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Spatial and Temporal Control of Surfactant Systems

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Abstract

This paper reviews some recent progress on approaches leading to spatial and temporal control of surfactant systems. The approaches revolve around the use of redox-active and light-sensitive surfactants. Perspectives are presented on experiments that have realized approaches for active control of interfacial properties of aqueous surfactant systems, reversible control of microstructures and nanostructures formed within bulk solutions, and *in situ* manipulation of the interactions of surfactants with polymers, DNA and proteins. A particular focus of this review is devoted to studies of amphiphiles that contain the redox-active group ferrocene – reversible control of the oxidation state of ferrocene leads to changes in the charge/hydrophobicity of these amphiphiles, resulting in substantial changes in their self-assembly. Light-sensitive surfactants containing azobenzene, which undergo changes in shape/polarity upon illumination with light, are a second focus of this review. Examples of both redox-active and light-sensitive surfactants that lead to large ($> 20\text{mN/m}$) and spatially localized ($\sim\text{mm}$) changes in surface tensions on a time scale of seconds are presented. Systems that permit reversible transformations of bulk solution nanostructures – such as micelle-to-vesicle transitions or monomer-to-micelle transitions – are also described. The broad potential utility of these emerging classes of amphiphiles are illustrated by the ability to drive changes in functional properties of surfactant systems, such as rheological properties and reversible solubilization of oils, as well as the ability to control interactions of surfactants with biomolecules to modulate their transport into cells.

1. Introduction

The ability of surfactants to modify interfacial properties and self-assemble into micelles or other nanostructures is crucial to many industrial processes, such as coating and spreading processes, formation of foams, detergency, micellar catalysis, separations processes, etc.¹ Recently, approaches leading to active and reversible control of surfactants have received substantial attention because they suggest ways to potentially optimize the utilization of surfactants in these traditional contexts (for example, by allowing re-use of surfactants through cycling of the molecules between “on” and “off” states) and also to create new types of processes based on surfactant-driven phenomena, such as pumping and control of flow in microfluidic devices,² development of new separation methods,³ the design of new agents for actively controlled gene delivery,⁴ and fundamental studies of the mechanisms of protein refolding.⁵

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The development of surfactant systems that can be placed under active control has been founded on the design and optimization of surfactants that respond to easily manipulated external stimuli, such as redox potentials (which can be manipulated electrochemically) or incident illumination. Examples of redox-active surfactants that have been studied include those surfactants that contain functional groups such as ferrocene, viologen, or N-alkylated nicotinamides.⁶ These surfactants allow facile manipulation of the charge of the surfactants. For example, ferrocene is an organometallic complex that is redox-active and is easily incorporated into synthetic schemes leading to ferrocene-modified surfactants.⁷ A wide range of ferrocene-modified surfactants have now been synthesized (see Figure 1): (1) single-chain surfactants with the ferrocenyl group incorporated near anionic (Figure 1a)⁸ or cationic head groups (Figure 1b);⁹⁻¹³ (2) single-chain surfactants containing ferrocenyl groups at the ends of hydrophobic tails, with either cationic (Figure 1c),^{2, 14-16} anionic (Figure 1d)¹⁷ or nonionic (Figure 1e) head groups;¹⁸⁻²³ (3) single-chain surfactants with hydrocarbon tails containing double bonds and ferrocenyl groups located adjacent to non-ionic and cationic head groups (Figure 1f and figure 1g);⁶ (4) double-tailed cationic surfactants with ferrocene groups attached to each hydrophobic tail (Figure 1h²⁴ and 1i²⁵⁻²⁸); (5) double-tailed surfactants with ferrocene located near anionic (Figure 1j²⁹) or nonionic (Figure 1k²⁹) head groups; (6) double-tailed surfactants in which one hydrophobic chain is attached to each of the two cyclopentadienyl rings of the ferrocene (Figure 1l²⁹); (7) amphiphiles that contain a carbohydrate head-group linked to an aliphatic chain via ferrocene (Figure 1m³⁰); and (8) fluorocarbon-hydrocarbon hybrid surfactants with a pendant ferrocene group (Figure 1n³¹). This remarkable diversity of ferrocene-containing amphiphiles has enabled a wide range of studies of the influence of the oxidation state of ferrocene on solution properties. For example, studies of BFDMA (bis(11-ferrocenylundecyl) dimethylammonium bromide, Figure 1i) have provided insights into approaches that permit active control of double-tailed lipid-like systems, whereas studies of FTMA ((11-ferrocenylundecyl)dimethylammonium bromide, Figure 1c) have allowed the influence of ferrocene on the properties of classical cationic surfactants to be investigated. Finally, we comment that the structures shown in Figure 1 include some rather exotic molecules, such as the fluorocarbon- hydrocarbon hybrid surfactant, FcFHUB (Figure 1n). These surfactants exhibit particularly unusual behaviors. As described in the sections below, the surfactants shown in Figure 1 have provided a rather comprehensive perspective on the use of ferrocene as a redox-active group to achieve spatial and temporal control over the properties of surfactant systems.

A number of light-sensitive surfactants have also been investigated in recent studies, including surfactants that incorporate photo-active groups such as azobenzene,³²⁻³⁶ spiropyran³⁷⁻³⁹ and stilbene.^{40, 41} These surfactants undergo reversible (to differing extents) changes in conformation upon sequential illumination with UV and visible light. Upon illumination with UV light, azobenzene and stilbene undergo a reversible photoisomerization from the thermodynamically stable *trans* form with a planar structure, to a bent *cis* form, which is less hydrophobic than the *trans* form due to the dipole moment associated with the bent conformation³⁵ (Figure 2A and 2B). In contrast, spiropyran changes from the energetically stable form, which is non-ionic and relatively hydrophobic, to the merocyanine form, which is zwitterionic, upon illumination with UV light (Figure 2C). Of these various light-sensitive groups that have been investigated in past studies, azobenzene is a particularly attractive photosensitive group because it has stable and simple photochemistry, and because it can be easily incorporated into various types of surfactant architectures (Figure 3).^{32-36, 42-48}

In this review, we discuss recent progress towards active control of surfactant systems based on a subset of the redox active surfactants and light-sensitive surfactants described above. We do not attempt to be comprehensive in our description of studies reported in the

literature, but rather focus on those advances that have come from our own laboratory. Where appropriate and useful, we do describe some companion studies reported from other laboratories. We have organized the presentation of the perspective below into three parts. First, we describe studies that have sought to achieve active control of interfacial properties of aqueous solutions of surfactants, and we discuss our current understanding of the molecular mechanisms that underlie the measured changes in interfacial properties. Second, we describe studies that have aimed to achieve active control of the self-assembly of surfactants in bulk solution, based on both redox-active surfactants and light-sensitive surfactants. Third, and finally, we describe the use of redox-active and light-sensitive surfactants to manipulate the interactions of surfactants with macromolecules, such as semi-synthetic polymers, DNA and proteins. For the case of redox-active surfactants, we also describe how actively controlled gradients in surfactant-based properties have been used to drive Marangoni flows (based on gradients in interfacial properties) and bulk solution transport processes in microscale systems (based on gradients in bulk solution properties such as micellization). These latter studies serve to illustrate the technological potential of the outcomes of this research.

2. Redox-Active Surfactants under Electrochemical Control

Because ferrocene is chemically stable over a wide range of solution conditions,⁴⁹ and because the redox potentials of ferrocene allow facile control of the oxidation state of ferrocene in aqueous solution (without substantial hydrolysis of water),¹² the majority of redox-active surfactant systems studied in the recent past have employed ferrocene as the redox group. For this reason, in the sections below, we focus our discussion on ferrocenyl surfactants. The ferrocene group is electrically neutral and sparingly soluble in water. However, when oxidized, it forms the ferricenium ion, which is cationic and hydrophilic. Changes in the oxidation state of ferrocenyl surfactants can thus lead to substantial changes in the charge and amphiphilic nature of the surfactants. Depending on the structure of the molecule that hosts the ferrocene group, and the location of the ferrocene within that structure, a wide range of surfactant-based properties of aqueous systems can be accessed by using ferrocene.

2.1 Active Control of Interfacial Properties

Several of the ferrocenyl surfactants shown in Figure 1 have been investigated for their ability to be used for active control of surface tensions of aqueous solutions. Tajima and coworkers reported that oxidation of $\text{FcCH}_2\text{N}^+(\text{CH}_3)_2(\text{CH}_2)_{10}\text{CH}_3$ (Figure 1b) with AgNO_3 at 25°C led to changes in the surface tension of aqueous solutions of less than 5mN/m.¹³ Those measurements, however, appear to have been influenced by the use of silver ions as the oxidizing agent and/or the choice of temperature (the temperature was below Kraft temperature of the system). Subsequent measurements of surface tensions of aqueous solutions of these surfactants at 40°C (above the Kraft temperature), which employed electrochemical oxidation, found that changes in surface tension as large as 15mN/m are possible using this system.⁹ Even larger changes in surface tension (>20mN/m), have been achieved by electrochemical control of the oxidation state of the monomeric ferrocenyl surfactant FTMA (Figure 1c), and a related dimeric ferrocenyl surfactant (Figure 1h).^{14, 15, 24} Because these changes were driven electrochemically, these latter studies also opened up the possibility of spatial and temporal control of surface tensions of aqueous solutions using redox-active surfactants, and associated phenomena (such as control of wetting behaviors), as described below.

