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THE COMPARISON OF STRUCTURE AND PROPERTY OF AZT CONFORMERS AND ITS ANALOGUE CS-87 USING DENSITY FUNCTIONAL THEORY CALCULATIONS: A STUDY OF ANTI-AIDS

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ABSTRACT. The compounds 3'-azido-3'-deoxythymidine (AZT), 3'-azido-2',3'-dideoxyuridine (CS-87) are active inhibitors of HIV-1 replication, the causative agents of AIDS. We report Abinitio, DFT results of two AZT conformers; A-AZT and CS-87 by different basis sets and on structural and electronic properties. It is shown that A-AZT and CS-87 are similar in structure and properties. The B-AZT conformer is different from them interestingly and it is predicted that B-AZT is to be the active form of AZT.

KEY WORDS: 3'-Azido-3'-deoxythymidine (AZT), 3'-Azido-2',3'-dideoxyuridine (CS-87), Inhibitors of HIV-1 replication, Causative agents of AIDS, AZT conformers, Abinitio, Density functional theory

INTRODUCTION

Analogues of nucleosides that lack the 3'-hydroxyl group are being studied extensively as potential therapeutic agents for the treatment of acquired immunodeficiency syndrome (AIDS). These compounds have been shown to be effective inhibitors of human immunodeficiency virus type-1 (HIV-1), the causative agents of AIDS [1, 2]. AZT, a thymidine analogue, is an integral component of anti-HIV therapy [3]. Although the drug was developed as an anti-cancer agent in 1964, its poor activity limited the interest in its use as an anti-cancer agent [4]. Pre-clinical evaluation of AZT in combination with other anti-cancer agents especially with thymidylate synthesis inhibitors and immune modulators and its toxicity during anti-AIDS therapy observed during the last decade has received interest in AZT as an anti-proliferate agent. Restoration of sensitivity to cis-platin and MTX in cells resistant to these drugs further suggested that AZT might have potential as an anti-cancer agent, especially when used in combination with other drugs. These studies have led to clinical and pharmacological evaluation of high-dose AZT alone and in combination with thymidylate synthesize inhibitors [5].

AZT, 3'-azido-3'-deoxythimydine (Figure 1) is a thymine analogue where the 3'-hydroxy (OH) group has been replaced by an azido one (N_3). The exact mechanism responsible for AZT's cytotoxicity is not clear. Furman *et al.* [6] have investigated the action mechanism of AZT and found it to be sequentially phosphorilated to the 5'-mono, -di, and -triphosphate analogues. As the tri-phosphate analogue, AZT inhibits the utilization of DTTP by reverse transcripts and may be incorporated in the terminal position of DNA chain and due to the absence of the OH group, thereby preventing elongation. CS-87, 3'-azido-2',3'-dideoxyuridine (Figure 1) were chosen not only because of their structural similarities to AZT but also for their promising biological activities. CS-87 is a potent anti-HIV-1 agent and currently a strong candidate for clinical studies [7].

The knowledge of geometric and conformational structure, electric properties and structure-activity relationships of AZT and related analogues could lead to a comprehensive understanding necessary for the development of effective drugs for the future. From this point of

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view, the computational approach can be a valuable tool to gain insight in the action mechanism of such drugs.

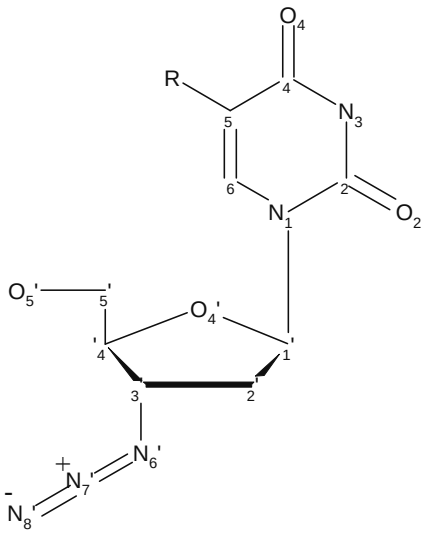

Figure 1. Schematic drawing of AZT (R = CH_3) and CS-87 (R = H).

