DFT Based Quantum Chemical Descriptors of Favipiravir Forms

Hakan Sayiner[1], Serap SENTURK DALGIC[2], and FATMA KANDEMIRLI[3]

[1]Adiyaman Universitesi Tip Fakultesi
[2]Trakya Universitesi
[3]Kastamonu Universitesi

May 29, 2020

Abstract

This research has focused on the chemical reactivity behavior of favipiravir forms and transition states of forms. These compounds are potential drugs for the Ebola virus and have shown its effectiveness for COVID-19. Geometry optimizations have been conducted by using the DFT method with the B3LYP/6-311G(d,p) method in the gas phase and 4 different solvent environments. Polarized Continuum Model has been used to evaluate the solvent effect on chemical stability and its related properties. Dipole moment, polarizability, and molecular first-order hyperpolarizability of the favipiravir forms were computed for gas and solvent phase. Also, thermodynamic properties such as heat capacity, entropy, and enthalpy of the A3 form of favipiravir at different temperatures were calculated in the gas phase.

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Hakan Sezgin SAYINER[1] , Serap SENTURK DALGIC[2], Fatma KANDEMIRLI[*3]

[1] Infectious Diseases, Medicine Department, Adiyaman University, Adıyaman, Turkey

[2] Atomic and Molecular Physics, Physics Department, Faculty of Science, Trakya University, Edirne, Turkey

[3*]Biomedical Engineering Department, Faculty of Engineering and Architecture, Kastamonu University, Kastamonu, Turkey

Corresponding author; Tel: +(90) 5439721281 e-mail:fkandemirli@yahoo.com

Abstract

This research has focused on the chemical reactivity behavior of favipiravir forms and transition states of forms. These compounds are potential drugs for the Ebola virus and have shown its effectiveness for COVID-19. Geometry optimizations have been conducted by using the DFT method with the B3LYP/6-311G(d,p) method in the gas phase and 4 different solvent environments. Polarized Continuum Model has been used to evaluate the solvent effect on chemical stability and its related properties. Dipole moment, polarizability, and molecular first-order hyperpolarizability of the favipiravir forms were computed for gas and solvent phase. Also, thermodynamic properties such as heat capacity, entropy, and enthalpy of the A3 form of favipiravir at different temperatures were calculated in the gas phase.

KEYWORDS Favipiravir, Covid-19, B3LYP, solvent effect, Tautomer.

INTRODUCTION

T-705 (favipiravir), a fluorinated pyrazinecarboxamide was initially developed against influenza virüs[1]. T-

705 (Favipiravir) is an antiviral pyrazinecarboxamide-based, an inhibitor of the influenza virüs with an EC90 of 1.3 to 7.7 uM (influenza A, H5N1). T-705 exhibits activity against type B and C viruses with EC90s of 0.25-0.57 uM and 0.19-0.36 uM, respectively.[2] Favipiravir acts as a purine analogue that selectively inhibits viral RdRps.[3] In addition to its potent anti-influenza activity, favipiravir has shown activity against a wide range of other RNA viruses, including enteroviruses, bunyaviruses, filoviruses, norovirus, arenaviruses, flaviviruses rhabdoviruses, and alphaviruses.[4-6]They reported that favipiravir had potent antiviral activity against henipaviruses and showed that In vitro, favipiravir inhibited Nipah and Hendra virus replication and transcription at micromolar concentrations. In the Syrian hamster model, either twice-daily oral or once-daily subcutaneous administration of favipiravir for 14 days fully protected animals challenged with a lethal dose of Nipah virüs.[7] In February 2020, the drug favipiravir began to be studied in China for its experimental treatment in COVID-19 (new coronavirus) disease, which appeared in China.[8] Parlak et al.[9]investigated the adsorption between favipiravir and undoped or silicon doped C60 fullerenes and to assess their possible usage as drug delivery vehicles and also they studied the possible interaction mechanism of C20 and Si-doped C20 fullerenes with favipiravir molecule.[10] They reported structural analysis of favipiravir performed by exploring tautomers formations. They reported that four tautomers could be possible for favipiravir and their stability could be different regarding the values of total energy and also reported that the results indicated that the structure given in Figure 1 was the most stable structure and the next one is F1 by 5 kcal/mol difference in the stability level.[11]

