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# A preliminary study of cyclic voltammetry in glassy carbon electrode. Redox Behaviour of 2-Amino-4-phenylthiazoles

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**Abstract.** In this work a voltammetric study of the reduction processes of five substituted 2-Amino-4-(4-X-phenyl) thiazoles (-X = -H, -OCH<sub>3</sub>, -CH<sub>3</sub>, -Cl, -NO<sub>2</sub>) in dimethylsulphoxido was performed. In the potential range considered (-2.0 to -2.9 V vs Ag<sup>+</sup>/AgCl), one signal (I<sub>c</sub>) were detected, which was associated with the electrochemical reduction of the corresponding of the heterocycle compound. The voltammetric analysis at the reduction signal showed that when in-creasing the sweep speed ( $0.1 < v < 1.0 \text{ Vs}^{-1}$ ), an oxidation signal associated with the I<sub>c</sub> wave was not observed. The linear dependence of the peak current with respect to the root of the velocity of the I<sub>c</sub> wave, showed that this was a process controlled by diffusion and showed an apparently irreversible behavior. Peak potential shifted to more negative values as the potential sweep speed was higher; this was indicative of irreversible behavior in this signal. The substitution changes influenced the electrochemical behavior, evidencing that a substituent, as in this case methoxy group compound -OCH<sub>3</sub>, causes a greater energetic demand for the reduction of the thiazole derivative it becomes evident in the most negative potential, with respect to the derivative without substituent -H. This was new evidence of the behavior electrochemical of 2-Amino-4-(4-X-phenyl) thiazoles derivates which had not been reported for these compounds.

## 1. Introduction

The thiazole ring represents an interesting class of heterocyclic compounds. Thiazole derivatives play an important role in biological functions, such as antibacterial [1, 2], anti-fungal [3, 4], anti-parasitic [5], antimicrobial [6], antitubercular [7, 8], anti-HIV [9-11], pesticidal [12], anti-inflammatory [12-15], antiprotozoal [16], hypertension [17], schizophrenia [18] and anticancer [19].

For several decades the researches have been working on the synthesis and evaluation of the physicochemical properties of this type of compounds [20]. In recent years the interest in the chemistry of heterocyclic compounds has increased considerably; this is related to many of the special properties shown by similar compounds. The great interest is represented by the derivatives of 2-Amino-4-(4-X-phenyl) thiazoles (APhTz) that can be used as potential biologically active compounds [1]. The APhTz derivatives are an important component in medicinal chemistry and research for drug discovery [21].

Derivatives of this type of compounds are known to have a wide range of biological activities. However, studies of the electrochemical behavior of APhTz have not been of great interest probably in the case of oxidation, due to its similarity with primary amines. Electrochemical oxidation of hazardous organic species is a promising method for the remediation of wastewater [20]. In the case of



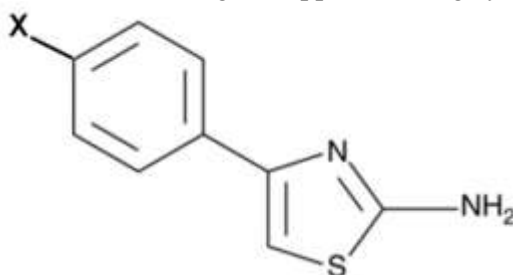
reduction, probably due to the need to use very negative potential values. Due to this fact, it is apparently not possible to study the effect of the structural properties on the electrochemical behavior of these compounds in acetonitrile solution. The electrochemical reduction of the derivatives APhTz has not been previously studied in aprotic media; neither is there information has been reported on the stabilization or destabilization of electrogenerated species during this process.

An interesting alternative to study the electrochemical behavior of organic compounds in aprotic medium is by modulating the structural properties of the compound. In the case of substituted derivatives APhTz, this can be achieved by modifying the chemical nature of a substituent group in the molecule, which can add or remove electron density within the chemical structure; modifying the reduction pathway, which would be particularly important for stabilization an anionic radical structure.

