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Electrochemical reduction processes on glassy carbon electrode of 2-Amino-4-phenylthiazoles.

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Abstract. In this work the electrochemical reduction of the compounds 2-Amino-4-(4-R-phenyl)thiazoles (1a, R = -H and 1b, R = -NHCOCH₃) was performed by cyclic voltammetry in dimethylsulfoxide (DMSO) + 0,1 M tetraethylammonium tetrafluoroborate (TEABF₄) and tetrabutylammonium hexafluorophosphate (TBAPF₆). Two reduction signals were observed, the I_c wave (EpI_c = -2.52 V) and wave II_c (EpII_c = -2.77 V) due to an electron transfer of the electrogenerated product in the I_c wave. The change of substituent influences the electrochemical behaviour, showing that an electrodonating substituent causes a higher energy requirement for the reduction of **1b**, which became evident in the more negative potential, with respect to **1a**. Additionally, it was observed that the peak potential in the first reduction signal I_c wave shifted to more negative values as the potential sweep rate was higher and this was indicative of an irreversible behaviour. A larger salt such as TBAPF₆ causes a decrease in the intensity of peak reduction currents, contrary to what was shown by a smaller salt such as TEABF₄. Also for both compounds, the cathodic peak potential of wave I_c and II_c is influenced by the effect of the size of salt used. A smaller salt favoured the electrochemical reduction of both heterocyclic compounds.

1. Introduction

The thiazole ring represents an interesting class of heterocyclic compounds. Thiazole derivatives play an important role in biological functions, such as antimicrobial, antidiabetic, antiviral, anti-inflammatory, antituberculous and anticancer [1]. For several decades we have been working on the synthesis and evaluation of the physicochemical properties of this type of compounds [2].

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-phenylthiazoles that can be used as potential biologically active compounds [3]. The 2-Amino-4-phenylthiazoles derivatives are an important component in medicinal chemistry and research for drug discovery [4].

Derivatives of this type are known for a wide range of antibacterial activities [5]. The 2-Amino-4-phenylthiazoles have been investigated due to their broad antiparasitic spectrum [6-7]. However a study of the electrochemical behavior of 2-Amino-4-phenylthiazoles has not been of great interest probably due to its similarity to primary aromatic amines. Electrochemical oxidation of hazardous organic species is a promising method for the remediation of wastewater [8]. The study of the electrochemical behavior when the molecule is reduced in an aprotic medium, will allow to mimic the behavior of these compounds in a similar electrical environment during their passage through the metabolism of a living being, which although an aprotic medium does not predominate in the



organism can be approximated the behavior of these molecules in aprotic zones of the cellular system [9]. In addition to providing useful knowledge for areas such as molecular design with different medical and industrial applications.

The aim of the present research is to study the behavior of derivatives 2-Amino-4-(4-R-phenyl)thiazoles ($R = -H, -NHCOCH_3$) (APhTz), whose reactivities depend in an essential way on the redox properties of the parent molecule and the properties of the intermediaries that are formed, in this case, by electrochemical reduction, in addition to the structural effect [10].

2. Experimental

2.1. Synthesis of 2-amino-4-(4-R-phenyl)thiazole (1a, $R = -H$).

The synthesis of the APhTz derivative **1a**, consisted in the reaction of acetophenone with thiourea and iodine [7]. The reaction mixture was stirred and heated to 120 °C in a thermostated oil bath for 8 hours. After completion of the reaction, the mixture was cooled to 70 °C and then triturated, filtered and washed with Et₂O. The crude product was dissolved in hot water and the pH was brought to 11 with NH₄OH. The precipitate was filtered and crystallized from EtOH-H₂O (1: 4) to obtain **1a**. Its characterization was carried out by infrared spectroscopy (IR), in an AGILENT CARY 630 FTIR spectrometer, and also using the technique of nuclear magnetic resonance (¹³C-NMR) and (1H-NMR). The APhTz derivative **1b** was supplied by the SIGMA brand ALDRICH.