X-ray crystallography studies show that AZT crystallized in the monoclinic space group $P2_1$ and has A and B conformers [2, 8] (Figure 2). Molecules A and B differ in the mutual orientation of the furanose and uridine rings, in the conformation of the hydroxyl groups and in the puckering of the furanose rings. In A-AZT, C2' is over and C3' is below the C1', C4', O4' plane, while in AZT-B both C2' and C3' are located at the same side of this plane [9]. The previous theoretical studies of conformers of AZT and its analogue have no report on the polarizability [10] or if they have it is without respect to the conformer type [11]. The factors such as dipole and quadrupole moments are very important quantities for determining and estimating lipophilicity of component that rightly related to anticancer and antiviral properties of biomolecules [12, 13]. We have evaluated molecular and electric structure properties of AZT conformers and its analogue using quantum mechanic methods. Usually, B3LYP/6-311++G** is effective in giving satisfactory calculated geometries [14] and the best correlation function on the calculation of the dipole moments for heterocycles molecules is the B3LYP/CBSB7 level, which predicts calculated values in good agreement with experimental spectroscopy data [15]. We have optimized A-AZT, B-AZT and CS-87 at the DFT method using different basis set and compete with experimental data and HF methods.

COMPUTATIONAL DETAILS

Gaussian 98 software package [16] is used to perform density functional theory (DFT) calculations on the compound of interest. The initial geometries were given from crystalline forms [2]. Geometry optimization and total molecular energy calculation (including the moments of molecules) were carried out at the density functional theory (B3LYP) on different basis sets including 6-31G**, 6-31+G**, 6-31++G**, 6-311++G** and CBSB7. Critical limit for geometry optimization and SCF-convergence were 10^{-7} hartree/Bohr and 10^{-9} hartree,

respectively. Structural molecular properties using DFT level were compared with that obtained using HF level [11] and by considering experimental data [2, 8]. Electronic structure properties were obtained at the DFT level and different basis set for optimized conformers of AZT and CS-87. Statistical calculations for obtaining the standard deviation were performed using the SPSS 12.0 for Windows.

RESULTS AND DISCUSSION

In the following sections, structural and electronic properties of two conformers (A and B forms) of AZT and its analogue CS-87 are presented. Such molecules were obtained as a result of the geometry-optimized procedure performed on the forms that exist in crystalline state. Figure 2 shows A-AZT, B-AZT and CS-87 optimized forms.

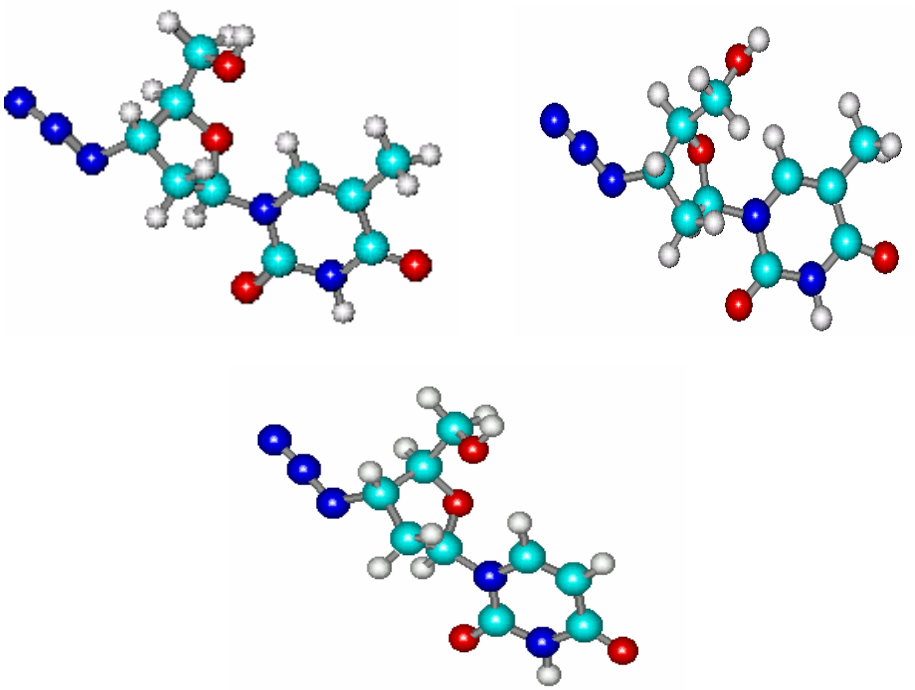

Figure 2. The optimized structures of A-AZT (right), B-AZT (left) and CS-87 (middle) at B3LYP/6-311++G** level.

