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Effects of Lewis Acid–Surfactant-Combined Catalysts on Aldol and Diels–Alder Reactions in Water

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Abstract: *Aldol and Diels–Alder reactions in water in the presence of various dodecyl sulfate and dodecanesulfonate salts as Lewis acid–surfactant-combined catalysts have been studied. In the aldol reactions, these salts differed from each other with respect to their catalytic ability at the initial stage of the reaction and to the final yields of the aldol product, while these salts did not affect the reaction rates of the Diels–Alder reactions. These results disclose the remarkable characteristics of Lewis acid catalysis in water.* © 1999 Elsevier Science Ltd. All rights reserved.

Introduction

Organic reactions in water without harmful organic solvents are of significant current interest, especially in relation to today's environmental concerns.[1,2] However, the use of water in organic reactions is limited because most organic compounds do not dissolve in water and, furthermore, many reactive substrates and catalysts are decomposed by water. Lewis acids are one of such catalysts. Although Lewis acid catalysis is one of the most powerful tools in modern organic synthesis, it must be generally carried out under strictly anhydrous conditions because of the water-labile nature of most Lewis acids. On the other hand, in the course of our investigations to develop new synthetic methods, we have found that rare earth metal triflates ($Sc(OTf)_3$, $Yb(OTf)_3$, etc.)[3–5] and some other metal salts[6] can be used as water-stable Lewis acids for organic reactions in water-containing solvents. While several reactions were smoothly catalyzed by these water-stable Lewis acids in aqueous media, a certain amount of organic solvents such as THF, EtOH, and acetonitrile still had to be combined with water to promote the reactions efficiently. To avoid the use of organic solvents, we have developed a new reaction system in which $Sc(OTf)_3$ catalyzes aldol reactions of aldehydes with silyl enol ethers (Mukaiyama aldol reactions) and allylation reactions in pure water in the presence of a small amount of a surfactant such as sodium dodecyl sulfate (SDS).[7,8] The surfactant molecules would form micelles and create hydrophobic reaction media in which the Lewis acid-catalyzed reactions proceed smoothly. Furthermore, in this micellar system, even ketene silyl acetals, which are known to be hydrolyzed easily in water, react with aldehydes to produce the corresponding aldol adducts in high yields. Quite recently, we have introduced new types of Lewis acids, scandium tris(dodecyl sulfate) (**1a**) and scandium trisdodecanesulfonate (**2a**).[9] These "Lewis acid–surfactant-combined catalysts (LASCs)" form stable colloidal dispersion systems with organic substrates in water and efficiently catalyze aldol reactions of aldehydes with very water-labile silyl enol ethers.

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$M(O_3SO\,C_{12}H_{25})_n$

1a: M = Sc, n = 3
1b: M = Cu, n = 2

$M(O_3S\,C_{12}H_{25})_n$

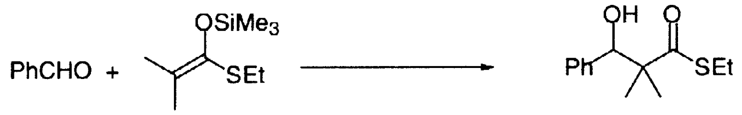
2a: M = Sc, n = 3
2b: M =Yb, n = 3
2c: M = Mn, n = 2
2d: M = Co, n = 2
2e: M = Cu, n = 2
2f: M = Zn, n = 2
2g: M =Na, n = 1
2h: M = Ag, n = 1

Our previous work[6] on Mukaiyama aldol reactions catalyzed by various metal chlorides, perchlorates and triflates in H_2O–THF (or H_2O–EtOH–toluene) suggested that the catalytic activity of each metal cation is correlated to its hydrolysis constant and exchange rate constant for substitution of inner-sphere water ligands (water exchange rate constant). Therefore, to investigate the LASC system in more detail and compare this system with the reactions in H_2O–THF, we have synthesized dodecyl sulfate and dodecanesulfonate salts with various metal cations and studied the effects of the metal cations on catalytic activity for Lewis acid-mediated reactions in water. Here we report that studies on Mukaiyama aldol and Diels–Alder reactions[10] in the presence of various LASCs have revealed the characteristics of each metal cation and the limitations of LASCs as effective Lewis acids in water.[11]

Results and Discussion

LASCs **1a**,[9] **b**,[12] **2a**–**h** were prepared from the corresponding metal chlorides and sodium dodecyl sulfate or sodium dodecanesulfonate in water. Generally, the dodecanesulfonates can be recrystallized from water more easily than the dodecyl sulfates.