Figure 4B shows the equilibrium surface tensions of aqueous solutions (0.1M Li_2SO_4 , pH2) of reduced and oxidized FTMA. Oxidation of FTMA in aqueous solution (Figure 4A) at concentrations of FTMA below 10mM resulted in an increase in surface tension, with a

maximum change of 23mN/m (from 49mN/m to 72mN/m) at a concentration of 0.1mM.¹⁵ Correspondingly, the excess surface concentrations of surfactant (estimated using the Gibbs adsorption equation) in equilibrium with bulk solution concentrations of FTMA of 0.1mM were shown to decrease from 2×10^{-6} mol/m² to less than 0.1×10^{-6} mol/m² upon oxidation.¹⁵ This result indicates that the increase in surface tension upon oxidation of FTMA under these conditions resulted from the desorption of FTMA from the surface of the solution. The desorption of FTMA upon oxidation of the ferrocene to ferrocenium is thought to be caused by two factors. First, oxidation of the sparingly water-soluble ferrocenyl moiety to the ferrocenium cation reduces the hydrophobic driving force for adsorption of surfactant to the surface of the aqueous solution; second, the increase in net charge of the ferrocenyl surfactant upon oxidation (from +1 to +2) leads to an increase in the electrostatic repulsion between FTMA molecules at the surface, which in turn limits adsorption of oxidized FTMA to the surface. In contrast to the increase in surface tension measured at low concentrations of FTMA in bulk solution, at higher concentrations (≥ 10 mM), oxidation of FTMA leads to a *decrease* in surface tension. Estimates of the limiting (maximum) excess surface concentrations of FTMA for both reduced and oxidized forms revealed the excess surface concentration of oxidized FTMA to be 2.3×10^{-6} mol/m², slightly higher than for reduced FTMA (2.0×10^{-6} mol/m²).¹⁵ That is, at high concentrations of FTMA in bulk solution (≥ 10 mM), oxidation of FTMA does not lead to desorption of surfactant from the surface of aqueous solutions but instead leads to its adsorption. The excess surface concentration of oxidized FTMA is greater than reduced FTMA at high bulk concentrations because oxidized FTMA does not form micelles whereas reduced FTMA does form micelles: The oxidation-induced disassembly of micelles in bulk solution leads to an increase in the cratic contribution to the chemical potential of the surfactant in bulk solution, which in turn drives the partitioning of the surfactant towards the surface of the solution. As is evident from Figure 4B, the increase in the excess surface concentration of oxidized FTMA molecules (with charge of +2) leads to a decrease in the surface tension of the solution.

A related observation derived from Figure 4B is that reduced and oxidized FTMA lower the surface tensions of aqueous solutions at surprisingly large values of area per molecule. By using the excess surface concentrations obtained from the plot of surface tensions of FTMA in Figure 4B, the *minimum* surface area occupied by each molecule ($A_{\min}$) is calculated to be 85 ± 5 Å² for reduced FTMA, and 75 ± 5 Å² for oxidized FTMA, respectively.¹⁵ To provide insight into these experimental observations, we developed a simple molecular-thermodynamic model of the FTMA-laden interfaces of aqueous solutions.⁵⁰ The model leads to the conclusion that both the reduced and oxidized states of FTMA adopt similar looped conformations at the surface of the aqueous solution (as shown in Figure 4C).^{15, 50} According to the molecular thermodynamic model, this looped conformation (and associated configurational entropy) plays a central role in the lowering of surface tension observed for the reduced state of FTMA, as shown in Figure 4B. In particular, we note that reduced FTMA lowers the surface tensions of aqueous solutions to 49mN/m at a limiting area per molecule of 85 Å². In contrast, experiment results show that under the same conditions (0.1M Li₂SO₄, pH 2), the cationic surfactant dodecyltrimethylammonium bromide (DTAB) reduces the surface tension to only 71mN/m when it occupies an interfacial area of 85 ± 5 Å².¹⁴ This comparison indicates that the ability of FTMA to lower surface tension to 49mN/m at a limiting area per molecule of 85 Å² is a consequence of the packing of the FTMA in a looped configuration at the surface of the solution (not the electrostatic contributions to the surface pressure).

Importantly, the changes in surface tension shown in Figure 4B that result from oxidation of FTMA can be reversed by reduction of the ferrocenium cation back to ferrocene. As shown in Figure 4D, the surface tensions of aqueous solutions can be cycled many times (>14 cycles) on time scales of minutes by using electrochemical methods.¹⁴ The rates of change

in surface tensions in these experiments were determined by mass transport of surfactants to electrodes, and thus faster changes in properties can be realized in microscale systems (see below).

2.2 Active Control of Surfactant Self-Assembly in Bulk Solution

As mentioned above, changes in the oxidation state of ferrocenyl surfactants can lead to large changes in the self-assembly of these surfactants in bulk solution, including changes in the critical micelle concentration (CMC), or changes in the microstructure of aggregates. For example, inspection of the surface tension measurements in Figure 4B reveals that the reduced state of FTMA possesses a CMC of 0.1mM (the surface tension changes little at bulk concentration of FTMA greater than 0.1mM) whereas oxidized FTMA does not measurably self-associate over the experimental conditions reported in the figure (up to 30mM in concentration of oxidized FTMA in 0.1M Li_2SO_4). These results indicate that oxidation of reduced FTMA at concentrations ranging from 0.1mM to 30mM leads to the disassembly of micelles formed by reduced FTMA to singly dispersed molecules of oxidized FTMA. This conclusion has been confirmed by several other studies, including studies that have involved light scattering measurements.¹⁷

It is important to note that the changes in self-assembly that can be induced by oxidation of ferrocene can be manipulated through design of the host surfactant structure. For example, substitution of the cationic group of FTMA ($\text{N}^+(\text{CH}_3)_3$) by an anionic head group (SO_3^-), as shown in Figure 1d, leads to substantially different bulk aggregation behavior.¹⁷ The changes in the aggregation behavior of $\text{Fc}(\text{CH}_2)_{11}\text{SO}_3^-$ are evident via their impact on interfacial properties of solutions of these surfactants. Measurements of the equilibrium surface tensions of aqueous solutions of $\text{Fc}(\text{CH}_2)_{11}\text{SO}_3^-$ and $\text{Fc}^+(\text{CH}_2)_{11}\text{SO}_3^-$ (10mM Li_2SO_4 , pH 5) at 37°C (results shown in Figure 5A) lead to several observations. First, in contrast to oxidized FTMA, which does not exhibit a measurable CMC, $\text{Fc}^+(\text{CH}_2)_{11}\text{SO}_3^-$ forms aggregates at bulk concentrations of 0.15mM, which is lower than the CMC of $\text{Fc}(\text{CH}_2)_{11}\text{SO}_3^-$ (0.4mM). This result is interpreted to indicate that oxidation of $\text{Fc}(\text{CH}_2)_{11}\text{SO}_3^-$ to $\text{Fc}^+(\text{CH}_2)_{11}\text{SO}_3^-$ decreases the repulsive electrostatic interactions between surfactant molecules thus facilitating their aggregation. Complementary dynamic light scattering measurements determined the hydrodynamic diameter (D_h) of the aggregates formed by the oxidized surfactant to be $70 \pm 8\text{nm}$, and static light scattering measured the radius of gyration (R_g) of the same aggregates to be $38 \pm 8\text{nm}$. The calculated ratio R_g/R_h of the aggregates formed by $\text{Fc}^+(\text{CH}_2)_{11}\text{SO}_3^-$ is 1.0 ± 0.3 , a value that is consistent with the presence of thin-shelled vesicles.⁵¹ At high surfactant concentrations ($c > 0.4\text{mM}$) where both $\text{Fc}(\text{CH}_2)_{11}\text{SO}_3^-$ and $\text{Fc}^+(\text{CH}_2)_{11}\text{SO}_3^-$ form aggregates, measurements based on quasi-elastic light scattering reveal the aggregates formed by $\text{Fc}(\text{CH}_2)_{11}\text{SO}_3^-$ are globular in shape with diameters of $6 \pm 2\text{nm}$. Thus, for bulk concentrations greater than 0.4mM, oxidation of $\text{Fc}(\text{CH}_2)_{11}\text{SO}_3^-$ to $\text{Fc}^+(\text{CH}_2)_{11}\text{SO}_3^-$ leads to the transformation of globular aggregates ($D_h = 6 \pm 2\text{nm}$) into vesicular aggregates ($D_h = 70 \pm 8\text{nm}$) (as shown in Figure 5B).

