

# THE MECHANISM OF ANODIC ELECTROOXIDATION OF GABAPENTINE AND ITS MATHEMATICAL EVALUATION

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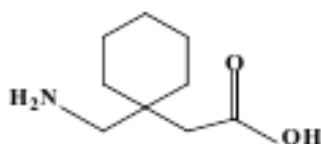
## ABSTRACT.

The mechanism for the electrooxidation of gabapentine in aqueous solutions has been suggested. and analyzed electrochemically and mathematically, by using linear stability theory and bifurcation analysis. The steady-state stability requirements, like also oscillatory and monotonic instability conditions, have been detected. The system tends to the similarity with another, describing the modification of conducting polymers

**Keywords:** gabapentine, electrochemical oxidation, oscillations, stable steady-state, polythiophene paradox

## 1.INTRODUCTION

Gabapentine [1] (1-(aminomethyl)cyclohexanecarboxylic acid) is an anticonvulsant drug, modeled as an analog of gamma-aminobutyric acid (GABA). Maintaining the curative functions of GABA, it is capable to trespass the blood-brain barrier, because of the presence of cyclohexan lipophilic fragment. [2]. Nevertheless, its excess in the organism may cause some toxic effects [3 – 4]. Moreover, its medical action is strongly depending on its concentration in the organism. Thus, the development of an analytical method, capable to detect the drug concentration by more precise and exact way, is, without a doubt, an actual task [5 – 20]. In this aspect, the chemical structure of gabapentine (Fig. 1) presents some inconvenience, due to the presence of little quantity of unsaturated bonds and viable chromophoric groups and easily oxidized fragments. So the use of non-electrochemical [5 – 14] and electrochemical [15 – 20] analytical methods, in this case, requires derivatization and modification of the proper gabapentine, or of an electrode with various substances, in order to enhance the sensitivity.



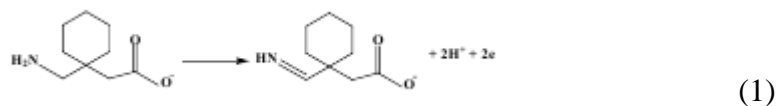
**Fig. 1.** Gabapentine

Other difficulty in the gabapentine electrooxidation is the problem of the most probable mechanism of gabapentine electrooxidation. Its suggestion would help in the development of the electrochemical sensors, efficient, rapid, precise and sensitive in chemical and pharmaceutical analysis [21 – 26]. Also, the gabapentine electrooxidation may be accompanied by oscillatory and monotonic instability [20]. Such behavior is characteristic for the similar systems of the electrooxidation of small organic molecules and hydrogen [27 – 42], including the electropolymerization, and, in the majority of cases, has only received a phenomenological explanation, caressing a rigid theoretical base, which may only be given by a mathematical model, capable to describe adequately the behavior of this system.

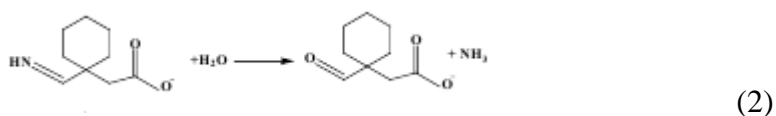
Moreover, it gives the possibility to compare and predict the behavior of this system with other systems without any experimental essay. So, in this work the mechanism of gabapentine electrooxidation and its mathematical representation are suggested and the system [20] compared with the cases of similar systems [43 – 56].

## 2.SYSTEM AND ITS MODELING

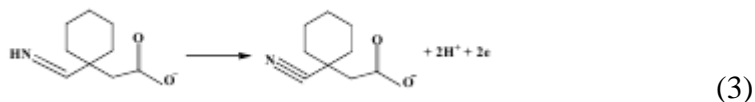
In aqueous solution, gabapentine is oxidized by the complex mechanism, described below [20]. As the amino-group is oxidized more easily than the rest of the molecule, at the first stage it's oxidized to imino-group:



This group is then hydrolyzed to form the corresponding aldehyd by:



or oxidized to corresponding nitrile by:



To describe the behavior of the system with gabapentine electrooxidation in aqueous solutions, we introduce three variables:

$c$  – gabapentine concentration in the pre-surface layer;

$\theta_1$  – gabapentine surface concentration;

$\theta_2$  – gabapentine imine surface concentration.

To simplify the modeling, we assume that the reactor is intensively stirred, so we can neglect the convecting flow. Also we assume that the background electrolyte is in excess, so it's possible to neglect the migration

flow. Yet the diffusion layer is supposed to be of constant thickness, equal to  $\delta$ , and of linear concentration profile of gabapentine.

Gabapentine enters the pre-surface layer by its diffusion and by means of its desorption and leaves it by adsorption. So, the balance equation for its concentration in the pre-surface layer will be rewritten as:

$$\frac{dc}{dt} = \frac{2}{\delta} \left( \frac{\Delta}{\delta} (c_0 - c) + r_{-1} - r_1 \right) \quad (4)$$

in which  $\Delta$  is the gabapentine diffusion coefficient,  $r_1$  and  $r_{-1}$  are gabapentine adsorption and desorption rates and  $c_0$  its bulk concentration.

