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THEORETICAL ASSESSMENT OF ACID STRENGTH OF ANTIVIRAL FAVIPIRAVIR MEDICATION

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Abstract: AB INITIO and DFT methods were used to perform a quantum-chemical calculation of antiviral drug favipiravir and theoretically estimated its acidic strength (pKa = 13-14, where pKa is a universal indicator of acidity). It was found that this antiviral medication belongs to the class of weak acids (9 <pKa <14). It has been suggested that a decrease in acidic strength of favipiravir may increase its effectiveness.

Keywords: favipiravir, acid strength, quantum-chemical calculation, AB INITIO method, DFT method, pKa.

Introduction

Favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamide, $C_5H_4FN_3O_2$) is an antiviral medication (drug) developed in Japan for treatment of viral diseases, including influenza viruses, rhinovirus, respiratory syncytial virus and other life-threatening viral diseases [1]. The principle of its action is based on elongation inhibition of forming RNA chain [2]. Currently, favipiravir is being studied as a potential medication for treatment other viral infections, including coronavirus infection (COVID-19) [3]. Therefore, the question of increasing the effectiveness of this medication currently remains open. One of the ways to increase the effectiveness of favipiravir (and any other medical drug), as it appears to the authors, is the ability to control the acidic strength of this medication in accordance with well-known rule: when the acidic strength of any chemical compound decreases, its selectivity increases (to a certain limit), while maintaining its sufficiently high activity [4].

In this regard, the aim of this work is to theoretically estimate the acidic strength of studied compound - 6-fluoro-3-hydroxypyrazine-2-carboxamide - by quantum-chemical calculation of its optimal geometric and electronic structure and obtaining various quantum-chemical parameters (the total energy of molecular system $C_5H_4FN_3O_2$ (E_o), electron energy (E_{el}), distribution of atoms electron density (q_A), where q_{max}^{H+} is the maximum hydrogen atom charge), etc.. These parameters can be used in other studies, for example, when studying the mechanisms of chemical and biochemical reactions in which favipiravir can participate.

Methodical part

Two methods - AB INITIO/6-311G* and DFT-PBEO/6-311G** - for quantum-chemical calculation of studied drug favipiravir were chosen. The calculation was carried out according to programs [5-7], similar to [8]. The choice of these methods was due to the fact that at present it reproduce both the energy characteristics of favipiravir and the distribution of its atoms electron density quite well and with high accuracy. The calculations were carried out within framework of gas phase molecular model [9-10].

Calculation data

The optimized geometric and electronic structure of favipiravir's molecule is shown in Figs. 1, 2. The quantum-chemical parameters (E_0, E_{el}, q_{max}^{H+}) and pKa of studied favipiravir are presented in Table 1. For model of favipiravir obtained by AB INITIO method, the optimized bond lengths between carbon atoms in the ring are within the range 1.38-1.51 Å, C-O-1.19-1.32 Å,C-H-1.07 Å, C-N-1.29-1.35 Å, F-C-1.32 Å, H-N-0.99 Å, H-O-0.94 Å.

The following corresponding optimized bond angles (in degrees) were obtained: N(6)-C(2)-C(1)-119,C(5)-N(6)-C(2)-119, C(2)-C(1)-N(3)-121, C(1)-N(3)-C(4)- 119,N(3)-C(4)-C(5)-120, C(4)-C(5)-N(6)-122, C(4)-C(5)-F(7)-120, C(2)-C(1)-O(8)- 122, N(6)-C(2)-C(9)-117, C(1)-C(2)-C(9)-124, C(2)-C(9)-N(10)-114, O(11)-C(9)-N(10)-124, C(2)-C(9)-O(11)-122, N(3)-C(4)-H(12)-119, C(1)-O(8)-H(13)-108, C(9)-N(10)-H(14)-122, C(9)-N(10)-H(15)-118.

The atomic charges: C(1)-(0.511), C(2)-(-0.033), N(3)-(-0.394), C(4)-(0.03), C(5)-(0.418), N(6)-(-0.378), F(7)-(-0.283), O(8)-(-0.378), C(9)-(0.579), N(10)-(-0.527), O(11)-(-0.458), H(12)-(0.143), H(13)-(0.265), H(14)-(0.261), H(15)-(0.245) (see Fig. 1).

For model of favipiravir obtained by DFT method, the optimized bond lengths between carbon atoms in the ring are within the range of 1.39-1.51 Å, C-O-1.21-1.33 Å, C-H-1.09 Å, C-N-1.30-1.35 Å, F-C-1.33 Å, H-N-1.00-1.01 Å, H-O-0.97 Å.

