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Extensive Molecular Dynamics of Chlorproguanil Molecule in Different Environments

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Abstract

This research explores the molecular dynamics of the Chlorproguanil molecule across various environments through computational simulations. The objective is to gain insights into the molecule's behavior under different conditions, which is essential for optimizing its pharmacological efficacy. In this research, comprehensive molecular dynamics (MD) simulations were performed using Gaussian 03W software to analyze the structural and dynamic characteristics of the Chlorproguanil molecule in three different environments: water, methanol, and gas. The aim was to investigate how the polarity of solvents affects the conformational stability, interaction profiles, and potential pharmacokinetic properties of the molecule, particularly related to its use as an antimalarial agent. The findings indicate that Chlorproguanil is significantly sensitive to environmental changes, with the aqueous setting fostering the most stable and compact molecular conformation.

This is linked to the reinforced hydrogen bonding network and beneficial electrostatic interactions between the molecule and water molecules. Methanol showed moderate stabilization effects, while the gas condition resulted in greater structural deviations and decreased intra-molecular cohesion. The comparative evaluation highlights that polar solvents, especially water, considerably enhance the molecular stability and interaction energetics of Chlorproguanil, indicating a better pharmacodynamic profile in physiological conditions. These results offer crucial insights into how Chlorproguanil's molecular behavior depends on its environment, which has significant implications for its bioavailability and therapeutic effectiveness. Additionally, the study emphasizes the value of molecular dynamics simulations in the early assessment of drugs, providing a computational framework for refining drug candidates based on their responses to different environments. The simulations shed light on structural changes, binding behaviors, and interaction energies, particularly in relation to its potential antimalarial activity. The results reveal significant conformational flexibility and adaptive interactions influenced by the surrounding medium, which could guide future drug design and delivery strategies.

Keywords: Chlorproguanil, solvation effects, Gaussian 03W Software, Density Functional Theory

Introduction

In 2022, malaria affected approximately 249 million individuals globally and resulted in around 600,000 fatalities, underscoring its persistent threat to public health [1]. For more than a century, extensive international collaboration and research have focused on enhancing malaria prevention strategies, diagnostic methods, and treatment options. Despite these advancements, the incidence of malaria and associated deaths remains alarmingly high, particularly in endemic regions [2]. Malaria is most prevalent in sub-Saharan Africa, representing a significant health challenge, but it also impacts several Asian countries, especially those in tropical climates that are home to the Anopheles mosquito vec-

tors. The global fatality rate for malaria ranges from 0.3% to 2.2%. However, in tropical areas where more severe forms of the disease, such as Plasmodium falciparum infections, are common, mortality rates can escalate significantly, reaching between 11% and 30% [3].

The World Health Organization (WHO) has identified the eradication of malaria as a key priority in its recently released Global Technical Strategy for Malaria 2016–2030. The main objectives are to achieve a 90% reduction in both malaria incidence and mortality by the year 2030, using data from 2015 as a baseline. Nonetheless, as of 2022, advancements have been minimal, with only a 2% decrease in incidence and a 6% decline in mortality [1]. Recent studies reveal a concerning trend: since 2015, the prevalence of malaria parasite infections has been on the rise, complicating ongoing eradication efforts. This situation calls for renewed attention on vaccine development, vector control strategies, and public health initiatives to mitigate transmission. Addressing the challenges posed by malaria continues to be a critical priority for health organizations worldwide as they work to protect millions at risk [2].

Malaria may be treated or prevented using a finite number of medications. Quinine and its derivatives (Chloroquine, Primaquine, and Mefloquine) are the most commonly used, followed by antifolate medications (Proguanil, Chloproguanil, Clociguanil, BRL 6231 (WR99210), Pryrimethamine, Sulfadoxine, Sulfalene, and Dapsone), as well as combinations of these medications (Atovaqone and Proguanil Hydro) [3,4]. In 1952, researchers Crud, Davy, and Rose synthesized pyrimethamine through the production of the antifolate medication known as Paludrine or proguanil (chloro hydrochloride). Pyrimethamine functions as an inhibitor of hydrofolate reductase and exhibits antiparasitic properties. As a folic acid antagonist, its therapeutic efficacy is attributed to the differential requirements for nucleic acid precursors utilized in growth by the host and the parasite. The compound demonstrates modest tissue and blood schizonticidal activity against the human malaria parasite [3,4].

The majority of drugs used in malarial therapy are effective against blood-borne parasites (the disease-causing kind). Currently used antimalarial drugs include artemisinin from the herb Qinghao (Artemisia annua L, China, 4th century) and quinine from South America, both of which are derived from plants with a long history of use in traditional medicine. Quinine is one of the most potent antimalarial medications on the market right now, along with artemisinin. For travel to endemic areas where malaria is prevalent, doxycycline is recommended. When ACT is not available or artesunate fails to treat severe malaria, it is often used in conjunction with quinine or artesunate to treat malaria. Doxycycline's drawback is that it cannot be used by minors [2].

Proguanil is a widely recognized prophylactic antimalarial medication, demonstrating considerable effectiveness against sporozoites, particularly during the early stages of malaria infection. Its mechanism of action involves inhibiting the reproduction of malaria parasites within the erythrocytes (red blood cells), thereby preventing the proliferation of the infection. Chlorproguanil, a synthetic derivative of Proguanil, is chemically characterized as 1- [Amino- (3,4-dichloroanilino) methylidene]-2-propan-2-ylguanidine, with the molecular formula C11H15Cl2N5 and a precise molecular weight of 288.18 g/mol. This compound was initially formulated as an alternative treatment in light of the increasing resistance observed in various strains of malaria to conventional therapies, including chloroquine and sulfadoxine/pyrimethamine.

