Tetrahedron 65 (2009) 7177–7185

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Electroorganic synthesis in oil-in-water (O/W) nanoemulsion: TEMPO-mediated electrooxidation of amphiphilic alcohols in water

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ARTICLE INFO

Article history:
Received 19 November 2008
Received in revised form 2 June 2009
Accepted 2 June 2009
Available online 10 June 2009

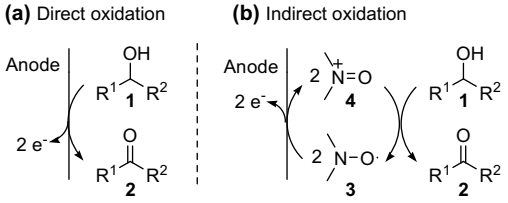
ABSTRACT

Oil-in-water nanoemulsion which consisted of TEMPO, amphiphilic alcohols, and water offered unique reaction environments for electrooxidation of the alcohols to give the corresponding carboxylic acids in good to excellent yields.

1. Introduction

Organic reactions in water attract great interest[1] since water is a cheap, safe, and inflammable solvent, offering environmental and economical advantages. Organic transformations in water are often accelerated and show unique reactivity and selectivity caused by hydrophobic interaction.[2,3] Solubility of the organic substrates in water is, however, generally poor, and a unique design and special care of the aqueous medium are required. To perform the organic reactions in water smoothly, oil-in-water (O/W)-emulsions using surfactants[4] and sonication[5] have been studied. Recently, nanoemulsions have been focused,[6] which are a type of thermodynamically stable liquid isotropic dispersions composed of water, oil, and surfactants. Nanoemulsions have been used widely in many fields, such as pharmaceuticals,[7] cosmetics,[8] lubricants,[9] surfactants,[10] and detergents.[11] However, the O/W-nanoemulsion has scarcely been used in organic synthesis and, to our best knowledge, the nanoemulsion has not been used in electroorganic synthesis.[12]

Electroorganic synthesis is an environmentally benign process because the desired oxidation and reduction are promoted by passage of electricity without any chemical oxidants and reductants, i.e., no waste generation. In the case of electrooxidation of alcohols **1** to the corresponding carbonyl compounds **2**, however, direct electrooxidation of alcohols are not efficiently achieved because of the high over-potential, and indirect methods using a mediator have been investigated (Scheme 1). In 1983, Semmelhack reported the first *N*-oxyl-mediated electrooxidation of alcohols.[13] In this reaction, *N*-oxyl **3** was oxidized to give the corresponding *N*-oxoammonium **4** at low oxidation potential (ca. 0.4 V vs $Ag/AgNO_3$), and **4** oxidized **1** to give **2**. A catalytic amount of **3** was enough to complete the oxidation since **3** was re-generated in this process.



Scheme 1. *N*-Oxyl-mediated electrooxidation of alcohols.

To execute the *N*-oxyl-mediated electrooxidation of alcohols in high current efficiency, electroreduction of the in situ generated *N*-oxoammonium **4** should be prevented. For this purpose, the electrooxidation was usually carried out in a divided cell to separate **4** from the cathode. This method was, however, not satisfactory in terms of operational simplicity. Furthermore, this electrooxidation was carried out in a polar organic solvent containing high concentration of supporting electrolytes, causing manufacturing cost and environmental stress.

Water is an ideal medium for electrolysis since its dielectric constant is high enough to pass the required electricity. Torii reported the *N*-oxyl-mediated electrooxidation of alcohols in CH_2Cl_2/H_2O two-phase solution.[14] We also reported the *N*-oxyl-mediated electrooxidation of alcohols in several aqueous electrolysis systems such as solid/water disperse systems (silica gel[15] and polymer particles[16]/water), and oil-in-water emulsion systems[17] (Scheme 2). These electrolyses are performed in an undivided cell under constant current conditions. In these heterogeneous systems, however, direct oxidation of *N*-oxyl **3** to *N*-oxoammonium **4** on the anode scarcely occurred because **3** is separated from the anode by dissolving in CH_2Cl_2 and/or immobilization on solid particles, and the second mediator such as bromide salt was

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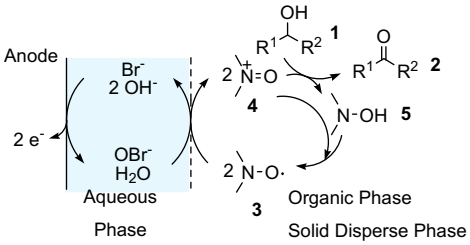
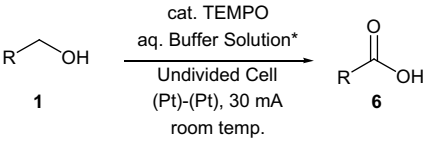
doi:10.1016/j.tet.2009.06.005



Scheme 2. A plausible mechanism of *N*-oxyl **3**/Br^--mediated indirect electrooxidation of alcohols **1**.

indispensable. Electrooxidation of Br^- in aqueous phase would give [Br^+] species such as OBr^- which oxidized **3** to give **4**. *N*-Hydroxylamine **5**, generated in the reaction between **1** and **4**, would subsequently react with another molecule of **4** immediately to form **3** (conproportionation). The [Br^+], however, caused undesirable side reactions such as bromination of the substrate, 'halogen-free' method has been investigated.

In 1999, Schäfer reported *N*-oxyl-mediated electrooxidation of sugar derivatives in water.[18] To our surprise, the electrooxidation proceeded smoothly without Br^- in an undivided cell under constant current conditions. This report prompted us to reinvestigate the electrooxidation of various alcohols in water. We analyzed the electrolysis media by dynamic light scattering (DLS) and cyclic voltammetry (CV) to find that this electrooxidation proceeded smoothly with amphiphilic alcohols, which formed O/W-nanoemulsion in water (Eq. 1).



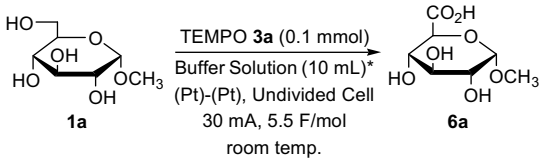
(1)

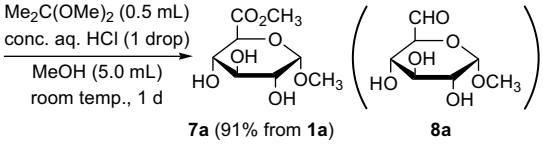
In contrast, water-soluble and -insoluble alcohols, which did not form nanoemulsion, were not efficiently oxidized. Herein we describe the details on the *N*-oxyl-mediated electrooxidation of nanoemulsion-forming alcohols in the O/W nanoemulsion system to form the corresponding carboxylic acids **6**.

2. Results and discussion

2.1. TEMPO-mediated electrooxidation of alcohols in buffer solution

Electrooxidation of methyl α-D-glucopyranoside **1a** was examined. A typical procedure was as follows (Scheme 3). A mixture of **1a** (0.5 mmol), 2,2,6,6-tetramethylpiperidyl 1-oxyl (TEMPO, **3a**) (0.1 mmol), and an aqueous carbonate buffer solution (1/1 mixture of Na_2CO_3 (0.4 M) and $NaHCO_3$ (0.3 M), 10 mL) was placed in a simple beaker-type undivided cell fitted with two Pt electrodes (1.5×1.0 cm^2). The mixture was electrolyzed under constant current conditions (30 mA) at room temperature. Passage of 5.5 F/mol of electricity (2 h)[19] gave the corresponding carboxylic acid **6a**.[20] The reaction mixture was further treated with 2,2-dimethoxypropane (0.5 mL, 4.1 mmol), MeOH (5 mL), and concd hydrochloric acid (one drop) at room temperature for 1 d. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (SiO_2, AcOEt/MeOH=5/1) to give methyl (methyl α-D-glucopyranosid)uronate **7a** in 91% yield. Neither aldehyde **8a** (intermediate) nor ketones (oxidation of *sec*-hydroxyl groups) were obtained.