Relative energetic stability

The molecular energies of the optimized structures were obtained at the density functional theory (B3LYP on different basis set). The molecular energies are listed in Table 1. As can be seen, the energy difference is 4 kcal/mole at the B3LYP levels, conformer A is more stable than conformer B. This case is analogous with the energy difference of crystalline A- and B-AZT forms (single point calculation) but there is a different in quantity of the energy difference (the energy difference of crystalline forms is 13 kcal/mole), resulting of optimization of A- and B-AZT. This is in agreement with biological considerations that the conformation of molecule B-AZT represents the biologically active form of AZT. The total molecular energies with

considering zero point energy of the two optimized structures of AZT were obtained by using of B3LYP/6-31++G** level that is -963.5615 hartree for A-AZT and -963.5558 hartree for B-AZT and the energy difference for two conformers is 3.603 kcal/mole, exactly similar with its quantity in Table 1, and the thermo-chemistry calculation obtains the same results.

Table 1. Total molecular energy (hartree) for the optimized structures of A and B conformers and the energy differences (kcal/mole) at the B3LYP method.

Basis set	A-AZT (hart)	B-AZT (hart)	ΔE (kcal/mole)[b]
B3LYP/6-31G**	-963.5217	-963.5162	3.407
B3LYP/6-31+G**	-963.5610	-963.5552	3.639
B3LYP/6-31++G**	-963.5615	-963.5557	3.603
B3LYP/6-311++G**	-963.7826	-963.7769	3.856
Crys. [a]	-963.4819	-963.4607	13.300

[a] The energies of crystalline A and B forms (B3LYP/6-31G** at the single point calculations). [b] 1 hartree = 207.212 eV = 627.51 kcal/mole.

Internuclear distances

The standard deviations for every method in considering with experimental data in reference 2 (exp. 1) and reference 8 (exp. 2) were calculated by SPSS. The results show the internuclear distances resulted at B3LYP methods are in agreement with experimental data with less standard deviation.

Table 2. Internuclear distances (Å) for the optimized structures of A-AZT conformer.

Group	Exp.1[a]	Exp.2[b]	6-31G**[c]	6-31+G**[c]	6-31++G**[c]	6-311++G**[c]	HF[d]	BLYP[d]
N1-C2	1.318	1.375	1.400	1.398	1.397	1.397	Θ 1.372	Ø 1.413
N1-C6	1.408	1.390	1.387	1.388	1.388	1.383	1.386	Q 1.399
C2-N3	1.391	1.368	1.383	1.383	1.384	1.383	1.368	1.395
C6-C5	1.360	1.337	1.352	1.353	1.354	1.350	1.332	1.367
N3-C4	1.420	1.386	1.406	1.404	1.404	1.405	1.384	1.423
C2-O2	1.253	1.232	1.220	1.223	1.224	1.215	O 1.201	1.238
C5-C7	1.536	1.504	1.501	1.502	1.502	1.501	1.503	1.512
C4-O4	1.252	1.230	1.222	1.227	1.226	1.218	O 1.197	Q 1.239
N1-C1'	1.46	1.468	1.461	1.461	1.461	1.46	1.463	Ø 1.494
C1'-O4'	1.432	1.424	1.429	1.432	1.432	1.432	O 1.391	1.435
O4'-C4'	1.378	1.454	1.430	1.433	1.432	1.431	1.414	1.460
C2'-C3'	1.504	1.520	1.527	1.527	1.528	1.525	1.529	Ø 1.549
C4'-C5'	1.536	1.520	1.524	1.524	1.524	1.522	1.515	1.535
C5'-O5'	1.424	1.422	1.425	1.431	1.430	1.430	O 1.402	Ø 1.448
C3'-N6'	1.487	1.507	1.487	1.487	1.488	1.487	O 1.467	1.495
N6'-N7'	1.232	1.230	1.236	1.236	1.236	1.230	1.231	Ø 1.249
N7'-N8'	1.122	1.135	1.142	1.142	1.143	1.135	O 1.100	Ø 1.159
Std deviation with Exp. 1			0.030	0.030	0.029	0.030	0.030	0.033
Std deviation with Exp. 2			0.013	0.012	0.012	0.013	0.017	0.013

[a] Experimental X-ray diffraction, Ref. [2]. [b] Experimental X-ray diffraction, Ref. [8]. [c] Level of these basis sets is B3LYP. [d] Theoretical values at 6-31+G**, Ref. [11]. O: DFT preference over HF, Θ: HF preference over DFT, Ø: B3LYP preference over BLYP, Q: BLYP preference over B3LYP.

Table 3. Inter nuclear distances (Å) for the optimized structures of B-AZT and CS-87 molecules.