In the research conducted by, a comprehensive study of the molecular dynamics of proguanil was carried out in different environments using advanced computational techniques such as Restricted Hartree Fock (RHF) and Density Functional Theory (DFT) [3]. More recently, our research group conducted an in-depth analysis of a specific derivative of Proguanil, namely 3-Chloroproguanil, also employing RHF and DFT methods [5]. This study aims to provide a thorough study and comparison of the molecular dynamics of chlorproguanil in various environments, addressing the current lack of literature and contributing to a more comprehensive understanding of anti-malarial drugs in response to solvation.

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 program for Physics and Chemistry that utilizes Gaussian type basis functions. It is employed for electronic and geometric structure optimization, molecular properties analysis, and vibrational analysis. The software supports both Density Functional Theory (DFT) and ab initio methods.

Geometry and Vibrational Frequency Optimization

Geometry optimization involves finding minima and transition states on the molecular orbital potential surface. It uses automatically generated Cartesian coordinates and can incorporate fixed constraints on distances, bond angles, and dihedral angles. The process is iterative, involving repeated calculations of energies, gradients, and estimations of Hessians until convergence is achieved. The calculation of free energy using electronic structure theory is computationally demanding, primarily due to the need to calculate the vibrational energy and entropy contributions. This expense arises from determining the Hessian or force constant matrix, which is essential for obtaining harmonic vibrational frequencies through diagonalization [4, 5].

Computation of Molecular Properties

The molecular geometries and structures of the Chlorproguanil was fully optimized through ab-initio quantum mechanical calculations using the DFT method utilizing the 6-31G basis set, a more computationally efficient method for incorporating electron correlations using the three-parameter density functional commonly referred to as Becke3LYP (B3LYP), which combines Becke's gradient exchange corrections (Becke, 1993), the correlation functional proposed by Lee, Yang, and Parr (1988), and the Vosko, Wilk, and Nusair correlation functional, all applied with a 6-31G basis set. Initially, geometry optimizations were performed, followed by the calculation of IR and Raman frequencies utilizing the Hessian matrix, which represents the second derivatives of energy concerning geometry.

As the results obtained in the gas phase are insufficient for accurately characterizing molecular behavior in solutions, the influence of surrounding solvents on the molecule in bulk was explored. For this analysis, the simplest Onsager reaction field model from the self-consistent reaction field (SCRF) theory was employed alongside the 6-31G basis set. In this computational framework, the solute is situated within a fixed spherical cavity inside the solvent medium. The solute's electric dipole induces a dipole in the solvent, and the electric field generated by this induced dipole will interact with the molecular dipole, impacting its behavior [3]. All calculations will be performed using Windows version of Gaussian 03W suit of ab initio quantum mechanical software.

Results and Discussions

Optimized Molecular Structures

The geometry of a molecule is vital and is done to reveal important information about its physical and chemical properties. The ground state geometry, or the most stable molecular configuration, was found through geometric optimization, which involves adjusting nuclear positions to identify the lowest energy arrangement. In the Born-Oppenheimer (BO) approximation, the total ground state energy is a function of the nuclei's coordinates, with electronic wave functions solved at fixed nuclear positions. The minimum energy point on this potential energy surface indicates the ground state geometry, while a first-order saddle point represents the transition state geometry, which is crucial for understanding reaction mechanisms and molecular transformations during chemical reactions [3].

Fig. 1 illustrates the optimized molecular structure of chlorproguanil, wherein carbon (C) atoms constitute the fundamental framework of the molecule. Nitrogen (N) atoms are integral components of the guanidine and pyrimidine rings, which are significant in facilitating hydrogen bonding with enzyme active sites and enhancing drug interactions with biological macromolecules. The chlorine (Cl) atom represents a critical functional group that affects lipophilicity and binding interactions, thereby improving membrane permeability and altering binding affinity to the target enzyme. Additionally, hydrogen (H) atoms are bonded to the carbon and nitrogen atoms within the structure [6- 8]. Also, the list and atom position of the molecule was presented in Table 1.

