Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Article
Volume 13, Issue 1, 2023, 74
https://doi.org/10.33263/BRIAC131.074

Theoretical Description for Anti-COVID-19 Drug Molnupiravir Electrochemical Determination over the Poly-((1,2,4-triazole)-co-(squaraine dye)) Composite with Cobalt (III) Oxyhydroxide

Volodymyr V. Tkach [1,2,*], Marta V. Kushnir [1], Sílvio C. de Oliveira [2], Inna M. Shevchenko [3], Vira M. Odyntsova [3], Volodymyr M. Omelyanchik [3], Ludmila O. Omelyanchik [4], Olga V. Luganska [4], Vira V. Kopiika [4], Zholt O. Kormosh [5,*], Yana G. Ivanushko [6], Viktor V.Kryvetskyi [6], Inna I.Kryvetska [6], Igor V.Kryvetskyi [6], Nataliia R.Yemelianenko [6], Vitalii F. Rusnak [6], PetroI. Yagodynets [1,*], Zoriana Z. Masna [7], Lucinda Vaz dos Reis [8]

1 Chernivtsi National University, 58001, Kotsyubynsky Str. 2, Chernivtsi, Ukraine
2 Instituto de Química, Universidade Federal de Mato Grosso do Sul, 79074 – 460, Av. Sen. FelintoMüller, 1555, Vila Ipiranga, Campo Grande, MS, Brazil
3 Zaporizhzhia State Medical University, 69600, Mayakovsky Ave. 24, Zaporizhzhia, Ukraine
4 Zaporizhzhia National University, 69600, Zhukovsky Str. 66, Zaporizhzhia, Ukraine
5 Volyn National University, 43000, Voli Ave., 13, Lutsk, Ukraine
6 Bukovinian State Medical University, 58001, TeatralnaSq, 9, Chernivtsi, Ukraine
7 Danylo Halytsky Lviv National Medical University, 79010, Pekarska Str. 69, Lviv, Ukraine
8 Universidade de Trás-os-Montes e Alto Douro, Quinta de Prados, 5001-801, Folhadela, Vila Real, Portugal
* Correspondence: nightwatcher2401@gmail.com (V.V.T.); zholt-1971@ukr.net (Z.O.K.); ved1988mid@rambler.ru (P.I.Y.);

Scopus Author ID 55758299100
Received: 24.11.2021; Accepted: 29.12.2021; Published: 6.02.2022

Abstract: The possibility of electrochemical determination of molnupiravir has been theoretically evaluated for the first time. The molnupiravir electrochemical oxidation over the poly((1,2,4-triazole)-co-(squaraine dye)) composite with cobalt (III) oxyhydroxide has been theoretically evaluated. The correspondent mathematical model analysis has shown that the composite is an efficient electrode modifier for molnupiravir electrochemical determination. As for the oscillatory behavior is more probable than for the simplest case, and its probability will be higher in alkaline media than in neutral.

Keywords: COVID-19; molnupiravir; conducting polymers; cobalt (III) oxyhydroxide; triazole; squaraine dye; electrochemical sensor; stable steady-state.

1. Introduction

For the last two years, the atypical pneumonia outbreak, caused by the newly found bat coronavirus, known as SARS-CoViD2, causing the COVID-19 infection [1 – 6], has influenced the situation in the world seriously. Despite different drugs and vaccines' proven efficiency, it becomes in jeopardy as novel coronavirus variants surge. Hence, developing 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 [7-17].

The COVID-19 clinical trial of molnupiravir has proven effective 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, like the exact action-concentration dependence. Therefore, developing an efficient methodology for its qualitative and quantitative determination is still an actual question [18-23].

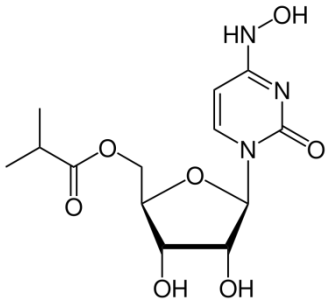

Figure 1. Molnupiravir.

As for now, no electroanalytical method for molnupiravir determination has been developed at this date. Nevertheless, considering that it possesses electroactive groups, it may be detected either anodically or cathodically. For anodic oxidation, the electrooxidation is realized by hydroxyl groups and hydroxylamine moiety, present in the analytes, which have been already detected electrochemically [24-29] on both conducting polymers and metal oxide nanoparticles. Also, as the electrochemical instabilities have already been predicted and observed in those electroanalytical systems [30-32], they may appear in this system.

