



**Research Paper / Makale**

**The Theoretical Evaluation For The Use of Vanadium (Iii) Oxyhydroxide  
For The Electrochemical Determination of Benzodiazepines**

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**Abstract:** The theoretical evaluation for the use of vanadium (III) oxyhydroxide as an electrode modifier for benzodiazepines' electrochemical determination in acid solutions has been made. The correspondent mathematical model has been developed and analyzed by means of the linear stability theory and bifurcation analysis. It was shown that VO(OH) may be an efficient electrode modifier for the benzodiazepines electrochemical determination in lightly and moderately acid solution. Its use in concentrated acidic solution may be compromised by modifier destruction. The oscillatory behavior in this system may be caused not only by the DEL influences of the electrochemical stage, but also by surface instabilities, caused by VO(OH) dissolution.

**Keywords:** Benzodiazepines, electrochemical sensor, chemically modified electrodes, vanadium(III)oxyhydroxide, stable steady-state

**Benzodiazepinlerin Elektrokimyasal Tayini İçin Vanadyum (Iii)  
Oksihidroksit Kullanımı İçin Teorik Değerlendirme**

**Öz:** Asit çözeltilerinde benzodiazepinlerin elektrokimyasal tayini için bir elektrot modifiye edici olarak vanadyum (III) oksihidroksit kullanımı için teorik değerlendirme yapılmıştır. Matematiksel model geliştirilmiş ve doğrusal kararlılık teorisi ile bifürkasyon analiziyle test edilmiştir. VO (OH), hafif ve orta asitli bir çözelti içinde benzodiazepinlerin elektrokimyasal tayini için etkili bir elektrot modifiye edici olabileceği gösterilmiştir. Konsantrasyon asidik çözelti içindeki kullanımı modifiye edici yıkımla tehlikeye girebilir. Bu sistemdeki salınım davranışı sadece elektrokimyasal evrenin DEL etkilerinden değil, aynı zamanda VO (OH) çözünmesinden kaynaklanan yüzey dengesizliklerinden de kaynaklanabilir.

**Anahtar Kelimeler:** Benzodiazepinler, elektrokimyasal sensör, kimyasal olarak değiştirilmiş elektrotlar, vanadyum (III) oksihidroksit, kararlı durum

**1.1.Introduction**

The benzodiazepines (named so according to the nomenclature of heterocyclic compounds by Hantsch – Widman, as being insaturated (-in) seven-atom heterocyclic compounds (-ep-),

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containing two nitrogen heteroatom (*-diaz-*) and condensed with benzoic ring (*benzo*) [1]), is the family of the most used sedative, anxiolytic, antipsychotic, neuroleptic and relaxant drugs [2 – 4]. Its mechanism of pharmacological action is based on the direct action on GABA receptors, which augments the diffusion of chloride-ions towards the neurons, which gives the relax effect [5]. Nevertheless, despite of their activity, these compounds aren't suitable for lasting and excessive use, due to their side effects [6] like excessive slumber, general paralysis, suppression of libido, dependence and even death. Thus, the development of a method, capable to detect its presence efficiently, is really actual [7]. Various electrode modifiers have been used for electrochemical determination of benzodiazepines [8 – 10]. One of interesting electrode modifiers could be vanadium (III) oxyhydroxide, a compound, with the similar structure to cobalt (III) oxyhydroxide and also with the tendency to flexible electrochemical behavior, but, contrarily to VO(OH), representing anodic behavior in neutral and alkaline media, VO(OH) is more inclined to the cathodic behavior in neutral, lightly and moderately acid solutions, in which benzodiazepines may be effectively reduced. Nevertheless, no works, concerning electroanalytical function of VO(OH) with benzodiazepines or other analytes, have been published for now. Only one work concerning the use of vanadium oxyhydroxide as an electrode modifier for condensers [11] is known. On the other hand, the development of a principally new electrode modifier may confront some problems, like:

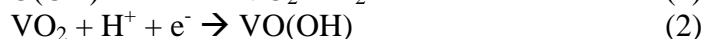
- The indecision about the mechanism of electrochemical action of the electrode modifier with the analyte;
- The possibility of the appearance of electrochemical instabilities, characteristic for the electrosynthesis and action of VO(OH), a similar compound [12 – 13].

