

# Size-Selective Phase-Transfer Catalysis with Interfacially Cross-Linked Reverse Micelles

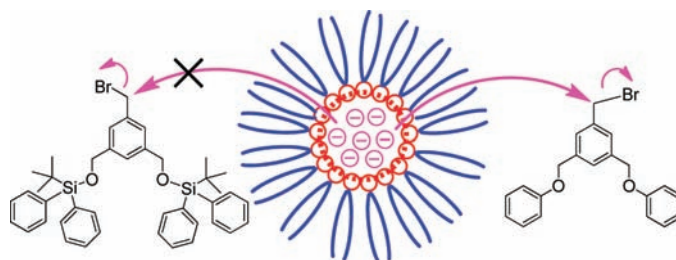
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Received December 12, 2011

## ABSTRACT



Cross-linking of the reverse micelles (RMs) of a triallylammonium surfactant afforded organic nanoparticles with introverted cationic groups. The cross-linked reverse micelles catalyzed size-selective biphasic reaction between sodium azide and alkyl bromides. Size selectivity of up to 9:1 was obtained for alkyl bromides with similar structures. The selectivity was influenced strongly by the size of the water pool and proposed to happen as a result of the “sieving” effect of the alkyl corona.

Enzymes carry out highly efficient and selective catalysis in active sites tailored for their specific functions. The active site not only has different polarity from the bulk solvent but also size, shape, and functional groups essential to the molecular recognition and catalysis of the enzyme.

Chemists have adopted a similar strategy and devoted much effort to the development of nanoreactors for enzyme-like catalysis.<sup>1</sup> By encapsulating orthoester in an anionic water-soluble nanoreactor, Bergman and Raymond were able to achieve acid catalysis in basic solution.<sup>2</sup> Rebek and co-workers placed a carboxyl group inside a cavitand for the regioselective ring-opening of epoxides.<sup>3</sup> Ramamurthy and Gibb were able to control the photoreactions of ketones using water-soluble molecular capsules.<sup>4</sup> Fujita

and colleagues demonstrated that, when packed in a metal–organic nanocapsule, unreactive naphthalenes could undergo regio- and stereoselective Diels–Alder reactions.<sup>5</sup> Badjic and co-workers developed cavitand “baskets” with conformational gating to control reactivity.<sup>6</sup> Warmuth employed hemiacarcerand to modulate the photochemical and thermal reactions of reactive intermediates such as nitrene and carbene.<sup>7</sup>

We recently reported the synthesis of interfacially cross-linked reverse micelles (ICRMs) from cationic surfactants **1** and **2** (Scheme 1).<sup>8</sup> These surfactants form RMs in a chloroform/heptane mixture in the presence of a small amount of water. The nanosized water pool in the middle of the RM concentrates the water-soluble dithiothreitol

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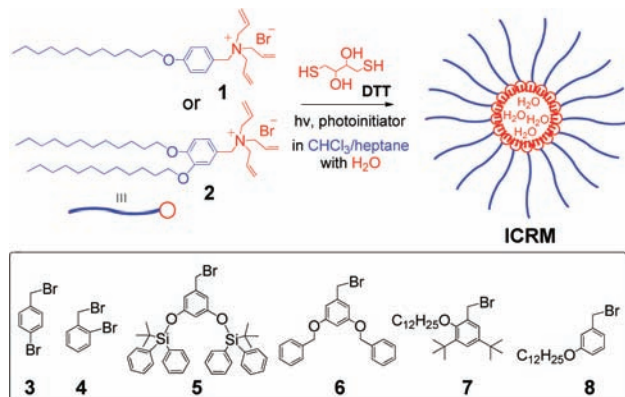
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**Scheme 1.** Preparation of the Interfacially Cross-Linked Reverse Micelle (ICRM) and the Benzyl Bromides Used in the Study



(DTT) near the headgroups of the surfactants. The high local concentrations of alkene and thiol near the water–surfactant interface facilitate the already efficient thiol–ene radical chain reaction,<sup>9</sup> enabling the dynamic self-assembled RMs to be captured in the original size by covalent bonds.<sup>10</sup>

