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Electrooxidation mechanism of non-steroidal anti-inflammatory drug piroxicam at glassy carbon electrode

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Abstract

The electrochemical oxidation behavior of the anti-inflammatory drug piroxicam at the glassy carbon electrode in 10% ACN + 90% 0.2 M Britton–Robinson Buffer is presented. Cyclic voltammetry, controlled potential electrolysis and spectroscopic techniques were used to obtain information about the reaction mechanism and product identification. After exhaustive electrolysis, the extraction followed by chromatographic separation of the reaction products gave the oxidized compounds. Using UV–Vis, GC–MS, ^{1}H and ^{13}C NMR techniques as well as the results of our preceding electrochemical investigation, 2-{[(carboxycarbonyl)(methyl)amino]sulfonyl}benzoic acid and 2-aminopyridine were identified. To account for the formation of these products, a detailed interpretation of the mechanism of the electrooxidation of piroxicam in acidic-buffered media was presented.
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1. Introduction

The project that produced the novel anti-arthritic and anti-inflammatory agent piroxicam (Scheme 1) [4-hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide] (Feldene; Pfizer) began in 1962 and led to the product launching into key European markets in 1980.

A detailed history of that 18-year-process, including the failures and setbacks along the way, has been described elsewhere [1]. This drug is the prototype of a class of non-steroidal anti-inflammatory drugs (NSAIDs) that has been named "oxicams" [2,3]. Piroxicam produces a rapid and effective response in the treatment of many diseases such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout juvenile rheumatoid arthritis, muscular skeletal disorders, postpartum pain and sport injuries [3]. The most important side effect that has been reported is gastrointestinal effect (ulcer, bleeding ulcers). Other side effects such as headache, dizziness, skin rashes, palpitations, edema, and tinnitus are less important and infrequent [3,4]. These drugs not only have great pharmacological and therapeutic potential, but also provide interesting chemical/spectral properties by virtue of their dynamic structural features [5–7]. However, with respect to electrochemical behavior of this molecule, only few studies were found in the literature. The first electrochemical study was related to the reduction of piroxicam at mercury pool electrode [8,9]; in the first one, the author gave the electrode reaction mechanism. The products of the reactions were identified using spectroscopic techniques, such as IR, ^{1}H and ^{13}C NMR [8]. In another paper, these authors completed the aspects of the electrode reactions using different pH media and gave a brief discussion of electrooxidation of this compound identifying only the oxidation site [9].

As regards electrooxidation, few papers were found [9–11]. Details, such as peak potential and peak current,

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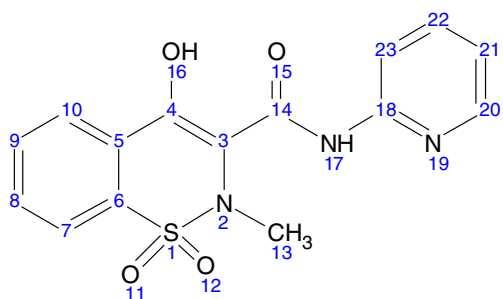
Scheme 1. Piroxicam.

for the oxidations of piroxicam and tenoxicam using carbon paste electrode were studied at different pH. The reported results suggested that the electrochemical methodology should be used for analytical determination of this compound, but these authors did not deepen in the electrode reaction mechanisms [10]. Other electrochemical studies, such as voltammetric polarographic and ion selective electrode techniques, were used for analytical purpose in the determination of piroxicam and tenoxicam in pharmaceutical preparations [12] (and references cited herein).

The aim of the present work is to identify the complex mixture of products formed during the electrooxidation of piroxicam employing cyclic voltammetry (CV) and controlled potential electrolysis in combination with UV–Vis, GC–MS and NMR analysis. In these experiments, controlled potential electrolysis was used both to produce the oxidation products and to examine the electrochemical properties of the compounds on an experimental time scale larger than the one used in the initial study. We believe that the aforementioned aspects are important when an electrochemical technique is applied for analytical purpose. Additionally, this study together with the previous reduction results [8,9] permits a better knowledge of the piroxicam electrochemical behavior.

2. Experimental

2.1. Reagents and solvents

Piroxicam (100.0%), working standard, was generously supplied by CASASCO, Argentina, and used without further purification. 2-Aminopyridine was purchased from Sigma–Aldrich and used as received. Acetonitrile (ACN) was purchased from Sintorgan, HPLC grade and was used without further purification. HClO$_4$ Merck p.a. was used as received.

A stock solution of 1×10^{-2} M piroxicam was prepared in ACN, and stored at 5 °C in the dark. Since piroxicam generally has a low solubility in water [13], the dilute solutions were prepared daily with solutions composed of 10% ACN + 1.58×10^{-2} M HClO$_4$ aqueous solutions; the concentration range was between 0.8×10^{-5} and 2×10^{-4} M. Higher concentrations could not be used due to the problem of stability of piroxicam, see below. This solution was used for most of the electrochemical studies.

