Mini Review Article

Tautomerism of Flutamide as a Biocatalyst: A Quantum Chemical Investigation

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Flutamide (FLUT) is an antitumor drug of importance capable of existing and making in solution and gas phase in two tautomeric types via prototrophic tautomerism. The two tautomer were examined here with a computational procedure. The calculation of relative energy levels at the B3LYP/6-311G++(d,p), 6-311++g, and 6-311++g(d) levels of theory suggest that T2 tautomer is the one with the utmost stability in the gas phase, which corresponds to NBO, dipole momentum, and thermochemistry parameters. The observations are helpful to better understand proton transfer tautomerization procedures. The findings are also discussed in the framework of chemoinformatics rules to handle tautomerism so that the findings of tautomer types can be helpful for a better action of chemical compounds in biologic milieus.

Keywords: Flutamide; DFT; Tautomerism; NBO; B3LYP

INTRODUCTION

Contrary to the competitive hormones, Flutamide (FLUT), 4-Nitro-3-trifluoromethyl-isobutilanilide, is not a steroid; instead, it is a replaced anilide. Thus, it is defined as a non-steroid compound to discriminate it from previous steroidal antiandrogens, including cyproterone acetate and megestrol acetate. In non-planar structures with the CF3 and the NO2 groups, FLUT adopts an out of the phenyl-plane conformation. After its discovery in 1967, the initial introduction of FLUT was for uses in medicine in 1983. Acting as a selective antagonist of the androgen receptor (AR), FLUT competes with androgens (e.g. testosterone and dihydrotestosterone, DHT) to bind to ARs in such tissues as the prostate gland, thereby preventing their impacts and inhibiting their stimulation of growing prostate cancer cells. FLUT is among antiandrogenic factors with the highest effectiveness that exert antiandrogenic activities in genitals. It has wide-ranging uses in prostate cancer and is mostly deemed an antiandrogenic drug lacking a steroidal construct (1) FLUT and its activated type remain in the body for a rather shortened duration, causing the need for taking FLUT several hours daily.

Tautomerization procedures are of importance in multiple biologic systems. In addition to its necessary influences, FLUT can lead to some adverse consequences, all of which may not happen at once, but medical care may be necessary in the case of occurring the fallouts. In an investigation, four (0.36%) out of 1,091 studied patients with prostate cancer under FLUT treatment and an LHRH agonist presented acute hepatotoxicity in the first 4 weeks of treatment. Serum aminotransferases rose over 4 times standard levels. Alkaline phosphatase rose over 6 times standard levels in one patient. Two patients showed an elevation in total bilirubin(2-5). Clinically manifested signs, such as fatigue, anorexia, weight loss, nausea, and vomiting, were observed in only two patients. Liver function assays did not significantly elevate in any of the rest 1,089 patients, but occasional, slight rises happened transiently in AST and ALT levels.

There are reports on a FLUT withdraw syndrome where prostate-specific antigen (PSA) concentrations decrease significantly when FLUT treatment is discontinued in patients with hormone-refractory prostate cancer.

Assessing the impact of concurrently discontinued FLUT and beginning of aminoglutethimide treatment was performed in patients with hormone-refractory prostate cancer. An investigation reported reduced serum PSA concentrations by > 80% for over 4 weeks in 14 out of 29 (48%) patients, along with clinically improved conditions. Protracted FLUT treatment has been proposed to probably lead to cancer cell lines to proliferate selectively with androgen receptors recognizing hydroxyflutamide as an androgenic agonist. Full evaluation of this phenomenon requires further investigations. The recognition and representation of the tautomers of drug-like small molecules have significant entailments, which have been established by tautomers recognized recently by reputed pharmaceutics. The tautomeric equilibrium can be influenced by the solvent, pH, and temperature. In the gas phase, the obtained tautomeric type can be different from that being predominate in solution and solid state. Various tautomers will oftentimes possess varying features physicochemically and a variety of reactivity modes, probably changing their metabolic profiles impressively. Hence, it is crucial to recognize the tautomeric type existing at every stage of medication and throughout the procedure of developing drugs. According to our results, the theoretical existence of FLUT is possible in two distinctive tautomeric types. FLUT displays prototropic tautomerism, the intramolecularly moved hydrogen from one atom to the other, and atom relocation tautomerism that is associated with moving the proton. The entire open-chain types of FLUT display keto−enol tautomerism at both the β-keto lactone and the sidechain keto moieties, each of which can be present in all tautomeric types.