Several recent studies from outside our laboratory also provide excellent examples of the diversity of changes in aggregate microstructures that can be achieved by manipulating in the oxidation states of ferrocenyl surfactants.⁵²⁻⁵⁵ For example, Abe and coworkers have reported that the mixing of the anionic surfactant, sodium dodecylbenzenesulfonate (SDBS) with the cationic surfactant, FTMA, leads to the formation of vesicles over a certain range of total surfactant concentrations and surfactant concentration ratios ($[\text{FTMA}]/[\text{SDBS}]$), and that the assembly and disassembly of vesicles can be controlled by changing the oxidation state of FTMA.⁵²⁻⁵⁴ For example, dynamic light scattering measurements of an aqueous solution (0.02M NaCl) containing 1wt% total surfactant with the ratio $[\text{FTMA}]/[\text{SDBS}] = 7:3$ (Figure 6 a-c) revealed the mixture of reduced FTMA and SDBS to form coexisting micelles (described as “swollen micelles”, with hydrodynamic diameters of $\sim 35\text{nm}$) and

vesicles (with diameters around 110nm and 570nm, as shown in Figure 6a). Oxidation of FTMA was shown to disassemble the large vesicles, leaving only small micelles with hydrodynamic diameters of ~10nm (Figure 6b). The changes in microstructure induced by oxidation of the FTMA were reported to be reversed upon reduction of the oxidized FTMA, although the hydrodynamic sizes of the vesicles were measured to increase slightly (Figure 6c). Optical micrographs (Figure 6d-f) supported these conclusions, showing the presence of vesicles in the solutions containing reduced FTMA (Figure 6d and 6f) and the absence of visible aggregates in solutions containing oxidized FTMA (Figure 6e). The authors suggested that FTMA and SDBS associate into an ion pair in aqueous solution, leading to formation of a so-called pseudo-double chain surfactant and vesicular assemblies (similar to mixtures of classical anionic and cationic surfactants). Oxidation of FTMA is proposed to disrupt the formation of the pseudo-double chain surfactant, and thereby prevents formation of the vesicles.

Ferrocenyl surfactants have also been formulated in aqueous solutions to permit active control of the formation of worm-like micelles. In particular, Tsuchiya and coworkers⁵⁵ reported that addition of 20mM sodium salicylate (NaSal) to an aqueous solution of 50mM reduced FTMA led to formation of a highly viscous solution, as depicted in Figure 7A. However, upon oxidation of the FTMA, the solution was observed to undergo a pronounced reduction in viscosity (Figure 7B). These qualitative observations were quantified by dynamic viscoelasticity measurements, revealing that the mixture of reduced FTMA and NaSal formed a non-Newtonian fluid with a zero shear viscosity of 15 Pa·s that decreased upon oxidation of FTMA by four orders of magnitude to 2.5×10^{-3} Pa·s.⁵⁵ The microstructure of the aggregates formed in the solution of reduced FTMA and NaSal was characterized by freeze fracture transmission electron microscopy (FF-TEM). The electron micrographs confirmed formation of worm-like micelles with diameters of 8nm and lengths in the micrometer range (depicted schematically in Figure 7C).⁵⁵ In contrast, no such large aggregates were observed in solutions containing the oxidized FTMA and NaSal. These results demonstrate that oxidation of FTMA can lead to the disruption of elongated worm-like micelles into smaller aggregates (Figure 7D).

2.3 Electrochemical Control of Interactions of Ferrocenyl Surfactants with Macromolecules

Whereas the studies described above have reported on oxidation-induced changes in the self-assembly of FTMA (and other related ferrocenyl surfactants) in aqueous solution, recent studies have moved to exploit the broad class of ferrocenyl amphiphiles to manipulate the interactions of surfactants with macromolecules in solution, including semi-synthetic polymers⁵⁶ and DNA.^{57, 58} These studies have been driven by the opportunity presented by ferrocenyl surfactants to provide fundamental insights into the interactions between surfactants and macromolecules species, as well as the technological promise of surfactant-macromolecular complexes that are placed under active control. Below, we provide highlights of some recent studies of electrochemical control of complexes formed by electro-active amphiphiles with either semi-synthetic polymers or DNA.

2.3.1 Interactions of FTMA and a Semi-Synthetic Polymer—The interactions of cationic and anionic surfactants (e.g., SDS and DTAB) with the polymer EHEC (ethyl (hydroxyethyl) cellulose, Figure 8A) have been studied in dilute aqueous solution (0.1%).^{56, 59} At concentrations below a CAC (critical aggregation concentration), the surfactants do not interact strongly with the polymer. Above the CAC, however, EHEC participates in the cooperative formation of a surfactant-polymer aggregate, which is thought to be formed through hydrophobic interaction with multiple polymers. The sizes of the mixed aggregates formed in these systems increase with addition of surfactants, until a characteristic concentration is reached, where sufficient surfactant is present to saturate the

EHEC molecules. Above this concentration, the addition of more surfactant causes dissociation of EHEC aggregates. Building on these observations involving classical surfactants, a recent study has characterized the extent to which EHEC-surfactant interactions can be modulated through control of the oxidation state of ferrocene-containing surfactants. Specifically, the interactions between EHEC and either reduced or oxidized FTMA in aqueous solution (0.1M Li₂SO₄, pH 2.5) were investigated by measuring clouding temperatures and dynamic light scattering.⁵⁶ Figure 8B shows clouding temperatures of aqueous solutions of reduced or oxidized FTMA containing 0.1% wt EHEC (0.1M Li₂SO₄, pH 2.5) as a function of FTMA concentration. In the absence of surfactant, the clouding temperature of the EHEC solution was 32.5±0.4°C. Inspection of Figure 8B reveals that the clouding temperature of the solution decreased upon addition of reduced FTMA at concentrations near its CMC (0.1mM in 0.1M Li₂SO₄), indicating that reduced FTMA promoted the aggregation of EHEC under these conditions. The clouding temperature decreased further with increasing concentration of reduced FTMA, and reached a minimum of 5°C at concentration of 9mM. The addition of reduced FTMA at concentrations greater than 9mM led to an increase in clouding temperature, which suggests that reduced FTMA dispersed the aggregates formed by reduced FTMA and EHEC under these conditions. In contrast to reduced FTMA, which behaves much like a classical surfactant, oxidized FTMA exhibited a qualitatively different effect on the clouding temperature of solutions of EHEC. Specifically, the clouding temperature was determined to decrease monotonically with increasing concentration of oxidized FTMA, showing no evidence of a minimum in the clouding temperature (as a function of concentration) over the concentration range of oxidized FTMA investigated. The magnitude of the decrease in clouding temperature caused by the oxidized FTMA was also found to be smaller than the decrease induced by reduced FTMA at the same concentration. These results indicate that EHEC and oxidized FTMA do not interact via a cooperative mechanism. Overall, the results in Figure 8B clearly demonstrate that the clouding temperatures of dilute EHEC solutions can be manipulated by changes in the oxidation state of FTMA.

Further insights into the interactions of EHEC with reduced or oxidized FTMA were obtained by measurements of dynamic light scattering at 25°C (Figure 8C).⁵⁶ Inspection of Figure 8C reveals that the hydrodynamic radii of EHEC aggregates (0.1% wt, 0.1M H₂SO₄, pH 2.5) without surfactant were measured to be 25±6nm. At concentrations of reduced FTMA lower than 0.05mM, the addition of reduced FTMA did not cause a measurable change in the hydrodynamic size of the aggregates. At slightly higher concentrations of reduced FTMA (0.1mM to 0.3mM), addition of reduced FTMA led to a rapid increase in hydrodynamic radius, with a maximum value of 900nm measured at 0.3mM of FTMA prior to onset of visible cloudiness at higher FTMA concentrations. At concentrations of reduced FTMA between 0.3mM and 20mM, the solutions were observed to be visibly cloudy (as shown in Figure 8C). At still higher concentrations of reduced FTMA (20mM to 25mM), the solutions became clear to the eye, and small aggregates with hydrodynamic radii around 3.5±1.1nm were measured by dynamic light scattering. The sizes of these aggregates are similar to those of micelles of reduced FTMA measured in the absence of EHEC.⁵⁶ Comparable measurements of oxidized FTMA with EHEC revealed hydrodynamic sizes of aggregates in solution that were strikingly different from reduced FTMA, and reminiscent of trends in aggregation induced by addition of simple salts (non-amphiphilic salts) to solutions of EHEC. In particular, oxidized FTMA caused no change in the state of aggregation of EHEC at concentrations below 1mM, and at concentrations above 1mM, the increase in size of the aggregates in solution was monotonic. In summary, these results confirm the strikingly different effects of reduced FTMA and oxidized FTMA on aggregates formed with EHEC that were inferred from the clouding temperature measurements. That is, reduced FTMA enhances aggregation of EHEC at concentrations above the CAC, and then disperses the aggregates at high concentrations, a behavior that is similar to other micelle-

forming surfactants. In contrast, oxidized FTMA does not interact with EHEC at low concentrations, and at high concentrations, it shows a behavior that is more similar to simple salts than classical surfactants. These results demonstrate that changes in the oxidation state of FTMA can be used to tune polymer-surfactant interactions.