2.2. Electrochemical study

A single cell with a three-electrode arrangement was used, using a working electrode of vitreous carbon with an area of 0.07 cm², and a steel wire as an auxiliary electrode. A silver wire was used as a reference electrode. The working electrode was polished before each electrochemical measurement, with an aqueous paste of alumina (0.05 μm). 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 of tetraethyl ammonium tetrafluoroborate (TEABF₄) 0.1 M in dimethyl-sulfoxide (DMSO), tetrabutylammonium hexafluoro-phosphate (TBAPF₆) 0.1 M also in 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 brand Autolab model PGSTAT128N connected to a personal computer for the acquisition and storage of data. The measurements were made in cathode scanning, from -1.16 to -2.46 V. In addition, experiments were carried out at different scanning speeds ($0.1 < v < 1.0 \text{ Vs}^{-1}$). The processing of the data was done through the OriginPro 8.0 program.

3. Results and discussion

3.1. Synthesis of 2-amino-4-(4-R-phenyl)thiazole (1a, $R = -H$).

A yield of 88% was obtained with melting point of 144 °C. By means of FTIR spectroscopy, were observed the valence vibrations NH characteristics of the NH₂ group (3433 cm⁻¹ and 3248 cm⁻¹), the aromatic overtone indicating the monosubstitution in the phenyl ring (771 cm⁻¹) and the vibrations of bonds of the thiazolic ring (1596 cm⁻¹ and 1201 cm⁻¹). In the ¹HNMR spectrum (data not shown) the characteristic signals of the 8 protons present in the molecule were observed, where the multiplicity of the signals can be analyzed, which are: two singlets corresponding to the hydrogens of the amino group and Adjacent to the sulphur 7.81 - 7.91 (s, 2H, NH₂), two triplets corresponding to the geometrically equivalent hydrogens of the phenyl having 2 neighboring hydrogens, and a doublet which is justified by the unique hydrogens of the phenyl, which have only one hydrogen in their immediate vicinity 7.64 (d, 1H, J = 8.36 Hz). Another important factor to analyze is the integral obtained, ie the area under the curve that is proportional to the number of hydrogens giving the signal, the sum of said values give a total of 9, which corresponds to the total hydrogens number of the

compound of interest. In the ^{13}C NMR spectrum the 7 different signals expected for the carbon nuclei were evidenced.

3.2. Electrochemical study

The voltammetric response of 4-(4-R-phenyl) -2-aminothiazole (**1b**, R = -NHCOCH₃) in DMSO is shown below with TEABF₄. From Figure 1, it was possible to infer that the I_c wave (EpI_c = -2.08 V) corresponds to the reduction of the compound structure [11-12].

