

Evaluation of Quantum Chemical Methods and Basis Sets Applied in the Molecular Modeling of Artemisinin

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ABSTRACT

In this paper, we evaluate semiempirical methods (AM1, PM3, and ZINDO), HF and DFT (B3LYP) in different basis sets to determine which method best describes the sign and magnitude of the geometrical parameters of artemisinin in the region of the endoperoxide ring compared to crystallographic data. We also classify these methods using statistical analysis. The results of PCA were based on three main components, explaining 98.0539% of the total variance, for the geometrical parameters C3O13, O1O2C3, O13C12C12a, and O2C3O13C12. The DFT method (B3LYP) corresponded well with the experimental data in the hierarchical cluster analysis (HCA). The experimental and theoretical angles were analyzed by simple linear regression, and statistical parameters (correlation coefficients, significance, and predictability) were evaluated to determine the accuracy of the calculations. The statistical analysis exhibited a good correlation and high predictive power for the DFT (B3LYP) method in the 6-31G** basis set.

Keywords: Artemisinin; Molecular Modeling; Quantum Chemical Methods; Statistical Analysis; B3LYP/6-31G**

1. Introduction

Artemisinin (or Qinghaosu, QHS, **Figure 1**) represents the most relevant advance in the treatment of malarial disease for the last 20 years [1]. Artemisinin is a sesquiterpene lactone with an endoperoxide group, which has been used in traditional Chinese medicine for many centuries as a natural product for fever and malarial treatment. This drug was isolated by Chinese chemists in the early 1970s from the ancient *Artemisia annua* L. Nowadays, artemisinin and derivatives are widely used around the world because of their potent antimalarial activity, fast action, and low toxicity. As a result, artemisinin and its derivatives have become recognized as a new generation of antimalarial drugs [2].

Many studies on the rational design of new antimalarial drugs have been performed using molecular modeling.

However, complex molecular systems containing external and internal transition atoms, proteins, polymers, or compounds with a higher molecular weight overestimate the ability of these methods and basis sets to obtain molecular properties, which can lead to inaccurate results when compared with experimental data. Therefore, an evaluation of these methods and basis sets will be strongly dependent on the system under consideration [3].

Costa *et al.* studied the interaction between heme and artemisinin using the PM3 method, which exhibited a potential energy barrier for the relative rotation of the artemisinin-heme complex being studied both *in vacuo* and partially solvated. The authors observed that the inclusion of water molecules did not significantly affect the stability of the heme-artemisinin complex [4].

Leite *et al.* conducted studies of 18 natural compounds from Brazilian flora, which possess a peroxide group and

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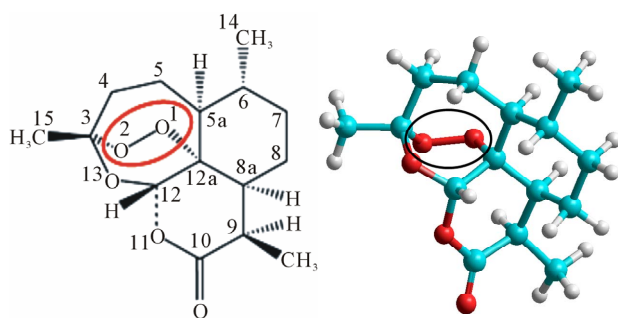


Figure 1. Artemisinin (structure) and region essential for the expression of biological activity (pharmacophore).

are assumed to act in heme protein, leading to a reduction in peroxide binding and the production of radicals that can kill the etiological agents of malaria (*Plasmodium falciparum* strains). These findings motivated the researchers to study the interactions among 18 natural peroxides. They initially performed a conformational search using the MM3 method for each molecule, and the most stable conformers were optimized by the PM3 (tm) method. The interactions between the peroxide-heme groups were then evaluated, and the results indicated that four of the compounds may exhibit desirable antimalarial activity [5].