COMPUTATIONAL METHOD

The reactivity of the tautomer of FLUT was investigated by doing the whole computations in the context of DFT with a spin unrestricted setting at Becke's three-parameter hybrids function in combination with the Lee-Yang-Parr correlation function, B3LYP. Then, computational levels for the entire atoms were determined by the 6-311++g and 6-311++g(d) and 6-311++g(d,p) pople basis set. The primary constructs were made with the gauss view 5.0 and underwent optimization by Gaussian 09 revision A 02 [38], considering various conformations of the tautomer. Stability energy, structural parameters, dipol moment, electronegativity, thermal features, IR frequency, and reactivity features were measured with the same technique.

RESULTS AND DISCUSSION

FLUT contains two tautomer structures (T) and Figures 1 and 2 depict their tautomerization structures. The formation of keto-enol and keto- imidic tautomerization was based on the carbonyl functional group. Of the two

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tautomerization types (T1 and T2) are produced with hydrogen atom movement. Optimal constructs of enol, imidic, and FLUT (T1, T2, and F, respectively) were estimated using three basis sets of the B3LYP quantum technique (6-311++g, 6-311++g(d), 6-311++g(d,p)), along with calculating the whole geometric and chemical features. The computed stability energy of molecules by the entire basis sets for better analysis is presented in Table 1. Figure 1 demonstrates the H transition to form the tautomer construct from αC to O caused the enol type(6-9). Figure 2 illustrates the H transition from N to O caused imidic type of tautomerization. The charge distribution of individual atoms in the FLUT molecule revealed the easy occurrence of these transitions (Table 2). The considerable changes in the charge distribution of transferred hydrogen throughout the tautomerization suggested the simultaneous transference of the proton and electron. According to the estimated stability energy, the use of the 6-311++g(d,p) basis set yielded the most negative energy for F, T1, and T2. + 0.9 kJ of ΔE between F and T1, indicating more stability of F than T1. Besides, +0.6 kJ of ΔE between F and T2 revealed more stability of F than T2. The ΔE = 0.03 kJ between T1 and T2 obtained T2 has more stability than T1 (see Table 1).

TABLE 1: Stability energy of molecules

Molecule structure	Name	E(kJ)B3LYP/3-311++g	E(kJ)B3LYP/6-33++g(d)	E(kJ)B3LYP/6-311++g(d,p)
	Flutamide	-2784.57	-2785.32	-2785.36
	Tautomer 1	-2784.49	-2785.21	-2785.27
	Tautomer 2	-2784.49	-2785.25	-2785.30

TABLE 2: Charge distribution of atom by three basis sets

Name/basis set	6-311++g	6-311++g(d)	6-311++g(d,p)
	C20(-0.351)	C20(-0.288)	C20(-0.145)
	C19(0.558)	C19(0.500)	C19(0.198)
	O22(-0.394)	O22(-0.363)	O22(-0.298)
	N17(-0.806)	N17(-0.315)	N17(0.085)
	H18(0.350)	H18(0.380)	H18(0.262)
	H21(0.230)	H21(0.365)	H21(0.223)
Flutamide			
	C20(2.141)	C20(1.744)	C20(1.050)
	C19(-1.227)	C19(-0.901)	C19(-0.627)
	O21(-0.416)	O21(-0.340)	O21(-0.250)
	H30(0.372)	H30(0.367)	H30(0.293)
	N17(-0.443)	N17(-0.274)	N17(-0.052)
	H18(0.433)	H18(0.376)	H18(0.278)
T1			
T2	C18(-0.526)	C18(-0.772)	C18(-0.489)
	C19(0.523)	C19(0.419)	C19(0.116)
	N17(0.071)	N17(0.350)	N17(0.316)
	O20(-0.352)	O20(-0.191)	O20(-0.115)
	H29(0.382)	H29(0.360)	H29(0.274)
	H30(0.287)	H30(0.215)	H30(0.151)