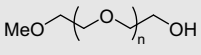
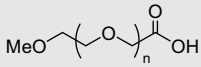
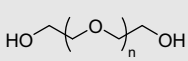
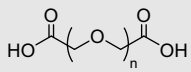




Scheme 3. Electrooxidation of sugar derivatives **1a**.

The electrooxidation of *prim*- and *sec*-alcohols was carried out in a similar manner to that described above (Table 1). In the case of *prim*-alcohols R-CH_2OH, the electrolysis was carried out until 4.5 F/mol of electricity was passed. The mixture was treated with cation exchange resin (Amberlite IR 120, room temperature, 30 min) and filtered, and the filtrate was concentrated in vacuo to give the corresponding carboxylic acid R-C(O)OH (**6**). Di-, tri- and hexa(ethylene glycol)

Table 1
TEMPO **3a**-mediated electrooxidation of alcohols

Run	Substrate	F/mol	Product	Yield[a] (%)	
				Prod.	**1**
Amphiphilic alcohols					
					
1	**1b** (*n*=1)	4.5	**2b** (*n*=1)	96	nd
2	**1c** (*n*=2)	4.5	**2c** (*n*=2)	99	nd
3	**1d** (*n*=6)	4.5	**2d** (*n*=6)	90	nd
					
4	**1e** (*n*=2)	9.0	**2e** (*n*=2)	94	nd
5	**1f** (*n*=8)	9.0	**2f** (*n*=8)	99	nd
Water-soluble alcohols					
6	$PhCH_2CH(OH)CH_2OH$ **1g**	4.5	$PhCH_2CH(OH)CO_2H$ **2g**	16	64
7	2-$PyCH_2OH$ **1h**	5.5	2-$PyCO_2H$ **2h**	nd	49
8	3-$HOC_6H_4CH_2OH$ **1i**	5.5	3-$HOC_6H_4CO_2H$ **2i**	nd	89
9	$PhCH(OH)CO_2H$ **1j**	2.5	$Ph(C{=}O)CO_2H$ **9j**	nd	77
10	$MeCH(OH)CO_2H$ **1k**	2.5	$MeC(=O)CO_2H$ **9k**	nd	76
11	$MeCH(OH)CH_2CO_2Me$ **1l**	4.5	$MeC(=O)CH_2CO_2Me$ **9l**	nd	98
12	$PhCH(CO_2H)CH_2OH$ **1m**	2.5	$PhCH(CO_2H)CO_2H$ **2m**	nd	99
Water-insoluble alcohols					
13	4-$ClC_6H_4CH_2OH$ **1n**	2.5	4-ClC_6H_4CHO **8n**	27[b]	40
14	$Ph(CH_2)_2CH_2OH$ **1o**	2.5	$Ph(CH_2)_2CHO$ **8o**	10[b]	59
15	**1o**	5.5	**8o**	14[b]	59
16	4-$ClC_6H_4CH(OH)Me$ **1p**	2.5	4-$ClC_6H_4C(=O)Me$ **9p**	48	41
17	$PhCH(OH)Et$ **1q**	2.5	$PhC(=O)Et$ **9q**	9	79
18	$Ph(CH_2)_2CH(OH)Me$ **1r**	2.5	$Ph(CH_2)_2C(=O)Me$ **9r**	nd	84

[a] Isolated yields. nd='not detected.'
[b] The corresponding carboxylic acids were not obtained.

monomethyl ether **1b**, **1c**, and **1d** were smoothly oxidized to give the corresponding carboxylic acids **6b** (96%), **6c** (99%), and **6d** (90%), respectively (Entries 1–3). The electrooxidation of tri- and nona-(ethylene glycol) **1e** and **1f** afforded the corresponding dicarboxylic acids **6e** (94%) and **6f** (99%), respectively, after 9 F/mol[21] of electricity was passed (Entries 4 and 5). The current efficiency and product selectivity were excellent in all cases: Neither starting materials **1b**–**1f** nor the corresponding aldehydes **8b**–**8f** were detected.

On the contrary, electrooxidation of water-soluble alcohols, such as 3-phenyl-1,2-propanediol **1g**, 2-pyridylmethanol **1h**, 3-hydroxybenzyl alcohol **1i**, and α- and β-hydroxy-carboxylic acids **1j**–**1m**, did not efficiently proceed. Electrooxidation of **1g** (30 mA, 4.5 F/mol) afforded 2-hydroxy-3-phenylpropanoic acid **2g** in 16% yield and most of **1g** (64%) was recovered (Entry 6). Aryl-substituted methanols such as **1h** and **1i** did not afford neither carboxylic acids **2h** and **2i** nor aldehydes **8h** and **8i**, resulting in recovery of the starting materials **1h** (49%) and **1i** (89%) (Entries 7 and 8). Mandelic acid **1j**, 2-hydroxypropanoic acid **1k**, 3-hydroxybutanoic acid **1l** and tropic acid **1m** also did not give ketocarboxylic acids **9j**, **9k**, **9l** and dicarboxylic acid **2m** at all, and the starting materials **1j** (77%), **1k** (76%), **1l** (98%) and **1m** (99%) were recovered (Entries 9–12).

The TEMPO-mediated electrooxidation of water-insoluble alcohols **1n**–**1r** also did not efficiently proceed. Electrooxidation of *prim*-benzylic alcohol **1n** was carried out (30 mA, 2.5 F/mol) to afford 4-chlorobenzaldehyde **8n** in 27% yield and the starting material **1n** (40%) was recovered (Entry 13). *prim*-Aliphatic alcohol, **1o**, gave **8o** in only 10% yield, and 59% of **1o** was recovered (Entry 14). The yield of **8o** was not improved (14%) even when 5.5 F/mol of electricity was passed (Entry 15). It is worthy to note that the aldehydes **8n** and **8o** were obtained selectively, and appreciable amount of the corresponding carboxylic acids **2n** and **2o** were not obtained at all. These water-insoluble alcohols formed oil droplets and were separated from water. Most of TEMPO **3a** would be dissolved in the alcohol phase and be isolated from the anode, retarding electron transfer from **3a** to anode. *sec*-Benzylic alcohols such as 1-(4-chlorophenyl)ethanol **1p** and 1-phenyl-1-propanol **1q** gave the corresponding ketones **9p** and **9q** in 48% and 9% yields together with the starting materials **1p** and **1q** in 41% and 79% yield, respectively (Entries 16 and 17). TEMPO **3a**-mediated electrooxidation of *sec*-aliphatic alcohol **1r** in water did not afford the corresponding ketone **9r** at all, and most of **1r** (84%) was recovered (Entry 18).

From these results, TEMPO-mediated electrooxidation of the amphiphilic alcohols in water proceeded smoothly, indicating that both hydrophobic and hydrophilic natures of the alcohols are necessary for smooth electrooxidation in water.

