# ELECTROCHEMICAL CHARACTERIZATION OF NEW 1,5-BENZODIAZEPINE DERIVATIVES

*PAOLA JARA-ULLOA*[1], SEBASTIÁN CATALÁN-CARO[1] AND CARLOS A. ESCOBAR[2]*

*Universidad Andres Bello, Facultad de Ciencias Exactas, Departamento de Ciencias Químicas*
*[1]Laboratorio de Electroquímica, Av. República 275, Santiago, Chile.*
*[2]Laboratorio de Síntesis Orgánica y Organometálica, Av. República 275, Santiago, Chile.*

## ABSTRACT

Cyclic voltammetry was used to study the electrochemical behavior of new 1,5-benzodiazepine derivatives on a glassy carbon electrode. Well-defined oxidation peaks were observed in DMSO. The Electrochemical response of the glassy carbon electrode was evaluated as function of the scan rate, showing that the electron transfer process for compound (**5**) and (**6**) resulted to be controlled by diffusion.

**Keywords:** Cyclic voltammetry, 1,5 benzodiazepines, Diffusive behavior.

## 1. INTRODUCTION

Benzodiazepines (BZP) are biologically active molecules widely used as analgesic, hypnotics, sedatives and antidepressants agents[1,2,3]. Among others, there are some differences between the pharmacological effects of 1,4 and 1,5-BZP, for the latter, therapeutic potential and lower incidence of side effects has been described[4].

In addition to the other electrochemically active groups present in BZP core, such as, nitro, *N*-oxide and carbonyl groups, the drugs bearing the 1,4-benzodiazepine core are characterized by the presence of a relatively easily reducible azomethine[5] moiety, many of the therapeutic 1,5-benzodiazepines, such as clobazam are reported to be electrochemically inactive[6], however, some others, such as the 3*H*-1,5-benzodiazepines[7] has been shown to undergo two 2e-, $2H^+$ reductions at their azomethine moieties.

Also, the dibenzo-substituted benzodiazepines such as clozapine undergo a reversible 2e-, H+ redox reaction involving a relatively stable nitrenium ion [8,9].

To study the electrochemical oxidation behavior, the electrical conductivity trough the electrodes is an important factor. Carbon-based electrodes usually have a wider potential range than the other solid electrodes, because of their broad potential window, low background current, rich surface chemistry[10], chemical inertness, low cost and suitability for various sensing and detection applications[11]. Glassy carbon electrode is commonly used because it's excellent mechanical and electrical properties, impermeability to gases and extremely low porosity[12]. Electro- analytical applications[13,14] of carbon based electrodes has been developed to determine pharmaceutical compounds in both their dosage forms and in biological samples.

In comparison to 1,4-BZP, the electrochemical information related to the electrochemical behavior of 1,5-BZP is scarce. Research has been focused mainly in the electrochemical cathodic behavior of the 1,4-BZP, for this reason, we conducted this study, to evaluate the electrochemical oxidation behavior of 4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine derivatives.

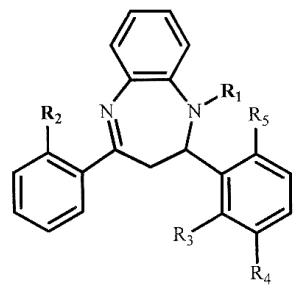
Recently, the synthesis of the 4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-Benzodiazepine, as well as, a new family of derivatives has been described[15-18], but its electrochemical behavior remains still unknown.

## 2. EXPERIMENTAL

### 2.1. Reagents

Dimethylsulfoxide (DMSO), used in the electrochemical experiments was purchased from Sigma and was dried with 3Å molecular sieves. All the electrochemical experiments were carried out in a non-aqueous medium (100% DMSO) with 0.1 M tetrabutylammonium perchlorate (TBAP) as the supporting electrolyte (Fluka).