FIGURE 1

In very recent studies, favipiravir has been studied for experimental treatments of COVID-19, where it is recommended as an effective drug recently. [12]

Previous studies have shown that quantum chemical calculations can very well evaluate molecular properties.[13-16] Over the past two decades, there has been a great deal of interest in studying the tautomerism of heterocyclic compounds to ensure that the effect of tautomerism on the chemical and biological properties of molecules can be determined. These structures and tautomers can occur if the energy required for tautomer formation is provided by other sources, such as intermolecular interactions and binding, and may be important in recognizing such structures before exploring their activity in the biological environment. [10]

This study aims to investigate two different structures (A and B) and three tautomers of structure A and two tautomers of structure B and transition states between the tautomers and conformer A and B in different environments as a quantum chemical. Besides, the temperature addiction of the thermodynamic parameters such as heat capacity (Cv), entropy (S), zero-point energy, heat capacity at constant pressure was calculated at B3LYP /6-311G(d,p) level in the gas phase for A3 form.

MATERIALS AND METHODS

Gaussian 09 program.[17] was used for all DFT calculations. Possible structures (Figure 2) in the gas phase, and different media have been analyzed by performing density functional theory (DFT) calculations at the B3LYP/6-311G(d,p) theoretical level. Frequency computations based on the same geometry optimization method were used to confirm the nature of the stationary points. Frequency calculations characterized all stationary points. The reaction pathway was determined by following the IRC procedure.[18,19] In addition, the effects of four solvents, ethanol, DMF, DMSO and water were studied through the self-consistent reaction-field (SCRF) method based one conductor-like polarisable continuum model (CPCM), which is often considered one of the most successful solvation models.[20]

The Polarizable continuity model (PCM) proposed by Born, Kirkwood and Onsager is an extension of the solvent reaction field models presented for charge distributions in space. PCM uses a more realistic shape of the void, simulates the dielectric response with separate charges on the void surface, and contains nonpolar additives to the solution.[21]

The electronic energies, NLO properties, the energy of the highest occupied molecular orbital (EHOMO),

and the lowest unoccupied molecular orbital (ELUMO) of the energy were computed. Also, some parameters related to HOMO and LUMO energies such as chemical hardness (h), chemical softness (S), electronegativity (χ), chemical potential (μ) and electrophilicity index (w) were computed. Nonlinear optical (NLO) properties such as dipole moment (μ), mean polarizability (αtotal), the anisotropy of the polarizability ([?]α) and first hyperpolarizability (β) were computed with the B3LYP/6-311G(d,p) theoretical level.

RESULT and DISCUSSION

Two different structures were considered (A and B). The features of three tautomers of structure A and two tautomers of structure B were examined. The transition states between the tautomers of structure A in gas and solvent phases were examined, and also the transition states of structure A and B were examined.

The optimized possible molecular conformations of favipiravir numbering of the atoms, and its transition states forms with the sum of electronic and zero-point Energies calculated using B3LYP/6311 G(d,p) theoretical method in the gas phase were given in Figure 2.

FIGURE 2

No imaginary frequencies were found in the calculated vibrational spectra of the stable A1, A2, A3, B1, B2 form of favipiravir while a single imaginary stretching frequency was found for each Transition State (TS). The value of imaginary frequencies are -1893 cm-1 for TS1, -515 cm-1 for TS2, -1903 cm-1 for TS3, in gas phase. The energies for the A1, A2, A3, B1, and B2 form of favipiravir and transition between A1 with A2, A2 with A3, and A3 with B1 are summarized in Table 1 for different media. The energies are sensitive to the gas phase and solvent used. On the other hand, transition states are characterized by higher energies compared to the other form. It is clear that the calculated values of the energies depend on the solvent media used.

Accordingly the energy is -381253.07 kcal/mol for A1 form, -381240.80 kcal/mol for A2 form and -381239.30 kcal/mol for A3 form. A1, A2 and A3 form are tautomer form each other. A1 is more stable than the others. A3 and B1 are different conformers of favipiravir molecule. B1 conformer is stable than A3 conformer however is less stable than A1 and A2 tautomer forms in gas phase and different media (Table 1). The order of stability of A1, A2, A3 tautomers studied in the gas phase and solvent media is A1 > A2 > A3.

