Adv. J. Sci. Eng.
Original Research

Advanced Journal of Science and Engineering
https://adv-j-sci-eng.com
eISSN: 2717-0705

Structural and Electronic Analysis of Tautomerism in 5,6-Difluor-2,4(1H,3H)-Pyrimidindion

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Advanced Journal of Science and Engineering. 2022;3(1):2-6. https://doi.org/10.22034/advjse22031002

Received: 05 October 2021 / ***Revised***: 31 January 2022 / ***Accepted***: 03 February 2022 / ***Published***: 15 February 2022

Abstract: Density functional theory (DFT) calculations were performed to analyze the structural and electronic features of tautomers of 5,6-difluor-2,4(1H,3H)-pyrimidindion, as a possible compound for pharmaceutical applications. To this aim, possible structures of tautomers were obtained by performing optimization calculations and their electronic features were investigated. The results indicated that the tautomerism process could change the original features of 5,6-difluor-2,4(1H,3H)-pyrimidindion, in which different impacts of such changes could be observed for the list of tautomeric structures. Finally, further pharmaceutical uses of 5,6-difluor-2,4(1H,3H)-pyrimidindion compound should be in accordance with the structural and electronic features of the tautomeric formations.

Keywords: Pyrimidindion; DFT; Tautomer; Conformation; Drug design.

Introduction

Tautomerism is a common occurring process among the organic compounds, in which one hydrogen atom will move usually among the oxygen atomic sites of a heterocyclic compound to produce keto-enol tautomeric structures [1]. Accordingly, the features of tautomeric structures should be investigated to recognize new characteristics of the tautomeric compounds in accordance with their behaviors [2]. Not only in the synthetic organic compounds, but the tautomerism will occur in the natural bioorganic compounds leading to appearance of mutagenic impacts [3]. Therefore, recognizing such features are important in both of synthetic and natural organic/bioorganic compounds [4]. Computational chemistry tools could help to approach such goals of materials characterizations [5]. Quantum chemical calculations are useful to provide insightful information for the characteristic features of matters [6]. To this point, the tautomerism in 5,6-difluor-2,4(1H,3H)-pyrimidindion (DfPy) compound (Figure 1) was investigated by such calculations to recognize structural variations and electronic features.

In the field of computer-aided drug design (CADD), quantum chemical calculations could help for investigating structural and electronic features of the pharmaceutical related compounds for predicting or interpreting the structure-activity relationship (SAR) concept [7]. To approach this goal, several practical and computational methodologies have been developed up to now [8]. DfPy (Figure 1) is a heterocyclic compound as could be known as a derivative of uracil, in which each of

5-flurouracil and 6-flurouracil have been seen as possible anticancer drugs [9]. Therefore, it could be an important issue to see their structural and electronic features for their further applications in pharmaceutical related fields [10]. Earlier works indicated the importance of tautomeric formations in the nature of pharmaceutical compounds leading to appearance of new behaviors [11]. Therefore, following such variations and examining the impacts on structural and electronic features is a must in the case of drug design and development [12]. For the current investigated compound, the original heterocyclic structure of DfPy makes it a potent compound for contributing to tautomerism process. In this regard, this work was performed to show occurrence of such tautomerism process for DfPy compound by means of performing quantum chemical calculations.

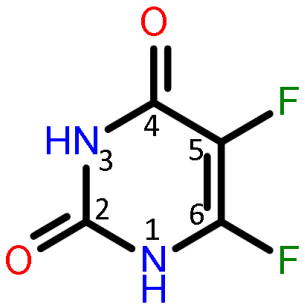

Figure 1: The original 5,6-difluor-2,4(1H,3H)-pyrimidindion (DfPy) compound.

Materials and Methods

In this work, the B3LYP/6-31+G* level of density functional theory (DFT) quantum chemical calculations were performed using the Gaussian program [13]. First, the original structure of DfPy (Figure 1) was optimized to obtain the minimized energy structure. Next, possible structures of tautomers of DfPy were investigated by movement of the hydrogen atoms of each of N1 and N3 among the oxygen atomic sites of 2 and 4 yielding formations of five tautomeric compounds in addition to the original compound (Figure 2). All models of tautomers were optimized to see their stability during geometrical relaxation, and their electronic features were subsequently evaluated to analyze the models systems. In Table 1, the results of calculations were included in terms of total energy (TE), delta-energy of tautomeric formation (DE), energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) levels, energy gap of HOMO and LUMO levels (EG), and dipole moment (DM). Additionally, qualitative features including distribution patterns of HOMO and LUMO and electrostatic potential (ESP) surfaces were exhibited in Figure 3. Indeed, *in silico* computer-based medium has been seen useful for investigating the biological environment besides the well-known *in vitro* and *in vivo* media avoiding the impacts of unexpected interferers of experiments [14, 15].

