# Molecular Dynamics of Malaria Drug Proguanil: DFT and ab Initio Study

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Quantum chemical calculations were carried out to investigate the molecular structure and vibrational frequencies of Malaria drug Proguanil. DFT and ab initio quantum mechanical calculations have been used to predict the optimized molecular structures, dipole moments, atomic charges, polarizability tensors, thermal energies, IR and Raman vibrational frequencies of the malaria drug, Proguanil.

# 1. Introduction

Over the years, Malaria has been known to be the most important parasitic infection of man in tropical regions. It is probably one of the oldest diseases known to mankind that has had profound impact on our history. Currently, about 2 billion people are at risk of malaria resulting in about 500 million cases annually and 1 million deaths. A major part of the burden exists in developing countries of the tropics and sub-tropics with the majority of casualties being among children. Malaria thus represents a significant impediment to economic development of these tropical countries [1-5].

There are only a limited number of drugs which can be used to treat or prevent malaria. The most widely used are Quinine and it derivatives (Chloroquine, Primaquine, Mefloquine), and the antifolate drugs (Proguanil, Chloproguanil, Clociguanil, BRL 6231 (WR99210), Pryrimethamine, Sulfadoxine, Sulfalene, Dapsone and their combination with other drugs (Atovaqone and Proguanil Hydrochloride, Pryrimethamine/Sulfadoxine, Pryrimethamine/Sulfadoxine/Artesunate) [6].

Proguanil is an antimalarial drug that is very effective against sporozoites and works by stopping the malaria parasites from reproducing inside the red blood cells. Based on the important role Proguanil plays in the fight against malaria, this work provides a systematic study of the molecular dynamics of Proguanil with the aid of RHF and B3LYP methods.

### 2. Computational Methodology

The Gaussian package is used. Geometry optimization is done by locating both the minima and transition states on the potential surface of the molecular orbital. The process is iterative, with repeated calculations of energies and gradients, and calculations or estimations of Hessian in every optimization cycle until convergence is attained. The calculation of the matrix of second energy-derivatives (the Hessian or force constant matrix) yields harmonic vibrational frequencies upon diagonalization [7].

The molecular structures and geometries of the two compounds are completely optimized using abinitio quantum mechanical calculations at the Restricted Hartree-Fock (RHF) level of theory (with 6-31G basis set) without using any symmetry constraints. The structures are refined further using Density Functional Theory (DFT) for inclusion of electron correlations with the three-parameter density functional generally known as Becke3LYP (B3LYP). As the first step, geometry optimizations are carried out and then the IR and Raman frequencies are calculated using the Hessian, which is the matrix of second derivatives of the energy with respect to geometry [7].

### 3. Results and Discussion

#### 3.1. Optimized molecular structure

The atom list for the molecule is shown in Table 1 and the optimized molecular structure is shown in Fig. 1. The optimized bond lengths at both levels of theory are listed in Table 2. The predicted bond lengths at RHF/6-31G level for both molecules are slightly larger than the corresponding values at B3LYP/6-31G level of theory except for R21. It can be predicted that the inclusion of electron correlation expands the molecule. It is also

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Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Symbol	С	С	С	С	С	Н	С	С	С	Η	Н	Н	Η	Н	Cl	Ν	Ν	Ν	Ν	Ν
Number	21	22	23	24	25	26	27	28	29	30	31	32	33							
Symbol	Η	Η	С	С	Н	Н	Н	С	Η	Н	Н	Н	Н							

Table 1: Atom list of Proguanil Molecule.

