



Computational study on the geometry optimization and excited-state properties triamterene by ArgusLab 4.0.1 software

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ABSTRACT

6-phenylpteridine-2,4,7-triamine (Triamterene) is used in the treatment of edema associated with congestive heart failure. Conformational analysis and geometry optimization of triamterene was performed according to the Hartree-Fock (HF) calculation method by ArgusLab 4.0.1 software. Heat of Formation of procarbazine was 764.8268 kcal/mol, the steric energy calculated for procarbazine was 0.05130821 a.u. (32.19641689 kcal/mol) and SCF energy was found to be -108.6545111064 au(-68181.7966 kcal/mol), which is the most feasible position for the drug to interact with the receptor.

Key words: Triamterene, Molecular mechanics, Arguslab software.

INTRODUCTION

6-phenylpteridine-2,4,7-triamine (Triamterene) is used in the treatment of edema associated with congestive heart failure, cirrhosis of the liver and the nephrotic syndrome[1]. Triamterene has a unique mode of action; it inhibits the reabsorption of sodium ions in exchange for potassium and hydrogen ions at that segment of the distal tubule under the control of adrenal mineralocorticoids (especially aldosterone)[2]. Triamterene occasionally causes increases in serum potassium which can result in hyperkalemia[3]. Molecular surface charges of drugs determines the level of interaction of the drugs with the receptor, these charges are partial atomic charges obtained from calculations carried out by the methods of computational chemistry which can be used to characterize the electronic charge distribution in a molecule and the bonding, antibonding, or nonbonding nature of the molecular orbitals for particular pairs of atoms[4-6]. To develop the idea of these populations, a real, normalized molecular orbital composed from two normalized atomic orbitals is taken into consideration by calculating the density matrix terms. From this calculations the difference between the number of electrons on the isolated free atom, and the gross atom population gives the values of the Mulliken charges[7-8]. ZDO charges can also be generated from Argus lab using the AM1 parameterized method. In the zero differential overlap (ZDO) approximation, the product of two different atomic orbitals is set to zero. The integral which survives the ZDO approximation was partly computed using the uniform charge sphere and the rest parameterized. The energies computed by molecular mechanics are usually conformational energies[9]. This means that the energy computed is meant to be an energy that will reliably predict the difference in energy from one conformation to the next.

MATERIALS AND METHODS

All conformational analysis (geometry optimization) study was performed on a window based computer using Argus Lab 4.0.1, molegro molecular viewer and ACD Lab Chem Sketch software. Triamterene structure was sketched with ACD Lab Chem Sketch software and saved as MDL molfiles (*.mol). The 6-phenylpteridine-2,4,7-triamine (Triamterene) structure was generated by Argus lab, and minimization was performed with UFF molecular mechanics method [10-12]. The minimum potential energy was calculated by using geometry convergence function

in Argus lab software. Surfaces created to visualize ground state properties as well as excited state properties such as orbital, electron densities, electrostatic potentials (ESP), spin densities and generated the grid data used to make molecular orbital surfaces to visualize the molecular orbital and making an electro static potential mapped on electron density surface. The minimum potential energy was calculated for Triamterene through the geometry convergence map. Mulliken Atomic Charges, ZDO Atomic Charges of Triamterene and Ground State Dipole of 6-phenylpteridine-2,4,7-triamine (Triamterene) were determined using AM1/RHF method when the net charge was -1 and valence electrons 84.

RESULTS AND DISCUSSION

Prospective view and calculated properties of 6-phenylpteridine-2,4,7-triamine (Triamterene) molecule are shown in figure1. Figure 5 shows Electrostatic potential of molecular ground state mapped onto the electron density surface for the ground state The colour map shows the ESP energy (in hartrees) for the various colours. The red end of the spectrum shows regions of highest stability for a positive test charge, magenta/ blue show the regions of least stability for a positive test charge. The active conformation of Triamterene by molegro molecular viewer software is shown in figure 2. Figure 3 and 4, shows the highest occupied molecular orbital and the lowest unoccupied molecular orbital of Triamterene molecule.

Fractional coordination of triamterene molecule is given in Table1, bond length and bond angles of triamterene are given in table 2 and 3 respectively, which are calculated after geometry optimization of molecule from ARGUS LAB by using molecular mechanics calculation. Table 5 shows calculated steric energy of Triamterene molecule. Table 4 shows the ZDO and mulliken atomic charges of Triamterene. The steric energy and heat of formation calculated for Triamterene are 0.05130821 a.u. (32.19641689 kcal/mol) and 764.8268 kcal/mol respectively. SCF energy was found to be -108.6545111064 au(-68181.7966 kcal/mol) as calculated by RHF/AM1 method, as performed by ArgusLab 4.0.1 suite.

