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Research Article

A DFT Study on the Radical Structures and HOMO-LUMO Analysis of Azathioprine

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Abstract

Azathioprine (Imuran) is used for to treat of numerous debilitating skin diseases. Azathioprine is an immunosuppressive antimetabolite used to prevent the body from rejecting a transplanted kidney. By means of EPR spectroscopy, this compound was studied experimentally before. But experimental searchers were only able to determine g value. For this reason, the EPR parameters (a and g value) have been determined theoretically in the present study. Furthermore HOMO and LUMO analysis have been carried out by density functional theory (DFT/B3LYP) method with 6-311++G (d,p) as basis set. Since HOMO and LUMO are most important orbitals in molecules, these orbitals are very useful to understand some molecular properties such as the chemical reactivity, kinetic stability, optical polarizability, chemical hardness and softness and electronegativity. Moreover, from the results of the DFT calculations, we obtained as follows: the total energy, the total dipole moment of the molecule (μ), absolute hardness (η), absolute electron negativity (χ) and reactivity index (ω).

Keywords: Azathioprine, DFT, HOMO-LUMO analysis, Radical Structure

Azatioprin Molekülünün Muhtemel Radikallerinin Yapısının Hesaplamalı Yöntemlerle İncelenmesi ve Homo-Lumo Analizi

Öz

Azatioprin (Imuran) çok sayıda güçten düşüren cilt hastalığını tedavi etmek için kullanılır. Azatioprin vücudun nakledilen böbreği reddetmesini önlemek için kullanılan bağışıklık bastırıcı bir anti-metabolittir. Bu bileşik, daha önce EPR spektroskopisi ile deneysel olarak incelenmiştir. Ama deneysel olarak sadece g değerini belirleyebilmişlerdir. Bu nedenle, çalışmamızda EPR parametreleri (a ve g değerleri) teorik olarak hesaplanmıştır. Ayrıca HOMO ve LUMO analizi DFT/B3LYP metot ve 6-311++G (d,p) baz seti ile yapılmıştır. HOMO ve LUMO, moleküllerdeki en önemli orbitaller olduğundan, bu orbitaller kimyasal tepkime, kinetik stabilite, optik polarizasyon, kimyasal sertlik ve yumuşaklık ve elektronegatiflik gibi bazı moleküler özellikleri anlamak için çok faydalıdır. Ayrıca, DFT hesaplamalarının sonuçlarından toplam enerji, molekülün toplam dipol momenti (μ), mutlak sertlik (η), mutlak elektron negatifliği (χ) ve reaktiflik indeksi (ω) elde edilmiştir.

Anahtar Kelimeler: Azatioprin, DFT, HOMO-LUMO analizi, Radikal yapı

1. Introduction

Azathioprine (AZA) is derived from 6-mercaptopurine. And the most recognized uses of azathioprine in dermatology are for immunobullous diseases, generalized eczematous disorders, and photodermatoses (Pillai & Levitsky, 2009). Moreover physicians had successfully employed azathioprine to treat myriad conditions,including inflammatory bowel disease, multiple sclerosis, myasthenia gravis, malignancies, and autoimmune conditions (Patel, Swerlick, & McCall, 2006).

As gamma radiation introduces both definite advantages such as the possibility of sterilization of drugs in packages and ensures a long period of validity, sterilization by gamma radiation has been successfully usedin many

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countries. Electron Paramagnetic Resonance (EPR) spectroscopy has been of use in the study of the characteristics of radicals that can occur because of gamma irradiation in drugs (Swarbrick, 2013). EPR is a very sensitive method for detection of free radicals. It can be used for a detailed study of radicals derived from amino acids and drugs which have unpaired electron (Osmanoğlu, Sütçü, & Başkan, 2017).

