Full Paper

The Theoretical Evaluation of the Possibility of Theacrine Electrichemical Detection over the Polymers of Quinonic Compounds

Volodymyr V. Tkach,[1,2,*] Yana G. Ivanushko,[1] Svitlana M. Lukanova[1], Marta V. Kushnir,[1] Sílvio C. de Oliveira,[2] Reza Ojani[3] and Petro I. Yagodynets´[1]

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

*Corresponding Author, Tel.: 380506400359,; Fax: +5521991809675
E-Mail:nightwatcher2401@gmail.com

Abstract- The possibility of theacrine electrochemical determination has been evaluated from the theoretical point of view. The correspondent mechanism has been suggested, and the correspondent model, developed and analyzed by means of linear stability theory and bifurcation analysis. It was verified that theacrine may be electrochemically detected in neutral media over the polymers of the compounds, belonging to the quinone-hydroquinone system, serving as mediator of electrons and protons transfer. The analytical signal has to be clear and easily interpreted. The possibility of oscillatory and monotonic instabilities has also been detected.

Keywords- Food security, Theacrine, Conducting polymers, Quinonic compounds, Electrochemical detection, Stable steady state

1. INTRODUCTION

Theacrine, also known as 1,3,7,9-tetramethyluric acid (Fig. 1) is an alkaloid, naturally occurring in cupuaçu plant, growing in the North of Brazil (mostly in the states of Pará,

Amazonas, Rondônia and Acre), like also in Colombia, Peru and Bolivia [1-2]. It is also found in a Chinese tea plant, kudingcha [3].
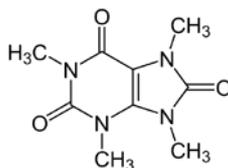

Fig. 1. Theacrine

It manifests anti-inflamatory and analgesic effecs [4-7] and affects adenosine signaling by mechanism, similar to that of caffeine [8-9].

Nevertheless, although theacrine is a relatively safe drug [10-11], its effect strongly depends on the concentration [12-13]. Moreover, while used in formulations, theacrine may be confused with other uric acid derivatives. Thus, the development of a cheap, precise, exact and sensitive method of its detection and quantification remains an actual problem [14-16].

Although the electrochemical techniques have been developed and successfully applied to other uric acid derivatives (the proper uric acid, caffeine, theobromine) [17-22], none of these methods have been applied to thecrine yet. The similarity of its composition to that of the mentioned compounds makes think that theacrine may also be subjected to electrochemical analysis. Moreover, the discovering of the proper theacrine has been realized recently, so this work has to be interesting also from this point of view.

On the other hand, the quinone-hydroquinonic systems and polymers, based on them The development of an electroanalytical method leads the research, *a priori,* to resolve some problems like:

- The indefinition in theacrine electrochemical detection mechanism;
- The possibility of electrochemical instabilities, characteristic for the anodic oxidation of small organic compounds (including the electropolymerization processes) [23];
- In case of use of chemically modified electrodes, the indefinition in applicability of a certain modifier.

Their resolution is impossible without development of a mathematical model, capable to describe adequately the system´s behavior. The modeling also lets us compare it with the behavior of other, similar systems.

So, the general goal of our work is the theoretical mechanistic investigation of theacrine electrochemical oxidation. It´s resolution is achieved by the realization of specific goals like:

- The suggestion of a mechanism of theacrine electrochemical oxidation;
- The development of a mathematical model, correspondent adequately to the process;
- The analysis of the model and steady-state stability investigation;
- The comparison of this system with the similar ones [24-28].

2. SYSTEM AND ITS MODELING

Theacrine may be either isolated from the above-mentioned plants, or acquired in the market of chemicals, like also in the market of food-additives. It is also possible to synthetize it, parting from related compounds.