These problems may be solved, if the experimental essays are preceded by an *a priori* theoretical investigation of the electroanalytical system. Moreover, the work, describing the general features of benzodiazepines' electrochemical reduction, has already been prepared by the authors of the present work [14]. So, the goal of our work is to investigate theoretically the possibility of benzodiazepines electrochemical quantification, assisted VO(OH). In order to achieve it, we realize the specific goals:

- suggestion of the mechanism of the electroanalytical reaction consequence, leading to the appearance of analytical signal;
- development of the balance equation mathematical model, correspondent to the electroanalytical system;
- analysis and interpretation of the model in terms of the electroanalytical use of the system;
- the superposition of the general case of benzodiazepines electrochemical reduction [14] and the case of VO(OH)-assisted electroanalytical system;
- the seek for the possibility of electrochemical instabilities and for the factor, causing them;
- the comparison of the mentioned system's behavior with the similar ones [14 – 17]

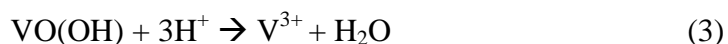
## 2. System and its modeling

**2.1. Reaction mechanism.** Schematically, the reaction sequence, leading to the appearance of the electroanalytical signal may be described as:



It is suitable to use VO(OH) as a modifier for carbon and (or) polymeric material.

From the equations (1 - 2) it may be concluded that the presence of an acid media is important for the electroanalytical system. Nevertheless, the excess of the protons may also lead to VO(OH) dissolution, realized without redox interaction and leading to the appearance of V<sup>3+</sup>



So, in order to describe the behavior of this system, we could introduce three variables:

- c – benzodiazepines concentration in the pre-surface layer;
- v – vanadium oxyhydroxide surface coverage degree;
- h – proton concentration in the pre-surface layer.

But, taking into account the excess of protons, relative to the electroanalytical system, occurring while  $\text{pH} < 3.5$ , the variable h will be dismembered from the equation set, which becomes bivariant. 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  $\delta$ , and the concentration profile in it is supposed to be linear. Taking this into account, we may represent the balance equation set as:

$$\begin{cases} \frac{dc}{dt} = \frac{2}{\delta} \left( \frac{\Delta}{\delta} (c_0 - c) - r_1 \right) \\ \frac{dv}{dt} = \frac{1}{G} (r_2 - r_1 - r_3) \end{cases} \quad (4)$$

In which  $\Delta$  is the diffusion coefficient,  $c_0$  is benzodiazepines' bulk concentration, G is VO(OH) maximal surface concentration and the parameters r are correspondent reaction rates, which may be calculated as:

$$r_1 = k_1 cv \quad (5)$$

$$r_2 = k_2 (1 - v) \exp\left(-\frac{F\varphi_0}{RT}\right) \quad (6)$$

$$r_3 = k_3 v \exp(-\beta v) \exp(-\rho\varphi_0) \quad (7)$$

in which the parameters k are correspondent reaction rate constants, F is the Faraday number,  $\varphi_0$  is the DEL potential slope in the double, related to the zero-charge potential, the parameters  $\beta$  and  $\rho$  describe the surface influences of the VO(OH) dissolution and its influence to the DEL capacitances, R is the universal gas constant and T is the absolute temperature. It is possible to show, that the excess of the protons makes the system's behavior more dynamic, and the oscillatory and monotonic instabilities more probable, which may be shown below.

### 3. Results and discussion

In order to describe the behavior of the system with benzodiazepines electrochemical detection, assisted by VO(OH), we analyze the equation set (1) by means of the linear stability theory. The steady-state Jacobian functional matrix elements for this system may be described as:

$$\begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \quad (8),$$

in which:

$$a_{11} = \frac{2}{\delta} \left( -\frac{\Delta}{\delta} - k_1 v \right) \quad (9)$$

$$a_{12} = \frac{2}{\delta} (-k_1 c) \quad (10)$$

$$a_{21} = \frac{1}{G} (k_1 v) \quad (11)$$

$$a_{22} = \frac{1}{c} \left( -k_2 \exp\left(-\frac{F\varphi_0}{RT}\right) - jk_2(1-v) \exp\left(-\frac{F\varphi_0}{RT}\right) - k_1c - k_3 \exp(-\beta v) \exp(-\rho\varphi_0) + \beta k_3 v \exp(-\beta v) \exp(-\rho\varphi_0) + \rho k_3 v \exp(-\beta v) \exp(-\rho\varphi_0) \right) \quad (12)$$

The main conditions for bivariate systems are described in the Table 1:

Table 1. The main conditions for bivariate systems.

