Electrochemical reduction of 2-nitroimidazole in aprotic medium: Influence of its dissociation equilibrium on the reduction mechanism

J.A. Squella [a,*], A. Campero [b], J. Maraver [b], J. Carbajo [b]

[a] *Bioelectrochemistry Laboratory, Chemical and Pharmaceutical Sciences Faculty, University of Chile, POB 233, Olivos 1007, Santiago, Chile*
[b] *Departamento de Ingeniería Química, Química Física y Química Orgánica, Facultad de Ciencias Experimentales, Universidad de Huelva, Huelva, Spain*

Abstract

The electrochemical reduction of 2-nitroimidazole in a non-aqueous medium using cyclic voltammetry (CV) at a mercury electrode was carried out.

The 2-nitroimidazole derivative in DMF + 0.1 M tetra(*n*-butyl)ammonium hexafluorophosphate (TBAHFP6) resulted in the following dissociation equilibrium:

$HNRNO_2 \leftrightarrows {}^{-}NRNO_2 + H^{+}$

The neutral species ($HNRNO_2$) and the corresponding conjugate base ($^{-}NRNO_2$) are characterized by UV absorption bands at 328 and 370 nm, respectively.

The voltammograms of 2-nitroimidazole produced two well-defined signals, which were determined by the above dissociation equilibrium. The first reduction peak was caused by the reduction of the neutral species according to the following overall mechanism:

$5HNRNO_2 + 4e^{-} \rightarrow 4\,{}^{-}NRNO_2 + HNRNHOH + H_2O$

The second quasi-reversible couple was caused by the reduction of the conjugate base according to the following equation:

${}^{-}NRNO_2 + e^{-} \rightarrow NRNO_2^{\bullet -}$

Keywords: 2-Nitroimidazole; Cyclic voltammetry; Electro-reduction

1. Introduction

Nitroimidazolic compounds display a wide range of biological activities, mainly their use as radiosensitizers, antibacterial and antiprotozoans drugs. Their use as radiosensitizers takes advantage of their cytotoxicity in hypoxic mammalian cells, increasing sensitivity to the radiation of cancerigenic tumors [1–4]. Their antimicrobial characteristic takes advantage of their selective toxicity towards anaerobic microorganisms, permitting their extensive use in the treatment of infectious diseases [5–11].

According to the position of the nitro substituent in the imidazolic ring, it is possible to classify the nitroimidazolic derivatives as 2-, 3- and 4-nitroimidazolic derivatives (Fig. 1). In relation to their biological activity, 2-nitroimidazolic derivatives are preferably used as radiosensitizers, while 5-nitroimidazolic derivatives are mainly used because of their toxicity towards microorganisms and 4-nitroimidazolic derivatives are relatively more inert [12]. However, the descriptions of the mutagenic and carcinogenic properties of some 2- and 5-nitroimidazole derivatives have also increased the interest in minor mutagenic 4-nitroimidazoles [13,14]. Although the nitro reduction is crucial for any biological activity, there are still no conclusive results about the incidence of the nitro position in their biological activity.

* Corresponding author. Tel.: +56 2 9782927; fax: +56 2 7371241.
E-mail address: asquella@ciq.uchile.cl (J.A. Squella).

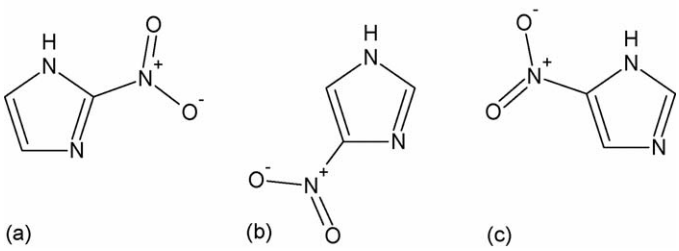

Fig. 1. Molecular structure of the isomers: (a) 2-nitroimidazole; (b) 4-nitroimidazole (tautomer); (c) 5-nitroimidazole (tautomer).

There are numerous studies aiming at the electrochemical aspects of nitroimidazolic compounds. Nevertheless, those works are mostly focused on the electroanalytical determination of some 5-nitroimidazoles of importance in medicine such as: metronidazol [15], ornidazol [16], secnidazol [17], tinidazol [18] and megazol [19]. In addition, cyclic voltammetry has been used in the study of nitro radical anions generated by 5-nitroimidazoles such as misonidazol, metronidazol and megazol [20–24]. These studies demonstrated the utility of cyclic voltammetry (CV) for the study of the formation and stability of nitro radical anions.

The studies of 4-nitroimidazole derivatives are restricted to a couple of works. The first report in the 1980s was done by Roffia et al. [25]. In that study, the voltammetric behavior of 4-nitroimidazole in an aprotic medium was presented. Two reduction peaks were displayed using CV. The first peak was irreversible, whereas the second was reversible. The first irreversible peak was attributed to the following global reaction:

$$5HRNO_2 + 4e^- \rightarrow HRNHOH + 4RNO_2{}^- + H_2O \quad (1)$$

The second reversible peak was attributed to Eq. (2):

$$RNO_2{}^- + e^- \leftrightarrows RNO_2{}^{2-} \quad (2)$$

From that study, it was concluded that the nitro radical anion decays fast because of a protonation reaction by the proton acid of the initial 4-nitroimidazole (father–son reaction).