As we mentioned in our previous studies such as amphi-chloroglyoxime (Sayin, Yuksel, Yildirim, & Birey, 2006; Turkkan, Dereli, Tasdemir, & Cavusoglu, 2009), "Radical is an atom, molecule or ion that has unpaired valence electrons. EPR spectroscopy is one of the most powerful methods in studying the structure and determining the identity of molecules containing unpaired electrons. There are two EPR parameters that contain valuable information about the geometry and electronic structure of the radical systems. One of them is known as isotropic hyperfine coupling constant (ihfcc), which is symbolized by A, another is isotropic g value. Extraction of these parameters from experimental spectra is not always straightforward. Beside, while radical types can be determined using these parameters, detailed radical structures cannot be determined (Dereli, Erdoğdu, Ateş, Sarıkaya, & Özturan, 2017)". In this study, it is aimed to determine hyperfine coupling constants, which could not be determined from experimental study performed before, by computational methods. Molecule and possible radicals were modeled for this purpose. Some molecular properties of title compound have also been calculated using this obtained molecular structure.

2. Material and Methods

2.1. Experimental

Experimental EPR study of Azathioprine ($C_9H_7N_7O_2S$) was reported by Ambroz and coworkers (Ambroż, Kornacka, Marciniec, Ogrodowczyk, & Przybytniak, 2000). Experimental parameters used in our study were taken from Ambroz et al. studies (Ambroż et al., 2000). The experimental spectrum taken from that article is shown in Fig. 1.

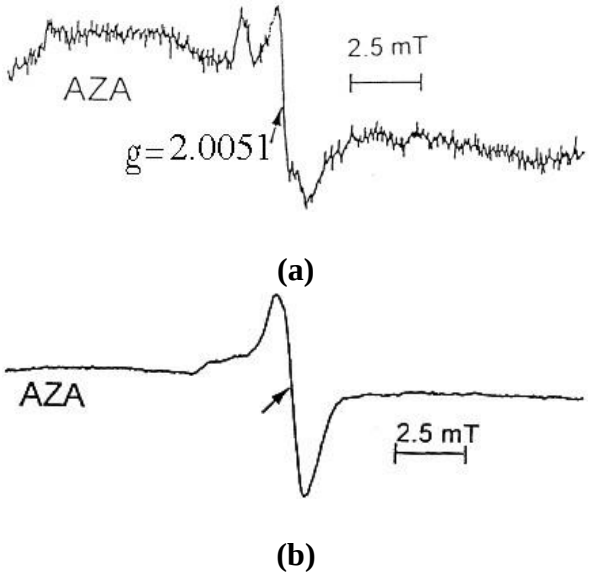

Figure 1. The experimental spectrum was taken from (Ambroż et al., 2000). (a) EPR spectrum of AZA un-irradiated (b) EPR spectrum of AZA irradiated with 10 kGy dose.

Ambroz et al.(Ambroż et al., 2000) investigated non-irradiated AZA molecule and they obtained weak EPR signal. According to this spectrum, they measured g value of AZA as 2.0051. And then they irradiated the compound with absorbed dose of 10 kGy at room temperature. Consequently they were observed anisotropic broad signal in the EPR spectrum of AZA. On account of an admixture of broad singlet in spectrum, they

didn't measure hyperfine coupling constants (hfccs) and g value of AZA.

2.2. Computational Details

The literature was investigated and it was determined that the molecular structure studies, vibrational analysis and NMR (Makhyoun, Massoud, & Soliman, 2013; Prasath, Govindammal, & Sathya, 2017) studies have been done, because this molecule is an important drug derivative. When these studies were examined, different methods and basis sets were used in these studies.

So conformational analysis of AZA was performed in our study and then six conformers have been obtained as shown in Fig. 2. These calculations were built by using semi empirical method (Milosavljević, Juranić, Aljančić, Vajs, & Todorović, 2003) and Spartan 08 (Irvine, 2008) was used for conformational analysis. The potential energy surface (PES) scan was performed by Spartan 08 program. As a result of these calculations, conformation space was obtained. Then geometry optimizations of all of the possible conformers was performed by B3LYP functional of Density Functional Theory (DFT) and standard 6-311++G(d,p) basis sets.

