Computational Study of Some Double Headed Acyclo-C-Nucleosides

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ABSTRACT. In the present paper we have a focus in a study of theoretical characterization of three double headed acyclo-C-nucleosides, which are a recent target of experimental studies. The structural and electronic properties of double headed acyclo-C-nucleosides, 1,4-bis(3-mercapto-1*H*-1,2,4-triazol-5-yl)butane-1,2,3,4-tetrol, 1,4-bis(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)butane-1,2,3,4-tetrol and 5,5'-(1,2,3,4-tetrahydroxybutane-1,4-diyl)bis(1,3,4-oxadiazole-2(3*H*)-thione), have been investigated theoretically by performing semi-empirical molecular orbital, ab initio Hartree-Fock (HF) and Density Functional Theory (DFT) calculations. Geometries of the three molecules are optimized at the level of Austin Model 1 (AM1). The electronic properties and relative energies of the molecules have been calculated by HF and DFT in the ground state.

1. INTRODUCTION

Many important advances have occurred in the field of acyclo-nucleosides [1,2] and C-nucleosides.[3-10] Indeed, the modern structural features of nucleosides are somewhat different from those present in poly-ribonucleotides RNA and DNA,[11] by means of variations in sugar, heterocyclic moieties and the various modes of attachments between the two major components (sugar and heterocycle).

The literature of the new kinds of nucleosides is increasing and a lot of variations and kinds of nucleosides with dinuclear nucleosides [12,13] and others were also reported.[14,15]

The wide occurrences of heterocyclic compounds in bioactive natural products and pharmaceuticals have made them as important synthetic targets. The 1,2,4-triazoles and 1,3,4-oxadiazoles represent classes of heterocyclic compounds of great importance in biological chemistry.[16-19] The therapeutic effects of compounds containing 1,2,4-triazole and 1,3,4-oxadiazole rings have been well studied for a number of pathological conditions.

1,2,4-triazoles and their derivatives are found to be associated with various biological activities such as anticonvulsant,[20,21] antifungal,[22-24] anticancer,[25-28] anti-inflammatory [29-31] and antibacterial properties.[32-34] Also, a series of 1,2,4-triazole derivatives have been patented and extensively employed in agriculture.[35]

Derivatives of 1,3,4-oxadiazole have been found to possess a wide spectrum of pharmacological, medical, and biological activities.[36,37]

In this study, double headed acyclo-C-nucleosides bearing 1,2,4-triazole and 1,3,4-oxadiazole rings, 1,4-bis(3-mercapto-1*H*-1,2,4-triazol-5-yl)butane-1,2,3,4-tetrol (**1**), 1,4-bis(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)butane-1,2,3,4-tetrol (**2**), and 5,5'-(1,2,3,4-tetrahydroxybutane-1,4-diyl)bis(1,3,4-oxadiazole-2(3*H*)-thione) (**3**) (Figure 1.), tested *in vitro* against some gram positive and gram negative bacteria,[38] have been investigated theoretically by performing semi-empirical molecular orbital, ab initio Hartree-Fock (HF) and Density Functional Theory (DFT) calculations.

Because of the antibacterial activity of these double headed acyclo-C-nucleosides, we have investigated the structural features and electronic properties theoretically in this work.

Fig. 1. Chemical structures of the studied molecules

2. COMPUTATIONAL METHODS

All theoretical calculations in this work were performed using the computational methods implemented in the GAUSSIAN09 package.[39] Geometry optimization of the studied compounds was done by performing the semi-empirical molecular orbital theory at the level AM1. The electronic properties have been calculated by applying ab initio Hartree-Fock (HF) calculations with 6-31+G(d,p) basis set and the Density Functional Theory (DFT) at the B3LYP/6-31+G(d,p) levels of theory. The hybrid Becke 3-Lee–Yang–Parr (B3LYP) exchange correlation functional was applied for DFT calculations.[40,41]

3. RESULTS AND DISCUSSION

Some molecular data for the studied molecules are given in Table 1.

Table 1. Some molecular data for the compounds studied

Molecules	(1)			(2)			(3)		
Chemical formula	$C_8H_{12}N_6O_4S_2$			$C_8H_{14}N_8O_4S_2$			$C_8H_{10}N_4O_6S_2$		
Quantity	Value			Value			Value		
	AM1	HF	DFT	AM1	HF	DFT	AM1	HF	DFT
Electrons	110	166	166	122	182	182	110	166	166
Doubly occupied levels	55	83	83	61	91	91	55	83	83
Total orbitals	92	448	448	102	496	496	90	438	438

The optimized structures of the studied molecules are shown in Figure 2.

Fig. 2. Optimized structures of the studied molecules
(Optimization performed by AM1 method)

The geometry optimizations of AM1 method yield non-planar structures for the molecules **1**, **2** and **3**.