Gabapentine enters the surface by its adsorption and leaves it by desorption. It is then oxidized to form gabapentine imine. So, the balance equation for its surface concentration will be described as:

$$\frac{d\theta_1}{dt} = \frac{1}{G} (r_1 - r_{-1} - r_2) \quad (5),$$

in which  $G$  is gabapentine maximal surface concentration and  $r_2$ , its electrooxidation rate.

Gabapentine imine is formed by electrooxidation of gabapentine and then hydrolyzed to form the aldehyd and electrooxidized to form a nitrile. Thus, the balance equation for its surface concentration will be rewritten as:

$$\frac{d\theta_2}{dt} = \frac{1}{J} (r_2 - r_3 - r_4) \quad (6),$$

in which  $J$  is the imine surface concentration,  $r_3$  and  $r_4$  are the hydrolysis and electrooxidation rates.

The rates of the reactions, mentioned in this section may be calculated as:

$$\begin{aligned} r_1 &= k_1 \exp(a\theta_1) c (1 - \theta_1 - \theta_2), & r_{-1} &= k_{-1} \exp(-a\theta_1) \theta_1, & r_2 &= k_2 \theta_1 \exp\left(\frac{2F}{RT} \varphi_0\right) \\ r_3 &= k_3 \theta_2 & r_4 &= k_4 \theta_2 \exp\left(\frac{2F}{RT} \varphi_0\right) \end{aligned} \quad (7-11),$$

In which the parameters  $k$  are correspondent rate constant, the constant  $a$  describes the interaction between adsorped particles, 2 is the number of electrons transferred,  $F=N_A \cdot e$  is a Faraday number,  $R$  is the universal gas constant,  $T$  is the absolute temperature and  $\varphi_0$  is the potential slope, related to the zero-charge potential.

As it is possible to see, this system represents the modified case of the general model of electrooxidation and electropolymerization (including the polythiophene paradox). The differences between this case and the general system will be discussed below.

### 3.RESULTS AND DISCUSSION

To investigate the mechanism for the electrochemical oxidation of gabapentine in water solutions, we analyze the equation set (4 – 6), taking in account the algebraic relations (7 – 11) by means of linear stability theory. The Jacobian matrix elements, calculated for a steady-state, will be represented as:

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{12} & a_{22} & a_{23} \\ a_{13} & a_{32} & a_{33} \end{pmatrix} \quad (12),$$

in which:

$$a_{11} = \frac{2}{\delta} \left( -\frac{\Delta}{\delta} - k_1 \exp(a\theta_1) (1 - \theta_1 - \theta_2) \right) \quad (13)$$

$$a_{12} = \frac{2}{\delta} (k_{-1} \exp(-a\theta_1) - ak_{-1} \exp(-a\theta_1)\theta_1 + k_1 \exp(a\theta_1)c - ak_1 \exp(a\theta_1)c(1 - \theta_1 - \theta_2)) \quad (14)$$

$$a_{13} = \frac{2}{\delta} (-k_1 \exp(a\theta_1)) \quad (15)$$

$$a_{21} = \frac{1}{G} (k_1 \exp(a\theta_1)(1 - \theta_1 - \theta_2)) \quad (16)$$

$$a_{22} = \frac{1}{G} \left( \left( -k_{-1} \exp(-a\theta_1) + ak_{-1} \exp(-a\theta_1)\theta_1 - k_1 \exp(a\theta_1)c + ak_1 \exp(a\theta_1)c(1 - \theta_1 - \theta_2) - \right) \right. \\ \left. - k_2 \exp\left(\frac{2F}{RT} \varphi_0\right) + pk_2\theta_1 \exp\left(\frac{2F}{RT} \varphi_0\right) \right) \quad (17)$$

$$a_{23} = \frac{1}{G} (k_1 \exp(a\theta_1)) \quad (18)$$

$$a_{31} = 0 \quad (19)$$

$$a_{32} = \frac{1}{J} \left( k_2 \exp\left(\frac{2F}{RT} \varphi_0\right) - pk_2\theta_1 \exp\left(\frac{2F}{RT} \varphi_0\right) \right) \quad (20)$$

$$a_{33} = \frac{1}{J} \left( -k_3 - k_4 \exp\left(\frac{2F}{RT} \varphi_0\right) + yk_4\theta_2 \exp\left(\frac{2F}{RT} \varphi_0\right) \right) \quad (21)$$

Observing the Jacobian elements, we can conclude that the *oscillatory behaviour* is possible in this system, like in the analogous [43 – 56], because the main diagonal of the matrix contains the positive elements, responsible for the positive callback. These are:

$$ak_{-1} \exp(-a\theta_1)\theta_1 + ak_1 \exp(a\theta_1)c(1 - \theta_1 - \theta_2)$$

in the case of the positivity of  $a$ , defining the attraction between adsorbed molecules. This is the common cause for the oscillatory behaviour in such type of systems [43 – 56], due to the presence of attracting and distracting forces between the adsorbed organic molecules and the electrode surface.

$$pk_2\theta_1 \exp\left(\frac{2F}{RT} \varphi_0\right) \text{ and } yk_4\theta_2 \exp\left(\frac{2F}{RT} \varphi_0\right) \quad -$$

in the case of the positivity of parameters  $p$  and  $y$ , defining the strong influences of two electrochemical stages on DEL rearrangement. This is one more factor defining the oscillatory behaviour, not only in analogous systems, but also in the case of electroanalytical function of conducting polymers, including the electrochemical stage of oxidation (be it by direct or mediated electron transfer) [57 – 63].