2.2. Electrooxidation of methyl α-D-glucopyranoside 1a with various *N*-oxyl derivatives

Electrooxidation of methyl α-D-glucopyranoside **1a** by use of various *N*-oxyl derivatives **3a**–**3f** in the aqueous carbonate buffer was carried out in a similar manner to that described above (Table 2, Fig. 1). In the absence of *N*-oxyl derivatives, no appreciable amount of the corresponding ester **7a** was obtained and the starting material **1a** was recovered quantitatively (Run 1), indicating that *N*-oxyl derivatives are indispensable for this electrooxidation. When water-soluble WS-TEMPO **3b**[17a] was used in place of **3a**, the yield of **7a** decreased to 69% (Entry 3). On the other hand, water-insoluble 4-benzoyloxy-TEMPO **3c** (Entry 4) and solid particles-immobilized TEMPO, such as silica gel-immobilized TEMPO (SiO_2–TEMPO, **3d**,[15] Entry 5) and poly-(ethylene-*co*-acrylic acid)-immobilized TEMPO (PE-*co*-AA-TEMPO, **3e**,[16b] Entry 6), did not promote the electrooxidation of **1a** at all.

So far as examined, unsubstituted TEMPO **3a**, which is slightly soluble in water, promoted the electrooxidation of **1a** in water most smoothly. Water-soluble **3b** was less effective, and water-insoluble **3c** and solid particle-immobilized TEMPO derivatives **3d** and **3e** were ineffective for the electrooxidation in water.

Table 2
Electrooxidation of methyl α-D-glucopyranoside **1a** with various *N*-oxyl derivatives[a]

Run	*N*-Oxyl derivatives	mg (mmol)	Yield/%[b]	
			7a	**1a**
1	—[c]	—[c] (—[c])	—	99
2	TEMPO **3a**	16 (0.1)	96	—
3	WS-TEMPO **3b**	45 (0.1)	69	—
4	4-Benzoyloxy-TEMPO **3c**	28 (0.1)	—	99
5	SiO_2–TEMPO **3d**[d]	500 (0.4)	—	99
6	PE-*co*-AA-TEMPO **3e**[e]	500 (0.3)	—	99

[a] Aq Na_2CO_3 (0.40 M) and $NaHCO_3$ (0.30 M).
[b] Isolated yields.
[c] Not used.
[d] 0.64 mmol-TEMPO/g-silica gel.
[e] 0.64 mmol-TEMPO/g-polymer.

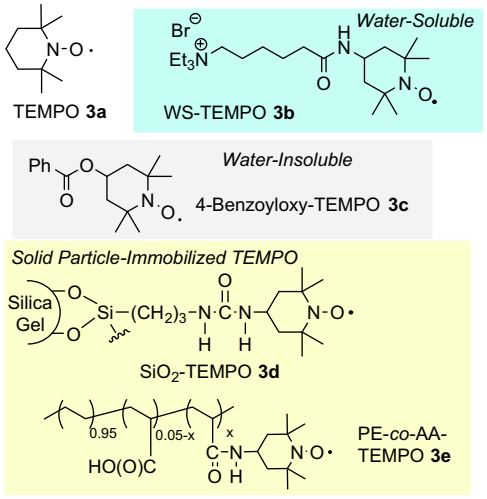


Figure 1. Various *N*-oxyl derivatives.

2.3. Cyclic voltammetry (CV) analysis of the electrolysis media

Electrochemical behavior of TEMPO **3a** was estimated by cyclic voltammetry (CV) in a carbonate buffer solution in the presence of amphiphilic alcohols, methyl α-D-glucopyranoside **1a** and MTEG **1c**, water-soluble mandelic acid **1j**, and water-insoluble 4-phenyl-2-butanol **1r** (Fig. 2). CV of **3a** (10 mM) in the buffer solution (aq Na_2CO_3 (0.4 M)/$NaHCO_3$ (0.3 M)) showed a set of reversible redox peaks at 0.57 V (E_{ox}) and at 0.48 V (E_{red}) versus Ag/AgCl (curve a),

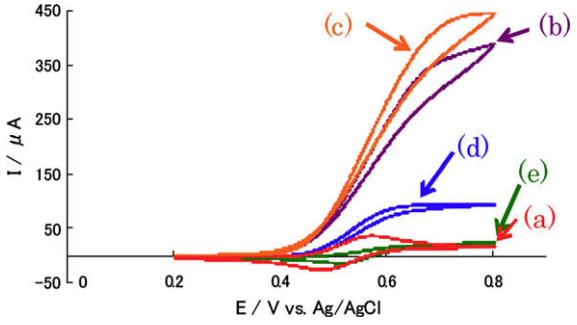


Figure 2. CV of an aqueous buffer solution of TEMPO **3a** (10 mM) in the absence (a) and in the presence of 100 mM of alcohols; (b) methyl α-D-glucopyranoside **1a**, (c) MTEG **1c**, (d) mandelic acid **1j**, and (e) 4-phenyl-2-butanol **1r**. Buffer Solution: Na_2CO_3 (0.4 M)/$NaHCO_3$ (0.3 M), Scan Rate: 100 mV s^{-1}. Glassy carbon, Pt wire, and Ag/AgCl were used as a working, counter, and reference electrode, respectively.

suggesting that (1) **3a** was oxidized directly on the anode to give *N*-oxoammonium **4a** and (2) **4a** is stable within the timescale of CV. Remarkable catalytic current appeared (curve b) when **1a** (10–100 mM) was added to the solution. A similar catalytic current was observed when **1c** was added (curve c). On the other hand, catalytic current was small when a water-soluble alcohol **1j** was added (curve d), and no catalytic current was observed in the presence of water-insoluble alcohol **1r** (curve e). These results indicate that amphiphilic alcohols **1a** and **1c** were oxidized with **4a** smoothly in the buffer solution, whereas the electron transfer from **1j** to **4a** occurred but not efficient. Water-insoluble alcohol **1r** was separated from water to form oil droplets and dissolved **3a**, which would retard electrooxidation of **3a** at the anode.

Though both amphiphilic alcohols **1a** and **1c** and water-soluble alcohol **1j** were soluble in the buffer solution to give a clear solution containing **3a**, electrochemical behavior of these solutions was totally different. These phenomena suggested that combination of water-soluble alcohol **1j** and **3a** forms a true homogeneous solution, whereas amphiphilic alcohols, **1a** and **1c**, and **3a** forms a 'submicroscopically' heterogeneous environment, i.e., nanostructure in the solution.

2.4. Dynamic light scattering (DLS) analysis of the electrolysis media

The nanostructure of the electrolysis media was investigated by dynamic light scattering (DLS). MTEG (**1c**, 5 mmol) was dissolved in the aqueous carbonate buffer solution (100 mL) to give a clear solution (50 mM). DLS analysis of the solution (5 mL), however, showed that nano-scale oil particles were formed which had a rather broad distribution of the particle size (100–1000 nm, Fig. 3a). The nanoparticles were dispersed in the aqueous carbonate buffer solution to make O/W nanoemulsion. When 1.0 mmol (0.2 molar equiv) of TEMPO **3a** was added to the solution, the distribution of the particle size became narrow (mean size: ca. 200 nm, Fig. 3b). Similarly, MDEG (**1b**, 50 mM) formed nanoparticles (φ 500–1000 nm, Fig. 4a) and the distribution of particle size became narrow (mean size: 161 nm, Fig. 4b) by addition of **3a** (10 mM).

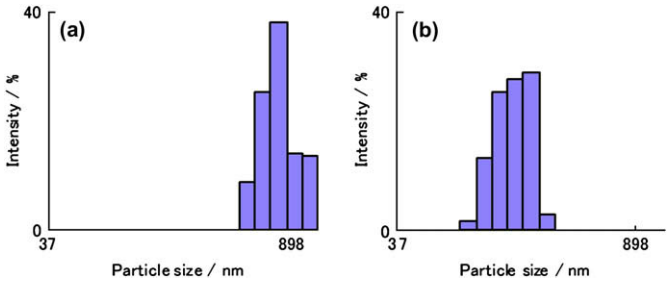


Figure 3. Particle size distribution of (a) the buffer solution of MTEG **1c** (50 mM) and (b) **1c** (50 mM)/TEMPO **3a** (10 mM).

