Binimetinib (Mektovi)

Structural Analysis using SPARTAN

CH231 – Organic Chemistry

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Abstract

Binimetinib, an enzyme inhibitor created by Array Biopharma, is an anti-cancer molecule that inhibits key enzymes that cause melanoma and colorectal cancer. Binimetinib was analyzed using SPARTAN '18, a quantum chemistry software created by Wavefunction. The equilibrium geometry of Binimetinib in the gas phase and ground state was computed using the Møller–Plesset model (MP) and Hartree-Fock model (HF) with a 6-31G* basis set. The equilibrium geometry in the gas phase and the ground state was also computed using the density functional theory (DFT) method with a basis set of 6-31G* and a ωB97X-D functional. The total energy of the molecule, LUMO and HOMO energies, net dipole moment, and electrostatic potential map were determined using these three calculation methods. Three different calculation methods were used to compare the results of each method and the duration it took to do the quantum computations. The total molecular energies of Binimetinib for the three calculation models were -3869.57273 au, -3865.77165 au, and -3874.6394 au for MP, HF, and DFT, respectively. The HOMO energies were -8.02 eV for MP, -7.98 eV for HF, and -7.46 eV for DFT. The LUMO energies were 2.16 eV for MP, 2.51 eV for HF, and 0.49 eV for DFT. The net dipole moments were 5.59 debye for MP, 7.19 debye for HF, and 6.42 debye for DFT. The direction of the dipole moment vectors were similar for all three calculation models. The electrostatic potential maps were also similar for all three calculations; it was analyzed to understand the direction of the dipole moment vector as well as the acidity and basicity of the molecule. The three methods produced similar results, but MP took 106 minutes, HF took 5 minutes, and DFT took 13 minutes to perform the calculations.

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Introduction

Molecular orbital theory utilizes the wave function (Ψ) of an electron to describe the distribution of electrons in molecules. The molecular orbital (MO) defines a probability region in space that a valence electron is most likely to be found in. The MOs are mathematically computed by combining the wave functions in a process called the linear combination of atomic orbitals (LCAO). When MOs combine in phase, they produce a bonding MO that holds the nuclei together, resulting in a lower energy (increased stability). Unlike bonding MOs, antibonding MOs form when MOs combine out of phase, resulting in higher energy (decreased stability) [1]. Figure 1, below, illustrates the LCAO of two hydrogen atoms to produce bonding and antibonding MOs.

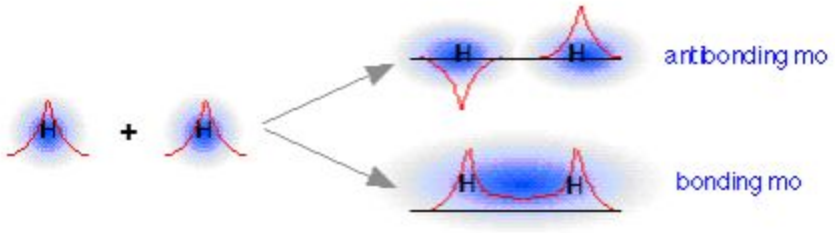

Figure 1. The combination of the 1s wave functions of two hydrogen atoms to form bonding and antibonding molecular orbitals [2].

Of all the resulting MOs in a molecule, the "frontier molecular orbitals," which involve the highest-energy occupied molecular orbital (HOMO) and lowest-energy unoccupied molecular orbital (LUMO), can be used to explain and predict the reactivity of molecules. The HOMOs of a molecule are nucleophilic, which tend to donate electrons, whereas the LUMOs of

a molecule are electrophilic, which tend to accept electrons. Thus, the LUMO of one molecule is likely to react at the site of another molecule's HOMO [3].

The partial atomic charges in a molecule are determined by the electronegativity differences between different atoms. Larger electronegativity differences result in larger partial atomic charges [1]. On a molecular level, the partial atomic charges create areas of high electron density and low electron density. These regions of differing electron densities determine the charge distributions of the molecule. The high and low electron densities result in negative and positive partial charges, respectively. The partial charges attract regions of a molecule with the opposite charge [4]. The spread of these charges can be more easily analyzed using an electrostatic potential map.

Electrostatic potential maps allow chemists to visualize the charge distribution of a molecule. These maps are often computed by a computer program that calculates the electrostatic potential energy at set distances from the nuclei of the molecule. Electrostatic potential maps are usually on a color spectrum from red to blue. Red areas indicate regions of low electrostatic potential energy (high electron density), and blue areas indicate regions of high electrostatic potential energy (low electron density). The electrostatic potential map shows regions of acidity and basicity of a molecule. Blue regions have high electrostatic potentials, so those regions accept electrons, acting as Lewis acids. Red areas, on the other hand, indicate regions of Lewis basicity [5].