As a uric acid derivative, bearing carboxyl moiety in the position 2, theacrine undergoes oxidation in neutral solution according to the equation (1)

$$(1)$$
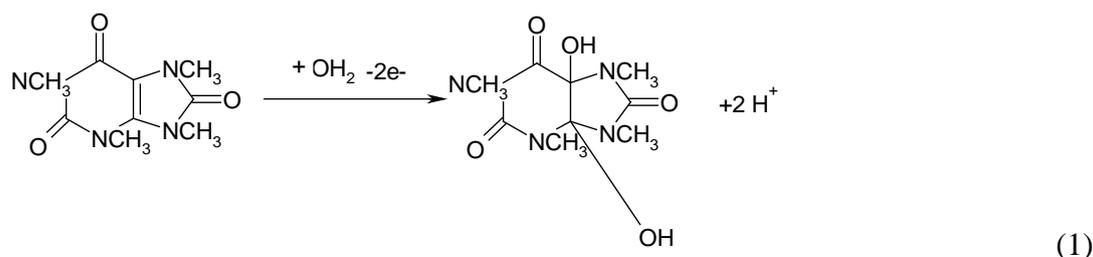
Due to the two-electron – two-proton character of the reaction, it is possible to predict that a conducting polymer, containing quinonic system, like polyalizarine in [24] and polydopamine (in its oxidized form) in [25], may serve as excellent modifier for it.

In this case, the sensing mechanism will be presented as:

$$+ H_2O + Q \rightarrow \qquad\qquad + H_2Q \qquad\qquad (2)$$

$$H_2Q – 2e^- - 2H^+ \rightarrow Q \qquad\qquad (3),$$
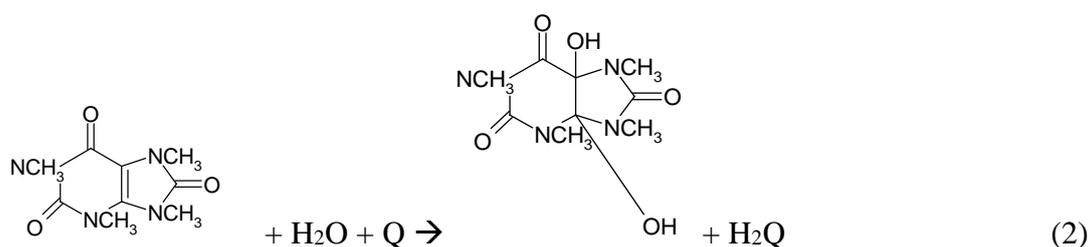
In which Q is a quinonic moiety.

Taking this in account, to describe the process mathematically, we introduce three variables:

θ – theacrine concentration in the pre-surface layer;

Θ – the polymer reduced form coverage degree;

h – the protons´ pre-surface layer concentration.

In order 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 is also supposed that at the null-moment of the reaction the oxidized polymer covers the entire anode surface.

Theacrine enters in the pre-surface layer by means of its diffusion, and reacts with quinonic compounds and, eventually, with protons, surging from the electrochemical reaction. Thus, taking in account the first Fick´s law, its balance equation will be described as:

$$\frac{d\theta}{dt} = \frac{2}{\delta}\left(\frac{\Delta}{\delta}(\theta_0 - \theta) - r_2 - r_h\right) \tag{1},$$

In which Δ is the theacrine diffusion coefficient, θ_0 is the theacrine bulk concentration, r_2 is the rate of the reaction (2), and r_h is the reaction rate of the reaction of analyte with protons. *The hydroquinonic form* of the polymer is formed by the reaction (2) and is reduced by theacrine by the reaction (3). So, its balance equation will be described as:

$$\frac{d\Theta}{dt} = \frac{1}{G}(r_2 - r_3) \tag{2},$$

In which G is the maximal concentration of the quinonic form of the polymer.

The protons are formed during the reaction (3), while the reduced form of the polymer is oxidized. Once formed, they may eventually attack either the analyte, or the polymer oxidized form. So, their balance equation may be described as:

$$\frac{dh}{dt} = \frac{2}{\delta}(r_3 - r_h - r_{h2}) \tag{3},$$

In which r_{h2} is the reaction rate of the protonic attack of the oxidized polymer form.
The correspondent reaction rates may be described as:

$$r_2 = k_2\theta(1 - \Theta) \tag{4}$$

$$r_3 = k_3\Theta\exp\left(\frac{2F\gamma\Theta}{RT}\right) \tag{5}$$

$$r_h = k_h h\theta \tag{6}$$

$$r_{h2} = k_{h2}h(1 - \Theta) \tag{7}$$

In which the parameters k are corresponding reactions rate constants, F is the Faraday number, γ is the coefficient, describing the influence of the electrochemical process on DEL capacitance, R is the universal gas constant, and T is the absolute temperature.