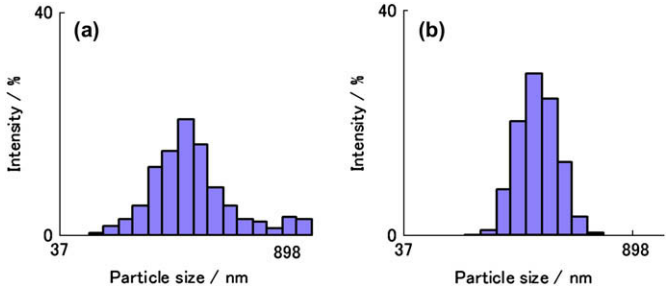


Figure 4. Particle size distribution of (a) the buffer solution of MDEG **1b** (50 mM) and (b) **1b** (50 mM)/TEMPO **3a** (10 mM).

Water-soluble 4-phenyl-1,2-propanediol (**1g**, 50 mM) gave broad distribution of the particle size (100–1000 nm, Fig. 5a). The distribution unchanged by addition of TEMPO **3a** (Fig. 5b), indicating that **1g** hardly interact with **3a**. On the other hand, water-insoluble 4-phenyl-2-butanol (**1r**) was separated from water and nanoparticles were not observed.

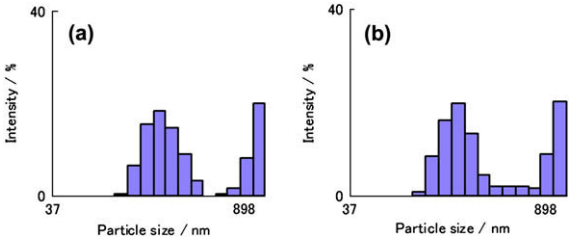


Figure 5. Particle size distribution of (a) the buffer solution of an aqueous 3-phenyl-1,2-propanediol **1g** (50 mM) and (b) **1g** (50 mM)/TEMPO **3a** (10 mM).

DLS measurement of the electrolysis solution (Fig. 6) and electrooxidation of MTEG **1c** with TEMPO **3a** (Fig. 7) were performed at various temperature. As mentioned above, a mixture of **1c** (50 mM) and **3a** (10 mM) in the carbonate buffer solution formed a stable O/W nanoemulsion (mean diameter: ca. 200 nm) at 20 °C (Fig. 6c). The size distribution of the nanoparticle was broadened from 100 to 1000 nm at 50 °C (mean size: ca. 300 nm, Fig. 6f). Accordingly, yield of **2c** decreased to 59%. On the other hand, the size of the nanoparticles became larger at 0 °C (mean diameter: ca. 300 nm, Fig. 6a) than that observed at 20 °C, and the yield of **2c** gradually decreased to 55%. These results indicate that at high temperature, hydrophobic interaction between **1c** and **3a** weakened, whereas at low temperature. The hydrophobic interaction might become more tight and particle size would increase (from 200 nm to 300 nm). Electrooxidation and formation of nanoparticle proceeded most smoothly at 20 °C, and the yield decreased and the particle size distribution was broadened at both higher and lower temperature.

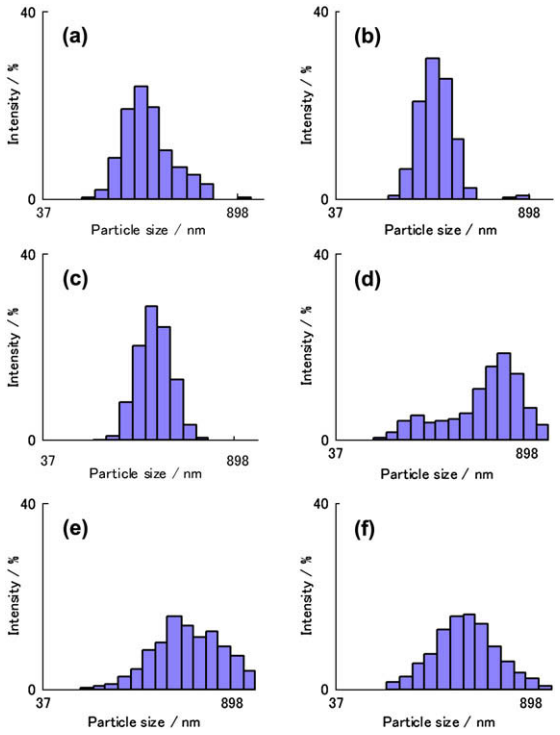


Figure 6. Particle size distribution of aqueous MTEG **1c** (50 mM) and TEMPO **3a** (10 mM) solution at (a) 0 °C, (b) 10 °C, (c) 20 °C, (d) 30 °C, (e) 40 °C, (f) 50 °C.

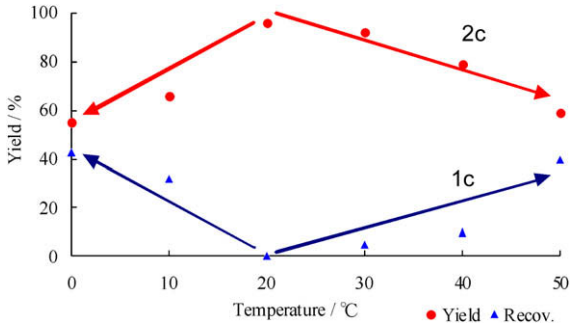
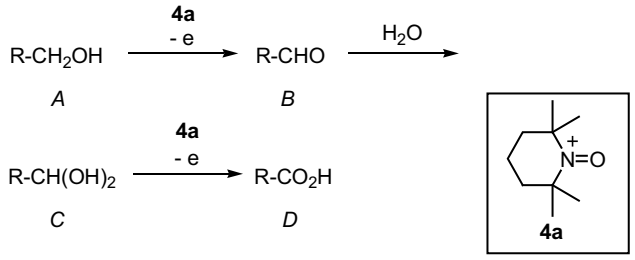


Figure 7. TEMPO **3a**-mediated electrooxidation of MTEG **1c** in buffer solution at various temperature.

Effect of CH_3CN as a *co*-solvent on formation of the O/W nanoemulsion was also investigated (Fig. 8). Addition of CH_3CN to the carbonate buffer solution broadened the distribution of the particle size of the O/W nanoemulsion. The yields of **2c** decreased with increase of CH_3CN (Fig. 9). For instance, the yield of **2c** decreased to 81% and 7% of **1c** was recovered by use of buffer/CH_3CN mixture (7/3). This is because that solvation of **3a** with CH_3CN would weaken the hydrophobic interaction between **1c** and **3a**. The solution was homogeneous when the buffer/CH_3CN ratio was in a range of 10/0 to 7/3. When more than 30 vol % of CH_3CN was used, the solution became heterogeneous and the nanoparticles were not observed. The yield of **2c** gradually decreased with increase the amount of CH_3CN. The best yield of **2c** was attained when electrooxidation was performed in the carbonate buffer solution without addition of CH_3CN.

It is very likely that formation of O/W nanoemulsion and its size are important for the electrooxidation. These results are also consistent with our hypothesis that amphiphilic alcohols would interact with TEMPO **3a** to form a 'submicroscopically' heterogeneous environment in water.

