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Article

A computational quantum chemical study of Fluorinated Allopurinol

MD Mostakim Khan[1] and Rafia Akter Tuly[2]

[1] A K High School, Dhaka, Bangladesh

[2] East-West University, Dhaka, Bangladesh

SUMMARY

Allopurinol is a two-ring heterocyclic drug. Allopurinol has several conveniences for medicinal chemistry, including easy preparation methods and low toxicity, which make it a preferable choice for researchers and scientists. However, it has some limitations such as a short half-life and low stability. Fluorination is one of the most effective ways to enhance a number of chemical properties and applications of a compound. The small and highly electronegative features of fluorine have thus made it a profitable choice to optimize a compound. The inclusion of fluorine atoms can improve the effectiveness and reduce the limitations of allopurinol was the presumption of this study. From that context, this research deals with an examination of the effect of fluorine atoms on allopurinol. We investigated several chemical properties of allopurinol with quantum chemistry calculations using Hartree-Fock theory. We evaluated the molecular geometry, Mulliken charge analysis, and frontier molecular orbitals calculations. We conducted a comparison of our calculated properties to determine the advantages and disadvantages of allopurinol and two simulated, fluorinated, hybrid compounds. We found higher chemical stability in the hybrid compounds. The first hybrid compound was more organic agent-friendly, whereas the second one was more ionic and polar agent-friendly. The fluorinated compounds showed their potential to prevent metabolic attacks and improve reactivity with different chemical agents.

INTRODUCTION

Allopurinol (1,5-dihydro-4H-pyrazolo[3,4-d] pyrimidin-4-on) is part of a class of pharmaceutical drugs known as xanthine oxidase inhibitors (1). Where xanthine oxidase inhibitors inhibit xanthine oxidase, an enzyme that decreases uric acid production. The usage of allopurinol is to treat gout attacks or kidney stones caused by high levels of uric acid (2). As a nitrogen-based heterocyclic compound, allopurinol shows diverse biological activity and has long been an attractive species for synthetic organic chemists (2). However, the structure of allopurinol is chemically unstable. Additionally, high level of basicity of the compound reduces the bioavailability (3). Thus, the application of allopurinol is somewhat limited. In this study, we focused on finding a way to overcome these limitations and enhance the ability of this nitrogen-based drug. We hypothesized that substitution of hydrogen bonds with halogen bonds would increase the stability and reactivity of allopurinol-derived compounds. Because the halogen atoms show the highest electronegativity on the periodic table, they can increase the charges of other atoms of the compound. As a result, the other bonds may get stronger and the compound may be more stable. Also, a hydrogen bond (H-bond) acceptor of a compound could also serve as a halogen bond (X-bond) acceptor, so it is possible to substitute an H-bond with an X-bond (4). We chose the fluorine atom because it has the highest electronegativity, and it is the smallest halogen atom on the periodic table. Also, fluorine has minimal steric effects on the compound due to its small size. Thus, we believed fluorine was the ideal atom to test our hypothesis.

We used Highest Occupied Molecular Orbital (HOMO)-Lowest Unoccupied Molecular Orbital (LUMO) analysis to explain information regarding energy transfer within the molecule (5). Higher HOMO energy means a stronger ionization potential of the compound (6). The energy gap between the HOMOs and LUMOs is the critical parameter in determining the molecular electrical transport properties which help in the measure of electron conductivity (7). This energy gap is also related to the chemical hardness, stability, and reactivity of a compound (5, 8). In addition, a larger energy gap means a smaller aromatic system (6) and chemically a harder compound (5). In most of the traditional and feasible nitrogen-based drugs, the range of HOMO-LUMO energy gap is within 3.5-4.5 eV (5, 7-12). Thus, we can assume that drug compounds with a HOMO-LUMO gap around this range contain proper stability and reactivity.