Therefore, the goal of this work is the mechanistic theoretical investigation of the molnupiravir on the composite of the copolymer of 1,2,4-triazole and squaraine dye with cobalt (III) oxyhydroxide, by the most probable mechanism suggestion and mathematical modeling development. By analyzing the mathematical model, we investigate the electroanalytical system stability and the possibility of electrochemical instabilities. Also, we compare the system´s behavior with the behavior of similar ones [33-35].

Figure 2. The schematic representation for molnupiravir CoO(OH)-assisted determination.

2. System and its Modeling

Molnupiravir may be electrooxidized on CoO(OH) by either the hydroxylamino group or by each of the hydroxy groups. The nitrogen heteroatom heterooxidation will be realized if a stronger oxidant is used. The electrooxidation is realized via a nitroso-intermediate, thereby oxidizing, yielding a nitro derivative. Schematically, the electroanalytical process may be described as in Figure 2.

As for the copolymer, it stabilizes the CoO(OH) nanoparticles in its matrix and implements the function of the electronic transfer mediator.

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

m – molnupiravir concentration in the pre-surface layer;

m* - molnupiravir nitroso-form concentration in the pre-surface layer;

c – cobalt (II) oxide polymer matrix coverage degree.

Taking some assumptions [26 – 28], we describe the system´s behavior by the three-dimensional equation set, exposed as:

$$\begin{cases} \frac{dm}{dt} = \frac{2}{\delta}\left(\frac{\Delta}{\delta}(m_0 - m) - r_{11} - r_{12}\right) \\ \frac{dm*}{dt} = \frac{2}{\delta}(r_{11} - r_{21} - r_{22}) \\ \frac{dc}{dt} = \frac{1}{C}(r_{11} + r_{12} + r_{21} + r_{22} - r_3) \end{cases} \quad (1)$$

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

$$r_{11} = k_{11} m (1 - c)^2 \quad (2)$$

$$r_{12} = k_{12} m (1 - c)^2 \quad (3)$$

$$r_{21} = k_{21} m * (1 - c)^2 \quad (4)$$

$$r_{22} = k_{22} m * (1 - c)^2 \quad (5)$$

$$r_3 = k_3 c \exp\left(\frac{F\varphi_0}{RT}\right) \quad (6)$$

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

As it is possible to see, the behavior of this system for neutral and slightly alkaline media is less dynamic than in similar systems. On the other hand, molnupiravir sensitivity is enhanced, as shown below.

3. Results and Discussion

The electroanalytical behavior of the system with molnupiravir electrochemical determination is described by analyzing the equation-set (1) using the linear stability theory. The steady-state Jacobian matrix members may be expressed as:

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

Herein:

$$a_{11} = \frac{2}{\delta}\left(-\frac{\Delta}{\delta} - k_{11}(1-c)^2 - k_{12}(1-c)^2\right) \quad (8)$$

$$a_{12} = 0 \quad (9)$$

$$a_{13} = \frac{2}{\delta}(2k_{11}m(1-c) + 2k_{12}m(1-c)) \quad (10)$$

$$a_{21} = \frac{2}{\delta}(k_{11}(1-c)^2) \quad (11)$$

$$a_{22} = \frac{2}{\delta}(-k_{21}(1-c)^2 - k_{22}(1-c)^2) \quad (12)$$

$$a_{23} = \frac{2}{\delta}(-2k_{11}m(1-c) + 2k_{21}m*(1-c) + 2k_{22}m*(1-c)) \quad (13)$$

$$a_{31} = \frac{1}{C}(k_{11}(1-c)^2 + k_{12}(1-c)^2) \quad (14)$$

$$a_{32} = \frac{1}{C}(k_{21}(1-c)^2 + k_{22}(1-c)^2) \quad (15)$$

$$a_{33} = \frac{1}{C}\left(-2k_{11}m(1-c) - 2k_{12}m(1-c) - 2k_{21}m*(1-c) - 2k_{22}m*(1-c) - k_3\exp\left(\frac{F\varphi_0}{RT}\right) + jk_3c\exp\left(\frac{F\varphi_0}{RT}\right)\right) \quad (16)$$

Contrarily to similar systems [33-35], in which the *oscillatory behavior* is highly probable, in this system, it is far less probable, is caused by a unique factor of the cyclic DEL capacitance changes during the electrochemical stage. Mathematically, this factor is described by the positivity of $jk_3c\exp\left(\frac{F\varphi_0}{RT}\right) > 0$ if j>0, and this is the unique positive Jacobian matrix element. The oscillations are expected to be frequent and of small amplitude.

