

Full Paper

The Electrochemical Oxidation of Procarbazine on Cobalt(III)oxyhydroxide and its Mathematical Evaluation

Volodymyr V. Tkach,^{1,2,*} Sílvio C. de Oliveira,² Severino C.B. de Oliveira,³ Virgínia S. Neves,⁴ Reza Ojani⁵ and Petro I. Yagodynets¹

¹*Chernivtsi National University, 58012, Kotsyubyns'ky Str., 2, Chernivtsi, Ukraine*

²*Universidade Federal de Mato Grosso do Sul, Av. Sen. Felinto. Müller, 1555, C/P. 549, 79074-460, Campo Grande, MS, Brazil*

³*Universidade Federal Rural de Pernambuco, Rua Dom Manuel de Medeiros, s/n, Dois Irmãos, 52171-900, Recife, PE, Brazil*

⁴*Instituto Federal de Educação, Ciência e Tecnologia da Bahia, 40301-015, Rua Emídio dos Santos, s/n, Barbalho, Salvador, BA, Brazil*

⁵*University of Mazandaran, 47416-95447, 3rd km. Air Force Road, Babolsar, Islamic Republic of Iran*

*Corresponding Author, Tel.: +5521991809675

E-Mail: nightwatcher2401@gmail.com

Received: 6 March 2016 / Received in revised form: 29 April 2016 /

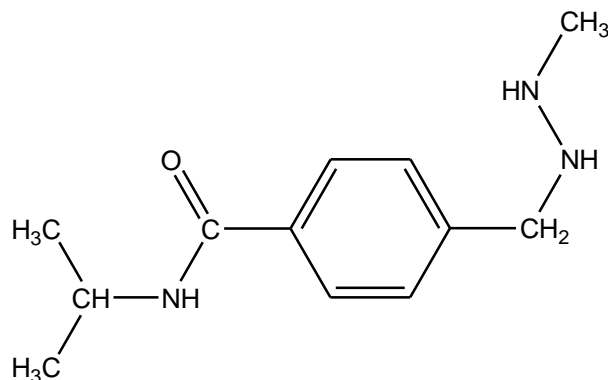
Accepted: 30 April 2016 / Published online: 30 June 2016

Abstract- The possibility of electrochemical oxidation of procarbazine on cobalt(III) oxyhydroxide in slightly alkaline medium, realized for electroanalytical purposes, has been investigated. The corresponding mathematical model has been analyzed by means of linear stability theory and bifurcation analysis. The optimal conditions for electrooxidation and electroanalytical efficiency of the process have been derived. The possibility of oscillatory and monotonic instabilities was also evaluated.

Keywords- Cobalt(III) oxy-hydroxide, Procarbazine, Electrooxidation, Electrochemical sensors, Stable steady-state

1. INTRODUCTION

Procarbazine, or, better saying, N-isopropyl- α -(2-methylhydrazino)-p-toluamide is one of the drugs commonly used in chemotherapy at different types of cancer [1-2].



Scheme 1. Procarbazine formula

The exact mechanism of its action has not been determined yet. However, it is already known that its interaction with various substances (such as enzymes or compounds of transition metals) in the human organism leads to the formation of toxins (aldehydes, hydrazine and metal complexes) [3]. Therefore, search of sensitive, precision and expeditious method for determining the concentration of the compound is a really actual task [4], and the electrochemical detection, yet used for other substances [5-15] seems to be an interesting resolution for it.

On the other hand, the chemically modified electrodes are an interesting tool for its realization, due to their efficiency, rapidity, exact and precise response and affinity to the analyte (due to the key – lock principle). The last factor is principal in the matter of choosing the electrode modifier. For example, for the hydroquinonic compounds different substances and objects are used – from specific molybdenic acid ester to banana tissue [5-12]. The proper quinonic compounds may be used for sulphite [13] and hydrazine [14]. Yet in [15], the quinonic system was present either in the analyte (omeprazole) or in the modifier (polyalizarine). In all cases, these modifiers are chosen due to their capacity to interact with an analyte.