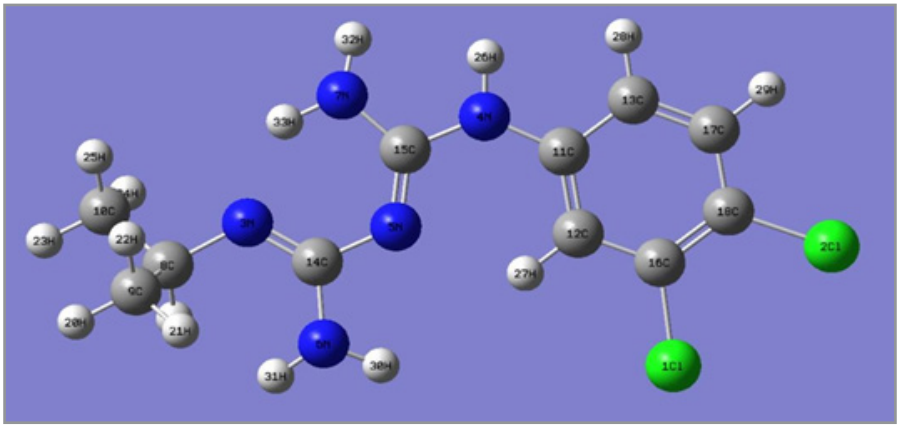

Figure 1: Optimized Structure of Chlorproguanil Molecules

Table 1: Atom List position of Chlorproguanil Molecule

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

The optimized raw bond lengths and bond angles in chloroform, ethanol, gas phase, and water are presented in Table 2. Table 3 summarizes the average measurements of bond lengths (in Å) for various chemical bonds (C-C, C-H, Cl-C, C-N, N-H) across different environments, including Chloroform, Ethanol, Gas, and Water. The C-C bond length exhibits slight variations among these environments; specifically, it is the longest in Water (1.432238 Å) and the shortest in Gas (1.431875 Å). The bond lengths recorded for Chloroform (1.432125 Å) and Ethanol (1.432212 Å) are nearly identical, both being somehow shorter than the value observed in Water. The discrepancies in C-C bond length are relatively minor, ranging from 1.431875 to 1.432238 Å, indicating that this bond is largely unaffected by environmental conditions. The C-H bond length demonstrates considerable stability across all environments, with values spanning from 1.090967 Å (Gas) to 1.091000 Å (Ethanol). The minimal difference of 0.000033 Å between the smallest and largest values suggests that the C-H bond is substantially resistant to environmental influences. In contrast, the Cl-C bond length displays greater variation compared to C-C and C-H bonds. It

presents its longest measurement in Water (1.75555 Å), whereas Ethanol (1.75535 Å) shows a slightly longer bond than that in Chloroform (1.75425 Å), which is shorter. The Cl-C bond is shortest in Gas (1.75000 Å), indicating that the bond length in the gaseous phase is reduced compared to other environments, potentially due to the absence of stabilizinginteractions observed in liquid settings.

The C-N bond length follows a similar trend to that of the Cl-C bond, being longest in Water (1.374012 Å), marginally shorter in Ethanol (1.373975 Å) and Chloroform (1.373863 Å), with the shortest measurement noted in Gas (1.373825 Å). Although the variations are minor, they suggest that polar solvents, such as Water and Ethanol, may contribute slightly to the elongation of C-N bonds. The N-H bond length remains consistent across all environments, with values ranging from 1.01398 Å (Gas) to 1.01410 Å (Ethanol). The small difference of 0.00012 Å indicates that the environment has minimal impact on the N-H bond. In summary, C-C and C-H bond lengths demonstrate little variation across the studied environments, suggesting that these bonds are less influenced by external factors. Conversely, Cl-C and C-N bonds are generally longer in liquid settings (Water, Ethanol) than in the Gas phase, potentially due to solvation effects wherein interactions with solvent molecules stabilize elongated bond configurations.

In gaseous states, all bonds, with the exception of C-H, tend to be shorter than their liquid counterparts, signifying that intermolecular interactions in solvents can produce slight elongation of bonds. Overall, bonds in Water are typically longer than in other environments, likely attributable to strong hydrogen bonding and solvation effects. The N-H bond length exhibits the most stability across all settings, indicating that robust internal bonding forces dominate over environmental influences. The data suggests that, while solvent effects may be minimal, they remain relevant, particularly for bonds involving chlorine and nitrogen, as these bonds are more responsive to their surrounding interactions.

Table 2: Optimized average Bond Lengths (Å) for chlorproguanil at different environment

Positions	Geometrical Parameter	Chloroform	Ethanol	Gas	Water
R1	R(1,16)	1.7556	1.7567	1.7512	1.7569
R2	R(2,18)	1.7529	1.754	1.7488	1.7542
R3	R(3,8)	1.4613	1.462	1.4593	1.4622
R4	R(3,14)	1.3008	1.3011	1.299	1.3012
R5	R(4,11)	1.3987	1.3982	1.4011	1.3981
R6	R(4,15)	1.3865	1.3859	1.388	1.3857
R7	R(4,26)	1.0099	1.0102	1.0092	1.0103
R8	R(5,14)	1.3913	1.3911	1.392	1.3911
R9	R(5,15)	1.3095	1.311	1.3047	1.3113
R10	R(6,14)	1.3859	1.3869	1.3837	1.3871
R11	R(6,30)	1.0097	1.0102	1.0085	1.0102
R12	R(6,31)	1.0093	1.0098	1.008	1.0098
R13	R(7,15)	1.3569	1.3556	1.3628	1.3554
R14	R(7,32)	1.0094	1.0095	1.0094	1.0095
R15	R(7,33)	1.032	1.0308	1.0348	1.0305
R16	R(8,9)	1.5388	1.5388	1.5388	1.5388
R17	R(8,10)	1.5326	1.5327	1.5324	1.5327
R18	R(8,19)	1.1055	1.1051	1.1068	1.1049
R19	R(9,20)	1.0955	1.0954	1.0956	1.0953
R20	R(9,21)	1.0938	1.0939	1.0938	1.094
R21	R(9,22)	1.0953	1.0954	1.0948	1.0954
R22	R(10,23)	1.095	1.095	1.0951	1.095
R23	R(10,24)	1.0943	1.0944	1.0942	1.0944
R24	R(10,25)	1.0957	1.0958	1.0955	1.0958
R25	R(11,12)	1.4023	1.4027	1.4009	1.4028
R26	R(11,13)	1.4077	1.4081	1.4063	1.4082
R27	R(12,16)	1.3941	1.3941	1.3942	1.3942
R28	R(12,27)	1.0789	1.079	1.0786	1.079
R29	R(13,17)	1.387	1.3869	1.3872	1.3869