Recent studies on 51 peroxides were conducted to identify correlations between *in silico* parameters and experimental data for identifying new antimalarial agents from natural sources. The interaction of the heme group was studied by molecular docking refinement followed by conformational analysis using semiempirical parametric method 6 (PM6). The results indicated that two of these compounds are promising antimalarials [6].

Artemisinin derivatives with antimalarial activity against *Plasmodium falciparum*, which is resistant to mefloquine, were studied using quantum chemical methods (HF/6-31G*) and the partial least-squares (PLS) method. Three main components explained 89.55% of the total variance, with $Q^2 = 0.83$ and $R^2 = 0.92$. From a set of 10 proposed artemisinin derivatives (artemisinin derivatives with unknown antimalarial activity against *Plasmodium falciparum*), a novel compound was produced with superior antimalarial activity compared to the compounds previously described in the literature [7].

Recently, Cristino *et al.* [8] used the B3LYP/6-31G* method to model artemisinin and 19,10-substituted deoxyartemisinin derivatives, with different degrees of activity against the *Plasmodium falciparum* D-6 strains of Sierra Leone. Chemometric methods (PCA, HCA, KNN, SIMCA, and SDA) were employed to reduce the dimensionality and to determine which subset of descriptors is responsible for the classification between more and less active agents.

Figueiredo *et al.* [9] conducted studies using the

B3LYP/6-31G* method for antimalarial compounds against *Plasmodium falciparum* K1. These studies led to multivariate models for artemisinin derivatives and series of dispiro-1,2,4-trioxolanes. The application of these models has enabled the prediction of activity for compounds designed without known biological activity. Moreover, a new series of antimalarial compounds is currently in the study phase.

Araújo *et al.* [10] used density functional theory (6-31G*) to verify the performance of a basis set in reproducing experimental data, particularly geometrical parameters, and to calculate the interaction energies, electronic states, and geometrical arrangements for complexes composed of a heme group and artemisinin. The results demonstrated that the interaction between artemisinin and the heme group occurs at long distances through a complex in which the iron atom of the heme group retains its electronic characteristics, with the quintet state being the most stable. These results suggest that the interaction between artemisinin and heme is thermodynamically favorable.

In this paper, we propose to identify the best method and basis set for molecular modeling of the pharmacophoric group of artemisinin and its derivatives. There is currently a diversity of methods and basis sets that can be applied to reproduce experimental data and to elucidate the biological significance of this compound. An identification of the best theoretical method for data acquisition is critical in achieving credible *in silico* results with respect to biological action. Artemisinin was modeled using five methods and seven basis sets (6-31G, 6-31G*, 6-31G**, 3-21G, 3-21G*, 3-21G**, and 6-311G) based on the properties of the endoperoxide group present in artemisinin, which is responsible for the biological activity, and the results were evaluated via principal component analysis (PCA), hierarchical cluster analysis (HCA), and statistical analysis using simple linear regression.

2. Experimental

2.1. Molecular Modeling of Artemisinin

The artemisinin compound was constructed as follows: initially, the structure of artemisinin was established with the Gauss View 3.0 program [11] and optimized using different methods and basis sets: semiempirical (AM1, PM3, and ZINDO), Hartree-Fock (HF/6-31G, HF/6-31G*, HF/6-31G**, HF/3-21G, HF/3-21G*, HF/3-21G**, and HF/6-311G), and DFT (B3LYP/6-31G, B3LYP/6-31G*, B3LYP/6-31G**, and B3LYP/3-21G) implemented with the Gaussian 03 program [12]. These calculations were performed to determine which methods and basis sets provide the best compromise between computational time and accuracy compared to the experimental data [13]. The experimental structure of artemisinin was re-

moved from the Database Cambridge Structural CSD with REFCODES: QNGHSU10, crystallographic R factor 3.6 [14]. The numbering of atoms adopted in this study is shown in **Figure 1** (artemisinin).