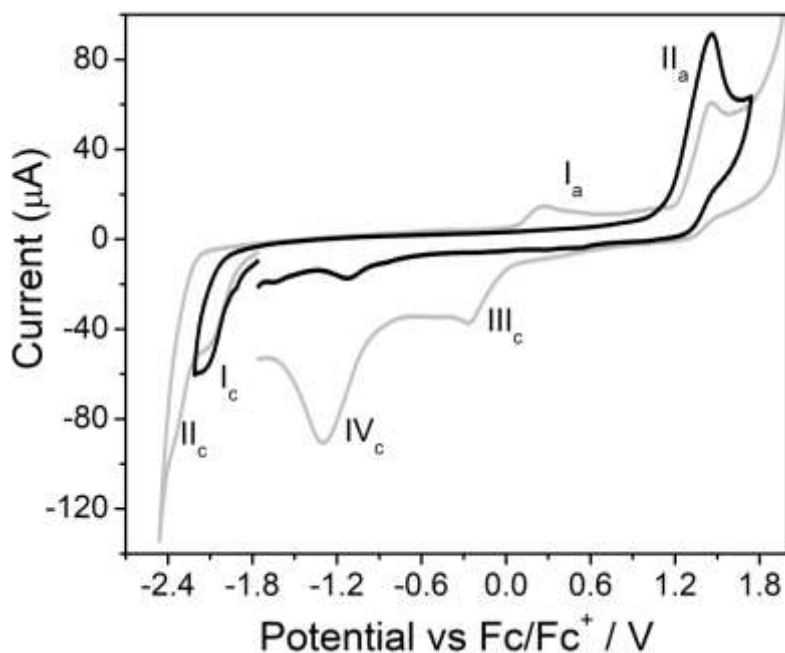


Figure 1. Cyclic voltamperogram of 3 mM 4-(4-R-phenyl) -2-aminothiazole (R = -NHCOCH₃) in DMSO + 0.1 M TEABF₄. With E_f -2.46 V and E_λ -2.16, v = 0.1 Vs⁻¹.

On the other hand, wave II_c (EpII_c = -2.33 V) is probably due to an electron transfer of the electrogenerated product in the I_c wave [13-15]. By reversing the potential sweep, the wave I_a corresponding to the oxidation process of the product formed in wave II_c, and the oxidation of the primary amino group of compound **1a** which is reflected in wave II_a (EpII_a = 1.45 V). Additionally, wave III_c and IV_c are probably due to reduction processes of the electrogenerated chemical species in the oxidation wave II_a. When the potential is reversed (E = -2.16 V) just after the reduction wave I_c and before process II_c, the first oxidation wave I_a disappears, and process II_a prevails and increases its current intensity. This is due to a greater concentration of parent compound species that are reduced on the surface of the electrode. Interestingly the processes III_c and IV_c were also inhibited during this procedure. This may mean that certain intermediates and associated processes are responsible for this phenomenon. The above is indicative of signal dependence. The voltammetric response **1a** was similar to that shown by the derivative **1b**.

A study of the electrochemical reduction of both compounds at different potential scanning speeds revealed the irreversible nature of both I_c and II_c waves. On this occasion only the result obtained for derivative **1b**, (Figure 2) is shown.

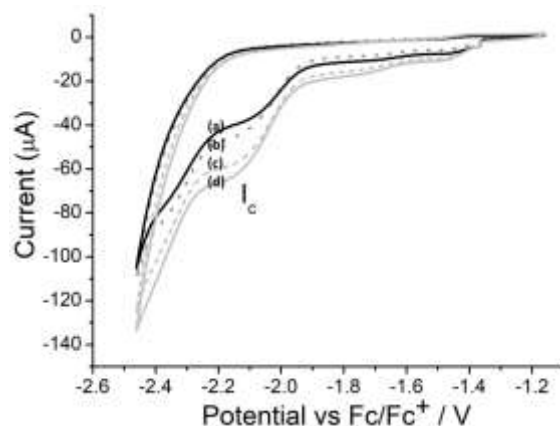


Figure 2. Cyclic voltamperograms at different scanning rates for 3 mM **1b** 4-(4-R-phenyl) -2-aminothiazole (R = -NHCOCH₃) in DMSO + 0.1 M TBAPF₆, (a) 0.07, (b) 0.08, (c) 0.09 and (d) 0.1 Vs⁻¹

In a small range of scanning speeds, the reduction signal I_{lc} practically disappears with increasing speed and apparently moves to less negative potential values, contrary to what happens with the signal I_c that moves to more negative values of potential.

Figure 3, shows the increase of the peak current I_c and also in I_{lc}, as consequence of the change in the support electrolyte.

