A CHRONOAMPEROMETRIC STUDY OF THE OXIDATIVE NUCLEATION OF NIAZID AND ISONIAZID ON MERCURY ELECTRODES IN BASIC SOLUTIONS

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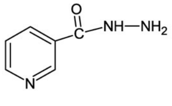
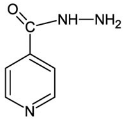
Using chronoamperometric measurements at pH 12 it is shown that the oxidation mechanism of niazid adsorbed on the mercury electrode changes with respect to the mechanism reported in the literature for the electrooxidation of the molecules reaching the electrode by diffusion. A compact monolayer of niazid molecules is formed on the electrode surface, being the hydrazide oxidized through a two-electron process. The oxidation product is not able to dissociate a H^+ ion, and the oxidation process does not proceeds beyond. For isoniazid the monolayer never becomes compact.

Keywords: Pyridine hydrazides; Niazid; Isoniazid; Oxidation; Nucleation; Electrode kinetics; Adsorption; Electrochemistry.

Niazid and isoniazid are the hydrazides derived from 3- and 4-pyridine carboxylic acid (nicotinic and isonicotinic acid respectively) whose structures are as follows.


Niazid


Isoniazid

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Isoniazid is widely used as an antitubercular and antiactinomycotic agent in medicine because of its antagonism for nicotinic acid and nicotinamide.

The polarographic and macroscale oxidation of isoniazid was first investigated by Lund[1] who found that this compound showed one oxidation wave in the pH range 8.5–13.5. The process corresponded to a four-electron process at the concentrations usually used in polarography. Controlled-potential macroelectrolysis performed at pH 11 in phosphate buffer gave 1, 2-diisonicotinoyl hydrazide as the product of the bielectronic oxidation together with traces of 4-pyridine aldehyde. In strongly basic solutions, formation of isonicotinic acid was also observed. This acid was not generated through hydrolysis of any of the above compounds, as was verified experimentally.

The electrochemical oxidation of niazid and isoniazid on mercury electrodes was also studied[2] by DC and differential pulse polarography and, in the case of isoniazid, by cyclic voltammetry in neutral and basic media. At pH > 8.5, the positive scans show a prewave, in addition to the main oxidation wave, which can be suppressed by changing experimental variables such as the concentration, temperature and ethanol content in the medium. In the absence of the prewave, Tafel slopes and reaction orders were obtained at the potentials corresponding to the foot of the polarographic waves. On the basis of polarographic, voltammetric and kinetic results, and taking into account the literature data, the oxidation processes were found to be of the ECE type, where the rate-determining step was the release of an H^+ ion from the intermediate formed after two reversible one-electron transfers.

The results obtained for the prewave agree with those expected for a process in which the product is more strongly adsorbed than the reactant. It was also shown that the adsorption follows a Langmuir isotherm for which the Gibbs energy of adsorption is potential dependent.

There are a variety of models to describe adsorption processes in which the rate determining step is kinetic, electronic transfer or diffusion. These processes can be divided into two-dimensional (2D), with possible further growth layer by layer, and three-dimensional (3D). For organic molecules the phase transition on the electrode surface, basically consists of the transition from a state with disordered distributed molecules and minimal interaction between them, to a state where the molecules are adsorbed in a fixed position, forming a ordered film with stronger cohesive interactions.

Two-dimensional (2D) phase transitions on electrode surfaces have been widely investigated[3–5] on account of the fact that the compact monolayers they form can take part in a large number of major electrochemical processes including electrocatalysis, corrosion inhibition, biosensing or the construction of electro-optical devices. Chronoamperometry has proved the most suitable technique for characterizing electrochemical 2D nucleation processes; also, special mathematical models have been developed that account accurately for the behavior of a wide variety of real systems[4,6–11].

On the other hand, a theoretical study of two-dimensional phase transitions taking place in electrode processes was carried out by using cyclic voltammetry[12]. The equations derived are obeyed only at low to moderately high scan rates (v) depending on the particular experimental system. The treatment used was applied on the assumption that the nucleation rate for the process is a function only of the concentration of nuclei of a critical size which depends on the overpotential. This approximation holds whether nucleation at a constant potential is instantaneous or progressive. Consequently, neither has physical significance under variable-potential conditions, at least at low scan rates. Theoretical relationships between the peak current, the peak half-width (the width, in V, at the peak half-height) and the difference between the reduction and oxidation peak potentials and the scan rate were proposed.