R30	R(13,28)	1.0862	1.086	1.087	1.0859
R31	R(16,18)	1.3977	1.3974	1.3988	1.3973
R32	R(17,18)	1.3968	1.397	1.3964	1.397
R33	R(17,29)	1.0841	1.0841	1.0841	1.084
A1	A(8,3,14)	120.577	120.5536	120.6529	120.5532
A2	A(11,4,15)	131.4816	131.4701	131.499	131.4682
A3	A(11,4,26)	114.0154	113.9948	114.0532	113.9904
A4	A(15,4,26)	114.4722	114.5257	114.1096	114.5359
A5	A(14,5,15)	121.504	121.5699	121.3772	121.5869
A6	A(14,6,30)	114.5745	114.3909	115.0318	114.3651
A7	A(14,6,31)	117.5357	117.3304	118.1111	117.2951
A8	A(30,6,31)	114.4947	114.0891	115.7967	114.0111
A9	A(15,7,32)	120.2498	120.4585	118.9115	120.4921
A10	A(15,7,33)	111.7743	112.0537	110.9056	112.1142
A11	A(32,7,33)	120.9358	121.0965	119.8231	121.1172
A12	A(3,8,9)	111.1043	111.1327	111.0387	111.1299
A13	A(3,8,10)	108.607	108.6055	108.5958	108.6055
A14	A(3,8,19)	111.0618	111.058	111.0403	111.0595
A15	A(9,8,10)	111.1224	111.0815	111.2365	111.0778
A16	A(9,8,19)	108.0303	108.017	108.096	108.0141
A17	A(10,8,19)	106.8422	106.8728	106.7613	106.881
A18	A(8,9,20)	110.9932	110.9578	111.052	110.9533
A19	A(8,9,21)	111.1951	111.2092	111.2129	111.2096
A20	A(8,9,22)	109.9601	110.0039	109.8462	110.0172
A21	A(20,9,21)	108.2857	108.2271	108.4114	108.2086
A22	A(20,9,22)	108.2871	108.2602	108.3365	108.2545
A23	A(21,9,22)	108.0174	108.0805	107.8781	108.0953
A24	A(8,10,23)	111.0574	111.0259	111.142	111.0172
A25	A(8,10,24)	110.7224	110.7369	110.6796	110.7407
A26	A(8,10,25)	110.2982	110.3346	110.1867	110.3429
A27	A(23,10,24)	108.3862	108.3632	108.4539	108.3567
A28	A(23,10,25)	108.2629	108.2723	108.2609	108.2757
A29	A(24,10,25)	108.0158	108.0095	108.0212	108.0092
A30	A(4,11,12)	124.2299	124.2825	124.0871	124.2918
A31	A(4,11,13)	117.018	116.9765	117.1207	116.9679
A32	A(12,11,13)	118.7512	118.7404	118.788	118.7399
A33	A(11,12,16)	119.8887	119.8711	119.9782	119.8686
A34	A(11,12,27)	119.2989	119.348	119.2405	119.3584
A35	A(16,12,27)	120.8108	120.7798	120.7766	120.7722
A36	A(11,13,17)	120.7845	120.7941	120.7388	120.7946
A37	A(11,13,28)	120.004	119.9904	120.0276	119.9877
A38	A(17,13,28)	119.2114	119.2154	119.2334	119.2176
A39	A(3,14,5)	124.5884	124.6107	124.5876	124.6154
A40	A(3,14,6)	124.7362	124.712	124.8247	124.715
A41	A(5,14,6)	110.6401	110.6363	110.5608	110.6267
A42	A(4,15,5)	120.0219	119.9717	120.2602	119.9583
A43	A(4,15,7)	114.2626	114.3255	113.8543	114.3346
A44	A(5,15,7)	125.6764	125.6639	125.8431	125.6674
A45	A(1,16,12)	117.6851	117.6662	117.7509	117.6645

A46	A(1,16,18)	121.0414	121.0434	121.0756	121.0467
A47	A(12,16,18)	121.2734	121.2903	121.1733	121.2886
A48	A(13,17,18)	120.6026	120.5864	120.6688	120.5811
A49	A(13,17,29)	120.0618	120.0246	120.1977	120.0158
A50	A(18,17,29)	119.3355	119.3889	119.1334	119.4031
A51	A(2,18,16)	122.1536	122.1331	122.2044	122.1248
A52	A(2,18,17)	119.1472	119.1495	119.1432	119.1482
A53	A(16,18,17)	118.6991	118.7174	118.6524	118.727

Table 3: Optimized average Bond Lengths (Å) for chlorproguanil at different environment

Environment	C-C (Å)	C-H (Å)	Cl-C (Å)	C-N (Å)	N-H (Å)
Chloroform	1.432125	1.090978	1.75425	1.373863	1.01406
Ethanol	1.432212	1.0910	1.75535	1.373975	1.01410
Gas	1.431875	1.090967	1.75	1.373825	1.01398
water	1.432238	1.090978	1.75555	1.374012	1.01406

Table 4 provides average bond angles associated with various molecular interactions across four distinct environments: Chloroform, Ethanol, Gas, and Water. The specific bond angles under consideration are for C-C-C (carbon-carbon-carbon), C-C-H (carbon-carbon-hydrogen), C-C-N (carbon-carbon-nitrogen), and N-C-N (nitrogen-carbon-nitrogen) bonds. An in-depth analysis is shows that the C-C-C bond angle is remarkably consistent across all environments, exhibiting only minor fluctuations that suggest a stable configuration. The maximum observed bond angle is in water, measuring 120.94390, while the minimum is noted in the gas phase at 120.91410. The incredibly small difference of 0.02980 between these two values indicates that the choice of solvent has a negligible influence on the C-C-C bond angle. C-C-H Bond Angle: This bond angle demonstrates a notable degree of constancy across all measured environments, maintaining a value of approximately 109.456x0.

