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Calix[6]arene derivatives bearing sulfonate and alkyl groups as surfactants in Sc(OTf)₃-catalyzed Mukaiyama aldol reactions in water

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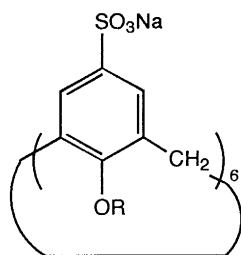
Abstract

Amphiphilic calix[6]arene derivatives **1a–b** were found to be efficient surfactants for Sc(OTf)₃-catalyzed Mukaiyama aldol reaction of silyl enol ethers with aldehydes in water. The results indicated that a hydrophobic microenvironment was formed in the reaction system, which is favorable to stabilize some labile silyl enol ethers and thus promotes the reactions. © 2000 Elsevier Science Ltd. All rights reserved.

The development of carbon–carbon bond-forming reactions in aqueous media is a challenging topic in organic synthesis.¹ The aldol-type reaction of silyl enol ethers with carbonyl compounds (the Mukaiyama reaction)² has been recognized as one of the most important carbon–carbon bond-forming reactions. Recently, great progress has been made on aqueous Mukaiyama aldol reactions by using a series of water-tolerant Lewis acids, such as lanthanide triflates, and metal salts.³ As Kobayashi⁴ reported, in order to promote the reactions in water alone, certain surfactants must be added to the lanthanide triflate catalyzed-reaction medium, such that a micellar system is formed. These surfactants can be anionic, such as sodium dodecyl sulfate (SDS), or nonionic. However, although some very labile silyl enol ethers could react smoothly with aldehydes in water in the presence of a surfactant Lewis acid, scandium trisdodecylsulfate (STDS),⁵ they decompose rapidly in the Sc(OTf)₃–SDS–H₂O system. For improving the reaction yield, it is necessary to use a large excess of the very labile silyl enol ethers in the Sc(OTf)₃–SDS–H₂O system.⁴ Previously, Shinkai and co-workers⁶ reported the synthesis and inclusion properties of some water-soluble calixarene derivatives with surfactant activity. It was found that the water-soluble *p*-sulfonated calixarenes could form host–guest type complexes with various organic guest molecules in water with the aid of hydrophobic interactions. We envisioned that the use of these calixarene derivatives as surfactants in the aqueous Mukaiyama aldol reaction would provide a hydrophobic cavity, which would be favorable to stabilize the labile silyl enol ethers and prevent them from being hydrolyzed in water. Herein, we wish to report that the calix[6]arenes **1a** and **1b** (bearing both sulfonates and alkyl groups) are efficient

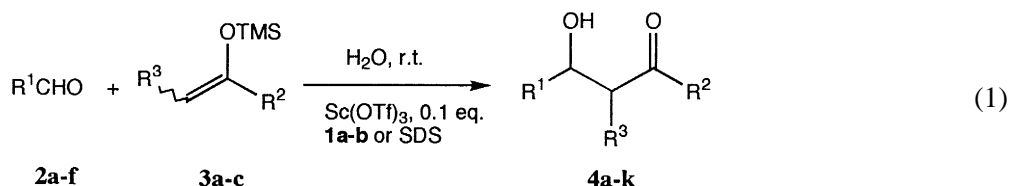
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surfactants in $\text{Sc}(\text{OTf})_3$ -catalyzed Mukaiyama reactions in water (Eq. (1)). The use of these surfactants can inhibit the hydrolysis of silyl enol ethers as well as promote the carbon–carbon bond formation reaction.



1a: R=*n*-C₄H₉; **1b**: R=*n*-C₆H₁₃; **1c**: R=H

Calix[6]arene derivatives **1a–b**, bearing sulfonate groups on the upper rim and the hydrophobic alkyl groups on the lower rim, were synthesized based upon the protocol by Shinkai.⁶ At the beginning of the investigation the aldol reactions of silyl enol ethers, 1-trimethylsiloxy-cyclohex-1-ene (**3a**) and 1-phenyl-1-trimethylsiloxyethylene (**3b**), with aldehydes **2a–d** were carried out in water at room temperature in the presence of the surfactants **1a–b** (20 mol%) and the catalyst $\text{Sc}(\text{OTf})_3$ (10 mol%) to afford the aldol adducts **4a–f** (Eq. (1)).⁷ For comparison, the $\text{Sc}(\text{OTf})_3$ -catalyzed reactions in water were also examined with 20 mol% of the surfactant SDS instead of **1a–b**. The experimental results are summarized in Table 1. In the case of SDS, the silyl enol ethers **3a–b** in the reaction mixture disappeared (as shown by TLC) after 1 h of the reaction; however, a large amount of the aldehyde remained, leading to lower yields of the aldol products. In contrast, when surfactants **1a** and **1b** were used, the silyl enol ethers **3a** and **3b** were still present after a longer reaction time in aqueous solution. Presumably, such an increased stability of the silyl enol ethers toward water in the presence of **1a** and **1b** resulted in higher yields of the aldol products. The calix[6]arene derivative **1b**, having a hexyl group exhibited an advantage over **1a** which bears a shorter chain (butyl group) in both reaction rates and yields (a shorter reaction time and a higher yield). This difference can be explained by the fact that the calix[6]arenes bearing alkyl groups on the lower rim could form a hydrophobic cavity, which associates with the molecule of the silyl enol ether in water. This complex effectively shields the labile silyl enol ethers from hydrolysis and increases the concentration of silyl enol ethers in the hydrophobic reaction field. The size of the cavity formed by **1b** with a longer chain is larger and better accommodates the molecule of silyl enol ethers.