Furthermore, the electrochemical behavior of 4-nitroimidazole was also exhaustively studied in a protic medium using a wide pH scale [26]. The results in a protic medium were substantially different from those previously described for aprotic medium, since they showed that the reduction of 4-nitroimidazole produced stable nitro radical anion within the time scale of the CV, which had not been possible in the aprotic medium. The nitro radical anion decayed according to a disproportionation reaction wherein the disproportionation constants (k_2) were calculated according to a CV approach. The disproportionation constants relied strongly on both pH and co-solvent content.

The electrochemical studies about the 2-nitroimidazole derivative are scarce and are restricted almost exclusively to a study where its electrocatalytic reduction on gold and modified gold electrodes is described [27]. The mechanism described in that report involved two different routes in acid medium, an electrocatalytic and an electronic interchange. There were no references in that study to the formation of radical intermediates. Moreover, it does not exist studies in the literature that demonstrate the reduction mechanism of 2-nitroimidazole.

Thus, the lack of electrochemical investigation in relation to 2-nitroimidazole and the importance of its reduction in medical applications have prompted us to carry out a study with the purpose of contributing to its basic REDOX understanding.

2. Experimental

2.1. Reagents and solutions

2-Nitroimidazole and 4-nitroimidazole (Fig. 1a), 97% pure, were obtained from Aldrich Chem. Co., and were used without prior purification. All the other reagents employed were of analytical grade. Nitrogen gas was obtained from ALPHAGAZ-AIR LIQUIDE with maximum impurities of $H_2O < 3$ ppm; $O_2 < 2$ ppm; $C_nH_m < 0.5$ ppm.

All the voltammetric experiments were obtained after bubbling with N_2 for 10 min in the cell before each run. Temperature was kept constant at 25 ± 0.1 °C in all experiments.

Solutions for cyclic voltammetry were prepared starting from a 0.2 M stock solution of the nitroimidazole derivative in DMF daily prepared. Final solutions in the voltammetric cell were prepared by diluting an appropriate quantity of the stock solution in order to obtain a final concentration of 1 mM.

Experiments in aprotic medium were made in DMF with 0.1 M tetra(*n*-butyl)ammonium hexafluorophosphate (TBAHFP6) as supporting electrolyte.

2.2. Apparatus and methods

Voltammetric curves were recorded on an Electrochemical Analyzer type BAS 100B/W (Bioanalytical System) attached to a PC computer with appropriate software (BAS 100W 2.3 for Windows) for total control of the experiments and data acquisition and treatment. A static mercury drop electrode (SMDE) (BASi EF-1400) with mercury drop area of 0.43 mm^2 was used as the working electrode and a platinum wire (BASi MW-1032) as the counter electrode. All potentials were measured against Ag|AgCl|NaCl (3 M) (BASi MF-2052).

Controlled potential electrolysis (CPE) was carried out at constant electrode potential (−1.1 or 2.0 V) on a mercury pool electrode. Oxygen was removed with pure and dry pre-saturated nitrogen. A three-electrode circuit with an Ag|AgCl|NaCl (3 M) electrode was used as reference and platinum wire as a counter electrode. A BAS-CV 50 assembly was used to electrolyze the 2-nitroimidazole solutions.

UV–vis spectra were recorded in the 200–600 nm range, using an UNICAM UV-3 spectrophotometer.

Temperature was controlled with a Thermostat/cryostat SELECTA Frigiterm-10, resolution of 0.1 °C.

3. Results and discussion

2-Nitroimidazole was reduced in a non-aqueous medium containing 0.1 M TBAHFP6 in DMF when it is subjected to a cyclic voltammetric (CV) experiment on Hg surface. As observed in

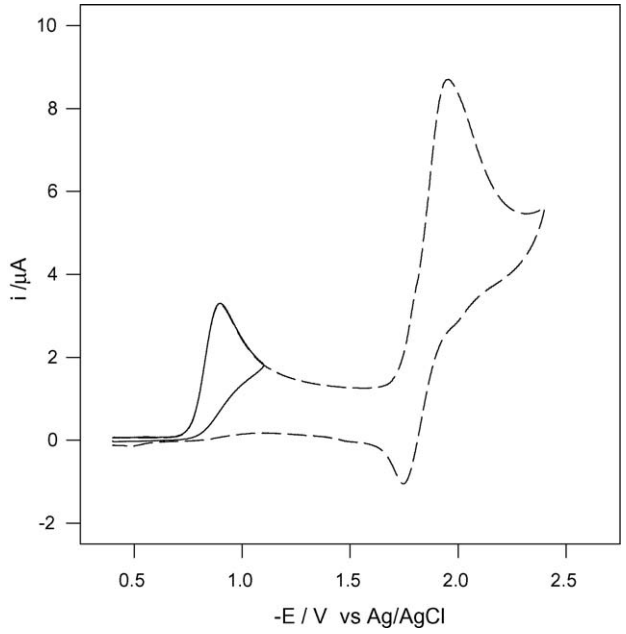

Fig. 2. Cyclic voltammograms (dotted line = large sweep and whole line = short sweep) of 1 mM 2-nitroimidazole in DMF, 0.1 M TBAHFP6. $v = 0.5$ V/s.