The 1,5-benzodiazepine derivatives, 4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-Benzodiazepine (**1**), 1-acetyl-4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-Benzodiazepine (**2**), 1-crotonyl-4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-Benzodiazepine (**3**), 4-(2-acetoxyphenyl)-1-acetyl-2-phenyl-2,3-dihydro-1*H*-1,5-Benzodiazepine (**4**), 4-(2-hydroxyphenyl)-2-(2,5-dimethoxyphenyl)-2,3-dihydro-1*H*-1,5-Benzodiazepine (**5**) and 4-(2-hydroxyphenyl)-2-(2,3-dimethoxyphenyl)-2,3-dihydro-1*H*-1,5-Benzodiazepine (**6**) (Figure 1) were synthesized as previously described by Escobar *et al.*[15-18]




| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|
| **(1)** | H | OH | H | H | H |
| **(2)** | $CO\text{-}CH_3$ | OH | H | H | H |
| **(3)** | $CO\text{-}CH{=}CH_2\text{-}CH_3$ | OH | H | H | H |
| **(4)** | $CO\text{-}CH_3$ | $O\text{-}CO\text{-}CH_3$ | H | H | H |
| **(5)** | H | OH | H | $OCH_3$ | $OCH_3$ |
| **(6)** | H | OH | $OCH_3$ | $OCH_3$ | H |

**Figure 1**. Chemical structures of 1,5-benzodiazepine derivatives studied in this work.

### 2.2. Apparatus

Electrochemical measurements were recorded on the Electrochemical Analyzer VOLTALAB PST50 (Radiometer) attached to a desktop computer with the appropriate software (VoltaMaster4 for Windows) for total control of the experiments and data acquisition and treatment, a conventional three-electrode cell was used. Glassy carbon electrode (GCE) of 3 mm diameter (model CHI104, CH Instruments) was used as working electrode. A 0.8 mm diameter Pt wire and a Ag|AgCl|KCl(sat.) electrode (model CHI111, CH Instruments) were used as the counter and reference electrodes, respectively. Before each experiment the GCE was polished with 0.3 and 0.05 µm alumina, and then rinsed with water. All the experiments were carried out at room temperature.

### 2.3 Work Solutions

Work Solutions were prepared by dissolving a calculated weight of each compound in study (*i.e.* compounds **1** to **6**) in 100% DMSO whit 0.1M TBAP.


*e-mail: paola.jara@unab.cl*

**2.4 Cyclic Voltammetry**

Voltammetric study was performed with solutions of each compound at a concentration of about 1mM in 100% DMSO media with 0.1M TBAP. Potential sweep were performed in anodic direction between 0.1 and 1.6 V. at the following scan rates: 0.1, 0.25, 0.5, 0.75, 1.0 and 1.5 V/s. To distinguish if the electron transfer process is adsorption or diffusion controlled the values of the anodic peak current (ip,a) as a function of the scan rate, were examined.

## 3. RESULTS AND DISCUSSION

Cyclic voltammograms were performed to compound (**1**) to (**6**). For compound (**1**) in a forward scan, two definite anodic peaks were observed at +0.975 and +1.435 V ($I_1$, $II_1$ respectively) in contrast in the reverse sweep no cathodic peak was observable, which indicates that the oxidation process for (**1**) is irreversible (Figure 2).

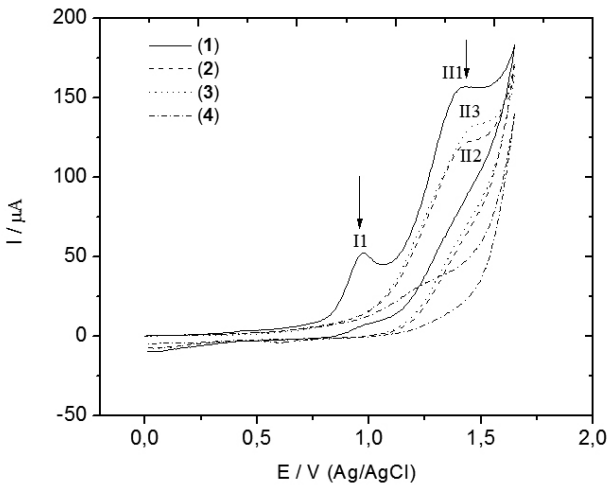
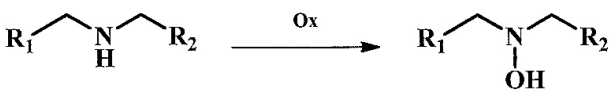