The net dipole moment of a molecule is a vector that indicates the direction and magnitude of the molecule's polarity. The net dipole moment of a molecule is the sum of the bond dipoles of each covalent bond in the molecule. The net dipole moment vector points from

regions of low electron density to regions of high electron density. Understanding the overall polarity of the molecule can help chemists understand the intermolecular interactions of the molecule. These intermolecular interactions affect the solubility of the molecule in different solvents. Polar molecules dissolve well in polar solvents, whereas nonpolar molecules do not. Understanding the net dipole moment can also help chemists understand how a molecule interacts with other molecules in order to react. The partially positive regions of a molecule, which usually have a low density of electrons, act as Lewis acids in reactions because these areas of high electrostatic potential will accept electrons during reactions.

The wave function calculations can be done using SPARTAN, a computer program that solves the Schrödinger equation numerically using various methods. These methods include the Møller–Plesset model (MP), Hartree-Fock model (HF), density functional theory model (DFT). MP uses perturbation theory to perform calculations. HF assumes that each electron in an atom or molecule is impacted by all other electrons when performing the calculations. DFT utilizes a functional that represents the electron density to compute the energy, rather than utilizing a wave function [6]. These three methods can use the same basis set for the calculations but have different strategies in determining the total molecular energy, HOMO and LUMO energies, net dipole moment, and electrostatic potential map for a molecule.

Procedure

SPARTAN ‘18 was used to determine the total energy, LUMO and HOMO energies, net dipole moment, and electrostatic potential map of Binimetinib. The molecular structure for Binimetinib was recreated using SPARTAN’s sketch feature. Drawing a 2D molecule with the sketch feature automatically generated a ball and stick model. The sketch feature was ideal for building multiple samples of Binimetinib because all the atoms in each sample were oriented in the same spatial location before the calculations were run. The sketch of Binimetinib was created by following the bond line structure of Binimetinib shown in Fig. 2, below.

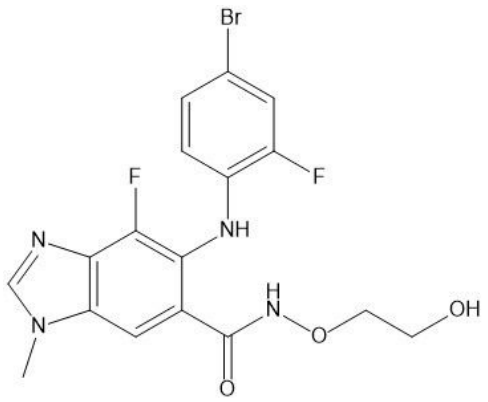

Figure 2. The bond line structure of Binimetinib [7].

The bond line structure was sketched starting with the benzene ring at the top in Fig. 2. The alkyl halides were then sketched. The nitrogen that connects the benzene ring and fused ring structure was sketched next. Then, the fused ring structure was sketched, followed by the fluoro group and methyl constituent. The carbon chain on the bottom right of Fig. 2 was sketched last from the fused ring structure to the alcohol at the end of the chain. After sketching the bond line structure, the structure’s energy was minimized. The sketch was then exited to the main screen that showed the ball and stick model. The energy of the structure was minimized again. Then, the

equilibrium geometry was calculated for Binimetinib in the ground state and gas phase with a 6-31G* basis set for the MP, HF, and DFT calculations. An MP2 calculation was performed for the MP model. A ωB97X-D functional was used for the DFT calculation. MP, HF, and DFT calculations were performed on each newly created Binimetinib sample. Binimetinib was set to a neutral charge with 0 unpaired electrons for all three calculations. The total molecular energy, HOMO and LUMO energies, electrostatic potential map, and dipole moment were recorded for each method. The duration of each quantum calculation was also recorded.

Results and Discussion

Three calculation methods were used to determine the total molecular energy, HOMO and LUMO energies, and net dipole moment of Binimetinib. Table 1 shows the result of the calculations done using SPARTAN '18 for Binimetinib at the ground state and gas phase with a basis set of 6-31G*.

Table 1: Properties of Binimetinib determined by three different calculation methods.