If the mentioned element is negative, the *steady-state stability* is realized. It may be shown by the Routh-Hurwitz criterion applied to the Jacobian matrix. Rewriting its determinant as (17):

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

and imputing the Det J<0 condition, salient from the criterion, we obtain the steady-state stability requirement (19):

$$\Lambda(2\Xi\Sigma + L\Sigma) - \Sigma\Omega(\kappa + \Xi + L) < 0 \quad (19)$$

which may be thereby rewritten as (20):

$$\Lambda(2\Xi\Sigma + L\Sigma) < \Sigma\Omega(\kappa + \Xi + L) \quad (20)$$

Describing either diffusion or kinetically controlled efficient electroanalytical system. The condition (20) corresponds to the linear current–concentration dependence, providing a facile analytical signal interpretation. Moreover, the system´s behavior becomes even more stable than [33-35].

From the electroanalytical point of view, the monotonic instability, correspondent to the detection limit, is also probable if the destabilizing and stabilizing influences are equal. Its conditions will be described as:

$$\Lambda(2\Xi\Sigma + L\Sigma) = \Sigma\Omega(\kappa + \Xi + L) \quad (21)$$

This system describes the electroanalytical behavior of the molnupiravir determination in a neutral and slightly alkaline medium. In a strongly alkaline medium, the electrooxidation will be accompanied by the stable ionic forms transformations, influencing the DEL. Also, if pH>0, cobalt (III) oxyhydroxide will be dissolved, making the system's behavior. This case will be evaluated in our next works.

4. Conclusions

From the system with the electrochemical determination of molnupiravir determination on the 1,2,4-triazole copolymer with the squaraine dye composite with CoO(OH), it was possible to conclude that the electroanalytical process is both diffusion and kinetically controlled;the linear dependence between the electrochemical parameter and concentration of the drug is realized in a broad topological parameter region. The composite is an efficient electrode modifier for molnupiravir electrochemical determination; the oscillatory behavior in this system is less probable than in similar systems, being caused uniquely and exclusively by the DEL influences of the electrochemical stage.

Funding

This research received no external funding.

Acknowledgments

This research has no acknowledgment.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Chauhan, S. Comprehensive review of coronavirus disease 2019 (COVID-19). *Biomed. J.* **2020**, *43*, 334-340, https://doi.org/10.1016/j.bj.2020.05.023.
2. Harapan, H.; Itoh, N.; Yufika, A.; Winardi, W.; Keam, S.; Te, H.; Megawati, D.; Hayati, Z.; Wagner, A.L.; Mudatsir, M. Coronavirus disease 2019 (COVID-19): A literature review. *Journal of Infection and Public Health* **2020**, *13*, 667-673, https://doi.org/10.1016/j.jiph.2020.03.019.
3. Tay, M.Z.; Poh, C.M.; Rénia, L.; MacAry, P.A.; Ng, L.F.P. The trinity of COVID-19: immunity, inflammation and intervention. *Nature Reviews Immunology* **2020**, *20*, 363-374, https://doi.org/10.1038/s41577-020-0311-8.
4. Alsayed, R.; Kadhom, M.; Yousif, E.; Sabir, D.K. An Epidemiological Characteristic of the COVID-19 Among Children, *Lett. Appl. NanoBioSci.* **2020,** *9*, 1156–1164, https://doi.org/10.33263/LIANBS93.11561164.
5. Figueroa-Valverde, L.; Díaz-Cedillo, F.; López-Ramos, M.; Rosas-Nexticapa, M.; Mateu-Armad, M.V.; Garcimarrero, R.A.; Cauich-Carrillo, R.; Ortiz-Ake, Y. Design and Synthesis of Five Cyclobuta-1,3-Dien-1-yl-Steroid Derivatives to Evaluate Their Theoretical Activity Against COVID-19. *Lett. Appl. NanoBioSci.* **2020,** *9*, 1177–1187, https://doi.org/10.33263/LIANBS93.11771187.
6. Hosny, N.M.; Sherif, Y. Molecular Docking Study on Some Isonicotinoyl Hidrazide Derivatives as Potencial Inhibitors of COVID-19. *Lett. Appl. NanoBioSci.* **2020,** *9*, 1217–1224, https://doi.org/10.33263/LIANBS93.12171224.
7. Cox, R.M.; Wolf, J.D.; Plemper, R.K. Therapeutically administred ribonucleoside analogue MK-4482/EIDD-2801 Blocks SARS-Cov-2 Transmission in Ferrets, *Nat. Microbiol.*, **2021**, *6*, 11-18, https://doi.org/10.1038/s41564-020-00835-2.