2.3.2 Interactions of DNA and Redox-Active Surfactants—Whereas the results above, involving interactions of EHEC with FTMA, demonstrate that reduced FTMA and EHEC undergo a cooperative association, past studies have revealed that cationic surfactants interact with DNA in a manner that is often coined “double cooperativity”.⁶⁰ The term “double cooperativity” is used to characterize the fact that, at concentrations above the CAC, surfactant tends to associate with a sub-population of the DNA molecules in solution. Only after molecules of DNA within this sub-population have been saturated with surfactant, does the additional FTMA associate with FTMA-free DNA molecules in solution. This behavior leads to the presence of coexisting populations of two distinct states of the DNA in solution – “extended, surfactant-free coils” and “compacted, surfactant-DNA aggregates”. A recent study has explored the extent to which this physical situation can be manipulated through changes in the oxidation state of FTMA in solutions containing DNA.⁵⁷

Figure 9(a-g) shows the results of dynamic light scattering measurements from aqueous solutions (1mM Li₂SO₄, pH 5) containing 5μM lambda phage DNA (with respect to DNA nucleotide units) and either reduced or oxidized FTMA. In the absence of FTMA, the DNA in solution exhibited a single broad distribution of hydrodynamic sizes, with an average value of 234nm (Figure 9a). Whereas addition of less than 1μM of reduced FTMA had no measurable impact on the size distribution (Figure 9b, Figure 9I), the presence of 2-5μM of reduced FTMA led to coexistence of extended DNA coils (~250nm) and compact DNA-FTMA globules (~55nm) (Figure 9c and d, Figure 9II). This result is consistent with the above-described notion of double-cooperativity. With increasing concentration of reduced FTMA, the peak in the size distribution corresponding to compacted DNA moved to larger sizes, and at concentrations of FTMA between 10 and 30μM, the peak corresponding to extend coils had disappeared (note that the peak corresponding to compact DNA globules was observed at 85nm) (Figure 9e, 9f, Figure 9III). This result indicated that the DNA in these solutions was condensed into compact globules. Finally, with further addition of reduced FTMA (50 μM or higher), higher order aggregates were formed, with hydrodynamic diameters greater than 1 μm (Figure 9g). In contrast to the above behavior of reduced FTMA, inspection of Figure 9(a-g) reveals the striking result that oxidized FTMA did not significantly change the hydrodynamic size of the DNA, allowing DNA to maintain an extended coil state in the presence of concentrations of oxidized FTMA that are as high as 75 μM (Figure 9a-g). These results, when combined, demonstrate that reduced FTMA, which self-associates in solution, complexes strongly with DNA in manner that is similar to other classic cationic surfactants (e.g. DTAB), causing formation of compact DNA-FTMA globules; in contrast, oxidized FTMA, which does not self-associate in solution, has no measurable impact on the conformations of DNA in solution. These results demonstrate that pronounced changes in DNA-surfactant interactions can be achieved by manipulation of the oxidation state of ferrocene-containing surfactants.

Building from the above study, it has also recently been reported that double-tailed surfactants containing ferrocenyl groups can be exploited to control the formation of complexes between double-tailed surfactants and DNA.^{28, 58} These complexes, which have microstructures that differ substantially from those formed by single-tailed cationic surfactants, are referred to below as lipoplexes. The focus on this class of ferrocenyl surfactants was motivated by the past observation that a range of double-tailed cationic lipids can form complexes with DNA to facilitate the delivery of DNA into cells.^{61, 62} The recent studies sought to determine if reversible control over the oxidation state of electro-

active lipids in complexes of DNA might be exploited as the basis of principles to achieve active, spatial and temporal control over DNA delivery. Towards this goal, several recent studies have shown that the double tailed, ferrocene-containing molecule bis-(11-ferrocenylundecyl) demethylammonium bromide (BFDMA, Figure 1i) transfects cells with an efficiency that depends strongly on the oxidation state of the lipid.^{4, 25} As described in detail below, reduced BFDMA, which possesses a single cationic head group, was shown to be an efficient transfection agent, whereas oxidized BFDMA did not cause high levels of transfection under the same solution conditions. Complementary measurements of the cytotoxicity of BFDMA have also been performed, and these measurements revealed a window of concentrations over which low levels of toxicity were observed.^{4, 25} To provide insights into these observations, the nanostructures and the physical properties of complexes formed by plasmid DNA and BFDMA have been studied.^{28, 58} Below we present an overview of these studies.

A summary of the physical characterization of lipoplexes formed by DNA and BFDMA is shown in Figure 10. Figure 10A shows the results of dynamic light scattering measurements of aqueous solutions (1mM Li₂SO₄, pH5) of 7.3μM plasmid DNA (with respect to DNA nucleotide units) containing either reduced or oxidized BFDMA.⁵⁸ These results revealed that complexes formed by reduced BFDMA and DNA exhibited a maximum in hydrodynamic size (around 2580nm) at a BFDMA concentration of 20μM (corresponding to a charge ratio of 2.75). Furthermore, analysis of the autocorrelation functions (ACFs) of the dynamic light scattering measurements revealed that the addition of reduced BFDMA to the DNA solutions resulted in the elimination of the contributions of DNA chain dynamics to the ACFs, consistent with formation of a structured lipoplex in which the DNA had limited mobility. This behavior was similar to that exhibited by many vesicle-forming cationic lipids such as DoDAB (dioctadecyldimethylammonium bromide). In contrast to these measurements involving reduced BFDMA, complexes formed by oxidized BFDMA and DNA exhibited a weak minimum in hydrodynamic size as a function of increasing concentration of oxidized BFDMA (between 6μM and 10μM). Furthermore, analysis of the ACFs of these solutions did yield evidence of relaxation processes associated with DNA chain dynamics, consistent with the condensation of DNA into loosely-packed aggregates with oxidized BFDMA. Finally, inspection of Figure 10A reveals that oxidized BFDMA, at concentrations between 60μM to 100μM led to formation of very large aggregates (2μm in diameter). Overall, these studies reveal that the behavior of oxidized BFDMA in DNA solutions is reminiscent of small (non-amphiphilic) organic molecules that possess multiple positive charges but do not self associate (such as spermidine, which possesses three charges).

The second set of results shown in Figure 10B involve measurements of ζ-potentials of aggregates formed by 7.3μM DNA and BFDMA (either oxidized or reduced state of BFDMA) at concentration ranging from 2μM to 100μM in aqueous solution from (1mM Li₂SO₄, pH 5)⁵⁸. As shown in Figure 10B, the ζ-potentials of lipoplexes formed by DNA and reduced BFDMA were measured to increase monotonically from -40mV to +40mV with increasing concentration of reduced BFDMA (2μM to 100μM), with the change in sign occurring at ~10μM BFDMA (corresponding to a CR of 1.38). This behavior of the ζ-potential is similar to that of conventional vesicle-forming cationic lipids (e.g., DoDAB and DOPE (dioleoylphosphatidylethanolamine)) when complexed with DNA. In contrast, however, the ζ-potentials of complexes of oxidized BFDMA and DNA were very different, with the sign of the ζ-potential remaining negative over the same concentration range (2-100μM). Similar to the light scattering results reported above, the general ζ-potential behavior exhibited by the oxidized BFDMA is comparable to that reported previously for complexes of DNA and non-self-associating molecules that possess multiple positive charges (e.g., spermidine).^{63, 64} These results are also interesting for at least two additional

reasons. First, inspection of Figure 10B reveals that changes in the oxidation state of BFDMA in complexes with DNA can lead to reversal of the sign of the zeta-potential, suggesting that substantial changes in the organization of the outer region of the lipoplexes must accompany changes in the oxidation state of BFDMA. Second, a number of past studies have correlated transfection efficiency of lipoplexes with ζ -potentials, with the general conclusion that positive values of ζ -potential correlate with higher transfection efficiencies.⁶⁵⁻⁶⁷ The results in Figure 10B thus suggest that the strong dependence of transfection efficiency on the oxidation state of BFDMA may be influenced by the changes in the ζ -potentials of these complexes that accompany the changes in oxidation state of BFDMA.²⁸