When measurements are made on a number of objects, the results are typically organized in a data matrix. The measures in this study (geometrical parameters) were organized in rows, and the objects (quantum chemical methods and basis sets) were organized in columns. Statistical analysis was conducted with the Piroutte 3.10 and Statistica 6.2 programs [15,16].

The statistical analysis of the geometrical parameters was based on the studies of Silva *et al.*, in which density functional theory (DFT) calculations (B3PW91/DGD-ZVP) were employed to determine ^{13}C and ^1H nuclear magnetic resonance (NMR) chemical shifts for the two dihydrochalcones: 3,4,5-tetramethoxydihydrochalcone and 2,3,4,4-trimethoxydihydrochalcone. The theoretical and experimental NMR data were analyzed by simple linear regression, and the most relevant parameters were selected. In addition, other statistical parameters (correlation coefficients, significance, and predictability) were employed to verify the accuracy of the calculations. The statistical analysis indicated a good correlation between the NMR experiment results and the theoretical data, with high predictive power [17].

2.2. Principal Component Analysis (PCA)

PCA was performed with autoscaled processing for a maximum of three factors (3PCS), using the “leave-one-out validation method and cross-validation” procedure. The data matrix was constructed from the combinations of methods and basis sets, resulting in a 15×18 matrix. Each column was related to five methods and seven basis sets, and one column was related to the experimental geometrical parameters [13]. Each row represents 18 geometrical parameters of the 1,2,13-trioxane ring (bond lengths, bond angles, and torsion angles). The final PCA results led to the selection of a small number of geometrical parameters that were most strongly related to the dependent variable, which was the standard deviation of the methods and basis sets in this case.

2.3. Hierarchical Cluster Analysis (HCA)

Similar to the PCA results, the HCA results are qualitative and are arranged in the form of a dendrogram to display the methods studied and the variables (geometrical parameters of artemisinin) in a two-dimensional space. The results illustrate the combinations or divisions made in each successive stage of analysis. The samples (methods and basis sets) are represented by the bottom branch of the dendrogram. The similarity between agglomerates is given by the length of each branch such that methods

and basis sets with low levels of similarity have long branches and methods and basis sets with high similarity have short branches [18]. In HCA, the distance between these variables is calculated and transformed into a similarity matrix S . A hierarchical cluster analysis aims to display data in a manner that accentuates the natural groupings and patterns. Statistical analysis was required in this study to group similar methods and basis sets in their respective categories. HCA is a statistical method that was developed for this purpose.

2.4. Statistical Analysis

Statistical analysis via simple linear regression can correlate data from more relevant parameters to estimate and predict values using a model built with a full dataset and actual values of y_i (r), the explained variance (R_A^2 , *i.e.*, adjusted R^2), Fisher ratio values (F), and the standard error of estimation (SEE). The equations were also tested for their predictive power using a cross-validation procedure. Cross-validation is a practical and reliable method for verifying the predictive power. In the so-called “leave-one-out” approach, a number of models are developed with one sample omitted in each step. After developing each model, the omitted data are predicted and the differences between the actual and predicted y values are calculated. The sum of squares of these differences is computed, and finally, the performance of the model (its predictive ability) can be given by the prediction residual error sum of squares (PRESS) and standard deviation of the cross-validation (S_{PRESS}), as shown in Equations (1) and (2) [19]:

$$\text{PRESS} = \sum_{i=1}^n (y_i - \hat{y})^2 \quad (1)$$

$$S_{\text{PRESS}} = \frac{\sqrt{\text{PRESS}}}{n - k - 1} \quad (2)$$

where y_i is the experimental value, \hat{y} is the predicted value, n is the number of samples used to build the model, and k is the number of geometrical parameters. The predictive ability of the model can also be quantified in terms of the cross-validated correlation coefficient (Q^2), which is defined as [19]

$$Q^2 = 1.0 - \frac{\text{PRESS}}{\sum_{i=1}^n (y_i - \bar{y})^2}; \text{ where, } \bar{y} = y_{\text{mean}} \quad (3)$$