Table 1. Conformational energies of AZA in gas phase

Conformations	Energies (Hartree)	Dipol Moment (D)
Conf1	-1279.22704834	4.9038
Conf2	-1279.22704833	4.9025
Conf3	-1279.22704832	4.9012
Conf4	-1279.22704831	4.9029
Conf5	-1279.22704829	4.9034
Conf6	-1279.22704828	4.9019

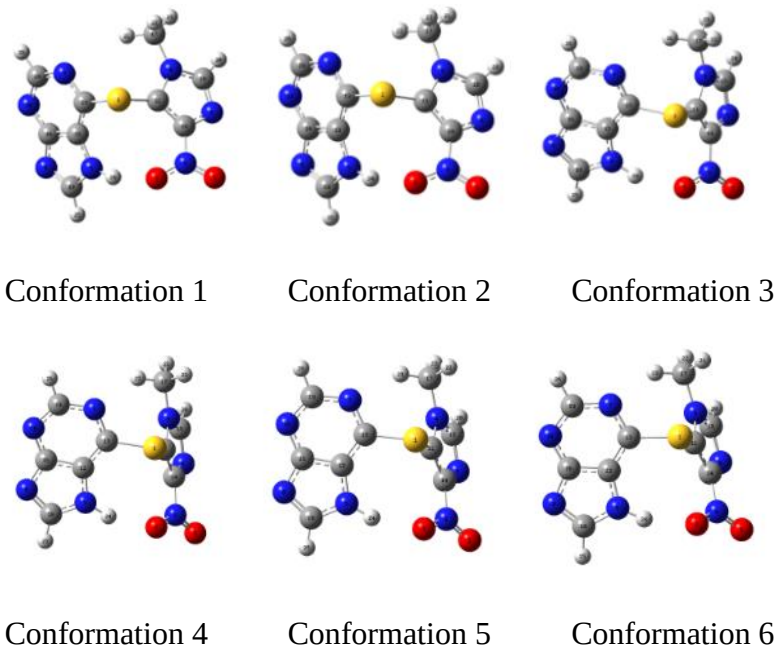

Figure 2. Stable conformers of the AZA molecule in gas phase

Hfccs(a) and g-factors of model radicals were also found by B3LYP/ 6-311++ G(d,p) computations. Hfccs and g-factor computations of model radicals were performed with NMR/GIAO method. Geometry optimizations were made by GAUSSIAN03 (Frisch, Rega, Jaramillo, Farkas, & Al-Laham, 2003) program. Conformational energies of conformers were given in Table 1. Because structural differences of conformers can easily be seen from dipole moments, these parameters were also given in Table 1. The most stable conformer was found as Conformation 1. As it is seen in Table 1, this conformation has the lowest energy. Energy and dipol moment values of the most stable conformer are -1279.22704834 Hartree and 4.9038 Debye, respectively.

Geometry parameters of this conformation was compared with the values found in the literature (W.J. Cook, 1975). This comparison was given Table 2. In addition to this, Makhyoun and coworkers (Makhyoun et al., 2013) determined the tautomer of AZA in their study. And they found the molecular structure and the relative stabilities of the four possible tautomers of AZA.