TABLE 1

HOMO, LUMO ESP of A1, A2, A3, B1, B2 form and transition states were given in Figure 3. HOMO is the outermost orbit filled with electrons; it can be thought of as a valance band as it is represented by the ionization potential of a molecule and acts as an electron donor. LUMO, on the other hand, represents the innermost orbital that is not filled by electrons and is directly related to electron affinity and it acts as an electron acceptor.

FIGURE 3

The main orbitals involved in the chemical reaction are the highest-occupied molecular orbital (HOMO) and the lowest-occupied molecular orbital (LUMO) since they act as electron acceptors.[22]

MEP map of the molecule is calculated in optimized geometries in estimating reactive regions for electrophilic and nucleophilic attack. In most MEPs, the maximum negative region is indicated in red for electrophilic attack indications and the maximum positive region in blue for nucleophilic attack symptoms. In terms of colour grading, it shows molecular size, shape, positive, negative and neutral electrostatic potential regions simultaneously and MEP is very useful in the investigation of molecular structure with its physicochemical property relationship.

The highest occupied molecular orbital (HOMO) and the lowest empty molecular orbital (LUMO) are called boundary orbitals, and these orbitals are key parameters in determining molecular properties and molecular electrical transport properties, the eigenvalues of HOMO (transmitter) and LUMO (receiver). Moreover, the energy difference between them determines the chemical activity of molecules. The Frontier molecular orbital

energies have been calculated with B3LYP/6–311G (d,p) level. Results obtained from solvent (ethanol, DMF, DMSO and water) and gas-phase for of A1, A2, A3, B1, B2 form and transition states are listed in Table-2 with the parameters obtained from frontier molecular orbital.

TABLE 2

Band gap, electronegativity (χ), global hardness (η), chemical potential (μ),, global electrophilic index (ω), spherical softness (σ), Nucleofugality ΔE_n and electrofugality ΔE_e and electronic charge ([?]N_{max}) can be calculated using the followng equations.[23-25]

$E_{gap} = E_{LUMO} - E_{HOMO}$ (1)

$$\eta \cong -\left(\frac{E_{HOMO} - E_{LUMO}}{2}\right)$$

$$\mu = -\chi \cong \left(\frac{E_{HOMO} + E_{LUMO}}{2}\right)$$

$$\sigma = \frac{1}{\eta} \cong -\left(\frac{2}{E_{HOMO} - E_{LUMO}}\right)$$

$$\omega = -\frac{\mu^2}{2\eta}$$

$$E_n = -A + \ \omega = \frac{(\mu + \eta)^2}{2\eta}$$

$$E_e = I + \ \omega = \frac{(\mu - \eta)^2}{2\eta}$$

$$N_{max} = -\mu/\eta$$

The electrophilic index, chemical hardness, the chemical potential is a global reactivity index. ΔN_{max} refers to the maximum charge transfer to the electrophile. ΔN_{max} was evaluated as showing the ability of the system to obtain additional electronic charge from the medium that defines the charge capacity of the molecule. This index measures energy stabilization when the system receives an additional electronic charge (ΔN_{max}) from the environment. With the electronic chemical potential of the molecule, the direction of charge transfer is completely determined. Since an electrophile is a chemical type that can accept electrons from the environment, after accepting the electronic charge, its energy should decrease and the electronic chemical potential should be negative.[26-29]

The global hardness index has changed as **A3 <B1 < A1 < A2 < B2** for gas phase and studied solvent phase. It seems the structure **A3**has the less hardness index and more reactive than the others Table 2 represents the solvent effect of the ΔN_{max} for A1, TS1, A2, TS2, A3, TS2, B1, and B2 in different solvents. The max charge transfer index (ΔNmax) of A1, T1, A2, A3, TS3, B1 decreases as follow: gas > ethanol > DMF > DMSO > water. ΔNmax of favipiravir forms increases in following order: B2 < A2 < A1 < B1 < A3 in gas phase, however in solvent phese (ethanol, DMF, DMSO, water) increase in following order: B2 < A1 < A2 < B1 < A3. According to these results, it can be easily estimated that B2 and A3 structures have the largest ΔNmax value in the gas phase and also in the solvent phase. Increase in the max charge transfer values of B2, A2, A1, B1, A3 in gas phase are 2.21 %, 3.09 %, 13.79 %, and 1.55 %.