Fig. 2, two cathodic peaks are displayed. The first peak has a cathodic peak potential, E_{pc}, of −0.9 V and the second one an E_{pc} of −1.96 V, at a sweep rate of 0.5 V/s. The last of these peaks shows an apparently reversible behavior, since the corresponding anodic peak is observed in the anodic sweep with an E_{pa} of −1.76 V. With the aim to study the voltammetric behavior at different time scales of the experiment, measurements were made at different sweep rates (Fig. 3). From the voltammograms shown in Fig. 3, the difference between cathodic and anodic peak potentials, ΔE_p, for the apparently reversible couple exceeds the theoretical value of 0.060 V for a one-electron reversible

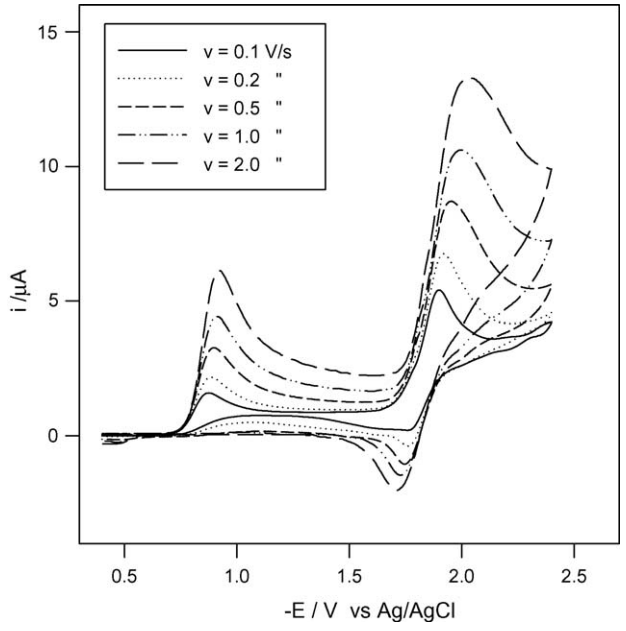

Fig. 3. Cyclic voltammograms of 1 mM 2-nitroimidazole in DMF, 0.1 M TBAHFP6 at different sweep rates.

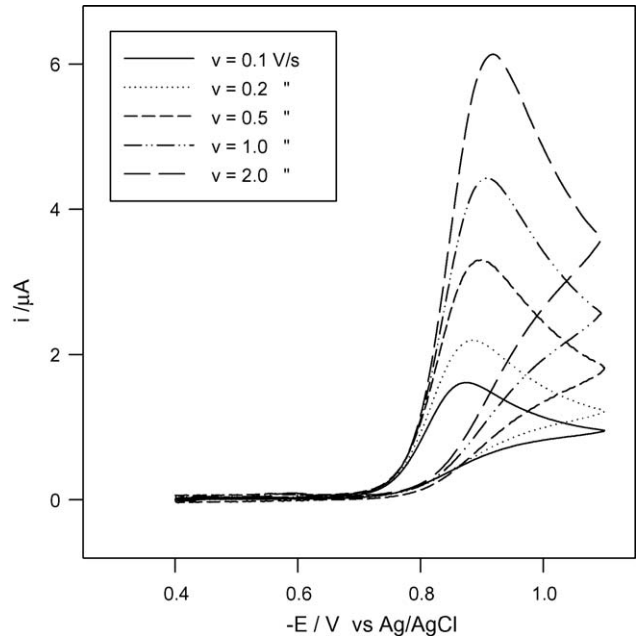

Fig. 4. First peak cyclic voltammograms of 1 mM 2-nitroimidazole in DMF, 0.1 M TBAHFP6 at different sweep rates.

process. This difference increases considerably with the sweep rate changing from approximately 0.12 V at the slowest rate to approximately 0.38 V at the fastest rate. This result led us to discard the reversibility of this wave since in fact the involved electron transfer would obey to a quasi-reversible process.

Cyclic voltammograms of the isolated first peak at different sweep rates are shown in Fig. 4. In addition, the data corresponding to the current intensities and the peak potentials of the first cathodic peak are shown in Table 1. From these data we obtained a linear relation between the cathodic peak current and the logarithm of the sweep rate with a slope of 0.45 as shown in the plot of Fig. 5a. This slope value is indicative of a diffusion-controlled process since it is near the theoretical value of 0.5 for this type of process. In Fig. 5a, on the other hand, a linear dependence between the peak potentials of the first cathodic peak and the logarithm of the sweep rate with a slope of 0.033 V is shown. From both plots in Fig. 5 we conclude that the first peak would obey to a diffusion controlled process wherein a slow one-electron process is followed by a first fast chemical reaction according to the following reaction scheme:

$$HNRNO_2 + e^- \rightarrow HNRNO_2^{\bullet -} \quad (3)$$

$$HNRNO_2^{\bullet -} \rightarrow \text{product} \quad (4)$$

Table 1
Current and potential values from the first peak obtained from CV of 1 mM 2-nitroimidazole in DMF, 0.1 M TBAHFP6 at different sweep rates

v (V/s)	log(v) (V/s)	i_{pc} (µA)	$-E_{pc}$ (V)	log(i_{pc}) (µA)
0.1	−1.00000	1.563	0.875	0.19396
0.2	−0.69897	2.13	0.885	0.32838
0.5	−0.30103	3.196	0.901	0.50461
1.0	0.00000	4.332	0.909	0.63669
2.0	0.30103	6.034	0.918	0.78061

