Enantioselective Oxidation of Amines on a Gold Electrode Modified by a Self-Assembled Monolayer of a Chiral Nitroxyl Radical Compound

Yoshitomo KASHIWAGI[†], Kazumi UCHIYAMA, Futoshi KURASHIMA, Jun-ichi ANZAI and Tetsuo OSA

Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Aoba-ku, Sendai 980-8578, Japan

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Organic nitroxyl radicals, such as 2,2,6,6-tetramethylpiperidin-*N*-oxyl (TEMPO), are known to be an effective redox mediator for the oxidation of amines.^{1,2} We have reported that a graphite felt electrode coated with a thin poly(acrylic acid) layer immobilizing 4-amino-TEMPO can be used for the electrocatalytic oxidation of amines.³ On the other hand, a self-assembled monolayer has attracted a great deal of interest because of its possible applications to many fields, such as biosensors and display devices.^{4,5} Many self-assembled monolayer-modified electrodes report on the monolayer-immobilization of thiols containing redox active functional groups on gold electrodes.⁶⁻¹⁰ Recently, Fuchigami *et al.*¹¹ have prepared a self-assembled TEMPO-modified electrode for the electrocatalysis of 4-methylbenzyl alcohol.

In this paper, we report on the enantioselective voltammetric behavior of chiral amines at gold electrodes modified with a mixed monolayer of chiral nitroxyl radical compound and hexadecanethiol.

Experimental

Reagents

(6*S*,7*R*,10*R*)-*N*-Oxyl-2,2,7-trimethyl-10-isopropyl-1-azaspiro[5.5]undecane-1,2-dithiolane-3-pentanecarboxamide (**1**) or *N*-oxyl-2,2,6,6-tetramethylpiperidin-1,2-dithiolane-3-pentanecarboxamide (**2**) was synthesized by the reaction of (6*S*,7*R*,10*R*)-4-amino-2,2,7-trimethyl-10-isopropyl-1-azaspiro[5.5]undecane-1-yloxyl¹² or 4-amino-2,2,6,6-tetramethylpiperidin-1-yloxyl (4-amino-TEMPO), respectively, with D,L- α -lipoic acid in the presence of *N,N*-dicyclohexylcarbodiimide. Hexadecanethiol (Tokyo Chemical Industry) was used as received. Acetonitrile (CH₃CN, guaranteed reagent, Nakarai Tesque Inc.) was stored over molecular sieves (4 Å, 1/16) for 24 h and then distilled in the presence of CaCl₂. Sodium perchlorate (NaClO₄, guaranteed reagent, Nakarai Tesque Inc.) was recrystallized from CH₃OH. All other reagents used as sub-

strates of electrocatalytic oxidation were of commercially available reagent grade.

Preparation of modified electrode

A gold (Au) disk electrode (1.6 mm diameter) was briefly etched in a 1:3:4 (in volume) mixture of conc. HNO₃/conc. HCl/ water before use. For preparing self-assembled monolayers on the surface of a Au electrode, the Au electrode was immersed in an ethanol solution containing a mixture of 1 mM **1** or **2** and 0.05 mM hexadecanethiol. The electrode was treated in the solution for at least 1 h and rinsed with ethanol and water. In the present study, mixed monolayers of **1** and **2** with hexadecanethiol (20:1 by mol) were used because the pure monolayer was reported to be somewhat unstable during electrochemical measurements.¹¹

Apparatus and procedure

Cyclic voltammetry was carried out in a CH₃CN solution containing 0.1 M NaClO₄ as a supporting electrolyte and 80 mM 2,6-lutidine as a deprotonating agent. The modified electrode was employed as a working electrode, and a platinum wire was used as a counter electrode. The anode potentials were referred to Ag/AgCl (0.1 M NaClO₄ in CH₃CN). Cyclic potential sweeps were generated by a Hokuto Denko Model HAB-151 potentiostat/galvanostat. Cyclic voltammograms were recorded on a Graphtec Model WX1200 X-Y recorder. All electrochemical measurements were carried out at room temperature.

Results and Discussion

Figure 1 shows the cyclic voltammograms (CVs) of the mixed monolayer containing **1** or **2** formed on the Au electrode. Both electrodes exhibited symmetrical reversible redox waves characteristic of a surface-confined species undergoing reversible redox reactions. The redox potential of **1** and **2** monolayer-modified electrodes was +0.62 V and +0.60 V vs. Ag/AgCl, respectively. The peak split between the anodic and cathodic peak potentials was *ca.* 20 mV and a linear

[†] To whom correspondence should be addressed.

relationships was observed between the anodic and cathodic current (i_{pa} and i_{pc}) and potential scan rate ranging from 10 to 200 mV s⁻¹. The amount of immobilized **1** and **2**, as determined by integration of current peak of the CVs, was 3.4×10^{-10} and 5.7×10^{-10} mol dm⁻², respectively. The surface coverage of **1** was slightly less than **2**, a monolayer-modified electrode, probably due to the bulkier nature of **1** than **2**. Both of the nitroxyl radical monolayer-modified electrodes were quite stable, and no decay in the CVs was observed after potential scanning many times.

