below ($[imine]_{total}$ = 2.7 mM) the CMC_{im} as a function of temperature. A significant decrease in imine conversion was observed in both samples upon heating from 25 to 75 °C (see Figure S9). Simultaneously, the position of the imine peak for **I** underwent a downfield shift until a plateau was reached at 55 °C. However, this peak position for **II** remained constant across the entire temperature range. These results show that a downfield shift of the imine peak accompanies the dissociation of the micellar aggregates with increasing temperature for **I**. A constant chemical shift was observed for **I** at temperatures of 55 °C and higher, indicating complete micelle dissociation. The total imine concentration at 55 °C was calculated to be 3.3 mM, which corresponds quite well with the CMC_{im} of C7IM at room temperature (3.8 mM) at pH 11.8. These observations indicate that the micelle dissociation is due to imine dissociation instead of a more general dependence of the CMC on temperature, as found for more common surfactants.[23]

In conclusion, this study represents a new approach for pH- and temperature-triggered on/off self-assembly of micellar aggregates by reversible displacement of the equilibrium between nonamphiphilic building blocks and their amphiphilic counterparts. The dynamic nature of the system and the use of nonamphiphilic starting materials provides facile entry into a variety of complex aggregates after just simple mixing using a library approach.[7,9] The potential for drug delivery was shown by reversible uptake and release of an organic dye in aqueous media. The stabilization of the dynamic covalent imine bonds by self-aggregation and their associated dynamic constitutional response to changes in pH and temperature make these structures highly interesting candidates for future smart drug-delivery vehicles and for the switchable formation of bilayers and polyelectrolytes.

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Supporting Information Available: Synthetic procedures and results of surface tension and ^{1}H NMR titration experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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