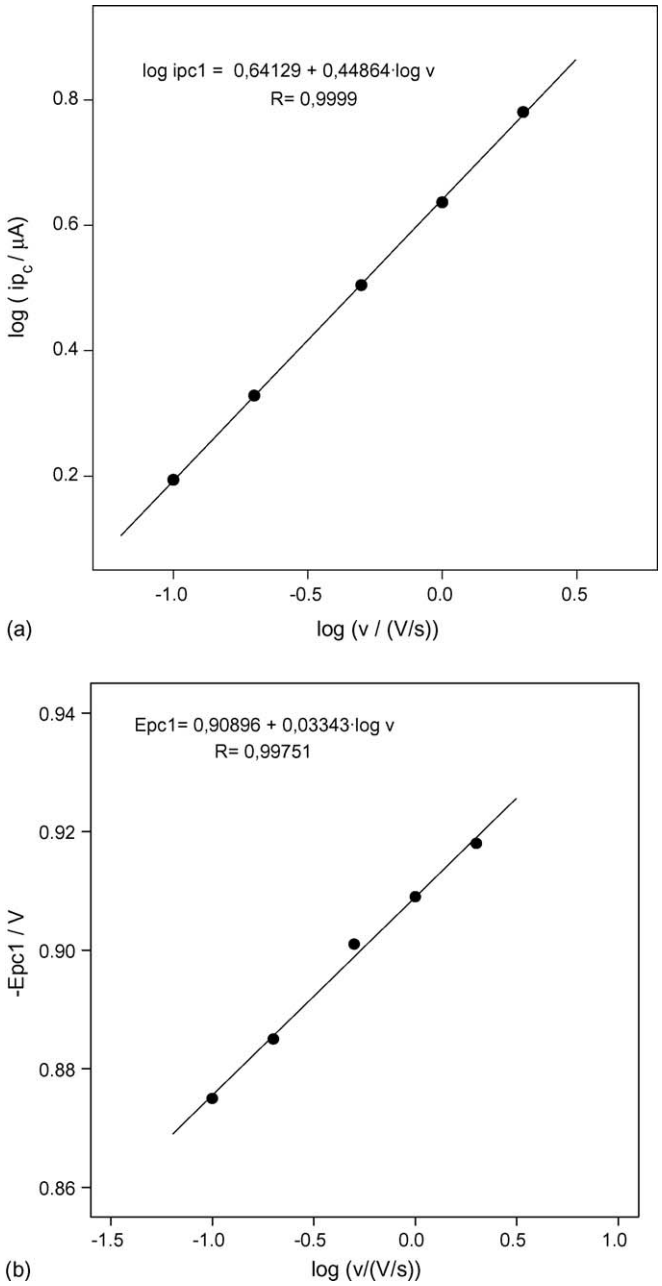

Fig. 5. (a) log i_{pc} vs. log v and (b) E_{pc} vs. log v, of the first peak of the reduction of 2-nitroimidazole in DMF with 0.1 M TBAHFP6. $C^0 = 1$ mm.

wherein $HNRNO_2$ represents the neutral species of 2-nitroimidazole and $HNRNO_2^{\bullet -}$ represents its radical anion.

This reaction scheme corresponds to a coupled process wherein the radical anion produced in the first step (Eq. (3)) decays chemically in a second step (Eq. (4)). As the chemical step is fast compared with the one-electron transfer, no back oxidation of the radical anion will be possible, thus the shape of the first peak will be irreversible (no anodic peak). However, there are several possibilities for the chemical decay of the radical anion, i.e. protonation, dimerization, dismutation or father–son reactions. Consequently, our next step will be to find the nature of the decay reaction.

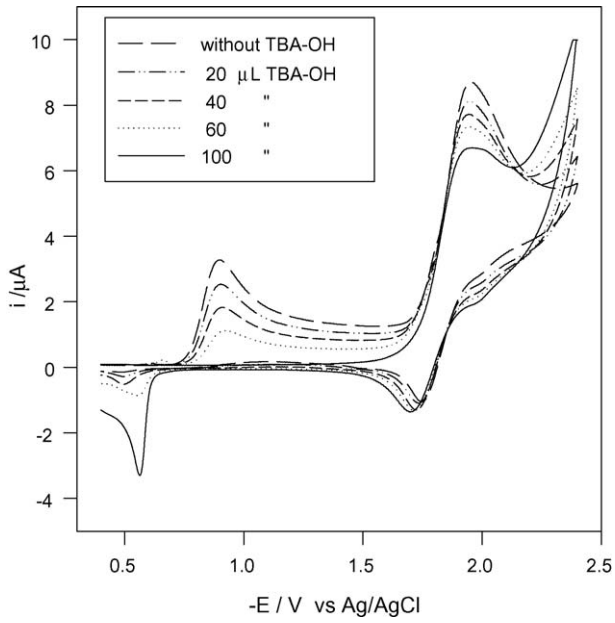

Fig. 6. Cyclic voltammograms of 1 mM 2-nitroimidazole in DMF, 0.1 M TBAHFP6 with different quantities of 0.1 M TBA-OH added. $v = 0.5$ V/s.