Although there has been a recent interest in studying the reactivity of derivatives APhTz an approach from the cyclic voltammetry to the electrochemical behavior in aprotic environment of such compounds has not been considered and the number of documents related to influence of the chemical structure on the electrochemical parameters of the electron transfer process neither has it been studied.

the above indicates that it is necessary to develop systematic studies focused on the characterization of the reactivity of these molecules, with the in order to predict qualitative tendencies of reactivity that also allow to design protocols for the design of new compounds. Therefore, it is important to approach from the cyclic voltammetry to the electrochemical behavior of the derivatives APhTz during their reduction in aprotic medium, evidencing the electronic effects of a particular substituent on said behavior in order to obtain more information about the parameters that can determine the chemical reactivity of the respective heterocyclic derivative.

In this work, the behavior of derivatives 2-Amino-4-(4-X-phenyl) thiazoles (APhTz) during their reduction in aprotic medium was studied, through an approach using cyclic voltammetry.



**Figure 1** Structure of 2-Amino-4-(4-X-phenyl) thiazoles (**1a**, X = -H; **1b**, X = -OCH<sub>3</sub>; **1c**, X = -CH<sub>3</sub>; **1d**, X = Cl and **1e**, X = -NO<sub>2</sub>).

## 2. Experimental

A single cell with a three-electrode arrangement was used, using a working electrode of vitreous carbon with an area of  $\sim 0.07 \text{ cm}^2$ , and a platinum wire (12 cm long) as an electrode auxiliary. A silver-silver chloride electrode in aqueous solution was used as a reference electrode. To minimize the effect of the liquid binding potential, the reference electrode was immersed for 30 minutes in DMSO before use, in order to saturate the porous glass of this electrode. The working electrode was polished before each electrochemical measurement, with an aqueous paste of alumina ( $0.05 \mu\text{m}$ ). The studies were carried out in an inert atmosphere by saturation with high purity nitrogen for 20 minutes before each measurement.

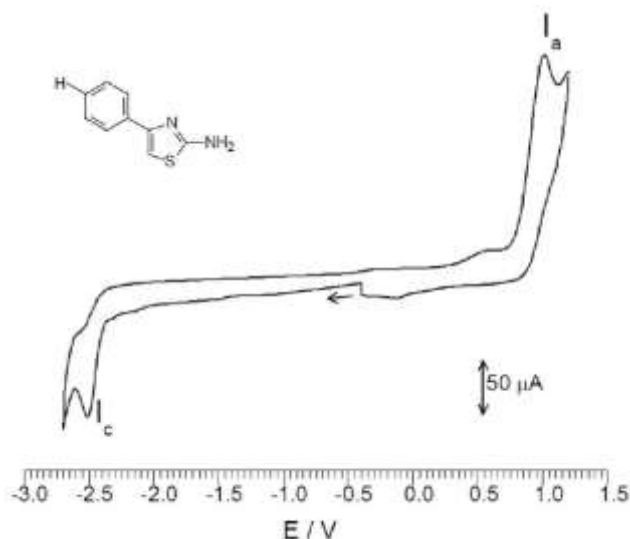
The compounds under study were prepared at a concentration of 3 mM, in solution 0.1 M of tetraethyl ammonium tetrafluoroborate (TEABF<sub>4</sub>) in dimethylsulphoxide (DMSO). All measurements were obtained by depositing 5 mL of the solution in the electrochemical cell.

The cyclic voltammetric was carried out in a Potentiostat Autolab model PGSTAT128N connected to a personal computer for the acquisition and storage of data. The measurements were made in cathode scanning, from +1.2 to -2.7 V at scan rate  $v = 0.1 \text{ Vs}^{-1}$ . The processing of the data was done through the Origin Pro 8.0 program.

### 3. Results and discussion

#### 3.1. Electrochemical study of 2-Amino-4-(4-X-phenyl) thiazoles

The typical cyclic voltammetry of 2-Amino-4-(4-X-phenyl) thiazole (1a, X = -H) at a potential sweep velocity  $v = 0.1 \text{ Vs}^{-1}$  is shown in Figure 2.