	B-AZT						CS-87				
Group	Exp.1[a]	Exp.2[b]	6-31[c]	6-31+[c]	6-31++[c]	6-311++[c]	Exp.1[a]	6-31[c]	6-31+[c]	6-31++[c]	6-311++[c]
N1-C2	1.302	1.366	1.391	1.390	1.389	1.389	1.381	1.380	1.403	1.403	1.402
N1-C6	1.388	1.380	1.383	1.384	1.384	1.382	1.367	1.380	1.383	1.382	1.380
C2-N3	1.394	1.369	1.382	1.381	1.381	1.380	1.386	1.368	1.383	1.383	1.383
C6-C5	1.378	1.342	1.355	1.357	1.358	1.353	1.361	1.330	1.352	1.352	1.348
N3-C4	1.422	1.399	1.408	1.407	1.408	1.406	1.386	1.388	1.409	1.409	1.410
C2-O2	1.255	1.232	1.224	1.227	1.228	1.220	1.242	1.967	1.223	1.223	1.214
C5-C7	1.509	1.498	1.502	1.504	1.503	1.502					
C4-O4	1.233	1.228	1.223	1.225	1.226	1.219	1.251	1.195	1.224	1.224	1.217
N1-C1'	1.525	1.505	1.491	1.493	1.493	1.494	1.494	1.453	1.463	1.463	1.462
C1'-O4'	1.335	1.405	1.410	1.411	1.412	1.410	1.415	1.402	1.431	1.431	1.430
O4'-C4'	1.490	1.443	1.433	1.436	1.436	1.434	1.438	1.409	1.433	1.433	1.431
C2'-C3'	1.465	1.517	1.533	1.534	1.534	1.532	1.534	1.522	1.527	1.527	1.525
C4'-C5'	1.530	1.521	1.530	1.529	1.529	1.528	1.524	1.516	1.524	1.523	1.522
C5'-O5'	1.441	1.425	1.418	1.423	1.423	1.422	1.475	1.404	1.431	1.431	1.430
C3'-N6'	1.497	1.508	1.484	1.485	1.485	1.483	1.490	1.475	1.487	1.487	1.486
N6'-N7'	1.234	1.211	1.236	1.237	1.237	1.232	1.230	1.229	1.235	1.236	1.231
N7'-N8'	1.115	1.143	1.142	1.142	1.142	1.134	1.152	1.101	1.142	1.143	1.135

[a] Experimental X-ray diffraction, Ref. [2]. [b] Experimental X-ray diffraction, Ref. [8]. [c] Performed at B3LYP/AG** e.g. B3LYP/6-31G**.

As in O assigned rows are seen, the bond distances obtained at DFT level in competition of experimental values is better than data obtained at HF methods except for Θ assigned item. The DFT methods because of considering electron correlations often obtain the better results than HF method. In competing B3LYP and BLYP as in Ø assigned rows are seen B3LYP method has the more accuracy than BLYP except in Q assigned items. As can be inferred from Table 3, DFT results for AZT-B and CS-87 are compatible with experimental data.

The glycoside bond N1-C1' length in B-AZT is 1.49 Å (at the highest level) which is longer than that in A-AZT and CS-87 (1.46 Å). The strain in B-AZT causes this different. The bond distances in atoms of azido group C3'-N6', N6'-N7' and N7'-N8' (1.48, 1.24 and 1.13 Å) are unique in the three molecules and it is indicated that there is the $C{-}N^{-}{-}N^{+}{\equiv}N$ more than $C{-}N{=}N^{+}{=}N^{-}$ resonance forms probably [14]. The bond lengths of C─N, N─N, N=N and N≡N are 1.47, 1.47, 1.24 and 1.10 Å, respectively.

Internal angles

The values of internal angles for two conformers of AZT and its analogue CS-87 are given in Table 4 and 5. As can be inferred from the standard deviations in Table 4 the internal angles resulted at DFT methods are in agreement with experimental data. The angles obtained at DFT level in comparison with experimental values especially in $ assigned rows is better than data obtained at HF methods, except for C2-N1-C6 group. With respect to Table 2 and 4 this matter is especially seen in ribose ring.

Table 4. Internal angles (°) for the optimized structures of A-AZT conformer.