Table 2. The calculated geometry parameters of AZA by B3LYP/6-311++G(d,p) method

Bond leng. (A°)	**Teo.**	**Exp.***	**Bond angles (^{0})**	**Teo.**	**Exp.***	**Dihedral angles (^{0})**	**Teo.**	**Exp.***
(S1,C11)	1.763	1.737	(O2,N9,O3)	124.3	123.8	(C15,N4,C17,H22)	110.3	-
(S1,C13)	1.819	1.768	(O2,N9,C14)	117.7	117.0	(C15,N4,C17,H23)	9.3	-
(O2,N9)	1.240	1.236	(O3,N9,C14)	118.1	119.2	(C18,N5,C12,C13)	179.5	-
(O3,N9)	1.214	1.217	(C16,N10,C19)	114.4	112.0	(C18,N5,C12,C16)	0.2	-
(N4,C11)	1.382	1.365	(S1,C11,N4)	122.0	124.2	(H24,N5,C12,C13)	2.9	-
(N4,C15)	1.365	1.360	(S1,C11,C14)	134.2	132.0	(H24,N5,C12,C16)	177.8	-
(N4,C17)	1.464	1.475	(N4,C11,C14)	103.4	103.5	(C19,N7,C13,S1)	176.4	-
(N5,C12)	1.370	1.387	(N5,C12,C13)	136.4	133.4	(C19,N7,C13,C12)	0.3	-
(N5,C18)	1.371	1.368	(N5,C12,C16)	105.5	110.8	(C13,N7,C19,N10)	0.5	-
(N5,H24)	1.019	0.920	(C13,C12,C16)	118.1	115.8	(C13,N7,C19,H26)	179.5	-
(N6,C14)	1.353	1.353	(S1,C13,N7)	118.2	120.9	(C18,N8,C16,N10)	179.2	-
(N6,C15)	1.313	1.305	(S1,C13,C12)	122.3	118.2	(C18,N8,C16,C12)	0.0	-
(N7,C13)	1.327	1.323	(N7,C13,C12)	119.5	120.9	(C16,N8,C18,N5)	0.2	-
(N7,C19)	1.351	1.335	(N6,C14,N9)	119.6	120.3	(C16,N8,C18,H25)	179.8	-
(N8,C16)	1.376	1.376	(C16,N8,C18)	104.4	105.6	(O2,N9,C14,N6)	156.4	-
(N8,C18)	1.312	1.363	**Dihedral angles**	**Teo.**	**Exp.***	(O2,N9,C14,C11)	24.9	-
(N9,C14)	1.450	1.435	(C13,S1,C11,N4)	81.6	-	(O3,N9,C14,N6)	23.6	-
(N10,C16)	1.334	1.336	(C13,S1,C11,C14)	107.8	-	(O3,N9,C14,C11)	155.1	-
(N10,C19)	1.329	1.334	(C11,S1,C13,N7)	110.5	-	(C19,N10,C16,N8)	179.3	-
(C11,C14)	1.392	1.371	(C11,S1,C13,C12)	72.9	-	(C19,N10,C16,C12)	0.2	-
(C12,C13)	1.387	1.387	(C15,N4,C11,S1)	173.8	-	(C16,N10,C19,N7)	0.3	-
(C12,C16)	1.421	1.394	(C15,N4,C11,C14)	0.6	-	(C16,N10,C19,H26)	179.8	-
Bond angles (^{0})	**Teo.**	**Exp.***	(C17,N4,C11,S1)	3.7	-	(S1,C11,C14,N6)	172.0	-
(C11,S1,C13)	100.8	102.1	(C17,N4,C11,C14)	176.8	-	(S1,C11,C14,N9)	6.8	-
(C11,N4,C15)	107.2	107.2	(C11,N4,C15,N6)	1.0	-	(N4,C11,C14,N6)	0.1	-
(C11,N4,C17)	126.6	127.7	(C11,N4,C15,H20)	178.3	-	(N4,C11,C14,N9)	178.7	-
(C15,N4,C17)	126.1	125.1	(C17,N4,C15,N6)	176.5	-	(N5,C12,C13,S1)	2.6	-
(C12,N5,C18)	105.8	103.0	(C17,N4,C15,H20)	4.2	-	(N5,C12,C13,N7)	179.2	-
(C14,N6,C15)	104.5	103.4	(C11,N4,C17,H21)	53.6	-	(C11,N4,C17,H23)	173.7	-
(C13,N7,C19)	118.0	117.6	(C11,N4,C17,H22)	66.7	-	(C15,N4,C17,H21)	129.4	-

*Values were taken from Ref.(W.J. Cook, 1975)

After obtaining the molecular structure, seventeen possible radicals were modeled. And EPR parameters were calculated for all modeled radicals after geometry optimizations of them. Model radicals were shown in Fig. 3.

