Electroorganic Synthesis in Oil-in-Water Nanoemulsion: TEMPO-Mediated Electrooxidation of Amphiphilic Alcohols in Water

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Abstract: Oil-in-water nanoemulsions, consisting of TEMPO, amphiphilic alcohols, and water, offer unique reaction environments for electrooxidation of the alcohols to give the corresponding carboxylic acids in good to excellent yields.

Key words: electrooxidation, alcohols, nanostructure, TEMPO, aqueous environment

A nanoemulsion is a type of thermodynamically stable liquid isotropic dispersion composed of water, oil, and surfactants, and the particle sizes of the dispersed phase are defined as less than 1000 nm.¹ Nanoemulsions have unique physical and chemical properties, and have been used widely in many different fields, such as pharmaceuticals,² cosmetics,³ lubricants,⁴ surfactants,⁵ and detergents,⁶ in the last decade. For example, oil-in-water nanoemulsions transport hydrophobic compounds (drugs) in water and have been used as drug delivery materials.⁷ However, these nanoemulsions have scarcely been used in organic synthesis, especially in electroorganic synthesis.⁸ This paper describes the first application of nanoemulsion to a potent electrolysis medium.

Electroorganic synthesis is one of the most promising environmentally benign processes because passage of electricity promotes the desired oxidation and/or reduction without oxidants or reductants and, therefore, wastes arising from these reagents are not produced. Electrolyses have been carried out in several reaction media such as organic solvents (DMF, MeCN, CH₂Cl₂, EtOAc, and so on), water, and their mixed systems. Water is an ideal medium for electrolysis: indeed, it is cheap, nonflammable, and nontoxic, and its dielectric constant is high enough to pass the required electricity. Solubility of the organic substrates in water is, however, generally poor, and a unique design and special care of the aqueous medium are required. We have reported N-oxyl-mediated electrooxidation of alcohols⁹ in several aqueous electrolysis systems, such as organic/aqueous two-phase system (CH₂Cl₂water),¹⁰ solid/water disperse systems (silica gel¹¹ and polymer particles¹²/water), and oil-in-water microemulsion systems.¹³ A representative mediatory system in the heterogeneous environment is illustrated in Scheme 1. Electrooxidation of Br⁻ would give OBr⁻. Oxidation of N-

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oxyl **3** with OBr^{-} would give *N*-oxoammonium **4**, which would oxidize alcohol 1 to the corresponding carbonyl compound 2. N-Hydroxylamine 5, generated in this step, would subsequently react with another molecule of 4 to form 2 mol of 3. This electrooxidation can be performed conveniently in an undivided cell under constant current conditions. This system always requires the second watersoluble mediator such as Br⁻ even in the microemulsion system,¹³ and the electrooxidation of alcohols scarcely occurred in the absence of NaBr. The Br- sometimes causes undesirable side reactions such as bromination of the substrate. Although the electrooxidation in the single-phase organic system proceeded without Br-, it proceeded only in a divided cell under constant potential conditions, and was not satisfactory in terms of operational simplicity, manufacturing cost, and environmental stress.



Scheme 1 N-Oxyl-mediated electrooxidation of alcohols in heterogeneous environments

In 1999, Schäfer et al. reported 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-mediated electrooxidation of sugar derivatives in water.¹⁴ To our surprise, the electrooxidation proceeded smoothly without use of bromide salt. This prompted us to reinvestigate the electrooxidation of various alcohols in water by dynamic light scattering (DLS) and cyclic voltammetry (CV) analyses, and we found that this electrooxidation proceeded smoothly only when a nanoemulsion was formed in the electrolysis medium (Equation 1). Only amphiphilic alcohols such as sugars and polyethylene glycols formed the nanoemulsion with TEMPO in water, while water-soluble and water-insoluble alcohols did not form nanoemulsions and were not efficiently oxidized.



Equation 1

A typical procedure is as follows (Table 1, entry 1): A mixture of diethylene glycol monomethyl ether (**1a**, 0.5 mmol) and TEMPO (0.1 mmol) in a carbonate buffer $[Na_2CO_3 (0.4 \text{ M}) \text{ and } NaHCO_3 (0.3 \text{ M}), 10 \text{ mL}]$ was electrolyzed in a simple beaker-type undivided cell fitted with two Pt electrodes ($1.5 \times 1.0 \text{ cm}^2$) under constant current density conditions (20 mA/cm²) at room temperature. The mixture of **1a** and TEMPO in the buffer solution gave a clear solution. After passage of 4.5 F/mol¹⁵ of electricity (2.5 h), the reaction mixture was treated with an ion-ex-

Table 1 Electrooxidation of Various Alcohols

change resin (Amberlite IR 120, 30 min) and filtered. The filtrate was concentrated in vacuo to give the corresponding carboxylic acid **6a** in 96% yield.

Results of the electrooxidation using various alcohols are summarized in Table 1. Electrooxidation of polyethylene glycol monomethyl ethers **1b–c** was performed in a similar manner to afford the corresponding carboxylic acids **6b–c** in good yields (entries 2 and 3). Diols **1d** and **1e** gave the corresponding dicarboxylic acids **6d** and **6e** quantitatively after passage of 9 F/mol¹⁵ of electricity (entries 4 and 5). Although water-soluble alcohols **1f–i** gave a similar clean aqueous solution, the electrooxidation did not efficiently give the corresponding carboxylic acid **6f** and ketones **8g–i** (entries 6–9). In cases of water-insoluble alcohols **1j–l** (entries 10–12), oil droplets were observed in the aqueous electrolysis medium, and the electrooxidation did not smoothly proceed to give the corresponding aldehydes **7j** and **7k** in low yields and no ketone **8l**.