EXPERIMENTAL

In all cases, Merck analytical grade reagents were used with the exception of niazid and isoniazid which were from Aldrich. Solutions of 0.1 M in both phosphoric acid and Na_2CO_3 were used as supporting electrolytes. Stock solutions of hydrazides were stored in darkness at 277 K to avoid decomposition. The aqueous solutions were prepared using ultrapure water type I (resistivity 18.2 MΩcm at 25 °C) obtained by an ultrapure water system Millipore Simplicity®. Ionic strength was adjusted to 0.5 M with solid NaCl and the pH was adjusted with solid NaOH. All potentials were measured against the Ag|AgCl||KClsat electrode. Triply distilled mercury was used.

Measurements were made on a CHI650A electrochemical workstation from IJCambria coupled to an EF-1400 controlled growth mercury electrode from BAS instruments. For voltammetric and chronoamperometric measurements the Hg drop area was 6.70×10^{-3} cm^2. Solutions were purged with purified nitrogen and the temperature was kept at 298 ± 0.1 K.

RESULTS AND DISCUSSION

Both for niazid and isoniazid, at basic pH values and concentrations higher than 0.2 mM, a prepeak was observed in addition to the main oxidation peak and sharper than this last (see Figs 7, 8 and 10 in ref.[2]). The prepeak is more defined and separated from the main oxidation peak at high scan rates, and at more basic media than at lower pH values, being both peaks best resolved in the case of niazid than for isoniazid. At scan rates high enough, the intensities of the prepeaks are roughly proportional to the scan rate, as expected for a process due to the oxidation of an adsorbed species[13,14]. At low scan rates the adsorption peak currents decrease more markedly than the diffusion peaks heights, being both peaks more overlapped. The proximity between both peaks prevents measurement of the half-width of the prepeak at low scan rates and thus, the diagnostic criteria to distinguish the possible nucleation acting at such potentials, which are derived for low scan rates[12] cannot be applied.

Chronoamperometric measurements have been made at different concentrations and at potentials corresponding to the prepeaks. As can be seen in Fig. 1, when the overpotentials were low or moderate, the *i*-*t* curves

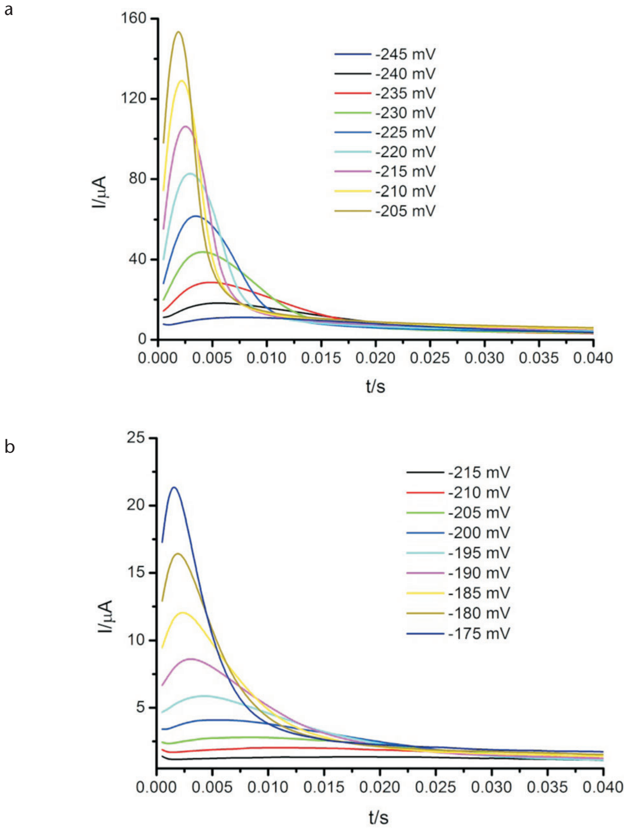


FIG. 1
Chronoamperometric curves of 2×10^{-3} M hydrazides on the mercury electrode at pH 12: niazid (a), isoniazid (b). Starting potential –0.35 V. Final potentials are given in the figures

showed a maximum value at a given time, characteristic of a phase transition of a thin layer of organic material, being the kinetic of the formation of the layer driven by nucleation and growth processes[6,7].