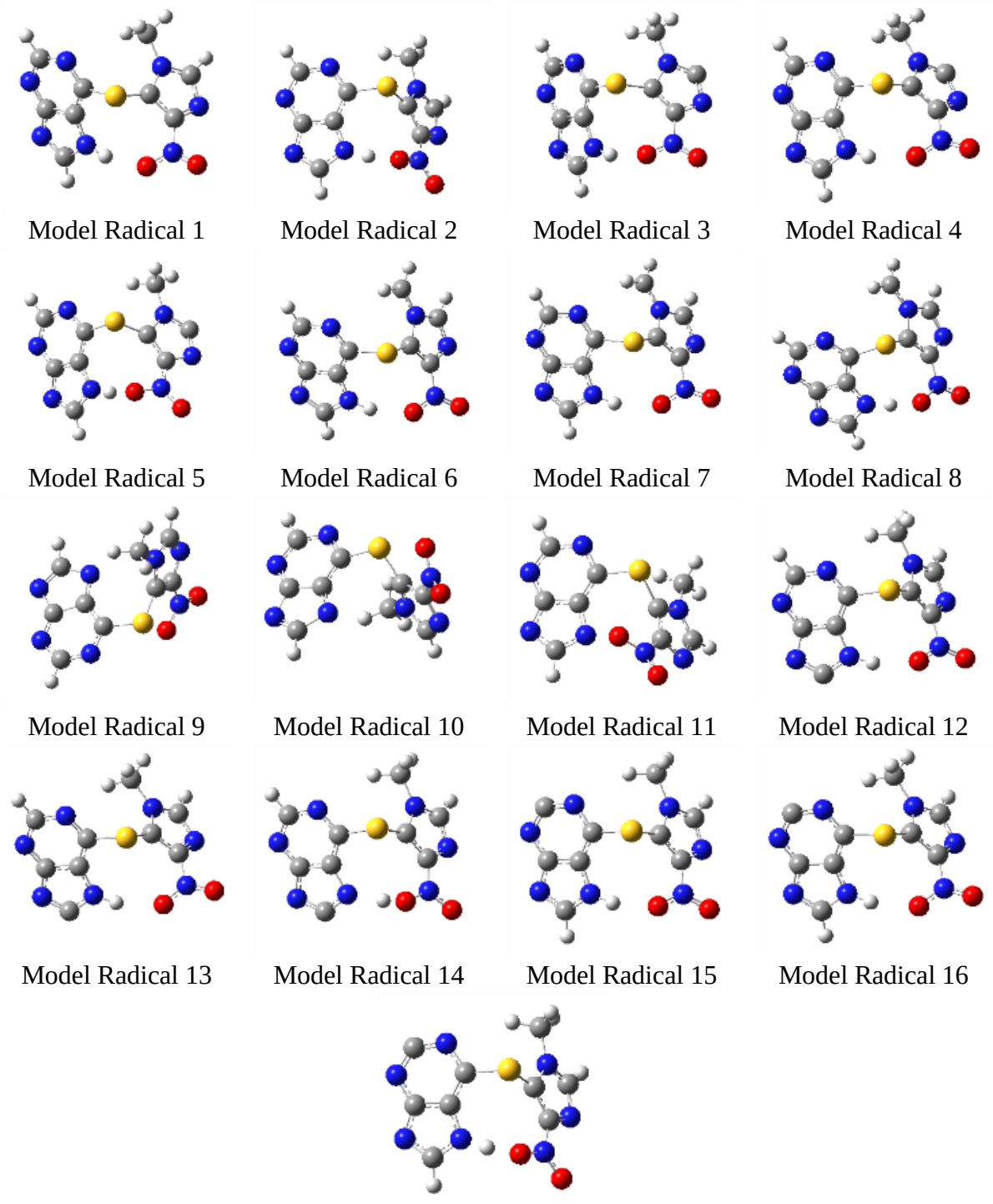

Figure 3. Model radicals of AZA molecule in gas phase

Model Radical 1 (MR1) is a radical cation and MR2 is radical anion of molecule. MR3 is a neutral radical formed by abstraction of H20 atom from the molecule. MR4 is cation form of MR3 and MR5 is anion form of MR3. MR6 is a neutral radical formed by abstraction of H21 atom from the molecule. MR7 and MR8 is cation and anion form of MR6, respectively. MR9 is a neutral radical formed by abstraction of H24 atom from the molecule. MR10 is cation form of MR9 and MR11 is anion form of MR9. MR12 is a neutral radical formed by abstraction of H24 atom from the molecule. MR13 is cation form of MR12 and MR14 is anion form of MR12. MR15 is a neutral radical formed by

abstraction of H25 atom from the molecule. MR16 is cation form of MR15 and MR17 is anion form of MR15. The theoretical hfccs and g-values of model radicals were shown in Table 3.

