

Novel Redox-Responsive Surfactant

by Yuming Yang

Vesicles have been identified as perfect small molecule containers and possess great potential to be used in drug delivery systems and microfluidic analysis devices.^{1,2} However, the controllable release of the encapsulated contents from vesicles is a significant technical barrier that limits their application. Currently, the main solution to this challenge is modification of the surfactant molecules which are used to construct the vesicles. The modifications allow the surfactants to respond to specific environmental signals, which in turn cause the vesicles to release their contents. By adjusting the structure or the morphology of the surfactant molecules, vesicle properties can be carefully controlled.^{3,4}

In my dissertation studies, I am developing a novel surfactant molecule-based system that is redox responsive, namely, Q9; see Fig. 1. Q9 is composed of a trimethyl quinone moiety and a 6-aminohexanoic acid chain structure, and it is proposed that Q9 will form vesicles in aqueous solutions based on previous work with *n*-alkanoic acids.^{5,6} Furthermore, work from Cohen on the “trialkyl lock” mechanism for carboxylic acid-functionalized quinones allows for the proposal that Q9 will undergo the intramolecular lactonization reaction shown in Fig. 1 upon reduction with sodium dithionite or at an electrode surface.⁷⁻⁹ Through this redox-induced destruction of the Q9 surfactant, it should be possible to open the Q9 vesicles and empty their contents in a highly controllable manner. Here, I report on the synthesis and some select properties of the Q9 surfactant molecules.

The synthesis of Q9 was achieved by a seven-step synthesis using standard conditions and reagents.⁹⁻¹¹ Products from each synthetic step were characterized by ¹H NMR and mass spectrometry (GC-MS, ESI-MS), and results indicated the presence of pure materials. The ¹H NMR spectrum of the final product Q9 is shown in Fig. 2a.

Once Q9 was synthesized, ¹H NMR experiments in aqueous milieu were used to ascertain whether the desired stimuli-responsive reaction could be achieved and if so, what the reaction rate was under these conditions. Q9 was dissolved in pure D₂O at a concentration of 10 mM. Na₂S₂O₄ was used as the reducing agent to trigger the reaction, as it has been previously shown that dithionite is efficient

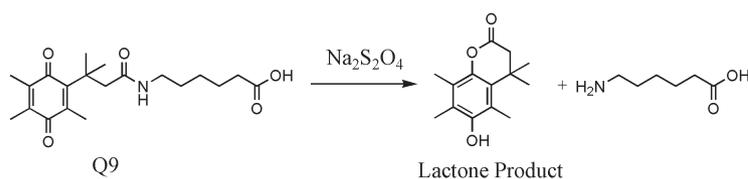


Fig. 1. Q9 structure and stimuli-response reaction.

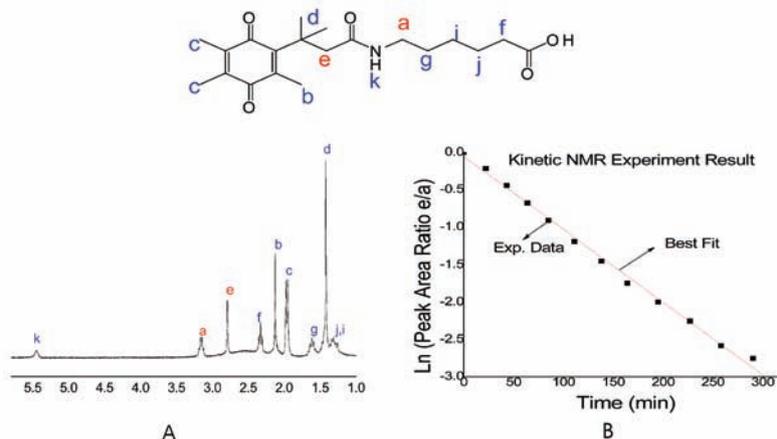


Fig. 2. NMR experiments with Q9: (a) ¹H NMR spectrum of Q9 alone in CDCl₃, chemical shifts are assigned in the structure at top with letters; and (b) NMR kinetic experiments for reduction of 10 mM Q9 in D₂O after Na₂S₂O₄ addition (5 equivalents).

in the reduction of carboxylic-acid functionalized quinones.¹⁰ Indeed, upon inspection of the NMR spectrum of Q9 after addition of dithionite, it was found that the intensity of peak *e* associated with the methylene protons to the ring (on the chain) decreased with time, as expected for the insoluble lactone product.¹⁰

The ratio of the integrated peak areas for the *e* and *a* signals (*e/a*) was picked to monitor this reaction, Fig. 2a. Peak *a* is associated with the methylene group of the aminohexanoic acid chain structure (α to the amine group), and its integrated peak area should remain constant during the course of the reaction. The insoluble nature of the cyclized lactone product will result in a time-dependent signal during the reaction. In this way, the ratio of *e/a* can be used as an index for monitoring the progress of the reaction. After 5 equivalents of Na₂S₂O₄ were added, ¹H NMR spectra were recorded at various points during the 300 min observation period. The results are plotted in a first-order fashion (ln(*e/a*) vs time) in Fig. 2b. The observed linear relationship (correlation coefficient $r = 0.997$) indicates that indeed the

reaction is first order in nature. The half-life $t_{1/2}$ is approximately 60 min, which is reasonable based on other quinone structures that have been reported.¹⁰ The outcomes from this work demonstrate that Q9 is a good candidate for the construction of controlled release vesicle systems that are sensitive to redox stimuli. ■

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