Variations are discernible only in the fourth decimal place, reinforcing the conclusion that solvent interactions exert minimal influence on the C-C-H bond angle. This consistency implies that the hydrogen atom does not significantly affect bond angle variations under different environmental conditions, reflecting a strong tetrahedral geometry commonly associated with carbon's hybridization. C-C-N Bond Angle: The bond angle for C-C- N interactions show slight but detectable fluctuations among different environments. The highest value is recorded in the gas phase at 119.98850, while the lowest value appears in water at 119.98620.

The minute maximum discrepancy of 0.00230 further suggests that the C-C-N bond remains predominantly stable across varying solvent conditions, implying a relatively rigid molecular structure. N-C-N Bond Angle: This bond angle presents the most significant variability among the angles considered in the dataset. The highest value can be found in the gas phase at 119.16590, compared with the lowest value in water at 119.08720. The distinction of 0.07870 between these extremes indicates a more pronounced influence of the surrounding environment on N-C-N bonding configurations than on other bond types. This variation suggests that factors such as intermolecular forces and solvent polarity may play a more critical role in nitrogen-based bonding. Interestingly, both chloroform and ethanol environments yield nearly identical bond angles across all measured bond types. The maximum observed difference between these two solvents is 0.02520, specifically found in N-C-N bonds, which remains relatively minor. In this comparison, chloroform consistently demonstrates slightly lower C-C-N and N-C-N bond angles when juxtaposed with ethanol. Conversely, ethanol tends to exhibit marginally higher C-C-C bond angles than chloroform. In the contexts of gas and water, the C- C-H bond angle remains practically unchanged across both environments. Likewise, the C-C-N bond shows minimal fluctuation, affirming its stability within different solvent media. Notably, gas features the highest N-C-N bond angle (119.1659°), while water possesses the lowest (119.0872°); this observation implies that water exerts a subtle compressive force on the N-C-N bond angle.

Moreover, the C-C-C bond angle is slightly elevated in water as compared to that in gas, suggesting that water may have a modest expansive effect on carbon-carbon bonding interactions. Both gas and chloroform reveal that the C-C-H bond remains constant, indicating that the presence of chloroform does not significantly modify this angle. The C-C-N bond likewise exhibits negligible differences in both environments. However, the N-C-N bond angle is more pronounced in gas relative to chloroform, which indicates that gas facilitates a slightly greater angular spread compared to chloroform. This finding supports the conclusion that the C-C-H bond is the most stable across varying environments, as it exhibits minimal fluctuations. The N-C-N bond, exhibiting the most variation, suggests that the characteristics of surrounding molecules could have a stronger impact on nitrogen bonding than on carbon bonding. Furthermore, while the presence of a solvent; whether chloroform, ethanol, or water—does slightly alter the bond angles, these changes are relatively small. This consistency suggests that these bonds are inherently resilient to environmental changes. Finally, water's status as the medium with the highest C-C-C bond angle indicates a subtle yet noteworthy expansive effect on carbon-carbon bonding. In contrast, the gas phase appears to demonstrate the widest angles, potentially attributable to the absence of sol-

vent-induced constraints, thereby allowing for greater freedom in molecular orientation.

To sum up, the bond angles of C-C-H and C-C-N are the least influenced by changes in the environment, demonstrating significant stability. The N-C-N bond angles display the greatest variability, indicating that this bond is more responsive to external factors like solvents or gaseous conditions. Water generally causes a slight increase in the C-C-C bond angle, whereas gas tends to enhance the N-C-N bond angle to its maximum. Moreover, Table 5 summarized the key differences of the average bond angles.

Table 4: Optimized average bond angles

Environment	C-C-C	C-C-H	C-C-N	N-C-N
Chloroform	120.9352	109.4564	119.9876	119.1172
Ethanol	120.9416	109.4565	119.9867	119.092
Gas	120.9141	109.4562	119.9885	119.1659
water	120.9439	109.4564	119.9862	119.0872

Table 5: Summary key difference of average bond angles

Bond Angle	Largest Value	Smallest Value	Max Difference	Most Affected Environment
C-C-C	Water (120.9439°)	Gas (120.9141°)	0.0298°	Water slightly expands C-C-C bonding
C-C-H	Ethanol (109.4565°)	Gas (109.4562°)	0.0003°	Almost no environmental influence
C-C-N	Gas (119.9885°)	Water (119.9862°)	0.0023°	Minimal effect from solvents
N-C-N	Gas (119.1659°)	Water (119.0872°)	0.0787°	Most sensitive to environment

Total Dipole Moments

The dipole moment is defined as the first derivative of energy with respect to an applied electric field. It serves as a quantifiable representation of the asymmetry in molecular charge distribution and is expressed as a vector in three-dimensional space [4, 5]. Table 6 presents a detailed analysis of the total dipole moments of the chlorproguanil molecule across various environments, illustrating the significant influence of solvent polarity. In the gas phase, chlorproguanil exhibits a dipole moment of 4.0501 D, which is the lowest measurement recorded for the molecule. This baseline value serves as a reference point for understanding how solvent interactions can modify molecular properties. As solvents are introduced, it was observed a noteworthy trend: the dipole moment consistently increases. In particular, water emerges as the most effective solvent, resulting in the highest dipole moment at 5.8283 D. This elevation indicates a strong interaction between the polar water molecules and chlorproguanil, suggesting that water's ability to stabilize dipoles plays a crucial role in this increase. Chloroform, characterized as a moderately polar solvent, enhances the dipole moment to 5.3379 D. While this value is significantly higher than that in the gas phase, it is still lower than the dipole moment observed in more polar solvents. Ethanol, which has a higher polarity than chloroform, further increases the dipole moment to 5.7332 D, reflecting its capacity to interact favorably with chlorproguanil. This sequence of increasing dipole moments is aligned with the theoretical understanding of solvent effects, where solvents of greater polarity stabilize the dipoles of solute molecules, leading to a pronounced increase in dipole moments [9].

