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Molecular mechanics studies of 5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine(trimethoprim) by ArgusLab 4.0.1 software

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ABSTRACT

5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine (Trimethoprim) is used mainly in the treatment of urinary tract infections. Molecular mechanics studies of 5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine (Trimethoprim) was performed according to the Hartree-Fock (HF) calculation method by Argus Lab 4.0.1 software. The molecular mechanics potential energy function were evaluated in terms of energies associated with bonded interactions (bond length, bond angle and dihedral angle) as well as non-bonded interactions (Vander Waals and electrostatic). Surfaces were created to visualize excited state properties such as highest occupied molecular orbital's, lowest unoccupied molecular orbital's and electrostatic potential (ESP) mapped density. The steric energy calculated for trimethoprim was 0.14364738 a.u. (90.14017290 kcal/mol), it Heat of Formation was estimated as 984.4882 kcal/mol and SCF energy was found to be -130.0072298778 au (-81580.8420 kcal/mol) as calculated by RHF/AM1 method at a net charge of 0 (zero) and valence electron of 94, as performed by ArgusLab 4.0.1 suite.These results could help us in understating the drug-receptor interactions.

Keywords: Trimethoprim, Molecular mechanics, Arguslab software.

INTRODUCTION

Antibiotic5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine (Trimethoprim) is used mainly in the treatment of urinary tract infections[1]. Other uses include for middle ear infections and travelers' diarrhea. When combined with sulfamethoxazole or dapsone it can be used treat *Pneumocystis* pneumonia in people with HIV/AIDS. This combination, also known as co-trimoxazole, TMP-sulfa, or TMP-SMX, results in an *in vitro* synergistic antibacterial effect by inhibiting successive steps in folate synthesis. Trimethoprim binds to dihydrofolate reductase and inhibits the reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF)[2-3]. THF is an essential precursor in the thymidine synthesis pathway and interference with this pathway inhibits bacterial DNA synthesis. Trimethoprim's affinity for bacterial dihydrofolate reductase is several thousand times greater than its affinity for human dihydrofolate reductase. Sulfamethoxazole inhibits dihydropteroate synthetase, an enzyme involved further upstream in the same pathway[4-5]. Trimethoprim and sulfamethoxazole are commonly used in combination due to claimed synergistic effects, and reduced development of resistance. The geometry of a molecule has a great impact on its energy level and physical and chemical properties. As the molecule rotates, it adopts different conformations and spatial arrangements to achieve one of the stable states of *lowest energy* [6]. The total molecular energy can be evaluated in terms of potential energy surface as a sum of energies associated with each type of bonded interactions i.e. bond length, bond angle and dihedral angle as well as non-bonded interactions (van der Waals and electrostatic) taking place in a molecule and on atomic properties of a molecule [7]. The present work describes the computer aided geometry optimization (active conformation) and calculation of excited state properties of Bicalutamide by ArgusLab 4.0.1 software.

MATERIALS AND METHODS

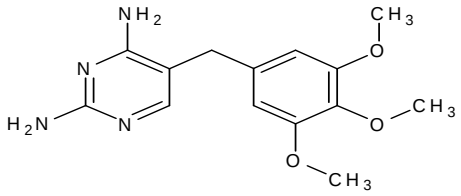
5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine (Trimethoprim) structure was sketched with ACD Lab Chem Sketch software and saved as MDL molfiles (*mol). 5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine (Trimethoprim) structure was generated by Argus lab, and minimization was performed with UFF molecular mechanics method [8-9]. The minimum potential energy was calculated 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 were used to make molecular orbital surfaces and electro static potential mapped on electron density surface [10-11]. The minimum potential energy was calculated for Trimethoprim through the geometry convergence map [12]. Mulliken Atomic Charges, ZDO Atomic Charges of Trimethoprim and Ground State Dipole (debye) of 5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine (Trimethoprim) were determined using AM1 method [13].