Calculation Method	Energy (au)	E HOMO (eV)	E LUMO (eV)	Dipole Moment (debye)
Møller–Plesset	-3869.57273	-8.02	2.16	5.59
Hartree-Fock	-3865.77165	-7.98	2.51	7.19
Density Functional Theory	-3874.6394	-7.46	0.49	6.42

The total energy of Binimetinib was quite similar for all three calculation methods. The HOMO energy determined by the three different methods were also relatively similar. The main difference appeared in the LUMO energy calculation. MP and HF resulted in similar LUMO energy values, 2.16 and 2.51. DFT, on the other hand, calculated a much lower LUMO value of 0.49. This result may have been caused by the fact that, unlike MP and HF, DFT uses a functional that represents electron densities rather than a wave function for its calculations [6]. The dipole moments were also dissimilar for all three calculation methods, but there was no clear reason for the disparity. The dipole moment of Binimetinib determined by the different calculation methods was high. Compared to water, a well-known polar molecule that has a dipole

moment of 1.84 debye [4], the dipole moment of Binimetinib was approximately 3 times higher. The high polarity of Binimetinib suggests that it will dissolve well in other polar solvents.

Although the calculation methods produced different magnitudes for the net dipole moment, the relative directions of the net dipole moment vectors stayed consistent for all three calculation methods. Fig.3 shows the dipole moment vector of Binimetinib calculated using DFT in the ball and stick model and bond line structure.

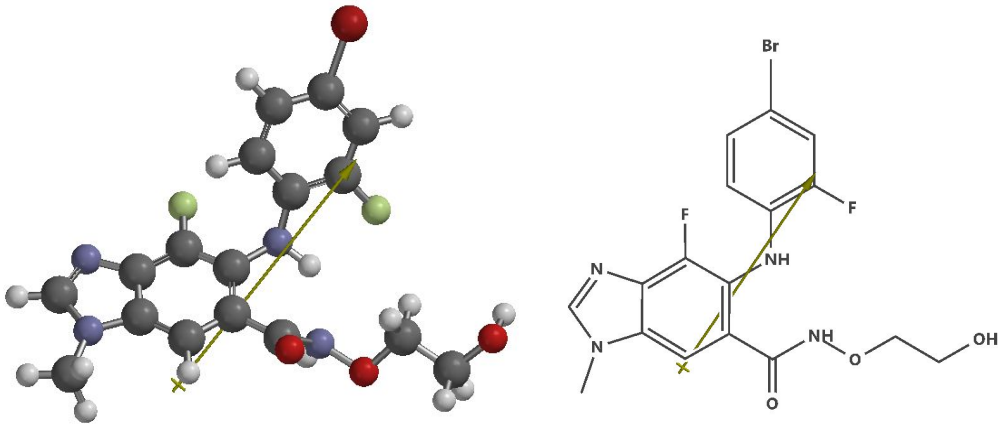

Figure 3. The net dipole moment vector of Binimetinib calculated using DFT in the ball and stick model (left) and the bond line structure (right).

The relative direction of the net dipole moment vector pointed from the hydrogen opposite of the fluoro group on the fused ring structure towards the carbon connected to the fluoro group on the benzene ring at the top (see Fig. 3). The reason for the net dipole moment vector's direction was better understood after analyzing the electrostatic potential map. The electrostatic potential map produced by the three different calculations were almost identical. Fig. 4 shows the electrostatic potential map for the "front" and "back" side of Binimetinib calculated using HF.