We reasoned that the introverted ammonium groups of the ICRMs should make them potential phase-transfer catalysts (PTCs). Unlike conventional PTCs, however, the ICRMs have the phase-transferred anions located in or near the nanosized internal cavity. Because both the surface alkyl density and the size of the water pool can be tuned easily in our synthesis, we hypothesized that only substrates small enough to access the nucleophilic anions would be able to react. The size selectivity is akin to the “reactive sieving” displayed by tRNA synthetase<sup>11</sup> and synthetic foldamers.<sup>12</sup>

To test the hypothesis, we examined the biphasic reaction between sodium azide and alkyl bromides (**3**–**8**) in a water/chloroform mixture. As shown in Table 1, in the absence of the ICRMs, most bromides were unreactive under our experimental conditions. The small bromides (**3** and **4**) had somewhat higher background reactivity, probably because their higher water-solubility allowed them to enter the azide-containing aqueous phase more easily. In the presence of both ICRMs, the small azides (**3** and **4**) reacted quantitatively. A bulky bromide (**5**), on the other hand, was only converted in 23 and 38% yield, respectively, by the two ICRMs. Because compound **6**, which is

**Table 1.** Percent Yield of Benzyl Azide Obtained in the Biphasic Reaction between  $\text{NaN}_3$  and Various Benzyl Bromides (RBr)<sup>a</sup>

| entry | RBr      | yield with ICRM (1) (%) | yield with ICRM (2) (%) | yield with no ICRM (%) |
|-------|----------|-------------------------|-------------------------|------------------------|
| 1     | <b>3</b> | >95                     | >95                     | 8                      |
| 2     | <b>4</b> | >95                     | >95                     | 9                      |
| 3     | <b>5</b> | 23                      | 38                      | 0                      |
| 4     | <b>6</b> | 82                      | 89                      | 0                      |
| 5     | <b>7</b> | 74                      | 74                      | 3                      |
| 6     | <b>8</b> | >95                     | >95                     | 2                      |

<sup>a</sup>The reactions were carried out with 0.1 mmol of RBr, 0.3 mmol of  $\text{NaN}_3$ , and 20 mol % of the cross-linkable surfactant in the ICRMs in a mixture of water (1 mL) and  $\text{CDCl}_3$  (1 mL) under vigorous stirring for 24 h.  $W_0 = [\text{H}_2\text{O}]/[\text{surfactant}] = 15$ . The ICRMs were prepared according to a previously published procedure.<sup>8</sup> The reaction yields were determined by  $^1\text{H}$  NMR spectroscopy.

similar to **5** electronically but less sterically demanding, gave 80–90% yield under the same conditions, steric interactions were mainly responsible for the selectivity. The ICRMs overall were amazingly “permeable”, as bromide **7** with two *tert*-butyl groups and a dodecyloxy chain gave over 70% yield. A single dodecyloxy chain was even less of a problem—bromide **8** reacted quantitatively in the biphasic reaction.

A surprising result in the phase-transfer catalysis is the similar activity of ICRM (**1**) and ICRM (**2**) for the majority of the substrates. Although an alkyl bromide may not have to get into the hydrophilic core of the ICRM to react with the azide, it has to penetrate the alkyl corona to a certain degree to access the nucleophiles in or near the ICRM core. For this reason, one would expect that the double-tailed surfactant should afford ICRMs with a stronger “sieving” effect. Nevertheless, the two ICRM(s) gave essentially indistinguishable results for the majority of the bromides. For the bulkiest bromide (**5**), the ICRM derived from the double-tailed surfactant actually was more active, giving 1.7 times as much product as that by the single-tailed one (Table 1, entry 3).