RESULTS AND DISCUSSION

Prospective view and calculated properties of Trimethoprim molecule are shown in figure1. The active conformation of Trimethoprim by Molegro molecular-3D viewer software are shown in figure 2. 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. Figure 3 and 4 shows the highest occupied molecular orbital and lowest unoccupied molecular orbital respectively.

Fractional coordination of Trimethoprim molecule is given in Table1 and bond length and bond angles are given in table 2 and 3 respectively, which are calculated after geometry optimization of molecule from ARGUS LAB by using molecular mechanics calculation. Tables 4 shows the Mulliken Atomic Charges, ZDO Atomic Charges. Table 5 and 6 shows, Ground State Dipole (debye) of and calculated steric energy of Trimethoprim molecule. The steric energy calculated for trimethoprim was 0.14364738 a.u. (90.14017290 kcal/mol), it Heat of Formation was estimated as 984.4882 kcal/mol and SCF energy was found to be -130.0072298778 au (-81580.8420 kcal/mol) as calculated by RHF/AM1 method at a net charge of 0 (zero) and valence electron of 94, as performed by ArgusLab 4.0.1 suite.

Molecular Formula	= $C_{14}H_{18}N_4O_3$
Formula Weight	= 290.31772
Composition	= C(57.92%) H(6.25%) N(19.30%) O(16.53%)
Molar Refractivity	= 80.25 ± 0.3 cm^3
Molar Volume	= 231.8 ± 3.0 cm^3
Parachor	= 628.2 ± 4.0 cm^3
Index of Refraction	= 1.608 ± 0.02
Surface Tension	= 53.9 ± 3.0 dyne/cm
Density	= 1.252 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 31.81 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 290.13789 Da
Nominal Mass	= 290 Da
Average Mass	= 290.3177 Da



5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine

Figure 1: Prospective view of trimethoprim by ACD/ChemSketch

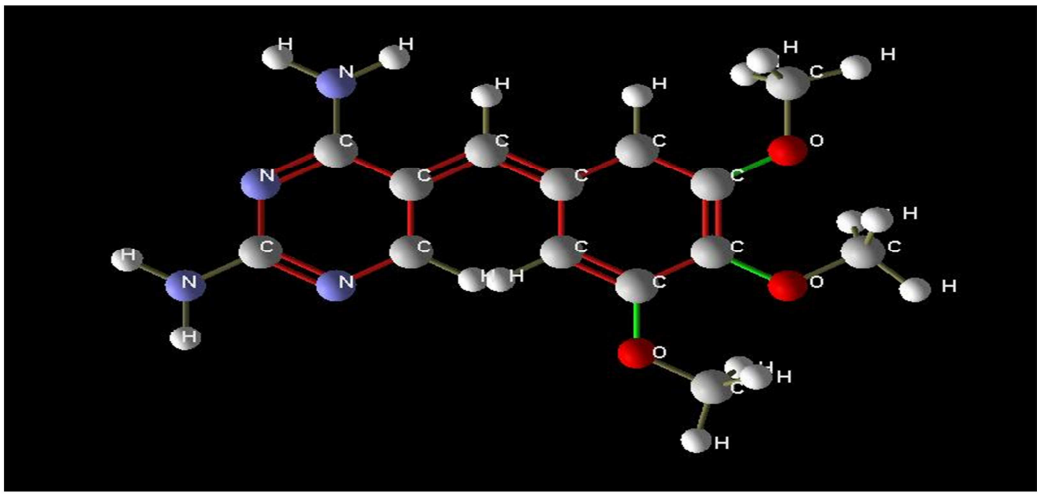


Figure 2: Prospective view of active comformation of Trimthoprime by Molegro molecular viewer