**Figure 2.** Cyclic voltammograms of 1,5-benzodiazepine derivatives (**1**) to (**4**) obtained onto GCE in DMSO 0.1MTBAP, scan rate: 0.1 V/s

In contrast with the findings for 1 (bearing any substitution at R1), for compound (**2**) and (**3**), only one oxidation peak was visible ($II_2$) and ($II_3$), respectively. Since a common feature for the last two compounds (*i.e.* compounds **2** and **3**) is the substitution at N1 position, we postulate that the first anodic peak, observed for 1, at ca. 0.975V, corresponds to the oxidation of NH to hydroxylamine derivative[19].




Since for compound (**4**) the previously mentioned oxidation peaks were absent, and the only one structural difference with compounds (**1**) to (**3**) is the presence of two acetyl groups located at R1 and R2, respectively, then is possible to establish that the signal (II) at Ca 1.3V (figure 2), observed for compounds (**1**), (**2**) and (**3**) is due to the oxidation of the R2 (*i.e.* 2´-OH group).

Cyclic voltammograms for Compounds (**5**) and (**6**), bearing methoxy groups located at 2-phenyl ring, were recorded with the aim to evaluate the effect of the substituent over the oxidation of R1 and R2 (*i.e.* NH y OH, Figure 3).

Again, for compound **1**, two definite anodic peaks were observed ($I_1$, $II_1$ respectively) as previously described above. For compounds (**5**) and y (**6**) In a forward scan, only one anodic peaks was observed about 1 V with no cathodic peak in the reverse sweep, which indicates that the oxidation process of (**5** and **6**) is irreversible. Demonstrating clearly in this way that the electron donor substituent located at 2-phenyl ring, has any incidence in the oxidation of the amino moiety. In contrast the oxidation of R2 was no observed in the range of applied potentials.

Oxidation potentials found for each of the compounds tested are summarized in table 1.

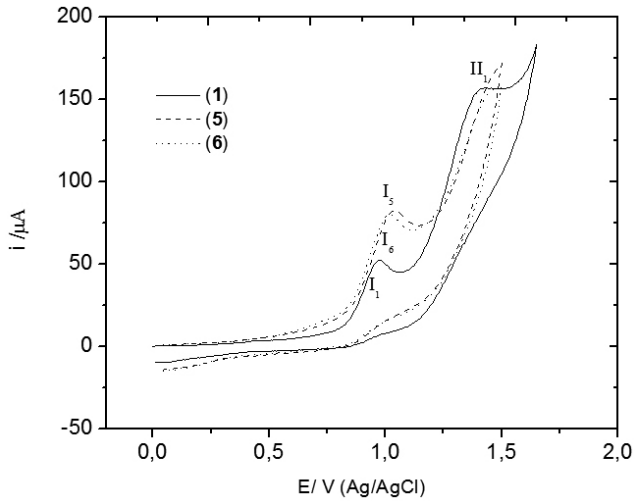



**Figure 3.** Cyclic voltammograms of 1,5-benzodiazepine derivatives **(1, 5 and 6)** obtained onto GCE in DMSO 0.1MTBAP, scan rate: 0.1 V/s

**Table 1.** Oxidation potential values of 1,5-BZP onto GCE in DMSO 0.1MTBAP.

| 1.5 BZP | Signal I ( Ep,a/V) | Signal I ( Ep,a/V) |
|---|---|---|
| ( 1) | 0.975 | 1.435 |
| ( 2) | – | 1.445 |
| ( 3) | – | 1.480 |
| ( 4) | – | – |
| ( 5) | 1.040 | – |
| ( 6) | 1.020 | – |

Although the structural differences between 1,4 and 1,5-BZP are minimal, it is difficult to propose a common oxidation mechanism for both compounds, due to their differences in both the functional groups present in each compound and the way they are affecting the electronic transfer.

From previous studies regarding the 1,4-BZP family, it has been postulated for flurazepam, that oxidation occurs at the N1-substituted atom (*i.e.* ca. 1 V, Acetonitrile), producing an N-oxide.[20]

Moreover, those 1,4-BZP who do not have substitution at N1 are oxidized to more positive potentials (*i.e.* ca. 1.5 V, pH = 4), however it is not possible to make a comparison with 1,5-BZP since experiments has been not performed in the same working environment.

