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The Theoretical Description for Chlorthalidone Electrochemical Sensing on Vanadium(III)Oxyhydroxide-Modified Electrode

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Abstract: The electroanalytical system for VO(OH)-assisted chlorothalidone electrochemical determination has been described for the first time. The electroanalytical process may be useful for pharmaceutical investigation or doping control in sports. The electrochemical process is given as a cathodic reduction, in which the sulfamide group and lactam moiety are reduced. Based on the most probable mechanism of the electrochemical process, the mathematical model confirms the efficiency of vanadium (III) oxyhydroxide as an electrode modifier. As for the stability analysis, it confirms that a mildly acidic medium, close to neutral, is the most efficient for chlorthalidone VO(OH)-assisted cathodic determination.

Keywords: chlorthalidone; electrochemical sensor; vanadium (III) oxyhydroxide; electrochemical oscillations; stable steady-state.

1. Introduction

In 2006, in Portugal, the UEFA European U-21 Championship took place [1, 2]. The Ukrainian team entered the final game, losing to the Netherlands. This event attracted the attention of many Ukrainian TV spectators, who saw how the young Ukrainian football player passed stage by stage, coming into the final, where they lost to the Dutch team.

Nevertheless, the Ukrainian participation was accompanied by a scandal. One of the Ukrainian midfielders, Dmytro Nevmyvaka, tested positive for chlorthalidone (Figure 1) [3–5]. Chlorthalidone is one of the components of the anti-hypotension drug, taken by the player by indication of the club doctor. Considering this, WADA and UEFA disqualified Nevmyvaka for only one season.

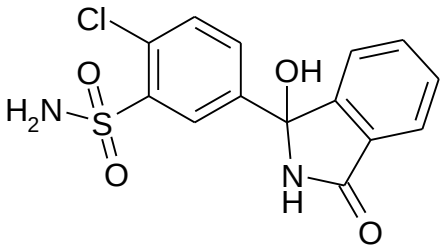

Figure 1. Chlorthalidone.

Taking into account that chlorthalidone, as a thiazide-like diuretic drug used for nephrotic syndrome, diabetes insipidus, and renal failure, possesses strong side effects and is banned in some sports [6–14], the development of an efficient method for chlorthalidone determination is actual.

Possessing electroactive groups, chlorthalidone may be detected by electroanalytical method [15, 16]. Both anodic and cathodic methods are compatible with them. Moreover, considering that the electrochemical methods are more rapid and more exact [17–24], which is really important for sports competitions, in which the interval between the games may be very rapid.

Nevertheless, for the same reasons, using the electroanalytical process in unstable modes may lead to the inexact determination and unjust decision to qualify or disqualify a player. Therefore, the stability investigation for the electroanalytical process is important, and the *a priori* mechanistic theoretical investigation is necessary for its implementation.

Therefore, the goal of this work is to investigate from the theoretical point of view the possibility of the electrochemical determination of chlorthalidone on VO(OH)-modified cathode. The investigation includes mechanism suggestions, the development and analysis of an adequate mathematical model via linear stability theory, and the comparison of the behavior of this system with that of similar ones.

2. Materials and Methods

In a neutral medium, neither the sulfamide group nor the alcoholic group is ionized and/or hydrolyzed. Vanadium (III) oxyhydroxide, transferring the electrons and protons, is reduced by both sulfamide and lactamic groups. Vanadium oxyhydroxide will be thereby regenerated by (1):

$$VO_2 + H^+ + e^- \rightarrow VO(OH) \quad (1)$$

or:

$$VO_2 + H_2O + e^- \rightarrow VO(OH) + OH^- \quad (2)$$

Either way, the pH value grows during the electroanalytical process, which is realized in Figure 2.