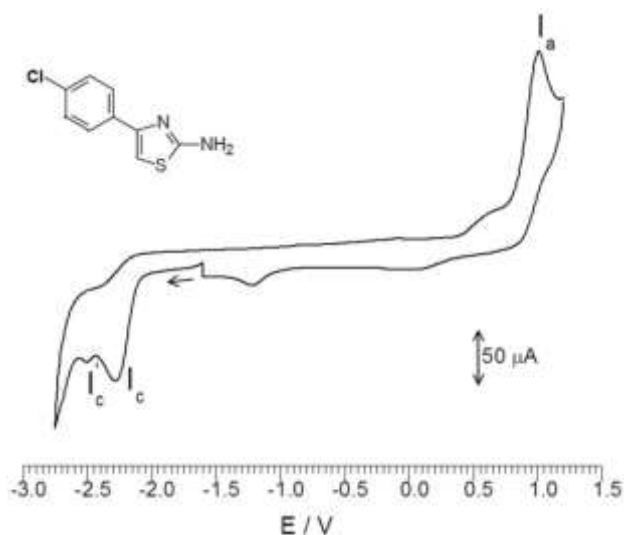
**Figure 2** Cyclic voltammetry of 3.0 mM 2-Amino-4-(4-H-phenyl) thiazole in DMSO + 0.1 M TBABF<sub>4</sub>. The potential sweep was initiated from -0.25 V vs. Ag / AgCl in the negative direction. The voltammetric response was obtained at a potential sweep speed  $v = 0.1 \text{ Vs}^{-1}$ .

In the figure 2, shown that a sweep in the cathode direction revealed the reduction wave ( $E_{pIc} = -2.5 \text{ V}$ ) signal Ic. This result, not been reported in the literature and corresponds to the reduction of the compound structure 1a.

When increasing the sweep speed ( $0.1 < v < 1.0 \text{ Vs}^{-1}$ ), an oxidation signal associated with the Ic wave was not observed. The linear dependence of the peak current with respect to the root of the velocity, of the Ic wave, showed that this was a process controlled by diffusion. This wave (Ic) showed an apparent irreversible behavior. Peak potential shifted to more negative values as the potential sweep speed was higher. This was indicative of irreversible behavior in this signal. The second wave (Ia) marked in the Figure 2 corresponded to the oxidation of the amino group present in the C2 position of the thiazole ring (checked with voltammetry of o-nitroaniline). It is important to note that in several of the studies reported in the literature, the voltammetric analysis is restricted to the potential window where the oxidation signal of the amino group appears. In general, the electrochemical behavior of 1a (X = -H) is followed by compounds 1b (X = -OCH<sub>3</sub>) and 1c (X = -CH<sub>3</sub>). However, the peak potential value of the Ic wave changes (1b,  $E_p = -2.63 \text{ V}$  and 1b,  $E_p = -2.56 \text{ V}$ ). This variation in the peak potential value shown by the Ic wave, indicated that the electron transfer process involves different amount of energy for it to occur, influenced by the substituent.

The voltammetric behavior for the derivative (1d, X = -Cl) is shown in Figure 3, and presents some differences in relation to the behavior described for derivatives 1a, 1b and 1c (Figure 2). In the voltammetric response above, a reduction signal Ic can was observed ( $E_p = -2.28 \text{ V}$  vs Ag / AgCl); this peak shows an irreversible behavior. A second reduction wave (Ic'  $E_{pIc'} = -2.5 \text{ V}$  vs. Ag (AgCl) corresponds to a reduction process whose peak potential coincided with the value of the peak potential of the reduction signal found for compound 1 (Figure 2). This result could indicate that the reduction

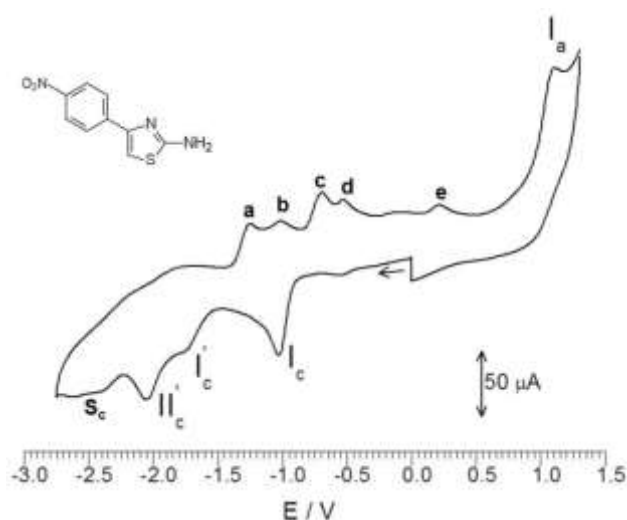
process followed a sequence of stages different from what the other compounds studied above showed.