The Energy Gaps (ΔE) for the favipiravir form studied increase in the following order: A3 < B1 < A1 < A2 <B2 for gas phase and the other solvent phases at B3LYP/6311G(d,p). Also, the energy gap of favipiravir form has depended on the solvent media. The most significant difference of energy gap for water and gas

phases is 0.05 eV, 0.12 eV, 0.13 eV respectively for A1, A2, and B2 forms, however, energy gap in water is smaller than gas phase only 0.01 eV for A3 and 0.04 for B1.

Dipol moment, which is a measurement of the asymmetry in the charge distribution, indicates the degree of separation of the charge in a molecule. The number of atoms in tautomers is constant, and it is stated that only the movement of the H atom between N and O atomic regions can bring important properties in tautomeric structures in which it is evaluated. The trends can be seen much better with the values of dipole moments (DM), where different values of the DM can detect different directions of the electronic directions.

The dipole moments of Favipiravir's A1, A2, A3, B1, B2 forms and transition states (TS1, TS2, and TS3) between A1 and A2, A2 and A3 and B1 and A3 were calculated in the gas and solvent phases and are given in Figure 4.

The values of the dipole moments in Figure 4 show that the presence of the solvent generally increases in the dipole moment of the A1, A2, A3, B1, B2 form of favipiravir and transition states relative to the gas phase. The dipole moments increase by changing the gas phase to the solution as well as by increasing the solvent polarity. In more polar solvents, Polar solvents have higher dipole moment values than non-polar solvents, so delocalization of loads is higher in polar solvents.[30-32] The gaseous A1, A2, A3, B1 and B2 forms have a dipole moment value of 1.28, 0.93, 2.03, 2.33 and 2.24 D in the gas phase. A2 tautomer has smaller dipole moments than the other forms, and B1 form has an enormous dipole moment.

FIGURE 4

The polarity of organic materials is usually due to the contributions of the components of the system (atoms, molecules) due to the molecules' Van der Waals, dipole-dipole interactions, hydrogen bond interactions. The nonlinear optical properties of molecular systems depend on the polarization of electrons in their bonding orbitals. The mean polarization and anisotropy of the polarization (αa and $\Delta\alpha$) were calculated as follows using the polarization components:

$\alpha = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz})$

$$\alpha = \left[\frac{(\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{yy} - \alpha_{zz})^2 + (\alpha_{zz} - \alpha_{xx})^2 + 6(\alpha_{xz}^2 + \alpha_{xy}^2 + \alpha_{yz}^2)}{2}\right]^{\frac{1}{2}}$$

The results of the static polarizability of A1, A2, A3, B1, B2 forms and TS1, TS2 and TS3 transition states of favipiravir calculated in the gas phase and different solvents are shown in Figure 5. The highest <α> value was found as 15.63 for A3 in water phases. Furthermore, the dipole moment difference between gas and water phase is the biggest; this difference is 3.53 esu, 3.48 esu, 3.76 esu, 3.75 esu, 3.46 esu, respectively for the forms A1, A2, A3, B1 and B2.

FIGURE 5

Static values of polarizability evolve in the following order B2<B1< in gas phase and different media, and static values of polarizability evolve in the following order A3<A2<A1 in gas phase, but A3<A2=A1.

The high polarity of a molecule means that the molecule has a small frontier orbital gap. [33-36] Form A3 has the smallest frontier orbital gap energy in the gas phase and the largest polarization of the favipiravir forms examined, so this is associated with a high chemical reactivity, low kinetic stability and is also termed as a soft molecule.