However, solutions composed of 10% ACN + Britton–Robinson buffer (0.1 M, pH 2.0–6.0) were also employed for performing studies of the dependence of E_p on the pH by using CV. The buffer as well as HClO$_4$ was also used as the supporting electrolyte in the electrochemical experiments. All the solvents used were of HPLC grade and all other reagents employed were of analytical grade and were used without further purifications. All solutions were prepared with ultra-high-quality water obtained from a Barnstead Easy pure RF compact ultra pure water system.

2.2. Apparatus and experimental measurements

Electrochemical experiments were performed in unstirred solutions using a BAS 100B/W electrochemical analyzer Bioanalytical System, West Lafayette IN, using a positive feedback routine to compensate the ohmic resistance. Cyclic voltammograms were obtained at scan rates (v) in the range 0.010–2.50 V s^{-1}, using a three electrodes system consisting of a glassy carbon (GC) working electrode model BAS MF-2012, 3.0 mm diameter, an Ag|AgCl|3 M NaCl reference electrode BAS MF-2052 and a Pt wire counter electrode of large area. Before each new solution was studied, the working electrode was carefully polished with PK-4 polishing Kits, BAS MF-2060, and rinsed following the general guideline for polishing electrodes recommended for BAS Electrode Polishing and Care, BAS A-1302. The polished electrode was further activated electrochemically in 1 M KOH (Merck p.a.) aqueous solution by a potential step of 1.2 V over 5.0 min according to a procedure described previously by Anjo et. al. [14]. Its electrochemical area ($A = 0.070$ cm^2) was calculated from the well known I versus $t^{1/2}$ Cottrell plots [15] by studying the oxidation of 1.99×10^{-3} M ferrocyanide in 0.5 M KCl, since the ferrocyanide diffusion coefficient in this reaction medium has already been reported $D = 7.0 \times 10^{-6}$ cm^2 s^{-1} [16]. All the solutions were free of oxygen bubbling nitrogen for 10 min and all experiments were carried out under a nitrogen atmosphere.

Controlled potential electrolysis was performed using BAS Bulk Electrolysis divide Cell, but glassy carbon plaques (2.1 cm × 2.0 cm × 0.25 cm) were used instead of reticulated glassy carbon as working electrode. A Pt wire, BAS MW-1033, as counter electrode and an Ag|AgCl|3 M NaCl BAS MF-2052 as reference electrode were used.

The electrolysis potential applied was +0.830 V for the oxidation. Corrections of the background current were made. The glassy carbon plaque used as working electrode was occasionally cleaned using the same method described previously.

The pH values of the solutions were recorded with an ORION 920 pH-meter with a combined glass electrode and Ag|AgCl|3 M NaCl reference electrode. This pH-meter was calibrated with two buffers: biphthalate buffers, prepared by dissolving 2.53 g of potassium biphthalate in 250.0 ml of deionized water for pH 4.0 and tetraborate

buffer, prepared by dissolving 0.95 g of sodium tetraborate in 250.0 mL of deionized water for pH 9.0.

The spectrophotometric investigation was performed with a Beckman DU® 920 spectrophotometer using 1.0 cm quartz cuvettes with pure $HClO_4$ aqueous solutions as reference solutions. Preparative thin-layer chromatography (t.l.c.) was carried out on glass plates (20 × 20 cm) coated with silica gel-G (Merck).

The ^1H nuclear magnetic resonance (NMR) spectra were recorded at 200 MHz on a Bruker AC 200 spectrometer with TMS as internal standard. The ^{13}C spectra were obtained with the same instruments at 50.23 MHz. 2D experiments were obtained using standard Bruker microprograms. Electron impact mass spectra (EIMS) were recorded at 70 eV using a Finnigan-Mat GCQ-Plus spectrometer.

2.3. Products identification

2-{[(Carboxycarbonyl)(methyl)amino]sulfonyl}benzoic acid (If): M.p. (dec.): >310 °C; ^1H NMR (CDCl₃), δ ppm: 8.05 (dd, 1H, 3-H), 7.83 (m, 3H, 4-H, 5-H and 6-H), 3.05 (s, CH₃,); ^{13}C NMR (CDCl₃), δ ppm: 163.6 (C, C-9), 159.7 (C, C-13), 159.3 (C, C-17), 139.8 (C, C-1), 137.1 (CH, C-5), 136.7 (CH, C-4), 131.9 (C, C-2), 129.5 (CH, C-3), 126.9 (CH, C-6), 34.8(CH₃, C-16); MS: *m/z* (relative intensity): 287 (72), 270 (16), 243 (41), 214 (38), 185 (33), 141 (15), 137 (55), 121 (100), 102 (18), 74 (23), 57 (16); Anal. Combustion for $C_{10}H_9NO_7S$. Found: C, 41.90; H, 3.22; N, 4.78; S, 11.0.2. Calc.: C, 41.81; H, 3.16; N, 4.88; S, 11.16%.