First, LASC-mediated aldol reactions in water were examined. Benzaldehyde (1 eq) and thioketene silyl acetal **3** (1.5 eq) were used as substrates. The reactions were carried out in the presence of 10 mol % LASC in water, and monitored by GC. Figure 1 shows the plot of GC yield (average value for two runs) versus time for the reaction catalyzed by the dodecanesulfonates (**2a–h**) at 30 °C. When the reactions were carried out at 23 °C, reproducible results for some dodecanesulfonate salts were not obtained, probably due to the low solubility of the salts in water at this temperature. On the other hand, the results were reproducible within experimental error at 30 °C.



3 **4**

The remarkable effects of the metal cations on the reaction are seen in Figure 1. These LASCs can be characterized in terms of catalytic activity at the initial stage and the yields at the final stage of the reactions. The order of catalytic activity at the initial stage is as follows: Cu (**2e**) > Zn (**2f**), Ag (**2h**) > Sc (**2a**), Yb (**2b**) > Na (**2g**) > Mn (**2c**), Co (**2d**). The Cu salt (**2e**) has the highest ability to catalyze the aldol reaction among the catalysts used. As far as the yields at the final stage of the reactions are concerned, the Cu salt (**2e**) was less effective than the Sc and Yb salts (**2a**, **2b**). When catalyst **2e** was used, the yield of **4** did not exceed 70%, because **2e** accelerated not only the aldol reaction but also hydrolysis of thioketene silyl acetal **3**. The same trend was observed for the Zn and Ag salts (**2f**, **2h**). On the other hand, the Sc and Yb salts (**2a**, **2b**) afforded the aldol product (**4**) in >90% final yields, although the catalytic activity of **2a** and **2b** at the initial stage of the reactions was slightly lower than those of **2e**, **2f**, and **2h**. It should be noted that, in the dispersion system derived from **2a** and **2b**, the hydrolysis of thioketene silyl acetal **3** was attenuated.

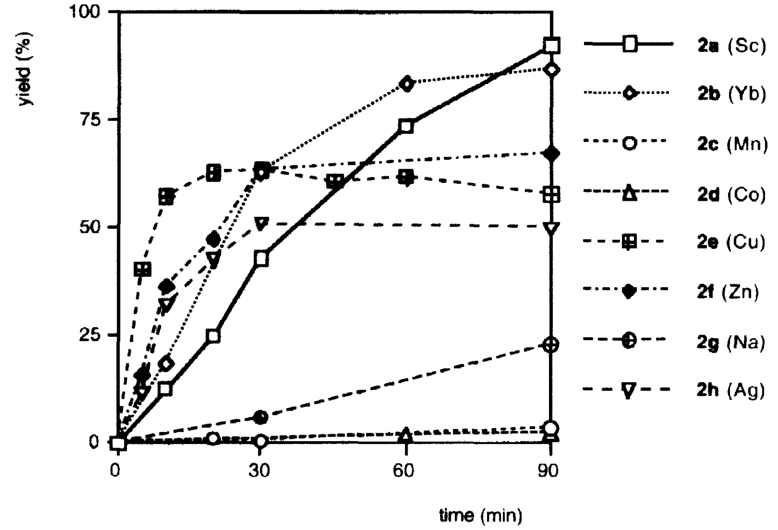


Figure 1. Plot of GC yield versus time for the aldol reaction of benzaldehyde with **3** in the presence of dodecanesulfonate salts in water.

Especially in the case of **2a**, a small amount of **3** still remained when the aldol reaction completed. When the Na, Mn, and Co salts (**2g**, **2c**, **2d**) were used as catalysts, the aldol reactions proceeded very slowly, and the yields of **4** did not exceed 70% because of the hydrolysis of **3**.

Similar effects of scandium and copper were observed in the dodecyl sulfate series (Figure 2). The Sc salt (**1a**) suppressed the hydrolysis of **3** more efficiently than the Cu salt (**1b**) did, whereas **1b** catalyzed the aldol reaction at the initial stage more effectively than **1a** did.