***Scan rate study***

The influence of the scan rate on the anodic peak current (Ip,a) was studied in the range of 0.1 – 1.5 V/s for compounds (**1**), (**2**), (**3**), (**5**) and (**6**), only the cyclic voltammogram for compound (**1**) is depicted in Figure 4A. As showed in figure 4A, the peak potential moves to a more positive potential with increasing the scan rate, which confirms the irreversibility of the process.

To distinguish if the electron transfer process is adsorption or diffusion controlled the values of the anodic peak current (ip,a) as a function of the scan rate, were examined plotting log Ip,a against log υ over the scan range of 0.1-1.5 V/s (Figure 4B). Slope values of 0.38; 0.33; 0.36; 0.43; 0.48 were found for compounds (**1**), (**2**), (**3**), (**5**) and (**6**) respectively, and these values are in accordance with the theoretically expected values of 0.50 for a diffusion controlled process.

## 4. CONCLUSION

This paper deal with the electrochemical oxidation behavior of 4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine derivatives on a glassy carbon electrode, all compounds were irreversibly oxidized at positive potentials. The first oxidation process occurs on N1 when R1 is H (compounds **1**, **5** and **6**), a second oxidation process was observed to high anodic potential, corresponding to the oxidation of the OH at R2 (compounds **1**, **2**, **3**, **5** and **6**). By including compound (**4**) were both the OH and the NH are protected, no signs of oxidation were observed in the applied potential range. The electron transfer process for compound (**5**) and (**6**) resulted to be controlled by diffusion.

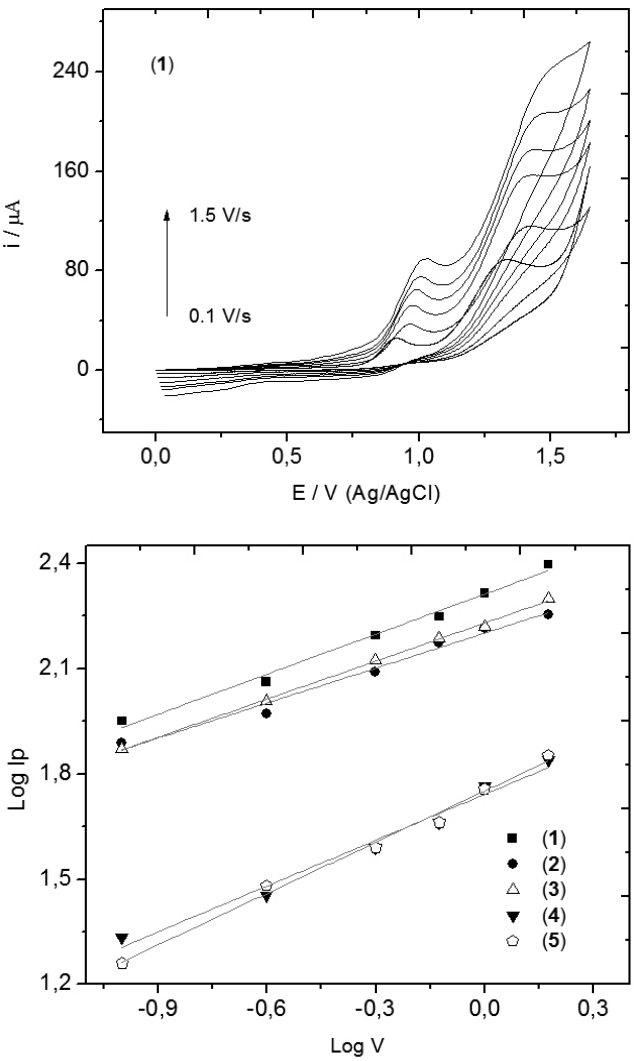



**Figure 4A** (upper) Cyclic voltammograms for (**1**), DMSO, 0.1M TBAP scan rate: 0.1-1.5 V/s ; 4B (Lower) Plot of Log Ip,a vs Log υ for all compounds in study.

## ACKNOWLEDGMENTS

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