2-Aminopyridine (Ig). M.p. = 58.3 °C; gives the spectral data (^1H NMR, EIMS) in agreement with previously reported data [17,18].

3. Results and discussion

3.1. Acid–base behavior of piroxicam

Several studies have been reported in the literature related with the acid–base behavior of piroxicam [19–23].

Being a diprotic amphoteric drug with pKa values differing by less than 4 units [24], the deprotonation–protonation of one group affects the other depending on the pH values of the media. The ionizable sites being two, the acidic (–OH 16) and the basic (–N 19) groups, the molecule may exist in four different structures. Usually, the two constants reported [22] describe the overall activity acid–base of the molecule but cannot be assigned to the individual functional group. However, the knowledge of protonation–deprotonation microconstants is required for complete characterization of the equilibria involved.

The four possible forms in which this kind of molecule can exist depending on the pH of the solution are: (i) as an acidic cation (A = AH ∼ BH⁺); (ii) as a neutral un-ionized species (N = AH ∼ B); (iii) as an intermediate zwitterion (Z = A⁻ ∼ BH⁺); and (iv) as a basic anion (B = A⁻ ∼ B). The acid–base equilibria defined in terms of microscopic constants are shown in Scheme 2. These constants are related to macroscopic constants Ka^{acidic} and Ka^{basic} by the following equations:

$$Ka^{acidic} = Ka^{AZ} + Ka^{BN} \tag{1}$$

$$1/Ka^{basic} = 1/Ka^{BZ} + 1/Ka^{AN} \tag{2}$$

$$Kz = (Ka^{AZ}/Ka^{BN}) = (Ka^{AN}/Ka^{BZ}) \tag{3}$$

The typical pKi values for piroxicam given in the literature [22] are: pKa^{acidic} = 1.88 ± 0.01, pKa^{basic} = 5.29 ± 0.02, pKa^{AZ} = 1.91, pKa^{AN} = 3.00 ± 0.02, pKa^{BZ} = 5.26, pKa^{BN} = 4.18, Log K^{NZ} = 1.09. Taking into account that piroxicam is more stable at low pH, most of the electrochemical studies were carried out at pH ≅ 2 (see below).

3.2. Stability of piroxicam solutions

There are some contradictory reports in the literature regarding the stability of piroxicam in aqueous media as a function of pH. While Fini et al. [25] considered that change in absorbance, observed in function of time, is probably due to the change of the position of the tautomeric equilibrium with the pH, Bartsch et al. [26] and
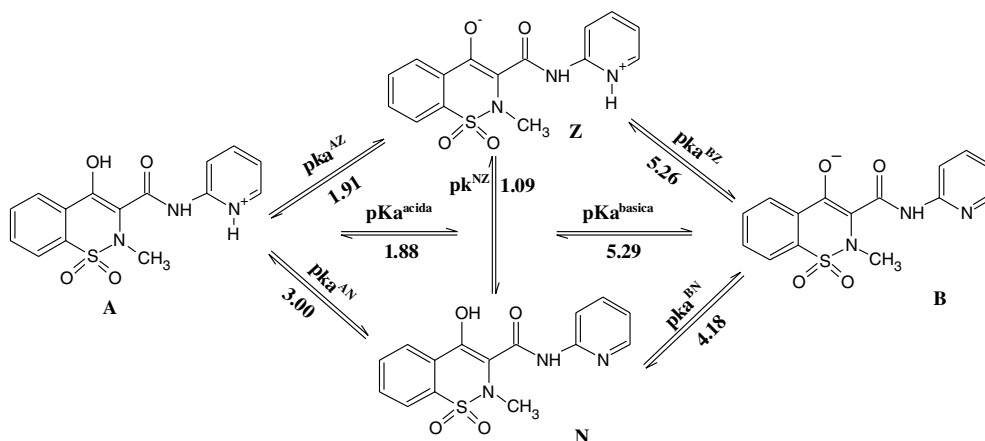
Scheme 2. Microscopic protonation/deprotonation equilibria of piroxicam.

Tománková et al. [27] attributed the degradations of piroxicam as a consequence of pH and light influence. The principal product of degradations is the synthesis precursor 2-aminopyridine, as well as 2-methyl-2H-1,2-benzotiazine-4(3H)-one 1,1-dioxide and N-methyl-N'-(2-pyridinyl)-ethane-diamide.

The presence of functional groups susceptible of hydrolysis, such as amide and sulfonamide moieties, suggested us to carry out out a stability test to find the optimal pH for the electrochemical study of the mechanism.