Molecular Formula	= C ₁₂ H ₁₁ N ₇
Formula Weight	= 253.26284
Composition	= C(56.91%) H(4.38%) N(38.71%)
Molar Refractivity	= 73.76 ± 0.3 cm ³
Molar Volume	= 188.5 ± 3.0 cm ³
Parachor	= 538.5 ± 4.0 cm ³
Index of Refraction	= 1.825 ± 0.02
Surface Tension	= 104.1 ± 3.0 dyne/cm
Density	= 1.502 ± 0.06 g/cm ³
Dielectric Constant	= Not available
Polarizability	= 29.24 ± 0.5 10 ⁻²⁴ cm ³
Monoisotopic Mass	= 253.107593 Da
Nominal Mass	= 253 Da
Average Mass	= 253.2628 Da

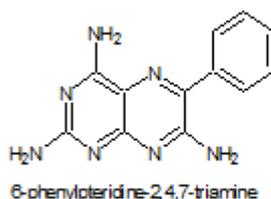


Figure 1: Prospective view of Triamterene by ACD/ChemSketch

6-phenylpteridine-2,4,7-triamine

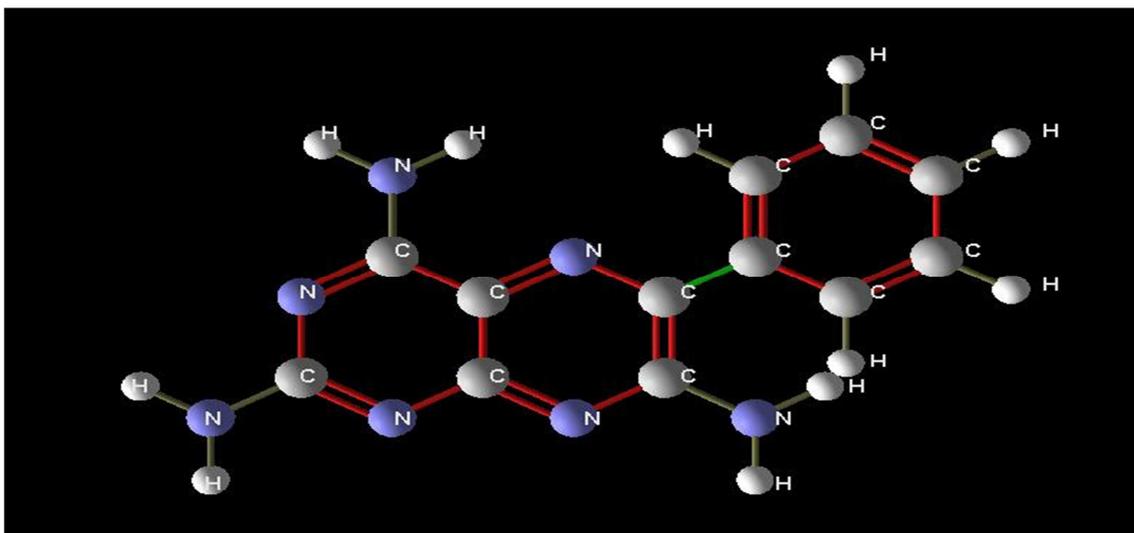


Figure 2: Prospective view of active conformation of Triamterene by Molegro molecular viewer