2-Nitroimidazole is a heterocyclic ring with two N atoms wherein one of them (N1) is linked to an H atom, which can act as a proton donor. On the other hand, the other N (N3) can act as a proton acceptor. Consequently, the molecule can act as acid or base, in such way that a dissociation equilibrium can affect its voltammetric behavior. Fig. 6 shows the effect of adding different quantities of a base as tetrabutyl ammonium hydroxide (TBA-OH) on a solution containing 1 mM of 2-nitroimidazole. From this figure, we observe that the addition of a base produces a decrease in the first cathodic peak, which means a decrease in the concentration of the initial reactant. Obviously, this result supports the existence of a dissociation equilibrium wherein probably the H linked to the N1 shows an acid behavior. If the hypothesis of a dissociation equilibrium is correct, the subsequent addition of an acid, to the previously alkalinized solution, would produce the reversion of the equilibrium to the initial condition. As observed in Fig. 7, the addition of an acid as $HClO_4$ (in ethanol) over the previous alkalinized solution produced the reversion of the reaction toward the regeneration of the electroactive species responsible for the first cathodic peak thus confirming the existence of dissociation equilibrium. The equilibrium can be represented by the following equation:

$$HNRNO_2 \leftrightarrows {}^{-}NRNO_2 + H^{+} \quad (5)$$

wherein the nitranion species $^{-}NRNO_2$ represents the conjugate base formed as a consequence of the loss of the weakly acid proton on the N1 of the neutral $HNRNO_2$ species in the alkalinized solution. The pK_a for 2-nitroimidazole in DMF have not been described but a value of 7.15 was informed for the pK_a of 2-nitroimidazol in a mixture CH_3OH–water, 1:1 [28]. So, considering this equilibrium we can explain both peaks for the reduction of 2-nitroimidazole. The electroactive species producing the first cathodic peak corresponds to the neutral

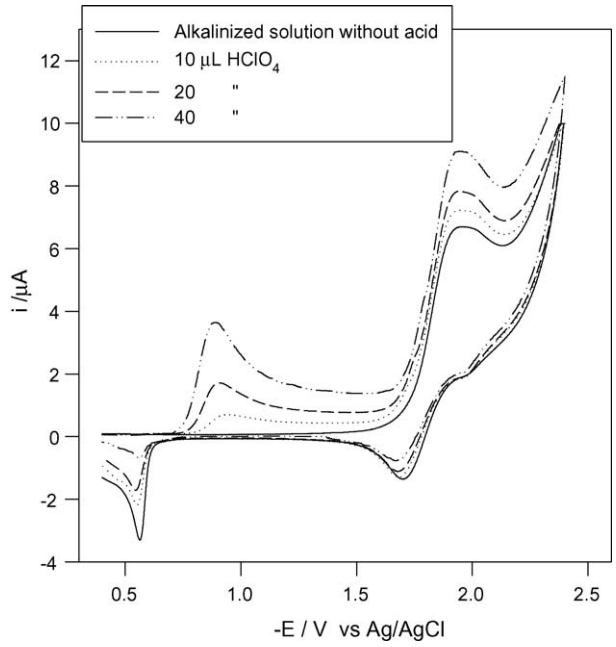

Fig. 7. Cyclic voltammograms of an alkalinized solution (100 µl of 0.1 M TBA-OH) of 1 mM 2-nitroimidazole in DMF, 0.1 M TBAHFP6 with different quantities of 0.2 M $HCLO_4$ (in ethanol) added. $v = 0.5$ V/s.

species $HNRNO_2$ and the electroactive species producing the second quasi-reversible couple corresponds to the conjugate base $^{-}NRNO_2$. The generation of this type of stable nitranion species has been also described for other nitrogen heterocycles in aprotic medium [29].

As can be appreciated from the voltammograms of Figs. 2, 3, 6 or 7 there are big differences between the reduction potential of both peaks (approximately, 1.0 V), meaning that the $HNRNO_2$ species is substantially more easily reducible than its corresponding nitranion. In the case of the nitranion, this difference can be explained by its negative center of charge that is localized very near the site of entrance of the electron, thus hindering its reduction.

According to the above experimental evidences, we can summarize that the first reduction peak is due to the above-mentioned Eqs. (3) and (4) and the second one by the following equation:

$$^{-}NRNO_2 + e^{-} \rightarrow \ NRNO_2^{\bullet -} \qquad (6)$$

where the nitranion species of the 2-nitroimidazole is reduced to the corresponding dianion radical (radical anion of the nitranion), which is oxidized in the reverse sweep in a quasi-reversible process. The heterogeneous electron transfer rate constant was calculated by CV from the variation of the ΔE_p values at different sweep rates according to the theoretical curve described by Nicholson [30]. We have obtained a heterogeneous electron transfer rate constant, k_{het}, of $(1.24 \pm 0.013) \times 10^{-3}$ cm/s for the quasi-reversible reduction of the nitranion.