A plausible mechanism of the electrooxidation of amphiphilic alcohols to the corresponding carboxylic acids in water is as follows: TEMPO **3a** was oxidized at the anode to give *N*-oxoammonium **4a**. **4a** would oxidize *prim*-alcohol *A* to give the corresponding aldehyde *B*. In the nanoemulsion system, *B* would react with water efficiently to afford the corresponding hydrate intermediate *C*. Oxidation of *C* with **4a** gave the corresponding carboxylic acid derivatives *D*. To perform this multistep reactions smoothly, both (1) oxidation of **3a** to **4a** and (2) hydration of *B* to *C* should proceed efficiently.



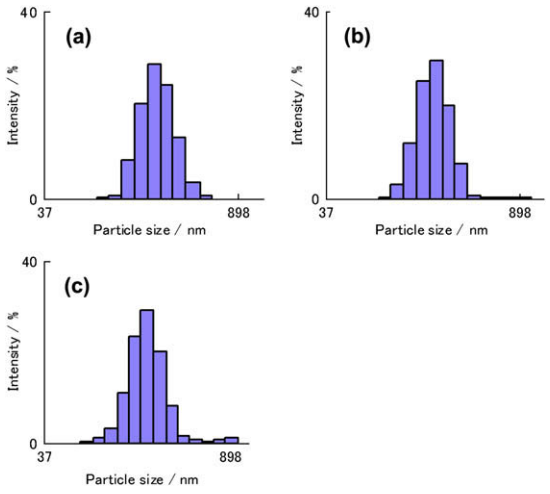


Figure 8. Particle size distribution of MTEG **1c**/TEMPO **3a** Solution using buffer/CH_3CN mixture: (a) 10/0, (b) 9/1, (c) 7/3.

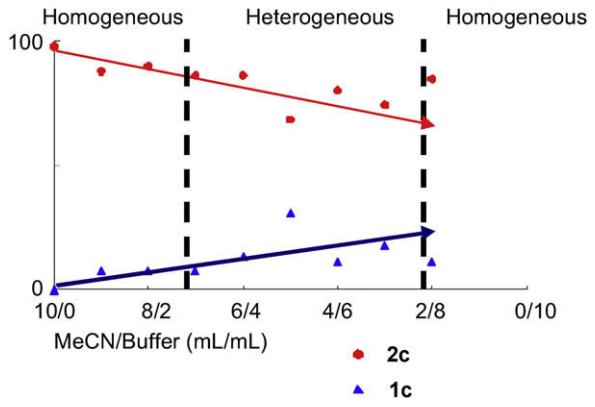


Figure 9. TEMPO-mediated electrooxidation of MTEG **1c** using buffer/CH_3CN mixture.

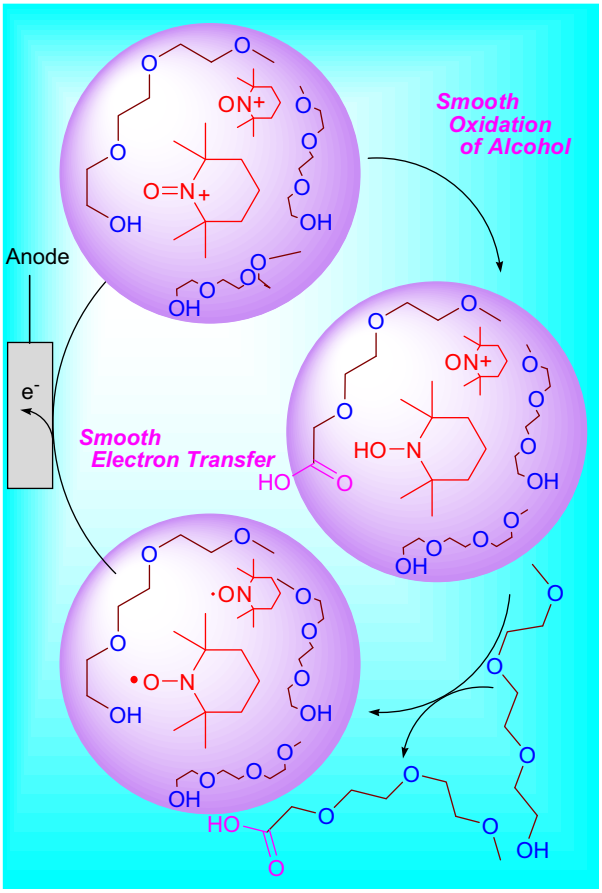


Figure 10. A plausible mechanism of TEMPO-mediated electrooxidation of amphiphilic alcohols in water.

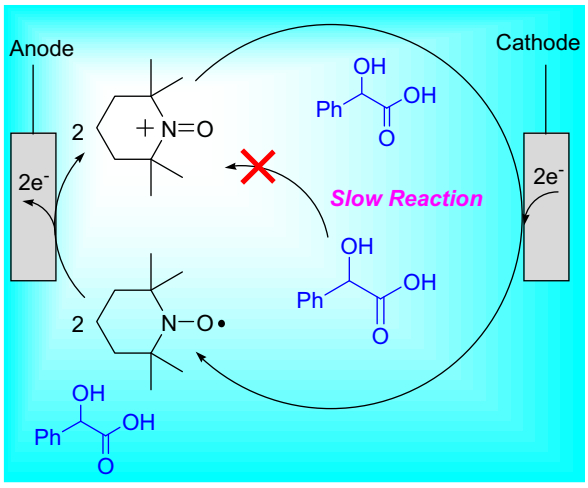


Figure 11. Electrooxidation of water-soluble alcohols.

In an aqueous solution of amphiphilic alcohol MTEG **1c** and TEMPO **3a**, small oil particles (100–1000 nm) was formed to make O/W nanoemulsion in which hydrophobic interaction between **1c** and TEMPO **3a** and hydrophilic interaction between **1c** and water would be balanced. Addition of **3a** to the O/W nanoemulsion of **1c** in water would stabilize the O/W nanoemulsion by hydrophobic interaction of **1c** with **3a** (Fig. 10). The nano-particle in the emulsion are small enough to diffuse quickly in water to carry **3a** to the anode surface efficiently. Electron transfer from **3a** to anode, i.e., oxidation of **3a**, would occur through the interface between the nanoparticle and the anode, i.e., surface of the nanoparticle. The electron transfer would occur efficiently in the nanoparticles because the relative surface area of the oil particles of the emulsion (i.e., $\pi r^2/(1/6\pi r^3)$) becomes larger as the diameter of the oil particles r becomes smaller. **4a** would oxidize the surrounding **1c** immediately. Water molecules, surrounding the nanoemulsion, would react with the aldehyde *B* to form the hydrate *C* which would be further oxidized to the carboxylic acid *D*.

Water-soluble alcohol **1j** gave a homogeneous solution, and would not form O/W nanoemulsion even in the presence of TEMPO **3a**. A small catalytic current was observed in CV of **3a** on addition of **1j**, suggesting that the electrogenerated **4a** would not efficiently contact with **1j** and the reduction of **4a** on the cathode would occur predominantly (Fig. 11).

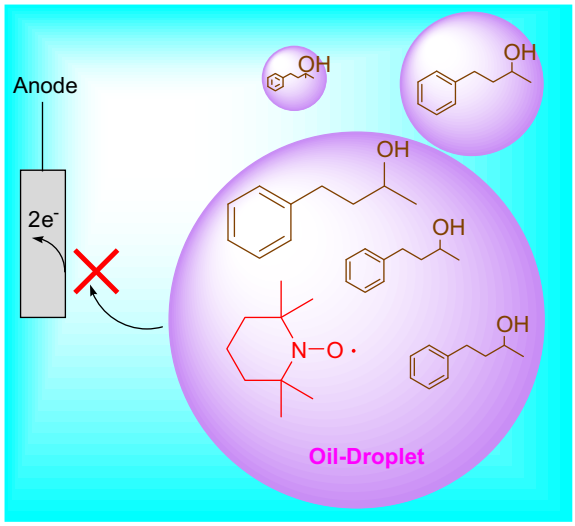


Figure 12. Electrooxidation of water-insoluble alcohols.

