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Density Functional Studies of Molecular Polarizabilities. Part 11. The Dipole Polarizability of the Most Stable Conformation of 3'–Azido–3'–deoxythymidine AZT

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Density Functional Studies of Molecular Polarizabilities. Part 11. The Dipole Polarizability of the Most Stable Conformation of 3'–Azido–3'–deoxythymidine AZT

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Abstract

We report an *ab initio* Hartree–Fock HF and Density Functional Theory DFT study of the dipole polarizability α of 3'–azido–3'–deoxythymidine (AZT) compound. Geometry was fully optimized at the HF/6–31+G(d,p) and BLYP/6–31+G(d,p) levels of theory using X–ray data as starting structure. These calculations have allowed us to find the most stable conformational structure of AZT. This structure shows a torsion angle between thymine and furanose rings larger than 90º and a nonlinear azido group located *trans* to the C2'–C3' bond of furanose ring. This conformation, verified by vibrational analysis, involves a hydrogen interaction between the oxygen atom in the position 2 of the thymine ring and the hydrogen atom in the position 3' of the furanose ring (O–H bond lengths are 2.4618 and 2.4536 Å at HF and BLYP, respectively). The calculated geometry of the furanose, azide and thymine fragments agree with X–ray AZT structure and with other DFT calculations, whereas the orientation of the thymine ring in the optimized structure shows strong discrepancies with the orientation in the crystal. The static dipole polarizability α was evaluated using the 6–311++G(3d,3p) basis sets with HF, BLYP and B3LYP methods. The polarizability results were compared with values from the empiric atomic methods of Miller, Thole, Swart and Jensen, giving average polarizability for AZT that range between 166 to 214 au values, whereas the corresponding values at HF/6–311++G(3d,3p), B3LYP/6–311++G(3d,3p) and BLYP/6–311++G(3d,3p) approaches are 157.27, 189.77 au and 182.34 au, respectively. These results indicated that the best value for AZT α lies in the middle of the range between the smaller and the largest empiric polarizability value, that correspond to the Miller and Thole methods.

Keywords. AZT; dipole polarizability; density functional theory.

1 INTRODUCTION

The 3'–azido–3'–deoxythymidine (AZT) is a thymidine analogue where the 3'–hydroxy (OH) group has been replaced by an azido (=N_3) group [1]. The AZT, together with other promising analogous of nucleosides, such as didanosine, zalcitabine, stavudine, etc., have a potential use as drugs for therapeutic treatment of acquired immunodeficiency syndrome (AIDS). The action of

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AZT compound has been explained taking in consideration that once AZT becomes attached to the DNA chain, no further growth can take place in the DNA chain due to the absence of the OH group, because this group is absolutely necessary for the triphosphorylated nucleotides be attached to the growing DNA chain [1]. Although, AZT is not triphosphorylated, it is though that the active form of AZT takes place in the cells by triphosphorylation, like in the natural nucleotides, and this form inhibits the replication of human immunodeficiency virus (HIV) [1]. However, the binding and inhibition mechanism of this kind of compounds have to be established.

The clinical usefulness of AZT has been recently questioned [2,3], in consequence new effective and nontoxic drugs are necessary for the treatment of antiviral illness. However, a fully understanding of the properties of the already used drugs is necessary in order to propose new ones. The knowledge of geometric and conformational structure, electric properties and structure–activity relationships of AZT and related drugs could lead to a comprehensive understanding necessary for the development of effective drugs for the future. From this point of view, the computational approach can be a valuable tool to gain insight in the action mechanism of such drugs. First principles calculations at *ab initio* and Density Functional Theory approaches have proved to be accurate methods for elucidation and predictions of molecular structures and properties [4].

Conformational analysis of AZT structure and other related drugs have been previously reported at semi–empirical and *ab initio* levels of theory [5,6,7]. However, to our knowledge, there is no report of dipole polarizability calculations for this very important molecule. To get inside on the chemical properties of AZT we have performed an *ab initio* HF and DFT study of the dipole polarizability of this drug. The dipole polarizability is a property of fundamental importance in structural chemistry [8], and can be considered as an index for the electronic nature of a molecule. This property can be either experimentally determined and theoretically calculated [9]. We are interested in the evaluation of the dipole polarizability of molecules of chemical and pharmacologic interest using quantum mechanic methods [10]. The aim of this work is to report the dipole polarizability of the most stable conformation of AZT.