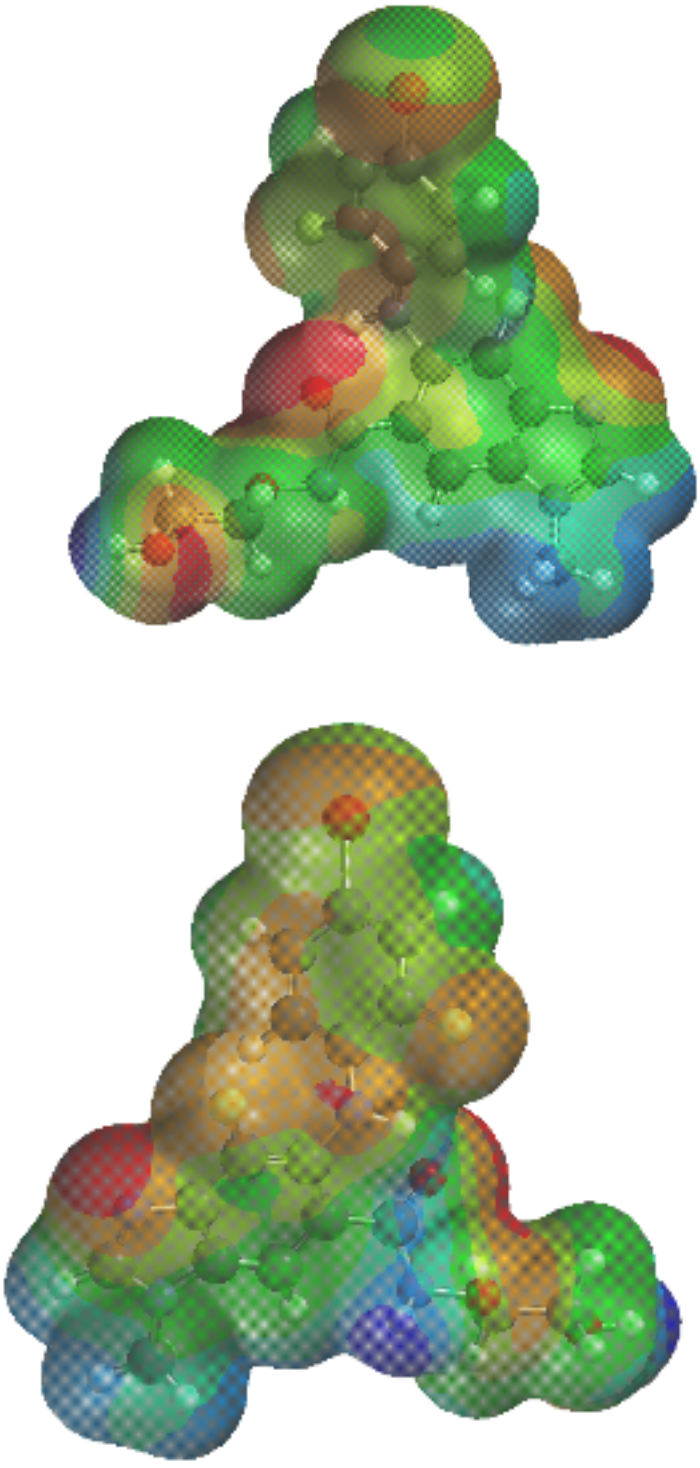

Figure 4. The electrostatic potential map of the “front” side (top) and “back” side (bottom) of Binimetinib determined by HF calculation.

Basic regions were indicated as red on the electrostatic potential map in Fig. 4. One main electron dense region was the area around the double bonded oxygen next to the fused ring structure. The oxygen atom was part of a secondary amine functional group, which had resonance as seen in Figure 5, below.

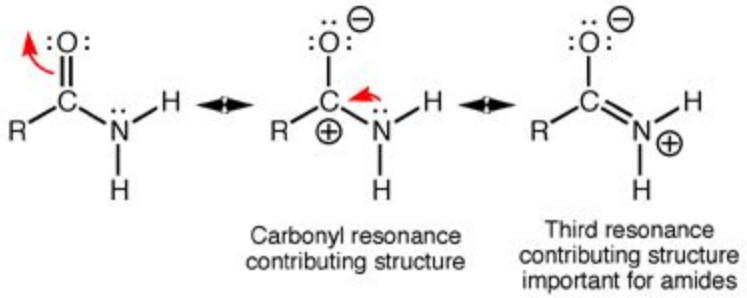

Figure 5. The resonance of a secondary amide [8].

Because of resonance, the delocalized electrons were able to stabilize around the more electronegative oxygen atom, creating a region of high electron density around the oxygen atom. This area with minimal electrostatic potential energy was a region of Lewis basicity.

The nitrogen atom on the fused ring also had a high electron density. This was also because of resonance. Figure 6, below, shows the resonance of the nitrogen in the five membered ring.

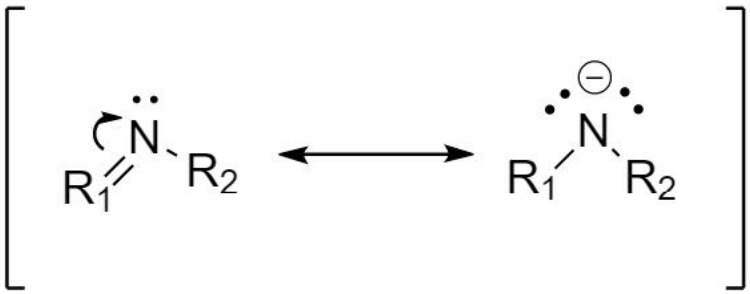

Figure 6. Resonance of the nitrogen atom in the five membered ring [9].

The electrons in the □ bond in the five membered ring had a resonance structure. The delocalized electrons were stabilized around the electronegative nitrogen atom, resulting in a higher electron density around the nitrogen. The nitrogen region in the fused ring structure is also an area of Lewis basicity.

The alcohol at the end of the carbon chain also had an oxygen atom with a high electron density because oxygen is much more electronegative than hydrogen. As seen in Fig. 4, the alcohol region had a much smaller area of low electrostatic potential compared to the nitrogen in the fused ring and secondary amine group. This is because of the lack of resonance in the alcohol group.