Water-insoluble **1r** formed oil droplets and **3a** would be included in it. The size of the oil droplets is much larger than that of emulsion. TEMPO **3a** would be almost completely separated from the anode so that electron transfer from **3a** to the anode would not occur efficiently (Fig. 12). Formation of the oil droplets would also retard the reaction of aldehyde with water, and aldehyde was obtained predominantly.

3. Conclusion

2,2,6,6-Tetramethylpyperidine-1-oxyl (**3a**)-mediated electrooxidation of amphiphilic alcohols in a carbonate buffer solution gave the corresponding carboxylic acids, whereas the oxidation of water-soluble and water-insoluble alcohols did not proceed efficiently. Among the *N*-oxyl mediators examined, unsubstituted TEMPO **3a** promoted the electrooxidation efficiently, while water-soluble, water-insoluble, and solid particle-immobilized TEMPO did not promote the electrooxidation.

Cyclic voltammetry (CV) of carbonate buffer solution of TEMPO **3a** and alcohol shows that (1) direct oxidation of **3a** on the anode proceeded in water to give the corresponding *N*-oxoammonium **4a**. (2) Amphiphilic alcohols would be in close contact with **4a** in aqueous solution. (3) Water-soluble alcohols would not effectively interact with **3a** in water. (4) Water-insoluble alcohols retard the oxidation of **3a** by inclusion. These results indicate that amphiphilic alcohols and TEMPO **3a** would form a 'microscopically' heterogeneous environment in an aqueous solution, though the solution seemed clear and homogeneous.

Dynamic light scattering (DLS) analysis of TEMPO/alcohol solution showed that (1) amphiphilic alcohols form nanoparticles having a broad distribution of the size (100–1000 nm) in a carbonate buffer solution. (2) The distribution of the particle size became narrow and the nanoparticles were stabilized by addition of TEMPO **3a** (mean size was ca. 200 nm). (3) The O/W nanoemulsion became unstable at higher temperature and/or addition of CH_3CN. As the results, the distribution of the size of the nanoparticles became broad, and the electrooxidation did not efficiently proceed. A key factor for the efficient electrooxidation in water is the fact that the combination of amphiphilic alcohols and TEMPO **3a** in a carbonate buffer solution form the nanoparticle (Fig. 12).

4. Experimental section

4.1. General

^{1}H NMR spectra were determined with a Varian Gemini-200 (200 MHz) instrument and a VXR-600 (600 MHz) instrument. ^{13}C NMR spectra were recorded on a Varian Gemini-200 (50 MHz) and a VXR-600 (150 MHz). IR spectra were obtained with a JASCO FT/IR-4100 spectrometer. Dynamic light scattering (DLS) measurements were performed on an FPAR 1000 light scattering system (Otsuka Electronics Co., Ltd, Osaka, Japan) equipped with a laser diode (30 mW) at λ_0=658 nm. Cyclic voltammetry (CV) was executed on the BAS 100B/W potentiostat (BAS, Tokyo, Japan). Elemental analyses were carried out with Perkin Elmer PE 2400 Series II CHNS/O Analyzer.

Unless otherwise noted, materials were obtained from commercial suppliers and reagent grade materials were used without further purification.

4.2. TEMPO-mediated electrooxidation of methyl α-D-glucopyranoside (1a)

Into an undivided cell equipped with two Pt plate electrodes (1.5×1.0 cm^2) and a stirring bar were placed methyl α-D-glucopyranoside (**1a**, 97 mg, 0.5 mmol), TEMPO **3a** (16 mg, 0.1 mmol), and

an aqueous carbonate buffer (Na_2CO_3 (0.40 M) and $NaHCO_3$ (0.30 M)). The solution was electrolyzed at room temperature under constant current condition (30 mA) until 5.5 F/mol of electricity was passed (2.5 h). The resulting solution was extracted with AcOEt (3×5 mL) to remove **3a**. To the aqueous layer was added cation exchange resin (Amberlite IR 120, 10 mL), and the whole mixture was stirred for 0.5 h. The resin was filtered off, and the filtrate was concentrated under reduced pressure. The residue was treated with 2,2-dimethoxypropane (0.5 mL, 4.1 mmol) and one drop of concentrated hydrochloric acid in MeOH (5 mL) at room temperature for 1 d. The resultant was concentrated under reduced pressure, and the residue was purified by column chromatography (SiO_2, AcOEt/MeOH, 5/1) to give the desired methyl (methyl α-D-glucopyranosid)uronate (**7a**, 95 mg, 0.43 mmol, 91%) as a colorless liquid:[22] R_f=0.32 (AcOEt/MeOH, 3/1); ^{1}H NMR (600 MHz, CD_3OD) δ 3.38 (s, 3H), 3.41 (dd, J=4.0, 9.5 Hz, 1H), 3.49 (t, J=9.5 Hz, 1H), 3.58 (t, J=9.5 Hz, 1H), 3.74 (s, 3H), 4.00 (d, J=9.5 Hz, 1H), 4.68 (d, J=4.0 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 51.2, 54.9, 71.6, 71.9, 72.1, 73.3, 100.7, 170.8; IR (neat) 3419 (br), 2939, 2844, 1744, 1645, 1442, 1050 cm^{-1}.

4.3. TEMPO-mediated electrooxidation of diethylene glycol monomethyl ether (1b)

Into an undivided cell equipped with two Pt plate electrodes (1.5×1.0 cm^2) and a stirring bar were placed di(ethylene glycol) monomethyl ether (**1b**, 60 mg, 0.5 mmol), TEMPO **3a** (16 mg, 0.1 mmol), and an aqueous carbonate buffer solution (Na_2CO_3 (0.40 M) and $NaHCO_3$ (0.30 M)). The mixture was electrolyzed at room temperature under constant current condition (30 mA) until 4.5 F/mol of electricity was passed (2 h). The resultant was extracted with AcOEt (3×5 mL) to remove **3a**. To the aqueous layer was added cation exchange resin (Amberlite IR 120, 10 mL), and the whole mixture was stirred for 0.5 h. The resin was filtered off, and the filtrate was concentrated under reduced pressure to give the desired 2-(2-methoxyethoxy)acetic acid (**2b**, 64 mg, 0.48 mmol, 96%) as a colorless liquid:[23] ^{1}H NMR (200 MHz, CD_3OD) δ 3.44 (s, 3H), 3.58–3.63 (m, 2H), 3.74–3.79 (m, 2H), 4.18 (s, 2H), 5.80–7.20 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 58.9, 68.4, 70.9, 71.5, 173.9; IR (neat) 3397, 2937, 2643, 2563, 1965, 1740, 1430, 1356, 1225, 1140, 1070, 886 cm^{-1}.

In a similar manner, electrooxidations of amphiphilic alcohols **1b**–**1e**, water-soluble alcohols **1g**–**1m**, and water-insoluble alcohols **1n**–**1r** were carried out.