2 METHODS AND THEORY

The molecular dipole polarizability α is the linear response of a molecular electronic distribution to the action of an external electric field $\Im$. Such an external field causes charge rearrangements that are reflected in changes in the permanent molecular dipole moment μ_e according to [8,9,10].

$$\mu_e(\Im) = \mu_e(\Im=0) + (1/2)\,\alpha.\Im + (1/6)\,\beta\,\Im^2 \qquad (1)$$

Here, $\mu_e(\Im = 0)$ is the dipole moment in the absence of the field and the higher terms are the dipole plarizability α and the first hyperpolarizability β, respectively. Similarly, a Taylor expansion for the energy E of the system has been defined in terms of the dipole polarizabilities and the field

$\mathfrak{I}$ as:

$$E(\mathfrak{I}) = E(0) - \mu\mathfrak{I} - (1/2)\,\alpha.\mathfrak{I}^2 - (1/6)\,\beta\,\mathfrak{I}^3 \tag{2}$$

where E(0) is the unperturbed energy. Hyperpolarizabilities are generally small and their effect is minimal for weak electric fields. They become important for large electric fields [11]. In polarizability studies, the quantities of experimental interest are the average polarizability:

$$\alpha_{\text{ave}} = \langle\alpha\rangle = \tfrac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \tag{3}$$

and the polarizability anisotropy:

$$\Delta\alpha = ((1/2)[(\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{xx} - \alpha_{zz})^2 + (\alpha_{yy} - \alpha_{zz})^2])^{1/2} \tag{4}$$

Accurate calculation of dipole polarizabilities requires the use of extended basis sets and high level of theory. In particular, these basis sets have to include sets of d and p polarization functions together with sets of s and p diffuse functions in order to give an appropriate description of the response function of the molecular charge distribution to the action of the external electric field.

Additionally to the basis sets, the requirements of the level of theory have to include the accounting of the exchange and correlation effects in an appropriate way for these electric properties. In recent years, density functional techniques have received a great deal of attention in the literature. In Density functional theory (DFT) we write the electronic energy expression as [12]:

$$\varepsilon_{el} = \mathrm{Tr}(\mathbf{h_1 P}) + (1/2)\mathrm{Tr}(\mathbf{PJ}) + \varepsilon_x + \varepsilon_c \tag{5}$$

which relates the electronic energy for one–determinant closed shell ε_{el} to the electron density matrix **P**, the matrix of one–electron integrals $\mathbf{h_1}$, the Coulomb matrix **J**, the exchange functional ε_x and the correlation functional ε_c, this is zero for Hartree–Fock (HF) wavefunctions. In this context, the evaluation of ε_x and ε_c potentials is done by the assumption of determined functional forms for these two potentials and then calculate the contribution to the electronic energy as an integral part of the electron density. These calculations are performed numerically and they consume less computing resources than standard second order perturbation theory Møller–Plesset MPn methodology [13].

There are different models to represent the forms for the exchange and correlation functionals [12]. In particular, the known BLYP [12] and B3LYP [14] hybrid functionals work very well in conjunction with 6–311++G(3d,3p) basis sets [16], and they have shown good performance for accounting the correlation effects in dipole polarizability calculations [9,10]. In the present work, we have used these functionals and basis sets for the theoretical determination of the static dipole polarizability of AZT molecule. For these calculations, the geometry of AZT was optimized by using gradient techniques at the HF/6–31+G(d,p) and BLYP/6–31+G(d,p) levels without symmetry constrains. Vibrational frequency analyses was performed at these levels of theory in order to characterize the nature of the stationary point of the potential energy surface corresponding to the AZT optimized structure. Additionally, dipole moment and Mulliken population analysis calculations were performed. All Calculations were carried out using the GAUSSIAN 98 [17] quantum chemistry package in an Origin 2000 Silicon Graphics workstation.

3 RESULTS

3.1 Structure and charges of AZT

Figure 1 display the AZT structure optimized at the BLYP/6–31+G(d,p) level of theory showing the atomic notation scheme and molecular orientation in the axis coordinate system. We have followed the Saenger's notation scheme for the atomic description of the molecule, how has been previously reported [18]. Table 1 shows optimized geometric parameters of AZT structure at different levels of theory HF and BLYP. Results indicate that bond distances and bond angles, important to describe geometric features of AZT, are very close to those reported from X–ray structure (values in parentheses) and other calculations [5,6,7]. The stationary point was found performing a fully geometry optimization without symmetry restrictions using X–ray structure of AZT [19] as starting point.