Table 3. The theoretical hyperfine-splitting parameters and g-values of model radicals

a_{iso}	MR 1	MR 2	MR 3	MR 4	MR 5	MR 6
S	0.55107	3.22640	-0.01789	-0.54099	1.78078	0.21772
N	-1.27732	0.14176	12.70198	5.77305	6.42524	-3.45827
N	-0.52378	1.35996	-0.00769	-0.26365	0.61853	0.00958
N	-0.34074	0.57673	35.72611	16.68901	19.82311	-0.08198
N	0.96254	0.36027	0.02326	1.03724	0.21998	0.41935
N	1.38052	-0.01445	-0.00178	0.71500	-0.00951	-0.00261
N	-0.73182	4.70004	-0.18787	-0.47304	1.90836	-0.53721
N	4.31404	-0.00102	0.00631	2.81036	0.00658	-0.00712
H	-4.99747	0.92432	-	-	-	-2.94187
H	-1.68781	1.52841	-0.70145	-1.31372	0.45929	-
H	-0.98842	2.18532	-0.86638	-0.64649	0.84688	-20.33130
H	-0.33123	-0.03916	-0.30940	-0.42655	-0.18452	-19.79257
H	-0.05442	1.24017	-0.00848	0.01554	0.24449	-0.01692
H	0.02962	-0.03042	-0.00751	0.11545	-0.02698	-0.01303
H	-0.47139	0.10432	0.00260	-0.05952	0.06099	-0.01508
g_{iso}	**2.00560**	**2.00519**	**2.00223**	**2.00790**	**2.00820**	**2.00271**
a_{iso}	**MR 7**	**MR 8**	**MR 9**	**MR 10**	**MR 11**	**MR 12**
S	0.35307	1.18398	2.54464	3.01217	1.12833	0.00489
N	-2.66454	-1.13979	0.43205	-1.11326	0.02643	-0.00174
N	-0.26782	0.66730	3.17690	2.44228	16.63489	16.05166
N	-0.34254	0.64121	0.19997	-0.17716	0.52834	0.00037
N	0.82430	0.25440	-1.18447	-0.73876	0.13298	-0.15444
N	0.73716	-0.00662	0.09858	0.13610	0.04435	37.24764
N	-0.66637	2.22170	-0.04412	-0.70616	2.76888	-0.00342
N	2.23782	-0.00288	-0.46589	-0.56835	-0.00047	1.40720
H	-4.83838	-0.92218	0.22982	-4.31795	0.32588	-0.00089
H	-	-	0.02421	-1.24067	0.56420	-0.00118
H	-10.08211	-10.08957	-0.00235	-0.28948	0.74850	-0.00138
H	-9.86478	-9.69775	0.02057	-0.25779	-0.01318	0.00034
H	-0.03323	0.47585	-	-	-	-0.24894
H	0.10107	-0.01487	-2.81492	-1.30966	0.02605	-
H	-0.10360	0.04006	-5.74234	-3.90530	-0.15111	-0.11382
g_{iso}	**2.00876**	**2.00916**	**2.00481**	**2.01096**	**2.01639**	**2.00181**
a_{iso}	**MR 13**	**MR 14**	**MR 15**	**MR 16**	**MR 17**	
S	1.10391	1.05534	0.04807	1.14178	1.60116	
N	-0.72471	-0.05917	0.00263	-0.61403	0.06930	
N	8.44068	12.73607	0.73047	0.12059	0.94235	
N	-0.17239	0.23628	-0.00168	-0.12063	0.28727	
N	-0.07949	0.09958	35.00543	18.11213	17.72614	
N	19.18462	15.59865	0.67701	0.63101	0.38022	
N	-0.41754	3.24710	-0.00281	-0.37266	2.37237	
N	1.25591	0.79141	36.32096	18.90337	17.90164	
H	-2.88452	0.20184	-0.01250	-2.52510	0.44313	
H	-0.96959	0.51019	-0.01791	-0.88034	0.76342	
H	-0.51193	0.78096	0.02914	-0.48053	1.07630	
H	-0.21107	-0.01594	0.01847	-0.18950	-0.01662	
H	-0.33682	4.14446	0.11102	-0.18261	0.84956	
H	-	-	0.01160	-0.41556	0.01384	
H	-0.63836	0.05898	-	-	-	
g_{iso}	**2.00977**	**2.00717**	**2.00191**	**2.00920**	**2.00739**	