The optimized structure parameters of each double headed acyclo-C-nucleoside by HF and DFT levels with 6-31+G(d,p) basis set are listed in Tables 2, 3 and 4, in accordance with the atom numbering scheme given in Figures 3, 4 and 5 respectively.

From the theoretical values it is found that general geometries of carbon chain moieties of the three molecules gave almost similar bond lengths, whereas the torsion angle C1-C2-C3-C4, is 164.272° (HF) and 164.064° (DFT), for the molecule **1**, -169.763° (HF) and -169.619° (DFT) for the molecule **2** and 85.244° (HF) and 85.003° (DFT) for the molecule **3**.

Fig. 3. Atom numbering adopted in this study for molecule **1**

Fig. 4. Atom numbering adopted in this study for molecule **2**

Fig. 5. Atom numbering adopted in this study for molecule **3**

The total energy, highest occupied and the lowest unoccupied molecular orbital (HOMO and LUMO, respectively) energies, energetic gap (LUMO–HOMO, ΔE) and the dipole moment μ (in Debyes) for the studied molecules are given in Table 5.

The molecule **1** has a total energy value of -1731.121 a.u. by HF and -1737.159 a.u. by DFT methods. The ΔE (LUMO – HOMO gap) of this molecule is 0.401 a.u. (HF) and 0.206 a.u. (DFT), the resultant dipole moment is 3.0 Debyes by HF and DFT methods.

The total energy of the molecule **2** is -1841.089 a.u. by HF and -1848.510 a.u. by DFT methods. This molecule needs energy of 0.378 a.u. according to HF calculations and 0.195 a.u. according to DFT calculations to reach the excited state. The resultant dipole moment is 6.8 and 7.0 Debyes by HF and DFT methods respectively.

Table 2. Geometrical parameters optimized of molecule 1

	HF/ 6-31+ G(d,p)	DFT/ 6-31+ G(d,p)
Bond lengths (Å°)		
Chain :		
C9-C1	1.507	1.502
C1-C2	1.528	1.537
C2-C3	1.536	1.542
C3-C4	1.530	1.538
C4-C14	1.509	1.507
C1-O8	1.411	1.445
C2-O5	1.403	1.428
C3-O6	1.407	1.434
C4-O7	1.392	1.416
Ring : A		
C9-N11	1.322	1.347
N11-N13	1.345	1.358
N13-C12	1.295	1.330
C12-S19	1.758	1.765
C12-N10	1.352	1.363
N10-C9	1.306	1.330
Ring : B		
C14-N16	1.322	1.344
N16-N18	1.349	1.365
N18-C17	1.293	1.327
C17-S20	1.758	1.765
C17-N15	1.354	1.366
N15-C14	1.304	1.327
Bond angle (°)		
N13-C12-S19	124.481	123.976
N18-C17-S20	124.603	124.189
C1-C9-N10	122.754	123.760
C4-C14-N15	122.944	123.009
Dihedral angle (°)		
C2-C1-C9-N10	161.166	157.741
C3-C4-C14-N15	137.453	136.960
C1-C2-C3-C4	164.272	164.064

Table 3. Geometrical parameters optimized of molecule2

	HF/ 6-31+ G(d,p)	DFT/ 6-31+ G(d,p)
Bond lengths (Å°)		
Chain :		
C9-C1	1.500	1.497
C1-C2	1.540	1.552
C2-C3	1.530	1.537
C3-C4	1.537	1.548
C4-C14	1.504	1.503
C1-O8	1.403	1.431
C2-O5	1.407	1.432
C3-O6	1.405	1.429
C4-O7	1.403	1.432
Ring : A		
C9-N11	1.365	1.380
N11-N19	1.383	1.403
N11-C13	1.354	1.370
C13-S20	1.755	1.761
C13-N12	1.283	1.314
N12-N10	1.367	1.386
N10-C9	1.280	1.311
Ring : B		
C14-N15	1.363	1.377
N15-N21	1.383	1.403
N15-C17	1.356	1.373
C17-S22	1.754	1.758
C17-N18	1.283	1.314
N18-N16	1.367	1.383
N16-C14	1.281	1.312
Bond angle (°)		
N11-C13-S20	122.291	121.879
N15-C17-S22	122.241	121.799
C1-C9-N11	126.900	126.587
C4-C14-N15	125.675	126.199
Dihedral angle (°)		
C2-C1-C9-N10	97.299	100.137
C3-C4-C14-N16	-16.196	-19.880
C1-C2-C3-C4	-169.763	-169.619