The structure reported in the present work corresponds to the most stable conformation of AZT at both levels of theory, HF and BLYP. For this structure only positive eigenvalues of the Hessian matrix of the potential energy were found, which mean that this conformation has no imaginary vibrational frequencies and that the calculated gas phase structure represent a global minima. A comparison of our structure with those calculated by Dayu *et al.* at B3LYP/6–31G(d) level of theory in their rotational study of AZT [7], shows that our conformation resemble the structure with the lowest energy conformation (named AZTB) reported by these authors.

Since the molecular point of view, the structure of AZT is dominated by three fragments, the thymine ring, the furanose ring and the azide one. Our results show that the azide group lies in a nonlinear conformation, where $N_{6'}$–$N_{7'}$–$N_{8'}$ bond angle range from 174.6º at HF to the value of 171.6º at BLYP level and is attached in *trans* position to the C_3'–C_2' bond of furanose ring. The azide group also has an *anti* conformation with respect to both, the hydroxyl group and the thymine ring. The thymine ring has nearly planar configuration, with a deviation from the plane no larger than 3º in the torsion angles. The furanose ring has a no planar conformation and the hydroxyl group forms a torsion angle (O5'–C5'–C4'–O4') of –179.7° and 175,7° at HF and BLYP levels of theory, respectively.

Table 1. BLYP/6–31+G(d,p) Optimized bond distances (in Angstron Å), bond angles and torsion angles (in degrees °) of AZT.

Bond distances/ Angstroms	HF	BLYP	Exp^b.	Angles/ Degrees	HF	BLYP	Exp ^{b}	Torsion Angles/ Degrees	HF	BLYP	Exp ^{b}
$N_1–C_2$	1.372	1.413	1.318	$C_2–N_1–C_6$	120.3	120.7	119.1	$N_1–C_2–N_3–C_4$	2.8	2.4	–2.4
$N_1–C_6$	1.386	1.399	1.408	$N_1–C_2–N_3$	115.0	113.8	113.0	$N_1–C_6–C_5–C_4$	–1.1	–0.8	–0.6
$C_2–N_3$	1.368	1.395	1.391	$N_1–C_6–C_5$	124.8	124.7	127.4	$N_3–C_2–N_1–C_6$	–4.2	–3.4	1.0
$C_6–C_5$	1.332	1.367	1.36	$N_1–C_2–O_2$	123.5	123.7	121.8	$C_2–N_1–C_6–C_5$	3.6	2.8	0.3
$N_3–C_4$	1.384	1.423	1.42	$C_2–N_3–C_4$	128.0	128.8	130.4	$O_2–C_2–N_3–C_4$	–178.0	–178.1	177.2
$C_2–O_2$	1.201	1.238	1.253	$C_6–C_5–C_4$	117.3	118.8	116.5	$O_2–C_2–N_1–C_1'$	5.9	4.1	–0.3
$C_5–C_7$	1.503	1.512	1.536	$C_6–C_5–C_7$	124.2	123.3	125.2	$C_2–N_1–C_1'–O_4'$	67.3	70.3 61.0^a	–123.3
$C_4–O_4$	1.197	1.239	1.252	$N_3–C_4–O_4$	120.5	120.2	123.1	$C_2–N_1–C_1'–C_2'$	–54.6	–52.2 –60.8^a	117.8
$N_1–C_1'$	1.463	1.494 1.476^a	1.46	$C_2–N_1–C_1'$	120.0	120.2	117.9	$N_1–C_1'–O_4'–C_4'$	–133.8	–128.9 –136.8^a	–133.6
$C_1'–O_4'$	1.391	1.435	1.437	$C_6–N_1–C_1'$	119.1	118.8	123.0	$O_5'–C_5'–C_4'–O_4'$	–179.7	175.7 –75.1^a	–67.6
$C_1'–C_2'$	1.535	1.551	1.497	$N_1–C_1'–O_4'$	109.7	109.8	107.8	$C_3'–C_4'–C_5'–O_5'$	–62.0	–65.9 42.6^a	–91.3
$O_4'–C_4'$	1.414	1.460	1.378	$N_1–C_1'–C_2'$	116.5	106.5	110.1	$C_2'–C_3'–N_6'–N_7'$	146.9	148.2 114.4^a	177.5
$C_2'–C_3'$	1.529	1.549	1.504	$C_1'–O_4'–C_4'$	108.9	111.6	110.2	$C_1'–C_2'–C_3'–C_4'$	21.3	21.2 20.4^a	–33.1
$C_4'–C_5'$	1.515	1.535	1.536	$C_1'–C_2'–C_3'$	104.9	105.5	98.8	$C_2'–C_3'–C_4'–O_4'$	–25.5	–22.3 –26.7^a	26.8
$C_5'–O_5'$	1.405	1.448	1.424	$O_4'–C_4'–C_3'$	106.0	106.6	104.7	$C_3'–C_4'–O_4'–C_1'$	20.6	15.1 23.6^a	–7.8
$C_3'–N_6'$	1.467	1.495 1.480^a	1.487	$C_2'–C_3'–C_4'$	102.8	103.6	105.6	$C_4'–O_4'C_1'–C_2'$	–6.5	–1.3 –10.3^a	–14.1
$N_6'–N_7'$	1.231	1.249 1.236^a	1.232	$O_4'–C_4'–C_5'$	107.5	107.3	108.1	$O_4'–C_1'–C_2'–C_3'$	–10.3	–13.1 –7.3^a	29.3
$N_7'–N_8'$	1.100	1.159 1.142^a	1.122	$C_4'–C_5'–O_5'$	106.9	106.3	113.5				
				$C_2'–C_3'–N_6'$	109.4	109.0	111.1				
				$C_3'–N_6'–N_7'$	114.4	116.8 116.2^a	115.0				
				$N_6'–N_7'–N_8'$	174.5	171.6 172.8^a	173.7				