The Mulliken atomic charge calculation has a significant role in the application of quantum chemical calculations to molecular systems (5). The higher negative partial charge the nitro groups possess, the more the compound is stable and has less electron affinity. Mulliken charge analysis can predict electrophilic and nucleophilic reactions of a compound (8). More electronegative compounds can prevent an electrophilic attack more effectively (3).

In this context, we conducted a computational fluorination procedure on this compound. We substituted a hydrogen bond with a non-covalent fluorine bond. To test the hypothesis, we needed to interpret the molecular structure, illustrate reaction pathways, and determine chemical mechanisms before and after the fluorination process. For that, we used quantum chemical computational methods, which helped us to understand these chemical notions (13). We calculated our substitutional changes using quantum chemical methods. We tried to visualize the effect of hydrogen-to-halogen bond substitution on the structure and biological diversity of the allopurinol compound. We fluorinated allopurinol in the H11 and H14 positions individually. The allopurinol-1 hybrid shows H11--F11 replacement and allopurinol-2 shows H14--F14 replacement. We conducted a comparison of the molecular

geometry of allopurinol and its hybrid compounds to see the changes in the molecular geometry.

The molecular geometry indicated there were no big structural changes in allopurinol after fluorination on both sites. Surprisingly, we found that the long bond length of the C-F bond created a stronger bond than the substituted C-H bond, which had a shorter bond length. The Highest Occupied Molecular Orbital and Lowest Unoccupied Molecular Orbital (HOMO-LUMO) gap revealed that the hybrid compounds have larger energy gaps than the primary compound. Larger energy gaps define better chemical stability, supporting our hypothesis (6). Mulliken atomic charge analysis indicated that fluorination resulted in an increase in electronegativity and a decrease in electronegativity in allopurinol-1. We found allopurinol-2 is a more stable, polar-agent-friendly compound and allopurinol-1 is a more stable, organic-agent-friendly compound which was a tremendous finding of this research. From our study, we concluded that the fluorination process is capable of reducing the current limitations of allopurinol and enhancing its clinical activity.

RESULTS

We conducted several quantum chemistry calculations to calculate the optimized geometries, atomic charges, and orbital energies for primary allopurinol and allopurinol-1, and allopurinol-2. For these calculations, we used the WebMO server.

Molecular Geometry

We calculated the bond angles, bond lengths, and dihedral angles between the atoms of allopurinol and fluorinated allopurinol-1 and allopurinol-2 using the WebMO server (**Figure 1**). In the primary allopurinol compound, the H11 atom took part in two angles. In allopurinol-1, the F11 atom changed these bonds. In both compounds, the H11/F11-C9-C10 angles were triangular-shaped bonds, and they had sp^2 hybridization. Both bonds had no lone pairs of electrons. The H11/F11-C9-N8 angles were angular (V) shaped bonds that had sp^2 hybridization. Both bonds had one lone pair of electrons. In both compounds, the bond angle values were similar (**Table 1**). From the bond length result, we found fluorination at the H11 position caused an increase in the bond length even though the molecular orbitals maintained sp^2 hybridization (**Table 1**). The dihedral angle related to the H11 position showed no noteworthy change in the compound (**Table 1**).

In allopurinol-2, we fluorinated the H14 position, wherein the primary compound H14 atom created two angles, and in allopurinol-2 F14 atom altered those angles. The angles related to position 14 were sp^2 hybridized V-shaped bonds in both compounds. These bonds had one lone pair of electrons. The bond angle values were similar in both compounds (**Table 1**)**.** The bond length of position 14 was increased by fluorination, but the orbital maintained sp^2 hybridization in both compounds (**Table 1**). The dihedral angles of related positions were also similar (**Table 1**)**.**

Mulliken Charge Calculation

We determined the electropositive and electronegative nature of the atoms inside the allopurinol and its fluorinated compounds. In the primary allopurinol compound, all the hydrogen atoms were electropositive, which showed as blue