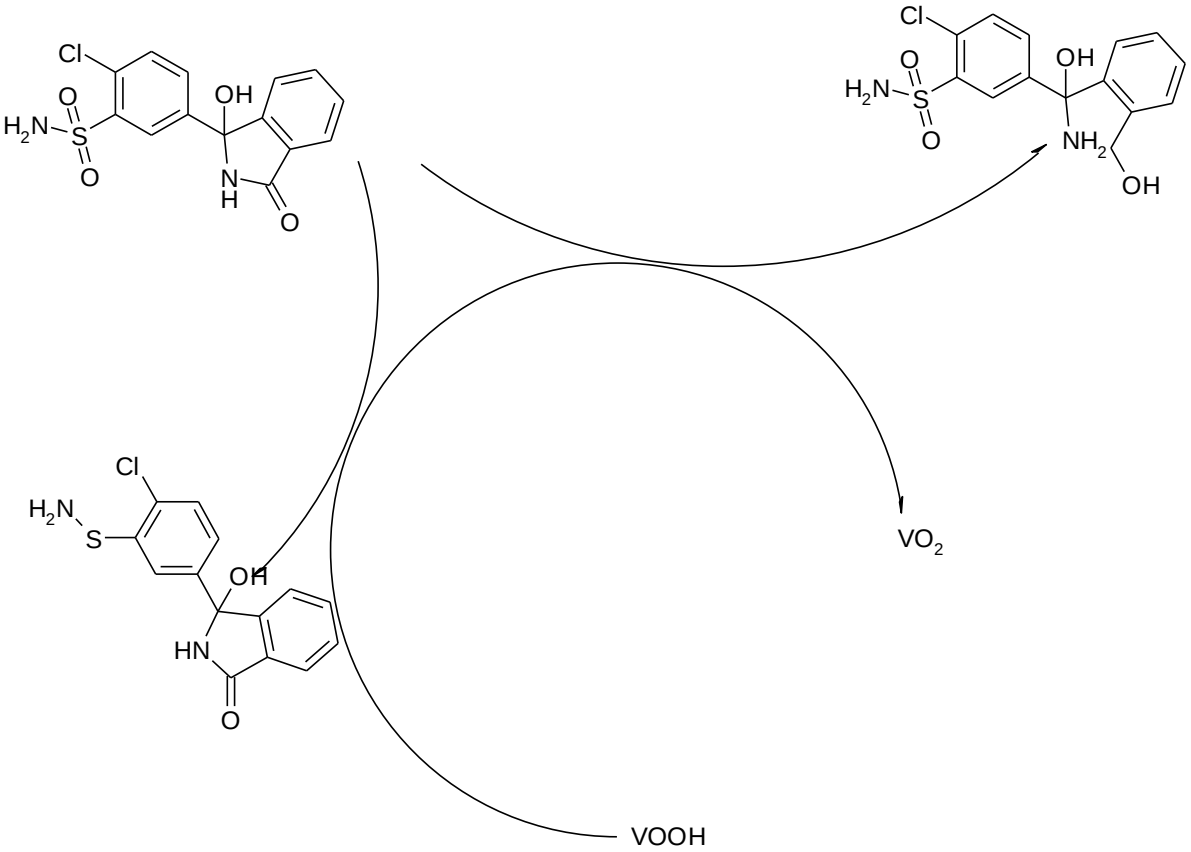

Figure 2. Chlorthalidone VO(OH)-assisted electrochemical determination.

Taking into account the pH growth during the process, such as the presence of a mildly alkaline medium, we include the alkali concentration in the model, as it is important for DEL stability and behavior.

Therefore, taking certain assumptions indicated in [27 – 28], we describe the electrochemical behavior of the system with chlorthalidone by trivariant equation-set (3):

$$\begin{cases} \frac{dc}{dt} = \frac{2}{\delta}\left(\frac{\Delta}{\delta}(c_0 - c) - r_1 - r_2\right) \\ \frac{da}{dt} = \frac{2}{\delta}\left(\frac{A}{\delta}(a_0 - a) + r_r - r_1\right) \\ \frac{dv}{dt} = \frac{1}{V}(r_1 + r_2 - r_r) \end{cases} \quad (3)$$