Group	Exp.1[a]	Exp.2[b]	6-31G**[c]	6-31+G**[c]	6-31++G**[c]	6-311++G**[c]	HF[d]	BLYP[d]
C2-N1-C6	119.1	120.9	121.9	121.7	121.7	121.7	120.3	120.7
N1-C2-N3	113.0	114.8	113.3	113.5	113.6	113.3	115.0	113.8
N1-C6-C5	127.4	123.5	123.6	123.8	123.7	123.9	124.8	124.7
N1-C2-O2	121.8	123.2	123.8	123.9	123.9	123.9	123.5	123.7
C2-N3-C4	130.4	127.8	128.7	128.5	128.4	128.7	128.0	128.8
C6-C5-C4	116.5	118.7	118.5	118.3	118.3	118.3	117.3	118.8
C6-C5-C7	125.2	121.8	123.7	123.5	123.5	123.5	124.2	123.3
N3-C4-O4	123.1	120.3	120.5	120.2	120.2	120.4	120.5	120.2
C2-N1-C1'	117.9	120.4	118.1	118.3	118.3	118.4	120.0	120.2
C6-N1-C1'	123.0	118.7	120.0	119.9	119.9	119.8	119.1	118.8
N1-C1'-O4	107.8	107.7	108.6	108.5	108.5	108.6	$ 109.7	109.8
N1-C1'-C2'	110.1	113.4	114.5	114.7	114.7	114.8	$ 116.5	106.5
C1'-O4'-C4'	110.2	111.2	111.2	111.3	111.3	111.2	$ 108.9	111.6
C1'-C2'-C3'	98.8	102.5	102.9	103.1	103.1	103.0	$ 104.9	105.5
O4'-C4'-C3'	104.7	105.0	106.5	106.5	106.5	106.5	106.0	106.6
C2'-C3'-C4'	105.6	104.2	102.6	102.9	102.9	103.0	$ 102.8	103.6
O4'-C4'-C5'	108.1	110.6	110.0	110.0	110.1	110.1	107.5	107.3
C4'-C5'-O5'	113.5	111.2	109.2	109.3	109.3	109.3	$ 106.9	106.3
C2'-C3'-N6'	111.1	107.1	107.9	108.2	108.1	108.2	109.4	109.0
C3'-N6'-N7'	115.0	113.4	115.7	115.6	115.5	115.9	114.4	116.8
N6'-N7'-N8'	173.7	173.5	173.4	173.6	173.7	173.7	$ 174.5	171.6
Std deviation with Exp1			2.59	2.59	2.61	2.57	3.08	3. 08
Std deviation with Exp2			1.25	1.17	1.15	1.20	1.90	2.49

[a] Experimental X-ray diffraction, Ref. [2]. [b] Experimental X-ray diffraction, Ref. [8]. [c] Level of these basis sets is B3LYP. [d] Theoretical values at 6-31+G**, Ref. [11]. $: DFT preference over HF.

For comparing the accuracy of the two experimental data [2, 8] in Table 5 the optimized angles of the cases which are near to the experimental data of reference 8 are assigned with #. Also the standard deviations show it clearly (Table 4). By considering that the structure optimization was performed using the crystalline forms reported in reference 2 (as initial geometries) and this fact that results of optimization often are comparable with A- and B-AZT structures in reference 8, it is inferred that the reference 8 has the more accuracy than the reference 2.

Dihedral angles

The torsion angles for optimized structures of A-, B-AZT and CS-87 are given in Tables 6 and 7. The data in these tables show that the B3LYP method has less standard deviation. A-AZT has two torsion angle C2-N1-C1'-O4' (x = -124^o) and C3'-C4'-C5'-O5' (y = 50.5^o). These values are calculated at B3LYP/6-311++G** level of the theory. B-AZT has x = -172^o and y = 175^o at the same level. These torsions values are specializations of A and B conformers of AZT (reference 9: x = -124^o and y = 51^o for A-AZT and x = -174^o and y = 173^o for B-AZT).

Table 5. Internal angles (°) for the optimized structures of B-AZT and CS-87 molecules.