Eventually HOMO and LUMO calculations were done using DFT- B3LYP/ 6-311++ G(d,p) level of theory. HOMO and LUMO are the most important orbitals in molecules. These orbitals are very useful to understand the chemical reactivity and kinetic stability of the molecule (Issaoui et al., 2017; Rauk, 2004; Streitwieser, 1961).

As it can be seen in the Table 4, we calculated the total energy (ET (eV)), E_{HOMO} (eV), E_{LUMO} (eV), difference between the LUMO and the HOMO energy (Gap), total dipole moment of the molecules (μ), absolute hardness (η), absolute electron negativity (χ) and reactivity index (ω), respectively.

Table 4. The theoretically calculated some molecular properties of AZA

ET(eV)	**E_{HOMO} (eV)**	**E_{LUMO} (eV)**	**Gap(eV)**
-34809.815	-7.429	-3.211	4.218
μ (Debye)	**η**	**χ**	**ω**
4.904	2.109	5.320	6.710

Gap, μ, η, χ and ω were calculated by equations taking from ref(Chtita et al., 2013)

HOMO-LUMO energies of the title compound were calculated and shapes of these orbitals were drawn, as it is seen in Figure 4.

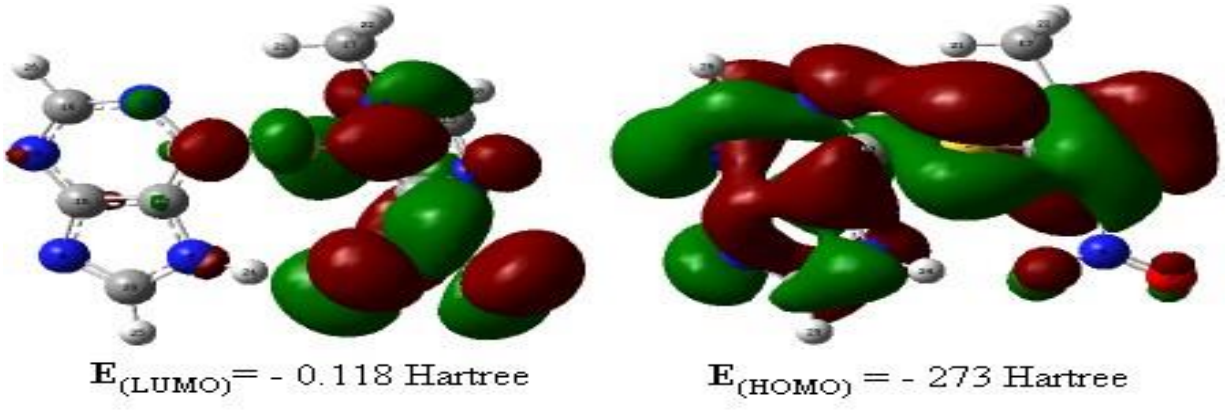

Figure 4. 3D plots of HOMO and LUMO of AZA

3. Research Findings

According to the experimental study, neither a nor g values could have not been determined. Even if the experiment is done again, determination of these values are seen difficult without the support of theoretical studies. Therefore, the structure of the molecule and all possible radicals of it were determined and presented to the literature, in this study. These structures and calculated values (both molecular properties such as HOMO-LUMO and radical parameters such as a values, g values and radical geometry parameters) of them will be useful for future experimental researchers of title compound.