UV–Vis spectra at different pH values for piroxicam (data not shown) were recorded for 4 h immediately after the preparation of solutions. At low value (pH ≅ 1.8), the absorbance did not appreciably change with time until about 60 min. This time was progressively shortened as the pH was increased, being about 8 min. at pH 12.

This study showed that although the source of this change (increasing) of absorbance with time was not very clear, this effect should be avoided in the electrochemical study. Therefore, we found that if the concentration was lower than 2×10^{-4} M, the pH was lower than 2, and special care was taken to protect the piroxicam solution from the laboratory radiations; the solutions were stable at least for 2 h. This time was sufficient for all electrochemical experiments (see Section 2). As a consequence, the major part of our study was carried out at pH 1.8, and only in a few cases at greater pH, but for a short time.

3.3. Electrochemical measurements

3.3.1. Cyclic voltammetry

A typical cyclic voltammogram of piroxicam in water–Britton–Robinson buffer at pH 1.8 is depicted in Fig. 1a. The first anodic scan shows only one peak (I), whose peak potential appears around 0.820 V depending on the pH and in less extension on the scan rate (v). On the reverse scan no complementary reduction peak is observed for peak I, in all the range of v studied (0.05–2.50 V s^{-1}). This behavior is typical for a fast irreversible chemical reaction couple to the charge transfer [28–30]. Moreover, in this case, the chemical reaction gives electroinactive products. In the cathodic zone, a new peak II is defined around −1.1 V, which corresponds to the reduction of piroxicam. This was established by beginning the scan in a point of current near to zero but in the cathodic direction as shown in Fig. 1b. These results agree with those of the previous report for piroxicam reduction [8,9].

More detailed studies of the electrooxidation of piroxicam were carried out registering voltammogram in the oxidation zone as shown in Fig. 2. As it can be observed in the second scan only peak I is detected, confirming that the coupled chemical reaction gives electroinactive products. The whole kinetic analysis is carried out under the assumption that the electron transfer is a fast process within the range of sweep rates used in this study. The principal results for peak I can be summarized as follows:
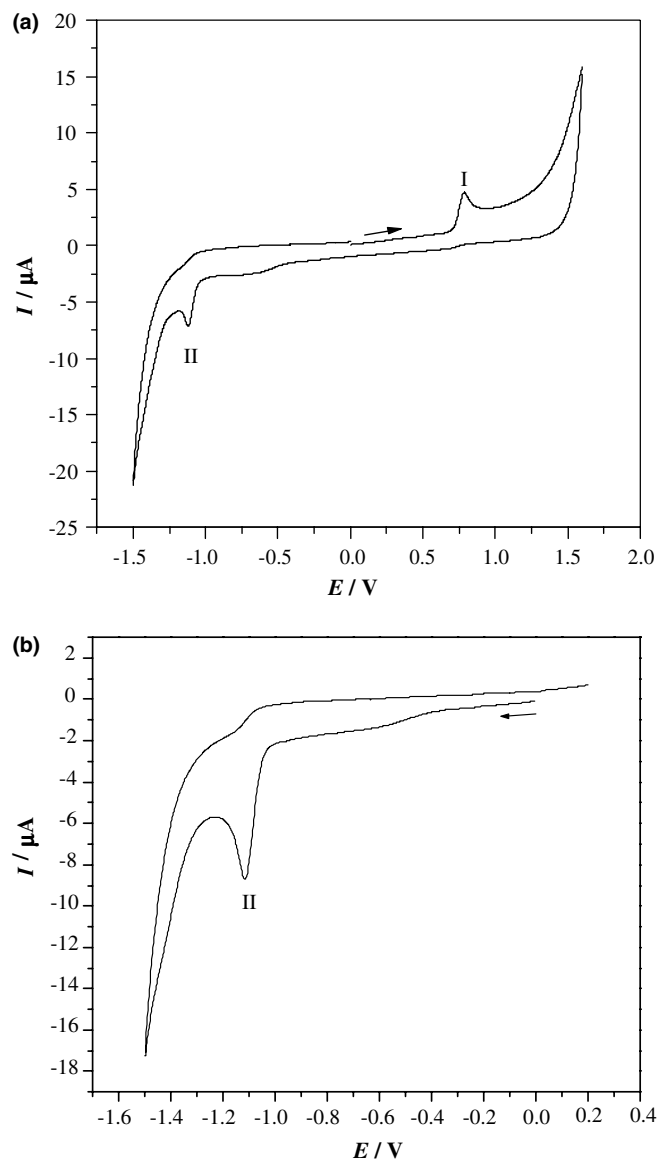

Fig. 1. Cyclic voltammograms of piroxicam, pH 1.8, $c_{piroxicam} = 1 \times 10^{-4}$ M, $v = 0.1$ V s^{-1}: (a) complete scan; (b) cathodic scan.