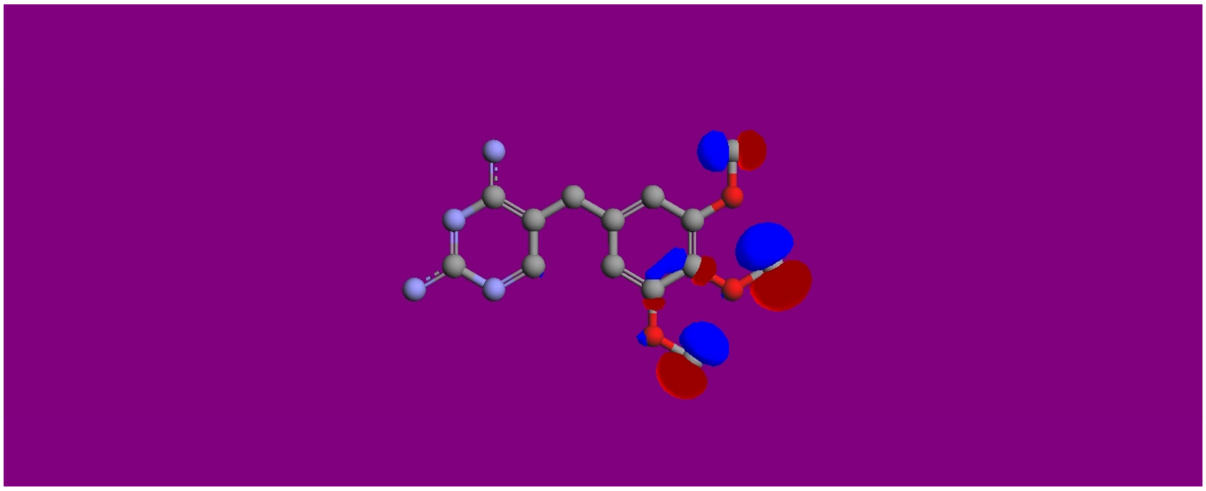


Figure 3 : Highest occupied molecular orbital's (HOMO) of Trimethoprim

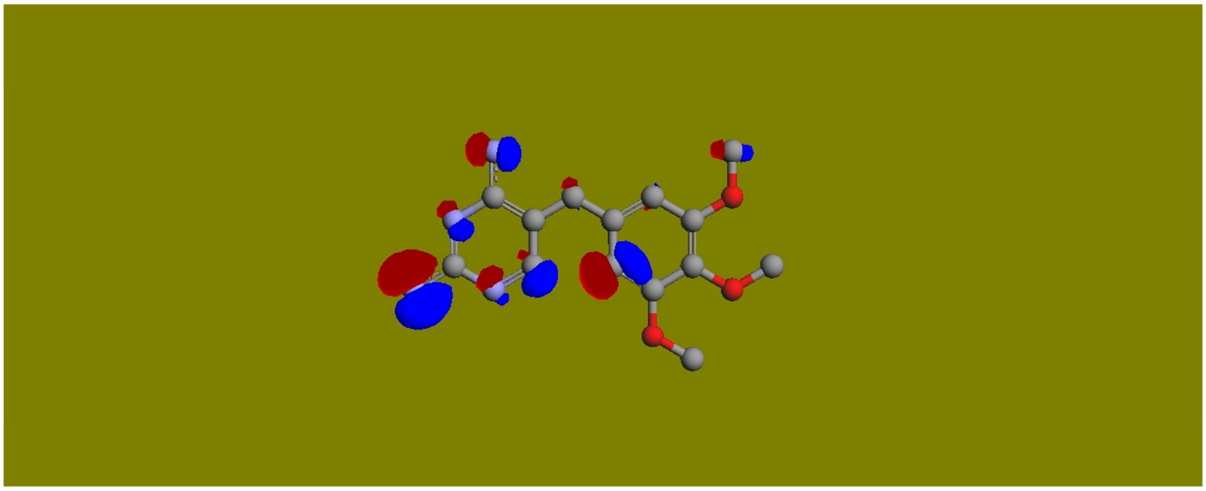


Figure 4 : Lowest unoccupied molecular orbital's (LUMO) of Trimethoprim

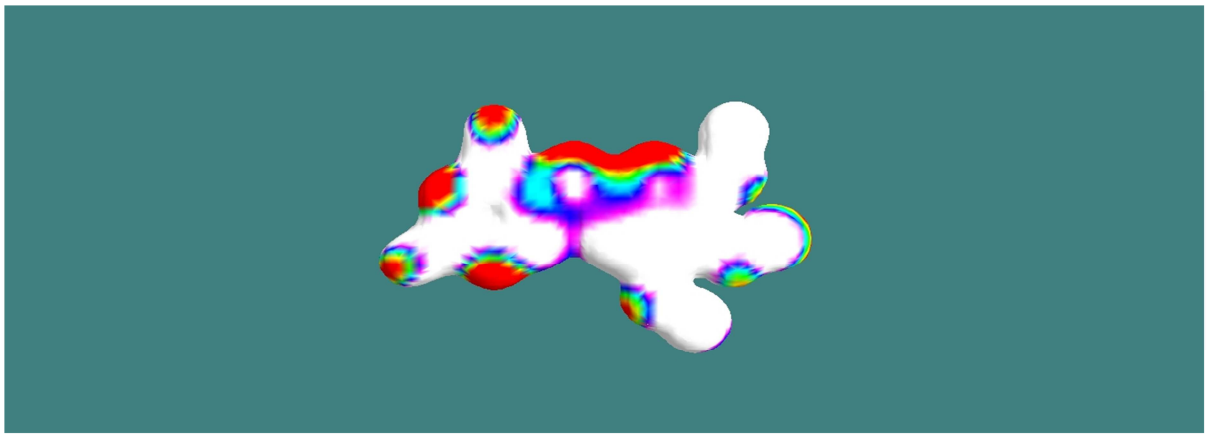


Figure 5: Electrostatic potential mapped density of Trimethoprim

Table 1: Atomic Coordinate of Trimethoprim

S.NO	Atoms	X	Y	Z
1	C	17.159900	13.195800	0.000000
2	C	17.159900	14.525800	0.000000
3	C	16.008000	12.530800	0.000000
4	N	16.008000	15.190800	0.000000
5	N	14.856200	13.195800	0.000000
6	C	14.856200	14.525800	0.000000
7	C	18.311700	12.530800	0.000000
8	C	19.463500	13.195800	0.000000
9	C	20.615400	12.530800	0.000000
10	C	19.463600	14.525900	0.000000
11	C	21.767200	13.195900	0.000000
12	C	20.615400	15.190900	0.000000
13	C	21.767200	14.525900	0.000000