4. References

Ambroż, H., Kornacka, E., Marciniec, B., Ogrodowczyk, M., & Przybytniak, G. (2000). EPR study of free radicals in some drugs γ-irradiated in the solid state. *Radiation Physics and Chemistry*, *58*(4), 357-366.

Chtita, S., Ghamali, M., Larif, M., Adad, A., Hmammouchi, R., Bouachrine, M., & Lakhlifi, T. (2013). Prediction of biological activity of imidazo [1, 2-a] pyrazine derivatives by combining DFT and QSAR results. *IJIRSET*, *2*(12), 7962.

Dereli, Ö., Erdoğdu, Y., Ateş, L., Sarıkaya, E. K., & Özturan, F. P. (2017). Molecule and Radical Structures of Isobutyronitrile. *Gazi University Journal of Science*, *30*(1), 161-165.

Frisch, M. J. T., G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; , Rega, N. P., G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.;, Jaramillo, J. G., R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.;Dapprich,S.Daniels, A. D.; Strain, M. C.; , Farkas, O. M., D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; , & Al-Laham, M. A. P., C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J.A. (2003). Gaussian 03. Wallingford CT: Gaussian, Inc. Retrieved from http://www.gaussian.com/g_misc/g03/citat ion_g03.htm

Irvine. (2008). Spartan 08. CA 92612, USA: Wavefunction Inc.

Issaoui, N., Ghalla, H., Bardak, F., Karabacak, M., Dlala, N. A., Flakus, H., & Oujia, B. (2017). Combined experimental and theoretical studies on the molecular structures, spectroscopy, and inhibitor activity of 3-(2-thienyl) acrylic acid through AIM, NBO, FT-IR, FT-Raman, UV and HOMO-LUMO analyses, and molecular docking. *Journal of Molecular Structure*, *1130*, 659-668.

Makhyoun, M. A., Massoud, R. A., & Soliman, S. M. (2013). Tautomerism and spectroscopic properties of the immunosuppressant azathioprine. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *114*, 394-403.

Milosavljević, S., Juranić, I. O., Aljančić, I., Vajs, V., & Todorović, N. (2003). Conformation analysis of three germacranolides by the PM3 semi-

empirical method. *Journal of the Serbian Chemical Society, 68*(4-5), 281-289.

Osmanoğlu, Y. E., Sütçü, K., & Başkan, M. H. (2017). EPR investigation of gamma-irradiated l-citrulline, α-methyl-dl-serine, 3- fluoro-dl-valine and N-acetyl-l-cysteine. *Journal of Molecular Structure, 1130*, 291-295.

Patel, A. A., Swerlick, R. A., & McCall, C.O. (2006). Azathioprine in dermatology: the past, the present, and the future. *Journal of the American Academy of Dermatology, 55*(3), 369-389.

Pillai, A. A., & Levitsky, J. (2009). Overview of immunosuppression in liver transplantation. *World Journal of Gastroenterology: WJG, 15*(34), 4225.

Prasath, M., Govindammal, M., & Sathya, B. (2017). Spectroscopic investigations (FT-IR & FT-Raman) and molecular docking analysis of 6-[1-methyl-4-nitro- 1H-imidazol-5-yl) sulfonyl]-7H-purine. *Journal of Molecular Structure, 1146*, 292-300.

Rauk, A. (2004). *Orbital interaction theory of organic chemistry*: John Wiley & Sons.

Sayin, U., Yuksel, H., Yildirim, B., & Birey, M. (2006). EPR of gamma irradiated single crystals of amphi-chloroglyoxime. *Radiation Effects & Defects in Solids, 161*(4), 241-245.

Streitwieser, A. (1961). *Molecular orbital theory for organic chemists*. New York: John Wiley and Sons, Inc.,.

Swarbrick, J. (2013). *Encyclopedia of pharmaceutical technology*: CRC Press.

Turkkan, E., Dereli, O., Tasdemir, H., & Cavusoglu, H. (2009). Density functional theory–electron paramagnetic resonance study of gamma-irradiated single crystal of amphi-chloroglyoxime. *Radiation Effects and Defects in Solids, 164*(2),73-82. W.J. Cook, C. E. B. (1975). *J. Pharm. Sci., 64* 221–225.