The measurements of physical properties described above all hint at the fact that the nanostructure of the lipoplexes formed by BFDMA and DNA is strongly dependent on the oxidation state of the BFDMA. Complementary measurements by small angle neutron scattering (SANS) and cryogenic transmission electron microscopy (cryo-TEM) have confirmed this proposition, and provided important insights into the nanostructure of these complexes.²⁸ As shown in Figure 10C, SANS revealed that 1mM reduced BFDMA and DNA at a CR(+/-) of 1.1:1 in aqueous solution (1mM Li₂SO₄, pH 5) formed multilamellar vesicles with a lamellar periodicity of 5.2nm (indicated by the single Bragg peak at 1.2nm^{-1}). The single peak was interpreted to indicate that the periodicity of the lamellar structure did not extend over large distances. In contrast, SANS of the complexes of oxidized BFDMA and DNA indicated formation of either large, loose non-lamellar aggregates or a network of lamellar structures (q dependence of -2.5) that did not possess measurable periodicity (absence of any Bragg peaks). These conclusions extracted from the SANS measurements were supported by cryo-TEM imaging, which confirmed that reduced BFDMA and DNA formed polydisperse complexes with a multilamellar shell and a compact core (Figure 10C, left). The periodicity of the multilamellar structure was 5.2 ± 0.2 nm, independent of the diameter of the lipoplex. The maximum number of layers per aggregate observed in micrographs was seven, a result that is consistent with the interpretation of the SANS. The cryo-TEM of the complexes formed by oxidized BFDMA and DNA (Figure 10C, right) was also found to be consistent with the SANS (absence of multi-lamellar nanostructure). Overall, these measurements reveal that the oxidation state of BFDMA strongly impacts the nanostructure of complexes of BFDMA and DNA. Although many details of the structure and properties of complexes of BFDMA and DNA remain to be understood, it is now evident that the above-described changes in nanostructure underlie the oxidation state-dependent values of the ζ -potentials of complexes formed by BFDMA and DNA, which in turn likely influence the efficiencies with which lipoplexes of BFDMA and DNA transfect cells.

2.4 Control of Gradients in Concentration of surfactants

The results described above demonstrate how properties of surfactant-based systems can be manipulated (in many cases reversibly) by changes in the oxidation states of ferrocene-containing surfactants. As described below, and of equal significance, these surfactants also provide the capability to direct these changes in properties to occur in localized regions of systems, thus providing means to generate spatial gradients in both interfacial and bulk solution properties of surfactant-based systems. The consequences of gradients in surfactant-based interfacial properties are well-known in the context of gradients in surface tension, which result in convection at interfaces. These surface-driven flows are often termed “Marangoni flows”, and they have been the subject of a wide range of fundamental studies as well as technological innovation.⁶⁸⁻⁷¹ For example, “Marangoni flows” have been reported to accelerate the spreading of fluids,⁶⁸ enhance the stability of surfactant-laden films of fluids, emulsions and foams,⁶⁹ lead to the assembly of ordered patterns of

nanoparticles,⁷⁰ and increase rates of mass and energy transfer at interfaces.⁷¹ In addition to interfacial gradients, below we describe studies that have revealed ways in which ferrocene-containing surfactants can be used to generate controlled gradients in the bulk solution properties of surfactant systems (such as concentration gradients of micelles). The exploratory studies described below suggest that these gradients might be exploited to control the solubilization and release of solutes, as well to create new processes leading to microscale separation and analysis.

2.4.1 Control of Interfacial Gradients in Surfactant Concentration—Because changes in the oxidation states of redox-active surfactants can be performed in a spatially localized manner, and because large changes in surface tension can result from these local changes in oxidation state (see Figure 4), redox-active surfactants provide a general and facile way to drive Marangoni flows of liquids.^{2, 72-74} For example, by oxidizing FTMA at one electrode while reducing it at a second electrode, a concentration gradient of reduced FTMA can be generated between the electrodes, thus leading to gradients in surface tension, and the resulting motion of fluid between the electrodes.^{2, 74} As illustrated by Figure 11A-C, this principle has been used to control the motion and position of oil droplets floating at the surfaces of aqueous solutions of FTMA in a simple fluidic network consisting of four intersecting channels.² The direction of motion of the droplets was manipulated by changing the electrical potential applied to the electrodes located at the end of each channel. As shown in Figure 11D, the velocity of fluid motion can also be manipulated by changing the magnitude of the potentials applied to the electrodes. Figure 11D reveals that the onset of the motion of fluid occurred at 0.1V (vs SCE), which approximately coincides with the half-wave potential for oxidation of FTMA. As discussed above, the maximum change in equilibrium surface tension measured to accompany oxidation of FTMA is 23mN/m (Figure 4), which was measured when the initial concentration of reduced FTMA was around the value of the CMC (0.1mM). It should be remembered, however, that the driving force for the motion of fluid is not the gradient in equilibrium surface tension, but rather the (local) dynamic surface tension. To this end, Figure 11E shows the change in dynamic surface tension ($\Delta\gamma$) measured using a maximum bubble pressure tensiometer as a function of concentration (Figure 11E) - the behavior of the surfactant system is qualitatively similar to the equilibrium surface tension measurements shown in Figure 4, although the maximum change in dynamic surface tension is achieved at higher concentrations of FTMA as compared to the case of equilibrium surface tensions (0.4mM vs 0.1mM). The maximum change in dynamic surface tension found to accompany the change in oxidation state of FTMA was also smaller than the maximum change in equilibrium surface tension (12 mN/m vs 23mN/m).⁷⁴ The measurements in Figure 11E (and others described in the papers cited above), however, clearly support interpretation of the flows shown in Figure 11A-D in terms of electrochemically generated gradients in concentration of FTMA (and thus gradients in surface tension). We also comment here that many prior reports of electrokinetic flows exist in the literature⁷⁵ – these prior examples, however, typically involve gradients in potentials (electric fields) that are many orders of magnitude larger than those present in the experiments described in Figure 11. In this respect, the results in Figure 11 are noteworthy for the realization of electrochemically-driven fluid flows using small voltages.

2.4.2 Control of Gradients in Surfactant Concentration in Bulk Solution—Early studies by Saji and coworkers reported that the solubility of dyes in aqueous solutions of ferrocene-containing surfactants depend strongly on the oxidation state of the ferrocene.^{18-21, 76-78} These observations have been the subject of more recent studies in the context of exploiting ferrocene-containing surfactants for separations processes.⁷⁹ In particular, it is well-known that the extent of solubilization of dyes into micellar solutions is dependent on the structure of the dyes. This point is illustrated in Figure 12A, where the dye

yellow AB is shown to be more soluble in a micellar solution of reduced FTMA than the dye orange SS. Furthermore, both dyes have been determined to not substantially solubilize in solutions of oxidized FTMA (solubilization < 5 μ M in Figure 12A). Building from these observations, the selective solubilization and deposition of sparingly water-soluble compounds from an aqueous solution of FTMA has been exploited as the basis of a novel microscale separations scheme.⁷⁹ In this scheme (Figure 12B), micelles formed by reduced FTMA were contacted with a mixture of yellow AB and orange SS, leading to solubilization of both compounds. Next, the solubilize-loaded micelles were locally oxidized at an electrode, leading to a spatially localized disassembly of FTMA micelles, and the (selective) capture of the contents of the micelles on the electrode surface. By repeatedly solubilizing and depositing a mixture that initially contained equal mole fractions of each dye, a purified product that contained 98.4% yellow AB was formed after six cycles.

Recent studies have also explored the generation of steady state gradients in concentration of FTMA as the basis of new principles for *continuous* separations processes and microanalytical systems, and more broadly, to provide new methods to achieve localized transport of biomolecules and to generate gradients in concentration of analytes that interact with surfactants.^{80, 81} These studies have shown that steady-state gradients in concentration of FTMA and spatially localized populations of FTMA micelles can be generated and measured by flowing aqueous solutions of FTMA through microfluidic channels fabricated with gold electrodes lining both side-walls of the microfluidic channels (Figure 13A).⁸¹ Measurements of the concentration of reduced and oxidized FTMA collected at the outlets revealed that a lateral concentration profile of FTMA was generated across the channel upon application of oxidizing and reducing potentials to the two electrodes that lined the channels. The concentration profile was shown to be consistent with the presence of slowly diffusing micelles of FTMA in a spatially localized region near the cathode and monomeric FTMA only near the anode (Figure 13B). Furthermore, as also shown in Figure 13B, the magnitude of the gradients and the fraction of the cross-sectional area of the microfluidic channel that contained micelles of reduced FTMA were shown to be easily manipulated by changing the potential applied to the electrodes (Figure 13B) or by changing the inlet concentration of FTMA. Because a wide range of solutes exhibit interactions with surfactants (see sections above), the lateral gradients in concentration of the surfactant monomers and micelles generated across the channel can be used to drive selective transport of analytes across the channels (unpublished results), which in turn might be exploited to realize continuous microscale separations and analytical processes. This topic will be the subject of future publications.