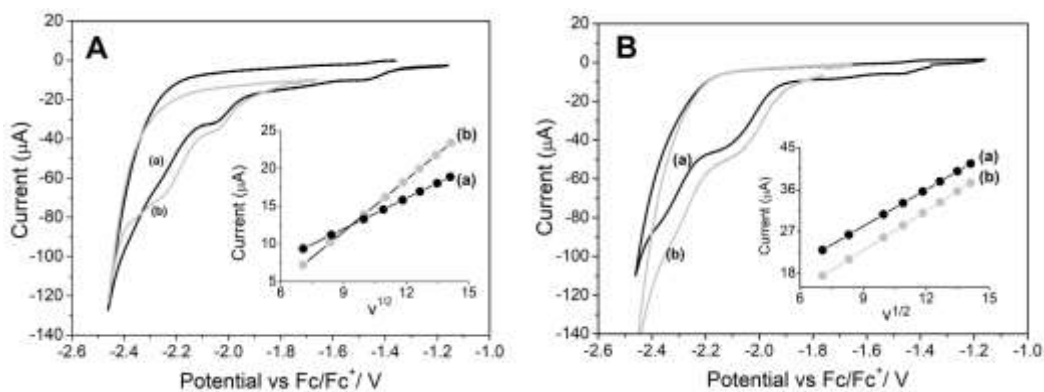


Figure 3. Cyclic voltamperogram A. 1a, R = -H and B. 1b, R = -NHCOCH₃ at 0.1 Vs⁻¹ (a) (TBAPF₆) and (b) (TEABF₄)

It was observed that a larger salt such as TBAPF₆ causes a decrease in the intensity of peak reduction currents, contrary to what was shown by a smaller salt such as TEABF₄ (Figures 3a and 3b). Also for both compounds, the cathodic peak potential of wave I_c and I_{lc} is influenced by the effect of the size of salt used. A smaller salt favoured the electrochemical reduction of both heterocyclic compounds.

It was observed that the potential required for the reduction of the compounds according to figure 4 is less negative for the compound without substituent **1a** compared to the substituent compound **1b** which has character electrodonator. It is an evidence of the effect of the substituent (*para*- in the benzene relative to the heterocyclic ring) on the process of reduction of these compounds. The values reported in Table 1 show the effect of the substituent and the size of the salt in the electrochemical reduction of the compounds. The peak current values are higher for compound **1b** than **1a**. This

behaviour is very interesting since, as we know, the current is dependent on the number of electrons, concentration and diffusion coefficient of the compound, since the other parameters are constant. Therefore, a possible explanation for this result is that the diffusional parameter for compound **1b** was higher. This can be inferred from the Randles-Sevcik equation [16].

Table 1 Voltammetric Data Obtained from reduction electrochemical of 2-Amino-4-(4-R-phenyl)thiazoles, wave Ic

	-R	E_{pIc}/V^a	$I_{pIc}/\mu A$	$D \times 10^{-6}$	αn_{α}	$\left(\frac{\Delta I_p}{\Delta \sqrt{v}}\right)$	$\left(\frac{\Delta \log(I_p)}{\Delta \log(v)}\right)$	$\left(\frac{\Delta E_p}{\Delta \log(v)}\right)$
1a	-H	- 2,04 (- 2,05) ^b	12,8 (11,8)	3,17 (1,11)	0,66 (0,60)	32,2 (19,0)	0,78 (0,53)	0,045 (0,050)
1b	-NHCOCH ₃	- 2,08 (- 2,12)	24,7 (30,3)	4,21 (4,70)	0,49 (0,35)	37,1 (39,2)	0,55 (0,45)	0,061 (0,085)

^a $v = 0.1 \text{ Vs}^{-1}$, ^b Data in parentheses for TBAPF₆.

Figure 3, shows the behaviour of the peak current of the wave Ic with respect to $v^{1/2}$. From Figure 3 and Table 1, it was evidenced that the smaller the electrolyte size, the diffusional character increases, as could be observed in the value of the slopes [17]. At a smaller electrolyte size, it was observed that the value of intercept was lower for derivative **1b** than the derivative without substituent **1a** as the electrolyte was larger, the result was the opposite. This supposes that the electronic transfer is associated to complications of the chemical type or adsorption. The values of the slope, in **1b** were higher than those obtained for **1a**, indicating that the diffusion coefficient would have a higher value than for the substituted derivative.

