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The Modeling for Anti-Covid-19 Drug Molnupiravir Electrochemical Sensing on C_3N_4

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Abstract: The cathodic electrochemical determination of molnupiravir on carbon nitride nanoparticles has been investigated for the first time. The electrochemical determination is given in neutral and mildly acidic media, and C_3N_4 plays the role of proton and electron transfer mediator. The analysis of the correspondent model confirms that the electrochemical determination of molnupiravir may be efficiently given with the easy interpretation of the analytical signal. As for the oscillatory behavior, its probability is more expressed than in the similar systems

Keywords: molnupiravir; carbon nitride; electrochemical sensor; electrochemical oscillations; stable steady-state.

1. Introduction

In 2019-2020 the world was influenced by strange virus infection [1-4]. The virus structure resembled the 2003 atypical pneumonia virus SARS, Middle East β-coronavirus MERS, and the newly found bat coronavirus, which received the code name SARS-CoViD2. Yet the proper infection has been put in the code name COVID-19. The pandemic outbreak has led to the cancellation and postposition of different events, including the European Football Cup and the Summer Olympics [5,6]. Despite the proven efficiency of different drugs and vaccines, the appearance of new variants puts them in check, which is why the development of an effective drug, vaccine, and specific treatment is still in progress.

Molnupiravir (Figure 1, also known as MK-4482 and EIDD-2801) is an experimental drug initially developed to treat different types of influenza. Its antiviral action includes the introduction of copying fails during the viral RNA replication, provoking a massive number of mutations, leading to error catastrophe and lethal mutagenesis [7-10].

The COVID-19 clinical trial of molnupiravir has shown its efficacy in reducing the hospitalization and death risk for newly-diagnosed high-risk patients. It was also efficient against delta, gamma, and mu variants. Nevertheless, the molnupiravir side effects haven´t been studied yet. Also, the molnupiravir action is dose-related. Therefore, developing an efficient analytical method for its quantification is actual [11-13].

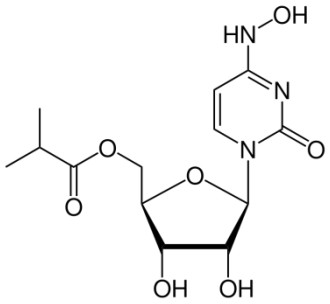

Figure 1. Molnupiravir.

As of now, no electroanalytical method for molnupiravir determination has been developed. Nevertheless, taking into account that it possesses electroactive groups, it may be detected either anodically or cathodically. The cathodic route includes the reduction of both hydroxylamine moiety and pyridone ring.

However, the use of novel electrode modifiers with novel analytes may be impeded by: the indecision concerning the exact mechanism of electrochemical reaction; the necessity of determination of the parameter region, correspondent to the most efficient active substance and mediating action; the presence of electrochemical instabilities, yet described for the electrooxidation and reduction of organic compounds [14 - 18].

The mentioned problems may only be solved by analyzing a mathematical model capable of adequately describing the molnupiravir electrochemical determination. It can also compare the behavior of this system with that of similar ones without any experimental essay.

So, the goal of this work is the mechanistic theoretic analysis of molnupiravir electrochemical determination over carbon (IV) nitride-modified cathode. The correspondent mathematical model is developed and analyzed by linear stability theory and bifurcation analysis. The behavior will be evaluated for electroanalytical efficiency and thereby compared to similar ones [19 – 21].

2. System and its Modeling

In acidic media, carbon nitride undergoes electrochemical reduction as follows:

$C_3N_4 + 2H^+ + 2e^- \rightarrow C_3H_2N_4$ (1)

The *in situ* formed reduction product, in its turn, provides the molnupiravir determination, given by the reduction of both pyridone and hydroxylamine moiety. Both of the processes may occur in the organism, leading to the appearance of potentially toxic metabolites. Schematically, the process may be described in Figure 2.

Therefore, in order to describe the system´s behavior, we introduce two variables:

m – molnupiravir concentration in the pre-surface layer;

c – carbon nitride surface coverage degree

and, taking some assumptions [19 – 21], describe the system´s behavior by a bivariant equation set, exposed as (2):

$$\begin{cases} \frac{dm}{dt} = \frac{2}{\delta}\left(\frac{M}{\delta}(m_0 - m) - r_{21} - r_{22}\right) \\ \frac{dc}{dt} = \frac{1}{C}(r_{21} + r_{22} - r_1) \end{cases} \quad (2)$$

Herein, Δ is the diffusion coefficient, m_0 is the molnupiravir bulk concentration, C is the C_3N_4 maximal matrix concentration, and the parameters r are the correspondent reaction rates, calculated as:

$$r_{21} = k_{21} m (1 - c)^2 \exp(-am) \quad (3)$$

$$r_{22} = k_{22} m (1 - c)^2 \quad (4)$$

$$r_1 = k_1 c \exp\left(-\frac{2F\varphi_0}{RT}\right) \quad (5)$$

W, the parameters k are the correspondent reaction rate constants, a is the parameter, related to DEL changes during the ionic form formation, as the amine group is formed and protonized, 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.