Frontier orbital gap energy of A3 form in the solvent phase is smaller than the gas phase so, it could be concluded that A3 form in the solvent phase is a higher chemical reactivity than the gas phase. Figure 5 shows that polar solvents increase the polarisability of all studied favipiravir tautomers in compare to the gas phase.

Results of polarization anisotropy calculated in the gas phase and different solvents of the forms of Favipiravir molecule A1, A2, A3, B1, B2 and their transition states are shown in Figure 6.

FIGURE 6

For these forms, the anisotropy of polarizability is found as 9.95, 9.76, 10.18, 10.57, 9.78 in the gas phase, and as 13.42, 13.16, 14.31, 14.64, 13.17 in the water phase. The most significant difference in polarization anisotropy value was found between the water and gas phases, which are 3.48 esu, 3.39 esu, 4.14 esu, 4.07 esu, 3.39 esu for A1, A2, A3, B1 and B2 forms, respectively.

The total hyperpolarizabilities in atomic units (a.u.) are related to the electrostatic units (esu) by the relation: 1 a.u. = 8.6393X10-33 esu. The first hyperpolarizability is a third-degree tensor that can be defined by a 3 x 3 x 3 matrix. Due to the Kleinman symmetry, 27 components of the 3-D matrix can be reduced to 10 components. The output of Gaussian 09 provides ten components of this matrix as βxxx, βxxy, βxyy, βyyy, βxxz, βxyz, βyyz, βxzz, βyzz, βzzz, respectively. The values of the first hyperpolarized tensors calculated in atomic units were converted to electrostatic units using 1au =0.0086393x10-30 esu. The calculated first static hyperpolarizability value for A1 is equal to 1.31x10-30, 2.09x10-30, 2.10x10-30, 2.11x10-30, and 2.12x10-30 calculated DFT level of theory in gas, ethanol, DMSO, DMF, and water respectively.

Thermodynamic parameters such as heat capacity ($C^o_{p,m}$), entropy ($S^o_{p,m}$) and enthalpy ($H^o_{p,m}$Hm*), changes Gibbs Free energy changes ($G^o_{p,m}$) were calculated for the A3 favipiravir form at temperatures ranging from 200 K to 1000 K, under 1 atm pressure and vacuum. Based on vibration analysis, these static thermodynamic functions were obtained from theoretical harmonic frequencies and their correlation graphs are shown in Figure 7.

FIGURE 7

It can be observed from Figure 7 that heat capacity, entropy, and enthalpy of favipiravir increase with temperatures ranging from 200 to 1000 K due to increased molecular vibration intensities with temperature and Gibbs free energy of For A3 favipiravir form decreases. It means that with increase of temperature, the stability of A3 favipiravir form increases. [37] Correlation equations between heat capacity, entropy, enthalpy, Gibbs Free energy changes and temperatures were placed by quadratic formulas as in the equation below

$$C^o_{p,m} = -6x10^{-5}T^2 + 0.1194T + 4.9341$$

$$S^o_{p,m} = -4x10^{-5}T^2 + 0.1491T - 56.726$$

$$H^o_{p,m} = 2x10^{-5}T^2 + 0.0264T - 3.3117$$

$$G^o_{p,m} = -5x10^{-5}T^2 + 0.0707T + 2.8816$$

with the corresponding fit factors (R2) for these thermodynamic properties are 0.9983, 0.9999 and 0.9997, 1.000 respectively.

All thermodynamics data can provide useful information for further study about 4Cl3NT and can be used to predict directions of chemical reactions according to the relationship of thermodynamic functions, other thermodynamic energies and the second law of thermodynamics in the thermochemical field.

4 . SUMMARY

In this research, we have tried to explain quantum chemical parameters of the A1, A2, A3, B1, B2 form of favipiravir and transition states TS1 between A1 and A2 forms, TS2, A2 and A3 forms and TS3 A3 and B1 forms in gas and studied solvent phase at B3LYPP/6-311G(d, p) to show the computed parameters strongly depend on the solvent media. The dipole moments, polarisability of all forms are affected by the solvent. With the increase of the polarity of solvents, the dipole moments of all tautomers were increased.

CONFLICT OF INTERES

The authors declare no competing financial interests.

ORCID https://orcid.org/ 0000-0001- 6097-2184

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