In the case of procarbazine, the main problem is the small amount of data on its electrooxidation [4,16]. In [4] an attempt to determine based on a purely experimental data the mechanism of the electrooxidation of the preparation under neutral conditions has been made. Yet in [17] there was made the theoretical investigation for the possibility for procarbazine oxidation in alkaline media and it was shown, that the alkaline solution has to be more favorable for procarbazine than neutral one (if side reactions are avoided). Such an investigation provides the facility in search of adequate electrode modifier for procarbazine, and cobalt(III) oxyhydroxide, a p-type semiconductor, seen by modern researchers as an

adequate alternative for titanium(IV) dioxide [18-20], and yet used for the detection of oxalates [21] and phenolic compounds [22] in neutral and alkaline solutions, looks like a good alternative.

Nevertheless, there are some difficulties in possible use of CoO(OH) as an electrode modifier. Firstly, its electroanalytical properties' investigation has been commenced recently, so there is still indecision, concerning the most probable mechanism of its action. Secondly, its electrosynthesis may be accompanied by electrochemical instabilities, also characteristic for the oxidation of small organic molecules and heterocyclic compounds' electropolymerization [23-30]. Both problems may obtain their solution, if the electrochemical system gains a rigid theoretical base, which may only be given by a development and an analysis of a mathematical model, capable to describe adequately the system's behavior. Such modeling also permits to compare the behavior of this system with that for the similar ones without any experimental essay.

So, the aim of our work is the theoretical investigation for the procarbazine electrooxidation on CoO(OH). For this purpose, we:

- Develop the correspondent mathematical model;
- Analyze it by means of linear stability theory and bifurcation analysis;
- Detect the steady-state stability requirements and oscillatory and monotonic instabilities' conditions;
- Interpret the obtained data in experimental terms.
- Compare the system's behavior with that for analogous systems [31-35].

2. SYSTEM AND ITS MODELING

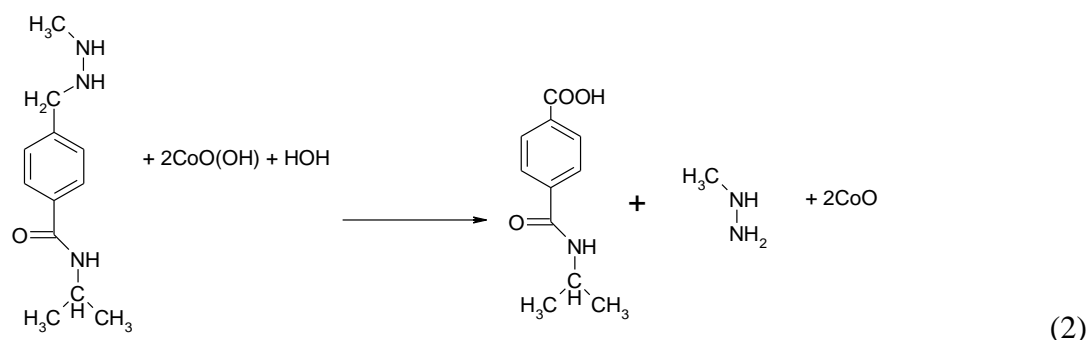
Cobalt (II) oxide film is obtained chemically, or electrochemically, parting from a soluble cobalt (II) salt. This salt, like also hydrazine for probes, may be acquired from Sigma Aldrich or Merck in analytically pure concentrations.

Procarbazine hydrochloride may be obtained from Sigma and used without further purification, as mentioned in [17].

In the presence of hydroxyle, CoO is oxidated to CoO(OH)



While reacting with CoO(OH), procarbazine may be oxidized by summary equation:



In the alkaline medium, the salt is formed, and it is solubilized.

As the reaction (2) has surface-controlled phases, it is realized *via* adsorbed state, so, supposing th

At the supporting electrolyte pH is maintained constant (and it is alkaline), we introduce three variables:

c – the procarbazine concentration in the pre-surface layer,

θ – the procarbazine surface concentration onto CoO(OH) ;

Θ – the CoO(OH) surface concentration.