	B-AZT						CS-87				
Group	Exp.1[a]	Exp.2[b]	6-31[c]	6-31+[c]	6-31++[c]	6-311++[c]	Exp.1[a]	6-31[c]	6-31+[c]	6-31++[c]	6-311++[c]
C2-N1-C6	119.0 #	121.3	122.1	121.8	121.9	121.8	120.2	121.1	121.6	121.6	121.6
N1-C2-N3	114.8	115.5	113.9	114.2	114.2	114.0	116.4	114.6	113.9	113.9	113.7
N1-C6-C5	126.9 #	123.0	123.1	123.3	123.3	123.5	123.1	123.3	122.9	122.9	123.1
N1-C2-O2	119.8 #	121.4	122.5	122.6	122.6	122.7	121.7	123.4	123.4	123.4	123.5
C2-N3-C4	129.8	126.9	128.1	128.0	127.9	128.2	126.2	128.2	128.5	128.5	128.6
C6-C5-C4	117.4	119.2	118.9	118.6	118.6	118.6	119.7	119.5	120.1	120.1	120.1
C6-C5-C7	125.9	118.8	123.3	123.2	123.2	123.1					
N3-C4-O4	123.5 #	119.5	120.3	120.1	120.1	120.2	118.9	120.6	120.3	120.3	120.3
C2-N1-C1'	115.0	115.7	115.1	115.5	115.5	115.6	118.3	118.9	118.3	118.3	118.4
C6-N1-C1'	125.9 #	123.0	122.6	122.4	122.4	122.3	121.4	119.9	120.0	120.0	119.9
N1-C1'-O4	106.8 #	108.4	109.6	109.4	109.4	109.3	109.3	108.4	108.4	108.4	108.5
N1-C1'-C2'	116.9 #	112.1	112.9	113.2	113.2	113.3	112.1	114.7	114.6	114.6	114.8
C1'-O4'-C4'	108.2 #	109.8	111.2	111.5	111.5	111.4	111.4	111.9	111.3	111.4	111.2
C1'-C2'-C3'	114.1 #	103.2	103.9	103.8	103.8	103.7	101.1	103.2	103.1	103.1	103.0
O4'-C4'-C3'	107.3 #	103.3	104.7	104.7	104.7	104.7	104.3	106.3	106.4	106.4	106.4
C2'-C3'-C4'	93.3 #	102.5	102.2	102.4	102.4	102.4	103.1	102.5	102.9	102.9	102.9
O4'-C4'-C5'	110.1 #	111.6	112.3	112.4	112.4	112.5	110.7	109.6	110.1	110.1	110.1
C4'-C5'-O5'	112.0	111.1	112.3	112.4	112.4	108.0	112.5	109.3	109.2	109.3	109.3
C2'-C3'-N6'	107.2	107.8	107.8	108.1	108.1	108.2	108.2	107.7	108.1	108.1	108.1
C3'-N6'-N7'	115.2	115.8	115.6	115.5	115.5	115.9	116.6	113.6	115.7	115.6	115.9
N6'-N7'-N8'	173.2	173.7	173.3	173.5	173.5	173.6	173.5	173.6	173.6	173.6	173.7

[a] Experimental X-ray diffraction, Ref. [2]. [b] Experimental X-ray diffraction, Ref. [8]. [c] Performed at B3LYP/AG** e.g. B3LYP/6-31G**. #: Ref. [8] preference over Ref. [2].

Table 6. Dihedral angles (°) for the optimized structures of A-AZT conformer.

Group	Exp.1[a]	6-31G**[c]	6-31+G**[c]	6-31++G**[c]	6-311++G**[c]		HF[d]	BLYP[d]
N1-C2-N3-C4	-2.4	-0.6	-0.4	-0.3	-0.5		2.8	2.4
N1-C6-C5-C4	-0.6	0.6	0.5	0.4	0.5		-1.1	-0.8
N3-C2-N1-C6	1.0	1.4	1.0	1.0	1.3		-4.2	-3.4
C2-N1-C6-C5	0.3	-1.5	-1.2	-1.1	-1.4		3.6	2.8
O2-C2-N3-C4	177.2	-179.8	-179.7	-176.6	-179.7		-178.0	-178.1
O2-C2-N1-C1'	-0.3	-2.1	-2.3	-2.2	-2.6		5.9	4.1
C2-N1-C1'-O4'	-123.3	-126.0	-125.0	-125.2	-124.0	$	67.3	70.3
C2-N1-C1'-C2'	17.8	116.2	117.3	117.1	118.3	$	-54.6	-52.2
N1-C1'-O4'-C4'	-133.6	-141.5	-142.5	-142.5	-143.1		-133.8	-138.9
O5'-C5'-C4'-O4'	-67.6	-70.1	-69.2	-69.2	-69.3	$	-179.7	175.7
C3'-C4'-C5'-O5'	48.5	49.5	50.6	50.6	50.5	$	-62.0	-65.9
C2'-C3'-N6'-N7'	177.5	173.9	171.5	171.4	172.1		146.9	148.2
C1'-C2'-C3'-C4'	-33.1	-31.9	-30.9	-30.9	-31.1	$	21.3	21.2
C2'-C3'-C4'-O4'	-7.8	-2.6	-1.0	-0.9	-0.6	$	20.6	15.1
C4'-O4'-C1'-C2'	-14.1	-18.2	-19.1	-19.3	-19.6		-6.5	-1.3
O4' C1'-C2'-C3'	29.3	31.4	31.3	31.4	31.7	$	-10.3	-13.1
Std deviation with Exp1		24.5	25.0	25.0	25.2		35.3	33.96

[a] Experimental X-ray diffraction, Ref. [2]. [b] Experimental X-ray diffraction, Ref. [8]. [c] Level of these basis sets is B3LYP. [d] Theoretical values at 6-31+G**, Ref. [11]. $: B3LYP preference over two other.