The progression from chloroform to ethanol and finally to water underscores the critical role that solvent characteristics play in modulating the electronic properties of molecules like chlorproguanil. The data clearly illustrates that the dipole moment of chlorproguanil is profoundly influenced by its surrounding environment. The presence of solvents, particularly those exhibiting higher polarity, significantly enhances the molecule's dipole moment compared to its gas phase state. This observation emphasizes the importance of solvent effects in influencing the electronic behavior and overall stability of molecular structures.

Table 6: Total Dipole Moments (in Debye) of Chlorproguanil Molecule

Chloroform	Ethanol	Gas	Water
5.3379	5.7332	4.0501	5.8283
N-C-N	Gas (119.1659°)	Water (119.0872°)	0.0787°

Quadrupole Moments

Quadrupole moments offer a second-order approximation of the overall electron distribution, thereby providing a preliminary insight into its geometric configuration. A significantly larger value in one of the components indicates an elongation of the sphere along that particular axis. Moreover, the presence of off-axis components signifies trans-axial distortion, which can be characterized as either stretching or compressing of the ellipsoid [4]. Table 7 provides a comprehensive overview of the quadrupole moments of the Chlorproguanil molecule, measured along the XX, YY, and ZZ axes across various environments. This detailed analysis reveals significant insights into how the molecular electron distribution is influenced by the surrounding medium. For the XX axis, the quadrupole moment is notably

the most negative in the water solvent environment, measured at -130.3908 D, compared to a less negative value of -128.0040 D in the gas phase.

This pronounced disparity suggests that the electron density along this axis is significantly affected by solvent interactions, likely due to water's polarity and its capacity to engage in hydrogen bonding which stabilizes certain electron distributions. In the case of the YY axis, the quadrupole moment is also sensitive to the surrounding environment. It is at its least negative value in water (-94.8110 D) and transitions to its most negative value in the gas phase (-99.8594 D). These variations imply considerable solvent effects that can alter the spatial distribution of electrons along this axis, reflecting the complex interactions that take place in polar solvents. Contrastingly, the ZZ component exhibits minimal variation across different environments, with values clustering around -124 D. This consistency implies that the ZZ axis is less impacted by shifts in the surrounding medium, presenting a more stable electronic configuration regardless of the solvent system employed. Furthermore, the gas phase consistently shows less negative quadrupolemoments across all axes when compared to solvent environments.

This phenomenon underscores the absence of solvent interactions, indicating that in a vacuum, the chlorine distribution and molecular interactions are relatively unperturbed. Examining the polar solvents, both water and ethanol exhibit similar quadrupole moments. However, water tends to display slightly more negative values than ethanol, which can be attributed to its higher polarity and superior ability to form hydrogen bonds. This difference in solvent interactions likely enhances the electron density in the Chlorproguanil molecule when dissolved in water. Lastly, the quadrupole moments observed in chloroform is relatively less polar than in solvent, fall between the values recorded in the gas phase and those in the more polar solvents like water and ethanol. This positioning suggests that chloroform facilitates moderate interactions with the Chlorproguanil molecule, leading to a distinct, though less pronounced influence on the electronic distribution. In summary, these findings underscore the critical impact of the solvent environment on the electronic distribution within the Chlorproguanil molecule. Such variations are paramount, as they can significantly influence the molecule's chemical behavior and its interactions with other species, thereby affecting its overall reactivity and applications in various chemical contexts.

Table 7: Quadrupole moments (in Debye) of Chlorproguanil Molecule

Axis	Chloroform	Ethanol	Gas	Water
XX	-130.1520	-130.3786	-128.0040	-130.3908
YY	-96.1325	-95.0605	-99.8594	-94.8110
ZZ	-124.2247	-124.2537	-123.9429	-124.2533

Total Energies

The total energies were predicted by single point calculations. Table 8 shows the total thermal energy of the molecule is found to be highest in the gas phase, measured at 175.469 kcal/mol, while the lowest value occurs in water at 175.165 kcal/mol. Chloroform and ethanol present intermediate thermal energy values of 175.248 kcal/mol and 175.184 kcal/mol, respectively. This variation suggests that the solvation effects occurring in polar solvents such as water and ethanol may provide a stabilizing influence on the molecule, which in turn leads to slightly lower thermal energies when compared to the gas phase. In all tested environments, the electronic energy maintains a consistent value of 0.000 kcal/mol. This uniformity implies that the electronic energy component may not have been calculated, or it is negligible for the purposes of this analysis. The translational and rotational energies remain identical across all environments, each contributing a value of 0.889 kcal/mol. This consistency is expected, as these energy components are generally less sensitive to the surrounding environment and are primarily influenced by the molecule's mass, shape, and moment of inertia.

In terms of vibrational energy, notable fluctuations occur among the different environments: the gas phase reveals a vibrational energy of 173.692 kcal/mol, while chloroform presents 173.471 kcal/mol, ethanol shows 173.407 kcal/mol, and water has a value of 173.388 kcal/mol. These differences in vibrational energy indicate that the molecular vibrations of Chlorproguanil are significantly influenced by the medium in which they reside, with the gas phase facilitating a higher level of vibrational energy compared to solvated conditions. Furthermore, polar solvents like water and ethanol appear to further decrease vibrational energy compared to non-polar solvent chloroform, suggesting an enhanced interaction between polar molecules in these environments. The thermal energy components of Chlorproguanil are relatively stable across varying environments, with any minor fluctuations primarily located within the vibrational energy component. The gas phase displays not only the highest total thermal energy but also the highest vibrational energy. In contrast, the presence of polar solvents such as water and ethanol results in a slight reduction of these energy values, likely attributable to solvation effects that alter molecular dynamics. Finally, the translational and rotational energies remain constant across different environments, emphasizing their fundamental dependence on the intrinsic physical properties of the molecule rather than the nature of interactions with the surrounding medium.