To simplify the modeling, we suppose that the reactor is intensively stirred, so we can neglect the convection flow. Also we assume that the background electrolyte is in excess, so we can neglect the migration flow. The diffusion layer is supposed to be of a constant thickness, equal to δ , and the concentration profile in it is supposed to be linear. It's also supposed that at the beginning of the reaction CoO covers the entire electrode surface and that procarbazine adsorbs only on CoO(OH) occupied surface areas.

The procarbazine enters the pre-surface layer by its diffusion, and also by its desorption. It also adsorbs and, by this way, leaves the surface. So, taking in account the first Fick's law, the balance equation for its pre-surface concentration will be rewritten as:

$$\frac{dc}{dt} = \frac{2}{\delta} \left(\frac{\Delta}{\delta} (c_0 - c) + r_{-1} - r_1 \right) \quad (3)$$

In which Δ is the diffusion coefficient, c_0 is the procarbazine concentration in the solution bulk, r_1 and r_{-1} are adsorption and desorption rates.

The procarbazine adsorbs on the surface and desorbs from it. It is also oxidized by CoO(OH) , according to the reaction (2). So, its balance equation will be described as:

$$\frac{d\theta}{dt} = \frac{1}{G} (r_1 - r_{-1} - r_2) \quad (4)$$

In which G is procarbazine maximal concentration on CoO(OH) and r_2 its reaction rate with CoO(OH) .

CoO(OH) is formed when CoO is oxidized (see the reaction (1)), and then reacts with procarbazine. When the pH is very high, it dissolves, forming a complex. Thus, its balance equation will be described as:

$$\frac{d\theta}{dt} = \frac{1}{\Gamma}(r_3 - r_2 - r_4) \quad (5)$$

In which Γ is the CoO(OH) maximal surface concentration, r_3 is CoO(OH) formation rate and r_4 is its dissolution rate by the reaction



The correspondent process rates may be described as:

$$r_1 = k_1 c(\theta - \theta) \exp(a\theta) \quad (7)$$

$$r_{-1} = k_{-1} \theta \exp(-a\theta) \quad (8)$$

$$r_2 = k_2 \theta \theta^2 \exp(-a\theta) \quad (9)$$

$$r_3 = k_3 (1 - \theta) \exp\left(\frac{F\phi_0}{RT}\right) \quad (10)$$

$$r_4 = k_4 \theta \exp(-a\theta) \quad (11),$$

In which a is a parameter, describing the interaction between the particles on the surface, the parameters k are corresponding rate constants, F is a Faraday number, ϕ_0 is the potential slope in double electric layer (DEL), R is the universal gas constant and T is the absolute temperature.

It's possible to affirm that this system resembles a classical organic electrooxidation system and the CoO(OH) electrosynthesis at the same time. So, the oscillatory behavior will be more probable for this case, than for each system separately. Yet, the steady-state stability will be defined by more factors, than in the previous cases. This behavior will be discussed below.

3. RESULTS AND DISCUSSION

To analyze the behavior of the system with procarbazine oxidation on CoO(OH), we investigate the equation set (3-5) with the algebraic relations (6-11) by linear stability theory. The Jacobi functional matrix steady-state members may be described as:

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \quad (12)$$

In which:

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

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

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

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

$$a_{22} = \frac{1}{G} (-k_{-1} \exp(-a\theta) + ak_{-1}\theta \exp(-a\theta) - k_1c \exp(a\theta) + ak_1c(\Theta - \theta) \exp(a\theta) - k_2\theta^2 \exp(-a\theta) + ak_2\theta\theta^2 \exp(-a\theta)) \quad (17)$$

$$a_{23} = \frac{1}{G} (k_1c \exp(a\theta) - 2k_2\theta\theta \exp(-a\theta)) \quad (18)$$

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

$$a_{32} = \frac{1}{F} (-k_2\theta^2 \exp(-a\theta) + ak_2\theta\theta^2 \exp(-a\theta)) \quad (20)$$

$$a_{33} = \frac{1}{F} \left(-k_3 \exp\left(\frac{F\varphi_0}{RT}\right) + \iota k_3(1 - \theta) \exp\left(\frac{F\varphi_0}{RT}\right) - 2k_2\theta\theta^2 \exp(-a\theta) - k_4 \exp(-a\theta) + \alpha k_4\theta \exp(-a\theta) \right) \quad (21)$$

In which $\varphi_0 = \iota\Theta$, and ι is the parameter, describing DEL influences of electrochemical reactions.

