Design of Electrode Providing Preparative Stereoselective Synthesis

Tetsuo OSA**, Yoshitomo KASHIWAGI***, Tetsuya ONO**, Futoshi KURASHIMA* and Uichi AKIBA***

*Graduate School of Pharmaceutical Sciences, Tohoku University, Aramaki, Aoba-ku, Sendai 980-8578 Japan
**Retired from*. The present home address: 7-37-15 Sakura-ga-oka, Aoba-ku, Sendai 981-0961 Japan
***School of Pharmaceutical Sciences, Ohu University, Tomita-machi, Koryoya, 963-8611 Japan

For the selective electrode-preparative syntheses of organic compounds, the electrode system composed of a graphite felt (GF) electrode coated with mediator-modified poly(acrylic acid) (PAA) was designed and prepared. In this study, characteristics of three GF electrodes differing from raw materials and the surface characteristics of these GF electrodes immobilizing redox mediator of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) were discussed. Among TEMPO-modified PAA-coated GF electrodes tested, the GF electrodes originated from pitch fibers was the best results for the enantio- and stereo-selective oxidations of geraniol and 2-naphthol, respectively, than the GF electrodes originated from polyacrylonitrile and phenolic resin fibers. The oxidation of racemic sec-alcohols and diols by chiral TEMPO of (6S, 7R, 10R)-4-amino-2,2,7-trimethyl-10-isopropyl-1-azaspiro[5,5]undecane-N-oxyl were carried out in high enantio- and stereo-selective yield and high isolated yield, respectively. The system can provide an ecologically clean process and will contribute to the development of green chemistry.

**Key Words**: TEMPO, poly(acrylic acid), graphite felt, mediator-modified electrode, macro-electrolysis

1 INTRODUCTION

For long period, organic macro-synthesis has been expected to provide an ecological and green process, if a suitable electrochemical system is constructed. Since preparative chemically modified electrodes for this purpose were first reported in the mid-1970’s [1], many reports along the purpose have been published. We confirmed that a large surface area of electrode such as graphite felt (GF) immobilizing electrocatalytic mediator can construct the system with high current density, high current efficiency, and high regio- or stereo-selectivity without any wastes of reagents [2].

In 1960’s, Osa, one of the present authors, successfully started the macro-electrochemical synthesis in The University of Tokyo [3] and has carried out many specific electrochemical trials. In 1986 when Bobbitt, J. M., University of Connecticut, USA, stayed in Sendai to cooperate with Osa’s group in Tohoku University, he brought GF and practiced to make reactive sites on its surface by air or reagent oxidation to immobilize functional materials with Akiba and Osa. The reactive groups on the GF surface were introduced by such oxidations smoothly, but simultaneously were decomposed. Therefore, the density of the reactive groups on the GF surface could not exceed ca. $10^5 \text{mol cm}^{-2}$. In 1987, Akiba newly adopted poly(acrylic acid) (PAA) coating to the GF surface and attained our research objectives with satisfaction [4].

Since then, Kashiwagi immobilized different types of mediators on GF and the electrochemical oxidation and reduction for many substrates were mainly examined in acetonitrile (AN) containing supporting electrolyte of sodium perchlorate (NaClO₄). Developing the system, high enantio- or stereo-selectivity, reactions were succeeded even if achiral mediator-modified GF electrode contains the additive of chiral base for dehydrogenation introduced in solution [5]. Furthermore, Kashiwagi and Kurashima developed the system of chiral mediator modified GF and succeeded in the reactions [6, 7]. Kashiwagi and his group are continuing this kind of study in Ohu University and clearing the differences upon the GF raw materials. So far, the effects of the different GF materials to organic macro-synthesis have not been reported, although it is especially important from the view-point of materials engineering for resources.

In this study, we would present the design, preparation and practice of different raw materials of GF electrodes and of several examples of electro-oxidation on a chiral mediator-modified GF electrode.