TABLE 3: Dipole moment of all molecules

Name	μ(Deby)B3LYP/ 6-311++g	μ(Deby)B3LYP/ 6-311++g(d)	μ(Deby)B3LYP/ 6-311++g(d,p)
Flutamide	8.9722	8.0011	7.9920
Tautomer 1	9.3297	7.9439	7.9741
Tautomer 2	11.4531	10.5199	10.4235

Figure 1: H transition for tautomer 1 structure of Flutamide

Figure 2: H transition for tautomer 2 structure of Flutamide

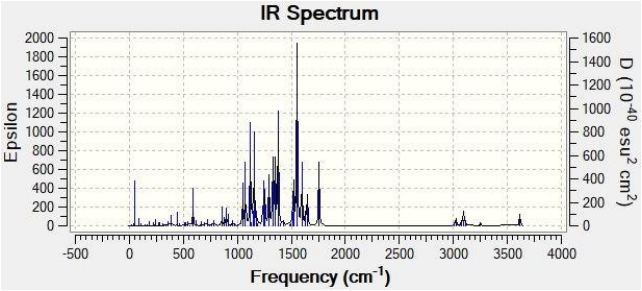


Figure 3: IR spectrum of Flutamide by B3LYP/6-311++g (d, p)

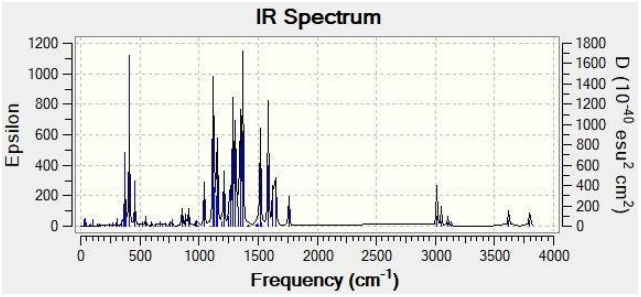


Figure 4: IR spectrum of T1 by B3LYP/6-311++g (d, p)

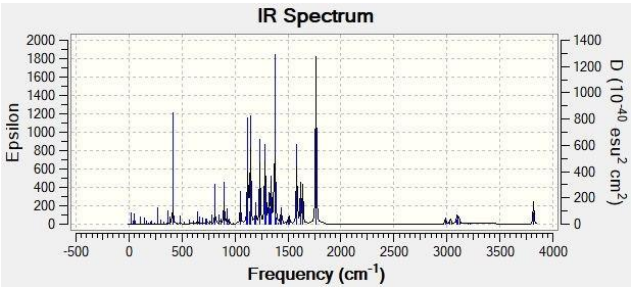


Figure 5: IR spectrum of T2 by B3LYP/6-311++g (d, p)

Table 4: Bond length(Å) of all compound H tautomer transition

Name/basis sets	6-311++g	6-311++g (d)	6-311++g (d, p)
Flutamide	R (17-18)1.0087	1.0089	1.0089
	R (17-19)1.3884	1.3866	1.3864
	R (19-20)1.5263	1.5323	1.5323
	R (19-22)1.2463	1.2162	1.2163
	R (20-21)1.0915	1.0940	1.0937
T1	R (19-20)1.3407	1.3392	1.3396
	R (19-21)1.4134	1.3795	1.3798
	R (20-22)1.5073	1.5046	1.5051
	R (17-18)1.0078	1.0085	1.0083
	R (21-30)0.9746	0.9665	0.9650
T2	R (18-19)1.5152	1.5167	1.5165
	R (17-18)1.2769	1.2668	1.2670
	R (20-29)0.9880	0.9658	0.9642
	R (30-19)1.0988	1.1003	1.0996
	R (18-20)1.4014	1.3629	1.3629

Table 5: Thermochemistry data of stabiliest compound according to basis set B3LYP/6-311++g (d, p)