Code	Bond	RHF/6-31	B3LYP/6-31	Code	Bond	RHF/6-31	B3LYP/6-31
R1	R(1,16)	1.3887	1.4014	R20	R(10,20)	0.9975	1.0189
R2	R(1,17)	1.4096	1.4274	R21	R(10,24)	2.8186	2.8034
R3	R(1,19)	1.2586	1.2808	R22	R(11,17)	0.9928	1.011
R4	R(2,17)	1.3913	1.405	R23	R(12,16)	0.9918	1.0095
R5	R(2,18)	1.3775	1.3917	R24	R(18,22)	0.9923	1.0102
R6	R(2,20)	1.2719	1.2958	R25	R(18,23)	1.4686	1.4793
R7	R(2,22)	2.0218	2.0495	R26	R(18,32)	2.0227	2.0442
R8	R(3,4)	1.394	1.4084	R27	R(19,21)	1.0023	1.0276
R9	R(3,9)	1.397	1.4103	R28	R(22,32)	2.1853	2.2289
R10	R(3,16)	1.4017	1.4077	R29	R(23,24)	1.5349	1.5438
R11	R(4,5)	1.3878	1.3988	R30	R(23,28)	1.5324	1.5397
R12	R(4,33)	1.0661	1.0808	R31	R(23,32)	1.0842	1.098
R13	R(5,6)	1.0709	1.0833	R32	R(24,25)	1.0824	1.0952
R14	R(5,7)	1.3774	1.3914	R33	R(24,26)	1.0831	1.0952
R15	R(7,8)	1.3791	1.3926	R34	R(24,27)	1.0842	1.0961
R16	R(7,15)	1.8137	1.833	R35	R(28,29)	1.0814	1.0937
R17	R(8,9)	1.3828	1.3951	R36	R(28,30)	1.0837	1.0954
R18	R(8,13)	1.0708	1.0831	R37	R(28,31)	1.0825	1.0944
R19	R(9,14)	1.0743	1.0873	R38	R(28,32)	2.1188	2.138

Table 2: Optimized bond lengths (Å) of Proguanil Molecule.



Fig.1: Optimized structure of Proguanil Molecules.

predicted that the longest and possibly weakest bonds are R7, R21, R26, R28 and R38 involving C-H, N-H and H-H bonds. The shortest and possibly strongest bonds are R20, R22, R23 and R24 involving N-H, C-H and C-N bonds. A similar trend is observed for the bond lengths as shown in Table 3. The smallest angles (acute) are A6 (N-C-H), A44 (H-C-C), A63 (N-H-C), A64 (H-H-C) and A45 (H-C-H). The largest angles are A7 (N-C-N), A8 (N-C-H), A35 (C-N-H), A47 (H-C-H), A59 (H-C-H) and A28 (C-N-C).

Code	Bond angle	RHF/6-31G	B3LYP/6-31	Code	Bond	RHF/6-31	B3LYP/6-31
A1	A(16,1,17)	109.2258	109.4071	A34	A(2,18,23)	127.4238	126.5019
A2	A(16,1,19)	123.4021	123.3927	A35	A(2,18,32)	158.1266	156.9713
A3	A(17,1,19)	127.3721	127.2002	A36	A(22,18,23)	115.6726	116.1827
A4	A(17,2,18)	111.132	111.2315	A37	A(1,19,21)	114.3922	111.5224
A5	A(17,2,20)	120.3953	119.87	A38	A(2,20,10)	116.7938	114.7427
A6	A(17,2,22)	86.812	87.5217	A39	A(2,22,32)	105.0694	103.8305
A7	A(18,2,20)	128.4708	128.8928	A40	A(18,23,24)	113.3064	113.3006
A8	A(20,2,22)	151.4036	150.7915	A41	A(18,23,28)	112.2006	111.8521
A9	A(4,3,9)	118.9127	119.1001	A42	A(24,23,28)	112.8656	112.8041
A10	A(4,3,16)	124.2336	123.6647	A43	A(24,23,32)	106.998	107.0764
A11	A(9,3,16)	116.8518	117.2325	A44	A(10,24,23)	72.4596	73.1134
A12	A(3,4,5)	119.782	119.8104	A45	A(10,24,25)	41.8969	40.7084
A13	A(3,4,33)	119.5012	118.741	A46	A(10,24,26)	112.3969	112.8607
A14	A(5,4,33)	120.7103	121.4362	A47	A(10,24,27)	135.1917	134.2131
A15	A(4,5,6)	119.6294	119.8122	A48	A(23,24,25)	112.4654	112.1318
A16	A(4,5,7)	120.214	119.899	A49	A(23,24,26)	110.5319	110.6735
A17	A(6,5,7)	120.1554	120.2867	A50	A(23,24,27)	110.0054	110.108
A18	A(5,7,8)	120.965	121.377	A51	A(25,24,26)	107.9116	107.8554
A19	A(5,7,15)	119.6894	119.5135	A52	A(25,24,27)	107.562	107.6413
A20	A(8,7,15)	119.3454	119.1088	A53	A(26,24,27)	108.2196	108.2943
A21	A(7,8,9)	119.0294	118.822	A54	A(23,28,29)	112.4558	112.0884
A22	A(7,8,13)	120.5345	120.6399	A55	A(23,28,30)	109.7782	109.8555
A23	A(9,8,13)	120.4358	120.5378	A56	A(23,28,31)	110.3042	110.3853
A24	A(3,9,8)	121.0949	120.9875	A57	A(29,28,30)	107.8556	108.0523
A25	A(3,9,14)	119.8409	119.8258	A58	A(29,28,31)	107.9666	107.883
A26	A(8,9,14)	119.0634	119.1858	A59	A(29,28,32)	141.7682	141.4579
A27	A(20,10,24)	119.9556	122.5652	A60	A(30,28,31)	108.3589	108.4693
A28	A(1,16,3)	129.0302	128.647	A61	A(30,28,32)	93.5883	94.4666
A29	A(1,16,12)	115.8741	115.9284	A62	A(31,28,32)	94.0433	93.3275
A30	A(3,16,12)	114.5899	114.9274	A63	A(18,32,28)	73.913	73.4142
A31	A(1,17,2)	126.7971	125.449	A64	A(22,32,23)	70.9467	70.3509
A32	A(1,17,11)	115.8202	116.4424	A33	A(2,17,11)	115.7978	115.8492