8. Mahase, E. Covid-19: Molnupiravir Reduces Risk of Hospital Admission or Death by 50% in Patients at Risk, MSD Reports, *BMJ* **2021**, *375*, https://doi.org/10.1136/bmj.n2422.
9. Abdelnabi, R; Foo, C.S; De Jonghe, S., Maes, P.; Weynand, B.; Neyts, J. Molnupiravir Inhibits Replication of the Emerging SARS-CoV-2 Variants of Concern in a Hamster Infection Model, *J. Inf. Dis.* **2021**, *224*, 749-753, https://doi.org/10.1093/infdis/jiab361.
10. Abdelnabi, R; Foo, C.S.; Kaptein S.J.F.; Zhang, X.; Do, T.N.D.; Langendries, L. *et al*. The combined treatment of Molnupiravir and Favipiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 Hamster Infection Model. *EBioMedicine* **2021,** *72,* 103595, https://doi.org/10.1016/j.ebiom.2021.103595.
11. Padhi, A.K; Shukla, R; Sauda, P; Tripathi, T. High throughput rational design of the remdesivir binding site in the RdRp of SARS-CoV-2: implications for potential resistance. *iScience* **2021,** *24*, 101992, https://doi.org/10.1016/j.isci.2020.101992.
12. Corey, L; Beyrer, C; Cohen, M.S. *et al.* SARS-CoV-2 variants in patients with immunosuppresion. The *New England J. Med.* **2021,** *385*, 562-566, https://doi.org/10.1056/NEJMsb2104756.
13. Blake, S; Shaabani, N; Eubanks, L. *et al.*, Salicylanilides Reduce SARS-CoV-2 Replication and Suppress Induction of Inflammatory Cytokines in a Rodent Model. *ACS Inf. Dis.* **2021,** *7*, 2229-2237, https://doi.org/10.1021/acsinfecdis.1c00253.
14. Forchette, L; Sebastian, W; Liu, T. A. Comprehensive Review of COVID-19 Virology, Vaccines, Variants and Therapeutics. *Curr. Med. Sci.* **2021,** *41*, 1037-1051, https://doi.org/10.1007/s11596-021-2395-1.
15. Menéndez-Arias, L. Decoding Molnupiravir-induced Mutagenesis in SARS-CoV-2. *J. Biol. Chem.* **2021,** *297*, 100867, https://doi.org/10.1016/j.jbc.2021.100867.
16. Painter, W.P; Holman, W; Bush, J.A. *et al.*, Human Safety, Tolerability and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2. *Antimicrob. Agents. Chemother.* **2021,** *65*, e02428-20, https://doi.org/10.1128/AAC.02428-20.
17. Chaplin, S. Molnupiravir: An Antiviral for the Prevention of Severe COVID-19, *Prescriber*, **2022,** *33*, 24 – 26, https://doi.org/10.1002/psb.1963
18. Li, P; Wang, Y; Lavrijsen, M. *et al.*, SARS-CoV-2 Omicron Variant Is Highly Sensitive to Molnupiravir, Nirmatrelvir and the Combination, *Cell Res.*, **2022,** https://doi.org/10.1038/s41422-022-00618-w
19. Pourkarim, F; Pourtaghi-Anvarian, S. Rezaee, H. Molnupiravir: A New Candidate for COVID-19 Treatment, *Pharmacol. Res. Perspect.*, **2022,** *10*, e00909, https://doi.org/10.1002/prp2.909
20. Singh, A.K.; Singh, Aç Singh, R. Misra, A. Molnupiravir in COVID-19: A Systematic Review of Literature, **2021,** *15*, 102329, https://doi.org/10.1016/j.dsx.2021.102329
21. Pouramini, A; Kafi, F; Hassanzadeh, Sh.; Saeifar, S; Jahantigh, H.R. Molnupiravir: An Effective Drug in Treating COVID-19? *J. Prev. Epidemiol.*, **2022,** *7*, e11, https://doi.org/10.34172/jpe.2022.11
22. Lee, Ch.-Ch; Hsieh, Ch.Ch.; Ko, W.-Ch. Molnupiravir – A Novel Oral Anti-SARS-CoV-2 Agent, *Antibiotics*, **2021,** *10*, 1294, https://doi.org/10.3390/antibiotics10111294
23. Zaranezhad, E; Marzi, M. Review on Molnupiravir as a Promising Oral Drug for the Treatment of COVID-19, *Europe PMC*, **2022,** *31*, 232 – 243, https://doi.org/10.1007/s00044-021-02841-3
24. El-Badawy, F.M.; Mohamed, M.A; El-Desoky, H.S. Fabrication of an Electrochemical Sensor Based on Manganese Oxide Nanoparticles Supported on Reduced Graphene Oxide for Determination of Subnanomolar Level of Antihepatitis C Daclatasvir in the Formulation and Biological Models. *Microchem. J.* **2020,** *157*, 104914, https://doi.org/10.1016/j.microc.2020.104914.
25. Ranganathan, P.; Mutharani, B; Chen, Sh.-M.; Sireesha, P. Polystyrene:β-Cyclodextrine Inclusion Complex-Supported Y_2O_3-Based Electrochemical Sensor: Effective and Simultaneous Determination of 4-Aminoantipyrine and Acyclovir Drugs. *J. Phys. Chem. C.* **2019,** *123*, 12211–12222, https://doi.org/10.1021/acs.jpcc.9b00465.
26. Annu; Sharma, S.; Jain, R.; Raja, N.A. Review–Pencil Graphite Electrode: An Emerging Sensing Material. *J. Electrochem. Soc.* **2019,** *167*, 037501, https://doi.org/10.1149/2.0012003JES.
27. Butnarasu, C.; Barbero, N.; Barolo, C.; Visentin, S. Squaraine dyes as fluorescent turn-on sensors for the detection of porcine gastric mucin: A spectroscopic and kinetic study. *Journal of Photochemistry and Photobiology B: Biology* **2020**, *205*, 111838, https://doi.org/10.1016/j.jphotobiol.2020.111838.
28. Maeda, T.; Liess, A.; Kudzus, A.; Krause, A.-M.; Stolte, M.; Amitani, H.; Yagi, S.; Fujiwara, H.; Würthner, F. Hydrogen bond-rigidified planar squaraine dye and its electronic and organic semiconductor properties. *Chemical Communications* **2020**, *68*, 9890-9893, https://doi.org/10.1039/D0CC04306K.
29. Gomes, V.S.D.; Gonçalves, H.M.R.; Boto, R.E.F.; Almeida, P.; Reis, L.V. Barbiturate squaraine dyes as fluorescent probes for serum albumins detection. *Journal of Photochemistry and Photobiology A: Chemistry* **2020**, *400*, 112710, https://doi.org/10.1016/j.jphotochem.2020.112710.
30. Das, I.; Goel, N.; Agrawal, N.R.; Gupta, S.K. Growth patterns of dendrimers and electric potential oscillations during electropolymerization of pyrrole using mono-and mixed surfactants. *J. Phys. Chem. B* **2010**, *114*, 12888-12896, https://doi.org/10.1021/jp105183q.
31. 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.