On the other hand, in the case of the radical anion generated in the first reduction peak (according to the above Eq. (3)) it has a sufficiently basic character to interact with the initial reactant, $HNRNO_2$, generating the following father–son reaction:

$$HNRNO_2 + HNRNO_2^{\bullet -} \rightarrow \ HNRNO_2H^{\bullet} + {}^{-}NRNO_2 \qquad (7)$$

where the sufficiently basic radical anion species ($HNRNO_2^{\bullet -}$) deprotonates the initial reactive ($HNRNO_2$), generating the protonated radical ($HNRNO_2H^{\bullet}$) and the nitranion species ($^{-}NRNO_2$). Obviously, the occurrence of the above reaction (7) explains the irreversible character of peak 1 because the formed radical anion reacts more easily with the parent compound than its possible oxidation in the reverse sweep, thus not producing the corresponding anodic peak.

Furthermore in order to prove the existence of the above Eq. (7) we have carried out experiments of controlled potential electrolysis (CPE) and then track both the consumption of the parent compound $HNRNO_2$ and the formation of the nitranion. In Fig. 8a, we show the cyclic voltammograms recorded before and after the CPE carried out at a controlled potential of −1.1 V. From this experiment, it is clear that the electrolytic process consumed all the electroactive specie responsible for the first cathodic peak. Moreover we have compared the UV spectra maxima of 2-nitroimidazole in DMF solution in order to show the similarity between the effect of both to alkalinize or to electrolyze the solution. According to the UV spectra in Fig. 8b, it is possible to distinguish two different absorption maxima for the initial solution of 2-nitroimidazole in DMF. The neutral species ($HNRNO_2$ according to Eq. (5)) shows a maximum at 328 nm and the conjugate base (the nitranion according to Eq. (5)) shows a shoulder at 370 nm. This result is in accord with the previously reported by Gallo et al. [28] wherein absorption bands at 372 nm (conjugate base) and 325 nm (neutral molecule) were informed for 2-nitroimidazole solutions. Furthermore, Fig. 8 shows the comparative spectra of both alkalinized and electrolyzed solutions of 2-nitroimidazole. The comparison shows that both procedures, addition of a base and electrolysis, produced the same effect i.e. the vanishing of absorption at 328 nm and the enhanced absorption at 370 nm. In the case of the electrolysis the explanation for this fact is that electrolysis produced the reduction of the initial $HNRNO_2$ (vanishing of 328 nm band), generating the radical anion, which is sufficiently basic to deprotonate the parent compound generating the nitranion derivative (increase of the 370 nm band) according to the above Eq. (7). Consequently, the above experiments support the occurrence of a father–son type reaction as the chemical reaction following the electron transfer, obeying the following scheme:

$$HNRNO_2 + e^{-} \rightarrow \ HNRNO_2^{\bullet -} \qquad (3)$$

$$HNRNO_2 + HNRNO_2^{\bullet -} \rightarrow \ HNRNO_2H^{\bullet} + {}^{-}NRNO_2 \qquad (7)$$

In order to obtain only stable products in the overall reaction and also based on previous evidences [31], where nitroso and hydroxylamine derivatives are intermediates or products in the reduction of nitro compounds, it is possible to postulate the following steps (8) and (9) and thus originate the following mechanism to explain the cathodic peak 1:

$$HNRNO_2 + e^{-} \rightarrow \ HNRNO_2^{\bullet -} \qquad (3)$$

$$HNRNO_2 + HNRNO_2^{\bullet -} \rightarrow \ HNRNO_2H^{\bullet} + {}^{-}NRNO_2 \qquad (7)$$