Table 4. Geometrical parameters optimized of molecule3

	HF/ 6-31+ G(d,p)	DFT/ 6-31+ G(d,p)
Bond lengths (Å°)		
Chain :		
C9-C1	1.505	1.506
C1-C2	1.537	1.548
C2-C3	1.543	1.549
C3-C4	1.541	1.550
C4-C14	1.507	1.506
C1-O8	1.384	1.407
C2-O5	1.396	1.419
C3-O6	1.404	1.429
C4-O7	1.388	1.414
Ring : A		
C9-O10	1.350	1.369
O10-C12	1.343	1.387
C12-S19	1.649	1.644
C12-N13	1.325	1.356
N13-N11	1.368	1.378
N11-C9	1.258	1.288
Ring : B		
C14-O16	1.348	1.366
O16-C18	1.350	1.398
C18-S20	1.641	1.636
C18-N17	1.328	1.358
N17-N15	1.367	1.376
N15-C14	1.258	1.288
Bond angle (°)		
O10-C12-S19	125.557	125.744
O16-C18-S20	125.275	125.408
C1-C9-N11	129.117	128.246
C4-C14-N15	127.078	125.991
Dihedral angle (°)		
C2-C1-C9-O10	60.187	62.016
C3-C4-C14-O16	-43.302	-43.022
C1-C2-C3-C4	85.244	85.003

Table 5. The Total energy, MO energy of HOMO, LUMO, ΔE (in a.u.) and the dipole moment, μ (in Debye) for the studied molecules

Molecule	Method	Total energy	HOMO	LUMO	ΔE	μ
1	HF/6-31+G(d,p)	-1731.121	-0.346	0.055	0.401	3.023
	DFT/6-31+G(d,p)	-1737.159	-0.244	-0.038	0.206	2.967
2	HF/6-31+G(d,p)	-1841.089	-0.333	0.045	0.378	6.812
	DFT/6-31+G(d,p)	-1848.510	-0.236	-0.041	0.195	6.972
3	HF/6-31+G(d,p)	-1770.744	-0.327	0.044	0.371	3.627
	DFT/6-31+G(d,p)	-1777.587	-0.233	-0.062	0.171	4.029

For the molecule **3**, the total energy value is -1770.744 a.u. by HF and -1777.587 a.u. by DFT methods. The ΔE (LUMO – HOMO gap) of this molecule is 0.371 a.u. (HF) and 0.171 a.u. (DFT), the resultant dipole moment is 3.6 Debyes according to HF calculations, while the calculated value according to DFT calculations is 4.0 Debyes.

The calculated dipole moments by the two methods indicate that each studied molecule is polar (hydrophilic) and active, and may interact with its environment strongly in solution. The high dipole moment value of the molecule **2** may make this double headed acyclo-C-nucleoside most reactive and attractive for the interaction with others systems than the molecules **1** and **3**.

The spatial distributions of HOMO and LUMO are shown in Figures 6, 7 and 8.

In general, HF and DFT methods give similar HOMO and LUMO orbitals.

According to DFT calculations, for the first molecule, the HOMO orbital is mainly localized on the two triazol rings (Ring A and B), while the LUMO orbital is mainly localized on triazol ring (Ring A) and around carbon chain.

For the second molecule, the HOMO orbital is mainly localized on amino-triazol ring (Ring A), while the LUMO orbital is mainly localized around carbon chain and on amino-triazol ring (Ring B).

However, for the molecule **3**, the HOMO orbital is mainly localized on the oxadiazol ring (Ring A). In contrast, the LUMO orbital is mainly localized on oxadiazol ring (Ring B) in molecule **3**.

Fig. 6. 3D HOMO and LUMO plots of the molecule **1** (HF and DFT results).

Fig. 7. 3D HOMO and LUMO plots of the molecule 2 (HF and DFT results).

Fig. 8. 3D HOMO and LUMO plots of the molecule 3 (HF and DFT results).

This means that these molecules don't have the same reactivity in the ground and excited states, and may be more active in the excitation state.

In order to probe the electronic differences between the molecules **1**, **2** and **3**, an electrostatic surface potential (ESP) was generated. Figures 9, 10 and 11 display the ESP surface of these molecules. The gross molecular electron distribution is relatively similar with a few key differences.

Fig. 9. The electrostatic potential energy surface of the molecule **1** (HF and DFT results).

Fig. 10. The electrostatic potential energy surface of the molecule **2** (HF and DFT results).

Fig. 11. The electrostatic potential energy surface of molecule **3** (HF and DFT results).

Regions colored red indicate negative ESP values and regions colored blue indicate positive values of the ESP with green being zero ESP.

1,4-bis(3-mercapto-1*H*-1,2,4-triazol-5-yl)butane-1,2,3,4-tetrol (1**):** The geometry optimization of AM1, HF and DFT methods yields a non-planar structure for the molecule **1**.