Name/Parameters	G (kJ)	S (calmol-1K-1)	Cv (calmol-1K-1)	Ln Q
Flutamide	-2784.47	140.577	65.586	-180.12
T1	-2784.38	140.923	67.774	-178.75
T2	-2784.42	141.975	66.296	-178.46

Table 6: NBO analysis of Flutamide (B3LYP/6-311++g(d, p))

Flutamide	Occupacy	Donor	Acceptor	E2(kCal/mol)
BD1 N17-H18	1.964	BD N17-H18	BD* C19-O22	4.25
BD1 N17-C19	1.981	BD C20-H21	BD* N17-C19	3.81
BD1 C19-C20	1.971	BD C19-C20	BD* C19-O22	1.20
BD1 C19-O22	1.98	BD C19-O22	BD* N17-H18	1.21

BD2 C19-O22	1.96	BD C19-O22	BD* C19-O22	0.65
BD1 C20-H21	1.96	BD C20-H21	BD* C19-O22	1.89

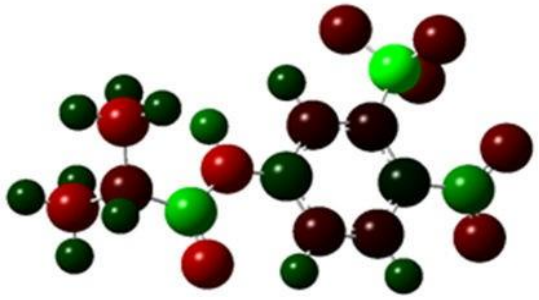


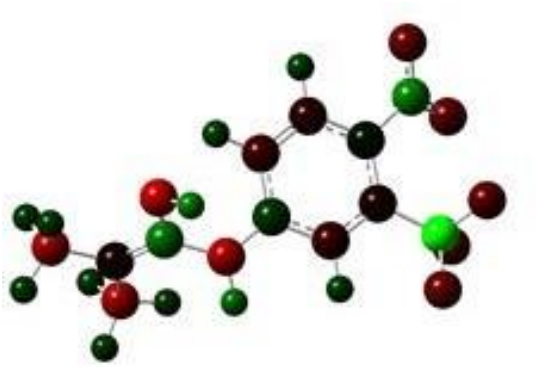
Figure 6: Flutamide Electron Density (NBO)

Table 7: NBO analysis of T1(B3LYP/6-311++g (d,

T1	Occupacy	Donor	Acceptor	E2(kCal/mol)
BD1 N17 -H18 BD1 N17 - C19	1.96266	BD N17-H18	BD* C19-O21	3.53
BD1 C19 - C20	1.97734	BD N17-C19	BD* C19-C20	0.94
BD2 C19 - C20	1.96153	BD C19-C20	BD* C19-C20	6.93
BD1 C19 - O21	1.91389	BD C19-C20	BD* O21-H30	1.67
BD1 C20 - C22	1.98877	BD C19-O21	BD* O21-H30	0.51
	1.98113	BD C20-C22	BD* C19-C20	1.77

Figure 7: T1 Electron Density (NBO)

Table 8: NBO analysis of T2 (B3LYP/6-311++g (d, p))



T2	Occupacy	Donor	Acceptor	E2(kCal/mol)
BD1 N17 - C18 BD1 C18 - C19	1.98431	BD N17 -C18 BD C18 - C19	BD* O20 - H29 BD* C19-H21	1.12
BD1 C18- O20	1.9725	BD C18- O20	BD* N17-C18	0.55
BD2 C19 - C21	1.9947	BD C19 - C21	BD* N17- C18	0.58
BD1 C19 - H30	1.9702	BD C19 – H30	BD* N17-C18	1.86
BD1 O20 - H29	1.9628	BD O20 – H29	BD* N17-C18	2.38
	1.98556			5.11

