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RHF AND DFT STUDY OF THE MOLECULAR PROPERTIES OF THE MALARIA DRUG PROGUANIL IN DIFFERENT ENVIRONMENTS

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ABSTRACT

The molecular geometries of the common malaria drug Proguanil in gas phase, water and Ethanol have been studied using ab- initio Quantum Chemical calculations at the Restricted Hartree-Fock (RHF) level of theory by employing 6-31+G basis set. Density functional calculation at the Becke3LYP (B3LYP) have been carried out by employing 6-31+G basis set for inclusion of electron correlation. The molecular structure, dipole moment, charge transfer, polarizability and energy were calculated. The shortest bonds were found to be H10-N20, H11-N17, H12-N16, N18-H22 with bond lengths less than 1 Å . The dipole moments, thermal energies and polarizabilities were found to be higher in water compared to gas phase and ethanol at both levels of theory.

Keywords: Proguanil, Molecular Dynamics, ab initio, DFT Calculations.

INTRODUCTION

Malaria is one of the oldest diseases known to mankind that has had profound impact on our history. Approximately 40% of the total global population is at risk of malaria infection. The disease was effectively eliminated in many of the non-tropical counties. Major parts of the burden exist in developing countries of the tropics and sub-tropics with the majority of casualties being among the children (Snow *et al*, 2005; Sach and Malaney, 2002; Singh *et al*, 2002; Rosenthal, 2003; Winstanley, 2000). According to the World Health Organization (WHO) about 660,000 people died from malaria in 2010 globally, most of them were African children. A limited number of drugs exist for the antimalarial medication which can be used to treat or prevent malaria. The most widely used are Quinine and its derivatives (chloroquine, primaquin, mefloquine), and the antifolate drugs (Proguanil, Chloproguanil, Cloliguanil, BRL6231 (WR99210), Pryrimethamine, Sulfadoxine, Sulfalene, Dapsone and their combination with drugs (Atevaqone and Proguanil Hydrochloride, Prymethamine/sulfadoxine, Pryrimethamine/Sulfadoxine/Artesunate) (Schwartz *et al*, 2002).

Proguanil is a prophylactic antimalarial drug that is very effective against sporozoites and works by stopping the malaria parasites from reproducing inside the red blood cells (Schwartz *et al*, 2002). In an earlier article (Ndikilar *et al*, 2013); a thorough study of the molecular dynamics of this molecule was carried out in gas phase at Restricted Hartree Fock (RHF) and Density Functional Theory (DFT) levels of theory. In this research article; we provide a systematic study of the effect of environment on the molecular dynamics of the malaria drug (Proguanil) by studying its molecular properties in water and ethanol and comparing them to those in gas phase.

COMPUTATIONAL METHODOLOGY

The computational methodology is described under the following headings: Gaussian package, geometry optimization and computation of molecular properties.

Gaussian package

The Gaussian package is a computational physics and chemistry program. The name comes from the fact that it uses Gaussian type basis functions. It is used for electronic and geometric structure optimization (single point calculation, geometry optimization, transition states, and reaction path modeling), and molecular properties and vibrational analysis (IR, Raman, NMR vibrational frequencies and normal modes, electrostatic potential, electron density, multi-pole moments, population analysis, natural orbital analysis, magnetic shielding induced current densities, static and frequency-dependent polarizabilities, and hyperpolarizabilities) using both DFT and ab initio methods (Frish *et al*, 2004) .

Geometry optimization

Geometrical optimization is done by locating both the minima and maxima states on the potential surface of the molecular orbital. It can be optimized in Cartesian coordinates that are generated automatically from the input Cartesian coordinates. It also handles fixed constraints on distances, bond angles and dihedral angles in Cartesian or (where appropriate) internal coordinates. 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. One of most computationally demanding aspects of calculating free energy using electronic structure theory is the calculation of vibrational energy and entropy contributions.

The computational expense is incurred by the calculation of the matrix of second energy-derivatives (i.e. the Hessian or force constant matrix), which yields harmonic vibrational frequencies upon diagonalization (Frish *et al*, 2004).

