Chapter 6

ELECTROCHEMICAL ENANTIOSELECTIVE REDUCTIONS

Abstract

This chapter considers the results received from enantioselective electrochemical reactions mainly from hydrogenations on metal (Pt, Ni), graphite, and Hg cathodes modified with chiral compounds (polyamino acids, alkaloids, and amino alcohols). Enantioselectivities of hydrogenation reactions were not effective, *ee* values did not exceed 50%, except in the cases of dehydrohalogenation and oxidation, from which optical yields reached above 90%.

6.1. General

Electrochemical reactions have some advantages in comparison with catalytic organic reactions. They do not need high hydrogen pressures in reaction vessels because hydrogen amounts and rates of reaction can be controlled by electrode potentials. This is a great advantage compared to the usual organic and catalytic reactions. But unfortunately, electrochemical enantioselective reactions in general have proved not to be very effective. The efficiency of enantioselectivity depends of many factors, such as the nature of the chiral inductor and its concentration, the electrode material, and the values of the potentials.

There are several methods for accomplishing electrochemical enantioselective reactions with the use of chiral inductors. They are the use of

a) chiral solvents
b) chiral supporting electrolytes
c) chiral electrode surface active material and
d) chiral modified catalytically active electrodes (see reviews [1-4]).

The first two methods, a) and b), are not very effective and need rather large amounts of chiral compounds as chiral inductors, although in some cases they give the products of reduction with *ee*'s up to 20% [1-5]. On the other hand processes c) and d) are more effective. They require only very small amounts of optically active compounds as asymmetric inductors and gave rather high optical yields.

The formation of optically active alcohol [6-8] and its pinacolinization [9] was observed in the reduction of acetophenone on a Hg cathode in the presence of (+) or (-)-ephedrine. (-)-Ephedrine resulted in the (*R*)-(+)-1-phenyl-

ethanol with an *ee* of 4.2% and (+)-ephedrine resulted in the (*S*)-(-)-1-phenylethanol with an *ee* of 4.6%.

The electrochemical reductions of prochiral carbonyl compounds like acetophenone and other carbonyl compounds in the presence of a number of alkaloids as chiral inductors have been described [10]. Thus, the reduction of phenylglyoxalic acid into mandelic acid was studied on a Hg cathode in the presence of a number of optically active alkaloids and other compounds which were strongly adsorbed on the cathode (strichnine, brucine, nicotine) and weakly adsorbed on the cathode (codeine, morphine) [11]. It was found that *ee* values increased with increasing adsorption of depolarizing molecules on the cathode, and the maximal *ee* was found in the presence of strychnine (*ee* was 22% at 0^0C).

It is interesting to note that quinidine promoted the formation of (*R*)-(-)-mandelic acid with low enantioselectivity (*ee* 2%), while quinine, cinchonine, and cinchonidine were ineffective [12]. If the alkaloid is not very strongly adsorbed on the cathode, it can be added in large amounts and play the role as the supporting electrolyte. If the alkaloid is strongly adsorbed, it needs only a small amounts to achieve a good effect [13].

Double asymmetric reduction was observed in the reduction of (-)-menthyl phenylglyoxilate into (*R*)-(-)-mandelate on a Hg cathode with an *ee* of 20.6% [14,15] and in the diastereoselective reduction of (*S*)-(-)-*N*-(*alpha*-methylbenzyl)benzoylformamide into the (*R,S*)-diastereomer with an *ee* of 12.5% [16].

Analogous to the reduction of phenylglyoxalic acid, strichnine proved to be moderately effective in the reduction of the oxime of this acid [17].

In acetate buffer and in the presence of strichnine the oxime of phenylglyoxalic acid was reduced into phenylglycine with either *R* or *S* configuration depending on the value of the cathode potential. The configuration of *R* in the potential interval of -0.95 V to -1.14 V was changed to *S* with an *ee* of 11.1% in the potential interval of -1.20 V to -1.35 V [17]. The polarographic reduction leads to phenylglycine with an *ee* of 17.1% [18,19].

Increasing the concentration of strichnine also reverses the stereochemical course of the electroreduction from an *ee* of 5% *R* at 0.1mM to an *ee* of 8% *S* at 3 mM [13]. The same effect was observed in the reduction of phenylglyoxalic acid to mandelic acid, in which an *ee* of 14% *R* resulted at 0.1 mM strychnine but an *ee* of 1% *S* resulted at 3.0 mM strychnine [13].