[a] Theoretical value, B3LYP/6–31G(d), Ref. [7]
[b] Experimental X–Ray Difraction, Ref. [19]

The calculated bond distances and angles are in agreement with the geometric features reported for X–ray structure of AZT [19]. A linear fit for bond distances between the calculated and experimental values shows a correlation coefficient of 0.97 and 0.96 at HF and BLYP levels, respectively. A statistical analysis shows a mean values of 0.030 Å and 0.026 Å and standard deviations of 0.016 ± 0.004 Å and 0.027 ± 0.006 Å for the differences between calculated and experimental distances using HF and BLYP methods.

Similarly, bond angles have a mean value of 2.4° and standard deviation of 1.854±0.405° at HF level and 2.562° and 1.659±0.362° for BLYP approach. However torsion angles for thymine and furanose rings, and also the hydroxyl group, differ significantly from the experimental structure.

Because of AZT forms a dimer structure through hydrogen bonding interactions, is expected that the structure from gas phase calculation differ from the crystal structure determined by X–ray technique.

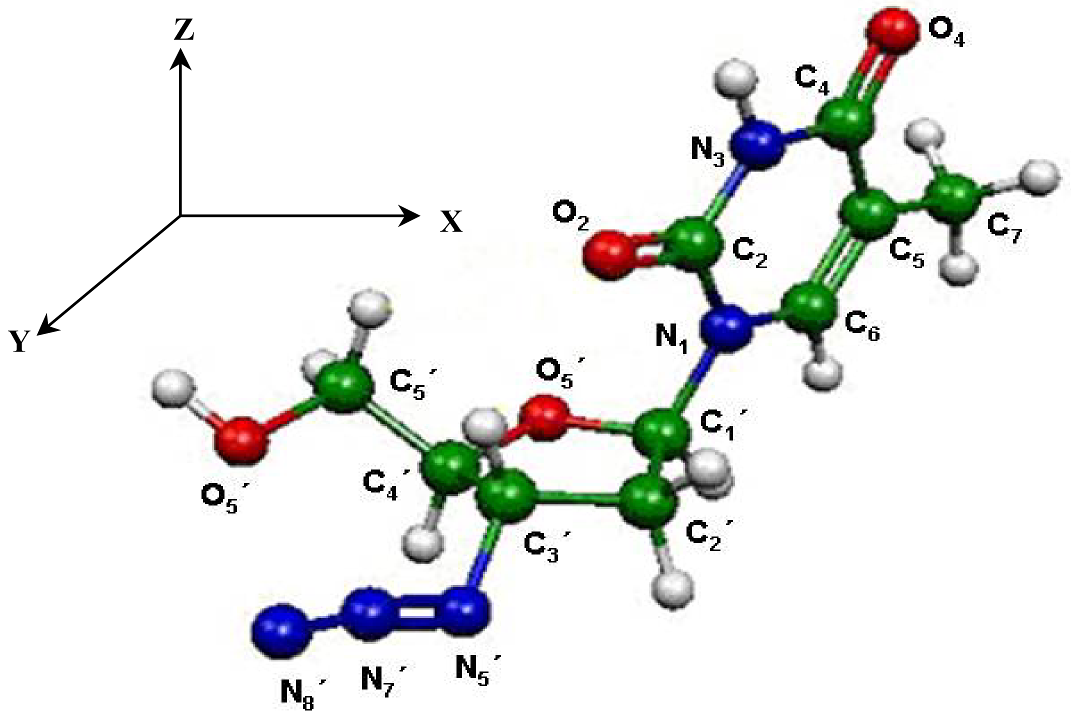

Figure 1. Axis orientation and atom numbering of the geometric structure of AZT optimized at the BLYP/6–31+G(d,p) level.

Theoretically, the structure of AZT has been previously reported using molecular mechanics, semi empirical and *ab initio* methods [5,6,7]. All these conformational studies of AZT showed structural discrepancies with respect to the experiment and other calculations. In this work we have determined the torsion angles C_2–N_1–C_1'–O_4' and C_2–N_1–C_1'–C_2' formed by thymine and furanose rings to be 67.3° and –54.6° at HF level and 70.3° and –52.2° at BLYP approach, which are close to the values report by Dayu and col. of 61.0 and –60.8 at B3LYP/6–31G(d) level (See Table 1). The differences between our values and those reported by Dayu *et al.* can be interpreted in terms of the differences in the basis set and the employed density functional approach.

In the previous semiempirical study of AZT conformation [5], four possibilities for hydrogen bonding were reported, all involving the hydroxyl and furan oxygen groups of furanose ring and hydrogen (H_6) and carbonyl group of thymine ring. Here, we report at *ab initio* and DFT levels a new possible hydrogen bonding for AZT. Our structural conformation leads to an interaction between the O atom of carbonyl group (O_2) of thymine ring and hydrogen atom (H_3') that is bonded to the C_3 atom of the furanose ring. The optimized distances between these atoms are 2.4618 Å and 2.4536 Å at HF and BLYP, respectively.