Computation of molecular properties

The molecular structure and geometry of Proguanil in gas phase, water, and ethanol have been fully optimized by using ab- initio quantum chemical calculations at the Restricted Hartree-Fock (RHF) level of theory without using any symmetry constraints. Initial geometry optimization was performed using the ab-initio RHF method with 3-21G basis set. Subsequently, the basis set was changed to 6-31+G basis set and final calculations were carried out. The structures was refined further using Density Functional Theory which is a cost effective method for inclusion of electron correlations with the three-parameter density functional generally known as Becke3LYP (B3LYP), which includes Becke's gradient exchange corrections (Becke, 1988), the Lee, Yang and Parr correlation functional (Lee *et al*, 1988) and the Vosko, Wilk and Nusair correlation functional (Vosco *et al*, 1980) with 6-31+G basis set. The basis set 6-31+G chosen here is quite moderate and is suitable for such molecules. Calculations have been carried out in two steps at each level of theory. At the first step geometry optimization has been carried out and then the IR absorption intensity calculation is made.

Since the gas phase results are inadequate for describing the behavior of molecules in solutions, therefore the effect of solvating the molecule in bulk water, and ethanol was investigated. For this purpose the simplest Onsager reaction field model of the self-consistent reaction field (SCRF) theory (Miertus *et al*, 1981; Miertus *et al*, 1982) was used with the 6-31+G basis set. In this calculation the solute occupies a fixed spherical cavity within the solvent field. The electric dipole of the solute molecule induces a dipole in the medium and the electric field applied by the induced solvent dipole will interact with the molecular dipole and affect its stabilization. The optimized molecular structure were tested by computing the second derivatives and checking that all the harmonic vibrational frequencies are found to be real at all level of calculations. All calculations in the present work were performed on Pentium IV PC using Windows version of Gaussian 03 (Frish *et al*, 2004) suit of ab initio quantum chemical program.

RESULTS AND DISCUSSION

The geometry of a molecule gives a lot of information that can be correlated with its physical and chemical properties. The ground state geometry of a system can be obtained by geometric optimization. In Born-Oppenheimer (BO) approximation the total ground state energy of a system is a function of the coordinates of the nuclei. The minimum energy corresponds to the ground state geometry whereas a first order saddle point on the BO surface gives the transition state geometry.

The optimized molecular structure of the molecule (Proguanil) is shown in figure 1. The atom list for the molecule is also shown in table 1. The calculated bond length at RHF/6-31+G level and DFT/B3LYP/6-31+G level is given in table 2 in gas phase, water and ethanol. Increase in bond length is noticed as one moves from gas to water to ethanol. Thus the bonds are weakest in ethanol and strongest in gas. This trend is observed at both RHF and B3LYP levels of theory. By implication, this molecule disintegrates more easily in ethanol than in water. This could be due to the polar nature of the solvent. A similar trend is also observed in the bond angles. The shortest bonds with bond lengths less than 1 Å at both levels of theory and in all solvents are R20, R21, R22 and R23 (Table 2). These are all N-H bonds and thus it is predicted that the shortest bonds in this molecule are the N-H bonds.