Taking in account the expressions (13), (17) and (21), one can observe that the *oscillatory behavior* for this system is possible. Moreover, it is more probable for this system than for analogous [31-35], because the main diagonal elements contain more positive elements (responsible for the positive callback), than in analogous cases. It is also possible to conclude that the oscillatory behavior will be defined mostly by surface behavior (particle attraction during the adsorption, desorption and dissolution processes) and, in least way, by DEL effect of CoO(OH) electrosynthesis.

In this case, the oscillations have to be frequent and of short amplitude.

The steady-state stability is corresponding to the linear part of electrochemical parameter – concentration curve and indicates the best sensor response. We investigate the *steady-state stability* using the Routh-Hurwitz criterion. To avoid the cumbersome expressions, we introduce new variables, for the determinant to be rewritten as:

$$\frac{2}{\delta FG} \begin{vmatrix} -\kappa_1 - X & -E & -I \\ X & E - \Sigma & I - P \\ 0 & -\Sigma & \Pi - P - T \end{vmatrix} \quad (22)$$

Applying to the system the stability requisite $\text{Det } J < 0$, salient from the criterion, we obtain the steady-state stability condition for this system, described as:

$$-\kappa_1(E\Pi - EP - ET - \Sigma\Pi + \Sigma T + \Sigma I) - X(\Sigma T - \Sigma\Pi + \Sigma I) < 0 \quad (23),$$

and transformed into:

$$\kappa_1(E\Pi - EP - ET - \Sigma\Pi + \Sigma T + \Sigma I) + X(\Sigma T - \Sigma\Pi + \Sigma I) > 0 \quad (24)$$

It is possible to see, that, due to the positivity of diffusion parameter κ_1 and adsorption parameter X , the negativity of the surface behavior parameter E , procarbazine electrooxidative dissolution parameter Σ and CoO(OH) dissolution parameter T , describing

the repulsion of adsorbed particles and the fragility of DEL influences of the CoO(OH) electrosynthesis, the inequation (24) will be satisfied, and the steady-state stability, warranted. In low procarbazine concentrations, the process will be diffusion-controlled, and in high concentrations, adsorption controlled. The topologic area of steady-state stability in this system continues being vast, but is narrower than in [31-35] (see the Table 1).

Table 1. The concentrational effects on steady-state stability of the system

| Procarbazine concentration | Stage rapidity | | Behavior character | Steady-state stability |
|----------------------------|----------------|------------|-------------------------------------|---|
| | Diffusion | Adsorption | | |
| Low | Slow | Rapid | Diffusion-controlled | Stable, surface instability is probable |
| Medium | Slow | Slow | Diffusion-and adsorption controlled | Stable, with more probabilities for surface instabilities |
| High | Rapid | Slow | Adsorption-controlled | Stable with high probability of surface instabilities |

The pH-dependence of the system is significant. The optimal pH for the electroanalytical system is $7 < \text{pH} < 8$. The lower and higher pH may destroy the electrode material and the analyte [17], in the case of acidic pH, the oxidation isn't favored. Thus, the pH – current peak curve has to be asymmetric, presenting its peak in pH, close to neutral (Table 2).

Table 2. pH-dependence of electroanalytical efficiency of CoO(OH) as a sensor of procarbazine

| pH | Material Stability | Procarbazine oxidation rate | Electroanalytical efficiency |
|-----|-----------------------------------|--------------------------------------|--|
| 0-7 | Unstable | Slow | Inefficient, material dissolution |
| 7 | Stable | Regular | Efficient |
| 7-8 | Stable | Rapid | Efficient |
| >8 | Unstable (with $\text{pH} > 12$) | Analyte destruction (side reactions) | Inefficient, material dissolution, analyte dissolution |

It permits the use of CoO(OH) in electrochemical micro- and nanosensors not only *in vitro*, but also *in vivo*, by monitoring of the cancer-suffering organs with the pH, correspondent to the table (like duodenum). So, CoO(OH) may be efficient electrocatalyst for electrooxidation of procarbazine in neutral and lightly alkaline media.