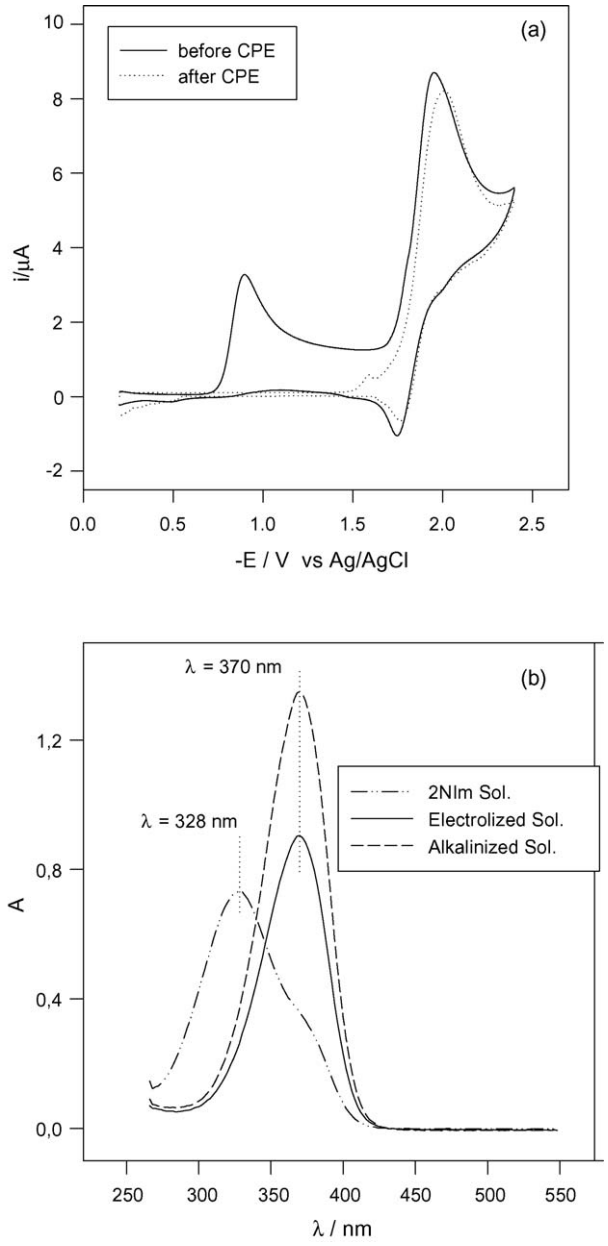

Fig. 8. (a) Cyclic voltammograms of 1 mM 2-nitroimidazole in DMF, 0.1 M TBAHFP6 before (whole line) and after (dotted line) controlled potential electrolysis at −1.1 V. $v = 0.5$ V/s. (b) Comparative UV spectra of 1 mM 2-nitroimidazole in DMF, 0.1 M TBAHFP6 solution and the corresponding alkalinized and electrolyzed solutions.

$$HRNO_2H^{\bullet} + HNRNO_2 + e^- \rightarrow HNRNO + {}^-NRNO_2 + H_2O \quad (8)$$

$$HNRNO + 2HNRNO_2 + 2e^- \rightarrow HNRNHOH + 2^-NRNO_2 \quad (9)$$

the overall reaction being the following Eq. (10):

$$5HNRNO_2 + 4e^- \rightarrow 4^-NRNO_2 + HNRNHOH + H_2O \quad (10)$$

The above overall reaction is in accord with the experimental evidences showing the consumption of the initial reactant ($HNRNO_2$) and the generation of the nitranion derivative ($^-NRNO_2$), furthermore, the proposed mechanism turns out to be analogous to the previously proposed for 4-nitroimidazole by Vianello and co-workers [25].

Moreover, according to the above proposed mechanism, the overall reaction would imply the consumption of 4 electrons for each five molecules of 2-nitroimidazole, consequently, the number of electrons per mol would be a value of (4 e)/(5 mol) = 0.8. In Fig. 9, we show the results of electrolysis at a controlled potential of −1.1 V for concentrations of 1 mM (Fig. 9a) and 4 mM (Fig. 9b) of 2-nitroimidazole in DMF. From Fig. 9a the charge accumulated during the electrolysis was 0.852 C. As we added 10 ml of 1 mM 2-nitroimidazole solution to the electrol-

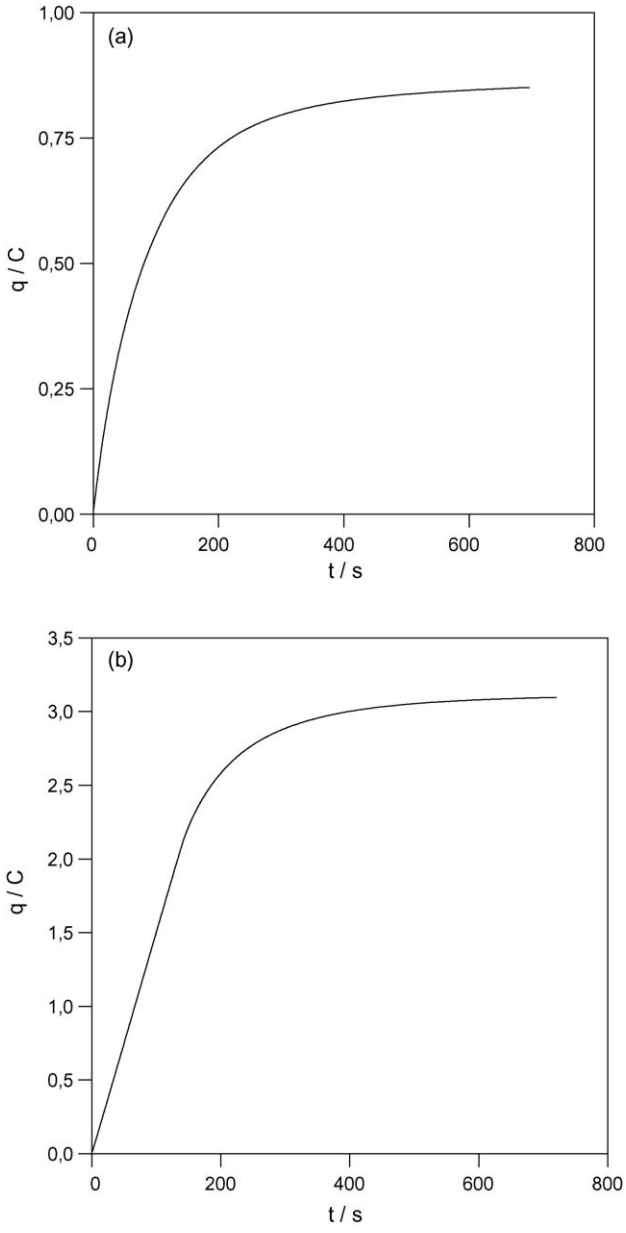

Fig. 9. Controlled potencial electrolysis of: (a) 1 mM and (b) 4 mM, of 2-nitroimidazole in DMF, 0.1 M TBAHFP6. $E = -1.1$ V.

ysis vessel, a value of 0.880 e mol^{-1} was obtained. Similarly, from the results of Fig. 9b, we obtained 0.801 e mol^{-1} of 2-nitroimidazole. Both results reveal a tendency to a value near 0.8, as theoretically predicted for the proposed mechanism, thus confirming this proposal.