Table 1: Results of calculations for the DfPy models.*

Model	TE	DE	HOMO	LUMO	EG	DM
T0	-16688.041	0	-6.950	-1.318	5.632	3.001
T1	-16687.795	0.247	-6.603	-1.186	5.417	4.596
T2	-16687.470	0.571	-6.669	-1.502	5.168	5.975
T3	-16687.191	0.850	-6.761	-0.823	5.938	6.175
T4	-16687.474	0.567	-6.712	-1.478	5.235	2.304
T5	-16687.665	0.376	-6.916	-1.011	5.905	3.748

*All energies are in eV. DM is in Debye.

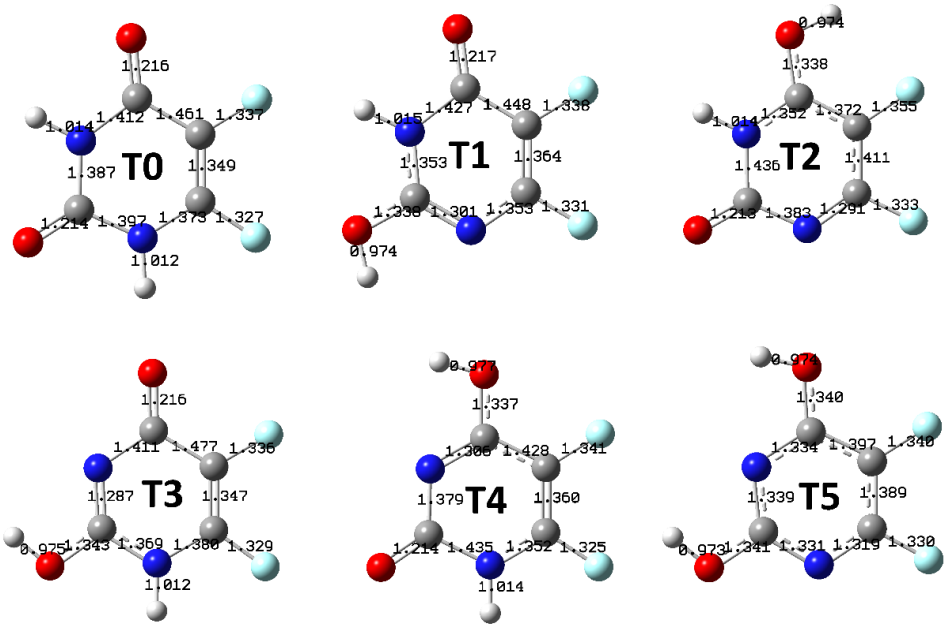

Figure 2: Tautomeric structures of 5,6-difluor-2,4(1H,3H)-pyrimidindion (DfPy) compound. The calculated bond distances are shown in Angstrom.

Results and Discussion

This work was aimed to analyze electronic and structural features of tautomers formations of 5,6-difluor-2,4(1H,3H)-pyrimidindion (DfPy) compound (Figure 1). As shown in Figure 2, five structures of tautomers; T1-T5, were obtained by the hydrogen atoms movements to the oxygen atomic sites of T0, the original structure. A quick look at the results of Figure 2 could show impacts of occurrence of such tautomerism processes on the structural bonds of the models, in which the bond distances and orientations were changed in the tautomeric models in comparison with the original model. The results of this work were obtained by performing DFT calculations for the 3D models of molecules of DfPy compound, in which the results of optimized structures were summarized in Table 1 besides representing their configurations in Figure 2. Besides the very light weight of hydrogen atom, its role is indeed dominant for putting serious impacts on the structural features of the tautomers besides conducting significant variations in the electronic features of the models. Accordingly, the optimized configurations and their related features could all show significance of such processes in determining the characteristic roles of an organic compound.

