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The theoretical evaluation of estradiol electrochemical determination, assisted by a new triazolic schiff base

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Abstract

The possibility of estradiol electrochemical determination on an anode, modified by a new triazolic Schiff base, has been theoretically evaluated. The correspondent mathematical model has been developed and analyzed by means of linear stability theory and bifurcation analysis. It was shown that the Schiff base provides an efficient estradiol electrochemical determination in neutral and basic media. The proper basicity of Schiff base and triazolic ring favors the process. The steady-state stability is easy to establish. The oscillatory behavior, in this case, is possible, due to the double electric layer influences of the electrochemical stage.

Keywords: ovarian hyperstimulation syndrome, estradiol, electrochemical sensors, chemically modified electrodes, fumigatin, stable steady-state

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a medical condition, occurring in women taking fertility medication to stimulate egg growth, and in other women in very rare cases [1 – 4]. Most cases are mild; rarely, the condition may become severe, leading to serious consequences.

Its occurrence may be mild, moderate, severe and critical [2 – 4], including symptoms from mild (abdominal pain, diarrhea) to severe (hemoconcentration, thrombosis). Mortality is low, but several fatal cases have been reported [5]. The predictor of the syndrome development is the enhance of the steroid sexual hormones' concentragtion. Estradiol (Fig. 1) is the basic hormone, influencing the

development of the OHSS [6 - 7], which makes it an interesting investigation object.Its biological activity is dose-related, thus, the development of a method, capable to detect and quantify this compound by rapid and efficient manner is really actual.
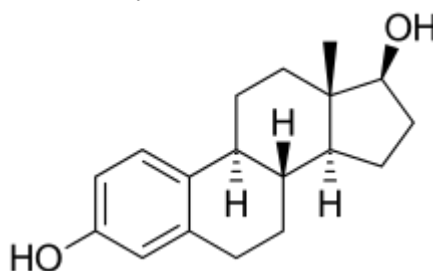

Fig. 1. Estradiol

For now, some methods of electrochemical determination have already been developed for steroid hormones [8 - 10]. Moreover, from its chemical composition, it is possible to suggest that it would be possible to determinate it by electrodes, using Schiff bases and their complexes, very popular in electroanalytics [11 - 18]. The list may even include some newly synthetized compounds.

Nevertheless, the use of the principally new electrode modifier requires an *a priori* mechanistic theoretical analysis of the electroanalytical system. It would help us to resolve some problems like:

- The indecision in interaction of the electrode with the analyte and on its role in electroanalytical system;

- The possibility of the appearance of electrochemical instabilities in similar systems with electrooxidation of different organic molecules [19 – 20], including electrochemical polymerization [20].

The *a priori* theoretical investigation provides us the possibility to resolve the mentioned problems during the elaboration of the sensor. Such an investigation includes the development and analysis of a mathematical model, capable to describe adequately the electroanalytical system. So, the principal objective of this work is the mechanistic investigation of an electroanalytical system with f estradiol electrochemical determination, assisted by a newly synthetized triazolic Schiff base. It is realized by achieving the specific goals like:

- Suggestion of the mechanism, presented as a sequence of chemical and electrochemical transformations, leading to the appearance of analytical signal;
- Development of a mathematical model, based on this mechanism;
- Analyze the model, obtaining the steady-state stability conditions (correspondent to the electroanalytical efficiency of the process) and of the oscillatory and monotonic instability;
- Compare the behavior of this system with that of the analogous systems [21 – 23].

System and Its Modeling

Materials and reagents.

5-(3-fluorophenyl)-4-amino-1,2-4-triazol-3-thiole has been provided as a courtesy by Zaporizhzhya State Medical University, and 5-phenylazosalicylic aldehyde has been used from the deposit of Chernivtsi National University. Butanol, ether and DMF have been acquired from Sfera Sim™ (Lviv, Ukraine) and used without further purification. The ^{1}H NMR experiment has been carried out in Enamin (Kiev, Ukraine), by Varian Mercury 400 spectrometer (400 MHz) in DMSO-d_6. The reaction has been realized as in the Fig. 2:
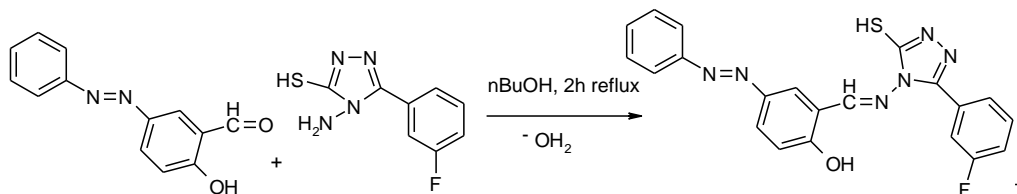

Fig. 2 The synthesis of the Schiff base

Experimental.