2 DESIGN AND PREPARATION OF MEDIATOR (TEMPO)-MODIFIED GRAPHITE FELT

2.1 Preferable property of graphite felt used in this study

To perform organic macro-electrolysis, large current passage is necessary. This objective can be attained by high current density electrolysis or by use of electrode having a large surface area. The latter can be realized by sponge like metal, felt, yarn or cloth of carbon materials. Carbon electrode materials have a long history of being used for industrial carbide production. Different carbon content and crystallinity of carbon electrode materials...
are commercially available from vitreous carbon to crystallized graphite of diamond providing a variety of shapes such as plate, ring, rod, yarn, fiber or felt. Here we show three kinds of GF materials different from raw materials: GF of PAN fibers obtained from ORAY Co. (PAN) (A), GF of pitch fibers originating from coal or petroleum obtained from National Electric Carbon Corp. (B) and GF of phenolic resin fiber from Gunei Chemical Co. Ltd. (C). Table 1 shows some of their physical properties.

2.2 Preferable coating of poly(acrylic acid) on graphite felt
To increase the density of mediators at the surface of GF, we have adopted an indirect mediator modification via polymer coating on GF electrodes. The PAA layer coated to GF yielded a high loading (20 μmol cm\(^{-2}\) level) of mediators, after trials to a various kind of polymers [5]. This PAA-coating GF has many favorable properties to prepare a polymer electrode as described below:
(a) Easy control of a layer thickness by dip-coating of electrode from the different concentration of PAA methanol solution.
(b) Strong physical adsorption of PAA to an electrode surface, particularly, to the GF surface.
(c) Easy chemical immobilization of functional groups of mediators to the PAA layer by the reactions of carboxyl groups of PAA.
(d) Control of hydrophilicity and lipophilicity by adjustment of the free carboxylate (-COOH) quantity of PAA.
(e) In the absence of free carboxylates in the PAA layer, organic compounds in the electrolyte solution can be condensed in the PAA layer.
(f) A suitable size of domain can be easily constructed and very important to a supramolecular structure.
(g) Chemical stability of the PAA layer.

2.3 Preferable mediators used for modified electrode
In general, the mediator-modified electrode has the following preferable properties over bare electrode:
(a) Electrochemical activation of electrochemically inactive substrates by depression of activation energy
(b) Increase in the reaction rate (increase in the electric current) by increase in mediator density at electrode interface
(c) Easy improvement of yield, selectivity and current efficiency of products by the control of electrode interface
(d) Decrease in the amount of expensive mediators by immobilization to electrode
(e) Attainment of clean and simple process, etc.

In order to achieve the above advantages, however, construction design at electrode interface such as highly efficient electron transfer or electric communications and high specificity is very important.

The optimum mediators for the preparation of modified electrode should use a reversible redox property of organic or metal coordination compounds for the following reasons. First, these mediators can be covalently attached to the PAA layer or strongly adsorbed on the electrode surface. Another point is that, due to the structural versatility of organic compounds and metal coordination compounds, the chemical structure of these mediators can be regulated to give a high degree of regio- and stereo-selectivity.

Here, we show a mediator adopted in our study since 1988, 2,2,6,6-Tetramethylpiperidinyl-1-oxyl (TEMPO) (1), which is a well known nitroxy radical mediator [8, 9]. The mediatory reaction of TEMPO is shown in Figure 1. Oxoammonium salt 2 can be easily prepared from 1 by treating with many methods such as positive halogen sources, m-chloroperbenzoic acid, high-valency metal salts, or electro-oxidation. Species 2 is a strong oxidant and is widely used for selective oxidation of several organic functional groups.

In this study, we demonstrate a chiral TEMPO of (6S,7R,10R)-4-amino-2,2,7-trimethyl-10-isopropyl-1-azaspiro-[5,5]undecane-N-oxyl ((6S,7R,10R)-SPIROXYL). This mediator was synthesized by the reaction of 2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyridine with (+)-dihydrocarvone and isolated from the formed 4 stereo-isomers by Kashiwagi and Kurashima [10].

2.4 Modification of (6S,7R,10R)-SPIROXYL to graphite felt as an example
The (6S,7R,10R)-SPIROXYL-modified electrode was prepared according to our established method [5] (Figure 2). A piece of GF (size: 1.0 x 1.0 x 0.5 cm\(^{3}\)) was usually dipped in 0.25 wt% PAA solution in methanol and then dried. This dipping condition gives ca. 40 nm thickness of the PAA layer. This layer was bonded with SPIROXYL to give a coverage of 20% (by titration), cross-linked with hexamethylenediamine to give a coverage of 10%, and, finally, butyl-esterified perfectly to remove any remaining free carboxylate groups. The density of SPIROXYL on the electrode was 8.4 mol cm\(^{-2}\). The effects of the PAA and SPIROXYL concentrations in methanol solution, and the effect of cross-linking of PAA with hexamethylenediamine or other dianimes were carefully examined and the proper treatment conditions were obtained.