Table 3: Optimized bond angles (°) of Proguanil Molecule.

# 3.2. Dipole moments, quadrupole moments and energies

The dipole moment is the first derivative of the energy with respect to an applied electric field. It is a measure of the asymmetry in the molecular charge distribution and is given as a vector in three dimensions. For Hartree-Fock calculations, this is equivalent to the expectation values of X, Y and Z, which are the quantities reported in the output. The predicted dipole moments (in Debye) at different levels of theory for both molecules are shown in Table 4. The dipole moment obtained at B3LYP/6-31+G level is slightly lower as compared to the corresponding values of the dipole moment at RHF/6-31+G level. Most of the negative charges

are predicted to reside mostly along the XX axis at both levels of theory.

The quadrupole moment for the molecule at different levels of theory is shown in Table 5. It predicts that the molecule is slightly elongated along the ZZ axis.

Thermo-chemical analysis of the molecular system at 298.15 K and 1 atmosphere of pressure, using the principal isotope of each element type in the molecular system were carried out. Predicted

total, electronic, translational, rotational and vibrational energies in kcal/mol for the molecule are listed in Table 6. It is seen that vibrational energy accounts for almost all of the total energy of the molecule at 298.15 K and 1 atmosphere of pressure. Inclusion of electron correlation reduces the predicted total energy from 195.095 kcal/mol at RHF level to 182.682 kcal/mol. This is expected as the inclusion of electron correlation increases the bond lengths (Table 2) thus weakening the bonds.

Table 4: Dipole moments (in Debye) of Proguanil Molecule.

	RHF/	6-31G		B3LYP/6-31G			
Х	Y	Ζ	Total	Х	Y	Ζ	Total
-8.4347	-5.6652	0.2435	10.1635	-8.3267	-5.3979	0.2188	9.9257

Table 5: Quadrupole moments (in Debye) of Proguanil Molecule.

	RHF/6-310	T T		B3LYP/6-31	G
XX	YY	ZZ	XX	YY	ZZ
-108.8825	-102.2247	-114.9042	-106.2946	-100.7662	-112.2982

Energy	RHF/6-31G	B3LYP/6-31G
Total Energy	195.095	182.682
Electronic Energy	0.000	0.000
Translational Energy	0.889	0.889
Rotational Energy	0.889	0.889
Vibrational Energy	193.317	180.904

Table 6: Predicted thermal energies (kcal/mol).

# 3.3. Charge transfer and polarizabilities

Within molecular system, atoms can be treated as a quantum mechanical system. On the basis of the topology of the electron density, the atomic charges in the molecule can be explained. The electrostatic potential derived charges using the CHelpG scheme of Breneman at different atomic positions for RHF/6-31G and B3LYP/6-31G levels of theories are given in Table 7. It is predicted that the bulk negative charge is shared among the Nitrogen atoms. Carbon and Hydrogen atoms share the bulk positive charge.

Polarizability refers to the way the electrons around an atom redistribute themselves in response to an electrical disturbance. The polarizability tensor components of the molecules at RHF/6-31+G and B3LYP/6-31+G levels of theory, is listed on Table 8. At both levels of theory, the molecule is highly polarized along the XX direction.