(a) Peak I only changes its peak potential (Ep_I) with the pH of medium, in the range $1.8 \leqslant pH \leqslant 4.0$ (see below), but does not change its appearance.

(b) The plots of peak current (Ip_I) versus $v^{1/2}$ show a linear behavior in the range of sweep rates used (Fig. 3). In addition, Ip_I varies linearly with the concentration of piroxicam in the range 5×10^{-5} M to 2×10^{-4} M. This behavior is typical for diffusion control of the overall electrode process, when the chemical reactions coupled are fast in the time scale of the experiment [31]. More details about the process involved in peak I are obtained by studying the dependence of the experimental current function (Ψ) on the scan rate and concentration. This parameter is more sensitive to the electrode processes [31–33]. The experimental Ψ may be defined as $\Psi = Ip_I/(Av^{1/2} c^*)$, where A is
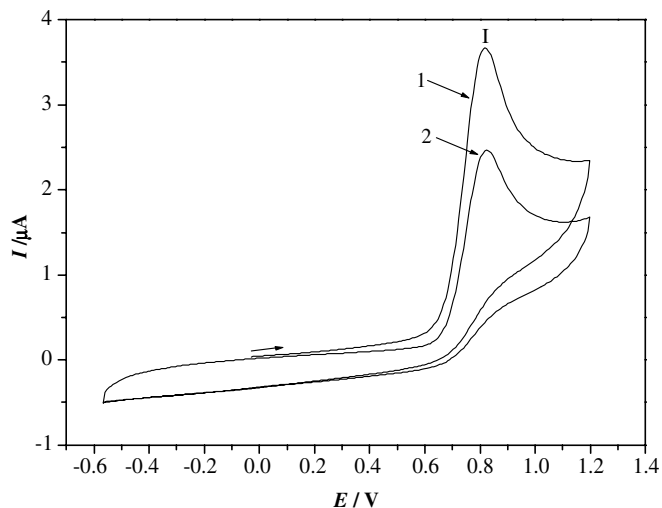
Fig. 2. Cyclic voltammograms of piroxicam, pH 1.8, $c_{\text{piroxicam}} = 2 \times 10^{-4}$ M, $v = 0.1$ V s^{-1}. The numbers indicate first and second scan, respectively.

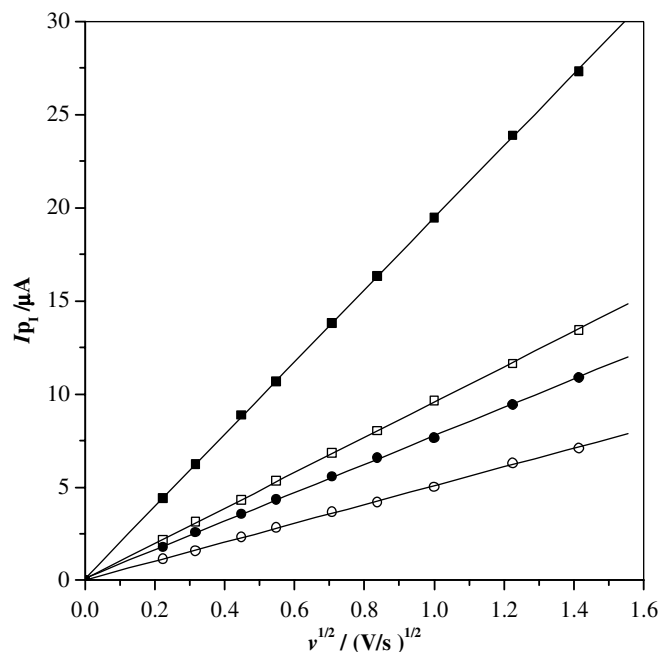Fig. 3. Dependence of I_{p_I} on sweep rate at different concentrations of piroxicam, pH 1.8, $c_{\text{piroxicam}}$: (○) 5×10^{-5} M; (●) 8×10^{-5} M; (□) 1×10^{-4} M; (■) 2×10^{-4} M.

the working electrode area, in cm^2, v the potential scan rate in V s^{-1}, and c^* the bulk concentration of piroxicam in M. Typical results for different concentrations and scan rates are Ψ 1.4 A. (V/s^{-1})$^{-1/2}$ cm^{-2} M^{-1}. The "apparent" number of electrons exchanged in the overall electrode process can be estimated with a 10% of error by using the experimental Ψ value and comparing with model compounds that exchange one and two electrons measured with the same working electrode in similar experimental conditions. Potassium ferrocyanide was selected as a model for one-

electron exchange $\Psi = 0.71$ A (V/s)$^{-1/2}$ cm^{-2} M^{-1}, and 1,4-hydroquinone as a two-electron exchange model [34], $\Psi = 1.59$ A (V/s)$^{-1/2}$ cm^{-2} M^{-1}. As can be observed, the value of $\Psi \cong 1.4$ A (V/s)$^{-1/2}$ cm^{-2} M^{-1} indicates that the overall electrode process for piroxicam involves two electrons per molecule. These data lead to the conclusion that at this pH the oxidation of piroxicam may comprise two successive one electron transfers at similar formal potential. Thus being $E_1^0 \cong E_2^0$, only one peak is detected in the first anodic scan [35].