In A-AZT and CS-87, quantity of the calculated glycoside torsion angle, (x = -124^o) is quite normal for a deoxynucleoside, but interestingly this parameter in conformer B is -172^o and unusual. This imposes significant changes in the geometry of molecule B. In a report on 138 uridine analogues only two structures are listed with a furanose ring in a similar conformation [18]. Furthermore, the gycosidic bond N1-C1' (1.494 Å) in B conformer is longer than the one in molecule A and CS-7 (1.46 Å). The strain also causes an increase of the optimized bond angle C6-N1-C1' to 122.3°, as compared to 119.8° in molecule A. (see Table 4 and 5).

The conformation of azido group is similar in three molecules, the torsion angles C2'-C3'-N6'-N7' being 171 to 175°. The $ assigned items show results that B3LYP is responsible better than two other methods.

Table 7. Dihedral angles (°) for the optimized structures of B-AZT and CS-87 molecules.

	B-AZT					CS-87				
Group	Exp.1[a]	6-31[b]	6-31+[b]	6-31++[b]	6-311++[b]	Exp.1[a]	6-31[b]	6-31+[b]	6-31++[b]	6-311++[b]
N1-C2-N3-C4	0.9	-0.8	-1.3	-1.2	-1.5	3.8	-0.2	-0.2	-0.3	0.4
N1-C6-C5-C4	0.4	1.0	0.9	0.9	0.9	-0.3	0.6	0.5	0.5	0.5
N3-C2-N1-C6	-0.4	2.1	2.6	2.6	3.0	-1.3	0.7	0.9	1.0	1.3
C2-N1-C6-C5	-0.3	-2.3	-2.6	-2.6	-2.9	-0.2	-1.0	-1.1	-1.1	-1.4
O2-C2-N3-C4	179.7	179.7	179.1	179.2	178.9	-176.8	-179.5	-179.7	-179.7	-179.8
O2-C2-N1-C1'	-2.7	-3.2	-3.2	-3.0	-3.1	4.5	-2.3	-2.5	-2.5	-2.8
C2-N1-C1'-O4'	-173.2	-170.3	-170.9	-170.9	-171.8	-159.9	-130.2	-125.7	-125.8	-124.3
C2-N1-C1'-C2'	70.4	70.4	70.0	69.9	68.9	82.3	112.7	116.7	116.6	118.0
N1-C1'-O4'-C4'	-114.2	-116.0	-117.6	-117.8	-117.7	-135.5	-145.4	-141.7	-141.8	-142.5
O5'-C5'-C4'-O4'	52.9	55.7	56.0	56.3	56.9	-61.2	-67.7	-68.7	-68.7	-68.8
C3'-C4'-C5'-O5'	173.5	173.3	173.7	173.9	174.6	56.8	51.5	51.0	51.0	51.0
C2'-C3'-N6'-N7'	-178.8	177.2	175.0	175.6	175.4	172.5	168.9	171.4	171.3	172.1
C1'-C2'-C3'-C4'	-29.4	-28.5	-28.6	-28.7	-28.8	-36.3	-31.6	-31.1	-31.1	-31.2
C2'-C3'-C4'-O4'	33.8	33.1	32.2	32.2	32.4	28.8	19.7	21.1	21.0	20.9
C3'-C4'-O4'-C1'	-30.2	-25.5	-24.0	-23.9	-24.1	-9.6	1.6	-1.8	-1.6	-1.3
C4'-O4'-C1'-C2'	10.3	6.8	5.4	5.2	5.3	-14.2	-22.4	-18.4	-18.6	-19.0
O4' C1'-C2'-C3'	14.1	14.7	15.5	15.7	15.7	31.4	33.6	31.0	31.1	31.5

[a] Experimental X-ray diffraction, Ref. [2]. [b] Performed at B3LYP/AG**, e.g. B3LYP/6-31G**.