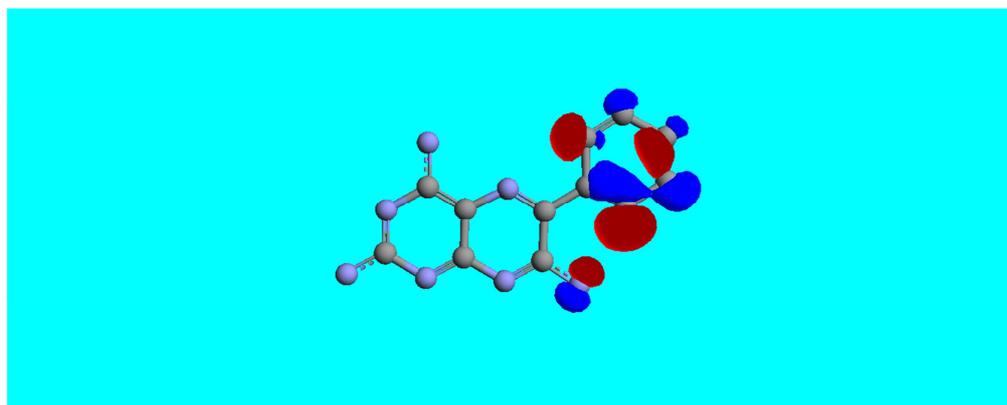


Figure 3 : Highest occupied molecular orbital's (HOMO) of Triamterene

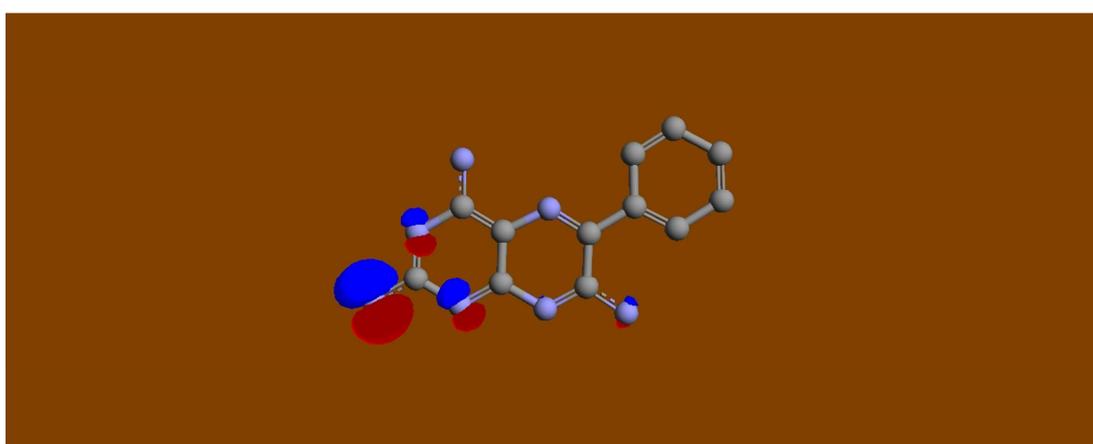


Figure 4 : Lowest unoccupied molecular orbital's (LUMO) of Triamterene

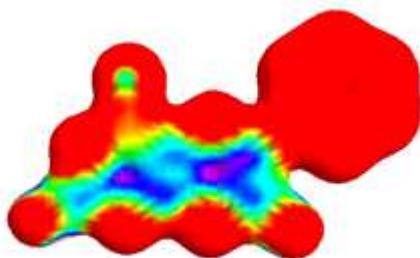


Figure 5: Electrostatic potential mapped density of Triamterene

Table 1: Atomic Coordinate of Triamterene

S.NO	Atoms	X	Y	Z
1	C	14.772300	13.580400	0.000000
2	C	14.772300	14.910400	0.000000
3	C	13.620400	12.915400	0.000000
4	N	13.620400	15.575400	0.000000
5	N	12.468600	13.580400	0.000000
6	C	12.468600	14.910400	0.000000
7	N	15.924100	12.915500	0.000000
8	C	17.075900	13.580600	0.000000
9	N	15.924000	15.575400	0.000000
10	C	17.075800	14.910500	0.000000
11	C	18.227700	12.915700	0.000000
12	C	18.227800	11.585700	0.000000
13	C	19.379600	13.580700	0.000000
14	C	19.379800	10.920700	0.000000
15	C	20.531400	12.915800	0.000000
16	C	20.531500	11.585800	0.000000
17	N	11.316800	15.575400	0.000000
18	N	13.620400	11.585400	0.000000
19	N	18.227600	15.575500	0.000000

Tables 2: Bond length of Triamterene

Atoms	Bond length
1 3 (C)-(C)	1.323387
1 7 (C)-(N)	1.433804
1 2 (C)-(C)	1.458000
2 4 (C)-(N)	1.301961
2 9 (C)-(N)	1.433804
3 5 (C)-(N)	1.433804
3 18 (C)-(N)	1.343384
4 6 (N)-(C)	1.433804
5 6 (N)-(C)	1.301961
6 17 (C)-(N)	1.343384
7 8 (N)-(C)	1.301961
8 10 (C)-(C)	1.458000
8 11 (C)-(C)	1.458000
9 10 (N)-(C)	1.301961
10 19 (C)-(N)	1.343384
11 12 (C)-(C)	1.458000
11 13 (C)-(C)	1.323387
12 14 (C)-(C)	1.323387
13 15 (C)-(C)	1.458000
14 16 (C)-(C)	1.458000
15 16 (C)-(C)	1.323387