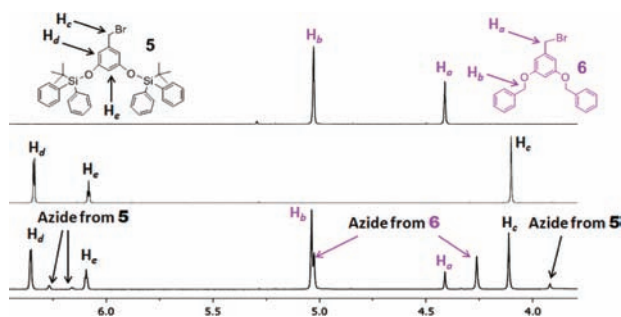
The above result may be explained by our previous study of the ICRMs.<sup>8</sup> Normally, one would anticipate an alkyl-covered organic nanoparticle to be fully soluble in nonpolar solvents. The ICRMs prepared from the single-tailed surfactant, however, have gaps in between the alkyl chains due to the bulkiness of the headgroup and the geometry of a spherical particle, i.e., more space at the periphery than at the center. These features make ICRM (**1**) extremely prone to interparticle aggregation even in nonpolar solvents such as chloroform. As aggregation occurs, the alkyl chains on the ICRM surface interdigitate, not only promoting the van der Waals interactions among the alkyl chains but also expelling solvent molecules trapped in between the alkyl chains into the bulk—an entropically favorable process. At the particles get closer, the (long-range) electrostatic interactions from the charged micellar cores also become significant. These interactions are sufficiently strong in ICRM (**1**) that it is completely insoluble in highly nonpolar solvents such as hexane.

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**Figure 1.** Competitive azidation of **5** and **6** at  $W_0 = 5$ . The  $^1\text{H}$  NMR spectra from top to bottom are for **6**, **5**, and the 1:1:1 mixture of **5/6/NaN<sub>3</sub>** at room temperature after 24 h.

In our previous study, ICRM (**2**) was found to be free of aggregation because the higher density of the alkyl chains on the surface makes alkyl-interdigitation sterically impossible.

Quite likely, it was the aggregation of ICRM (**1**) that made it much less “permeable” to bromide **5**. Although this PTC has larger gaps in between the surface alkyl groups, the gaps are closed by the alkyl interdigitation.

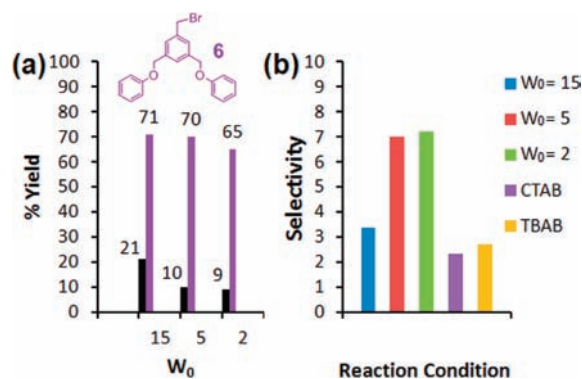
Conceivably, the larger the gap, the higher is the driving force for the interparticle aggregation and the “tighter” the alkyl shell, making the ICRM of the single-tailed surfactant more discriminating.

The reactions in Table 1 were performed with an excess of azide. To better characterize the size selectivity, we carried out competitive azidation with two bromides present in the same solution and only 1 equiv of azide. Figure 1 shows the  $^1\text{H}$  NMR spectra of bromides **5**, **6**, and a 1:1:1 mixture of **5/6/NaN<sub>3</sub>** after 24 h at room temperature. According to the integration, while ca. 70% of **6** was converted to the azide, barely 10% of **5** reacted.

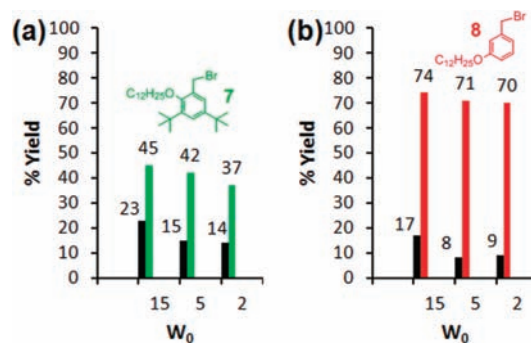
The size of the hydrophilic core can be tuned by the amount of water used in the RM formulation.<sup>13</sup> Figure 2a shows the yields in the competitive azidation of bromides **5** and **6**. The ICRMs prepared at  $W_0 = [\text{H}_2\text{O}]/[\text{surfactant}] = 15$  was clearly less selective than those at lower  $W_0$ . Note that it was the bulkier substrate (**5**) that was affected more by the size of the water pool, not the smaller one. As shown by Figure 2b, the highest selectivity for **6/5** was  $\sim 7:1$ , which was significantly higher than that displayed by conventional phase-transfer catalysts such as CTAB (cetyltrimethylammonium bromide) or TBAB (tetrabutylammonium bromide).