Such chronoamperometric curves were analyzed using the BFT model for 2D nucleation and growth. So, in this model, the current can be described by the Eq. (*1*)[6]

$$i_{2D}(t) = (n-1)\beta q_m t^{(n-1)} \exp(-\beta t^n) \tag{1}$$

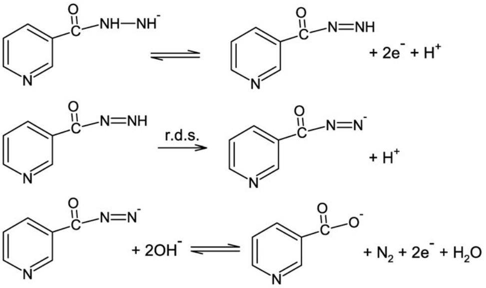
with $n = 2$ for an instantaneous 2D nucleation and $n = 3$ for a progressive 2D nucleation.

First, the BFT model with progressive nucleation has been applied to the data corresponding to niazid, but there is not any set of parameters, meeting the theoretical constraints, able to fit theoretical curves to the experimental ones, this ruling out the hypothesis of the occurrence of this type of nucleation. On the contrary, when instantaneous nucleation is assumed, the good agreement between experimental and theoretical values is evident, as can be seen in Fig. 2.

The curve parameters are consistent for each concentration and for each not excessively low final overpotential. From such parameters the charge value, q_N, corresponding to the nucleation process is easily obtained.

The charge q_N increased as the concentration was increasing until a limiting value of 0.52 μC above a concentration value of ca. 9×10^{-4} M, as can be seen in Fig. 3.

Above this concentration, q_N remains constant, this indicating that the mentioned limiting value is the concentration necessary for the formation of a monolayer on the electrode surface. This is in agreement with the results obtained in ref.[1] using voltammetric measurements. At very low concentration values the monolayer is not complete, this explaining the low q_N values. The mechanism of the electro-oxidation process in basic media on mercury electrodes can be written[2] as follows.



Niazid has been written as the anionic form because the pH is greater than the pK of the hydrazide group[15].

Using the abovementioned charge value, the number of electrons involved in the oxidation process $n = 4$, and taking into account the electrode area and that the monolayer must be compact, it is easy to conclude that the area covered by one molecule of niazid must be around 82 Å^2. Using Arguslab v. 4.01 [16], a model of niazid has been constructed and its geometry has been optimized. The area of the projection of the molecule in the most