3. Light-Sensitive Surfactants

The second broad class of surfactants that has been explored for active control of surfactant systems is the class of light-sensitive surfactants. The light-sensitive surfactants that are the focus of this review contain the azobenzene moiety (Figure 2A). Azobenzene is a widely studied chromophore, capable of assuming either a *trans* conformation (planar) or *cis* conformation (bent). As mentioned above, the *trans* conformation is the thermodynamically stable state of the molecule, but upon absorption of light with a wavelength of 360nm, it can be promoted to the *cis* conformation. Similarly, the *cis* isomer will absorb light with a wavelength of 460nm (visible light), and will relax back to the *trans* state. In practice, because the absorption spectra of the *trans* and *cis* isomers overlap, illumination of azobenzene with UV or visible light leads to the formation of a photostationary state of the system comprised of a mixture of *cis* and *trans* isomers.⁸² The relative proportion of the two states is dependent on the wavelength of illumination and the microenvironment of the azobenzene.⁸² Below we describe a series of studies that have employed azobenzene in the context of active control of water-soluble surfactant solutions. We note that azobenzene has

been the subject of many prior studies of Langmuir films of amphiphiles⁸³⁻⁸⁵ – those studies fall outside the scope of this perspective.

3.1 Active Control of Surface Tension using Light-Sensitive Surfactants

Figure 14 shows an example of a surfactant system containing azobenzene that leads to large changes in dynamic surface tension upon illumination. The surfactant used in these studies was bis(trimethylammoniumhexyloxy)azobenzene bromide (BTHA) (Figure 3b). Although early studies with this surfactant revealed that illumination of BTHA with UV light led to photoisomerization of solutions of BTHA, only small changes in dynamic surface tension (less than 1mN/m) were recorded to accompany the change in photostationary state.³⁶ However, by mixing BTHA with sodium dodecyl sulfate (SDS) (1.6mM), as shown in Figure 14A, large changes in dynamic surface tension (a maximum value of 25 mN/m at the concentration of BTHA 0.02mM) were achieved upon illumination.³⁶ Insights into this interfacial phenomenon were provided by dynamic light scattering measurements, which revealed that a solution containing 0.1mM *cis*-BTHA and 1.6mM SDS possessed only half the number density of aggregates as the solution of *trans*-BTHA and SDS (the sizes of aggregates were similar: 140nm for the *cis*-rich sample versus 150nm for the *trans*-rich sample). It was proposed that the decrease in the extent of aggregation upon illumination with UV light (see below for additional details regarding nanostructural characterization) led to a decrease in the characteristic time required to transport the surfactant to the surface of the solution, thus resulting in low dynamic surface tensions after illumination. It is significant to note that illumination with UV light allowed the characteristic time for the decrease in surface tension to be manipulated by over an order of magnitude (a few seconds to a min). The potential utility of light-induced changes in dynamic surface tension was illustrated by triggering the release of pendant droplets of solution from capillaries (Figure 14B). Specifically, patterned illumination of an array of pendent drops was used to selectively release particular drops from the array (Figure 14B). As seen in Figure 14B, illumination of the second and fourth droplets caused their release from the capillary while the other drops remained attached. We end this brief perspective by noting that since our early studies with BTHA and SDS, several additional studies of the surface tensions of aqueous solutions of azobenzene surfactants have appeared in the literature.^{35, 42, 43} These studies have identified surfactant systems that permit large changes (although relatively slowly) in equilibrium surface tensions to be achieved upon illumination.³⁵ The interested reader is referred to these studies for additional detail.

3.2 Active Control of Microstructure of Aggregates

Building from the observations reported above that illumination of solutions of BTHA and SDS can lead to changes in the states of aggregation of these surfactants, several detailed investigations of the microstructures of aggregates containing light-sensitive surfactants have been reported. These studies have unmasked light-induced changes in microstructure such as a vesicle-to-spherical micelle transition,^{41, 86} a vesicle-to-cylindrical micelle transition,⁸⁷ and a vesicle-to-lamellae phase transitions.³⁴ In particular, the microstructures of aggregates formed by BTHA and SDS have been studied by SANS and quasi-elastic light scattering (QLS).^{86, 87} These studies have established that the microstructures formed in aqueous solutions of SDS and BTHA are a strong function of composition, and photostationary state (*cis* or *trans*), as summarized in Figure 15A.⁸⁷ The black solid line from the apex to the base of Figure 15A indicates a composition of 33 mol% BTHA, where all samples were observed to precipitate because the system is charge neutral. The dashed lines represent the boundaries of regions of composition containing a particular microstructure formed from *trans*-BTHA and SDS. Inspection of Figure 15A reveals that all *trans*-BTHA-rich samples (all samples on the right of the black solid line) form vesicles after 1 day of equilibration. However, after 6 months, precipitates were observed in some

samples, as indicated by the dashed line on the right of the black solid line. SDS-rich samples containing *trans*-BTHA also form vesicles at very dilute concentrations (0.1wt%) of total surfactant. As the total surfactant concentration is increased, mixed micelles form at high SDS/BTHA ratios, indicated by the dash line on the left of the black solid line. The microstructures formed after illumination with UV light are indicated by regions separated by red lines in Figure 15A. By comparing the locations of the solid red and dashed black lines in Figure 15A, it is apparent that there exist three regions where significant changes in phase behavior or aggregate microstructure occur upon photo-isomerization. These regions are marked with red arrows, and are discussed below.

The first region discussed is labeled with “R/M+V” in Figure 15A, which corresponds to a region where the total surfactant concentration is below 0.3 wt% and the percent of BTHA is between 5-15 mol%. Measurements using SANS (Figure 15B) and QLS of samples in this region (e.g., 0.1 wt% total surfactant, 15 mol% BTHA/85 mol% SDS)⁸⁶ revealed that the mixture of *trans*-BTHA and SDS formed vesicles with average hydrodynamic diameters of 135 ± 5 nm and a vesicle-shell thickness of 3.5 ± 0.2 nm (a slope of -2 is consistent with bilayer-like shell). Upon illumination of these samples with UV light, the aggregates present in the solution changed to cylindrical micelles with cross-sectional radii of 1.9 ± 0.3 nm and average hydrodynamic diameters of 24 ± 5 nm (a slope of -1 is consistent with the presence of rod-like aggregates in solution). This change in microstructure was shown to be reversible. As shown in Figure 15B, samples that were cycled from *trans*-to-*cis*-to-*trans* were denoted “tct”, and found to possess microstructures that were almost the same as *trans* samples (except for an oscillation in the range $0.008 \text{ \AA}^{-1} < q < 0.015 \text{ \AA}^{-1}$, which indicates that the distribution of aggregates in the “tct” sample has a low polydispersity).

The second region of interest in Figure 15A is designated with a red “M”, where the total surfactant concentration is higher than 0.3wt% and the percentage of BTHA is 15-20 mol%. Measurements using SANS (Figure 15C) and QLS in this region⁸⁷ of composition space indicated that both the *trans*-rich sample and the “tct” sample formed vesicles with nearly identical sizes (hydrodynamic diameter of 162 nm and bilayer thickness of 2.8nm for the *trans*-rich sample versus a hydrodynamic diameter of 131nm and bilayer thickness of 2.7nm for the “tct” sample). In contrast, the *cis*-rich sample did not form either vesicles or rod-like aggregates. Instead, the SANS spectra showed a distinct maximum, followed by a slope of zero at low q values, which is consistent with the presence of small, globular micelles (the length of the major axis of the globular micelles was determined to be ~ 2.7 nm).

The third region lies in the BTHA-rich region of Figure 15A, corresponding to 40mol% BTHA and total surfactant concentration of 0.1wt% to 0.7wt%. In this region, illumination of the solutions with UV light led to precipitation, with less than 4% of BTHA remaining in solution. The formation of the precipitate was not reversed by illumination with visible light.⁸⁷

In summary, the results in Figure 15 shown that in two regions located on the SDS-rich side of the composition diagram, UV illumination transforms vesicles formed by *trans*-BTHA and SDS into either rod-like aggregates or small globular micelles (Figure 15D). These transformations can be reversed by illumination with visible light or by equilibration of the solutions overnight in the dark. However, in a region of composition space which lies on the BTHA-rich side of the composition diagram, precipitation occurs upon illumination with UV light and this precipitation is irreversible. For compositions outside of these three regions, illumination with UV light was observed to lead to surprisingly modest changes in the microstructure, sizes or numbers of aggregates in solution.