Table 1: Atom List of Proguanil Molecule

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

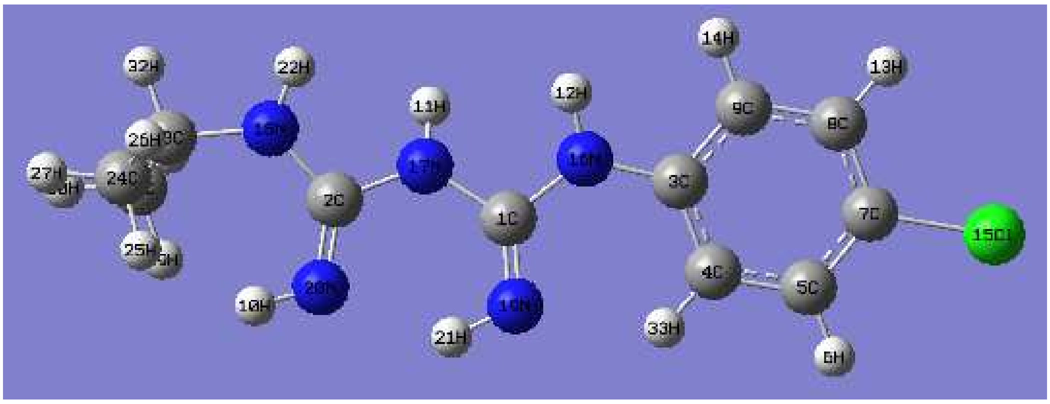

Figure 1: Optimized Structure of Proguanil Molecules

Table 2: Optimized Bond Lengths (Å) of Proguanil Molecule

Code	**Bond**	**RHF/6-31G**			**B3LYP/6-31G**		
		gas	**water**	**ethanol**	**gas**	**water**	**ethanol**
R1	R(1,16)	1.3887	1.3958	1.4029	1.4014	1.4128	1.412
R2	R(1,17)	1.4096	1.399	1.4046	1.4274	1.4131	1.414
R3	R(1,19)	1.2586	1.2615	1.2541	1.2808	1.2833	1.2831
R4	R(2,17)	1.3913	1.4003	1.4062	1.405	1.4174	1.4166
R5	R(2,18)	1.3775	1.3671	1.3708	1.3917	1.379	1.3798
R6	R(2,20)	1.2719	1.2742	1.2675	1.2958	1.2975	1.2974
R7	R(2,22)	2.0218	2.0221	2.026	2.0495	2.0497	2.0499
R8	R(3,4)	1.394	1.3979	1.3968	1.4084	1.4132	1.4129
R9	R(3,9)	1.397	1.3995	1.3975	1.4103	1.4138	1.4135
R10	R(3,16)	1.4017	1.3929	1.391	1.4077	1.3967	1.3974
R11	R(4,5)	1.3878	1.3863	1.3821	1.3988	1.3977	1.3977
R12	R(4,33)	1.0661	1.0663	1.0656	1.0808	1.0822	1.0821
R13	R(5,6)	1.0709	1.0712	1.0702	1.0833	1.0838	1.0838
R14	R(5,7)	1.3774	1.377	1.3732	1.3914	1.3906	1.3906
R15	R(7,8)	1.3791	1.3782	1.3732	1.3926	1.3914	1.3914
R16	R(7,15)	1.8137	1.8304	1.8379	1.833	1.8554	1.8538
R17	R(8,9)	1.3828	1.3834	1.3806	1.3951	1.3959	1.3958
R18	R(8,13)	1.0708	1.0707	1.0698	1.0831	1.0831	1.0831
R19	R(9,14)	1.0743	1.0736	1.0723	1.0873	1.0865	1.0865
R20	R(10,20)	0.9975	0.9977	1.0032	1.0189	1.0184	1.0184
R21	R(11,17)	0.9928	0.9928	0.998	1.011	1.0109	1.0109
R22	R(12,16)	0.9918	0.9923	0.9976	1.0095	1.0101	1.01
R23	R(18,22)	0.9923	0.9926	0.9976	1.0102	1.0105	1.0105
R24	R(18,23)	1.4686	1.4772	1.4817	1.4793	1.4894	1.4887
R25	R(19,21)	1.0023	1.0044	1.0123	1.0276	1.0329	1.0325
R26	R(23,24)	1.5349	1.5332	1.5409	1.5438	1.5413	1.5415
R27	R(23,28)	1.5324	1.5314	1.5385	1.5397	1.5384	1.5385
R28	R(23,32)	1.0842	1.0828	1.0816	1.098	1.0963	1.0964
R29	R(24,25)	1.0824	1.0832	1.083	1.0952	1.0961	1.096
R30	R(24,26)	1.0831	1.0828	1.0829	1.0952	1.0947	1.0947
R31	R(24,27)	1.0842	1.083	1.0831	1.0961	1.0949	1.095
R32	R(28,29)	1.0814	1.0823	1.0818	1.0937	1.0947	1.0946
R33	R(28,30)	1.0837	1.0828	1.0829	1.0954	1.0945	1.0945
R34	R(28,31)	1.0825	1.0825	1.0826	1.0944	1.0943	1.0943