In addition, other statistical parameters are available to verify the accuracy of the calculation, but none of these parameters are fully satisfactory if taken alone. For each system, we present parameters a and b from linear regression $\delta_{\text{calcd}} = a + b\delta_{\text{exptl}}$; the mean absolute error (MAE) defined as $\text{MAE} = \sum_n |\delta_{\text{calcd}} - \delta_{\text{exptl}}|/n$, and the corrected mean absolute error, CMAE [20], defined as

$CMAE = \sum_n |\delta_{corr} - \delta_{exptl}| / n$, where $\delta_{corr} = (\delta_{calcd} - a) / b$ to correct for systematic errors.

3. Results and Discussion

3.1. Determination of the Theoretical Geometrical Parameters of Artemisinin

We determined the geometrical parameters for the 1,2,13-trioxane ring of artemisinin (bond length, bond angle, and torsion angle of atoms in this ring), as shown in **Table 1**. **Table 1** illustrates that for the DFT method, all four basis sets (B3LYP/6-31G, B3LYP/6-31G*, B3LYP/6-31G**, and B3LYP/3-21G) can accurately describe all of the structural parameters with respect to their magnitude and sign when compared with the experimental values. Meanwhile, the semiempirical (AM1, PM3, and ZINDO) and Hartree-Fock (HF/6-31G, HF/6-31G*, HF/6-31G**, HF/3-21G, HF/3-21G*, HF/3-21G**, and HF/6-311G) methods exhibited standard deviations of 4.776, 8.388, and 4.372 and 1.663, 2.484, 1.762, 1.722, 1.714, 1.797, and 1.658, respectively. By comparing these methods with the DFT method, we find that all of the basis sets (B3LYP/6-31G, B3LYP/6-31G*, and B3LYP/6-31G**) have low standard deviations in relation to the semiempirical and Hartree-Fock methods at 0.843 (B3LYP/6-31G), 1.227 (B3LYP/6-31G*), and 1.103 (B3LYP/6-31G**). The variation was ± 0.384 be-

tween B3LYP/6-31G and B3LYP/6-31G*, ± 0.260 between B3LYP/6-31G and B3LYP/6-31G**, and ± 0.124 between B3LYP/6-31G* and B3LYP/6-31G**.

3.2. PCA and HCA

The advantage of the PCA and HCA methods in this study is that all structural parameters are considered simultaneously and all of their correlations are considered.

Figure 2 presents the PC1-PC2 scores for the five methods and seven basis sets and one score related to the experimental geometrical parameters of the 1,2,13-trioxane ring. The methods are divided into two groups according to PC2, where the semiempirical and Hartree-Fock methods are located at the bottom and the experimental data and the DFT/B3LYP method and basis sets (B3LYP/6-31G, B3LYP/6-31G*, B3LYP/6-31G**, and B3LYP/3-21G) are located at the top.

Figure 3 presents the PC1-PC2 loading for the four most important geometrical parameters related to the trioxane ring, namely, C3O13, O1O2C3, O13C12C12a, and O2C3O13C12. These geometrical parameters are responsible for the separation of the methods and basis sets into three groups, namely, semiempirical, Hartree-Fock, and DFT methods, as shown in **Figure 2**. The four geometrical parameters related to the trioxane ring are identified by atoms C3O13, which provides the interplanar distance between these two atoms (bond length),