Whereas the results above address the microstructures formed by mixtures of BTHA and SDS, a number of other studies have shown that light sensitive surfactants, when mixed with cationic surfactants,⁴⁸ or polymers³³ can lead to active control of microstructures (such as worm-like micelles) that exhibit very high viscosity in aqueous solution. In particular, Abe and coworkers have reported that the azobenzene-based cationic surfactant, 4-butylazobenzene-4'-(oxyethyl)-trimethylammonium bromide (AZTMA, Figure 3c) can lead to dramatic changes in viscosity (upon illumination) when mixed with the CTAB-NaSal system.⁴⁸ Addition of 10mM *trans*-AZTMA to 50mM CTAB and 50mM NaSal enhanced the degree of entanglement of worm-like micelles, resulting in a solution that possessed a very high viscosity (Figure 16A, left; zero-shear viscosity of 100 Pa·s). Illumination with UV light was shown to lead to disruption of the worm-like micelles, and formation of smaller aggregates (probably short rods). The resulting solution exhibited a low viscosity (Figure 16A, right): The zero shear viscosity was 4 orders in magnitude smaller than that measured prior to illumination (0.1 Pa·s). Interestingly, measurements of the zero shear viscosity (η_0) revealed that the change in viscosity was reversible over multiple cycles (Figure 16B).

3.3 Interaction of Light-Sensitive Surfactants with Biomolecules

Because the *trans* isomer of light-sensitive surfactants containing azobenzene is more hydrophobic than the *cis* isomer (due to the larger dipole moment across the azobenzene group in the *cis* state), it has been proposed that the *trans* form of azobenzene-based surfactants are more likely to interact with biomolecules, such as DNA and proteins than the *trans* isomer. This proposition has led to a series of recent investigations in which the interactions of azobenzene-based surfactants with DNA^{32, 88, 89} or proteins^{5, 46, 47, 90, 91} have been reported.

The first study that we mention here involves the surfactant azoTAB (Figure 3e).³² This surfactant, when in the *trans* form, preferably binds to negatively charged DNA and has been reported to lead to the compaction of DNA from a coil-like configuration (with an end-to-end distance of 1.27 μ m) to a compact globular state (with a hydrodynamic radius of 120 nm). However, illumination by UV light has been reported to result in the dissociation of the surfactants and DNA, and a return of the DNA to an expanded configuration. These changes in conformation of DNA induced by azoTAB were imaged by fluorescence microscopy (Figure 17A) and confirmed by measurements of diffusion coefficients by using dynamic light scattering (Figure 17B). Moreover, precipitation of the DNA upon addition of azoTAB was also reversed by illumination with UV light.³²

Complementary studies with *trans*-azoTAB have also provided evidence that *trans*-azoTAB can bind more strongly than *cis*-azoTAB to hydrophobic domains of some proteins, and lead to light-induced changes in the secondary,⁴⁶ tertiary,^{5, 90} and quaternary structure⁹¹ (i.e., degree of unfolding of proteins). For bovine serum albumin, a series of structural transitions was identified, and addition of *trans*-azoTAB led to transitions between the structural states denoted as N, N_d, F and E. The concentrations required for *trans*-azoTAB to cause the N to N_d, N_d to F, and F to E were 0.55mM, 0.8mM and 2.83mM, respectively. In contrast, the concentrations of *cis*-azoTAB required to cause each transition in tertiary structure (N to N_d, N_d to F, and F to E) were shown to be higher for the *trans* isomer, namely 1.6mM, 2.21mM, and 8.45mM, respectively. This observation led to the demonstration that it was possible to control transitions in protein conformation reversibly by illumination of azoTAB with light at the appropriate wavelength (Figure 18).^{5, 46} It was suggested by the authors that the capability to use light sensitive surfactants to control protein folding states could be exploited to characterize partially folded proteins in non-native conformations. It is noteworthy, however, that the effects of azoTAB on protein conformation are different for different proteins. For α -chymotrypsin, which self-associates to form either a dimer at pH 3

or a hexamer at pH 7,⁹¹ addition of *trans*-azoTAB converted the native structure (dimers or compact hexamers) into expanded corkscrew-like hexamers. It was observed that the *trans*-to-*cis* photoisomerization led to changes in the quaternary structure, with the hexamers aggregating laterally into rope-like dodecamers. For lysozyme,^{47, 90} the *trans*-to-*cis* photoisomerization resulted in a reversible structural change from a native-like structure to a partially unfolded conformation, and an 8-fold increase in enzymatic activity.

4. Conclusion

This paper has presented perspectives on several approaches leading to spatial and temporal control of surfactant systems that are based on use of redox-active and light-sensitive surfactants. To date, the most widely studied redox-active surfactant system is based on ferrocene. The electrochemical characteristics of ferrocene, namely the ability to control the oxidation state of ferrocene at potentials that do not lead to electrolysis of water, makes ferrocene particularly attractive for use in redox-active surfactants. We comment, however, that there exist a range of metallocenes beyond ferrocene that have not been investigated in the context of surfactant systems. Because a number of metallocenes are known to be effective catalysts, such metallocene-based surfactant systems may also possess functional properties not realized in existing systems. Although ferrocenyl surfactants are likely to be more expensive than commodity surfactants used in shampoos and detergents, we comment that only small quantities of surfactants will be required in the many of the applications envisaged for redox-active and light sensitive surfactants (e.g., gene delivery or microfluidic-based separations). In addition, because these surfactants undergo reversible changes in state, they can potentially be used many times in closed-loop processes. The majority of light-sensitive systems studied to date have involved azobenzene. While the ability to pattern light on a system makes these surfactants appear attractive for active control, a limitation of this approach is the limited depth of penetration of light into solutions of azobenzene surfactants. Also, the UV wavelengths associated with the *trans*-to-*cis* isomerization can also potentially drive unwanted side-reactions in biological systems containing labile molecules. The development of light-sensitive surfactant systems that can be driven through reversible changes in state upon illumination with visible wavelengths of light would potentially address both of these limitations of existing systems. That said, the recent studies reported in this review demonstrate that reversible changes in the charge of ferrocene-modified surfactants, and reversible changes in the conformation of azobenzene-containing surfactants can lead to large changes in both interfacial and bulk solution properties of these surfactants. The ability to achieve reversible control of surfactant-biomolecule interactions, as well as the capability to generate controlled gradients in both interfacial and bulk properties, suggests the basis of new types of surfactant-based processes where the gradient can be used to spatially localize phenomena (such as solubilization) or drive transport processes. Applications of these surfactants to templated materials synthesis are also envisaged.

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Figure 1.
Molecular structures of ferrocenyl surfactants

Figure 2.
Molecular structures of photo-sensitive groups that have been incorporated into surfactants.

Figure 3.

Molecular structures of light-sensitive surfactants containing the azobenzene group. (a) C4AzoOC6E2 (diethylene glycol mono(4',4-hexyloxy, butyl-azobenzene));^{35, 42-44} (b) BTHA (4,4'-bis(trimethylammoniumhexyloxy)-azobenzene bromide);^{36, 45} (c) AZTMA (4-butylazobenzene-4'-(oxyethyl)trimethylammonium bromide);^{34,48} (d) azoTAB (azobenzene trimethylammonium bromide);^{46, 47} (e) azoTAB³²

Figure 4.

(A) Molecular structures of FTMA (B) Equilibrium surface tensions of aqueous solutions (0.1 M Li₂SO₄, pH 2, 25°C) of reduced FTMA (○) and oxidized FTMA (●). (C) Cartoon of possible conformations of reduced FTMA (top row) and oxidized FTMA (bottom row) at the surface of an aqueous solution. (D) Dynamic surface tension of an aqueous solution of 0.3 mM reduced/oxidized FTMA (0.1M Li₂SO₄, pH 2, 20°C) measured during the repeated cycling of the surfactant between oxidation states. (B) and (C) were reproduced from ref¹⁵ with permission. Copyright 1995 Am. Chem. Soc. (D) was reproduced from ref¹⁴ with permission. Copyright 1996 Am. Chem. Soc..

Figure 5.

(A) Equilibrium surface tensions of aqueous solutions of $\text{Fc}(\text{CH}_2)_{11}\text{SO}_3^-$ (○) and $\text{Fc}^+(\text{CH}_2)_{11}\text{SO}_3^-$ (□) in 10 mM Li_2SO_4 , at 37 °C and pH 5. Reproduced from ref¹⁷ with permission. Copyright 2001 Am. Chem. Soc. (B) Schematic representation of aggregates formed in reduced state (left) and oxidized state (right) of surfactant.

Figure 6.

(a-c) Particle size distributions measured for aqueous FTMA/SDBS mixtures (1.0 wt% surfactant, FTMA:SDBS = 7:3) containing (a) reduced, (b) oxidized, and (c) re-reduced FTMA. The size distributions were determined from dynamic light scattering measurements. (d-f) Optical micrographs of mixed solutions of FTMA and SDBS (1.0 wt% surfactant, FTMA:SDBS = 7:3) containing (d) reduced, (e) oxidized, (f) re-reduced FTMA prepared by bulk electrolysis. The scale bar corresponds to 17 μm. Modified from ref⁵⁴ with permission. Copyright 2004 Elsevier.

Figure 7.