Table 2. Energy, dipole moment and Mulliken atomic charges of AZT

	HF	BLYP
Energy/Hartrees	–957.9499	–963.2888
μ/Debyes	2.90	3.20
Atom	Charge	Charge
N_1	–0.27	0.08
C_2	1.00	0.63
O_2	–0.60	–0.45
N_3	–0.76	–0.51
C_4	0.30	0.12
O_4	–0.58	–0.47
C_5	0.74	0.97
C_6	–0.47	–0.55
C_7	–0.49	–0.73
$C_{1'}$	0.03	–0.28
$C_{2'}$	–0.13	–0.29
$C_{3'}$	–0.39	–0.21
$C_{4'}$	0.01	0.03
$O_{4'}$	–0.49	–0.26
$C_{5'}$	0.27	–0.10
$O_{5'}$	–0.65	–0.51
$N_{6'}$	–0.58	–0.45
$N_{7'}$	1.04	1.37
$N_{8'}$	–0.36	–0.76

In Table 2 are displayed the total energy, dipole moment and the values of atomic charges of the relevant atoms in the most stable structure of AZT. The atomic symbols follow the notation in Figure 1. It is observed that AZT is a polar molecule with high value of dipole moment in gas phase (3.20 Debyes at the BLYP/6–31+G(d,p) level). This value can be understood in terms of the asymmetry of the charge distribution as is given by the Mulliken atomic charges. For instance, the extremes of the structure of AZT (O_4, $O_5^{'}$ and the region of the azide group) are negative strongly charged. While some internal N and C atoms are charged positively.

3.2 Polarizability Calculations

Table 3 reports the static dipole polarizability α_{xx}, α_{yy}, α_{zz} components and the average polarizability $\bar{\alpha}$ of AZT evaluated at HF, BLYP and B3LYP methods using the 6–31+G(d,p) and 6–311++G(3d,3p) basis sets with optimized geometries. There do not appear to be any corresponding experimental data in the literature, neither are there any other *ab initio* calculations. Additionally, in Table 3 are reported for comparison purposes the polarizability average values calculated with the atomic empiric methods from Miller [20], Thole [21], Thole–Swart [22], optimized Thole–Jensen and modified Thole from Jensen *et al.* [23]. From these empiric methods, the AZT polarizability values range between 166 to 214 au, whereas the corresponding value at HF/6–311++G(3d,3p) level and at the BLYP/6–311++G(3d,3p) and B3LYP/6–311++G(3d,3p) approaches are 157.27, 189.77 au and 182.34 au, respectively.