As either the stability of the analyte, or the electrochemical reactions, involving its oxidation, depend on pH, the protons play an important role in the electroanalytical process for theacrine. It will be discussed below.

3. RESULTS AND DISCUSSION

We investigate the behavior of theacrine electrochemical oxidation over a quinone-containing conducting polymer, analyzing the equation set (1-3) by means of linear stability theory. The steady-state Jacobi functional matrix elements may be represented as:

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \tag{8}$$

In which:

$$a_{11} = \frac{2}{\delta}\left(-\frac{\Delta}{\delta} - k_2(1-\Theta) - k_h h\right) \tag{9}$$

$$a_{12} = \frac{2}{\delta}(k_2\theta) \tag{10}$$

$$a_{13} = \frac{2}{\delta}(-k_h\theta) \tag{11}$$

$$a_{21} = \frac{1}{G}(k_2(1-\Theta)) \tag{12}$$

$$a_{21} = \frac{1}{G}(k_2(1-\Theta)) \tag{13}$$

$$a_{22} = \frac{1}{G}\left(-k_2\theta - k_3\exp\left(\frac{2F\gamma\Theta}{RT}\right) + \gamma k_3\Theta\exp\left(\frac{2F\gamma\Theta}{RT}\right)\right) \tag{14}$$

$$a_{23} = 0 \tag{15}$$

$$a_{31} = \frac{2}{\delta}(-k_h h) \tag{16}$$

$$a_{32} = \frac{2}{\delta}\left(k_3\exp\left(\frac{2F\gamma\Theta}{RT}\right) - \gamma k_3\Theta\exp\left(\frac{2F\gamma\Theta}{RT}\right) + k_{h2}h\right) \tag{17}$$

$$a_{33} = \frac{2}{\delta}(-k_{h2}h(1-\Theta) - k_h\theta) \tag{18}$$

Observing the expressions (9), (14) and (18), it is possible to see that the *oscillatory behavior* in this system is possible, as the main diagonal element (14) contains the positive element, referring to the positive callback.

The unique cause of the oscillatory behavior in this system are the influences of the electrochemical processes in DEL, described by the positivity of the element $\gamma k_3\Theta\exp\left(\frac{2F\gamma\Theta}{RT}\right)$. This factor is also common for similar systems [24-28]. The oscillations are expected to be frequent and of little amplitude.

To investigate the *steady-state stability* in the system, we apply the Routh-Hurwitz criterion to the equation set (1-3). To avoid the appearance of cumbersome expressions, we introduce new variables, so the jacobian determinant will be described as:

$$\frac{4}{\delta^2 G} \begin{vmatrix} -\kappa - \Omega - P & \Lambda & -X \\ \Omega & -\Lambda - \Xi & 0 \\ -P & \Xi + \xi & -X - \Pi \end{vmatrix} \tag{19}$$

Opening the brackets, and applying the steady-state stability requirement Det J<0, salient from the criterion, we obtain the steady-state stability condition as:

$$(-X - \Pi)(\kappa\Lambda + P\Lambda + \kappa\Xi + \Omega\Xi + P\Xi) - X(\Omega\Xi + \Omega\xi - P\Lambda - \Xi P) < 0 \tag{20}$$

After the rearrangement and annihilation of equal elements with opposite signs, the inequation (20) will be transformed in:

$$-\Pi(\kappa\Lambda + P\Lambda + \kappa\Xi + \Omega\Xi + P\Xi) - X(\kappa\Lambda + \kappa\Xi + 2\Omega\Xi + \Omega\xi) < 0 \tag{21}$$

Or even

$$\Pi(\kappa\Lambda + P\Lambda + \kappa\Xi + \Omega\Xi + P\Xi) + X(\kappa\Lambda + \kappa\Xi + 2\Omega\Xi + \Omega\xi) > 0 \tag{22}$$

The inequation (22) is warranted to be satisfied, if the parameter Ξ, describing the electrochemical reaction is positive, defining the fragility of the influences of electrochemical reaction on DEL capacitances. This requisite is also common for the similar systems [24-28].