(A and B) Photographs showing the appearance of aqueous 50 mM FTMA/NaSal at a molar ratio of $C_{\text{NaSal}}/C_{\text{FTMA}}$ of 0.4: (A) reduced FTMA; (B) oxidized FTMA. (C and D) Schematic representation of aggregates formed in solutions containing the (C) reduced and (D) oxidized states of FTMA. Modified from ref ⁵⁵ with permission. Copyright 2004 Am. Chem. Soc.

Figure 8.

(A) Molecular structure of EHEC. (B) Clouding temperatures of aqueous solutions of 0.1% (w/w) EHEC, 0.1M Li_2SO_4 , at pH 2.5, containing reduced FTMA, or oxidized FTMA. (C) Hydrodynamic radii of assemblies formed in aqueous solutions of 0.1% (w/w) EHEC, 0.1M Li_2SO_4 , pH 2.5, and reduced FTMA (●) or oxidized FTMA (■). Modified from ref⁵⁶ with permission. Copyright 2005 Am. Chem. Soc.

Figure 9.

(a-g) Distribution of hydrodynamic diameters of complexes formed between $5\ \mu\text{M}$ DNA and FTMA (in $1\text{mM Li}_2\text{SO}_4$) obtained using an intensity-based CONTIN analysis at a scattering angle of 90° and temperature of $25\ ^\circ\text{C}$: (a) no surfactant, (b) $1\ \mu\text{M}$ FTMA, (c) $2\ \mu\text{M}$ FTMA, (d) $5\ \mu\text{M}$ FTMA, (e) $10\ \mu\text{M}$ FTMA, (f) $30\ \mu\text{M}$ FTMA, and (g) $50\ \mu\text{M}$ FTMA. For graphs (b-g), the filled squares correspond to samples prepared using reduced FTMA and the open circles correspond to samples prepared using oxidized FTMA. The error bars were calculated as the standard deviation of two to five different samples, with five measurements per sample. (I-III) Schematic illustration of the structures of complexes formed by interactions between DNA and cationic surfactants: (I) extended, surfactant-free coils; (II) coexistence of extended coils and compacted aggregates; (III) compacted, surfactant-DNA aggregates. Reproduced from ref⁵⁷ with permission. Copyright 2007 Am. Chem. Soc.

Figure 10.

(A) Hydrodynamic diameters of lipoplexes formed from DNA and BFDMA (oxidized or reduced) as a function of the concentration of BFDMA. The solid squares are reduced BFDMA and the open circles are oxidized BFDMA. (B) ζ -potentials of complexes formed from DNA and lipid (BFDMA) in 1 mM Li_2SO_4 . The symbols correspond to the ζ -potentials of complexes prepared using DNA and reduced BFDMA (■), oxidized BFDMA (○). (C) SANS spectra obtained using solutions of reduced (dark symbols, charge ratio 1.1:1) and oxidized (light symbols, charge ratio 3.3:1) BFDMA (1 mM) mixed with a solution of plasmid DNA (2.9 mg/mL). A line with a slope of -2.5 is included for comparison. (D) Cryo-TEM images of complexes formed by BFDMA (1 mM) and DNA (2.9 mg/mL): (left) reduced BFDMA (charge ratio is 1.1:1) and (right) oxidized BFDMA (charge ratio is 3.3:1). (A) and (B) were reproduced from ref⁵⁸ with permission. Copyright 2007 Elsevier. (C) and (D) were modified from ref²⁸. Copyright 2008 Am. Chem. Soc.

Figure 11.

Time-lapse images of the pumping of LC droplets across the surface of an aqueous solution of 0.3 mM FTMA (0.01M Li₂SO₄) contained within a simple fluidic network. Platinum electrodes protrude through the surface of the solution at the ends of the left, right, and lower channels (widths ~4 mm). The end of the top channel contains a SCE and Pt counterelectrode. (A) applying a potential of +0.3 V to the bottom Pt electrode and -0.3 V to the right Pt electrode. (B) applying a potential of +0.3 V to the right Pt electrode and -0.3 V to the left Pt electrode. (C) applying a potential of +0.3 V to the bottom Pt electrode and -0.3 V to the left Pt electrode. (D) The velocity of fluid indicates the magnitude of the anodic and cathodic potentials. (E) Dependence of dynamic surface tension (γ) and change in dynamic surface tension ($\Delta\gamma$) on concentration of FTMA in aqueous solutions of 100 mM Li₂SO₄, pH 2.0: reduced FTMA (●), oxidized FTMA (■), and change in dynamic surface tension upon oxidation of I⁺ to I₂⁺ (▲). (A-D) were reproduced from ref² with permission. Copyright 1999 AAAS; (E) was reproduced from ref⁷⁴ with permission. Copyright 1996 Am. Chem. Soc.

Figure 12.

(A) Equilibrium solubilities of yellow AB and oil orange SS in reduced FTMA solutions. (B) Schematic illustration of a separations process based on the electrochemical assembly and disassembly of micelles. Reproduced from ref⁷⁹ with permission. Copyright 2001 Am. Chem. Soc.

Figure 13.

(A). (a) Expanded view of a microfluidic channel with two independent electrodes lining the vertical walls of the channel. (b) Schematic illustration of the microfluidic channel used to electrochemically generate and measure lateral gradients in the concentration of redox-active surfactants generated across microfluidic channels (B) Lateral concentration profiles of reduced and oxidized FTMA generated electrochemically across a microfluidic channel as a function of potentials applied to the electrodes. (a) 0.5V to the left electrode (anode) and 0.4V to the right electrode (cathode); (b) 0.3V to the left electrode (anode) and 0V to the right (cathode); (c) 0.1V to the left electrode (anode) and -0.05V to the right electrode (cathode). The electrodes line the walls of the microfluidic channel. The inlet solution is 0.5mM reduced FTMA and 0.2mM oxidized FTMA (in 0.1M Li_2SO_4 , pH=2). The flow rate was 0.04ml/h. The hashed regions indicate the micelle-containing volumes of the microfluidic channel (see right axis). Reproduced from ref⁸¹ with permission. Copyright 2009 Am. Chem. Soc.

Figure 14.

(A) Surface tensions of aqueous solutions of mixtures of BTHA and SDS (1.6 mM) measured as a function of BTHA concentration before (●) and after (○) illumination with UV light (du Nouy ring method); (B) Light-directed release of droplet of aqueous solutions containing 0.04mM BTHA, 0.16mM SDS, and 0.1M NaCl from an array of five capillaries. Reproduced from ref³⁶ with permission. Copyright 1999 Am. Chem. Soc.

Figure 15.

(A) Microstructure diagram for SDS/BTHA/H₂O. Dashed lines represent the boundaries for *trans*-BTHA, and the solid lines indicate the new boundaries formed after isomerization with UV light. Samples that undergo a change in microstructures upon isomerization are marked in red. (B) SANS from D₂O solutions containing 0.1 wt % total surfactant (15 mol % BTHA/85 mol % SDS). Tct sample is scaled by a factor of 10 for clarity. (C) SANS data for solutions containing 0.3 wt % total surfactant and 15 mol % BTHA/85 mol % SDS, before and after isomerization with UV light, and after isomerization with UV and then visible light. The data have been offset by the indicated factors for clarity. In Figure (B) and (C), the markers represent the data, and the solid lines represent fits to the data using an appropriate form factor model. (D) Schematic representation of aggregates of BTHA and SDS formed in *trans* (left) and *cis* (right) isomers. (A) and (C) were reproduced from ref⁸⁷ with permission. Copyright 2007 Am. Chem. Soc. (B) was reproduced from ref⁸⁶ with permission. Copyright 2005 Am. Chem. Soc.

Figure 16.

(A) Photographs showing the appearance of aqueous CTAB/NaSal/AZTMA mixture before (left) and after (right) UV light irradiation. (B) Zero shear viscosities (η_0) of an aqueous solution of CTAB(50 mM)/ NaSal (50 mM)/AZTMA(10 mM) measured during the repeated cycling of AZTMA between the *trans*-form and *cis*-form. The high values of η_0 correspond to the *trans*-AZTMA solution, and the low values correspond to *cis*-AZTMA solution. Reproduced from ref⁴⁸ with permission. Copyright 2005 Am. Chem. Soc.

Figure 17.

(A) Fluorescence images of T4-DNA molecules in the elongated-coil conformation in TBE buffer solution, in the globular conformation upon addition of azoTAB surfactant ($r=250$) under visible light, and the resulting reexpansion of DNA with UV light illumination. [T4-DNA]=0.6 μM. (B) Translational diffusion coefficient measurements of λ-DNA at a scattering angle of 20° at $r=11.5$ as a function of time upon repeated visible/UV light cycles. [λ-DNA]=0.05 mM, $T=25$ °C. Reproduced from ref³² with permission. Copyright 2006 Am. Chem. Soc.

Figure 18.
Transformation of structure of BSA as a function of azoTAB concentration and light illumination. Modified from ref ⁵ with permission. Copyright 2005 Am. Chem. Soc.