Taking into account that the ionic form is formed in only one of two scenarios, we conclude that the oscillatory behavior is less probable than in some dynamic electroanalytical systems, although it is more probable than in the simplest cases [19 – 21]. The behavior of the system permits the efficient electrochemical determination of molnupiravir in a cathodic way, as shown below.

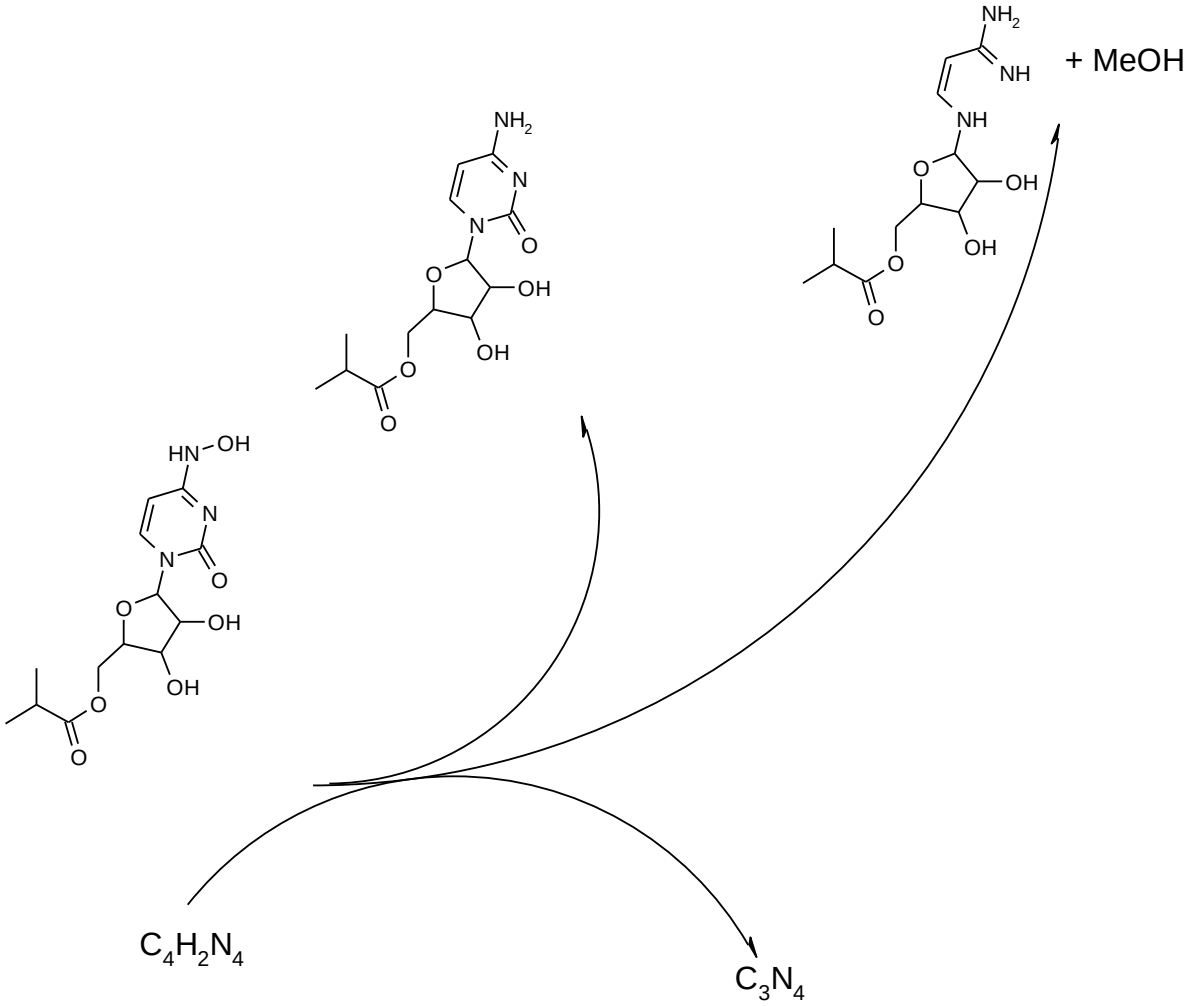

Figure 2. The schematical representation of the electroanalytical process.