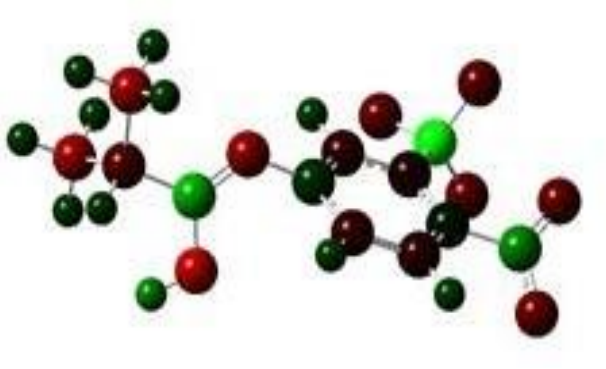


Figure 8: T2 Electron Density (NBO)

As the energy value of the ground state of individual compounds is determined with various base sets (because of changes in the precision and polarization of the base sets), using the base set 6-311 ++ g (d, p) affirms the real energy level of the ground state of every compound (10). Table 1 represents the negative level of the stability energy for individual compounds by the base set 6-311 ++ g (d, p).

Based on the estimated energy levels (Table 1) and the energy difference of -0.9 kJ between the composition F and T1, the F structure has greater stability than the T1 structure. The energy difference of -0.3 kJ between T2 and T1 and, thus, the energy difference of -0.06 kJ suggest that the compounds F and T2 are stable. Besides, such a tendency of stability series is acceptably observable by other arrays of assemblages. Thus, a conclusion can be drawn that the combined F has greater stability compared to the tutomer type state T2 and T2 in comparison to the tautomerform state T1. The stableness of the composition is indicative of existing greater activity and stability in the chemical and biochemical mediums. The stability of a compound regarding energy than its tautomerform compounds, it has higher formability and experiences chemical reactions in the same structural site.

The energy stability of the compounds is also indicative of the type of chemical structure and tautomorphism that are in equilibrium are more toward the composition(11) F, T2, and T1. This is favorable, and concerning stability, the structure is expectable that F and T2 to partake in chemical and biologic reactions. An alteration in the bipolar momentum of a molecule suggests that the molecule regarding the magnetized field participates in the interplays of the electrician and becomes magnetic with other molecules with varying radiation. Changes in the dipole momentum of F, T1, and T2 compounds by altering the base sets avered differences of magnetic orientation and polarization of the intended compounds (see Table 3). The magnetic impact of the milieu on the compounds induces various electrostatic interplays because of bipolar moments owing to changes in the dipole moment and the passing rate of every environment. The bipolar momentum will influence the polarization and the reactivity of the compounds. The combined T2, T1, and F is indicative of a more (12) prolonged bipolar momentum, suggesting its further exposure to the biologic milieu relative to the other compounds and raises the bio interplays. The chemical structure in compound T2 also undergoes an alteration in the orientation of the dipole momentum vector because of changing the position of the atoms.

Due to the changed position of H from N, the value of bipolar momentum has altered markedly to oxygen (Table 3). C = O vibrational frequency ranging from 1850 to 1650 (Fig. 3) displays the infrared spectrum of compound F. This vibrating frequency possesses a high intensity and vibrational frequency of CO and NH and OH in the range of 1700-3400 and 3200-3600 cm-1 as depicted in Figure 4 for compound T1, which is a proper equivalent for this. This is also true for the vibrating frequency of CO and CH at 1700 and 3000 cm-1 and two vibrating frequencies for NO at 1350 cm-1 and 1550 cm-1 (Fig. 5) for the combined tautomers T2. Table 2 represents the diffusion of contractual loadings on the atoms of every compound by altering the base set. The base set is changed to demonstrate the accurateness of the set of bases and the uniformness of the procedure of variation in load dispersion.The difference between the intrusive orbits was utilized in the base set technique on the distribution of atomic loads. The shorter bond length in the G molecule enables it to partake in all reactions superior to the other tautomers T1 and T2 (see Table 4). The calculated Gibbs free energy revealed that the F molecule had the utmost stableness to react in the entire chemical mediums. A stable molecule always performs the finest interplay in standard conditions (see Table 5). Analyzing F by NBO (Fig. 6) indicates that N17, C20, and C19 function as donor atoms and O22 functions as the acceptor atom in F compound. The color of individual atoms also led to this finding and demonstrated the function of individual atoms (see Table 6). NBO analysis data about T1 (Fig. 7) demonstrated N17, C19, C20 act as donor atoms and O21 act as acceptor atom. As NBO analysis of F active side of both compounds is the same as each other (see Table 7). The NBO assay of T2 (Fig. 8) displays a dissimilar active side of the molecule to act in reactions (see Table 8). C19 in combination with F are attached to atoms N and O. This is because the electrons pull electronegative atoms N and O and become positively charged. Since C20 is coupled to two groups of electrically charged alkylene, this leads to a negative charge value. Forming a double bond between the two carbons is facilitated by forming these two poles and will also expedite transferring hydrogen.