Table 3 : Bond Angles of Triamterene

Atoms	Bond angles	Alternate angles
3 1 7 (C)-(C)-(N)	120.000000	295.980973
3 1 2 (C)-(C)-(C)	120.000000	216.488007
1 3 5 (C)-(C)-(N)	120.000000	295.980973
1 3 18 (C)-(C)-(N)	120.000000	327.778708
7 1 2 (N)-(C)-(C)	120.000000	257.053574
1 7 8 (C)-(N)-(C)	120.000000	227.506158
1 2 4 (C)-(C)-(N)	120.000000	294.480480
1 2 9 (C)-(C)-(N)	120.000000	257.053574
4 2 9 (N)-(C)-(N)	120.000000	402.764879
2 4 6 (C)-(N)-(C)	120.000000	227.506158
2 9 10 (C)-(N)-(C)	120.000000	227.506158
5 3 18 (N)-(C)-(N)	120.000000	385.642256
3 5 6 (C)-(N)-(C)	120.000000	227.506158
4 6 5 (N)-(C)-(N)	120.000000	402.764879
4 6 17 (N)-(C)-(N)	120.000000	385.642256
5 6 17 (N)-(C)-(N)	120.000000	446.697620
7 8 10 (N)-(C)-(C)	120.000000	294.480480
7 8 11 (N)-(C)-(C)	120.000000	294.480480
10 8 11 (C)-(C)-(C)	120.000000	188.442082
8 10 9 (C)-(C)-(N)	120.000000	294.480480
8 10 19 (C)-(C)-(N)	120.000000	282.167276
8 11 12 (C)-(C)-(C)	120.000000	188.442082
8 11 13 (C)-(C)-(C)	120.000000	216.488007
9 10 19 (N)-(C)-(N)	120.000000	446.697620
12 11 13 (C)-(C)-(C)	120.000000	216.488007
11 12 14 (C)-(C)-(C)	120.000000	216.488007
11 13 15 (C)-(C)-(C)	120.000000	216.488007
12 14 16 (C)-(C)-(C)	120.000000	216.488007
13 15 16 (C)-(C)-(C)	120.000000	216.488007
14 16 15 (C)-(C)-(C)	120.000000	216.488007

Tables 4: ZDO atomic charges and Mulliken atomic charges of Triamterene

S.NO	Atoms	ZDO	Mulliken
1	C	-0.1176	-0.1174
2	C	0.0972	0.1442
3	C	-0.0267	-0.0060
4	N	-0.1495	-0.1892
5	N	-0.0869	-0.1347
6	C	-0.0068	0.0535
7	N	-0.1287	-0.1658
8	C	0.1506	0.1709
9	N	-0.2212	-0.2525
10	C	-0.0161	0.0054
11	C	-0.0881	-0.1072
12	C	-0.1197	-0.0943
13	C	-0.0822	-0.0289
14	C	-0.2160	-0.2265
15	C	-0.2090	-0.2027
16	C	-0.0140	-0.0519
17	N	-0.0454	-0.0510
18	N	0.1450	0.1311
19	N	0.1352	0.1229

Table 5: Final energy evaluation

S. No.	Force field	Energy components (au)
1	Molecular mechanics bond (Estr)	0.00542444
2	Molecular mechanics angle (Ebend)+ (Estr-bend)	0.00542444
3	Molecular mechanicsdihedral (Etor)	0.00000000
4	Molecular mechanicsImpTor (Eoop)	0.00000000
5	Molecular mechanicsvdW (EVdW)	0.04241079
6	Molecular mechanics coulomb (Eqq)	0.00000000
Total		0.05130821 a.u. (32.19641689 kcal/mol)

CONCLUSION

The present work indicates that the best conformation of triamterene is found to be at -108.6545111064 au (-68181.7966 kcal/mol) which is the minimum potential energy by using Argus Lab software. At this point triamterene will be more active as a sodium ion reabsorption inhibitor. All geometric variables were completely optimized for triamterene and the lowest energy conformations were used in molecular modelling studies.

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