Herein, c is the chlorthalidone concentration in the pre-surface layer, c_0 is its bulk concentration, a and a_0 are correspondent to pre-surface and bulk concentrations of alkali, Δ and A are the correspondent diffusion coefficients, v is the vanadium dioxide coverage degree, V is its maximal surface concentration, and the parameters r are the correspondent reaction rates, calculated as (4 – 6):

$$r_1 = k_1 ca(1 - v)^4 \exp(-\alpha a) \quad (4)$$

$$r_2 = k_2 c(1 - v)^4 \quad (5)$$

$$r_r = k_r v \exp\left(-\frac{F\varphi_0}{RT}\right) \quad (6)$$

Herein, the parameters k are the correspondent reaction rate constants, α is a parameter describing the DEL influence of the ion formation during the alkaline lactam reduction, F is the

Faraday number, φ_0 is the zero-charge-related potential slope, R is the universal gas constant, and T is the absolute temperature.

Alkaline pH favors one of the electrochemical stages of the process. Nevertheless, as the pH growth may destabilize the system, it has to be kept in mind during the electroanalytical process. Taking these measures, vanadium (III) oxyhydroxide becomes an efficient modifier for chlorthalidone determination, as shown below.

3. Results and Discussion

To describe the steady-state stability of the system with chlorthalidone electrochemical determination, we analyze the equation-set (3) via linear stability theory, thereby exposing the Jacobian matrix members as (7).

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \quad (7)$$

In which:

$$a_{11} = \frac{2}{\delta}\left(-\frac{A}{\delta} - k_1 a(1-v)^4 \exp(-\alpha a) - k_2(1-v)^4\right) \quad (8)$$

$$a_{12} = \frac{2}{\delta}(-k_1 c(1-v)^4 \exp(-\alpha a) + \alpha k_1 c a(1-v)^4 \exp(-\alpha a)) \quad (9)$$

$$a_{13} = \frac{2}{\delta}(4k_1 c a(1-v)^3 \exp(-\alpha a) + 4k_2 c(1-v)^3) \quad (10)$$

$$a_{21} = \frac{2}{\delta}(-k_1 a(1-v)^4 \exp(-\alpha a)) \quad (11)$$

$$a_{22} = \frac{2}{\delta}\left(-\frac{A}{\delta} - k_1 c(1-v)^4 \exp(-\alpha a) + \alpha k_1 c a(1-v)^4 \exp(-\alpha a)\right) \quad (12)$$

$$a_{23} = \frac{2}{\delta}\left(k_r v \exp\left(-\frac{F\varphi_0}{RT}\right) - j k_r v \exp\left(-\frac{F\varphi_0}{RT}\right) - 4k_1 c a(1-v)^3 \exp(-\alpha a)\right) \quad (13)$$

$$a_{31} = \frac{1}{V}(k_1 a(1-v)^4 \exp(-\alpha a) + k_2(1-v)^4) \quad (14)$$

$$a_{32} = \frac{1}{V}(k_1 c(1-v)^4 \exp(-\alpha a) - \alpha k_1 c a(1-v)^4 \exp(-\alpha a)) \quad (15)$$

$$a_{33} = \frac{1}{V}\left(-4k_1 c a(1-v)^3 \exp(-\alpha a) - 4k_2 c(1-v)^3 - k_r v \exp\left(-\frac{F\varphi_0}{RT}\right) + j k_r v \exp\left(-\frac{F\varphi_0}{RT}\right)\right) \quad (16)$$

Taking into account the elements (8), (12), and (16), we can see that they contain two positive elements - $\alpha k_1 c a(1-v)^4 \exp(-\alpha a) > 0$, if $\alpha > 0$ and $j k_r v \exp\left(-\frac{F\varphi_0}{RT}\right) > 0$, if j>0. Both of them describe the positive callback, corresponding to the oscillatory behavior caused by DEL influences on chemical and electrochemical stages. Both behavior types are characteristic for similar systems [25–28] and will be observed here. This factor explains the dependence of the oscillation pattern on the background electrolyte composition, including pH. In this system, the pH growth enhances the probability of the oscillatory behavior, yet reported in [25–28].