The dipole moments (in debye), Quadra pole moments and total electronic energies (Kcal/mol) without zero point correlation for the molecule both in gas phase and in different solvents are listed in tables 3, 4 and 5 respectively. It is seen that the total dipole moments of the molecule is highest in water. Inclusion of electron correlation increases the value of the dipole moments at B3LYP level of theory using 6-31G basis set. It has a value of 14.7507 Debyes in water and 14.4286 Debyes in ethanol. The quadrapole moment reduces in magnitude as one move from RHF to B3LYP. However at all levels of theory and in all media considered, it predicts that the molecule is slightly elongated along the ZZ axis.

Table 3: Total Dipole Moments (in Debye**) of Proguanil Molecule**

RHF/6-31G			B3LYP/6-31G		
Gas	**water**	**ethanol**	**Gas**	**water**	**ethanol**
10.1635	13.8760	13.6746	10.9245	14.7507	14.4286

Table 4: Quadrupole moments (in Debye**) of Proguanil Molecule**

Axis	**RHF/6-31G**			**B3LYP/6-31G**		
	Gas	**Water**	**Ethanol**	**Gas**	**Water**	**Ethanol**
XX	-108.8825	-111.1696	-111.0259	-106.2946	-108.3329	-108.1864
YY	-102.2247	-101.3562	-101.3597	-100.7662	-99.9282	-99.9307
ZZ	-114.9042	-114.8688	-114.8732	-112.2982	-111.7959	-111.8036

Table 6: Predicted thermal energies (kcal/mol)

	RHF/6-31G			B3LYP/6-31G		
Energy	**Gas**	**Water**	**Ethanol**	**Gas**	**Water**	**Ethanol**
Total Energy	195.095	194.066	193.128	182.682	181.102	181.002
Electronic Energy	0.000	0.000	0.000	0.000	0.000	0.000
Translational Energy	0.889	0.889	0.889	0.889	0.889	0.889
Rotational Energy	0.889	0.889	0.889	0.889	0.889	0.889
Vibrational Energy	193.317	192.288	191.350	180.904	179.324	179.224

The molecule has the highest energy in gas phase and the lowest in ethanol at both levels of theory. Thus; the molecule is weakest in ethanol and strongest in gas phase.

The electrostatic potential derived charges using the CHelpG scheme of Breneman at different atomic positions in gas phase and in different medium (water and ethanol) of proguanil molecule at RHF/6-31G and B3LYP/6-31G level of theories are given in table 6. There is no general trend of charge transfer. C1, C2, C3 and C23 are electropositive in all media and at all levels of theory; while C4, C5, C6, C7, C8, C9 and C24 are electronegative.