# 3.4. Vibrational frequencies and assignments

In this work, Gaussian software was used to predict the vibrational spectra of Proguanil molecule at their ground state. Some IR and Raman intense vibrational frequencies and their approximate descriptions for the molecule at RHF and B3LYP levels with 6-31G basis set are shown in Tables 9 and 10. At both levels of theory it is observed that the IR intensities are significantly greater than the Raman intensities (Figs. 2 and 3).

S/N	Atom	RHF/6-31G	B3LYP/6-31G	S/N	Atom	RHF/6-31G	B3LYP/6-31G
1	С	0.976490	0.648307	18	Ν	-0.936630	-0.669053
2	С	0.969836	0.641150	19	Ν	-0.682662	-0.523881
3	С	0.400314	0.331644	20	Ν	-0.717806	-0.554773
4	С	-0.162712	-0.086445	21	Н	0.378954	0.310666
5	С	-0.157513	-0.130396	22	Н	0.366916	0.308298
6	Н	0.233742	0.154501	23	С	0.052778	0.037460
7	С	-0.320813	-0.223696	24	С	-0.434365	-0.391179
8	С	-0.141288	-0.108919	25	Н	0.156297	0.141370
9	С	-0.256173	-0.169662	26	Н	0.165603	0.141888
10	Н	0.308058	0.258726	27	Н	0.160782	0.141604
11	Н	0.376324	0.313108	28	С	-0.440639	-0.395064
12	Н	0.367656	0.306058	29	Н	0.169032	0.151034
13	Н	0.231051	0.150377	30	Н	0.159899	0.140136
14	Н	0.195488	0.115910	31	Н	0.170891	0.147155
15	Cl	0.073142	0.041830	32	Н	0.180310	0.139886
16	Ν	-1.090577	-0.810122	33	Н	0.301918	0.200941
17	Ν	-1.054303	-0.758860		•	•	•

Table 7: Electrostatic potential derived charges on different atomic positions.

Table 8: Polarizabilities of PCP and PFP at different levels of theory.

Orientation	XX	ху	уу	XZ	yz	ZZ
RHF/6-31G	212.713	0.212	141.850	3.145	0.043	70.598
B3LYP/6-31G	260.854	0.853	149.854	3.847	-0.090	74.213

Table 9: Some IR intense vibrational frequencies and their approximate description.

RHF	B3LYP	Approximate Description
Frequency	Frequency	
1714.61	1558.72	Anti-symmetric stretching of the C-C and C-N bonds in phase
1444.07	1538.41	Symmetric stretching of the C-C and C-N bonds in phase
1678.66	1509.32	Anti-symmetric stretching of the C1-N17-C2 bonds in phase
1934.26	1759.33	Symmetric stretching of the double bonds between C1 and N19 and C2 and N20
1730.57	1584.71	Anti-symmetric stretching of the N17-C1-N16 bonds in phase
1261.37	1324.67	Anti-clockwise symmetric twisting of the N-H bonds
1059.53	1151.26	Symmetric stretching of the C-N bonds
1416.36	1308.09	Anti-symmetric stretching of the benzene ring

Table 10: Some intense Raman vibrational frequencies and their approximate description.

<b>RHF Frequency</b>	B3LYP	Approximate Description
	Frequency	
3211.5	3062.17	Symmetric stretching of the C-H bonds in the methyl groups
3832.8	3531.6	Stretching of the N20-H10 bond
3883.93	3626.42	Symmetric stretching of the N16-H12, N17-H11 and N18-H22 bonds
3403.55	3238.66	Anti-symmetric stretching of the C-H bonds in the benzene ring
3276.24	3137.19	Symmetric stretching of the C-H bonds in the methyl groups
3761.45	3402.49	Symmetric stretching of the N19-H21 and N20-H10 bonds



Fig.2a: IR spectrum of Proguanil Molecule at RHF level of theory.



Fig.2b: IR spectrum of Proguanil Molecule at B3LYP level of theory.



Fig.3a: Raman spectrum of Proguanil Molecule at RHF level of theory.



Fig.3b: Raman spectrum of Proguanil Molecule at B3LYP level of theory.

#### 4. Conclusion

In this article, computational methods are used to predict the molecular dynamics of the malaria drug, Proguanil. This work provides a base for more studies of this molecule and it is hoped that in no distant future, the experimental part of this work will be carried out to confirm the predictions given in this work. Also, environmental studies can be carried out to predict changes in the behavior of this molecule in different media.

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