Based on the movements of hydrogen atoms, five tautomeric structures were obtained. As could be found by the results of Table 1, different values of TE were calculated for the tautomeric structures affirming the impact of occurrence of tautomerism on the structural stability of T1-T5 in comparison with the original T0 compound. Interestingly, T0 was placed at the highest stability in comparison with other T1-T5 structures showing the impact of tautomerism for making the structures unstable. Accordingly, their energies and relaxation configurations were changed. Comparing the models based on the obtained values of DE, which are energy differences of each of tautomeric structure and T0, could show that the lowest stability was found for T3, and each of T2, T4, T5, and T1 were places at the next orders. It is indeed benefit of performing computer-based works to achieve such detailed results for investigating the features of chemical compounds. Besides the observed variations of energies, variations of HOMO and LUMO levels were found to be significant among T0 and T1-T5 structures. The values of both of HOMO and LUMO levels were changed in the tautomeric structures and their energy distance, indicated by EG, were also changed

for the models. Indeed, it is an important issue to explore such features of the organic molecules especially for those molecules with significant roles in the biological systems. Accordingly, the values of DM were also changed for the tautomeric models systems. To better characterize the features of DfPy models, HOMO and LUMO distribution patterns and ESP surfaces were visualized in Figure 3.

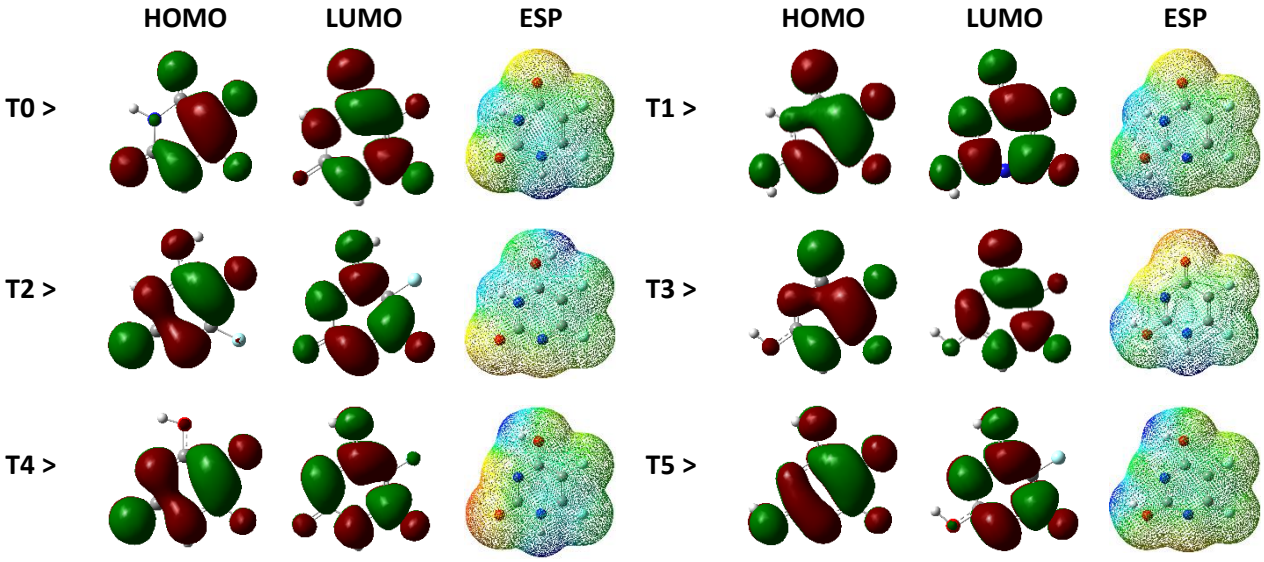

Figure 3: HOMO and LUMO distribution patterns and ESP surfaces.

As could be seen by panels of Figure 3, the electronic molecular orbital environments of the tautomeric forms of DfPy were detected the effects of occurrence of such tautomerism process by the observed colorful variations in the patterns and surfaces. As could be seen in details, the concentration of distribution patterns were also changed in this regard. Especially for the cases of ESP surfaces, tautomeric formations put significant impacts on the charge distribution of the models, in which the range of red-yellow-green-lightblue-blue could imply for negative to positive charges variations with the neutral green in the middle. This is indeed an important achievement for showing the importance of performing such investigations on those organic/bioorganic compounds for predicting or interpreting their features in accordance with their expected applications and behaviors. Such variations in the tautomerism processes could lead to appearance of several other features, which are not always favorite ones for this issue. As a consequence, the impacts of tautomerism were significant for structural and electronic features of DfPy compound.