Table 6: Electrostatic Potential Derived Charges on different atomic positions

		RHF/6-31G			B3LYP/6-31G		
S/N	**Atom**	**Gas**	**Water**	**Ethanol**	**Gas**	**Water**	**Ethanol**
1	C	0.976490	0.997149	1.097752	0.648307	0.664889	0.663842
2	C	0.969836	0.992035	1.104368	0.641150	0.665715	0.664159
3	C	0.400314	0.409335	0.412408	0.331644	0.337913	0.337525
4	C	-0.162712	-0.160636	-0.245402	-0.086445	-0.084907	-0.085017
5	C	-0.157513	-0.159677	-0.190687	-0.130396	-0.134322	-0.134046
6	H	0.233742	0.208617	0.249571	0.154501	0.125890	0.127575
7	C	-0.320813	-0.302120	-0.302586	-0.223696	-0.203013	-0.204526
8	C	-0.141288	-0.142772	-0.185080	-0.108919	-0.113084	-0.112765
9	C	-0.256173	-0.254030	-0.263856	-0.169662	-0.167773	-0.167910
10	H	0.308058	0.319476	0.305530	0.258726	0.272282	0.271327
11	H	0.376324	0.381529	0.356288	0.313108	0.318989	0.318645
12	H	0.367656	0.379046	0.356193	0.306058	0.317689	0.317004
13	H	0.231051	0.228230	0.263461	0.150377	0.142509	0.143269
14	H	0.195488	0.218482	0.247992	0.115910	0.138093	0.136894
15	Cl	0.073142	-0.002905	-0.001357	0.041830	-0.046122	-0.040109
16	N	-1.090577	-1.095095	-1.067506	-0.810122	-0.811227	-0.811271
17	N	-1.054303	-1.060944	-1.023464	-0.758860	-0.763474	-0.763286
18	N	-0.936630	-0.939520	-0.909566	-0.669053	-0.669209	-0.669255
19	N	-0.682662	-0.715081	-0.795235	-0.523881	-0.551051	-0.549380
20	N	-0.717806	-0.747711	-0.804949	-0.554773	-0.582987	-0.581198
21	H	0.378954	0.386189	0.362180	0.310666	0.315179	0.314805
22	H	0.366916	0.372719	0.348813	0.308298	0.317193	0.316677
23	C	0.052778	0.041127	-0.052151	0.037460	0.024045	0.024910
24	C	-0.434365	-0.437631	-0.568859	-0.391179	-0.395030	-0.394784
25	H	0.156297	0.141408	0.186786	0.141370	0.126971	0.127808
26	H	0.165603	0.170221	0.215321	0.141888	0.149108	0.148728
27	H	0.160782	0.191751	0.231889	0.141604	0.176477	0.174210
28	C	-0.440639	-0.442666	-0.570221	-0.395064	-0.397617	-0.397446
29	H	0.169032	0.150433	0.196804	0.151034	0.132077	0.133173
30	H	0.159899	0.189871	0.229698	0.140136	0.173569	0.171353
31	H	0.170891	0.170524	0.215562	0.147155	0.148183	0.148170
32	H	0.180310	0.205949	0.259795	0.139886	0.169297	0.167509
33	H	0.301918	0.306698	0.340508	0.200941	0.203752	0.203409

Polarizability is a property which depends on the second derivative of the energy with respect to the applied electric field. It gives information about the distribution of electrons in the molecule. Molecular polarizability plays an important role in determining the structure, orientation dynamics and thermodynamics properties of a system. The polarizability tensor components of the molecule (Proguanil) in gas phase as well as in water and ethanol obtained at RHF/6-31G andB3LYP/6-31 G levels of theory are listed in table 7. At both levels of theory, the molecule is highly polarized along XX direction. The highest polarizabilities are obtained in water at all levels of theory.

Table 7: Polarizabilities of Proguanil at Different Levels of Theory

	Medium	XX	XY	YY	XZ	YZ	ZZ
RHF/6-31G	Gas	212.713	0.212	141.850	3.145	0.043	70.598
	Water	284.713	4.316	167.898	-3.944	-0.032	63.702
	Ethanol	280.706	4.128	166.563	-3.873	-0.033	76.106
B3LYP/6-31G	Gas	260.854	0.853	149.854	3.847	-0.090	74.213
	Water	357.845	5.934	174.000	-4.559	-0.217	78.996
	Ethanol	351.348	5.632	172.561	-4.461	-0.214	78.705

CONCLUSION

The dipole moment of Proguanil at both levels of theory and in all media is far greater than that obtained for another malaria drug Daraprim. This indicates that Proguanil responds significantly more than Daraprim to an applied electric field. Also, compared to Daraprim, Proguanil has shorter bond lengths and bond angles and higher total energy thus suggesting that the molecule is more stable than Daraprim in gas phase (Geh, 2013). This article provides baseline data for the modeling and subsequent development of future malaria drugs which are derivatives of Proguanil. It is hoped that experimental work will be done in the near future to complement the findings in this work.

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