These metal effects cannot be explained only by the hydrolysis constants and water exchange rate constants of the metal cations.[6] The molar ratio of the metal cations to dodecyl sulfate or dodecanesulfonate anions should be also an important factor in determining the effectiveness of the catalysts. The LASCs whose molar ratios of the metal cations to counteranions are small (1/3 for the Sc(III) and Yb(III) salts) effectively protect the silyl enolate from hydrolysis to afford the aldol product in high final yields. On the other hand, for the LASCs whose molar ratios of the metal cations to counteranions are larger, the hydrolysis of the silyl enolate cannot be suppressed, resulting in lower yields of the product. Furthermore, the cation-to-anion ratios would also affect the catalytic activity at the initial stage. The order of the catalytic activity of Sc, Yb, Cu, Zn, and Ag differs from the one in metal chlorides- or perchlorate-catalyzed aldol reactions in H_2O–THF.[6] In this organic solvent-containing system, catalytic activities of Sc(III) and Yb(III) salts are higher than those of Cu(II), Zn(II), and Ag(I). On the other hand, catalytic activities of Cu(II), Zn(II), and Ag(I) are higher than those of Sc(III) and Yb(III) in the present LASC system. This difference in the order of the catalytic activity may be ascribed to low cation-to-anion ratios of Sc(III) and Yb(III) salts compared with those of Cu(II), Zn(II), and Ag(I) salts. In the LASC system, highly charged metal cations, which form salts of low cation-to-anion ratios, should attenuate the headgroup repulsion of the anionic surfactant. As a result, the packing of the headgroups becomes tight.[10] We assume that the tighter packing reduces the chance for the aldehyde to coordinate to the metal cations, resulting in the lower catalytic activity.

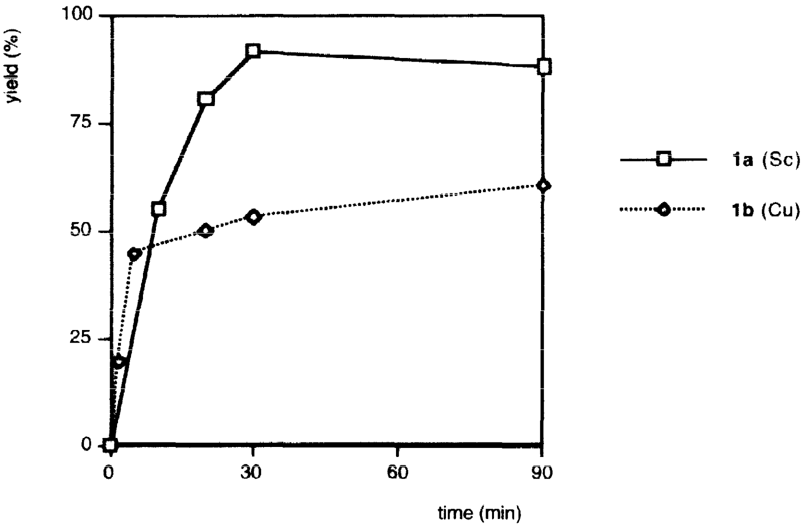


Figure 2. Plot of GC yield versus time for the aldol reaction of benzaldehyde with **3** in the presence of dodecyl sulfate salts in water.

Water plays an essential role in the present reaction system. The reaction of benzaldehyde with **3** in the presence of **2a** without water (neat conditions) gave no aldol product after 1.5 h, probably because water molecules create a catalytically active species or the reaction environment necessary for the aldol reaction.

Next, we turned our attention to the effect of LASCs on Diels–Alder reaction, which is also a representative Lewis acid-catalyzed reaction. While the Diels–Alder process was reported to be accelerated in water without catalysts,[13,14] several examples of Lewis acid catalysis in aqueous media have been disclosed recently.[15–21] Quite recently, Engberts and co-workers reported copper dodecyl sulfate-catalyzed Diels–Alder reactions in water using 3-phenyl-1-(2-pyridyl)-2-propen-1-one derivatives,[10] which can coordinate to a copper cation with exceptional strength as bidentate dienophiles. Since monodentate dienophiles have been used in many other examples of Lewis acid-catalyzed Diels–Alder reactions, we expected that LASCs might also catalyze the reactions of monodentate dienophiles such as *N*-butylmaleimide **5**.

The Diels–Alder reactions of **5** with 2,3-dimethylbutadiene[22] were carried out in the presence or absence of the several LASCs, and monitored by GC. The results are shown in Figure 3. Unexpectedly, all the LASCs exhibited almost identical reaction profiles. Furthermore, no rate retardation was observed even for the reaction without LASCs. Apparently, the reaction proceeded through an uncatalyzed pathway even in the presence of LASCs due to the rate enhancement by water itself.[13,14] We assume that the dienophile cannot effectively coordinate to a metal cation in the LASC system, and that the uncatalyzed pathway consequently predominates.