Also it's possible to conclude that the oscillatory behavior in this system is more probable than in the case of the electropolymerization of heterocyclic compounds in general [43 – 48], but less probable, than for the system with electropolymerization in strong acid media [49 – 51] and polythiophene paradox [52 – 56], due to the absence of autocatalytic factor, characteristic for the mentioned type of systems. The oscillations have to be frequent and of small amplitude.

The *steady-state stability* is analyzed by Routh-Hurwitz criterion. In order to simplify the analysis, we introduce new variables and the Jacobian determinant will be rewritten as:

$$\frac{2}{GJ\delta} \begin{vmatrix} -\kappa - \Xi & -\Lambda & -\xi \\ \Xi & \Lambda - \Omega & \xi \\ 0 & \Omega & -\Upsilon - \Theta \end{vmatrix} \quad (22)$$

Opening the brackets and introducing the  $\text{Det } J < 0$  requirement, we obtain the steady-state stability condition for this system as:

$$(-\kappa - \varepsilon)(-\Lambda\gamma - \Lambda\theta + \Omega\gamma + \Omega\theta - \Omega\xi) + \varepsilon(-\Omega\xi - \Lambda\gamma - \Lambda\theta) < 0 \quad (23)$$

The inequation (23) may be satisfied in the case of the negativity of  $\Lambda$  (defining the repealent interaction between adsorped particles with  $a < 0$ ) and the positivity of  $\Omega$  (the absence of significant influences of the electrochemical processes on the DEL capacitances). Like in the analogous systems [43 – 56], these factors warrant the steady-state stability, added, in this case, to the low value of  $\xi$  (desorption unity rate). When these conditions are satisfied, the reaction is controlled by the diffusion of gabapentine towards the pre-surface layer.

*The monotonic instability* in this system is possible, when the influences, stabilizing and destabilizing the steady-state, are equal. It is represented by equality of the left and right sides of (23).

In this case, the steady-state voltamperogram of the system will represent the N-shaped wave. Various steady-states coexist in this point (each one unstable) and the system chooses one. This steady-state is destroyed, while the system conditions are changed.

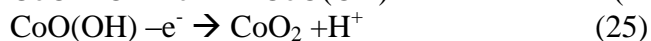
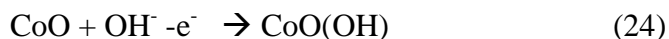
*Autocatalysis* in this concrete process isn't possible, but the model lets the possibility to introduce autocatalytic elements in it (if it is licit). One of the possible examples of it will be exposed below.

*Adaptability of the model to the analogous processes* permits that the analysis of one system gives an approach to more than one process. In the “gabapentine case” it is possible to give the adaptation of the model to the polythiophene paradox case and to electroanalytic systems.

For the polythiophene paradox system, in which the polythiophene, besides of its overoxidation, reacts with another substance to form a different polymer, the equation set (4 – 6) will be the same, but with different rate element for electropolymerization, including the autocatalytic chain propagation (see, for example, [52 – 53]). In this case the oscillatory behavior will be more probable, than in the “gabapentine” case.

For the electroanalytic system, in which the active substance, modified by an analyte is electrooxidized twice and the preliminary product enters the side reaction, the equation set will remain, but the rate expressions, not. The oscillatory behavior will be less probable, than for the “gabapentine” case, due to specific features of electroanalytical systems, described in [57 – 63].

It's possible to adapt the model to inorganic systems by the same way. For example, for the case of cobalt(III) oxyhydroxide synthesis in alkaline media, accompanied with its oxidation to  $\text{CoO}_2$  and dissolution:



In this case, due to the  $\text{CoO(OH)}$  film properties, the equations will be more or less similar to “gabapentinic” and the probability of oscillatory behavior will be equal.

#### 4.CONCLUSIONS

The gabapentine electrooxidation in aqueous solution is a two-step process with the side reaction on the second step. In this case, the steady-state stability is warranted by repealent interaction of adsorped particles and the absence or weakness of influences of the electrochemical stages on DEL capacitances and is defined by gabapentine diffusion towards the pre-surface layer.

The oscillatory behavior for this system is possible, being caused by surface and electrochemical factor. It is more probable, than for the case of the common electropolymerization, but less probable, than for the case of the polythiophene paradox. The oscillations have to be frequent and of short amplitude.

The “gabapentine” model may be suitable for other organic and inorganic electrochemical systems, and for their mutual comparison.

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