The electrocatalytic activity of the monolayer-modified electrodes towards the oxidation of chiral amines was investigated. Figure 2 shows the CVs of 10 mM (*R*)-(+)- and (*S*)-(-)-1-phenylethylamine measured on the nitroxyl radical monolayer-modified electrodes in the presence of 80 mM 2,6-lutidine as a deprotonating agent. When a self-assembled chiral **1** monolayer-modified electrode was used, the anodic peak for the oxidation of (*R*)-(-)-1-phenylethylamine was slightly larger than that for a blank (the electrode itself). On the contrary, the anodic peak for the oxidation of (*S*)-(-)-1-phenylethylamine was highly enhanced, and no cathodic peak was observed on the reverse scan, showing

Chart 1 Structures of **1** and **2**.

that (*S*)-(-)-1-phenylethylamine was oxidized into the imine form electrocatalytically.¹ In other words, the **1** monolayer-modified electrode discriminates (*R*)- and (*S*)-isomer in the electrocatalytic oxidation reaction. The direct oxidation of both (*R*)-(+)- and (*S*)-(-)-1-phenylethylamine was observed to be more positive at +0.8 V vs. Ag/AgCl, which is an enormous increase in the anodic current. The achiral **2** monolayer-modified electrode, on the other hand, exhibited a large electrocatalytic wave for both (*R*)-(+)- and (*S*)-(-)-1-phenylethylamine along with the disappearance of the cathodic peak. This means that monolayer-modified electrode **2** is electrocatalytically active equally for the

Fig. 1 Cyclic voltammograms of **1** (—) and **2** (---) monolayer-modified electrode in 0.1 M NaClO₄/CH₃CN at the scan rate of 100 mV/s.

Fig. 2 Cyclic voltammograms of **1** (left) and **2** (right) monolayer-modified electrode in 0.1 M NaClO₄/CH₃CN at the scan rate of 100 mV/s. —: in the presence of 10 mM (*R*)-(+)-1-phenylethylamine and 80 mM 2,6-lutidine; ---: in the presence of 10 mM (*S*)-(-)-1-phenylethylamine and 80 mM 2,6-lutidine.

Table 1 Catalytic efficiency of **1** monolayer-modified electrode for the oxidation of chiral amines

Substrate	Config.	$i_{\text{cat.}}$ /mA	Ratio ^a
<i>R</i>	1.37	2.24
	<i>S</i>	3.07
<i>R</i>	1.44	2.98
	<i>S</i>	4.29
<i>R</i>	1.42	2.65
	<i>S</i>	3.76
<i>R</i>	6.00	1.00
	<i>S</i>	5.97	

a. $i_{\text{cat.}}$ of *S*/ $i_{\text{cat.}}$ of *R*.

oxidation of both (*R*)-(+)- and (*S*)-(-)-1-phenylethylamine.

Table 1 gives the catalytic efficiency of the monolayer-modified electrodes **1** for the oxidation of several chiral amines. The ratios between R - $i_{\text{cat.}}$ (catalytic peak current ($i_{\text{cat.}}$) for the oxidation of *R*-isomer) and S - $i_{\text{cat.}}$ ($i_{\text{cat.}}$ for the oxidation of *S*-isomer) of 1-phenylethylamine, 1-(1-naphthyl)ethylamine and 1-cyclohexylethylamine, which has a chiral center at the α -position to the amino group, were 2.98, 2.65 and 2.24, respectively. This results suggest that the electrocatalytic oxidation of *S*-isomers on a monolayer-modified electrode **1**, was prior to *R*-isomers. On the contrary, the ratio between R - $i_{\text{cat.}}$ and S - $i_{\text{cat.}}$ of 2-phenylpropylamine, which has a chiral center at the β -position to the amino group, was unity, which suggests no enantioselectivity of the electrode to 2-phenylpropylamine. These facts mean that an α -hydrogen of the chiral center adjacent to the amino group will be necessary to attain enantioselective oxidation in the present electrochemical method. On the other hand, the ratio between i_{cat} for the oxidation of *R*-isomer and *S*-isomer in all chiral amines by the monolayer-modified electrode **2** was

unity. This results suggest that the monolayer-modified electrode **2** afforded no enantioselectivity for chiral amines. The enantioselective oxidation on the electrode modified with the chiral nitroxyl radical-terminated self-assembled monolayer may be applied to the determination of optical purity of chiral amines.

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