Table 3. Static dipole electronic polarizability components ($\alpha_{xx}, \alpha_{yy}, \alpha_{zz}$) and average polarizability ($\bar{\alpha}$), in atomic units (au), of AZT at HF, BLYP and B3LYP levels of theory, and the average polarizability obtained with the Thole modified, Thole/Swart, Thole/Jensen and Thole empiric models. %€ corresponds to the percent relative error of $\bar{\alpha}$ from these empiric models with respect to that at B3LYP/6–311++G(3d,3p).

Geometry/Property		HF	BLYP	B3LYP [a]
6–31+G(d,p)//6–31+G(d,p)	α_{xx}	132.31	156.50	–
	α_{yy}	106.58	124.90	–
	α_{zz}	211.45	266.72	–
	$\bar{\alpha}$	150.11	182.70	–
6–31+G(d,p)// 6–311++G(3d,3p)	α_{xx}	138.88	162.91	157.03
	α_{yy}	113.90	132.13	127.80
	α_{zz}	219.03	274.27	262.18
	$\bar{\alpha}$	157.27	189.77	182.34
Atomic Static Polarizability Models				
				%€
Modified Thole Model [b]	$\bar{\alpha}$		214.43	17.6
Thole / Swart Model [c]	$\bar{\alpha}$		210.45	15.4
Thole / Jensen Model [d]	$\bar{\alpha}$		208.21	14.2
Thole Model [e]	$\bar{\alpha}$		200.29	9.8
Miller Model [f]	$\bar{\alpha}$		166.46	–8.7

[a] Geometric structure optimized at BLYP/6–31+G(d,p)

[b] Ref. [23]; [c] Ref. [22]; [d] Ref. [23]; [e] Ref. [21]; [f] Ref. [20]

Inclusion of electron correlation through the BLYP/6–31+G(d,p) procedure increases α_{xx}, α_{yy}, α_{zz}, components and the $\bar{\alpha}$ average by 18%, 17%, 26% and 22%, respectively. While, the extension to the 6–311++G(3d,3p) basis set, the BLYP affects the HF components and the average polarizability in 17%, 16%, 25%, and 21%, respectively. These effects are reduced when the electron correlation effects are considered in the polarizability property with the B3LYP approach, being of 13%, 12%, 20% and 16%, respectively. These results show that the BLYP overestimate the correlation effects in about 4% to 5% with respect to the corresponding B3LYP values. In previous work, it has been shown that the B3LYP/6–311++G(3d,3p) methodology is able to give average values for the molecular polarizability that lies within the 3% of experimental error [9]. In this context, we expect that our best prediction for the AZT polarizability is about 182.34 au, obtained with the mentioned procedure. This result lies in the middle of the range between the smaller and the largest empiric polarizability value, that correspond to the Miller and Thole modified methods, respectively.

In Table 3 also there are reported the relative differences between the AZT best $\bar{\alpha}$ value with those from the empiric methods as %€. The smaller values of %€ corresponds to the Miller method that underestimate the polarizability in about 8.7%, while the variant Thole methods overestimate the polarizability in about 9.8% to 17.6%.

4 CONCLUSIONS

We have calculated the static dipole polarizability of 3$'$–azido–3$'$–deoxythymidine (AZT) molecule by using *ab initio* Hartree–Fock and Density Functional Methods DFT at the BLYP and B3LYP hybrid approaches with 6–311++G(3d,3p) standard basis set. We have used HF/6–31+G(d,p) and BLYP/6–31+g(d,p) optimized geometries, and a vibrational analysis was performed (not reported here) and the nature of the stationary points were characterized as absolute minumum at these levels of theory, that correspond to the most stable conformation of AZT. The comparison with experimental X–ray structure of AZT leads to agreement regarding the bond distances and geometric angles of the thymine, furanose and azide fragments, but discrepancies there exist in the orientation of these groups in the overall structure. For the BLYP/6–31+G(d,p) geometry was found that the predicted value for the B3LYP/6–311++G(3d,3p) static dipole average polarizability $\bar{\alpha}$ is about 182.34 au. The comparison of this value with corresponding from empiric models leads to relative variations that ranges from –9% to 18%. However, according to variations shown in Table 3, the Miller and Thole models give an appropriate interval to define static dipole polarizability of large molecules.

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