The *monotonic instability* for this system is possible, when the stabilizing and destabilizing influences on the surface and in DEL are equivalent. It is revealed by N-shaped part of voltamperogram and the condition of its appearance may be described as:

$$\kappa_1(\varepsilon\Pi - \varepsilon P - \varepsilon T - \Sigma\Pi + \Sigma T + \Sigma I) + X(\Sigma T - \Sigma\Pi + \Sigma I) = 0 \quad (25)$$

Yet, for the case of the presence of complex-forming substances as interfering substances and analytes in the solution, the material is destroyed, but the point of discussion is the electroanalytical use of complex-forming reactions. This case will be observed in one of our next works.

4. CONCLUSIONS

From the analysis of the system with the electrooxidation of procarbazine over CoO(OH) it was possible to conclude that:

- CoO(OH) has perspective of use as an efficient electrocatalyst for electrooxidation of procarbazine in neutral and lightly alkaline media. The curve pH – electrochemical parameter has to be asymmetric, having its peak in pH value, close to 7.
- The steady-state stability is maintained by the repulsion of adsorbed particles and fragility of DEL influences of CoO(OH) electrosynthesis. Depending on analyte concentration, the reaction may be diffusion- or adsorption-controlled.
- The steady-state stability topological region remains vast, but it is narrower, than for analogous systems.
- The oscillatory behavior, caused by surface and electrochemical factors, is more probable, then for analogous systems, due to the high probability of surface instability of procarbazine and CoO(OH).
- The monotonic instability for this system is possible, and it may occur in the case of equality of stabilizing and destabilizing influences in DEL and on surface.
- The presence of complex-forming substances as interfering compounds or analytes for CoO(OH)-assisted sensor destroys the modifying material, as it is capable to form complex with it, but the electroanalytical use of complex-forming reaction may be posed in discuss.

REFERENCES

- [1] H. B. Newton, Handbook of Brain Tumor Chemoterapy, Elsevier (2006).

