Evidence for Ionic Interaction between Cationic Surfactant and Anionic Intermediate Generated in Cathodic Reduction of Acetophenone

Yorimitsu Kodama,* Akihito Fujiwara, Hideki Kawamoto, Nobuaki Ohta, Akira Kitani,† and Sotaro Ito
Department of Applied Physics and Chemistry, Faculty of Engineering, Hiroshima University, 1-4-1 Kagamiyama, Higashi-Hiroshima 739-8527
†*Department of Applied Chemistry, Faculty of Engineering, Hiroshima University, 1-4-1 Kagamiyama, Higashi-Hiroshima 739-8527*

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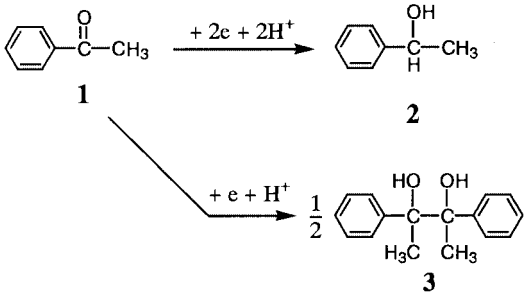
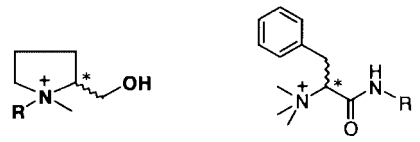
The cathodic reduction of acetophenone in the presence of a chiral cationic surfactant in aqueous media gave *S*- or *R*-1-phenylethanol with 8–12 % ee. The observed enantioselectivity clearly suggests the interaction between the cationic surfactants and the anionic intermediate generated from the one-electron reduction of acetophenone.

The electrolytic reactions of organic compounds have been usually carried out in organic solvents such as acetonitrile, dichloromethane and DMF.[1] The use of water instead of organic solvents is strongly desired from the viewpoint of environmental safety and economical cost. The electrolyses of organic compounds in aqueous media are, however, very limited, because of their low current efficiency and low selectivity. Recently, we have reported that the cathodic reduction of acetophenone **1** in the presence of cationic surfactants forms 1-phenylethanol **2** selectively in aqueous solutions.[2,3] The high selectivity of **2** observed in aqueous solutions is unusual, because the selective electroreduction of **1** to **2** is known to be achieved only in organic solvents. The selective formation of **2** was explained in terms of the electrostatic interaction between the negative charge on the intermediate anion derived from acetophenone and the positive charge on the micelle formed from cationic surfactants, though the direct evidence for this explanation was not present.[2,3] In this study, we would like to report the enantioselective reduction of **1** in the presence of chiral cationic surfactants. The present observations will hardly explained without postulating the electrostatic interaction between the cationic surfactants and the anionic intermediate generated from the one-electron reduction of acetophenone.



1 **2** **3**

Four chiral cationic surfactants **4**–**7**, which have an asymmetric carbon near the ammonium nitrogen with a positive charge, were synthesized[4–6] and the additive effect of the chiral surfactants on the product distribution in cathodic reduction of **1** was examined.



4: R = $C_{12}H_{25}$
5: $C_{16}H_{33}$

6: R = $C_{12}H_{25}$
7: $C_{18}H_{37}$

The electrolytic apparatus and conditions were essentially the same as the previous ones.[2,3] Acetophenone (2.2 mmol) in 100 mL of an aqueous sodium sulfate solution (0.05 M (1 M = 1 mol dm^{-3})) containing 10 mL of acetonitrile and 2.7 mmol of surfactant was electrolyzed on Pb cathode (12 cm^2) at room temperature under the constant-potential conditions at –2.1 V vs SCE. The catholyte was stirred in nitrogen atmosphere during the electrolysis. After passing 5 mF (1.2 F mol^{-1} (1 F = 96484.56 C)) of electric charge, the catholyte was subjected to HPLC analysis. HPLC analysis conditions were: Chiralcel OB (250 × ϕ 4.6 mm) column (Daicel Chemical Industries, LTD.), an eluent with 9:1 hexane/2-propanol at 1.0 mL/min.

The additive effect of the surfactants on the product distribution in the electroreduction of **1** was summarized in Table 1. In the presence of the cationic surfactants **4** and **5**, the selectivity of **2** was increased up to the ratio observed in the presence of hexadecyltrimethylammonium bromide (CTAB), a typical cationic surfactant commercially available. Likewise, the addition of **6** and **7** to the catholyte accelerated the formation of **2**. From the results in Table 1, it is understood that the additives **4**–**7** act as a cationic surfactant and favor the formation of **2**, as CTAB does.

The enantioselectivity of **2** in the electroreduction of **1** was summarized in Table 2. In the absence of surfactant and in the presence of achiral surfactants, the enantiomer excess (ee) was essentially zero. The addition of the chiral surfactants *S*-**4**, *S*-**5**, *R*-**6** and *R*-**7** to the catholyte, on the contrary caused an asymmetric reaction to give *R*-**2** on the ee values of 3.4–12 %. It is also noteworthy that if the *S*-surfactant accelerates the formation of *S*-**2**, the corresponding *R*-surfactant favors the *R*-isomer, and vice versa. Successful examples of the enantioselective conversions in electroreduction are quite few. On electroreduction of ketones in the presence of chiral additive such as ephedrine derivatives,[7,8] alkaloids,[7,9] and poly(pyrroles),[10] the corresponding alcohols were obtained enantioselectively with 20, 20, and 17 % ee, respectively. Shäfer studied the electroreduction of 4-methylcoumarin in the presence of chiral alkaloid, yohimbin, to get (+)-*R*-4-methyl-3,4-dihydrocoumarin with 47 % ee.[11]

It is well known that the electroreduction of carbonyl compounds proceeds in two-step one-electron transfer, as illustrated in Scheme 1.