Cyclic voltammogram (CV) of SPIROXYL-modified GF electrode (size: 1.0 x 1.0 x 0.5 cm\(^{3}\)) at 50 mV s\(^{-1}\) in 0.1 mol l\(^{-1}\) (M) NaClO\(_4\), /CH\(_2\)CN itself is shown in curve (a) of Figure 3. The CVs of 0.1 M and 0.2 M methyl-1,5-pentanediol with 0.2 M 2,6-lutidine afforded a well defined electro-catalytic peak at ca. +0.58 V vs. Ag/AgCl as shown in curves (b) and (c), respectively, in Figure 3. The CV of 0.1 M 3-methyl-1,5-pentanediol with 0.2 M 2,6-lutidine on
a bare GF electrode did not appear any peak as shown in curve (d) of Figure 3.

3 MACRO-ELECTROLYSIS ON MEDIATOR-MODIFIED GRAPHITE FELT ELECTRODE

A divided, H-type cell separated by Nafion 117 membrane is used for macro-electrolysis. The size of mediator-modified PAA coating GF electrode was: 5.0 x 2.0 x 0.5 cm$^3$ or 1.0 x 1.0 x 0.5 cm$^3$. The anode compartment contained 15-30 mmol of substrate, 30 mmol of 2,6-lutidine and several mmol of gas chromatography (GC) standard (tetralin or fluorene) in 40 ml 0.2 M NaClO$_4$/AN. The cathode was 40 ml of 0.2 M NaClO$_4$/AN. The cell was operated at a constant potential of 0.8-1.0 V vs. Ag/AgNO$_3$ under N$_2$ atmosphere. During electrolysis, samples were removed and analyzed by GC. After electrolysis, the electrolyte solution of AN was evaporated and the residuals were extracted by organic solvent and dried. The residual materials were mainly reaction product, small amount of starting substrate, added base and NaClO$_4$ of supporting electrolyte. Therefore, any waste materials were not formed in this process. Isolation, identification and amounts of substrates and products were conducted by conventional methods. Surface characteristics on GF electrodes and electrocatalytic results greatly depend on the raw materials producing GF. Table 2 shows the characteristics of TEMPO-modified GF electrodes produced from different raw materials. Thickness of PAA layer, ratio of reacted carboxyl groups of PAA layer with TEMPO, cross-linker of hexamethylenediamine and esterification by di-n-butyl sulfate, and density of TEMPO in the surface of GF differed from the raw materials of GF electrodes, but the oxidation potential of electrodes was same.

The results of electrocatalytic oxidation of geraniol on the above electrodes in the presence of 2,6-lutidine are shown in Table 3. All the GF electrodes oxidized the OH group of geraniol to CHO group almost quantitatively. The best results of current efficiency and conversion were obtained on the electrode from pitch (B), but the results of other 2 electrodes from PAN (A) and phenolic fibers (C) were moderate.

On the other hand, stereo-selective oxidation of 2-naphthol in the presence of (-)-sparteine are shown in Table 4. The GF electrode from pitch (B) gave the highest current efficiency, conversion, yield, ee% and turnover number among 3 GF electrodes. Therefore, GF electrode from pitch might be most preferable to stereo-selective synthesis. We found chiral TEMPO-, namely, SPIROXYL-modified PAA-coated GF electrode can give enantio-selective or stereo-selective electrooxidation without any chiral materials of additive. Here,
The results from the enantio-selective oxidation of several racemic alcohols are shown in Table 5. In the reactions of the racemic \(\text{sec}\)-alcohols, which contain a chiral centre \(\alpha\) to the hydroxyl group, the \((\text{S})\)-isomers were preferably oxidized to the \((\text{R})\)-isomers and form the corresponding ketones in 92-99% current efficiency, 50-53% yield and 100% selectivity. The turnover numbers based on SPIROXYL are greater than 74. The enantio-purity of the remaining \((\text{R})\)-isomers was 93-99%. On the contrary, the electrooxidation of 2-phenylproylalcohol, which has a chiral centre \(\beta\) to the hydroxyl group, was not enantio-selective, although it was oxidized to the corresponding aldehyde in 95% current efficiency, 96% yield and 100% selectivity.