14	N	16.008000	11.200800	0.000000
15	N	13.704400	15.190800	0.000000
16	O	22.919100	12.530900	0.000000
17	O	22.919000	15.190900	0.000000
18	O	20.615400	16.520900	0.000000
19	C	22.919100	11.200900	0.000000
20	C	24.070800	14.525900	0.000000
21	C	21.767200	17.185900	0.000000

Table 2: Bond length of Trimethoprim

Atoms	Bond length
1 2 (C)-(C)	1.458000
1 3 (C)-(C)	1.323387
1 7 (C)-(C)	1.461000
2 4 (C)-(N)	1.301961
3 5 (C)-(N)	1.433804
3 14 (C)-(N)	1.343384
4 6 (N)-(C)	1.433804
5 6 (N)-(C)	1.301961
6 15 (C)-(N)	1.343384
7 8 (C)-(C)	1.461000
8 9 (C)-(C)	1.323387
8 10 (C)-(C)	1.458000
9 11 (C)-(C)	1.458000
10 12 (C)-(C)	1.323387
11 13 (C)-(C)	1.323387
11 16 (C)-(O)	1.407689
12 13 (C)-(C)	1.458000
12 18 (C)-(O)	1.407689
13 17 (C)-(O)	1.407689
16 19 (O)-(C)	1.436155
17 20 (O)-(C)	1.436155
18 21 (O)-(C)	1.436155