Entry	F/mol	Substrate	Product	Yield (recov., %) ^a
Amphilic				
		MeO (O) OH	MeO (O) OH	
1	4.5	1a (n = 1)	6a (n = 1)	96 (-)
2	4.5	1b $(n = 2)$	6b (n = 2)	99 (-)
3	4.5	1c(n=6)	6c $(n = 6)$	90 (-)
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4	9.0	1d(n=2)	6d $(n = 2)$	94 (-)
5	9.0	1e(n=8)	6e (n = 8)	99 (-)
Water-solu	ble			
6	4.5	PhCH ₂ CH(OH)CH ₂ OH 1f	PhCH ₂ CH(OH)CO ₂ H 6f	16 (64)
7	2.5	PhCH(OH)CO ₂ H 1g	PhC(O)CO ₂ H 8g	- (77)
8	2.5	MeCH(OH)CO ₂ H 1h	MeC(O)CO ₂ H 8h	- (76)
9	2.5	MeCH(OH)CH ₂ CO ₂ H 1i	MeC(O)CH ₂ CO ₂ H 8i	- (98)
Water-inso	luble			
10	2.5	4-ClC ₆ H₄CH₂OH 1j	4-ClC₀H₄CHO 7j	27 (40) ^b
11	5.5	Ph(CH ₂) ₂ CH ₂ OH 1 k	Ph(CH ₂) ₂ CHO 7k	14 (59) ^b
12	2.5	Ph(CH ₂) ₂ CH(OH)Me 11	Ph(CH ₂) ₂ C(O)Me 81	- (86)

^a Isolated yields.

^b The corresponding carboxylic acids were not obtained.

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The electrolysis media were analyzed by dynamic light scattering (DLS, Otsuka Denshi Corp., FPAR 1000R). Triethylene glycol monomethyl ether (MTEG, 1b) dissolved in water to give a clear solution, in which broad distribution of the particle size (100-1000 nm) was observed (Figure 1, a). When TEMPO (3) was added to the solution, nanoparticles in narrow distribution of size (ca. 220 nm) were formed (Figure 1, b). Similarly, diethylene glycol monomethyl ether (1a) formed particles (50 mM, \emptyset 500–1100 nm) in water, which turned into nanoparticles (95-210 nm) when 10 mM of 3 were added. From these results, hydrophobic interaction between 3 and amphiphilic alcohols, 1a and 1b, would be strong enough to form stable nanoemulsions in buffer solution (Scheme 2), and the nanoparticles would be finely dispersed in water by hydrophilic interaction between alcohols, **1a** and **1b**, and water. The balance of these two interactions is a key factor for the efficient TEMPO-mediated electrooxidation of alcohols in water.



Figure 1 Particle-size distribution of an aqueous (a) triethylene glycol monomethyl ether (MTEG, 1b) and (b) 1b/TEMPO solution



Scheme 2 TEMPO/1b nanoemulsion

The close lipophilic interaction between the alcohols and TEMPO (3) was also confirmed by cyclic voltammetry (CV, Figure 2). An aqueous solution of 3 (2.5 mM) showed a small reversible redox peak at ca. 0.5 V vs. Ag/AgCl, indicating that 3 was oxidized on the anode to give the *N*-oxoammonium (4). A significant catalytic current

was observed when **1b** and methyl α -D-glucopyranoside¹⁴ were added to the solution, indicating that 1) direct oxidation of **3** at the anode occurs to give **4**, and 2) **3** seems to interact lipophilically with **1b** and methyl α -D-glucopyranoside so closely in water that the electrogenerated **4** would react with these alcohols immediately. On the other hand, only a small catalytic current was observed with water-soluble mandelic acid (**1g**). Water-insoluble 4-phenyl-2-butanol (**11**) gave no catalytic current and the redoxpeak current became small. These results show that electrogeneration of **4** and/or subsequent reaction with alcohols would not efficiently occur with water-soluble and water-insoluble alcohols.



Figure 2 Cyclic voltammograms of TEMPO in the presence of alcohols

A plausible mechanism of the electrooxidation in water is illustrated in Scheme 2. In an aqueous solution of alcohol 1b, 1b would interact lipophilically with TEMPO (3) and hydrophilically with water to form the nanoemulsion. The nanoemulsion would disperse in water and bring 3 to the anode by diffusion. Electron transfer from **3** to the anode, i.e., oxidation of 3, would occur efficiently in the nanoemulsion to afford N-oxoammonium ion 4, which would oxidize the surrounding 1b immediately. In the case of primary alcohols, oxidation occurred repeatedly, and finally gave the corresponding carboxylic acid. N-Hydroxylamine (5) would react with another molecule of 4 in the nanoemulsion to give 2 mol of 3. Water-soluble alcohols dissolved in water to give homogeneous solutions and would not form the nanoemulsion. As the result, the electrogenerated 4 would not efficiently oxidize the alcohols, and reduction of 4 on the cathode would occur predominantly. In cases of water-insoluble alcohols, 3 would be included in oil droplets (much larger than a microemulsion), and be separated from the anode so that oxidation of TEMPO did not occur efficiently.

In conclusion, TEMPO-mediated electrooxidation in water proceeded smoothly in the case of amphiphilic alcohols wherein nanoemulsion of TEMPO, alcohols, and water was formed; while the electrooxidation of watersoluble and water-insoluble alcohols did not proceed efficiently. Formation of the nanoemulsion is a key factor for the efficient electrooxidation.

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 1 F = 96500 C.

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