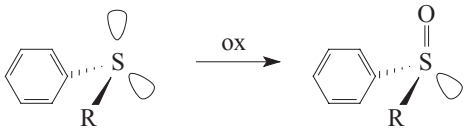
The 2-, 3-, and 4-acylpyridines were chosen as substrates on the Hg electrode because they are reducible at the potential ranges where alkaloids used as chiral inductors are electroinactive [10]. It was found that the stereochemical reduction was more effective in the case of 2-acetylpyridine (buffer acetate-EtOH, 0.5 mmol strychnine, 0^0C), the *ee*'s proved to be a function of the electrode potential, and the maximal *ee*'s were observed at very small concentrations of alkaloid. All characteristics indicate that the reactions pro-

ceeded on the surface of the electrode in the presence of the alkaloid as chiral inductor. The reduction proved to be very sensitive for the structure of alkaloids. In the cases of reductions of 2-acetylpyridine the following *ee* values were found with alkaloids: strychnine (47.5%), brucine (27%), cinchonine (2.5%), cinchonidine, (2%), yohimbine (5%), and sparteine (2%). The alkaloids quinine, quinidine, reserpine, and eserine proved to be inactive. In the reduction of 4-acetylpyridine only strychnine (*ee* 40%), brucine (18%), and yohimbine (4%) were stereochemically active (all alkaloids gave (+)-rotating products except yohimbine which gave (-)-rotating products). The reduction of 3-acetylpyridine resulted in only racemic products probably because it could not form an enol as a reactive intermediate.

The hydrogenolysis of carbon-halogen bonds were rather successful. The hydrogenolysis of the C-Cl bond in *N*-Methyl-3,3-dichloro-4,4-diphenyl-succinimide at a Hg electrode resulted in the (-)-monochloro-compound with an *ee* of 3% (in the presence of emetine), 2.7% (presence of yohimbine) and 26.5% (strichnine), while the hydrogenolysis of the C-Br bond in 1,1-dibromo-2,2-dimethylcyclopropane produced an *ee* of 44.3%. More negative working potentials gave higher *ee*'s [20,21].

Very innovative methods were attempted in the use of asymmetrically modified electrodes, although the first experiments were not very successful.

A graphite electrode modified chemically with L-phenylalanine gave an *ee* of 9.7% in the reduction of phenylglyoxalic acid into mandelic acid [22] and an *ee* of 2.5% in the oxidation of methyl *p*-tolyl sulfide into its sulfoxide [23]. Later this oxidation reaction was improved [24].



Scheme 6.1.

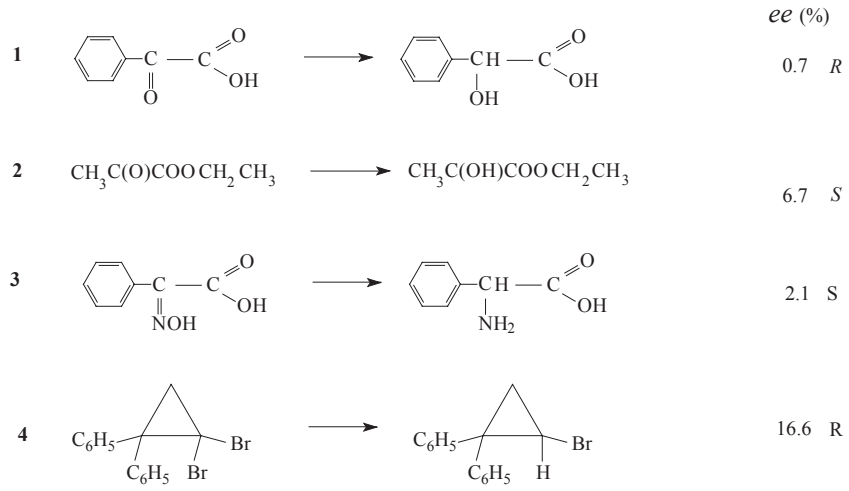
Oxidation of prochiral sulfides to chiral sulfoxides (Scheme 6.1.) was performed using a Pt electrode coated with a chiral polymer film consisting of the pyrrol-species [Ph-**C**H(Me)-NH-CO-CH_2CH_2-Pyrrol]$_n$. The reaction occurred in an acetonitrile solution containing 0.1mol nBu_4N-BF_4 at 1.3V vs. SCE (saturated calomel electrode) and gave the results shown below in Table 6.1.