CONCLUSIONS

T2 is the bioactive type and the tautomer of FLUT with the utmost stability. The physical features and chemical reactivity of FLUT is only understandable by considering the interconversion between varying tautomeric types. A computational instrument capable of predicting a tautomer the utmost stability should be beneficial, but calculating the necessary quantum is fairly time-taking. These findings are evidently not generalizable for predicting that greater stability of T2 tautomers would always be determined by the same calculations for other molecules. In addition, it should be borne in mind that the solvent and other settings affect the equilibrium, which is possible or impossible to be accounted for in the computations. It can be principally be considered to implement this type of advanced computational tautomerism analysis on a high number (hundreds or even thousands) of varied molecules. Then, the outcomes should be used for building quantitative structure−tautomerism relationship models that can predict the tautomers of utmost stability for all small molecules (in the model practicality domain) with suitable molecular descriptors. The authors intend to discover these and other methods in future investigations on the tautomerism of other molecules.

COMPUTATIONAL METHOD

The reactivity of the tautomer of FLUT was investigated by doing the whole computations in the context of DFT with a spin unrestricted setting at Becke's three-parameter hybrids function in combination with the Lee-Yang-Parr correlation function, B3LYP. Then, computational levels for the entire atoms were determined by the 6-311++g and 6-311++g(d) and 6-311++g(d,p) pople basis set. The primary constructs were made with the gauss view 5.0 and underwent optimization by Gaussian 09 revision A 0238, considering various conformations of the tautomer. Stability energy, structural parameters, dipol moment, electronegativity, thermal features, IR frequency, and reactivity features were measured with the same technique.

REFERENCES

1. H. M. Badawi, W. Forner and S. A. Ali, Spectrochim Acta A Mol Biomol Spectrosc, 2014; 131: 249–260.
2. C. P. Firme and P. R. Bandaru, Nanomed-Nanotechnol, 2010; 6:245-256
3. M. Kamel, H. Raissi and A. Morsali, J. Mol. Liq., 2017; 248: 490-500
4. W. Hart and B. H. Stricker, Ann. Intern. Med, 1989;110: 943-944
5. P. Moghetti, R. Castello, C. Negri, F. Tosi, et al., Int J Fertil Steril, 1995; 64: 511-517

6. S. Moller, P. Iversen, M. B. Franzmann and S. Mller, J. Hepatol, 1990; 10: 346-349.
7. R. L. Crownover, J. Holland, A. Chen, R. Krieg and et al., Int. J. Radiat. Oncol. Biol. Phys, 1996; 34: 911-915.
8. Y. Kosar, N. Sasmaz, P. Oguz and S. Kucukbas, Am. J. Gastroenterol, 1995; 90: 1027-1028
9. C. J. Tyrrell, J. E. Altwein and F. Klippel, J. Urol, 1991; 146: 1321-1326.
10. J. L. Gulley, Prostate Cancer, Demos Medical Publishing, Vol. 2011, Hindawi Publishing Corporation, 81 (2011).
11. T. William, O. Foye, T. L Lemke and D. A Williams, Foye's Principles of Medicinal Chemistry, Lippincott Williams & Wilkins, 2008.
12. L. J. Denis, K. Griffiths, A. V. Kaisary and G. P. Murphy, Textbook of Prostate Cancer: Pathology, Diagnosis and Treatment: Pathology, Diagnosis and Treatment, CRC Press, 199; 1–99
13. Index Nominum, 2000: International Drug Directory, Vol. 17 (Eds.: Swiss Pharmaceutical Society), Taylor & Francis, 1-1877 (2000).