To simplify the stability analysis, we introduce new variables and thereby rewrite the determinant as (17):

$$\frac{4}{\delta^2 V}\begin{vmatrix} -\kappa - \Xi - \Sigma & -\Lambda & \Phi \\ -\Sigma & -\xi - \Lambda & \Omega + \Phi \\ \Xi + \Sigma & \Lambda & -\Phi - \Omega \end{vmatrix} \quad (17)$$

Taking into account the determinant properties, we add the third line to the second, rewriting the determinant as (18):

$$\frac{4}{\delta^2 V}\begin{vmatrix} -\kappa - \Xi - \Sigma & -\Lambda & \Phi \\ \Xi & -\xi & 0 \\ \Xi + \Sigma & \Lambda & -\Phi - \Omega \end{vmatrix} \quad (18)$$

Opening the straight brackets, applying the Det J>0 condition, salient from the criterion, and changing the signs, we obtain the steady-state stability condition expressed as (19).

$$\Phi(\kappa\xi - 2\Xi\Lambda) + \Omega(\kappa\xi + \xi\Xi + \Sigma\xi + \Lambda\Xi) > 0 \quad (19)$$

Defining an efficient either diffusion or kinetically controlled system. The requisite (19) is readily satisfied if the parameters Λ and Ω are positive.

Considering that no side reaction compromising the analyte and(or) modifier stability is realized in this system, the steady-state stability will correspond to the linear dependence between the electrochemical parameter and concentration, providing efficient analytical signal interpretation. Nevertheless, the pH growth during the process may make possible a side reaction, as mentioned below.

The detection limit is defined by the monotonic instability, which depicts the margin between the stable steady-states and unstable states. It is described mathematically by the nullity of the Jacobian determinant, or (20):

$$\Phi(\kappa\xi - 2\Xi\Lambda) + \Omega(\kappa\xi + \xi\Xi + \Sigma\xi + \Lambda\Xi) > 0 \quad (20)$$

When the pH crosses the pH=10 threshold, the system's behavior changes, making a hydrolytic scenario possible via chlorine and lactam moieties. In those conditions, the model (3) won't be able to describe this process adequately.

Bi- and trivariant models are possible for that case. Their analysis shows that the pH growth during the process destabilizes the system. Therefore, in order to stabilize the system, organic basic media is recommended. The use of small concentrations of weak acid to neutralize the pH growth may also be admitted.

4. Conclusions

From the analysis of the system with the electrochemical determination of chlorthalidone on VO(OH)-modified cathode, it is possible to conclude that the electroanalytical process is efficient. Nevertheless, it is necessary to neutralize the pH growth for better analytical signal interpretation. As for the oscillatory behavior, it is possible due to the DEL influence of the electrochemical and chemical stages in one of two reduction scenarios.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Diaconu, M.; CAS 2018/A/5800 *Samir Arab v. Union Européenne de Football Association (UEFA),* Award of 14 November 2018, *Yearbook Int. Sports. Arbitr.*, **2022,** *3*, 3 https://doi.org/10.1007/15757_2022_37.