Similar competitive azidation was performed for **7/5** and **8/5** (Figure 3). When another bulky bromide (**7**) was present, **5** became more reactive, affording 14–23% azidation under the same reaction conditions. Meantime, the total yields decreased, ranging from 51–68% for **7/5** to 74–92% for **6/5** and 79–91% for **8/5**. Clearly, bulky substrates in general have difficulty approaching the entrapped azide ions.

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**Figure 2.** (a) Competitive azidation of **5** and **6** catalyzed by ICRM(**1**) with different  $W_0 = [\text{H}_2\text{O}]/[\text{Surfactant}]$ . The figure is color-coded according to the molecules, with the black bars showing the conversion of **5**. The numbers over the bars are the percent yields of the corresponding azides. (b) Comparison of the substrate-selectivity in the competitive azidation under different conditions. CTAB = cetyltrimethylammonium bromide. TBAB = tetrabutylammonium bromide.



**Figure 3.** Competitive azidation of (a) **5** and **7** and (b) **5** and **8** catalyzed by ICRM (**1**) with different  $W_0$ . The figure is color-coded according to the molecules, with the black bars showing the conversion of **5**.

For all three pairs, the selectivity was the lowest at the highest  $W_0$ . In general, the bromides were more reactive at higher  $W_0$  but the effect was more pronounced for the bulkier bromide (**5**) than for the less bulky ones (**6** and **8**). An increase of  $W_0$  from 5 to 15, for example, doubled the product yield for **5** while **6** and **8** were hardly affected (Figures 2a and 3b).

The ICRMs could be affected by the water/surfactant ratio in several ways. As  $W_0$  decreases, the water pool inside the ICRM becomes smaller, the number of the (cross-linked) surfactants in the ICRM decreases, and the curvature of the nanoparticle becomes larger. The first two factors affect the number of azide ions per ICRM and the last the aggregation of the ICRMs. For an  $\text{S}_{\text{N}}2$  reaction in a homogeneous solution, the reaction rate depends on the inherent reactivity of the reactants, their concentrations, and temperature. For a microphase-separated

system such as what we have, many factors could affect the reaction rates including the local concentration of the azide ions and how the bromide approaches the azide.

Although the total concentration of azide ions was the same under in all the experiments, the local concentration of azide could be different at different  $W_0$ . Because all the bromides in our study became more reactive at higher  $W_0$ , it is possible that the local concentration of azide ions might have increased with the  $W_0$ . The higher local concentration of azide, however, could not explain why the sterically most demanding bromide (**5**) always benefited most from the increase in the water-to-surfactant ratio. Since the smaller or slimmer bromides should be better able to react with the entrapped azide (as evident from their higher yields), they should benefit more from an increase in the effective concentration of azide ions if no other factors are involved.

Our current postulation is that the alkyl density outside the ICRM core is the main determining factor for the size selectivity. For the single-tailed ICRM, as discussed earlier, interparticle aggregation “tightens” the alkyl shell and increases the selectivity. A lower  $W_0$  increases the curvature of the ICRM core, widens the gaps in between the alkyl chains, and leads to stronger interparticle aggregation. The alkyl density around micellar core would increase

as a result, making it more difficult for the bulky substrate to react. The smaller bromides were not affected significantly by the  $W_0$  possibly because they could penetrate the alkyl corona fairly easily at all  $W_0$ .

ICRMs are prepared in a one-step synthesis from the cross-linkable surfactant. Their facile synthesis represents a tremendous benefit when they are compared with other functionalized nanoreactors such as dendrimers. Selectivity up to 9:1 has been achieved for similar bromides such as **5** and **8**. Further derivatization of these organic core–shell nanoparticles should provide additional functions and convert them into useful biomimetic nanoreactors.

**Acknowledgment.** We thank the U.S. Department of Energy Office of Basic Energy Sciences (Grant No. DE-SC0002142) for supporting the research.

**Supporting Information Available.** Experimental procedures, additional  $^1\text{H}$  NMR spectra for the competitive azidation, and the NMR data of the newly synthesized compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.