The mixture of 0,57 g (0,0025 mol) of 5-phenylazosalicylic aldehyde with 0,53 g (0,0025 mol) of 5-(3-fluorophenyl)-4-amino-1,2,4-triazolyl-3-thiole in 20 ml of butanol were refluxed during 2 hours. The reaction mixture has been kept on room temperature during 12 hours. The deposit has been filtered out and rinsed by ether, yielding 0,43 g of the Schiff base (m. p >250^0 C, chrystallized from DMF). Found: C: 60,56 %, H: 3,43%; N: 20,04 %; $C_{21}H_{14}FN_6OS$. Calculated: C: 60,42 %, H: 3,38%; N: 20,13 %. ^{1}H NMR shifts of the molecule are represented on the Fig. 3:
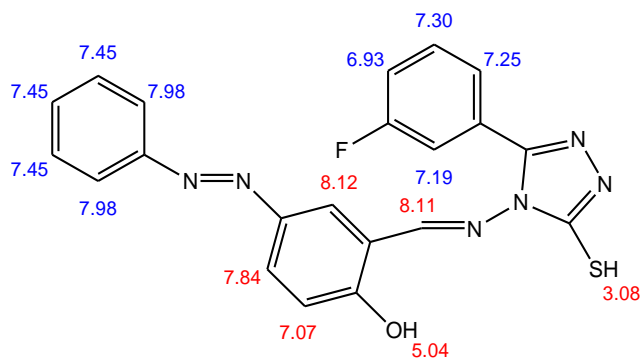

Fig. 3. The ^{1}H NMR shifts for the Schiff base

As the compound contains either the diazogroup or the Schiff bond, the electroanalytical process may occurred by two parallel mechanisms, using the azo-group (Fig. 4):
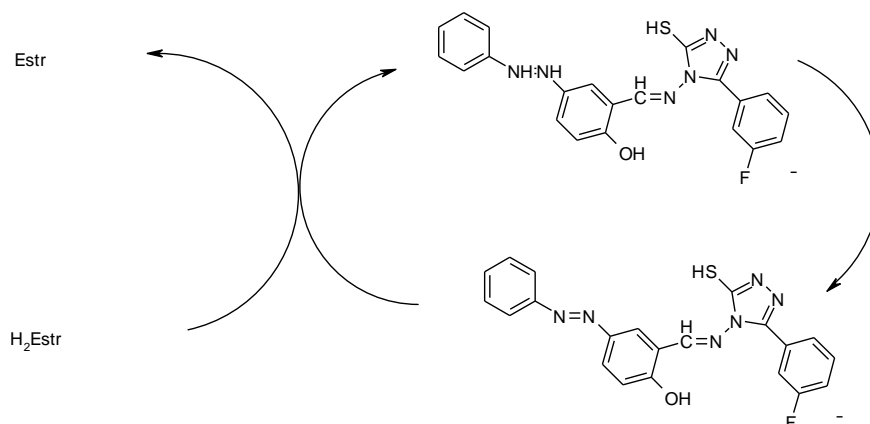
Fig. 4. The scheme of the electroanalytical process with the participation of azo-group
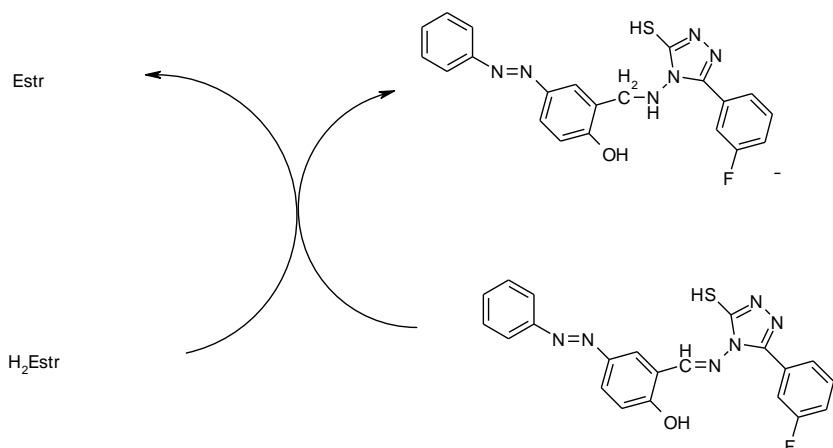
or via the azomethine moiety (Fig. 5)