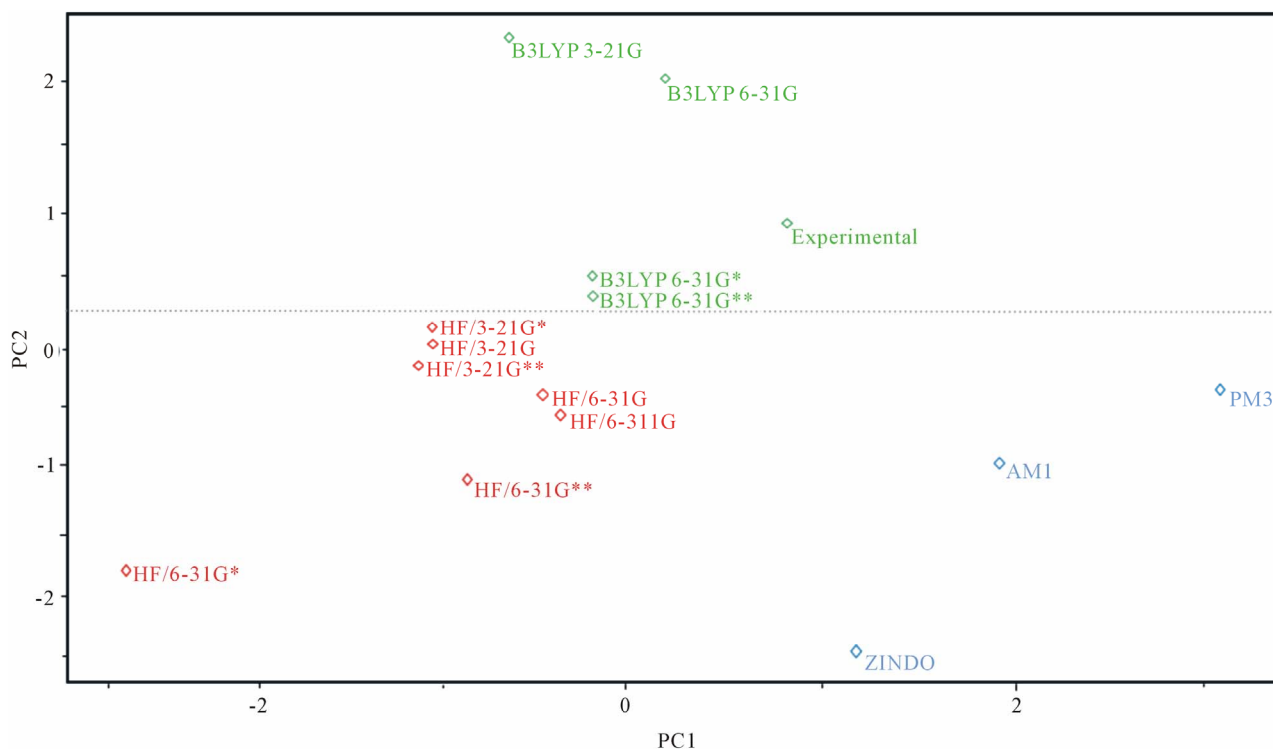


Figure 2. Plot of PC1-PC2 scores for the five methods and seven basis sets and the experimental geometrical parameters of the 1,2,13-trioxane ring.

Table 1. Theoretical and experimental parameters for the 1,2,13-trioxane ring in artemisinin.