2. Pérez-González, B.; León-Quismondo, J.; Bonal, J. *et al.,* The New Generation of Professional Soccer Talent is Born under the Bias of the RAE. Relative Age Effect in International Male Youth Soccer Championships, *Children*, **2021,** *8*, 1117, https://doi.org/10.3390/children8121117.
3. Ishani, A.; Cushman, W.C.; Leatherman, S.M. *et al.,* Chlorthalidone vs Hydrochlorothiazide for Hypertension-Cardiovascular Events, *New Engl J. Med.,* **2022,** *387,* 2401 – 2410, https://doi.org/10.1056/NEJMoa2212270.
4. Agarwal, R.; Should we CLICK on Chlorthalidone for Treatment-Resistant Hypertension in Chronic Kidney Disease, *Clin. Kindey J.,* **2023,** *272,* 1 – 4, https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.122.060167.
5. Furgeson, S.B.; Stuart, L. Chlorthalidone and Advanced Chronic Kidney Disease, *Clin. J. Amer. Soc. Neprhol.*, **2022,** *17*, 1076 – 1078, https://doi.org/10.2215/CJN.01380222.
6. Agarwal, R.; Sinha, A.D; Tu, W. Chlorthalidone for Resistant Hypertension in Advanced Chronic Kidney Disease, *Circulation*, **2022,** *146*, 718 – 720, https://doi.org/10.1161/circulationaha.122.060167.
7. Bashir, Kh.; Burns, T.; Pirruccello, S.J. *et al.,* Comparative Antiplatelet Effects of Chlorthalidone and Hydrochlorthalidone, *J. Clin Hypertension*, **2022,** *24*, 1310 – 1315, https://doi.org/10.1111/jch.14564.
8. Solís-Jiménez, F.; Perez-Navarro, L.M.; Cabrera-Barron, R. *et al.,* Effect of the Combination of Bumetanide plus Chlorthalidone on Hypertension and Volume Overload in Patients with Chronic Kidney Disease Stage 4-5 KDIGO Without Renal Replacement Therapy: A Double-Blind Randomized HEBE-CKD Trial, *BMC Nephrology*, **2022,** *23*, 316, https://doi.org/10.1186/s12882-022-02930-4.
9. Allisson, S.J. Chlorthalidone in Advanced CKD, *Nature Rev. Nephrol.*, **2022**, *18*, 3, https://doi.org/10.1038/s41581-021-00514-3.
10. Berlitz, S.M.; Reginatto, P.; Monte Machado, G.R. *et al.,* Development of a Clioquinol Nanocarrier as a New, Promising Option for the Treatment of Dermatomycosis. *Pharmaceutics,* **2023**, *15*, 531, https://doi.org/10.3390/pharmaceutics15020531.
11. Zhang, M.; Li, L.; Li, S. *et al.,* Development of Clioquinol Platinum (IV) Conjugates as Autophagy Targeted Antimetastatic Agents. *J. Med. Chem.,* **2023,** *66*, 3393 – 3410, https://doi.org/10.1021/acs.jmedchem.2c01895.
12. Olaleye, O.A.; Kaur, M.; Onyenaka, C. *et al.,* Discovery of Clioquinol and Analogues as Novel Inhibitors of Severe Acute Respiratory Syndrome Coronavirus 2 Infection, ACE2 and ACE2-Spike Protein Interaction. *In Vivo Heliyon* **2021,** *7*, e06426, https://doi.org/10.1016/j.heliyon.2021.e06426.
13. Kehwinde, A.I.; Egbeyemi, A.; Kaur, M. *et al.,* Inhibitory Mechanism of Clioquinol and Its Derivatives at the Exopeptidase Site of Human Angiotensin-Converting Enzyme-2 and Receptor Binding Domain of SARS-CoV-2 Viral Spike, *J. Biomol. Struct. Dyn.,* **2023,** *41*, 2992 – 3001, https://doi.org/10.1080/07391102.2022.2043938.
14. Debbarma, J.; Debnath, R.; Saha, M. Graphene from Sugarcane Bagasse for Nonenzymatic Electrochemical Determination of Glucose *Lett. Appl. NanoBioSci.,* **2023,** *10*, 115, https://doi.org/10.33263/LIANBS124.115.
15. Oliveira, R.W.; Gomes, P.; Ribeiro, J.; Reis, J.; Fontenele, M.; Everton, G.; Lyra, W.; Louzeiro, H.; Paula, M.; Filho, V. Determinação espectrofotométrica de Cobre(II) em aguardente de mandioca (Tiquira). *Revista Colombiana de Ciencias Químico-Farmacéuticas* **2020**, *49*, 353–371, https://doi.org/10.15446/rcciquifa.v49n2.89507.
16. Bagheri, A.; Hassani Marand, M. Voltammetric and Potentiometric Determination of Cu^{2+}, using an Overoxidized Polypyrrole Based Electrochemical Sensor.*Russ. J. Electrochem.***2020,** *56*, 453–461, https://doi.org/10.1134/S1023193520060026.
17. Nair, A.B.; Dalal, P.; Kadian, V. *et al.,* Formulation Strategies for Enhancing Pharmaceutical and Nutraceutical Potential of Sesamol: A Natural Phenolic Bioactive. *Plants*, **2023,** *12*, 1168, https://doi.org/10.3390/plants12051168.
18. Tesfaye, G.; Hailu, T.; Ele, E. *et al.,* Square-Wave Voltammetric Determination of Quercetin in Wine and Fruit Juice Samples at Poly(Safranine O) Modified Glassy Carbon Electrode, *Sens. Bio-Sens. Res.,* **2021,** *34*, 100466, https://doi.org/10.1016/j.sbsr.2021.100466.
19. Ziyatdinova, G.; Yakupova, E.; Zhupanova, A. Voltammetric Sensors Based on the Electropolymerized Phenolic Acids or Triphenylmethane Dyes for the Antioxidant Analysis. *Eng. Proc.*, **2022,** *27*, 2, https://doi.org/10.3390/ecsa-9-13178.
20. Holze, R. Overoxidation of Intrinsically Conducting Polymers. *Polymers*, **2022,** *14*, 1584, https://doi.org/10.3390/polym14081584.