Steady-state stability	Tr J<0, Det J>0
Oscillatory instability	Tr J=0, Det J>0
Monotonic instability	Tr J<0, Det J=0

In order to simplify the analysis of the matrix, we introduce new variables, so the matrix determinant will be described as:

$$\frac{2}{\delta c} \begin{vmatrix} -\kappa & -\varepsilon & -\Omega \\ \varepsilon & & -X - \Omega - \Lambda \end{vmatrix} \quad (13)$$

It is possible to see that in this system *the oscillatory behavior* in this system is more probable, than in similar ones, as there are three factors, causing oscillatory behavior against one or two in the similar systems [14 – 17]. The main condition of the oscillatory behavior via Hopf Bifurcation (Tr J = 0) is satisfied if the main diagonal Jacobian elements (9) and (12) contain positive elements, which represent the positive callback. The main diagonal contains three positive elements. Besides of the element  $-jk_2(1-v) \exp\left(-\frac{F\varphi_0}{RT}\right) > 0$  if  $j < 0$ , describing the DEL influences of VO<sub>2</sub> electrochemical reduction and typical for the similar systems [14 – 17], it contains the element  $\beta k_3 v \exp(-\beta v) \exp(-\rho\varphi_0) > 0$  if  $\beta > 0$ , describing the adsorbed particle attraction during VO(OH) electrodisolution and  $\rho k_3 v \exp(-\beta v) \exp(-\rho\varphi_0)$  if  $\rho > 0$ , describing oscillatory behavior, caused by DEL capacitance changes, caused by V<sup>3+</sup> formation in the vicinity of the cathode. The oscillations are expected to be frequent and of the small amplitude. The steady-state stability condition for a two-dimensional system may be described as: Tr J<0, Det J>0. For this system, it will be rewritten as:

$$\begin{cases} -\kappa - \varepsilon - X - \Omega - \Lambda < 0 \\ \kappa X + \kappa \Omega + \kappa \Lambda + \varepsilon X + 2\varepsilon \Omega + \varepsilon \Lambda > 0 \end{cases} \quad (14)$$

It is warranted to be satisfied, in the case of the positivity of the element  $j$  and of the negativity of  $\beta$  and  $\rho$ , describing the fragility or absence of the destabilizing influences on the electrode surface and in DEL. So, the steady-state is maintained stable easily. Nevertheless, in the case of relatively low pH, VO(OH) will be dissolved (even without destabilizing surface and DEL influences), and the system won't be electroanalytically efficient, although the steady-state remains stable. So, in order to maintain the electroanalytical efficiency of this system, one should use lightly and moderately acidic solutions. In this case, the element  $\Lambda$  will be equal to nil or have minimal values, and the electroanalytical process will be diffusion-controlled. In the terms of electroanalytical efficiency of stable steady-state, it will be correspondent to the linear dependence between benzodiazepines' concentration and electrochemical parameter. So, it is possible to conclude that in lightly and moderately acidic solutions, the electroanalytical process will be efficient. The *monotonic instability* in this system is possible, being caused by the equality between the stabilizing influences and the destabilizing ones of the electrochemical process influences on DEL. It is correspondent to the detection limit and its condition may be described as:

$$\begin{cases} -\kappa - \Xi - \Omega - \Lambda < 0 \\ \kappa\Omega + \kappa\Lambda + \Xi\Lambda > 0 \end{cases} \quad (16)$$

It is also possible to prepare the CP – VO(OH) composite, in order to use the mediated electron transfer. In this case, the presence of a polymer may make the system more stable and more efficient. It will be described in our next works. The use of  $V^{2+}/V^{3+}$  redox pair in benzodiazepines electrochemical reduction is also viable. The ions, in this case, may be intercalated into a graphene or polymeric matrix, or to be present on the cathode surface as complex compounds. The  $V^{2+}/V^{3+}$  pair may be alternative to VO(OH) in highly concentrated acidic solutions, in which the oxyhydroxide is dissolved. The system, using the  $V^{2+}/V^{3+}$  redox pair, intercalated into a matrix, will be described in our next works.

#### 4. Conclusions

From the theoretical investigation of the possibility of the Benzodiazepines electrochemical detection, assisted by vanadium oxyhydroxide we may conclude that:

- VO(OH) may serve as an excellent modifier for Benzodiazepines quantification. The VO(OH) acts as an active substance in mildly and moderately acidic solutions;
- In these conditions, The stable steady-state is maintained easily. The system is electroanalytically efficient. The electroanalytical process is diffusion -controlled;
- The oscillatory behavior in this system is possible, being caused by three factors. Two of them are linked to the VO(OH) dissolution in strongly acidic media.

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