4.4. 3,6,9-Trioxadecanoic acid (2c)[24]

A colorless liquid; ^{1}H NMR (200 MHz, CD_3OD) δ 3.39 (s, 3H), 3.56–3.77 (br s, 8H), 4.18 (s, 2H), 7.35–7.70 (br s, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 59.1, 69.0, 71.3, 71.5, 71.7, 72.9, 174.0; IR (neat) 3448, 2896, 2629, 2362, 1740, 1456, 1355, 1246, 1202, 1123, 1027, 936, 852, 673 cm^{-1}.

4.5. 3,6,9,12,15,18,21-Heptaoxadocosanoic acid (2d)[24]

A colorless liquid; ^{1}H NMR (200 MHz, CD_3OD) δ 3.39 (s, 3H), 3.54–3.78 (m, 24H), 4.16 (s, 2H), 5.70–6.10 (br s, 1H); IR (neat) 3479, 2877, 1959, 1744, 1644, 1457, 1351, 1292, 1248, 1201, 1106, 947, 853 cm^{-1}.

4.6. 3,6-Dioxaoctanedioic acid (2e)[25]

A colorless liquid; ^{1}H NMR (200 MHz, CD_3OD) δ 3.80 (s, 4H), 4.18–4.21 (m, 4H), 4.60–5.80 (br s, 2H); IR (neat) 3510, 2956, 1752, 1439, 1285, 1215, 1132, 1005, 855, 705 cm^{-1}.

4.7. 3,6,9,12,15,18,21,24-Octaoxahexacosanedioic acid (2f)[26]

A colorless liquid; ^{1}H NMR (200 MHz, CD_3OD) δ 3.25–3.95 (m, 28H), 4.10–4.30 (br s, 4H), 6.05–6.75 (br s, 2H); IR (neat) 3515, 2879, 1755, 1638, 1440, 1351, 1289, 1216, 1118, 945, 855 cm^{-1}.

4.8. 2-Hydroxy-3-phenylpropanoic acid (2g)[15]

A colorless liquid; R_f=0.00 (Hexane/AcOEt, 1/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.10 (s, 1H), 2.98 (dd, J=7.2, 14.0 Hz, 1H), 3.19 (dd, J=4.2, 14.0 Hz, 1H), 4.50 (dd, J=4.2, 7.2 Hz, 1H), 5.67 (s, 1H), 7.23–7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.5, 72.3, 127.4, 129.1, 130.7, 138.9, 175.6; IR (neat) 3417, 3064, 3031, 2928, 2624, 1725, 1498, 1455, 1094, 700 cm^{-1}.

4.9. 4-Chlorobenzaldehyde (8n)[27]

White solids; R_f=0.44 (Hexane/AcOEt, 5/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52 (d, J=8.5 Hz, 2H), 7.84 (d, J=8.5 Hz, 2H), 9.99 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 129.4, 130.8, 134.6, 140.9, 190.8; IR (KBr) 2860, 1694, 1589, 1576, 1485, 1388, 1208, 840, 816 cm^{-1}.

4.10. 3-Phenylpropanal (8o)[28]

A colorless liquid; R_f=0.47 (Hexane/AcOEt, 5/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.79 (t, J=7.3 Hz, 2H), 2.97 (t, J=7.3 Hz, 2H), 7.18–7.35 (m, 5H), 9.83 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.9, 45.1, 126.1, 128.2, 128.4, 140.2, 201.4; IR (neat) 3064, 3030, 2973, 2931, 1732, 1497, 1455, 1375, 1362, 1133, 1045 cm^{-1}.

4.11. 1-(4-Chlorophenyl)ethanone (9p)[29]

A colorless liquid; R_f=0.47 (Hexane/AcOEt, 5/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.59 (s, 3H), 7.43 (d, J=8.8 Hz, 2H), 7.99 (d, J=8.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.4, 128.7, 129.6, 135.3, 139.4, 196.7; IR (neat) 3005, 1686, 1590, 1488, 1398, 1358, 1262, 829, 762 cm^{-1}.

4.12. 1-Phenyl-1-propanone (9q)[30]

A colorless liquid; R_f=0.63 (Hexane/AcOEt, 5/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (t, J=7.3 Hz, 3H), 3.00 (q, J=7.3 Hz, 2H), 7.40–7.60 (m, 3H), 7.97 (d, J=6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.4, 30.9, 127.1, 127.8, 132.1, 136.2, 199.6; IR (neat) 3086, 3062, 3028, 2978, 2938, 2905, 2877, 1686, 1596, 1582, 1449, 1220, 951, 746, 690 cm^{-1}.

4.13. Preparation of 3-phenyl-1,2-propanediol (1g)

To a solution of allylbenzene (1.18 g, 10 mmol) in *tert*-butyl alcohol (50 mL) and water (60 mL) was added $K_3Fe(CN)_6$ (9.88 g, 30 mmol), K_2CO_3(4.14 g, 30 mmol), and the $K_2OsO_2(OH)_4$ (0.03 g, 0.1 mmol). The reaction mixture was stirred at room temperature for 24 h. To this solution was added Na_2SO_3, and the resultant was stirred for further 2 h. The reaction mixture was concentrated under reduced pressure to remove *tert*-butyl alcohol, and the residue was extracted with ether. The combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Hexane/AcOEt=1/1) to give the desired 3-phenyl-1,2-propanediol (**3g**, 1.38 mg, 9.1 mmol, 91%) as a colorless liquid:[31] R_f=0.15 (Hexane/AcOEt, 1/1); ^{1}H NMR (200 MHz, CD_3OD) δ 2.67 (d, J=6.8 Hz, 2H), 3.35–3.57 (m, 4H), 3.80–3.84 (m, 1H), 7.15–7.29 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 39.8, 66.0, 73.2, 126.6, 128.6, 129.4, 129.5, 138.0; IR (neat) 3363 (br), 3086, 3063, 3027, 2927, 2879, 1496, 1455, 1091, 1031, 746, 700 cm^{-1}.

4.14. Preparation of 4-(6-bromohexanoylamino)-2,2,6,6-tetramethylpiperidine-1-oxyl (1g)[17a]

Into a 50 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a three-way cock, and a rubber septum was placed 6-bromohexanoic acid (720 mg, 3.7 mmol), and the flask was purged with argon. A dichloromethane (12.5 mL) solution of 4-amino-TEMPO (518 mg, 3.0 mmol) was added portionwise, and the resulting mixture was stirred for few minutes. To the mixture were added DCC (880 mg, 4.3 mmol) and DMAP (45.3 mg, 0.37 mmol) at room temperature. The mixture was further stirred at room temperature for 16 h under argon atmosphere. The resulting mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved into AcOEt and washed with 5% HCl and ice (2×5 mL). The organic layer was washed with an aqueous saturated $NaHCO_3$ (2×5 mL) and brine (5 mL), successively, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Hexane/AcOEt, 3/1) to afford 4-(6-bromohexanoylamino)-2,2,6,6-tetramethylpiperidine-1-oxyl (**1g**, 890 mg, 2.56 mmol, 85%) as orange solids: R_f=0.67 (AcOEt/Hexane, 1/1); ^{1}H NMR (200 MHz, $CDCl_3$ containing 1,2-diphenylhydrazine) δ 1.18 (s, 6H), 1.19 (s, 6H), 1.30 (t, J=12.6 Hz, 2H), 1.41–1.52 (m, 2H), 1.58–1.72 (m, 2H), 1.81–1.94 (m, 4H), 2.14 (t, J=7.4 Hz, 2H), 3.41 (t, J=6.8 Hz, 2H), 4.06–4.25 (m, 1H), 5.24–5.28 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$ containing 1,2-diphenylhydrazine) δ 19.6, 24.7, 27.7, 32.4, 33.6, 36.4, 41.0, 45.6, 58.9, 171.9; IR (KBr) 3300, 2999, 2975, 1640, 1550, 1459, 1243, 1179 cm^{-1}. Anal. Calcd for $C_{15}H_{28}BrN_2O_2$: C, 51.73; H, 8.10; N, 8.04. Found: C, 51.80; H, 8.28; N, 8.03.