Parameters ^a	Semiempirical			Hartree-Fock/HF						DFT/B3LYP				EXP [13]	
	AM1	PM3	ZINDO	6-31G	6-31G*	6-31G**	3-21G	3-21G*	3-21G**	6-311G	6-31G	6-31G*	6-31G** ^b	3-21G	EXP [13]
Bond length/Å															
O1O2	1.288	1.544	1.237	1.447	1.391	1.390	1.461	1.461	1.462	1.429	1.524	1.459	1.459	1.524	1.469
O2C3	1.447	1.403	1.400	1.435	1.393	1.396	1.440	1.440	1.439	1.432	1.452	1.413	1.414	1.455	1.416
C3O13	1.427	1.428	1.396	1.435	1.388	1.408	1.436	1.435	1.435	1.434	1.473	1.441	1.441	1.473	1.445
O13C12	1.416	1.403	1.392	1.403	1.400	1.376	1.407	1.407	1.407	1.401	1.425	1.395	1.396	1.430	1.379
C12C12a	1.537	1.555	1.513	1.533	1.533	1.532	1.529	1.529	1.530	1.530	1.438	1.539	1.539	1.535	1.523
C12aO1	1.468	1.427	1.416	1.469	1.429	1.429	1.477	1.477	1.477	1.438	1.499	1.455	1.455	1.504	1.461
Bond angle/°															
O1O2C3	112.530	110.340	114.310	108.800	106.100	109.460	107.100	107.080	107.060	109.210	107.300	108.280	108.280	105.590	108.100
O2C3O13	103.600	104.810	105.370	106.760	110.800	107.800	107.270	107.285	107.300	106.670	107.730	108.490	108.490	108.220	106.600
C3O13C12	115.480	116.010	115.843	117.300	112.800	115.300	115.670	115.680	115.710	116.960	114.990	114.080	114.060	113.200	114.200
O13C12C12a	113.510	115.200	113.270	112.280	108.700	112.300	112.080	112.080	112.030	112.360	113.640	113.250	113.240	113.300	114.500
C12C12aO1	111.070	113.180	107.290	110.910	110.500	110.545	111.570	111.600	111.600	110.760	111.740	111.290	111.280	112.410	110.700
C12aO1O2	113.740	112.290	118.380	113.240	112.700	112.700	111.290	111.290	111.290	113.360	111.400	111.600	111.590	109.620	111.200
Torsion angle/°															
O1O2C3O13	-77.800	-73.310	-70.403	-71.840	-73.369	-73.400	-74.670	-74.700	-74.690	-71.940	-73.460	-73.900	-73.910	-76.610	-75.500
O2C3O13C12	42.070	52.700	36.370	33.390	31.034	31.100	32.300	32.360	32.180	33.010	34.970	32.800	32.780	33.750	36.000
C3O13C12C12a	11.400	2.811	17.420	25.320	27.432	27.400	28.290	28.190	28.330	25.380	26.260	27.460	25.500	29.060	25.300
O13C12C12aO1	-41.770	-40.510	-46.610	-49.410	-50.100	-50.143	-50.860	-50.770	-50.700	-49.470	-51.200	-51.270	-51.340	-52.190	-51.300
C12C12aO1O2	12.050	19.940	18.110	12.510	10.900	10.924	9.989	9.940	9.750	12.480	12.740	11.730	11.780	9.060	12.700
C12aO1O2C3	47.050	35.630	40.130	46.700	48.700	48.674	50.330	50.350	50.530	46.870	46.900	47.850	47.830	51.060	47.800
Standard Deviation	4.776	8.388	4.372	1.663	2.484	1.762	1.722	1.714	1.797	1.658	0.843	1.227	1.103	1.915	-

^aThe atoms are numbered according to Figure 1; ^bValence basis set separately validated for calculating the molecular properties.