So, the steady-state is stable and easy to maintain. Nevertheless, its electroanalytical efficiency will also depend on pH of the solution. As the pH is decreasing during the electrochemical reaction, if the relatively big concentrations of the analyte are used on a relatively small electrode, the protons' interference will be significant, although the steady-state remains stable. So, the purely neutral (pH=7) solutions may be used only with electrodes, possessing a relatively big active area.

Nevertheless, with small analyte concentrations, the concentration of protons formed is very small and insufficient to disturb greatly the electroanalytic process.
The process is diffusion-controlled with small analyte concentrations. Yet in big analyte concentrations, the protons' formation will be another factor controlling it. While electroanalytically efficient, the stable steady-state describes the liner dependence between the electrochemical parameter and the analyte concentration.

In the case of the equality of the influences stabilizing and destabilizing the system, the *monotonic instability* is realized, and its realization is correspondent to the detection limit. Its condition is

$$\Pi(\kappa\Lambda + P\Lambda + \kappa\Xi + \Omega\Xi + P\Xi) + X(\kappa\Lambda + \kappa\Xi + 2\Omega\Xi + \Omega\xi) = 0 \tag{23}$$

The use of lightly alkaline solution (7<pH<8) suppresses the effect of protons' formation. In this case, the hydroquinonic form oxidation will be realized by the reaction:

$$H_2Q + 2OH^- -2e^- \rightarrow Q + H_2O \qquad (4)$$

In this case, the electroanalytical process will be favored, as it is observed in other systems with caffeine and uric acid electrochemical detection systems [17-22]. The model for this system will be described in one of our next works.

Applicability. The working pH let determine the theacrine concentrations *in vitro* and, limitedly, *in vivo* (inclusively in teas and juices). Polymer composites may be used to separate the oxidation peaks of theacrine from those correspondent to interfering substance.

In the case of the use of big electrode and small concentrations, the protons' influence may be neglected, and the equation (3) will be eliminated from the set. The model will be transformed to that described in [26].

In the case of the use of a *polyelectrolyte* as a modifying polymer, the solution pH has to be prepared by manner to neutralize the polyelectrolyte proton or hydroxyl activity, in order to avoid the electroanalytical inefficiency of the steady-state.

4. CONCLUSIONS

The theoretical investigation of theacrine electrochemical analysis let conclude that:

- The steady-state stability is easy to maintain. Nevertheless, the electroanalytical efficiency of the steady-state will depend on the pH. In the case of the use of small electrodes in big analyte concentrations, the protons´ behavior will drive the steady-state to its electroanalytical inefficiency;
- The electroanalytical process is diffusion-controlled. The unique cause, capable to destabilize the steady-state is the influences of the electrochemical process on DEL capacitances;
- These influences are the unique factor, capable to cause the oscillatory behavior in the system;
- The working pH let determine the theacrine concentrations *in vitro* (inclusively in teas and juices) and, limitedly, *in vivo*. Polymer composites may be used to separate the oxidation peaks of theacrine from those correspondent to interfering substance;
- In the case of the use of a polyelectrolyte as a modifying polymer, the solution pH has to be prepared by manner to neutralize the polyelectrolyte proton or hydroxyl activity, in order to avoid the electroanalytical inefficiency of the steady-state;
- In the case of the lightly alkaline solutions (7<pH<8), the electroanalytical process will be more efficient, due to protons´ influence suppression;

- In the case of the use of big electrode and small concentrations, the protons' influence may be neglected, and the model will be simplified.

REFERENCES

[1] Hector L Lopez, Shawn Wells, Tim N. Ziegenfuss, Theacrine-based supplement and method of use thereof. US Patent US20150132280.

[2] A. Clewell, G. Hirka, R. Glavits, P. A. Palmer, J. R. Endres, T. S. Murbach, T. Marx, and I. Pasics Szakonyiné, J. Toxicol., 2016 (2016) 17 p.

[3] X. Q. Zheng, C. X. Ye, M. Kato, A. Crozier, and H. Ashihara, Phytochemistry 60 (2002) 129.

[4] Y. Wang, X. Yang, X. Zheng, J. Li, C. Ye, and X. Song, Fitoterapia 81 (2010) 627.

[5] A. A. Feduccia, Y. Wang, J. A. Simms, H. Y. Yi, R. Li, L. Bjeldanes, C. Ye, and S. E. Bartlett, Pharm. Biochem. Behavior 102 (2012) 241.