21. Can, Y.; Mohamed, A.M.; Mousavi, M.; Akinay, Y. Poly(pyrrole-co-styrene sulfonate)-Encapsulated MWCNT/Fe-Ni Alloy/$NiFe_2O_4$ Nanocomposites for Microwave Absorption. *Mat. Chem. Phys.*, **2021,** *259*, 124169, https://doi.org/10.1016/j.matchemphys.2020.124169.
22. Shukla, P.; Mishra, A.; Manivanna, S.; Mandal, D. Metal-Organic Frames (MOFs) Based Electrochemical Sensors for Sensing Heavy Metal Contaminated Liquid Effluents: A Review., *Nanoarchitectonics*, **2022,** *3*, 46 – 60, https://doi.org/10.37256/nat.3220221272.
23. Machindra, L.A.; Yen, Y.-K. A Highly Sensitive Electrochemical Sensor for Cd^{2+} Detection Based on Prussian Blue – PEDOT – Loaded Laser-Scribed Graphene-Modified Glassy Carbon Electrode. *Chemosensors*, **2022,** *10*, 209, https://doi.org/10.3390/chemosensors10060209.
24. Sharma, T.S.K.; Ganguly, A.; Santhan, A.; Hwa, K.-Y. Gadolinium Oxide Nanorods Anchored on C_3N_4 Nanosheets for Dual-Mode Electrochemical Determination of Clioquinol in Real-Time Analysis. *ACS Appl. Nano Mater.*, **2022,** *5*, 5208 – 5222, https://doi.org/10.1021/acsanm.2c00268.
25. Akinay, Y.; Çolak, B.; Turan, M.E. *et al.*, The Electromagnetic Wave Absorption Properties of Woven Glass Fiber Composites Filled with Sb_2O_3 and SnO_2 Nanoparticles Doped Mica Pigments. *Polym. Comp.* **2022,** *43*, 8784 – 8794, https://doi.org/10.1002/pc.27061.
26. Bazzaoui, M.; Bazzaoui, E.A.; Martins, L.; Martins, J.I. Electropolymerization of pyrrole on zinc–lead–silver alloys electrodes in acidic and neutral organic media. *Synthetic Metals* **2002**, *130*, 73-83, https://doi.org/10.1016/S0379-6779(02)00101-7.
27. Tkach, V.V.; Kucher, M.M.; Kushnir M.V. *et al.*, The Theoretical Description for Psilocin Electrochemical Determination over Cobalt Oxyhydroxide. *Orbital Elec J. Chem.*, **2023,** *15*, 27 – 30.
28. Tkach V.V.; Kushnir, M.V.; de Oliveira, S.C. *et al.*, The Theoretical Evaluation of the Hydrogen Peroxide Electrochemical Sensing Based on $CoSn(OH)_6$. *Appl. J. Env. Eng. Sci.*, **2023,** *9*, 16 – 22, https://doi.org/10.48422/IMIST.PRSM/ajees-v9i1.33281.