In this molecule, some of the carbon atoms have positive excess charge, some of them have negative excess charge, the magnitude of positive charges vary from + 0.046 to + 0.937 (HF) and + 0.113 to + 0.406 (DFT), whereas the magnitude of negative charges vary from - 0.296 to - 0.148 (HF) and - 0.277 to - 0.034 (DFT). All the oxygen atoms have negative excess charge, their

magnitude vary from - 0.706 to - 0.613 (HF) and - 0.632 to - 0.524 (DFT). Similar to oxygen atoms, all the nitrogen atoms have negative excess charge, their magnitude vary from - 0.395 to - 0.143 (HF) and - 0.318 to - 0.084 (DFT). The sulfur atoms have positive excess charge, their magnitude vary from + 0.041 to + 0.052 (HF) and + 0.110 to + 0.124 (DFT). Finally, all the hydrogen atoms have positive excess charge, their magnitude vary from + 0.054 to + 0.442 (HF) and + 0.077 to + 0.427 (DFT).

1,4-bis(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)butane-1,2,3,4-tetrol (2): Similar to the molecule **1**, the geometry optimization of AM1, HF and DFT methods yields also a non-planar structure for the molecule **2**.

For the carbon atoms, some of the carbon atoms have positive excess charge, the others have negative excess charge. According to HF calculations, the magnitude of positive charges vary from + 0.035 to + 0.961, whereas the magnitude of negative charges vary from - 1.109 to - 0.427. However, by DFT calculations, the magnitude of positive charges vary from + 0.013 to + 0.547, whereas the magnitude of negative charges vary from - 1.077 to - 0.088. All the oxygen atoms have negative excess charge, their magnitude vary from - 0.713 to - 0.611 (HF) and - 0.616 to - 0.536 (DFT). For the nitrogen atoms, some of the nitrogen atoms have positive excess charge, the others have negative excess charge. The magnitude of positive charges vary from + 0.026 to + 0.247 (HF) and + 0.107 to + 0.381 (DFT). However, the magnitude of negative charges vary from - 0.897 to - 0.096 (HF) and - 0.888 to - 0.071 (DFT). The sulfur atoms have positive excess charge, their magnitude vary from + 0.013 to + 0.082 (HF) and + 0.080 to + 0.150 (DFT). Finally, the hydrogen atoms have positive excess charge, their magnitude vary from + 0.068 to + 0.451 (HF) and + 0.088 to + 0.429 (DFT).

5,5'-(1,2,3,4-tetrahydroxybutane-1,4-diyl)bis(1,3,4-oxadiazole-2(3*H*)-thione) (3): For the molecule **3**, the geometry optimization of AM1, HF and DFT methods yields also a non-planar structure.

For the carbon atoms, some of the carbon atoms have positive excess charge, the others have negative excess charge. The magnitude of positive charges vary from + 0.015 to + 0.704 (HF) and + 0.050 to + 0.255 (DFT). However, the magnitude of negative charges vary from - 0.437 to - 0.173 (HF) and - 0.080 to - 0.065 (DFT). The oxygen atoms have negative excess charge, their magnitude vary from - 0.670 to - 0.316 (HF) and - 0.581 to - 0.206 (DFT). For the nitrogen atoms, one of them has positive excess charge, the others have negative excess charge. According to HF calculations, the value of positive charge is + 0.022, the magnitude of negative charges vary from - 0.523 to - 0.013. However, by DFT calculations, the value of positive charge is + 0.028, the magnitude of negative charges vary from - 0.425 to - 0.025. The sulfur atoms, have negative excess charge, their magnitude vary from - 0.323 to - 0.280 (HF) and - 0.084 to - 0.039 (DFT). Finally, the hydrogen atoms have positive excess charge, their magnitude vary from + 0.130 to + 0.422 (HF) and + 0.145 to + 0.400 (DFT).

The large charge accumulation takes place on the oxygen and nitrogen atoms. These results shown that oxygen and nitrogen atoms have more negative excess charges in compare with other atoms. This means that oxygen and nitrogen atoms undergo protonation reaction with acidic reagents.

4. CONCLUSION

In conclusion, the theoretical study of double headed acyclo-C-nucleosides, 1,4-bis(3-mercapto-1*H*-1,2,4-triazol-5-yl)butane-1,2,3,4-tetrol (**1**), 1,4-bis(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)butane-1,2,3,4-tetrol (**2**) and 5,5'-(1,2,3,4-tetrahydroxybutane-1,4-diyl)bis(1,3,4-oxadiazole-2(3*H*)-thione) (**3**), indicates that these molecules are polar and active molecules, and may interact with its environment strongly in solution. The indications reveal useful information about the

reactivity of such molecules and about the active sites in the molecules; also, clarify the sites of molecules which undergo nucleophilic substitution or electrophilic substitution reactions.

However, further work is necessary to complete a full analysis of these double headed acyclo-C-nucleosides at a higher level of theory. The relationship between structure and biological activity of variety of double headed acyclo-C-nucleosides, appears to be one of the next logical steps.

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