Fig. 5. The scheme of the electroanalytical process with the participation of the Schiff bond

in which Estr stands for the oxidized estradiol fragment.

In the both of cases, the initial Schiff base is regenerated during the electrochemical stage. So, taking into account the above mentioned statements, in order to describe theoretically the system´s behavior, we introduce three variables:

  c – estradiol concentration in the pre-surface layer;

  θ_4 – the anode coverage degree of the reduction product from the Fig. 4;

  θ_5 – the anode coverage degree of the reduction product from the Fig. 5.

To simplify the modeling, we suppose that the reactor is intensively stirred, so we can neglect the convection flow. Also we suppose that the background electrolyte is in excess, so we can neglect the migration flow. The pre-surface layer thickness is assumed to be constant, equal to δ, and the concentration profile of the analyte and the alkali, to be linear.

It is possible to show that the system´s behavior will be described by the following trivatiant equation set:

$$\begin{cases} \dfrac{dc}{dt} = \dfrac{2}{\delta}\left(\dfrac{\Delta}{\delta}(c_0 - c) - r_{41} - r_{51}\right) \\[2mm] \dfrac{d\theta_4}{dt} = \dfrac{1}{G_4}(r_{41} - r_{42}) \\[2mm] \dfrac{d\theta_5}{dt} = \dfrac{1}{G_5}(r_{51} - r_{52}) \end{cases} \qquad (1)$$

In which c_0 is estradiol bulk concentration, Δ is the diffusion coefficient, G_4 and G_5 are the reduction products maximal concentrations, and the parameters r are the rates of the correspondent chemical and electrochemical stages, related to the figures (4) and (5), which may be described as:

$$r_{41} = k_{41}c(1 - \theta_4 - \theta_5) \qquad (2)$$
$$r_{51} = k_{51}c(1 - \theta_4 - \theta_5) \qquad (3)$$
$$r_{42} = k_{42}\,\theta_4\exp\left(\dfrac{2F\varphi_0}{RT}\right) \qquad (4)$$
$$r_{52} = k_{52}\,\theta_5\exp\left(\dfrac{2F\varphi_0}{RT}\right) \qquad (5)$$

Where the parameters k are the correspondent rate constants, F is the Faraday number, φ_0 is the potential slope related to the zero-charge potential, R is the universal gas constant and T is the absolute temperature.

Although accomplished, while compared to the simple case, the behavior in this electroanalytical process will be efficient, which will be shown below.

Results and Discussion

In order to investigate the behavior of the electroanalytical process of the estradiol determination, assisted by a new Schiff base, we analyze the equation set (1) by means of linear stability theory. The steady-state Jacobi functional matrix members will be described as:

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \qquad (6)$$

In which:

$$a_{11} = \dfrac{2}{\delta}\left(-\dfrac{\Delta}{\delta} - k_{41}(1 - \theta_4 - \theta_5) - k_{51}c(1 - \theta_4 - \theta_5)\right) \quad (7)$$

$$a_{12} = \dfrac{2}{\delta}(k_{41}c + k_{51}c) \qquad (8)$$

$$a_{13} = \dfrac{2}{\delta}(k_{41}c + k_{51}c) \qquad (9)$$

$$a_{21} = \dfrac{1}{G_4}(k_{41}(1 - \theta_4 - \theta_5)) \qquad (10)$$

$$a_{22} = \dfrac{1}{G_4}\left(-k_{41}c - k_{42}\exp\left(\dfrac{2F\varphi_0}{RT}\right) - jk_{42}\,\theta_4\exp\left(\dfrac{2F\varphi_0}{RT}\right)\right) \qquad (11)$$