4.15. Preparation of triethyl[5-(2,2,6,6-tetramethylpiperidine-1-oxyl-4-yl-carbamoyl)pentyl]-ammonium bromide (3b)[17a]

Into a 50 mL round-bottomed flask equipped with a magnetic stirring bar, a Dimroth condenser, and a three-way cock were placed **1g** (1.02 g, 2.9 mmol) and ethanol (10 mL). The flask was purged with argon. Freshly distilled triethylamine (1.23 mL, 8.8 mmol) was added to the solution, and the mixture was stirred at 80 °C for 24 h under argon atmosphere. The reaction mixture was concentrated under reduced pressure, and the residual solid was washed with hexane and diethyl ether (×3), successively. The solids were dried under reduced pressure to afford triethyl[5-(2,2,6,6-tetramethylpiperidine-1-oxyl-4-yl-carbamoyl)-pentyl]ammonium bromide (WS-TEMPO **1b**, 1.23 g, 3.95 mmol, 89%) as orange solids: R_f=0.00 (EtOAc); ^{1}H NMR (200 MHz, CD_3OD containing 1,2-diphenylhydrazine) δ 1.15–1.46 (m, 23H), 1.51–1.89 (m, 6H), 2.20 (t, J=7.2 Hz, 2H), 2.40 (t, J=7.2 Hz, 2H), 3.08–3.32 (m, 9H), 4.00–4.36 (m, 1H); IR (KBr) 3230, 2931, 1656, 1537, 1454, 1242, 1181 cm^{-1}.

4.16. Preparation of silica gel-immobilized TEMPO (3d)[15]

A 100 mL two-necked flask fitted with a three-way cock was evacuated to dry up and filled with argon. In the flask was placed a benzene (20 mL) solution of 3-(triethoxysilyl)propyl isocyanate (2.60 g, 10.5 mmol). To the solution was added a benzene (10 mL) solution of 4-amino-TEMPO (1.71 g, 10.0 mmol) dropwise, and the resulting mixture was stirred at room temperature for 9 h to yield a benzene solution of the corresponding urea. To the solution was added benzene (20 mL) and silica gel (10.0 g). The resultant mixture was heated to gently reflux for 61 h without stirring. The resultant was cooled to room temperature and filtered, and the solids were washed with hot benzene by use of Soxhlet's extractor for 8 h. The solids were dried under reduced pressure to afford silica gel-immobilized TEMPO **3d** (12.8 g) as pale orange solids: **IR** (KBr) 3420, 2924, 2855, 1636, 1570 cm^{-1}. The content of the immobilized TEMPO moiety was estimated to be 0.64 mmol/g by elemental analysis: Found: C, 11.37; H, 1.86; N, 2.74%; Anal. Calcd for 0.64 mmol/g silica gel-immobilized TEMPO **1e**: C, 11.53; H, 1.94; N, 2.69.

4.17. Preparation of poly(ethylene-*co*-acrylic acid)-immobilized TEMPO (3e)[16b]

Poly(ethylene-*co*-acrylic acid) particles (5.0 g) were treated with 4-amino-TEMPO (688 mg, 4.0 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCI·HCl, 1033 mg, 5.0 mmol) in chlorobenzene (30 mL) at 50 °C for 2 d. The poly(ethylene-*co*-acrylic acid) particles were filtered and washed with chlorobenzene (20 mL), water (20 mL), methanol (20 mL), and ether (20 mL), successively. The solids were dried under reduced pressure to afford poly(ethylene-*co*-acrylic acid)-immobilized TEMPO **3e** (4.90 g) as orange solids: IR (KBr) 3325, 2903, 2855, 1702, 1636, 1467, 1377, 1243 cm^{-1}.

4.18. Electrooxidation of methyl α-D-glucopyranoside (1a) using triethyl[5-(2,2,6,6-tetramethylpiperidine-1-oxyl-4-yl-carbamoyl)pentyl]ammonium bromide (WS-TEMPO, 1b)

Into an undivided cell equipped with two Pt plate electrodes (1.5× 1.0 cm^2) and a stirring bar were placed **1a** (97 mg, 0.5 mmol), WS-TEMPO **3b** (45 mg, 0.1 mmol), and an aqueous carbonate buffer (10 mL, aqueous Na_2CO_3 (0.40 M) and $NaHCO_3$ (0.30 M)). The mixture was electrolyzed at room temperature under constant current condition (30 mA) until 5.5 F/mol of electricity was passed (2.5 h). The polymer was filtered off, and the filtrate was extracted with AcOEt (5 mL×3). Cation exchange resin (Amberlite IR 120, 10 mL) was added to the aqueous layer and the whole mixture was stirred for 0.5 h to remove Na^+. The resin was filtered off, and the filtrate was concentrated under reduced pressure. The crude product was dissolved in MeOH (5 mL) and treated with 2,2-dimethoxypropane (0.5 mL, 4.1 mmol) and one drop of concentrated aqueous HCl at room temperature for 1 d. The resultant was concentrated under reduced pressure, and the residue was purified by column chromatography (SiO_2, AcOEt/MeOH, 5/1) to give the desired methyl (methyl α-D-glucopyranosid)uronate (**7a**, 77 mg, 0.35 mmol, 69%) as a colorless liquid.

Electrooxidation of methyl α-D-glucopyranoside **1a** was also carried out by use of various TEMPO derivatives, e.g., 4-benzoyloxy-TEMPO **3c**, SiO_2–TEMPO **3d**, and PE-*co*-AA-TEMPO **3e**. The results are summarized in Table 2.

4.19. Cyclic voltammetry of TEMPO

Cyclic voltammetry (CV) was measured on the BAS 100B/W potentiostat (BAS, Tokyo, Japan). A glassy carbon electrode (GC, φ 3 mm), a platinum wire electrode (φ 1 mm), and an Ag/AgCl electrode (Ag wire in 3 M aqueous NaCl) were used as a working, a counter, and a reference electrode, respectively. The working electrode was polished with 5 μm diamond slurry and with 0.5 μm alumina slurry, successively, and washed with deionized water. These electrodes were dipped into an aqueous solution of TEMPO **3a** (10 mM), Na_2CO_3 (0.4 M), and $NaHCO_3$ (0.3 M) in a beaker-type electrochemical cell. The solution was degassed with argon for 10 min before measurement. Cyclic voltammogram was measured in a potential range from 0.2 V to 0.8 V versus Ag/AgCl at a scan rate of 10 mV/s.

Cyclic voltammograms of alcohols (100 mM)/TEMPO **3a** (10 mM) solutions were obtained in a similar manner.

4.20. Particle size distribution

Particle size distribution was measured by dynamic light scattering (DLS) method. DLS measurements were performed on an FPAR 1000 light scattering system (Otsuka Electronics Co., Ltd, Osaka, Japan) equipped with a laser diode (30 mW) at λ_0=658 nm. A typical procedure is as follows: an aqueous solution of MTEG **3b** (100 mM), Na_2CO_3 (0.4 M), and $NaHCO_3$ (0.3 M) was sonicated for 10 min and was stood for 12 h at 20 °C before measurement. The solution was analyzed every 3 s for 3 min at 20 °C under the dust cut conditions. Peaks attributable to particles larger than 1200 nm are omitted. The analyses were repeated for 15 times and the observed intensity were averaged.

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