Conclusion

In the current research work, structural and electronic features of tautomers of DfPy were investigated by performing DFT calculations. The optimization calculations yielded five tautomeric structures (T1-T5) besides the original the original DfPy compound (T0). The calculated bond distances and orientations showed the impacts of occurrence of tautomerism on the structural features, in which the stabilities were also found different by the calculated energy values. T0 compound was at the highest stability and all tautomers were at lower stability levels. Furthermore, variations of HOMO and LUMO levels indicated changes of electronic environments in the tautomeric structures. The visualized distribution patterns of HOMO and LUMO and ESP surfaces also showed changes of electronic environments of atomic sites of the structures. Consequently, the models were varied by their features among the occurrence of tautomerism processes.

Disclosure Statement

The author(s) did not report any potential conflict of interest.

References

1. Harismah K, Fazeli F, Zandi H. Barbituric acid tautomers: DFT computations of keto-enol conversions, frontier molecular orbitals and quadrupole coupling constants. Biointerface Research in Applied Chemistry. 2021;12:244-52.
2. Dhaked DK, Guasch L, Nicklaus MC. Tautomer database: a comprehensive resource for tautomerism analyses. Journal of Chemical Information and Modeling. 2020;60:1090-100.
3. Kondrashova SA, Polyancev FM, Latypov SK. Tautomeric preference in lumazines, deazalumazines, isoalloxazines and pyrimidines and its effect on the reactivity of alkyl groups. Bioorganic Chemistry. 2021;109:104725.
4. Slocombe L, Al-Khalili JS, Sacchi M. Quantum and classical effects in DNA point mutations: Watson–Crick tautomerism in AT and GC base pairs. Physical Chemistry Chemical Physics. 2021;23:4141-50.
5. Smalley CJ, Logsdail AJ, Hughes CE, Iuga D, Young MT, Harris KD. Solid-state structural properties of alloxazine determined from powder XRD data in conjunction with DFT-D calculations and solid-state NMR spectroscopy: unraveling the tautomeric identity and pathways for tautomeric interconversion. Crystal Growth & Design. 2021;22:524-34.
6. Ibrahim AA, Ibrahim MA, Sulliman EA, Daood SM, Ismael GQ. Comparison study of HOMO-LUMO energy gaps for tautomerism of triazoles in different solvents using theoretical calculations. NTU Journal of Pure Sciences. 2021;1:38-43.
7. Li N, Wang C, Georgiev MI, Bajpai VK, Tundis R, Simal-Gandara J, Lu X, Xiao J, Tang X, Qiao X. Advances in dietary polysaccharides as anticancer agents: structure-activity relationship. Trends in Food Science & Technology. 2021;111:360-77.
8. Barley MH, Turner NJ, Goodacre R. Improved descriptors for the quantitative structure–activity relationship modeling of peptides and proteins. Journal of Chemical Information and Modeling. 2018;58:234-43.
9. Zhang M, Xu J, Wang X. The theoretical investigation on the properties of fluorine-substituted uracil. Computational and Theoretical Chemistry. 2019;1156:43-51.
10. Gmeiner WH. Chemistry of fluorinated pyrimidines in the era of personalized medicine. Molecules. 2020;25:3438.
11. Wang Q, Xue J, Wang Y, Jin S, Zhang Q, Du Y. Investigation into tautomeric polymorphism of 2-thiobarbituric acid using experimental vibrational spectroscopy combined with DFT theoretical simulation. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2018;204:99-104.
12. Borbulevych OY, Martin RI, Westerhoff LM. The critical role of QM/MM X-ray refinement and accurate tautomer/protomer determination in structure-based drug design. Journal of Computer-Aided Molecular Design. 2021;35:433-51.
13. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, et al. Gaussian 09 Program. Gaussian Inc., Wallingford, CT. 2009.
14. Zandi H, Harismah K. Computer-based tools for structural characterizations and activity specifications of natural products: a quick review. Lab-in-Silico. 2021;2:50-4.
15. Mousanasab B, Mirzaei M. PNA-CNT interacting system: in silico investigation of nanocarbon sensors for PNA detection. Lab-in-Silico. 2021;2:15-9.

- **How to cite this article:** Zandi H. Structural and electronic analysis of tautomerism in 5,6-difluor-2,4(1H,3H)-pyrimidindion. Advanced Journal of Science and Engineering. 2022;3(1):2-6.
- https://doi.org/10.22034/advjse22031002