Then, surfactants **1a–b** were examined for the aldol reactions of 1-phenyl-1-trimethylsiloxypropene (**3c**) ($\text{R}^2=\text{Ph}$, $\text{R}^3=\text{CH}_3$) with aldehydes in water by the same experimental procedure. The results are summarized in Table 2. Since **3c** is relatively stable to water, both the calix[6]arene surfactants **1a–b** and SDS gave high yields of the aldol adducts **4g–k**. However, if a sulfonated calix[6]arene without alkyl groups on the lower rim (**1c**, R=H) was used instead of **1a–b**, the aldol reactions of **3c** with aldehydes did not proceed at all and **3c** was still present in the **1c**– $\text{Sc}(\text{OTf})_3$ – H_2O system even after 10 h of stirring. These results indicate that the alkyl group on the lower rim does not only play a role in stabilizing the silyl enol ethers, but also promotes the aldol reaction in water. Comparing **1a** with **1b**, **1a** is less effective in promoting the aldol reaction of **3c** (a longer reaction time) but gave a slightly higher diastereoselectivity (*syn/anti*) of the aldol products. It can be assumed that **1a**, having a shorter alkyl chain, results in a

Table 1
Aldol reactions of **3a–b** with aldehydes in water using **1a–b** and SDS as surfactants

| Entry | Aldehyde R ¹ | Silyl enol ether R ² R ³ | Surfactant | Reaction time (h) | Product | Yield (%) (syn/anti) |
|-------|-----------------------------------|---|------------|----------------------|-----------|-------------------------|
| 1 | 2a , Ph | 3a , (CH ₂) ₄ | SDS | 1 | 4a | 47 (72/28) |
| 2 | | | 1a | 7 | | 88 (75/25) |
| 3 | | | 1b | 4 | | 94 (77/23) |
| 4 | 2b , p-ClPh | | SDS | 1 | 4b | 74 (77/23) |
| 5 | | | 1a | 6 | | 95 (78/28) |
| 6 | | | 1b | 3.5 | | 96 (81/19) |
| 7 | 2c , p-CH ₃ OPh | | SDS | 1 | 4c | 40 (61/39) |
| 8 | | | 1a | 10 | | 63 (56/44) |
| 9 | | | 1b | 6 | | 97 (67/33) |
| 10 | 2d , PhCH=CH | | SDS | 1 | 4d | 54 (52/48) |
| 11 | | | 1a | 8 | | 75 (54/46) |
| 12 | | | 1b | 4 | | 95 (57/43) |
| 13 | 2a | 3b , Ph H | SDS | 1 | 4e | 34 |
| 14 | | | 1b | 8 | | 79 |
| 15 | 2e , p-NO ₂ Ph | | SDS | 1 | 4f | 68 |
| 16 | | | 1b | 5 | | 94 |

Table 2
Aldol reaction of **3c** with aldehydes in water using **1a–b** and SDS as surfactants

| Entry | R ¹ CHO | Surfactant | Reaction Time (h) | Product | Yield (syn/anti) (%) |
|-------|---|------------|----------------------|-----------|-------------------------|
| 1 | 2a | 1a | 8 | 4g | 90 (31/69) |
| 2 | | 1b | 3.5 | | 92 (40/60) |
| 3 | | SDS | 2 | | 90 (40/60) |
| 4 | 2b | 1a | 6 | 4h | 95 (34/66) |
| 5 | | 1b | 4 | | 96 (40/60) |
| 6 | | SDS | 2 | | 93 (41/59) |
| 7 | 2e | 1a | 5 | 4i | 94 (20/80) |
| 8 | | 1b | 4 | | 96 (30/70) |
| 9 | | SDS | 1.5 | | 96 (30/70) |
| 10 | 2d | 1a | 6 | 4j | 90 (36/64) |
| 11 | | 1b | 4 | | 93 (49/51) |
| 12 | | SDS | 3 | | 92 (41/59) |
| 13 | 2f , CH ₃ (CH ₂) ₄ | 1a | 19 | 4k | 75 (38/62) |
| 14 | | 1b | 9 | | 77 (43/57) |
| 15 | | SDS | 4 | | 65 (50/50) |

hydrophobic cavity which is too small to accommodate both substrates properly but is favorable for selectively hosting a substrate molecule.

In conclusion, the calix[6]arene derivatives **1a–b** were found to be effective surfactants for the aqueous Mukaiyama aldol reactions of silyl enol ethers with aldehydes catalyzed by Sc(OTf)₃ to afford the aldol products in high yields. Both **1a** and **1b** can provide a proper size of hydrophobic cavity to host and stabilize some labile silyl enol ethers in water, and to promote the aqueous aldol reactions.

Acknowledgements

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7. A typical experimental procedure: To a mixture of the surfactant (0.04 mmol) in water (1 mL) was added Sc(OTf)₃ (0.02 mmol), aldehyde (0.2 mmol), and the silyl enol ether (0.3 mmol). The mixture was stirred at room temperature until the silyl enol ether disappeared on TLC. Then the mixture was passed through a short silica gel pad and extracted with ethyl ether. The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired aldol adduct.