A new set of electrodes were described that consisted of a graphite electrode covered with an optically active polyamino acid, such as poly-L-valine [1,25]. With this electrode a product with an *ee* of 43% from the reduction of 4-methylcoumarin was obtained [26], while a more effective result, an *ee* of 54%, in the oxidation of cyclohexyl phenyl sulfide on a Pt electrode coated with poly-L-valine was obtained [27].

R in sulfoxide	Chemical yield (%)	Optical yield (%)
Me	24	4 (S)
*n*Bu	15	67 (S)
*t*Bu	15	> 99 (S)
Hexyl	22	50 (S)

Table 6.1. Oxidation of prochiral sulfides into chiral sulfoxides.

According to Abe et al. [5] the reduction on graphite-poly-L-valine electrode was extended to prochiral compounds other then olefins. As shown below carbonyl compounds were reduced in reactions **1**-**3** (Scheme 6.2.) and a cyclopropane derivative was hydrogenolysed in reaction **4**.



Scheme 6.2.

On a poly-L-valine-coated graphite electrode, the asymmetric reduction of the C=C bond in 2-methylcoumarin and in citraconic acid produced *ee*'s of 43% and 25%, respectively [25,19]. Earlier, methyldihydrocoumarin was obtained only with an *ee* of 18.6% using spartein as an asymmetric inductor [26].

The low enantioselectivity in these cases can be explained by low coverage of chiral species on electrode surfaces. Therefore, some attempts were undertaken to use metal hydrogenating catalysts as electrode materials. But at first [28] only *ee* values of 2-6% were obtained in the reduction of 2-oxo compounds into alcohols using Raney-Ni powder electrodes modified with

(2*R*,3*R*)-tartaric acid (like Ni catalysts modified with hydroxy or amino acids elaborated earlier [29,30], see also Chapter 4 of this book).

Twice modified Raney-Ni powder was deposited on a Ni plate electrode. Reduction of 2-hexanone or 2-octanone was performed in MeOH + LiCl electrolite at -1.0 V vs SCE (saturated calomel electrode). Modification of the electrode with (2*R*,3*R*)-(+)-tartaric acid resulted in (*S*)-(+) alcohols with *ee*'s of about 9%, and modification with (2*S*,3*S*)-(-)-tartaric acid produced (*R*)-(-)-alcohols with the same *ee*'s [28].

Electrodes made from Pt covered with Ni powder or Ni-black and modified with (2*R*,3*R*)-(+)-tartaric acid were more effective [31,32]. In the reduction of ethyl acetoacetate *ee* values of 8-12% were obtained.

A cathode containing a Raney-Ni-Tartaric acid catalyst coated with CdS particles proved to be rather effective. Irradiation of this electrode by a xenon-lamp during reduction of methyl acetoacetate in EtOH solution leads to methyl 3-hydroxybutyrate with an *ee* of 67% [33].

According to Kambe et al.[33], the mechanism of reaction consists not in the reduction of methyl acetoacetate by photochemically produced hydrogen, but in the electrochemical reduction of the C=O bond and proton by photogenerated electrons. Thus, the hydrogen production sites on the surface of Raney Ni are different from methyl 3-hydroxybutyrate production sites.

Some special methods of enantioselective electrochemical reactions should be mentioned. D-Alanine was prepared with an *ee* close to 100% using the electrochemical reduction of pyruvic acid using an electrode on which amino acid oxidase and electron mediator were immobilized [34].

A strange method of preparation of optically active compounds without any chiral inductors was described using an electrochemical cell with electrodes of special asymmetric configuration made of barium titanate [35]. Reduction of fumaric acid resulted in (*R*)-(+)-malic acid with an *ee* of 17%, or (*S*)-(-)-malic acid, with 18% *ee*, depending on the orientation of the cathode. In this case perhaps the mica plates are the asymmetric inductors present in the electrochemical cell construction materials; however, the effect on the configuration of product of the orientation of the cathode inside the electrolytic cell remains incomprehensible.

In 1986 Takahashi et al. [36] alleged that the electrolytic reduction of 2-oxocarboxylic acids into 2-hydroxycarboxylic acids at a Hg-cathode, perpendicular to a magnetic field of 0.168T (1680 Gauss) resulted in chiral products with an *ee* up to 25%. These experiments were checked by Bonner [36] using a more powerful magnetic field of 7.03T (70300 Gauss) and found the products were totally racemic.

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