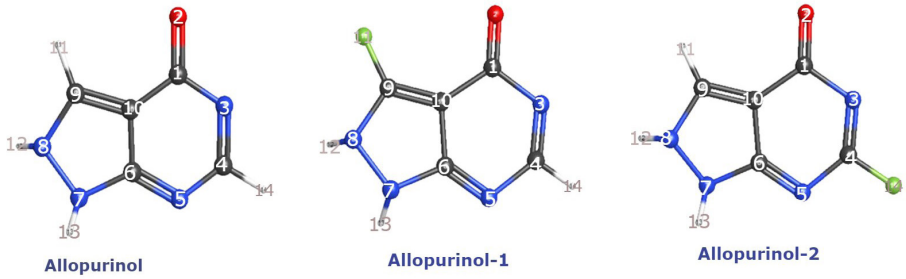

Figure 1: Molecular structure of allopurinol and its hybrid compounds. All atoms are labeled by their respective numbers. This figure shows the geometry parameters and atomic positions inside the compound. Atoms are defined by the color code: white as hydrogen, blue as nitrogen, red as oxygen, black as carbon, and green as fluorine.

Geometry Parameters	Allopurinol	Allopurinol-1	Geometry Parameters	Allopurinol	Allopurinol-2
H11/F11-C9-C10Bond angle	129.650°	130.535°	N5-C4-H14/F14 Bond angle	111.922°	110.629°
H11/F11-C9-N8 Bond angle	118.434°	116.973°	N3-C4-H14/F14 Bond angle	116.460°	116.964°
C9-H11/F11 Bond length	1.086 Å	1.332 Å	C4-H14/F14 Bond length	1.093 Å	1.345 Å
N8-C9-H11/F11-C10 dihedral angle	177.061°	177.602°	N3-C4-H14/F14-N5 dihedral angle	179.990°	-179.667°

Table 1. Geometry Optimization. This table shows a comparison of geometry parameters between allopurinol and its fluorinated compounds. The orange color indicates an increase in the fluorinated compound relative to allopurinol, while the blue color indicates a decrease.

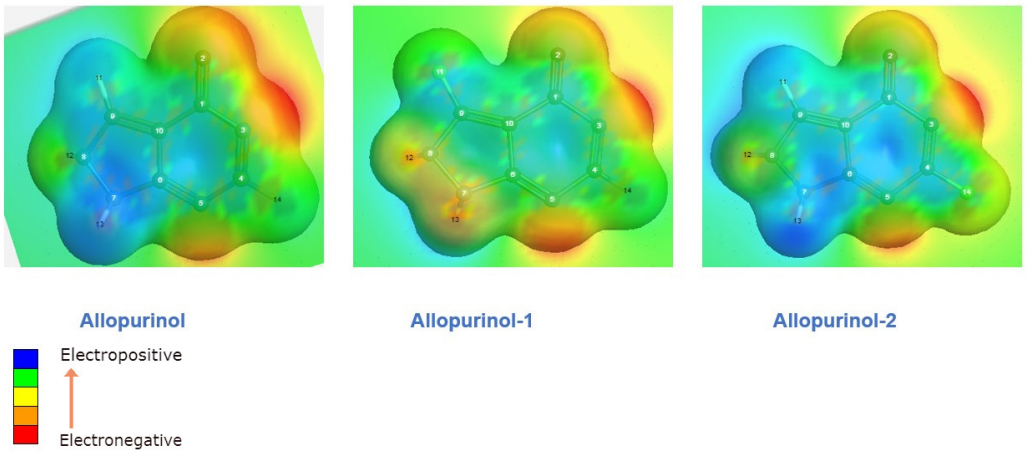

Figure 2: MEP surface map of allopurinol and its hybrid compounds. This figure shows the partial charge state of each atom. Atomic charges are defined by the color code in the legend.

in the electrostatic potential map (**Figure 2**). The molecular electrostatic potential map (MEP) shown in (**Figure 2**) demonstrates the partial charges of atoms on structures by colors.