**Figure 3** Cyclic voltammetry of 3.0 mM 2-Amino-4- (4-Cl-phenyl) thiazole in DMSO + 0.1 M TBABF<sub>4</sub>. The potential sweep was initiated from -1.6 V vs. Ag / AgCl in the negative direction. The voltammetric response was obtained at a potential sweep speed  $v = 0.1 \text{ Vs}^{-1}$ .

For 2-Amino-4-(4-X-phenyl) thiazoles derivatives compounds is a result that has not been reported in previous works. The wave (Ia) marked in Figure 3 is corresponded to the oxidation of the amino group present in the C2 position of the thiazole ring.

The voltammetric behavior for the derivative (1e, X = -NO<sub>2</sub>) is shown in Figure 4, and presented differences in relation to the behavior described for derivatives 1a, 1b, 1c and 1d (Figures 2 and 3).



**Figure 4.** Cyclic voltammetry of 3.0 mM 2-Amino-4- (4-NO<sub>2</sub>-phenyl) thiazole in DMSO + 0.1 M TBABF<sub>4</sub>. The potential sweep was initiated from 0,0 V vs. Ag / AgCl in the negative direction. The voltammetric response was obtained at a potential sweep speed  $v = 0.1 \text{ Vs}^{-1}$ .

It was possible to observe a reduction signal Ic, ( $E_{pico} = -1.0$  V vs Ag / AgCl) which has been associated to some of the oxidation waves (letter a) and corresponds to the first reduction wave of the nitro group -NO<sub>2</sub>, present in derivative 1e. Two reduction waves I'c ( $E_p = -1.75$  V and II'c,  $E_p = -2.0$  V). One of them (wave II'c) corresponding to the second reduction process of the nitro group and the other to the reduction process described by the voltammetric response of compound 1a (Figure 2). The above could be explained, due to the possibility of reducing the nitro group, which when reduced modified its effect on the site susceptible to being reduced in a similar way to derivatives 1a and 1b.

In addition, the reduction wave II'c have associated oxidation signals probably to those observed in the figure marked with letter (a, b, c and d). This would imply the oxidation of the products generated in the second reduction process of the nitro group.

A reduction signal Sc appears almost at the end of the reduction window, which is very long and of very low current intensity. This last case should be more studied, due to the complexity of the voltammogram that makes it difficult to know which signal corresponds to each of the reduction processes mentioned. The wave (Ia) marked in Figure 4 is due to an oxidation process corresponding to the oxidation of the amino group present in the C2 position of the thiazole ring.

The voltammograms shown in Figures 2-4 illustrate an increase in the complexity of the reduction process involved in the electronic transfer of the compounds studied and also showed the influence of the effects of the substituents on the reactivity of the electrogenerated species. From the preliminary study of cyclic voltammetry of the studied compounds (Figure 1), the peak potential value of the Ic wave could be determined (Figure 2 - 4). These data were analysed in order to find some correlation with free energy relationships data, Table 1.

**Table 1** Data obtained from the voltammetric analysis of the 2-Amino-4-(4-X-phenyl) thiazoles derivatives studied

Compounds	-X	Hammett $\sigma_p^a$	$E_{peak}/V^b$	$\Delta(E_{peak})^c$
<b>1b</b>	-OCH <sub>3</sub>	-0,288	-2,63	-0,13
<b>1c</b>	-CH <sub>3</sub>	-0,170	-2,56	-0,06
<b>1a</b>	-H	0,0	-2,50	0,0
<b>1d</b>	-Cl	+0,227	-2,28	+0,22
<b>1e</b>	-NO <sub>2</sub>	+0,778	-1,75	+0,75

<sup>a</sup> Taking [22].

<sup>b</sup> Reduction potential of the thiazide ring with respect to Ag<sup>+</sup>/ AgCl electrode.