- [2] D. A. Shiba, R. J. Weinkam, *Cancer Chemoter. Pharmacol.* 11 (1983) 124.
- [3] J. K. Aronson, *Meyler's Side Effects of Drugs in Cancer and Immunology*, Elsevier (2010).
- [4] S. C. B. Oliveira, C. H. S. Mendes, F. F. S. Filho, N. L. Queiroz, J. A. M. Nascimento, and V. B. Nascimento, *J. Electroanal. Chem.* 746 (2015) 51.
- [5] L. H. de Oliveira, A. C. Dias Souza, L. Pizzuti, V. Souza Ferreira, L. A. Pradela Filho, R. M. Takeuchi, A. L. dos Santos, and M. A. Gonçalves Trindade, *Orbital. Elec. J. Chem.* 6 (2014) 255.
- [6] L. Sasso, A. Heiskanen, F. Diazzi, M. Dimaki, J. Castillo-León, M. Vergani, E. Landini, R. Raiteri, G. Ferrari, M. Carminati, M. Sampietro, W. E. Svendsen, and J. Emnéus, *Analyst* 138 (2013) 3651.
- [7] T. Qian, C. Yu, X. Zhou, P. Ma, S. Wu, L. Xu, and J. Shen, *Biosens. Bioelectron.* 58 (2014) 237.
- [8] M. Lin, *RSC Adv.* 5 (2015) 9848.
- [9] C. C. Vishwanath, and B. Kumara Swamy, *Anal. Bioanal. Electrochem.* 6 (2014) 573.
- [10] H. Beitollahi, H. Karimi-Maleh, and I. Sheikhoae, *Casp. J. Chem.* 1 (2012) 17.
- [11] L. Scarpetta, A. Mariño, K. Bolaños, Y. Leiva, P. Castiblanco, É. Nagles, *Rev. Col. Cien. Quím. Farm.*, 44(2015), 311.
- [12] J. B. Raof, A. Kiani, R. Ojani, and R. Valliolahi, *Anal. Bioanal. Electrochem.* 3 (2011) 59.
- [13] T. Khajvand, R. Ojani, and J. B. Raof, *Anal. Bioanal. Electrochem.* 6 (2014) 501.
- [14] S. Z. Mohammadi, H. Beitollahi, and E. B. Asadi, *Environm. Monit. Assess.* 187 (2015) 121.
- [15] K. R. Mantasha, B. E. Kumara Swamy, and K. Vasantakumar Pai, *Anal. Bioanal. Electrochem.* 6 (2014) 234.
- [16] J. P. McCue, and J. H. Kennery, *J. Bioinorg. Chem.* 7 (1977) 5.
- [17] V. V. Tkach, R. Ojani, M. O. G. Espínola, P. Yagodynets', S. C. de Oliveira, *ans Química: ciência, tecnologia e sociedade* 3 (2014) 35.
- [18] J. Yang, H. Liu, W. N. Martens, and R. L. Frost, *J. Phys. Chem. C* 114 (2010) 111.
- [19] J. W. Wang, and Y. M. Kuo, *Phys. Stat. Sol.* 210 (2013) 494.
- [20] A. D. Jagadale, D. P. Dubal, and C. D. Lokhande, *Mat. Res. Bull.* 47 (2012) 672.
- [21] A. Stadnik, E. M. Caldas, A. Galli, F. J. Anaissi, *Orbital. Elec. J. Chem.* 7 (2015) 122.
- [22] J. S. Bonini, F. Quadros Mariani, E. Guimarães de Castro, A. Gali, R. Marangoni, F. J. Anaissi, *Orbital Elec. J. Chem.* 7 (2015) 318.
- [23] A. J. Pearlstein, and J. A. Johnson, *J. Electrochem. Soc.* 136 (1991) 1290.
- [24] I. Das, N. R. Agrawal, S. A. Ansari, and S. K. Gupta, *Ind. J. Chem.* 47 (2008) 1798.
- [25] S. U. Rahman, and M. S. Ba-Shammakh, *Synth. Met.* 140 (2004) 207.
- [26] A. S. Liu, and M. A. S. Oliveira, *J. Braz. Chem. Soc.* 18 (2007) 143.

- [27] D. Sazou, *Synth. Met.* 130 (2002) 45.
- [28] O. Stadnik, N. Ivanova, and Y. Boldyrev, 218th Int. Electrochem. Soc. Meeting. Abstract # 2240, [Online] available at: <http://ma.ecsdl.org/content/MA2010-02/38/2240.full.pdf> Accessed at 8th of August (2015).
- [29] O. Stadnik, *Synthesis, Electrochemical and Photoelectrochemical Properties of the Oxide-hydroxide Compounds of Cobalt*, Diss. Kand. Chim. N. – Kyiv. (2011).
- [30] I. Das, N. Goel, N. R. Agrawal, and S. K. Gupta, *J. Phys. Chem.* 114 (2010) 12888.
- [31] V. V. Tkach, S. C. de Oliveira, G. Maia, F. C. Dall’acqua Hirschmann, G. Karim-Nezhad, R. Ojani, and I. Y. Petro, *Mor. J. Chem.* 4 (2016) 112.
- [32] V. V. Tkach, S. C. de Oliveira, F. J. Anaissi, R. Ojani, U. Páramo-García, O. Yelenich, and P. I. Yagodynets, *Anal. Bioanal. Electrochem.* 8 (2016) 1.
- [33] V. Tkach, B. Kumara Swamy, R. Ojani, M. Blanes, and P. Yagodynets, *Orbital. Elec. J. Chem.* 7 (2015) 1.
- [34] V. V. Tkach, R. Ojani, M. O. G. Espínola, P. Yagodynets, S. C. de Oliveira, *Química: ciência, tecnologia e sociedade* 3 (2014) 35.
- [35] V. Tkach, V. Nechporuk, and O. Slipenyuk, *Eclet. Quím.* 37 (2012) 74.