In position 11, the H11 atom was paired with an electropositive C9 carbon atom. Fluorination caused an increase in electropositivity of C9 the atom (**Table 2**).Two electronegative carbon and nitrogen atoms (C10 and N8) surround these bonds, where the electronegativity of these two atoms is also slightly increased by fluorination (**Table 2**). In position 14, the H14 atom was paired with an electropositive C4 carbon, and addition of the fluorine atom increased the electropositivity of C4 atom (**Table 2**). N3 and N5 were the two electronegative atoms that surrounded these bonds. Where the electronegativity of these two atoms is also slightly increased by fluorination (**Table 2**).

Atoms	Allopurinol (Hartree)	Allopurinol-1 (Hartree)	Allopurinol-2 (Hartree)
C1	0.262	0.266	0.270
O2	-0.209	-0.210	-0.211
N3	-0.275	-0.271	-0.306
C4	0.141	0.141	0.346
N5	-0.300	-0.296	-0.302
C6	0.231	0.230	0.234
N7	-0.243	-0.236	-0.239
N8	-0.219	-0.231	-0.228
C9	0.073	0.285	0.079
C10	-0.072	-0.100	-0.074
H11-F11	0.112	-0.083	0.115
H12	0.198	0.203	0.208
H13	0.215	0.214	0.218
H14-F14	0.088	0.089	-0.111
Dipole Moment	5.2308 Debye	5.1324 Debye	5.7422 Debye

Table 2: Mulliken Atomic Charge. This table shows the partial charge on different atoms of allopurinol and its fluorinated compounds. The orange color indicates negative charges and blue indicates positive charges. Charges are calculated in hartree unit where 1 hartree= 27.2114 eV.

Comparing the overall molecular dipole moments, we found that the dipole moment of allopurinol-2 (5.74 D) increased compared to the primary allopurinol compound (5.23 D) while that of allopurinol-1 decreased slightly (5.13 D) (**Table 2**).

Frontier Molecular Orbitals Calculation

We evaluated the HOMO and LUMO orbitals of allopurinol and its fluorinated compounds (**Figure 3**). In both fluorinated compounds, the HOMO energy was increased by fluorination (**Table 3**). The HOMO-1 (molecular orbital one energy level below the HOMO, also known as NHOMO) energy was also increased, as expected. On the other hand, the LUMO energy was decreased in both compounds. The LUMO+1 (molecular orbital one level above the LUMO, also known as SLUMO) energy was also decreased (**Table 3**). The increase of the HOMO energy and the decrease of the LUMO energy in the fluorinated compounds caused an increase in the HOMO-LUMO and HOMO-1-LUMO+1 energy gaps (**Table 3**). As a result, allopurinol-2 had the highest HOMO-LUMO and HOMO-1-LUMO+1 energy gap (ΔE= 3.17 eV, ΔE1= 1.19 eV). Allopurinol-1 had a higher energy gap than primary allopurinol (ΔEp= 2.63 eV ΔEAllo-1= 2.93 eV) but a lower energy gap than allopurinol-2 (ΔEAllo-1= 2.93 eVΔEAllo-2= 3.17 eV) (**Table 3**).

DISCUSSION

Our bond angle and bond length analysis denotes the number of lone pairs and bonded electrons (the bond order). A higher bond order represents a strong chemical bond and stronger pull between the two atoms, which results in a shorter bond length. From the fluorinated positions, we observed that the fluorination process did not create any big impact on the structure of the compound. Most of the bond angles and bond lengths in the fluorinated compounds were slightly altered from the primary compound. The bond length of the fluorinated positions increased in both hybrid compounds.