On the other hand, CPE carried out at −2.0 V potential causes the disappearance of the first cathodic peak without appreciable modification of the second peak. After disappearance of the first peak, i.e. for $Q > 0.8$ e mol^{-1}, the second peak continues even if electrolysis is continued for long times and the electrolysis current reached a steady-state value, significantly higher than the background. Furthermore we have detected tri-*n*-butyl amine and 1-butene in the electrolyzed solution. All of these aspects suggest that protons would have come from the electrolyte through a Hoffmann degradation.

According to our results, although 2-nitroimidazole differs structurally from 4-nitroimidazole, both molecules follow exactly the same reduction mechanism in non-aqueous medium. However, the energetics of both reduction reactions is different. In Fig. 10 shows comparative CV of equimolar solutions of 2-nitroimidazole and 4-nitroimidazole in DMF plus 0.1 M TBAHFP6. From these voltammograms, it is clear that there is a great difference in the reduction potential of the first cathodic peak, wherein the $HNRNO_2$ species in the 2-nitroimidazole derivative is more easily reduced (approximate difference, 0.3 V) than the corresponding species in the 4-nitroimidazole derivative. This difference is explained because the nitro group in 2-position possesses two electronegative N atoms adjacent, thus diminishing the electronic density on the nitro group. On the other hand, in the case of the second cathodic peak, the reduction peak potential for both 2-nitroimidazole and 4-nitroimidazole are similar, which means that the nitranion species on both derivatives are reduced with similar energy requirements. This

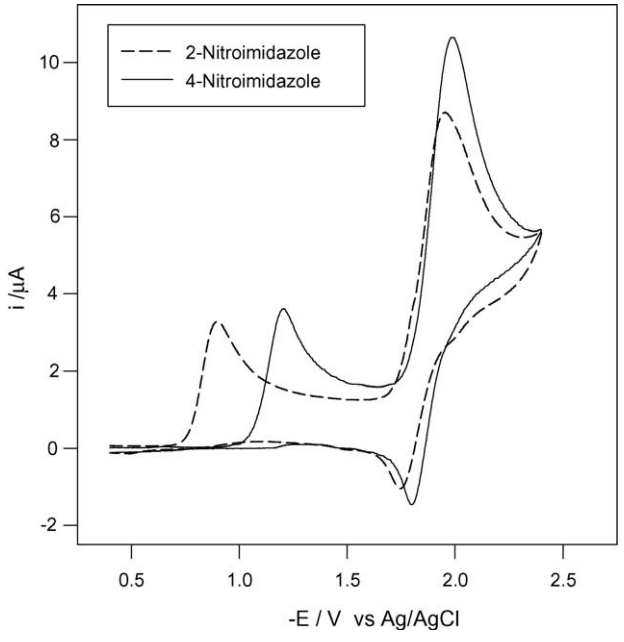

Fig. 10. Cyclic voltammograms of 1 mM 2-nitroimidazole (dotted line) and 4-nitroimidazole (whole line) in DMF, 0.1 M TBAHFP6. $v = 0.5$ V/s.

fact can be explained if we consider that in the case of the nitranion species there is a ionic negative charge on the N(1) whose effect is predominant over the effect caused by the charge densities that accounted for the first peak differences.

4. Conclusions

In the studied medium containing DMF + 0.1 M tetra(*n*-butyl)ammonium hexafluorophosphate (TBAHFP6) the 2-nitroimidazole derivative originates an equilibrium between the neutral species ($HNRNO_2$) and the corresponding conjugate base ($^{-}NRNO_2$) according to the following equation:

$$HNRNO_2 \leftrightarrows {}^{-}NRNO_2 + H^{+}$$

This equilibrium is caused by the ionization of the imino-nitrogen N(1) and determined the electro-reduction mechanism. Furthermore, the $HNRNO_2$ (neutral species) showed an UV absorption maximum at 328 nm and the nitranion $^{-}NRNO_2$ (conjugate base) showed a maximum at 370 nm. The reduction CV of the $HNRNO_2$ species produced an irreversible reduction peak with a cathodic peak potential of −0.9 V versus Ag|AgCl. On the other hand, the CV of the nitranion species ($^{-}NRNO_2$) produced a quasi-reversible couple with a cathodic reduction peak of −1.96 V versus Ag|AgCl and a heterogeneous electron transfer rate constant, k_{het}, of $(1.24 \pm 0.013) \times 10^{-3}$ cm/s.

According to the above results we demonstrated that 2-nitroimidazole follows a similar reduction mechanism that the previously described by Roffia et al. [25] for the 4-nitroimidazole derivative. This is a non-obvious matter because both isomers are structurally different with nitro groups suffering different electronic influences from its neighborhood, aspects that could affect its mechanism. In fact there is not information in the state of the art revealing that 2- and 4-isomers would share a similar mechanism. However, in spite of sharing the same mechanism, both derivatives differ strongly in the energetic of the reaction, being 2-nitroimidazole far more easily reduced than the 4-nitroimidazole derivative, thus confirming that 2-nitroimidazole derivatives are better radiopotentiators than 4-nitroimidazole derivatives.

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