$$a_{23} = \dfrac{1}{G_4}(-k_{41}c) \qquad (12)$$

$$a_{31} = \dfrac{1}{G_5}(k_{51}(1 - \theta_4 - \theta_5)) \qquad (13)$$

$$a_{32} = \frac{1}{G_5}(-k_{51}c) \qquad (14)$$

$$a_{33} = \frac{1}{G_5}\left(-k_{51}c - k_{52}\exp\left(\frac{2F\varphi_0}{RT}\right) - vk_{52}\theta_5\exp\left(\frac{2F\varphi_0}{RT}\right)\right) \qquad (15)$$

Taking into account the expressions (7), (11) and (15), one can see that the main diagonal of the Jacobian contains two elements, capable to be positive, and, in consequence, describe the positive callback. It makes this system different from the similar ones [21 – 23], for which only one positive element may be possible. Both of these elements: $-jk_{42}\theta_4\exp\left(\frac{2F\varphi_0}{RT}\right) > 0$, if j>0 and $-vk_{52}\theta_5\exp\left(\frac{2F\varphi_0}{RT}\right) > 0$, if j<0 describe the DEL capacitance influence of the electrooxidation of two reduction products of Schiff base. Nevertheless, it is observed beyond the detection limit and won't influence strongly the electroanalytical properties of this process.

Avoiding the appearance of cumbersome expression during the analysis of the Jacobian determinant, we introduce new variables, for it to be rewritten as:

$$\frac{2}{\delta GQ}\begin{vmatrix} -\kappa_1 - \Xi - \Lambda & \Pi & \Pi \\ \Xi & -V - \Omega & -V \\ \Lambda & -W & -W - K \end{vmatrix} \qquad (16)$$

The steady-state stability criterion for the dynamic systems is the so called Routh-Hurwitz criterion, and it may be shown that, for the trivariant systems, it may be transformed into the inequity of –Det J>0 or Det J<0. Opening the straight brackets of the determinant, applying to it the inequity, salient from the criterion, and taking into account that V+W=Π, we may obtain the steady-state stability condition, described as:

$$-\kappa_1(\Omega W + VK + \Omega K) - \Xi(\Omega W + \Omega K - WK) - \Lambda(VK + \Omega K - \Omega V) < 0 \quad (17)$$

Which is warranted to be satisfied if the parameters j and ν are positive (which is realized in the majority of the cases). So, the steady-state is stable in relatively vast parameter topological region, which, from the electroanalytical point of view, will mean that the system is electroanalytically efficient, as the dependence between the electrochemical parameter (in this case, current) and estradiol concentration is linear, and the analytical signal is easy to interpret. The electroanalytical process, in this case is mostly kinetically controlled, being diffusion-controlled with relatively large working electrodes.

The detection limit is defined by the realization of monotonic instability, correspondent to the saddle-node bifurcation, separating the stable steady-states and unstable states. The condition of its appearance is:

$$-\kappa_1(\Omega W + VK + \Omega K) - \Xi(\Omega W + \Omega K - WK) - \Lambda(VK + \Omega K - \Omega V) = 0 \quad (18)$$

The behavior of this system will be much less dynamic, if the Schiff base is incorporated into a conducting polymer as a part of macromolecule. Thus, both of the reduced forms will be present in the reduced macromolecules, which let us reduce the number of variables to two and approximate the behavior of the system to that described in [21 – 23].

Conclusions

The theoretical analysis of the estradiol electrochemical determination, assisted by a new Schiff base, let us conclude that:

- it may be an excellent electrode modifier for estradiol electroanalytical electrooxidative quantification. The system is electroanalytically efficient, as the steady-state stability is easy to obtain and maintain;
- The electroanalytical process is mostly reaction-controlled, being diffusion-controlled, if the working electrode is relatively large;
- The oscillatory behavior in this system is possible, being caused by influences of two electrochemical stages on double electric layer;
- The realization of the oscillatory behavior occurs beyond the detection limit.

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