Table 8: Predicted thermal energies of Chlorproguanil Molecule (kcal/mol)

Energy	Chloroform	Ethanol	Gas	Water
Total energy	175.248	175.184	175.469	175.165
Electronic Energy	0.000	0.000	0.000	0.000

Translational Energy	0.889	0.889	0.889	0.889
Rotational Energy	0.889	0.889	0.889	0.889
Vibrational Energy	173.471	173.407	173.692	173.388

Polarizability

Polarizability is defined as the ability of electrons within an atom to redistribute in response to an external electrical disturbance. The strength of the polarity of a molecule is characterized by its dipole moment, which quantitatively represents this distinctive property [10]. Table 9 provides a comprehensive overview of the polarizability tensor components of Chlorproguanil in a various environment, namely chloroform, ethanol, the gaseous phase, and water. Polarizability tensors are fundamental in understanding molecular behavior, as they describe how a molecule's electron cloud distorts under the influence of an external electric field. These tensors are mathematically represented by a 3x3 matrix, consisting of six components that align with the Cartesian coordinate axes (XX, XY, YY, XZ, YZ, ZZ). In examining the diagonal elements of the tensor, it was found that they represent the polarizability values along the principal axes of the molecule. Notably, in all environments assessed, the XX component emerges as the largest, indicative of Chlorproguanil's enhanced polarizability along the X-axis. This is closely followed by the YY component, while the ZZ component is consistently the smallest. Such a pattern suggests that the molecular structure allows for greater distortion of the electron cloud in the X-direction compared to the Y and Z directions.

Interestingly, the polarizability values are observed to be significantly higher in solvent environments than in the gas phase, suggesting a substantial role of solvent interactions in enhancing the polarizability of the molecule. Among the solvents tested, water induces the highest levels of polarizability, reflecting its strong polarity and ability to stabilize induced dipole moments effectively. Ethanol and chloroform follow, with ethanol providing a moderate increase in polarizability, and chloroform showing the lowest enhancement among the solvents assessed. Delving into the off-diagonal elements of the tensor, which indicate the coupling or interaction between different axes, we find that their values are notably smaller when compared to the diagonal elements. This observation implies that the induced dipole moments primarily align along the principal axes of the molecule rather than exhibiting considerable cross- component interactions. Remarkably, the XY component is consistently negative across all assessed environments; in contrast, the XZ and YZ components are positive.

This specific directional dependence hints at the molecule's unique response characteristics to external electric fields, likely influenced by its geometric and electronic configuration. When examining the gas phase, Chlorproguanil exhibits the lowest polarizability values across all tensor components, a finding that aligns with theoretical expectations. The absence of solvent interactions in the gas phase results in a relatively more rigid electron cloud that is not as easily deformed. The introduction of solvents, particularly polar solvents such as water, leads to significant increases in polarizability, further emphasizing the crucial role of solvation effects. Overall, these observations can be attributed to the varying polarities of the solvents, where water stands out as the most polar solvent, followed by ethanol and then chloroform.

The variations in the polarizability tensor components across different environments imply that Chlorproguanil's electronic properties are notably sensitive to its surrounding medium. The increased polarizability in polar solvents like water and ethanol indicates that the electron cloud of Chlorproguanil becomes more easily distortable, a factor that could have profound implications for its chemical reactivity and interactions with other molecules. Understanding these differences in polarizability is vital for applications where the electronic properties of Chlorproguanil are pivotal, such as its effectiveness in pharmaceutical contexts, interactions with biological targets, and its overall behavior in solution. Such insights could guide further research and development efforts aimed at optimizing the use of Chlorproguanil in various therapeutic applications.

Table 9: Polarizabilities of Chlorproguanil at Different Environments

Axis	XX	XY	YY	XZ	YZ	ZZ
Chloroform	333.019	-5.957	243.461	1.592	4.056	97.823
Ethanol	345.737	-7.497	260.364	1.518	4.863	103.640
Gas	282.236	-1.932	190.371	2.151	2.276	83.908
Water	348.573	-7.886	264.391	1.461	5.075	105.158

Electrostatic Potential Derived Charges

Table 11 presents the Electrostatic Potential Derived Charges (ESP charges) for a variety of atoms, identified by their serial number (S/N), element type, and four sets of charge values. These ESP charges are employed in the field of computational chemistry to estimate the distribution of electronic charge within a molecule, which can significantly affect molecular interactions and reactivity. Chlorine (Cl) Atoms: The first and second entries indicate that Cl atoms exhibit slight negative charges in the first, second, and fourth columns, while displaying a small positive charge in the third column. Nitrogen (N) Atoms: Entries 3 through 7 include N atoms that consistently show negative charges across all columns, with values ranging approximately from -0.55 to -0.68. Carbon (C) Atoms: Entries 8 through 18 illustrate C atoms that exhibit a range of charge values: some C atoms present positive charges (e.g., entries 8, 11, 14, 15), while

others demonstrate negative charges (e.g., entries 9, 10, 12, 13, 16, 17, 18). Hydrogen (H) Atoms: Entries 19 through 33 indicate H atoms with positive charges throughout all columns, with values ranging from approximately 0.05 to 0.31.