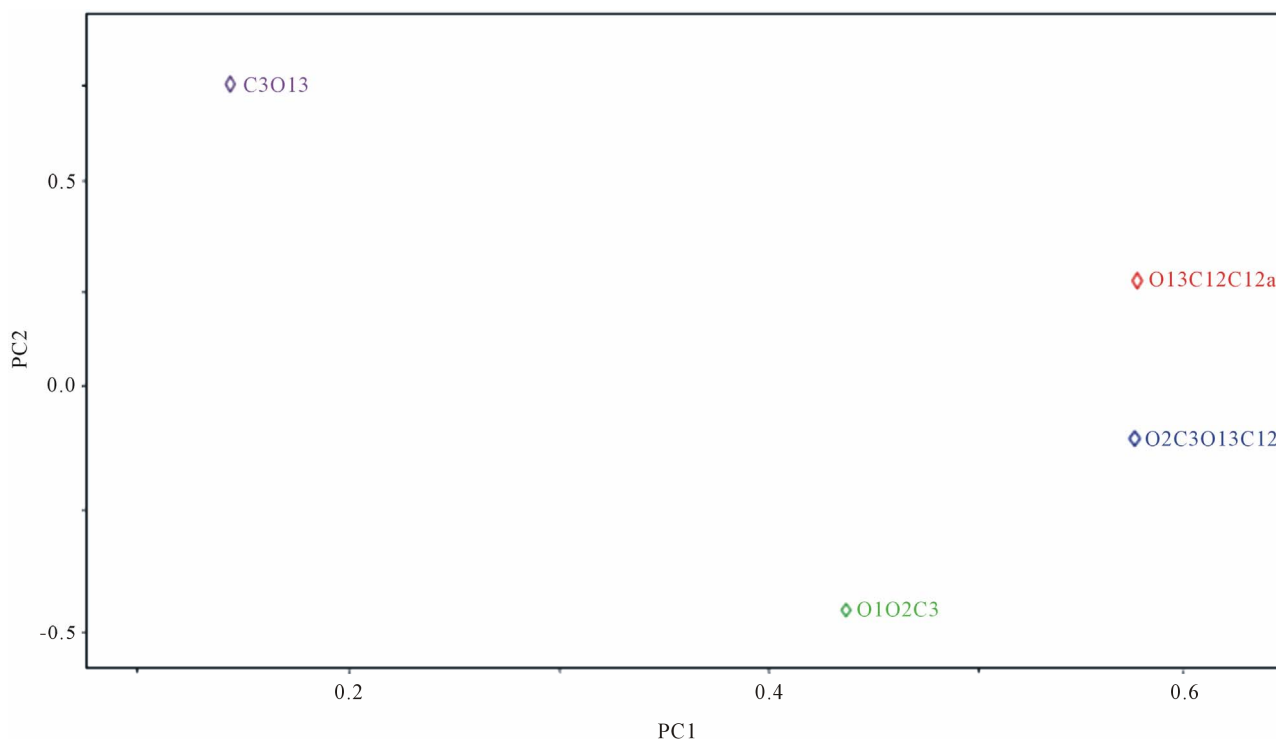


Figure 3. Plot of PC1-PC2 loadings using the four geometrical parameters selected by PCA.

O1O2C3 and O13C12C12a, corresponding to the bond angle between three atoms, and O2C3O13C12, which is related to the dihedral angle or torsion. The semiempirical (AM1, PM3, and ZINDO) and Hartree-Fock methods (HF/6-31G, HF/6-31G*, HF/6-31G**, HF/3-21G, HF/3-21G*, HF/3-21G**, and HF/6-311G) have a greater contribution from geometrical parameters O1O2C3 and O2C3O13C12, which are responsible for the low scores of these methods and basis sets. In contrast, the DFT method (B3LYP/6-31G, B3LYP/6-31G*, B3LYP/3-21G**, and B3LYP/6-31G) has a high contribution from the geometrical parameters C3O13 and O13C12C12a, which are responsible for the higher scores of these methods and basis sets. As shown in **Figure 3**, the given method and basis set have larger values as the contribution of geometrical parameters O3C13 and O13C12C12a in the second main component increase, resulting in improved scores and a closer agreement with the crystallographic experimental data. The geometrical parameters O1O2C3 and O2C3O13C12 contribute to a lesser degree, with a negative weight in PC2, demonstrating that the methods and basis sets generally have higher values for these geometrical parameters.

The values of the geometrical parameters selected based on PCA, their standard deviation, and the Pearson correlation matrix are shown in **Table 2**, which presents the correlation matrix between the geometrical parameters and their standard deviations. The correlations between geometrical parameters are less than or equal to

0.639, whereas the correlations between the geometrical parameters and standard deviations are less than or equal to 0.863. The geometrical parameters selected using PCA represent characteristics required to evaluate the methods and basis sets applied in the molecular modeling of artemisinin and its derivatives.