3. Results and Discussion

We investigate the system's behavior with molnupiravir cathodic determination linear stability analysis of the equation set (1). The Jacobian matrix members may be described as:

$$\begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \quad (6)$$

In which:

$$a_{11} = \frac{2}{\delta}\left(-\frac{M}{\delta} - k_{21}(1-c)^2\exp(-am) + ak_{21}m(1-c)^2\exp(-am) - k_{22}(1-c)^2\right) \quad (7)$$

$$a_{12} = \frac{2}{\delta}(2k_{21}m(1-c)\exp(-am) + 2k_{22}m(1-c)) \quad (8)$$

$$a_{21} = \frac{2}{\delta}(k_{21}(1-c)^2\exp(-am) - ak_{21}m(1-c)^2\exp(-am) + k_{22}(1-c)^2) \quad (9)$$

$$a_{22} = \frac{2}{\delta}\left(-2k_{21}m(1-c)\exp(-am) - 2k_{22}m(1-c) - k_1\exp\left(-\frac{2F\varphi_0}{RT}\right) + jk_1c\exp\left(-\frac{2F\varphi_0}{RT}\right)\right) \quad (10)$$

Avoiding the cumbersome expressions, we introduce new variables, rewriting the determinant as (11)

$$\frac{2}{\delta C}\begin{vmatrix} -\kappa - Y - Z & \Lambda \\ Y + Z & -\Lambda - \Omega \end{vmatrix} \quad (11)$$

The general singular point conditions for the bivariant systems may be joined in Table 1.

Table 1. The main singular point conditions for the bivariant systems.

Stable steady-state	Tr J<0, Det J>0
Oscillatory behavior	Tr J=0, Det J>0
Monotonic instability	Tr J<0, Det J=0

Considering elements (7) and (10), oscillatory behavior can take place in this system, due to the possibility of Hopf bifurcation realization and, therefore, of the positive callback

Besides the element $jk_1c\exp\left(-\frac{2F\varphi_0}{RT}\right) > 0$, if j>0, describing the influences of the electrochemical stage on the double electric layer and surface electrophysical properties, another element capable of describing it is the element $ak_{21}m(1-c)^2\exp(-am) > 0$, if a>0, describing the analogous influences of the chemical stage.

It is important to mention that only one of two chemical stages may be responsible for the oscillatory behavior in mildly acidic media, as the second product is far less basic. On the other hand, a decrease in the pH will make increase its ionization degree, making it, thereby, more ionic. Therefore, the oscillatory behavior will be highly dependent on the pH.

Mathematically, the condition for the oscillatory behavior will be described as (12):

$$\begin{cases} -\frac{2}{\delta}(\kappa + Y + Z) - \frac{1}{C}(\Lambda + \Omega) = 0 \\ \frac{2}{\delta C}(\kappa\Lambda + \kappa\Omega + Y\Omega + Z\Omega) > 0 \end{cases} \quad (12)$$

Yet, if the mentioned elements are negative, steady-state stability will be obtained. Really. Opening the brackets and applying the stability requisite, we obtain the steady-state stability requisite exposed as (13):

$$\begin{cases} -\frac{2}{\delta}(\kappa + Y + Z) - \frac{1}{C}(\Lambda + \Omega) < 0 \\ \frac{2}{\delta C}(\kappa\Lambda + \kappa\Omega + Y\Omega + Z\Omega) > 0 \end{cases} \quad (13)$$

Defining a diffusion-controlled system efficient for molnupiravir cathodic determination in biological liquids. This condition is satisfied in a relatively vast parameter

region, in which the dependence between the electrode current and copper concentration will be linear.

The monotonic instability, corresponding to the detection limit, separates the steady stable and unstable states. Its condition is mathematically exposed as (14):

$$\begin{cases} -\frac{2}{\delta}(\kappa + Y + Z) - \frac{1}{C}(\Lambda + \Omega) < 0 \\ \frac{2}{\delta C}(\kappa\Lambda + \kappa\Omega + Y\Omega + Z\Omega) = 0 \end{cases} \quad (14)$$

In the case of very low pH values, both of the products will be ionized, providing the enhancement of the oscillatory behavior. In this case, the oscillatory behavior will be far more probable. This case will be analyzed in our next works.

4. Conclusions

From the theoretical investigation of the possibility of the C_3N_4-assisted molnupiravir electrochemical detection, it is possible to confirm the efficiency of carbon nitride as an electrode modifier. The system is an electroanalytical efficient diffusion-controlled process. The oscillatory behavior in this system is possible, being caused by DEL influences of both chemical and electrochemical stages in basic media. Only one chemical stage is responsible for the oscillatory behavior in mildly acidic conditions and concentrated acidic solutions.

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Conflicts of Interest

The authors declare no conflict of interest.

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