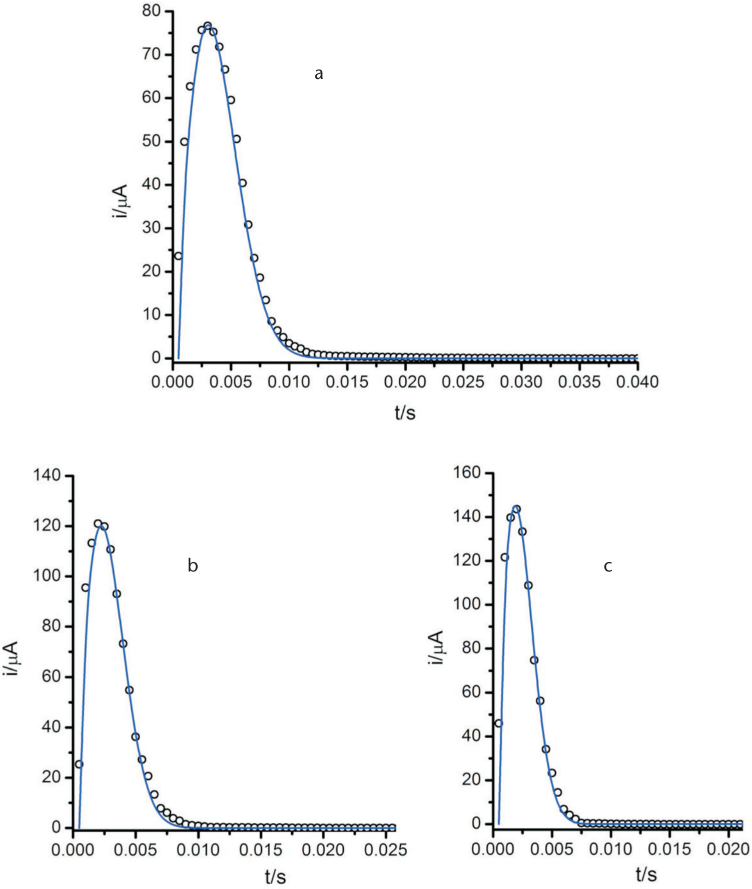


FIG. 2

Fitting of the theoretical BFT 2D instantaneous nucleation (line) to experimental values (circles) for niazid at pH 12 after substraction of the *i*-*t* curve in the same conditions and in the absence of depolarizer. Starting potential –0.35 V. Final potentials (in V): –0.220 (a), –0.210 (b), –0.200 (c) extended planar form possible was around 38 Å^2. It could be argued that niazid molecules are negatively charged due to the dissociation of the NH_2 group taking place above pH 11.5 [16], this charge implying the occurrence of repulsive interaction between the adsorbed molecules, increasing the effective coverage per molecule. Nevertheless, the increase of effective area covered should be twice the molecular area and this seems unlikely. An alternative explanation could be that the electrode surface is not fully covered by the niazid molecules. Nevertheless, the limiting charge value observed in Fig. 3 as the niazid concentration increased and the full coverage found above ca. 1×10^{-3} M niazid[2] indicate that the maximum coverage has been reached.

All these facts can be explained if the number of electrons involved in the oxidation process at the potential values of the prepeak were $n = 2$. In effect, from this value and q_N follows that the area covered by one molecule of niazid must be around 41 Å^2, only slightly higher than the molecular area. So, it seems reasonable to think that the oxidation of adsorbed niazid consists only of reaction 2 and the release of the H^+ ion from the oxidized product is very difficult in the adsorbed state.

For isoniazid it is evident that the monolayer never becomes compact (at least until accessible concentration values). This conclusion is supported by several evidences. First, as can be seen in Fig. 1, the charge values obtained from the integration of the chronoamperometric curves are much lower than those found for niazid in the same conditions. In addition, these charge values do not reach a limiting value but increase as the isoniazid concentration was increased.

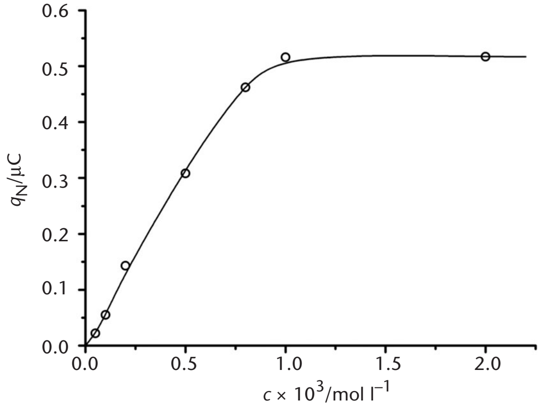


FIG. 3
Plot of nucleation charge, q_N, versus niazid concentration, c, at pH 12

Second, any of the 2D nucleation models (progressive and instantaneous) fit the experimental chronoamperometric curves. The Scharifker–Hills model described the 3D growth under diffusion control[7]. An attempt has been made to fit the data to the equations derived for 3D nucleation either instantaneous or progressive, but there is not an adequate set of parameters. So, the additional contribution to the current appearing at high time values can be attributed to the occurrence of the diffusion-controlled oxidation process, which for isoniazid takes place at potential values closer to the adsorptive oxidation than in the case of niazid[2]. So, as the layer of isoniazid is being formed on the electrode surface, new isoniazid molecules reaching the electrode are directly oxidized rather than incorporated to the layer and then oxidized. This contribution of the "homogeneous" oxidation prevents the formation of the monolayer and causes the distortion of the chronoamperometric curves.

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