Table 3: Bond Angles of Trimethoprim

Atoms	Bond length	Alternate angles
2 1 3 (C)-(C)-(C)	120.000000	216.488007
2 1 7 (C)-(C)-(C)	120.000000	187.861407
1 2 4 (C)-(C)-(N)	120.000000	294.480480
3 1 7 (C)-(C)-(C)	120.000000	215.760874
1 3 5 (C)-(C)-(N)	120.000000	295.980973
1 3 14 (C)-(C)-(N)	120.000000	327.778708
1 7 8 (C)-(C)-(C)	120.000000	187.283630
2 4 6 (C)-(N)-(C)	120.000000	227.506158
5 3 14 (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 15 (N)-(C)-(N)	120.000000	385.642256
5 6 15 (N)-(C)-(N)	120.000000	446.697620
7 8 9 (C)-(C)-(C)	120.000000	215.760874
7 8 10 (C)-(C)-(C)	120.000000	187.861407
9 8 10 (C)-(C)-(C)	120.000000	216.488007
8 9 11 (C)-(C)-(C)	120.000000	216.488007
8 10 12 (C)-(C)-(C)	120.000000	216.488007
9 11 13 (C)-(C)-(C)	120.000000	216.488007
9 11 16 (C)-(C)-(O)	120.000000	238.736810
10 12 13 (C)-(C)-(C)	120.000000	216.488007
10 12 18 (C)-(C)-(O)	120.000000	275.575962
13 11 16 (C)-(C)-(O)	120.000000	275.575962
11 13 12 (C)-(C)-(C)	120.000000	216.488007
11 13 17 (C)-(C)-(O)	120.000000	275.575962
11 16 19 (C)-(O)-(C)	104.510000	293.439812
13 12 18 (C)-(C)-(O)	120.000000	238.736810
12 13 17 (C)-(C)-(O)	120.000000	238.736810
12 18 21 (C)-(O)-(C)	104.510000	293.439812
13 17 20 (C)-(O)-(C)	104.510000	293.439812

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

S.NO	Atoms	ZDO	Mulliken
1	C	-0.2554	-0.2925
2	C	-0.0459	0.0286
3	C	0.0903	0.1023
4	N	-0.2091	-0.2642
5	N	-0.2596	-0.2905
6	C	0.0455	0.0926
7	C	0.1242	0.1640
8	C	-0.1160	-0.1706
9	C	-0.1081	-0.0664
10	C	0.1753	0.2408
11	C	-0.1080	-0.1180
12	C	-0.1971	-0.2249
13	C	0.0675	0.0906
14	N	0.0807	0.0667
15	N	0.0394	0.0298
16	O	-0.1899	-0.2452
17	O	-0.2474	-0.3019
18	O	-0.1290	-0.1882
19	C	0.5467	0.5801
20	C	0.2058	0.2424
21	C	0.4901	0.5247

Table 5: Ground State Dipole (debye) of Trimethoprim

X	Y	Z	Length
17.35198165	0.25969023	-0.00000000	17.35392480

Table 6 : Final energy evaluation of Trimethoprim

S.No.	Force field	Energy components (au)
1	Molecularmechanics bond (Estr)	0.01001617
2	Molecular mechanics angle (Ebend)+ (Estr-bend)	0.03037486
3	Molecularmechanicsdihedral (Etor)	0.04780800
4	MolecularmechanicsImpTor (Eoop)	0.00000000
5	MolecularmechanicsvdW (EVdW)	0.05544835
6	Molecularmechanics coulomb (Eqq)	0.00000000
Total	0.14364738 a.u. (90.14017290 kcal/mol)	

CONCLUSION

The present work indicates that the best conformation of 5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine (Trimethoprim) is found to be -130.0072298778 au (-81580.8420 kcal/mol) which is the minimum potential energy by using Argus Lab software. At this point Trimethoprim will be more active as a chemotherapy agent.

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