J. Am. Chem. Soc. **2001,** *123,* 10101−10102 10101

Dehydration Reactions in Water. Surfactant-Type Brønsted Acid-Catalyzed Direct Esterification of Carboxylic Acids with Alcohols in an Emulsion System

Kei Manabe, Xiang-Min Sun, and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences
The University of Tokyo, CREST
Japan Science and Technology Corporation (JST)
Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received June 4, 2001
Revised Manuscript Received July 22, 2001

Recently, organic reactions in water have received much attention, because water is a cheap, safe, and environmentally benign solvent.[1] Our and others' studies on surfactant-type Lewis[2] or Brønsted acid[3] catalysts revealed that carbon−carbon bond-forming reactions proceeded in the presence of these catalysts in water. Under the reaction conditions, emulsion droplets were formed from catalytic amounts of these catalysts and reaction substrates.[2c,3c,4] These droplets, although dispersed in water, are hydrophobic enough for protecting water-labile substrates such as silyl enolates from hydrolytic decomposition. These results prompted us to realize *dehydration reactions in water*.

Acid-catalyzed direct esterification[5] of carboxylic acids with alcohols was selected as a representative dehydration reaction. Generally, direct esterification is carried out in organic solvents and needs either of two methods to shift the equilibrium between reactants and products.[6] One is removal (azeotropically or using dehydrating agents) of water generated as the reactions proceed, and the other is use of large excess amounts of one of the reactants. On the other hand, our idea is that the esterification would be realized even in water without using a large excess of reactants. The concept is shown in Figure 1. The surfactant-type catalysts and organic substrates (carboxylic acids and alcohols) in water would form the droplets whose interior is hydrophobic. The surfactants would concentrate a catalytic species such as proton onto the droplets' surfaces, where the reaction takes place, and then enhance the rate to reach equilibrium. For lipophilic substrates, the equilibrium position between the substrates and the products (esters) would lie at the ester side, because water molecules would be expelled out of the droplets due to hydrophobic nature of their interior. As a result, the dehydration reactions would efficiently proceed even in the presence of a large amount of water as a solvent. Dehydration in water is really unusual and exciting because in water usually hydrolysis occurs. Indeed, the acid-catalyzed direct formation of esters with the aid of surfactants in water has not been reported as far as we know, although surfactants have been occasionally used to accelerate the reactions to the opposite direction: hydrolysis of esters.[7] Here we show that direct esterification in water was realized using a surfactant-type Brønsted acid and that selective esterification was also observed in this system.

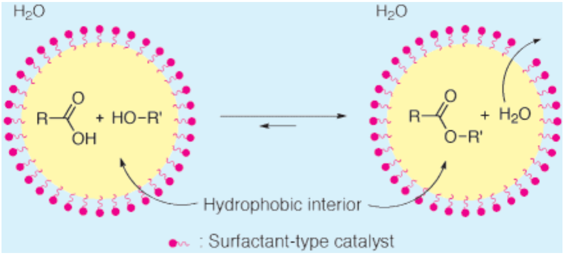


Figure 1. Illustration of direct esterification by dehydration in the presence of a surfactant-type catalyst in water.

First, we carried out the esterification of carboxylic acids with 3-phenyl-1-propanol (the molar ratio of a carboxylic acid to the alcohol = 1:1) in the presence of 10 mol % *p*-dodecylbenzenesulfonic acid (DBSA),[8] a surfactant-type Brønsted acid, at 40 °C for 24 h in water. When acetic acid was used as a substrate, the yield of 3-phenylpropyl acetate was only 6% (determined by ^{1}H NMR). To our delight, however, the reactions of more lipophilic carboxylic acids proceeded in water to afford the corresponding esters in acceptable yields (butyric acid: 31% yield; caprylic acid: 61% yield; lauric acid: 63% yield).[9] It should be noted that the ester formation was realized at 40 °C in water in contrast to high temperatures which are required for conventional azeotropic removal of water in organic solvents.

Sodium *p*-dodecylbenzenesulfonate instead of DBSA did not catalyze the esterification of lauric acid (1% yield), indicating that the catalytic species is proton. It is also noteworthy to mention that the esterification in the presence of *p*-toluenesulfonic acid (TsOH) as a catalyst proceeded very slowly. According to a study on the initial rates of the esterification of lauric acid with 3-phenyl-1-propanol, DBSA was found to catalyze the reaction 60 times faster than TsOH did (for DBSA, 5.41×10^{-3} M h^{-1}; for TsOH, 9.05×10^{-5} M h^{-1}). These results clearly demonstrate that both the long-chain alkyl and the sulfonic acid moiety of DBSA are crucial for efficient catalysis. In the case of using DBSA, the reaction mixtures became white turbid emulsions, as in the case of DBSA-catalyzed Mannich-type reactions, in which the formation of white turbid mixtures was important for good yields of the desired Mannich adducts.[3a−c] Formation of emulsion droplets in the present reaction system was confirmed by optical microscopy (Figure 2).[10]

---

(1) (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*: John Wiley & Sons: New York, 1997.