(c) Another property of peak I is the difference between the peak potential, Ep, and the half-peak potential, $E_{\text{p/2}}$, in this case the result was of about 45 mV, which again can be interpreted as the small difference between E^0 values for the two individual one electron transfers or ($E_1^0 \cong E_2^0$), in agreement with the previous discussion, but in this case the criterion is applied at oxidation process [36,37].

(d) To obtain more insight about the mechanism of electrooxidation of piroxicam, an analysis of the dependence of Ep versus pH was performed. In water the proton transfer from or toward organic molecules is usually considered fast [38], meaning that H$^+$ are in equilibrium in solution near the electrode. This type of situation should prevail in acidic or not excessively basic media, especially when the site of protonation is an oxygen atom [39].

A plot of Ep versus pH is shown in Fig. 4. A linear portion was observed at low pH with a slope of 0.058 V/pH. This slope is close to that expected for a monoelectronic/monoprotonic electrode reaction, which is 0.0592 V/pH at 25 °C. As it was previously shown, the experimental Ψ value indicates 2e$^-$ in the same pH range studied. The only possibility for the pH below 4 is that the number of proton transfers is also 2. That is 0.0592 (h/n)V/pH, where h and n are the number of protons and electrons involved in the
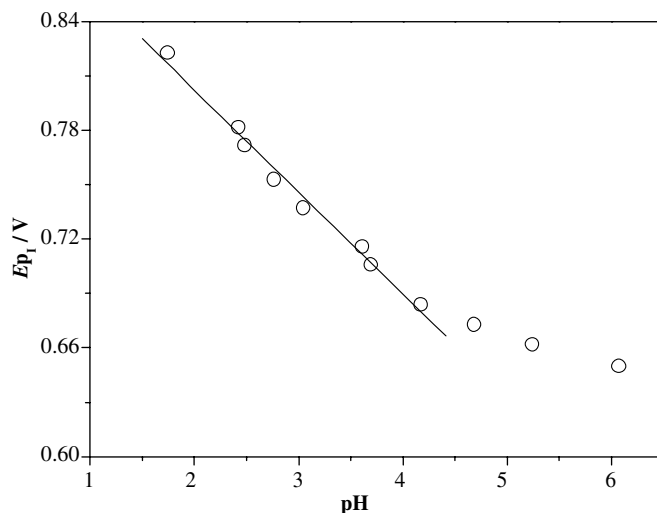

Fig. 4. Dependence of E_{p_I} on pH, $c_{\text{piroxicam}} = 1 \times 10^{-4}$ M, $v = 0.05$ V s^{-1}.

electrode process ($h = n = 2$). This behavior may be understood by considering that the loss of a second proton should involve a second homogeneous chemical reaction.

(e) The peak potential Ep_I versus $\log(v)$ was linear with a slope of 29 mV per decade^{-1} ($R = 0.998$) in good agreement with the theoretical value predicted for the $E_1C_1E_2$ type mechanism (theoretical value 29.6 mV per decade at 25 °C [40]). However, the dependence of Ep_I with $\log(c°)$, ($c°$ is the concentration of piroxicam) is practically constant within the experimental error, at least on the range of concentrations studied (5×10^{-5} to 2×10^{-4} M) thus meaning $\Delta\log(c°) \cong 0.6$.

3.3.2. Controlled-potential electrolysis

In order to obtain more insight regarding the apparent number of electron exchanges (n_{app}) in the global process of electrooxidation of piroxicam, a controlled-potential electrolysis was carried out. The current was registered as a function of time until it was about 2% of the initial values. In the same experimental condition, a blank experiment was performed and this current was subtracted to the total current in order to obtain the effective current. The plots $\ln(I)$ versus t [31] were linear in the overall time of electrolysis. A typical result is depicted in Fig. 5. This is indicative that all the chemical reactions coupled to charge transfer are fast and the same distribution of products is obtained at each time [41]. From the slope and intercept at $t = 0$, a n_{app} of 2.0 ± 0.07 electron per molecule of piroxicam can be calculated [42]. On the other hand, the total
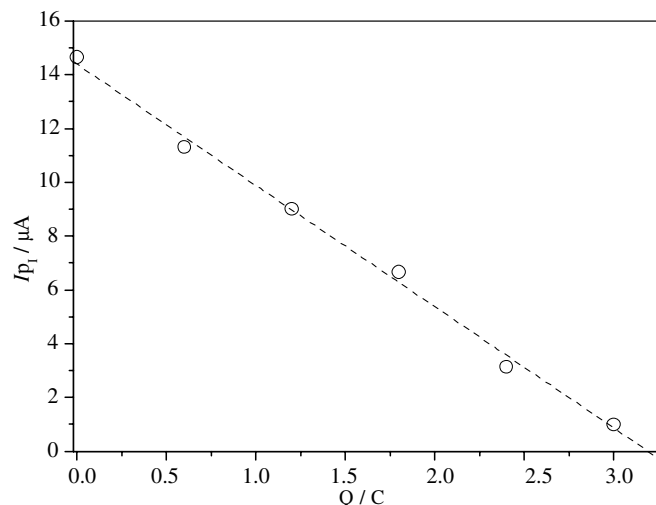
Fig. 6. Dependence of Ip_I on colorimetric charge, $E = 0.830$ V, pH 2, cell volume = 50.0 mL, $c_{piroxicam} = 3.02 \times 10^{-4}$ M.