[6] W. X. Li, Y. F. Li, Y. J. Zhai, W. M. Chen, H. Kuriharaand, and R. R. He, J. Agric. Food Chem. 61 (2013) 6328.

[7] [Online] available at: http://www.mountaindogdiet.com/nutrition/nutrition-basic/theacrine-supplementation/, accessed at 31st of October, (2016)

[8] S. Hayward, J. Mullins, S. Urbina, E. Santos, K. Villa, N. Viana, S. Perkins, J.Ander, A. Olivencia, S. McGorty, C. Wilborn, and L. Taylor, J. Int. Soc. Sports Nutr. 12 (2015) P59.

[9] S. M. Habowski, J. E. Sandrock, A. W. Kedia, and T. N. Ziegenfus, J. Int. Soc. Sports Nutr. 11 (2014) P49.

[10] L. Taylor, P. Mumford, M. Roberts, S. Hayward, J. Mullins, S. Urbina, and C. Wilborn, J. Int. Soc. Sports Nutr. 13 (2016) 2.

[11] D. Wang, J. Lu, Y. Cheng, X. Shi, X. Song, C. Ye, Acta Sci. Nat. Univ. Sun yat seni 49 (2010) 76.

[12] J. K. Xu, H. Kurihara, L. Zhao, X. S. Yao, J. Asian Nat. Res. Prod. 9 (2007) 665.

[13] Y. Wang, M. F. Yang, S. Gang, Y. Ch. Hing, S. Xiaohong, Zh. Xinjang Lishizhen, Med. Pharm. 10 (2010) [online] http://www.taozhy.com/baokan/7114.thtml, article in Chinese.

[14] T. N. Zeigenfuss, S. M. Habowski, J. E. Sandrock, A. W. Kedia, C. M. Kerksick, and H. L. Lopez, J. Diet Suppl. 10 (2016) 1.

[15] W. K. Zhang, J. K. Xu, J. Q. Hu, S. B. Wang, P. Li, K. Hiroshi, X. S. Yao, and B. H. Tang, Zhonqquo Zhong Yao Za Zhi 38 (2013) 753.

[16] X. R. Yang, C.X. Ye, J. K. Xu, and Y. M. Jiang, J. Food Chem. 100 (2007) 1132.

[17] L. Peng, X. Song, X. Shi, J. Li, and C. Ye, J. Food Comp. Anal. 21 (2008) 559.

[18] Y. Cheng, Y. Zh. Yan, J. Lu, C. Ye, D. Wang, Acta Sci. Nat. Univ. Sunyatseni 49 (2010) 65.

[19]   L. Svorc, Int. J. Electrochem. Sci. 8 (2013) 5755.

[20] A. J. Jeevagan, and S. Abraham John, Electrochim. Acta. 77 (2012) 137.

[21] A. C. Torres, M. M. Barsan, and C. M. A. Brett, Food Chem. 149 (2014) 215.

[22] W. Y. H. Khoo, M. Pumera, and A. Bonanni, Anal. Chim. Acta 804 (2013) 92.

[23] B. H. Hansen, and G. Dryhurst, J. Electroanal. Chem. Interf. Electrochem. 30 (1971) 407.

[24] I. Das, N. R. Agrawal, S. A. Ansari, and S. K. Gupta, Ind. J. Chem. 47A (2008) 1798.

[25] K. R. Mahantesha, B. E. Kumara Swamy, and K. Vasantakumar Pai, Anal. Bioanal. Electrochem. 6 (2014) 234.

[26] M. Amiri, E. Amali, A. Nematollhzadeh, and H. Salehniua, Sens. Actuator B 228 (2016) 53.

[27] V. Tkach, V. Nechyporuk, and P. Yagodynets´. Rev. Colomb. Cien. Quím. Farm. 41 (2012) 203.

[28] V. V. Tkach, B. Kumara Swamy, R. Ojani, O. Aksimentyeva, J. Zerbino, P. Agodynets, and R. Mascarenhas, Rev. Colomb. Cien. Quím. Farm. 44 (2015) 148.

[29] V. V. Tkach, B. Kumara Swamy, and R. Ojani, Orbital Elec. J. Chem. 7 (2015) 1.