Table 1. Effect of additive on product distribution in constant potential electrolysis of acetophenone

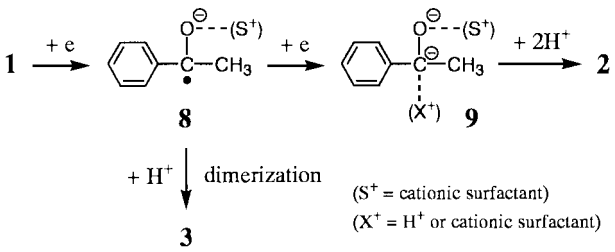
Additive	Solvent[a]	Yield/%[b]			Current efficiently/%		
		2	**3**	[**2**]/[**3**]	**2**	**3**	Total
CTAB	A	50	3.3	15	44	2.9	47
S-**4**	A	48	0.77	62	42	0.70	43
R-**4**	A	52	0.77	67	45	0.70	46
S-**5**	A	52	1.0	52	45	0.87	46
R-**5**	A	46	0.85	54	40	0.73	41
none	A	15	11	1.4	13	9.7	23
CTAB	B	22	8.0	2.8	20	7.8	28
S-**6**	B	15	9.1	1.6	13	8.1	21
R-**6**	B	15	9.5	1.6	13	8.4	21
S-**7**	B	15	3.8	3.9	13	3.0	16
R-**7**	B	16	4.6	3.5	14	4.1	18
none	B	13	22	0.59	11	20	31

[a]A: CH_3CN/H_2O = 1/9; B: CH_3OH/H_2O = 1/4.
[b][product]/[initial acetophenone].

Table 2. Effect of additive on enantioselectivity of **2** in constant potential electrolysis of acetophenone

Additive	Solvent[a]	Yield/%[b]		ee/%
		R-**2**	*S*-**2**	
CTAB	A	25	25	0.0
S-**4**	A	26	22	8.3
R-**4**	A	24	28	7.7
S-**5**	A	29	23	12
R-**5**	A	20	25	11
none	A	7.3	7.3	0.0
CTAB	B	11	11	0.0
S-**6**	B	7.2	7.8	3.9
R-**6**	B	7.7	7.2	3.4
S-**7**	B	6.8	8.3	10
R-**7**	B	8.8	7.3	9.3
none	B	6.5	6.5	0.0

[a]A: CH_3CN/H_2O = 1/9; B: CH_3OH/H_2O = 1/4.
[b][product]/[initial acetophenone].



Scheme 1.

In our previous work,[2,3] we suggested that the monomeric product **2** was selectively formed through the formation of an ion-pair between the negatively charged intermediate **8** and the positively charged micelle, which are formed by aggregation of cationic surfactant molecules. The results in Tables 1 and 2 unambiguously indicate that the anionic intermediate **8** so strongly interacts with the micelle of the chiral surfactant as to recognize an asymmetric center of the surfactant moiety.

In conclusion, the present study provides a strong evidence for the electrostatic interaction between the cationic surfactant and the intermediate **8**. Both the selective formation of the monomeric product **2** and the enantioselective reduction to *R*- or *S*-**2** can be explained in terms of the formation of an ion-pair.

References and Notes

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3 Y. Kodama, M. Imoto, N. Ohta, A. Kitani, and S. Ito, *J. Electroanal. Chem.*, in press.
4 Surfactant **4** was synthesized as follows; *S*- or *R*-prolinol and 1-bromododecane were heated at 60 °C with potassium carbonate in acetonitrile for 2 days to obtained *N*-dodecylprolinol, and then, the intermediate and methyl iodide were heated at 60 °C in methanol to obtained **4**. The chirality of new surfactant was determined on ^{1}H NMR with chiral shift reagent, europium tris[3-(trifluoromethylhydroxymethylene)-(+)-campharate] (Eu(TFC)$_3$). Surfactant **5** was synthesized from prolinol and 1-bromohexadecane under the same conditions as those of **4** .
5 Surfactants **4** and **5** were used without the separation of epimer according to the method proposed in E. V. Dehmlow, R. Klauck, S. Düttmann, B. Neumann, and H. -G. Stammler, *Tetrahedron: Asymmetry*, **9**, 2235 (1998). We estimated the epimer ratios of **4** and **5** by ^{1}H NMR. *S*-**4**: (1*R*,2*S*)/(1*S*,2*S*) = 93/7; *R*-**4**: (1*S*,2*R*)/(1*R*,2*R*) = 92/8; *S*-**5**: (1*R*,2*S*)/(1*S*,2*S*) = 80/20; *R*-**5**: (1*S*,2*R*)/(1*R*,2*R*) = 82/18.
6 Surfactant **6** was synthesized by follows; *N*-benzyloxycarbonyl-(*S*- or *R*-)phenylalanine and dodecylamine were heated at 60 °C in CH_2Cl_2 for 1 day to obtain *N*-benzyloxycarbonylphenylalanine dodecyl amide, and then, after the deprotection on amine by use of Pd/C and H_2, the intermediate and methyl iodide were heated at 60 °C with potassium hydrogencarbonate in MeOH for 1 day to obtain **6**. The chirality of new surfactant was determined on ^{1}H NMR with chiral shift reagent, Eu(TFC)$_3$. Other surfactant **7** was synthesized from phenylalanine and octadecylamine under the same conditions as those of **6** .
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