The oxidation results of some diols are shown in Table 6. \((\text{S})\)-(+)1,4-Pentanediol was converted to \((\text{S})\)-(+)2-methyl-\(\gamma\)-butyrolactone in high enantiomeric excess of 99%. \(\text{cis}\)-(1\(\text{R},6\text{S})\)-(+)8-oxabicyclo[4.3.0]-nonan-7-one was also oxidized to the corresponding lactone of \(\text{cis}\)-(1\(\text{R},6\text{S})\)-(+)8-oxabicyclo[4.3.0]-nonan-7-one in 82% enantio-selectivity. The results in Table 6 mean that the substrates are oxidized to the corresponding lactones in 94-97% current efficiency and 92-96% yield. The turnover numbers based on SPIROXYL are greater than 430. \((\text{S})\)-(+)1,3-Butanediol did not lead directly to the corresponding \(\beta\)-lactone; however, it was oxidized to an optically active hydroxyaldehyde without loss of

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Characteristics of TEMPO-modified GF Electrodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrode</td>
<td>Thickness of the PAA layer</td>
</tr>
<tr>
<td></td>
<td>nm</td>
</tr>
<tr>
<td>A</td>
<td>1400</td>
</tr>
<tr>
<td>B</td>
<td>40</td>
</tr>
<tr>
<td>C</td>
<td>850</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Electro catalytic Oxidation of Geraniol on TEMPO-modified GF Electrodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMPO-modified GF electrode</td>
<td>Current efficiency (%)</td>
</tr>
<tr>
<td>A</td>
<td>78</td>
</tr>
<tr>
<td>B</td>
<td>94</td>
</tr>
<tr>
<td>C</td>
<td>85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Stereo-selective Electro catalytic Oxidation of 2-Naphthol on TEMPO-modified GF Electrodes in the Presence of (-)-Sparteine</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMPO-modified GF electrode</td>
<td>Current efficiency (%)</td>
</tr>
<tr>
<td>A</td>
<td>69.1</td>
</tr>
<tr>
<td>B</td>
<td>88.8</td>
</tr>
<tr>
<td>C</td>
<td>75.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Enantioselective Electro catalytic Oxidation of Racemic A lcohols Using the ((6\text{S},7\text{R},10\text{R}))-SPIROXYL-modified GF Electrode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>Product</td>
</tr>
<tr>
<td>(\text{OH})</td>
<td>(\text{O})</td>
</tr>
<tr>
<td>(\text{OH})</td>
<td>(\text{O})</td>
</tr>
<tr>
<td>(\text{OH})</td>
<td>(\text{O})</td>
</tr>
<tr>
<td>(\text{OH})</td>
<td>(\text{CHO})</td>
</tr>
<tr>
<td>(\text{OH})</td>
<td>(\text{CHO})</td>
</tr>
</tbody>
</table>
optical purity (99% ee).

4 EVALUATION OF ELECTROLYSIS DATA

The TEMPO-modified PAA coating GF electrode has high current density, high stability and long life. The current density of the electrode for organic compounds easily exceeds ca. 0.1 A cm\(^{-2}\). Therefore, when the substrate of molecular weight 100 is electrocatalytically oxidized by 2 electrons transfer, this electrochemical cell is estimated to provide a current charge concentration of ca. 3600 C l\(^{-1}\) hr\(^{-1}\), that is, ca. 2 g of product is produced per liter of electrolytic cell per hr. This value corresponds to that of a conventional organic reactor. Furthermore, conversion yield and current efficiency of product are also very high as well as low applied potential electrolysis using this mediator-modified electrode.

The electron transfer mechanism between electrode and substrate will be smoothly carried out via PAA polymer layer on the surface of GF

5 CONCLUSIONS

It is demonstrated that the mediator-modified PAA coating GF electrode can provide an ecologically clean, green electrochemical system. This conclusion suggests to evoke an important attention to electrochemical production of organic compounds in future.

Acknowledgements — The authors are grateful to Professor Bobbitt, J. M., University of Connecticut for providing GF (WDF) in 1986 and then giving useful many comments to our study. —

References