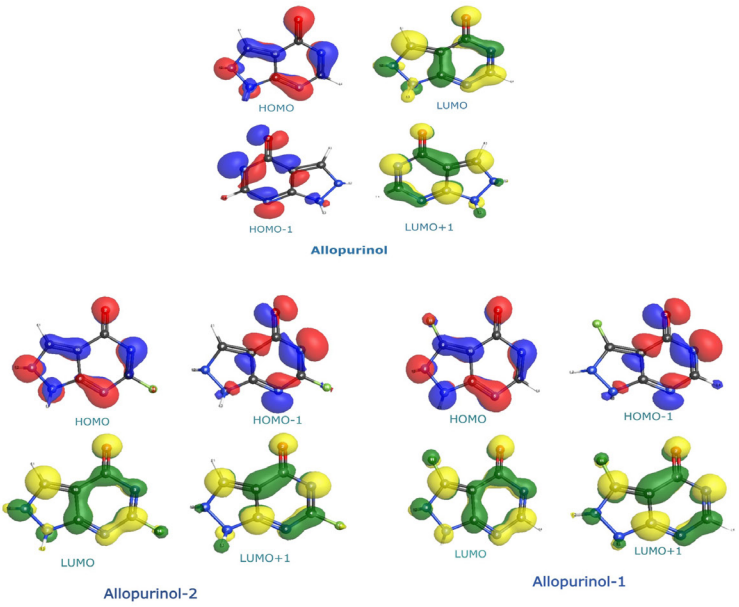

Figure 3: FMOs for allopurinol and its hybrid compounds. This figure shows the HOMO, HOMO-1, LUMO, and LUMO+1 orbitals for each structure. Blue and red colors show the occupied orbital phases. Green and yellow show the unoccupied orbital phases.

	Allopurinol (eV)	Allopurinol-1 (eV)	Allopurinol-2 (eV)
HOMO	-6.7756	-6.9116	-7.1103
HOMO-1	-8.2994	-8.4627	-8.6260
LUMO	-4.0817	-3.9728	-3.9320
LUMO+1	-8.0545	-7.5103	-7.4287
ΔE= LUMO-HOMO	2.6939	2.9388	3.1783
ΔE= LUMO+1-HOMO-1	0.2449	0.9524	1.1973

Table 3: HOMO-LUMO Energy. This table shows Frontier Molecular Orbital (FMO) energies of allopurinol and its fluorinated compounds. The orange color indicates an increase in the fluorinated compound relative to allopurinol and the blue color indicates a decrease.

In that fact, the fluorination process should have decreased the bond energy. But because of the higher electrostatic attractions, the bond energy of the C-F bond was higher than that of the C-H bond (3). This means the experimented bonds have become less reactive than the primary compound. The bond angles and dihedral angles of the experimental positions of all three compounds were almost the same. In allopurinol-1, the F11-C9-C10 bond was slightly more linear and the F11-C9-N8 bond was slightly less linear and more angular than the primary compound. In allopurinol-2, the difference between fluorinated angles with primary angles was less than 1°. This explains why there was no such noticeable change and means the fluorine atom replaced the hydrogen atom properly and the compound structure adopted the halogen very well.

In our Mulliken charge analysis, we found important details on charge distribution across the atoms to describe the donor and acceptor pairs and to obtain insights into the overall chemical activity of the compound. In analyzing these fluorination processes, our notion was that the partial electronic charges of the primary allopurinol compound and its hybrids would be correlated at the experimentally modified atomic positions (8). In the primary allopurinol compound, we found two electropositive atoms paired with hydrogen. All carbon atoms except for C10 and hydrogen atoms were electropositive. These atoms were surrounded by electronegative nitrogen and oxygen atoms. C10 shared its electrons with three electropositive carbons by forming two sigma and one pi bond. Also, there was no electronegative atom nearby; this is why C10 was negatively charged. The highest positive and negative partial charges were on C1 (0.26 Hartree) and N5 (0.300 Hartree). For the fluorinated allopurinol compounds, we found the atomic charges on experimental bonds were becoming more electronegative as the addition of an electronegative atom was extracting more electrons from the carbon atom. The electronegative atoms surrounding the δ+ carbon and of the experimental bond were more negatively charged because of increased electronegativity. This electronegativity gap increase in the bond caused a more polar covalent bond.