The adsorbent character of **1a** and **1b** derivatives on the glassy carbon electrode was identified from the dependence of the peak current of the wave Ic with the potential sweep velocity (v). Graphs of $\log i_p$ vs $\log v$, resulted in straight lines whose values were less than the theoretical value of 1.0 expected for an ideal surface species reaction, see Table 1. For the first wave Ic The slope (0.78) obtained in the $\log(I_{pIc})$ vs $\log(v)$ graph was lower than the theoretical one and probably because the general electrode process could be mainly diffusion controlled with Adsorption of the electrogenerated products from **1a** on the surface of the electrode. The data in Table 1 suggest that the adsorption of the derivative **1a** relative to **1b** was adsorbed in the electrochemical reduction process. An analysis of the dependence of the peak potential of the Ic wave with respect to the variation of the potential sweep speed indicated a controlled diffusion of the system of irreversible nature [18], where the potential is given by:

$$\ln E_p = E^o - \left(\frac{RT}{\alpha n_{\alpha} F}\right) \left[0.78 - \ln \frac{k^o}{D^{\frac{1}{2}}} + \ln \left(\frac{\alpha n_{\alpha} F v}{RT}\right)^{\frac{1}{2}}\right] \quad (1)$$

Where α is the cathodic charge transfer coefficient, n_{α} is the number of electrons involved in the speed determining step, D is the diffusion coefficient and k^o is the standard rate constant of the electrochemical reaction. In Table 1, the data obtained from E_{pIc} vs. $\log v$ for derivatives **1a** and **1b**, which was linear where the potential change was observed towards more negative values with increasing scanning speeds of potential, behaviour that is consistent with an EC mechanism, where the electronic transfer is coupled with a chemical reaction [19].

The αn_{α} value was calculated from the slope of the graph between E_{pIc} and $\log v$. In most irreversible cases, α is in the range of 0.30 to 0.70, so it is likely that the number of electrons transferred in the Ic wave is 1.

Finally, protonator additions were made, Figure 4, to demonstrate its effect on the electrochemical reduction process that occurs in waves Ic and IIc.

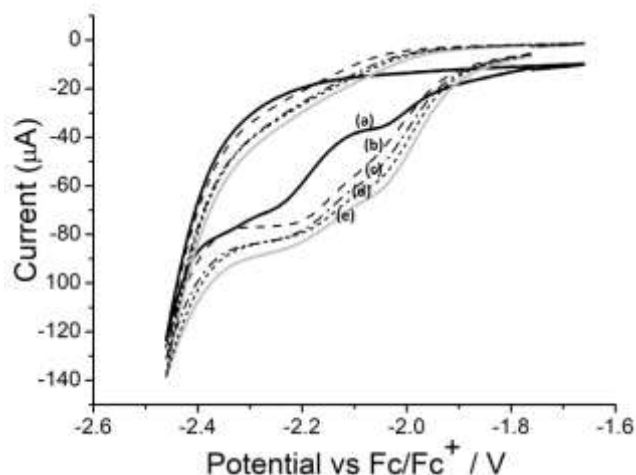


Figure 4. Cyclic voltamperograms at different scanning rates for 3 mM 4-(4-R-phenyl) -2-aminothiazole **1b**, in DMSO + 0.1 M TBAPF₆, (a) 0.07, (b) 0.08, (c) 0.09 and (d) 0.1 Vs⁻¹

From figure 4, it was observed that the addition of a protonator in the solution of **1a** with TEABF₄ shows the reduction signal I_{lc} to move towards less negative potential values. This is due to interfacial acidity changes and association processes between the electrogenerated intermediate in the I_c wave and the water molecules, whose concentration in the solvent increases, which is an evidence of the basic character of the same.

4. Conclusions

In this work the electrochemical reduction signal of 2-amino-4-phenylthiazole derivatives was evidenced. This is an opportunity to expand the information related to the behavior of these compounds. The results of the electrochemical reduction study show that the substitution change influenced the electrochemical behavior, evidencing that a substituent, 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. Peak potential shifted to more negative values as the potential sweep speed was higher. This was indicative of irreversible behavior in this signal.

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