integrated current gives $n_{app} = 2.0 \pm 0.1$ electrons per molecule. These results agree with the previous one obtained by cyclic voltammetry with Ψ. Finally the effect of charge injected can be followed by recording cyclic voltammograms of piroxicam oxidation at each time; no new peaks are detected in this potential zone. The Ip_I is a linear function with the injected charge as shown in Fig. 6. This is consistent with the behavior of $\ln(I)$ versus t. In conclusion, piroxicam oxidation exchanges $2e^-$ per molecule either in the cyclic voltammetry or controlled-potential electrolysis. Keeping in mind these facts, one could expect that the mechanism of reaction detected for both techniques is the same.

3.3.3. Products isolation

With the purpose of identifying the reaction products, several controlled-potential electrolyses were carried out of piroxicam solution. In a typical procedure, 50 mL of 10% ACN + 1.58×10^{-2} M HClO$_4$ + $\approx 1.5 \times 10^{-5}$ mol of piroxicam, a higher concentration cannot be used for problems of stability of the piroxicam. The electrolysis was stopped when the current reached approximately the value of the current of the baseline.

At the end of each electrolysis, the solution was neutralized with sodium bicarbonate. The mixture of several neutralized solutions was extracted with ethyl acetate (4×20 mL) and finally was dried over anhydrous sodium sulfate, and filtered. By t.l.c. analysis with toluene:acetone (80:20), only two products were detected. The extract was evaporated under reduced pressure, and the products were separated by preparative t.l.c on Sigel plates; the same solvent mixture as the eluent. The pure solids obtained were recrystallized from toluene. The products were identified as 2-{[(carboxycarbonyl) (methyl)amino] sulfonyl}benzoic acid (**If**) and 2-aminopyridine (**Ig**). These products may be due to a further decomposition of the