(2) (a) Kobayashi, S.; Wakabayashi, T.; Nagayama, S.; Oyamada, H. *Tetrahedron Lett.* **1997**, *38*, 4559. (b) Kobayashi, S.; Wakabayashi, T. *Tetrahedron Lett.* **1998**, *39*, 5389. (c) Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 7202. (d) Mori, Y.; Kakumoto, K.; Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 3107. (e) Manabe, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal.* **2001**, *343*, 174. (f) Otto, S.; Engberts, J. B. F. N.; Kwak, J. C. T. *J. Am. Chem. Soc.* **1998**, *120*, 9517. (g) Rispens, T.; Engberts, J. B. F. N. *Org. Lett.* **2001**, *3*, 941.

(3) (a) Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* **1999**, 1401. (b) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965. (c) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537. (d) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1426. (e) Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* **1999**, *40*, 7831.

(4) Emulsion systems have been used for organic reactions. One successful example is emulsion polymerization. For example: Harkins, W. D. *J. Am. Chem. Soc.* **1947**, *69*, 1428.

(5) (a) Larock, R. C. *Comprehensive Organic Transformations*; John Wiley & Sons: New York, 1999. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999.

(6) (a) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307. (b) Izumi, J.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1995**, 141. (c) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196. (d) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140. (e) Masaki, Y.; Tanaka, N.; Miura, T. *Chem. Lett.* **1997**, 55. (f) Storck, S.; Maier, W. F.; Salvado, I. M. M.; Ferreira, J. M. F.; Guhl, D.; Souverijins, W.; Martens, J. A. *J. Catal.* **1997**, *172*, 414. (g) Zhang, G.-S. *Synth. Commun.* **1999**, *29*, 607. Esterification under water−toluene two-phase conditions has been reported, although the yields of esters are low: (h) Okuhara, T.; Kimura, M.; Kawai, T.; Xu, Z.; Nakato, T. *Catal. Today* **1998**, *45*, 73.

(7) Feiters, M. C. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds; Elsevier Science: Oxford; 1996; Vol. 10.

(8) *p*-Dodecylbenzenesulfonic acid (soft type) was purchased from Tokyo Kasei Kogyo Co., Ltd. This is a mixture of linear alkylbenzenesulfonic acids. Its molecular weight was regarded as 326.50.

(9) The esterification of lauric acid with ethanol (a more hydrophilic alcohol) resulted in 6% yield.

(10) Stirring (usually 1400 rpm) of the reaction mixture was not very important to keep it an emulsion system. Without stirring, large, visible droplets were formed, but the aqueous phase was still a white turbid solution (the yield of 3-phenylpropyl laurate is 58% after 24 h at 40 °C without stirring). Cf. ref 2c.

10.1021/ja016338q CCC: $20.00 © 2001 American Chemical Society
Published on Web 09/22/2001

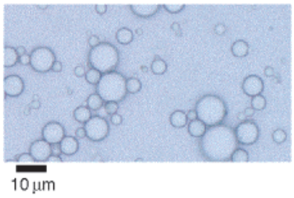


Figure 2. Optical micrograph of the reaction mixture of DBSA (10 mol %)-catalyzed esterification of lauric acid with 3-phenyl-1-propanol (1:1) in water.

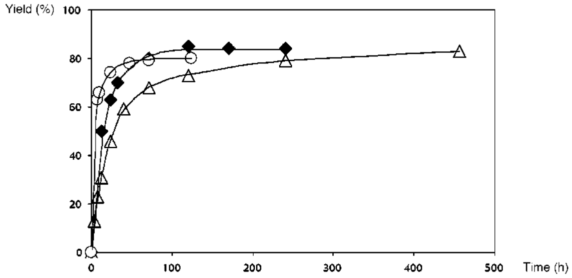
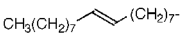


Figure 3. Reaction profiles for esterification of lauric acid with 3-phenyl-1-propanol (1:1) in the presence of DBSA (10 mol %) in water. (△) at 30 °C; (♦) at 40 °C; (○) at 60 °C.

Table 1. Esterification Catalyzed by DBSA in Water

$$\underset{(1.0\ \text{equiv.})}{RCO_2H} + \underset{(2.0\ \text{equiv.})}{HOR'} \xrightarrow[H_2O,\ 40\ °C,\ 48\ h]{\text{DBSA (10 mol \%)}} RCO_2R'$$

R	R'	Yield (%)[a]
$CH_3(CH_2)_{10}$-	-$(CH_2)_3Ph$	89
$CH_3(CH_2)_{10}$-	-$(CH_2)_{11}CH_3$	97
$CH_3(CH_2)_{10}$-	-$(CH_2)_{13}CH_3$	>99
$Ph(CH_2)_4$-	-$(CH_2)_{13}CH_3$	97
	-$(CH_2)_{13}CH_3$	97
c-Hex	-$(CH_2)_{13}CH_3$	95

[a] Isolated yield.