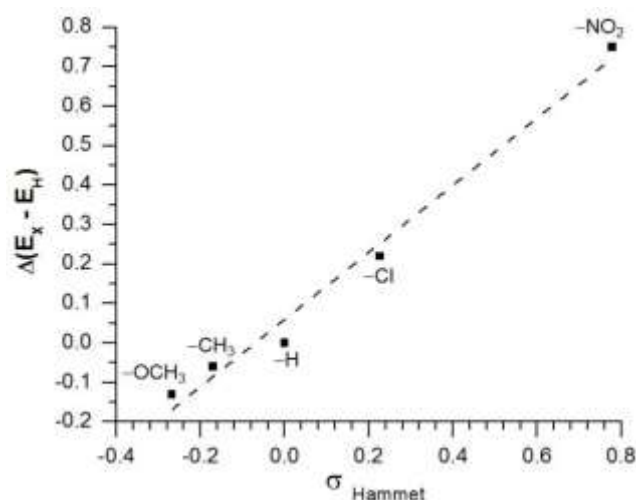
<sup>c</sup> Difference between the values of reduction potential of the derivative with substituent and the derivative without substituent, with respect to Ag / AgCl electrode.

These values were correlated to the corresponding Hammett sigma parameter, for the proper substituent -X in the C4 position with respect a p-thiazole cycle (Figure 1). For the signals Ic, this correlation showed that compound 1b, which has an electron-donating inductive substituent effect ( $\sigma_p < 0$ ), has a peak potential value more negative than that of the 2-Amino-4-(4-NO<sub>2</sub>-phenyl) thiazoles having an electron with drawing inductive effect (1d, 1e,  $\sigma_p > 0$ ).

An acceptable correlation was found when determining peak potential values and observing the trend or change in that value (Figure 5). The voltammetric behavior of every 2-Amino-4-(4-X-phenyl) thiazoles studied suggests changes in the stability of the electrogenerated intermediates during the electronic transfer process Ic (Figure 2). These changes can be directly related to inductive effects that is, the energetics of the reduction process is influenced by the inductive effect of the substituents in position 4 (for with respect to the thiazole ring, Figure 1).

The corresponding Hammett-Zuman-type relationship ( $\Delta E_{peak}$ )  $(E_{peak})_X - (E_{peak})_H$ , where  $(E_{peak})_X$  is the  $E_{peak}$  value for a compound bearing a given substituent (X) and  $(E_{peak})_H$  is the value obtained from

the compound bearing a proton (-H) as a substituent, presented a linear relationship with the  $\sigma_p$  values, leading to the linear equation ( $\Delta E_{peak}$ ) =  $0.85\sigma_p + 0.059$ ,  $r$  0.9802) Figure 5. It was found that for oxidation wave, peak Ia, there is relative correlation between the  $\sigma_p$  values and the  $E_{pIa}$  data.



**Figure 5.** Relationship between  $\Delta(E_{peak})$  with  $\sigma_p$  of Hammett.  
Linear trend: ( $\Delta(E_{peak})$ ) =  $0.85\sigma_p + 0.059$ ,  $r$  0.9802)

#### 4. Conclusions

The voltammetric signal of the electrochemical reduction of the derivatives of 2-amino-4- (4-X-phenyl) thiazoles, is a new evidence of the electrochemical behavior that had not been re-reported for these compounds. The results of the electrochemical reduction study showed that the substitution change influenced the electrochemical behavior, evidencing that a substituent, as in this case methoxy group compound 1b, causes a greater energetic requirement for the reduction of the thiazole derivative. It becomes evident in the most negative potential, with respect to the derivative without substituent 1a.

Considering the result of the present work, it could be suggested that the reduction path that leads to the formation of a arylthiazole radical anion intermediate would not be taking place in the cells. On the other hand, the formation of free radicals is attributed to the transfer of electrons that is favored in anaerobic cells or hypoxic conditions. Since oxygen is very electronegative, the bio-reduction of substances with low redox potential is favoured under conditions of hypoxia and anoxia. For example, the nitro group has low redox potential and thus its bioreduction is unlikely in oxygenated cells. The bioreduction of these substances (derived from the compound 2-aminothiazole), could occur under these conditions when the dose is high due to the effect of the law of mass action. The absence of genotoxic effects could be associated with the low reduction of the thiazide ring in the doses tested and the aerobic and oxidative condition of the cells.

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