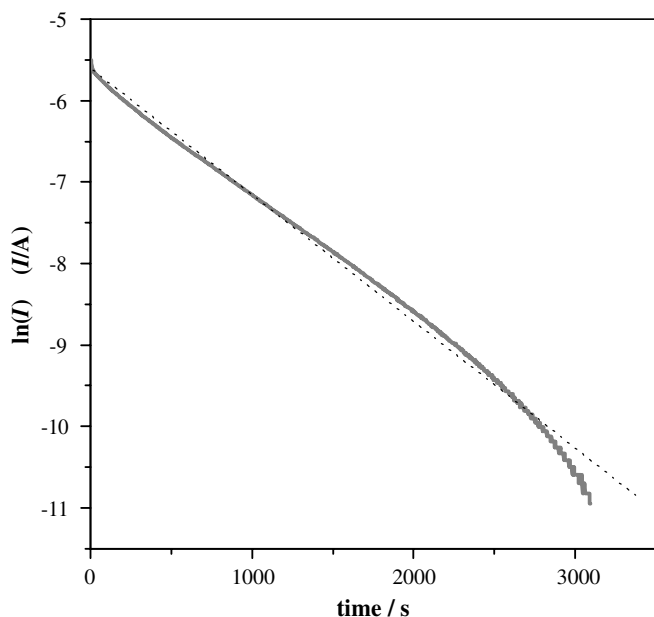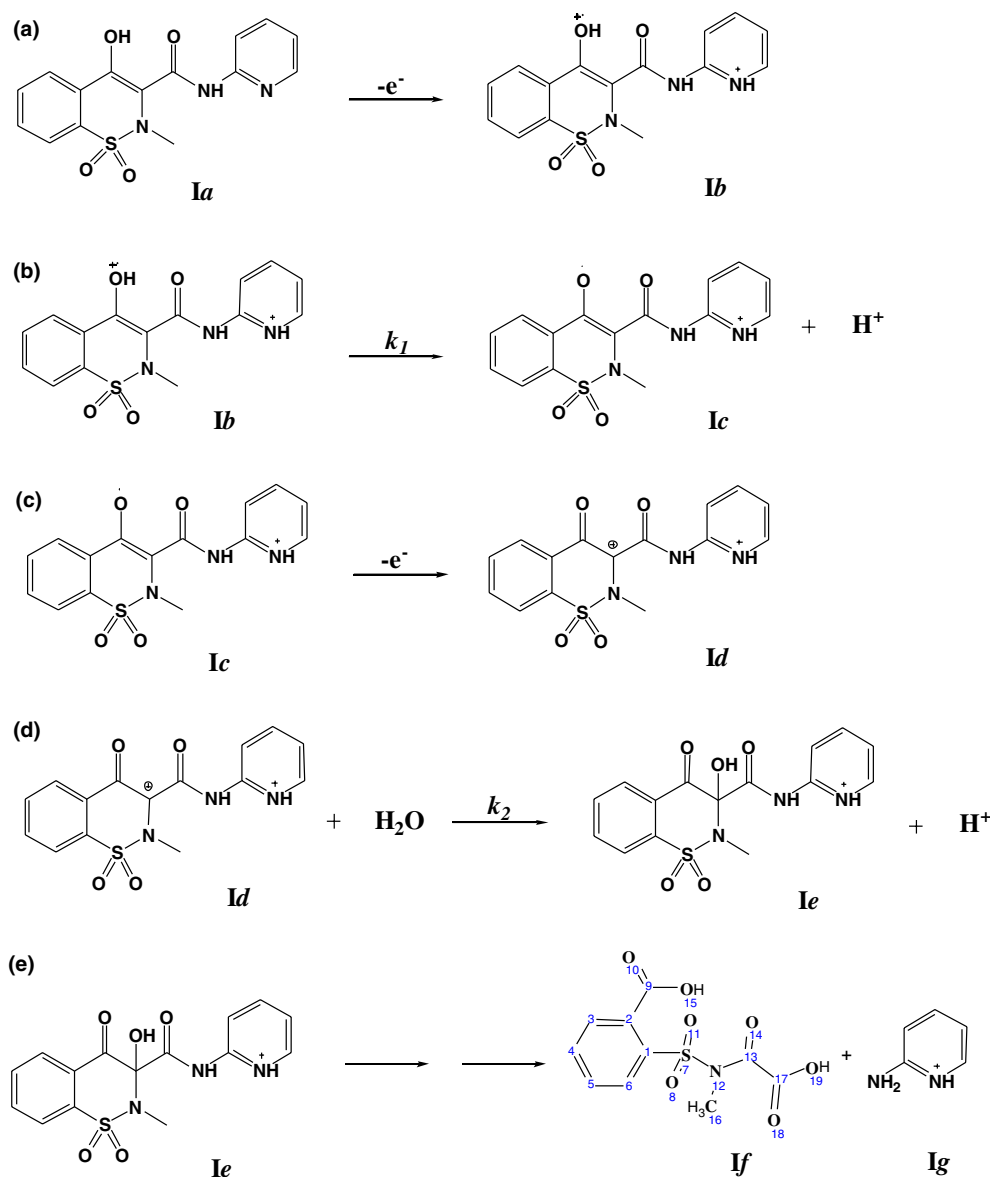

Fig. 5. Dependence of $\ln(I)$ versus time, pH 2.0, (—) experimental value, (---) best linear fit, $\ln(I) = -5.6$ at $t = 0$, slope $= p = 1.55 \times 10^{-3}$ s^{-1}, $n_{app} = 2.0 \pm 0.07$, potential of electrolysis $E = 0.830$ V, pH 2, cell volume = 40.0 mL, $c_{piroxicam} = 3 \times 10^{-4}$ M.

Scheme 3. Probable reaction mechanism for electrooxidation of piroxicam at pH 2.

primary electrolysis product during the workup of the reaction mixture.

3.3.4. Probable reaction mechanism

In summary taking into account the properties of peak I and the coulometric result, it can be concluded that the general scheme for electrooxidation of piroxicam in acidic media might be represented by $E_1C_1E_2C_2$ type's mechanism, where E_1, E_2 mean electron transfers with similar formal potential. $(E_1^0 \cong E_2^0)$ and C_1, C_2 are irreversible chemical reactions to give electroinactive products.

According to the electrochemical results and products isolation, the mechanism proposed is depicted in Scheme 3. After the first charge transfer in Eq. (a), the obtained cation radical **Ib** deprotonates to give **Ic** which is further oxidized in Eq. (c), to **Id**. This cation is susceptible of nucle-

ophilic attack by the solvent in step (d) to give **Ie**. This latter compound decomposes in the media in several unknown steps to the isolated products **If** and **Ig** (Eq. (e)). It should be noted that the appearance of **If** not only requires hydrolysis of **Ie** but also requries a homogeneous oxidation addition during the workup.

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