32. Das, I.; Goel, N.; Gupta, S.K.; Agrawal, N.R.J.J.O.E.C. Electropolymerization of pyrrole: Dendrimers, nano-sized patterns and oscillations in potential in presence of aromatic and aliphatic surfactants. *J. Electroanal. Chem.* **2012**, *670*, 1-10, https://doi.org/10.1016/j.jelechem.2012.01.023.
33. Tkach, V.V.; Kushnir, M.; Ivanushko, Y.; de Oliveira, S.; Reis, L.; Yagodynets´, P.; Kormosh, Z. The Theoretical Description for Neotame Electrochemical Determination, Assisted by Vanadium Oxyhydroxide Composite with a Squarainic Dye. *Appl. J. Env. Eng. Sci.* **2020,** *6*, 109-115, https://doi.org/10.48422/IMIST.PRSM/ajees-v6i2.18524.
34. Tkach, V.V.; Kushnir, M.; Storoshchuk, N.; Ivanushko, Y.; de Oliveira, S.; Yagodynets´, P.; Kormosh, Z. The Theoretical Description for the Confection of the Novel Thiourea-Based Active Surface for Cathodic Conducting Polymer Deposition. *Appl. J. Env. Eng. Sci.* **2020**, *6*, 143-148, https://doi.org/10.48422/IMIST.PRSM/ajees-v6i2.18543.
35. Tkach, V.V.; Kushnir, M.; Ivanushko, Y.; de Oliveira, S.; Reis, L.; Yagodynets´, P.; Kormosh, Z. The Theoretical Description for the Electrochemical Synthesis of Squaraine Dye Doped Conducting Polymer. *Appl. J. Env. Eng. Sci.* **2020,** *6*, 51–56, https://doi.org/10.48422/IMIST.PRSM/ajees-v6i1.17419.