Looking closely, we found that in the allopurinol-1 compound, charges of the several remote atoms get

reduced to accommodate the charge distribution across the compound. This is why allopurinol-1 was overall less polar and less interactive with polar and ionic agents according to our calculation. The dipole moment of allopurinol-1 is also lower than primary allopurinol, which agreed with this fact (6). Because of this decreased polarity, it is not suitable for polar and ionic agents and also has less solubility in polar solvents. On the contrary, allopurinol-1 is more suitable for organic agents. But in the allopurinol-2 compound, the remaining electropositive atoms became more partially positively charged and electronegative atoms became more partially negatively charged even though the atoms were far away from the fluorinated region. As a result, this hybrid compound is more acidic than the primary compound. Therefore, the allopurinol-2 compound has more capability to interact with polar and alkylating agents or for an electrophilic attack.

The calculated HOMO-LUMO and HOMO-1 - LUMO+1 energy gaps revealed that the allopurinol-2 compound has the highest energy gap followed by the allopurinol-1 compound. This demonstrated that the allopurinol compound has become less reactive and chemically more stable because of this fluorination process (3). Also, the increase of HOMO energy indicates ionization potential increment of the molecule. The allopurinol-1 compound is chemically softer and has higher chemical reactivity and lower kinetic stability than allopurinol-2 compound, but lower reactivity and higher stability than the primary compound. Allopurinol-1 is a smaller aromatic system than primary allopurinol but larger than allopurinol-2. The allopurinol-2 compound is chemically harder and more stable than the other two compounds. Also, the larger energy gap of allopurinol-2 defines it as a smaller aromatic system than allopurinol-1 and primary allopurinol compounds.

The higher stability of the fluorinated hybrid compounds means that fluorinated compounds may likely prevent a metabolic attack better than the primary compound (3). The energy gaps of fluorinated compounds are also closer to the conventional energy gap range. This means the compound has improved stability, but it did not become too inert. Also, fluorinated compounds have lower basicity than the primary compound, which means an improved bioavailability (3). Further, the addition of a fluorine atom may improve the binding affinity of allopurinol to a targeted protein (3). With this in mind, our research can help a synthetic chemist to design this drug in a new way. We have shown the possibility of enhancing a drug molecule through fluorination in this research. As most nitrogen-based drugs show a similar type of reactivity, this method could help a synthetic chemist to improve other drug molecules too.

MATERIALS AND METHODS

In our paper, we conducted computational chemical analyses to visualize our results. We used the WebMO guest server for our calculations (14). WebMO is a web-based interface to computational chemistry packages and programs.

For the calculations of bond lengths, bond angles, electrostatic potentials, HOMO-LUMO gaps, and dipole moments, we used the buchner.chem.hope.edu server with the Gaussian16 software package (15). Gaussian is an *ab initio* and semi-empirical calculations engine. To find the partial charge on each atom of the molecule, we used the MOPAC2016 program (16). We used the Hartree-Fock method (17) with the minimal STO-3G basis set for all of our calculations. We made sure that there was no unwanted ionization charge and the multiplicity was set to singlet. Mulliken charge analysis alongside Molecular Electrostatic Potential maps was studied to understand reactivity and chemical applications. The values of electrostatic potential of different atoms were defined by different colors in the surface map.

The chemical hardness and chemical potential of the molecules were evaluated using the WebMO HOMO-LUMO plot. The HOMO-LUMO energy gap is defined as the difference between the HOMO and LUMO energies.

The convergence criterion was set to 0.001% for geometry parameters, 0.02% for Mulliken charge calculation, and 0% for HOMO-LUMO gap, and it took three iterations to find these changes. These percentage values define that the output values in this research can be that much higher or lower than the given values in this article.

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