The following corresponding optimized bond angles (in degrees) were obtained: N(6)-C(2)-C(1)- 119,C(5)-N(6)-C(2)- 119, C(2)-C(1)-N(3)- 121, C(1)-N(3)-C(4)- 119, N(3)-C(4)-C(5)- 120, C(4)-C(5)-N(6)- 123, C(4)-C(5)-F(7)- 120, C(2)-C(1)-O(8)- 122, N(6)-C(2)-C(9)- 117, C(1)-C(2)-C(9)- 124, C(2)-C(9)-N(10)- 113, O(11)-C(9)-N(10)- 124, C(2)-C(9)-O(11)- 123, N(3)-C(4)-H(12)-119, C(1)-O(8)-H(13)- 106, C(9)-N(10)-H(14)- 120, C(9)-N(10)-H(15)-118.

The atomic charges: C(1)-(0.416),C(2)-(-0.033), N(3)-(-0.347), C(4)-(-0.014),C(5)-(0.337), N(6)-(-0.357),F(7)-(-0.207), O(8)-(-0.294), C(9)-(0.439), N(10)-(-0.466), O(11)-(-0.361), H(12)-(0.148), H(13)-(0.249), H(14)-(0.25), H(15)-(0.24) (see Fig. 2).

Using formula pKa = 49.04 - 134.61 q_{max}^{H+} [**11**], obtained by authors for AB INITIO/6-311G** (q_{max}^{H+} = +0.265), we find the value pKa = 13.

For DFT-PBE0/6-311G** method the acidity index is calculated by formula pKa = 51.048-150.078q_{max}^{H+} [**7**] (q_{max}^{H+} = +0.25). Calculated value pKa = 14.

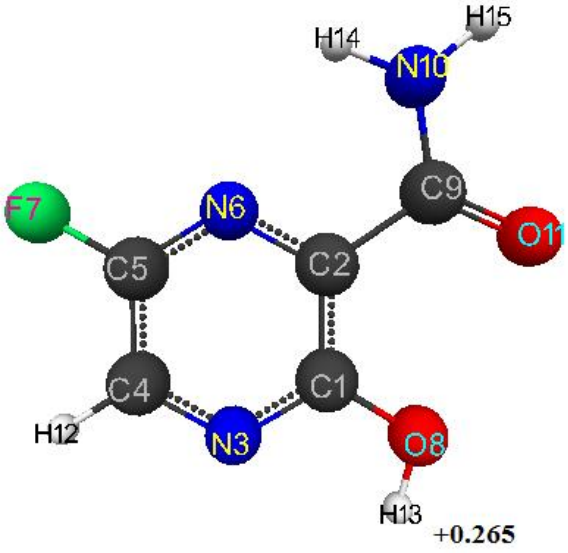

Figure 1. *Geometric and electronic structure of favipiravir's molecule obtained by AB INITIO method.*

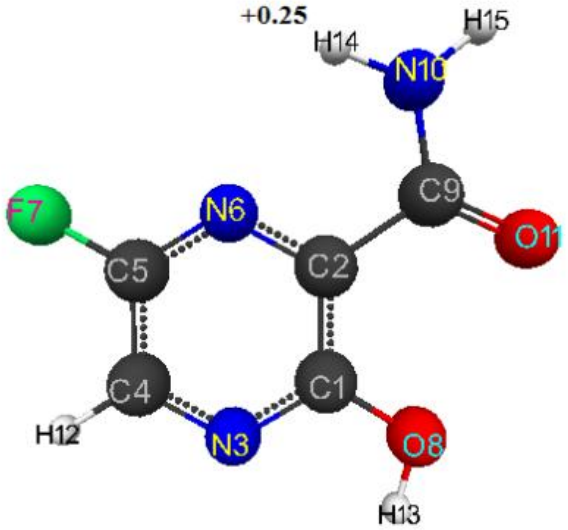

Figure 2. *Geometric and electronic structure of favipiravir's molecule obtained by DFT method.*

Table 1. *Quantum-chemical parameters (E_0, E_{el}, q_{max}^{H+} and pKa) of favipiravir studied.*

Preparation	**Method**	**E_0,** kJ/mol	**E_{el},** kJ/mol	**q_{max}^{H+}**	**pKa**
Favipiravir	AB INITIO	-1586398	-3182282	+0.265	13
	DFT	-1593396	-3178870	+0.25	14

Thus, the optimized atomic-molecular structures of studied favipiravir were obtained by DFT and AB INITIO methods. At the same time, the quantum-chemical parameters (E_0, E_{el}, q_{max}^{H+}), dipole moments, distribution of electron density on atoms were calculated, and also it was

proved that studied favipiravir belongs to the class of weak acids (9 <pKa≤14). It is obvious that proposed hypothesis for dependence of favipiravir's efficiency on its acidic strength requires experimental verification.

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