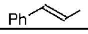
Figure 3 shows the profiles of the DBSA-catalyzed reaction of lauric acid with 3-phenyl-1-propanol (1:1) at various temperatures. At 40 °C, the reaction reached its equilibrium position in 120 h with a maximum yield of 84%. Raising the temperature to 60 °C made the reaction faster, although its maximum yield slightly decreased to 80%. At 30 °C, the time required to reach the equilibrium position increased significantly.

This catalytic system was applied to other substrates as shown in Table 1. The use of 2 equiv of alcohols improved the yields to greater than 90% for most cases.

We next investigated selective esterification in this system. When a 1:1 mixture of lauric acid and acetic acid was esterified with 3-phenyl-1-propanol in the presence of DBSA in water, 3-phenylpropyl laurate was selectively obtained (Table 2, entry 1). This selectivity is attributed to the hydrophobic nature of lauric acid and is unique to the present reaction system. Selective esterification based on the difference of hydrophobicity was also observed for other substrates (entries 2 and 3). Furthermore, preferential esterification of nonconjugated carboxylic acids over aromatic or conjugated carboxylic acids[11] was also attained (entries 4 and 5). These results of the selective esterification significantly expand the utility of the DBSA-catalyzed reactions in water.

Table 2. Selective Esterification Catalyzed by DBSA in Water

$$\underset{(1.0\ \text{equiv.})}{R^1CO_2H} + \underset{(1.0\ \text{equiv.})}{R^2CO_2H} + \underset{(x\ \text{equiv.})}{HOR} \xrightarrow[H_2O,\ 40\ °C,\ 48\ h]{\text{DBSA (10 mol \%)}} \begin{array}{c} R^1CO_2R\ (\mathbf{A}) \\ + \\ R^2CO_2R\ (\mathbf{B}) \end{array}$$

Entry	R^1	R^2	R (x equiv.)	Yield (%)[a] **A**	Yield (%)[a] **B**
1[b]	$CH_3(CH_2)_{10}$-	CH_3-	-$(CH_2)_3Ph$ (1)	78	trace
2	$CH_3(CH_2)_{10}$-	CH_3-	-$(CH_2)_{11}CH_3$ (1)	81	4
3	*c*-Hex	CH_3-	-$(CH_2)_{11}CH_3$ (1)	65	5
4	*c*-Hex	Ph	-$(CH_2)_{11}CH_3$ (2)	83	5
5	$Ph(CH_2)_2$-		-$(CH_2)_{11}CH_3$ (1)	78	trace

[a] Determined by ^1H NMR. [b] 120 h.

In conclusion, dehydration reactions were conducted to yield esters in water using DBSA as a surfactant-type Brønsted acid catalyst, and unique selective esterification was also attained. The reactions need neither dehydrating agents nor azeotropic removal of water. Instead, the catalyst and substrates in the present system assemble together through hydrophobic interactions to form devices for dehydration reactions ("dehydrating devices"), in which the catalyst enhances the reaction rate and hydrophobic interior of emulsion droplets facilitates exclusion of water molecules. Furthermore, since both of the sole byproduct and the solvent in the esterification are water, the reactions are atom-economical[12] and may lead to a method which solves some environmental problems. This work will not only lead to a practical synthetic method but also provide a new aspect of chemistry in water.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental details for the esterification and the initial rate kinetics, and characterization of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA016338Q

---

(11) (a) Blossey, E. C.: Turner, L. M.; Neekers, D. C. *Tetrahedron Lett.* **1973**, 1823. (b) Bertin, J.; Kagan, H. B.; Luche, J.-L.; Setton, R. *J. Am. Chem. Soc.* **1974**, *96*, 8113. (c) Rehn, D.; Ugi, I. *J. Chem. Res. Synop.* **1977**, 119. (d) Banerjee, A.; Sengupta, S.; Adak, M. M.; Banerjee, G. C. *J. Org. Chem.* **1983**, *48*, 3106. (e) Matsumoto, I. Jpn. Kokai Tokkyo Koho JP 59 152,347 [84 152,347] (Cl. C07C67/08); *Chem. Abstr.* **1985**, *102*, 5952w. (f) Ogawa, T.; Hikasa, T.; Ikegami, T.; Ono, N.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3473. (g) Ram, R. N.; Charles, I. *Tetrahedron* **1997**, *53*, 7335. (h) Rodríguez, A.; Nomen, M.; Spur, B. W. *Tetrahedron Lett.* **1998**, *39*, 8563. (i) Lee, A. S.-Y.; Yang, H.-C.; Su, F.-Y. *Tetrahedron Lett.* **2001**, *42*, 301.

(12) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233.