The regions in blue in Fig. 4 were regions of Lewis acidity. The highly electronegative oxygen and nitrogen atoms pulled the electrons from surrounding atoms, primarily carbon and hydrogen atoms that do not have high electronegativities. Therefore, the carbon and hydrogen atoms on the opposite side of the oxygen and nitrogen atoms had a very high electrostatic potential. These regions had low electron densities and, therefore, behaved as Lewis acids.

It was expected that the regions around oxygen and nitrogen, highly electronegative molecules, had high electron densities. However, it was surprising that the fluoro groups, which are more electronegative than oxygen and nitrogen, had significantly lower electron densities. The lower electron densities were indicated by the yellow-green and orange colors in Fig. 4.

The benzene rings in Binimetinib had a slightly lower electron density compared to the fluoro groups as seen by the yellow-green and green regions around both benzene rings. Figure 7 shows the resonance of a benzene ring.

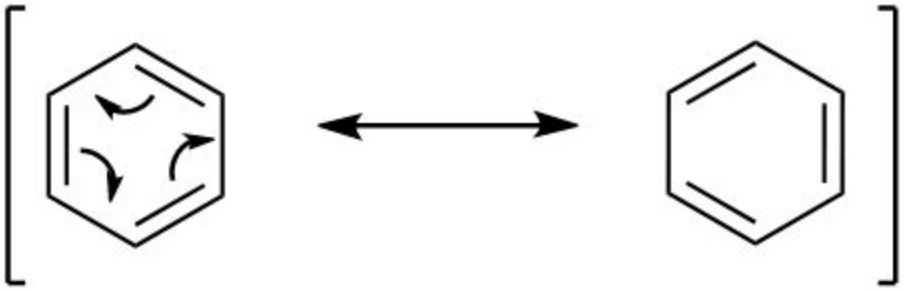

Figure 7. The resonance structure of a benzene ring [9].

Because the electrons in the benzene are delocalized, they have a lower electrostatic potential.

The electrostatic potential map also indicated that the reason the dipole vector in Fig. 3 pointed towards the fluoro group in the lone aromatic ring was not only because the fluoro group was electronegative. The regions of low electron density, indicated in blue regions in Fig. 4, and regions of high electron density, indicated in the red regions in Fig. 4, created a local dipole moment vector that pointed from the blue region to the red region. The various local dipole moment vectors combined to point in the direction from the hydrogen opposite to the fluoro group on the five-membered ring towards the fluoro group in the aromatic ring.

MP, HF, and DT took vastly different times to compute the total molecular energy, HOMO and LUMO energies, electrostatic potential map, and dipole moment for Binimetinib. Table 2 shows the duration of the quantum calculation for all three calculation methods.

Table 2: Duration of the quantum calculations for MP, HF, and DFT.

Calculation Type	Time (min)
Møller–Plesset	106
Hartree-Fock	5
Density Functional Theory	13

MP took about 21 times longer than HF and 8 times longer than DFT to perform the calculations. HF finished the calculations fastest, but DFT was only about 2.5 times slower than HF. Since MP and HF produced almost the same results, it would be more practical to use HF rather than MP to run more sample calculations on Binimetinib to determine its total energy, HOMO and LUMO energies, dipole moment, and electrostatic potential map. DFT is also reasonably efficient to run quantum calculations on Binimetinib.

Conclusion

Binimetinib was analyzed using SPARTAN ‘18 to determine the molecule’s total energy, HOMO and LUMO energies, electrostatic potential map, and net dipole moment of the molecule. The Møller–Plesset, Hartree-Fock, and density functional theory models were used to determine these properties. The equilibrium geometry energies of the molecule for the three calculation methods were -3869.57273 au, -3865.77165 au, and -3874.6394 au for the Møller–Plesset, Hartree-Fock, and density functional theory calculations, respectively. The HOMO energies were -8.02 eV, -7.98 eV, and -7.46 eV. The LUMO energies were 2.16 eV, 2.51 eV, and 0.49 eV. The dipole moments were 5.59 debye, 7.19 debye, and 6.42 debye. These three methods computed similar values for the total energy and HOMO energy. However, the LUMO energy of DFT, 0.49 eV, was significantly lower than the LUMO energies of MP and HF, 2.16 eV and 2.51 eV, which was likely due to the fact that DFT uses a functional rather than a wave function to perform the calculations. To perform more equilibrium geometry calculations for Binimetinib, either HF or DFT is recommended because it is significantly faster than MP when performing quantum calculations.

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