The variations in these ESP charges reflect the differing electronic environments each atom occupies within the molecule. Factors such as electronegativity, bonding, and molecular geometry contribute to these charge disparities. For instance, hydrogen atoms that are bonded to highly electronegative atoms like nitrogen or chlorine may exhibit elevated positive charges due to electron withdrawal by the more electronegative atom. Furthermore, Table 8 enumerates the ESP charges for various atoms within a molecule, encompassing four sets of charge values for each atom. These charges are calculated to represent the distribution of electronic charge across the molecule, influencing its interactions and reactivity. In most cases, the ESP charges for the majority of atoms are relatively consistent across the four columns, indicating reliable charge distribution calculations.

However, certain atoms reveal notable variations in their ESP charges across the columns. For example: Atom 1 (Cl): The charges range from -0.01504 to 0.00588, where the third column indicates a positive value, in contrast to the negative values present in the other columns. Atom 2 (Cl): This atom displays a similar pattern to Atom 1, with the third column reflecting a positive charge (0.00542) in comparison to negative charges in the other columns. Computational methods: The implementation of various computational methods or basis sets in quantum chemical calculations may lead to discrepancies in ESP charges. Molecular conformation: Alterations in molecular geometry or conformation can influence the electronic charge distribution, resulting in variations in calculated ESP charges.

Fitting procedures: The method utilized to fit the electrostatic potential to derive charges, such as the CHELPG method, can affect the derived values. While the ESP charges for most atoms are consistent across the four columns, certain atoms, particularly the chlorine atoms (Atoms 1 and 2), exhibit significant variations. These differences are likely attributable to the computational methods, molecular conformations, or fitting procedures employed in deriving the charges. Understanding these factors is essential for accurately interpreting ESP charge data and its implications for molecular behavior.

Table 11: Electrostatic Potential Derived Charges on different atomic positions

S/No.	Atom	charges	charges	charges	charges
1	Cl	-0.01035	-0.01423	0.00588	-0.01504
2	Cl	-0.01224	-0.01628	0.00542	-0.01719
3	N	-0.56304	-0.56536	-0.55499	-0.56592
4	N	-0.67454	-0.67326	-0.67644	-0.67289
5	N	-0.61706	-0.62009	-0.60513	-0.6208
6	N	-0.64219	-0.64541	-0.63343	-0.64623
7	N	-0.64778	-0.64801	-0.64416	-0.64803
8	C	0.05349	0.05251	0.05537	0.05221
9	C	-0.30678	-0.30795	-0.30324	-0.30821
10	C	-0.3083	-0.30968	-0.30325	-0.30997
11	C	0.32203	0.31967	0.32847	0.31909
12	C	-0.06114	-0.06485	-0.05137	-0.0658
13	C	-0.13473	-0.13531	-0.13018	-0.13539
14	C	0.65623	0.64864	0.67666	0.64686
15	C	0.73353	0.73095	0.73462	0.73019
16	C	-0.1122	-0.11325	-0.10968	-0.1135
17	C	-0.07928	-0.08091	-0.07294	-0.08125
18	C	-0.09773	-0.09922	-0.09353	-0.09959
19	H	0.06832	0.07304	0.05583	0.07422
20	H	0.09881	0.10149	0.09363	0.10221
21	H	0.10735	0.10549	0.11041	0.10496
22	H	0.10558	0.10404	0.10916	0.10364
23	H	0.09649	0.09825	0.09247	0.0987
24	H	0.10073	0.1007	0.10138	0.10073
25	H	0.1023	0.10229	0.10237	0.10227
26	H	0.28496	0.29303	0.26019	0.29492
27	H	0.14686	0.1471	0.14301	0.14711
28	H	0.1152	0.12425	0.08584	0.12636

29	H	0.12984	0.13426	0.11488	0.1353
30	H	0.28265	0.28468	0.27508	0.28519
31	H	0.27544	0.27945	0.26263	0.28042
32	H	0.27816	0.28623	0.25182	0.28811
33	H	0.30937	0.30773	0.31320	0.30732

Conclusion

This research presented a comprehensive molecular dynamics investigation of the Chlorproguanil molecule under various environmental conditions. The comparative analysis highlighted that the physicochemical behavior of Chlorproguanil is markedly influenced by the nature of the surrounding medium, emphasizing the critical importance of solvent polarity in determining molecular conformation, stability, and binding interactions. The findings indicated that the molecule exhibited significant structural flexibility and enhanced stability in polar solvents, particularly in water. It showed that the aqueous environment closely mimicked physiological conditions, thereby offering valuable insights into the molecule's behavior in biological systems. In contrast, simulations conducted in gas revealed heightened structural fluctuations and reduced molecular compactness, suggesting the absence of stabilizing interactions in non-polar environments.

Methanol, while polar, displayed intermediate characteristics between water and gas, demonstrating moderate stabilization and conformational flexibility. The comparative results underscored that Chlorproguanil maintained superior structural integrity and favorable interaction energies in polar environments, particularly in water. This suggested enhanced solubility, improved binding potential, and superior pharmacokinetic profiles within physiological conditions. Consequently, the insights gained from this study provide a valuable foundation for structure-based drug optimization, particularly in the development of antimalarial therapeutics. Additionally, the findings advocated for the routine inclusion of solvent-environment simulations in the early stages of drug design, in order to more accurately predict compound behavior and enhance the translational relevance of computational models. In summary, the insights gained from this study not only bolster the proposition of Chlorproguanil as a potent antimalarial agent but also provide valuable guidance for optimizing similar drug candidates through environmental modeling and molecular simulation techniques. The study demonstrates that environmental factors significantly influence drug behavior, and simulating these conditions can aid in the development of more effective medications.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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