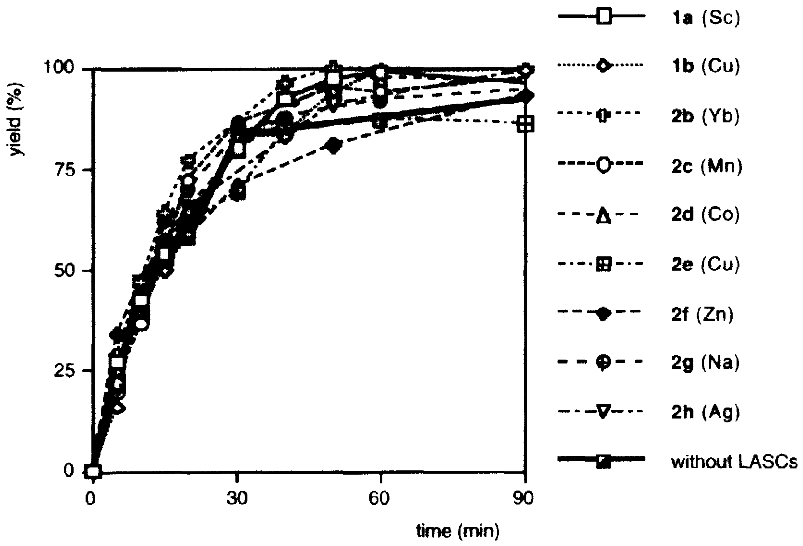
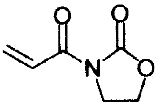


Figure 3. Plot of GC yield versus time for the Diels–Alder reaction of 5 with 2,3-dimethylbutadiene in the presence or absence of LASCs.

We also carried out a Diels–Alder reaction of bidentate dienophile **6**[23,24] with cyclopentadiene in the presence or absence of **1a**,**b**. Again, no significant rate enhancement by the LASCs was observed. Therefore, the results shown here imply that LASCs are poor catalysts for Diels–Alder reactions of dienophiles (both monodentate and bidentate) which are generally subject to Lewis acid catalysis in organic solvents.



6

In summary, LASCs with various metal cations were used for Mukaiyama aldol and Diels–Alder reactions in water. From the investigations, including kinetic studies, the copper salt was found to catalyze the aldol reaction efficiently at the initial stage compared with the other salts, whereas the scandium and ytterbium salts were found to afford the aldol product in high final yields. For the Diels–Alder reaction, the LASCs did not affect the reaction rate. These results show the remarkable characteristics of Lewis acid catalysis in water, since it is well-known that both aldol and Diels–Alder reactions are catalyzed by Lewis acids in organic solvents. It is expected that these results would enable us to gain insight into the precise mechanism of Lewis acid catalysis in water. Further investigations along this line as well as development of other Lewis acid-catalyzed reactions of water-labile substrates in water are now in progress.

Experimental

General. Melting points are uncorrected. IR spectra were recorded on a JASCO FT/IR-610 infrared spectrometer. GC analysis was performed on a Shimadzu gas chromatograph GC-17A with a capillary column (Silicone OV-101, Gasukuro Kogyo, Inc.). LASCs **1a**,[9] **b**,[12] were prepared according to the reported procedures.

Typical procedure for the preparation of LASCs. Sodium dodecanesulfonate (1.96 g, 7.19 mmol) was dissolved in H_2O (70 mL) at 70 °C. To this was added a solution of $CuCl_2•2H_2O$ (0.613 g, 3.60 mmol) in H_2O (1 mL) at the same temperature. The mixture was cooled to room temperature, and the resulting precipitate was collected and purified by recrystallization from H_2O to give **2e** as pale blue leaves (1.99 g, 99%). The other new LASCs were prepared in a similar way.

Typical procedure for LASC-mediated reactions. 2,7-Dimethylnaphthalene was used as an internal standard. To a mixture of 2,7-dimethylnaphthalene (ca. 5 mol %) and benzaldehyde (0.25 mmol, 1 eq) were added a LASC (10 mol %) and water (1.5 mL) under Ar. After 10 min at 30 °C, thioketene silyl acetal **3** (1.5 eq) was added. The resulting cloudy mixture was stirred at 30 °C and monitored by GC.

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