Intramolecular hydrogen bonding

Table 8 gives the values of distances and angles for intramolecular hydrogen bonding from the experiment and theoretical calculation. In conformer A, the C6-H group forms an intramolecular hydrogen bond with the hydroxyl oxygen O5'. The length of this hydrogen bonding is decreased by calculation and goes toward involving C6-H group with ribose oxygen, O4'. Neither experiment nor calculation is shown O5-H...O4' intramolecular hydrogen bonding in A conformer. For B-AZT both the C6-H...O4' and C6-H...O5' intramolecular hydrogen bonds are postulated. This fact is in agreement with calculation. Intramolecular hydrogen bonding in CS-87 molecule is not reported in the literature but the calculation showed the intramolecular hydrogen bonding in C6-H...O5' position for CS-87 molecule.

Table 8. Distances and angles for intramolecular hydrogen bonds.

	Crystal		B3LYP/6-311++G**	
D A	H...A dist.[a] (Å)	D-H...A ang.[a] (°)	H...A dist (Å).	D-H...A ang. (°)
A-AZT: C6-H . . .O5'	1.99(2.06)[b]	161.3 (175)[b]	2.44	161.8
A-AZT: C6-H . . .O4'	2.764	88.2	2.58	92.8
A-AZT: O5-H . . .O4'	3.79	25.0	3.77	24.3
B-AZT: C6-H . . .O4'	2.37 (2.19)[b]	97.4 (106)[b]	2.23	103.8
B-AZT: C6-H . . .O5'	2.34 (2.34)[b]	139.7 (144)[b]	2.6	149.5
CS-87: C6-H . . .O5'			2.41	161.7
CS-87: C6-H . . .O4'			2.6	92.5

[a] Experimental X-ray diffraction, Ref. 2. [b] Quantities in parentheses, Ref. 8.

Molecular moments

For obtaining of molecular moments, B3LYP/6-311++G** and also B3LYP/CBSB7 level, a sufficient level for description of the total dipole moments of heterocycles are used [15]. The B-AZT molecule has lower dipole and higher quadrupole moment related to the other two molecules and it is seems to have higher lipophilicity, resulting in the highest antiviral property. The property of lipophilicity causes to diffuse the antiviral molecule from cellular membrane to cytoplasm and effective activity of the molecule.

Table 9. Calculated total dipole (debye) and quadrupole moments at B3LYP method.

	A-AZT	B-AZT	CS-87
μ (6-311++G**)	6.90	5.42	6.96
μ (CBSB7)	6.59	5.26	6.68
XX(6-31++G**)	-140.3	-142.67	-136.19
YY(6-31++G**)	-106.3	-111.2	-99.5
ZZ(6-31++G**)	-110.5	-108.13	-104.4
α (6-31++G**)	-119.0	-120.7	-113.4
XX(CBSB7)	-136.4	-138.6	-131.8
YY(CBSB7)	-104.0	-108.8	-97.2
ZZ(CBSB7)	-109.4	-107.2	-103.2
α (CBSB7)	-116.6	-118.2	-110.7

α: the middle of XX,YY and ZZ.

CONCLUSION

The conformer A of AZT and CS-87 molecule are usual and similar in most of the properties such as N1-C1' distance, C6-N1-C1'-O4' torsion, intramolecular hydrogen bonding, atomic charges and dipole moment and probably have the same therapeutic properties. The structural similarity can be seen in Figure 2 clearly.

B-AZT conformer is different from the other two molecules, interestingly. The energy difference of two AZT conformers has shown the higher energy for B-AZT and it seems that conformation of molecule B-AZT represents the active form of AZT.

B-AZT has a C2-N1-C1'-O4'(x) torsion angle of 172° whereas only two of the 138 uridine analogues have this quantity of x. Furthermore, the gycosidic bond N1-C1' (1.494 Å) in B conformer is longer than the one in molecule A and CS-7 (1.46 Å). The strain also causes an increase of the optimized bond angle C6-N1-C1' to 122.3°, as compared to 119.8° in molecule A. These parameters further increase the potential energy of molecule B. Also this molecule has lower dipole and higher quadrupole moment related to the other two molecules and it is seems to have higher lipophilicity resulting in the highest antiviral property. The property of lipophilicity

causes to diffuse the antiviral molecule from cellular membrane to cytoplasm and results effective activity of the biochemistry molecule, and this fact is also shown that B-AZT has the highest activity in comparison to the other two molecules in bioenvironmental systems.

The azido group is relatively similar in three molecules in view of bond lengths, angles, torsion angles and atomic charges. As considering bond distances between C3, N6', N7' and N8', there are $C{-}N^{-}{-}N^{+}{\equiv}N$ and $C{-}N{=}N^{+}{=}N^{-}$ resonance forms.

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