The results of the selection model in **Table 3** illustrate that the model was built with three main components (3PCs), where the first principal component (PC1) describes 28.3156% of the total information, the second principal component (PC2) describes 21.0067%, and the third (PC3) describes 5.5879%. Furthermore, the table illustrates that PC1 contains 50.5635% of the original data, the first two (PC1 + PC2) contain 88.0755%, and the first three (PC1 + PC2 + PC3) can explain 98.0539% of the total information, losing only 1.9461% of the original information. In the same table, descriptors O13C12C12a (0.6125) and O2C3O13C12 (0.6152) appear to be the main contributors to PC1, whereas descriptors C3O13 (0.7947) and O13C12C12a (0.3424) are the main contributors to PC2.

Recently, Santos *et al.* [21] validated computational methods applied in the molecular modeling of artemisinin, proposing a combination of chemical quantum methods and statistical analysis to study the geometrical parameters of artemisinin in the region of the endoperoxide ring (1,2,13-trioxane). The PCA results indicated that their model was built with three main components (3PCs), explaining 97.0861% of the total variance.

Table 2. Geometrical parameters selected by PCA, standard deviations, and the Pearson correlation matrix.

METHODS	Bond length/Å	Bond angle/°	Bond angle/°	Torsion angle/°	Standard deviation
	C3O13	O1O2C3	O13C12C12a	O2C3O13C12	
AM1	1.427	112.530	113.510	42.070	4.776
PM3	1.428	110.340	115.200	52.700	8.388
ZINDO	1.396	114.310	113.270	36.370	4.372
HF/6-31G	1.435	108.800	112.280	33.390	1.663
HF/6-31G*	1.388	106.100	108.700	31.034	2.484
HF/6-31G**	1.408	109.460	112.300	31.100	1.762
HF/3-21G	1.436	107.100	112.080	32.300	1.722
HF/3-21G*	1.435	107.080	112.080	32.360	1.714
HF/3-21G**	1.435	107.060	112.030	32.180	1.797
HF/6-311G	1.434	109.210	112.360	33.010	1.658
B3LYP/6-31G	1.473	107.300	113.640	34.970	0.843
B3LYP/6-31G*	1.441	108.280	113.250	32.800	1.227
B3LYP/6-31G**	1.441	108.280	113.240	32.780	1.103
B3LYP/3-21G	1.473	105.590	113.300	33.750	1.915
Experimental	1.445	108.100	114.500	36.000	0.000
C3O13		-0.453	0.522	-0.002	-0.360
O1O2C3			0.360	0.483	0.564
O13C12C12a				0.639	0.281
O2C3O13C12					0.863

Table 3. PCA of selection model for the methods and basis sets.

	Principal component		
	PC1	PC2	PC3
Variance/%	28.3156	21.0067	5.5879
Cumulative Variance/%	50.5635	88.0755	98.0539
Geometrical Parameters	Contribution		
	PC1	PC2	
C3O13	0.0806	0.7947	
O1O2C3	0.4898	-0.4989	
O13C12C12a	0.6125	0.3424	
O2C3O13C12	0.6152	-0.0478	

The main components can be written as linear combinations of the four geometrical parameters selected by PCA. The mathematical expressions for PC1 and PC2 are shown:

$$\begin{aligned} \text{PC1} = & 0.0806(\text{C3O13}) + 0.4898(\text{O1O2C3}) \\ & + 0.6125(\text{O13C12C12a}) \\ & + 0.6152(\text{O2C3O13C12}) \end{aligned} \quad (4)$$

$$\begin{aligned} \text{PC2} = & 0.7947(\text{C3O13}) - 0.4989(\text{O1O2C3}) \\ & + 0.3424(\text{O13C12C12a}) \\ & - 0.0478(\text{O2C3O13C12}) \end{aligned} \quad (5)$$

The geometrical parameters C3O13, O1O2C3, O13C12C12a, and O2C3O13C12 are of great importance in this study because according to the proposal made by Jefford *et al.*, the iron in heme attacks artemisinin at position O1 and generates a free radical at position O2. After the ligation at C3-C4 is broken, a home carbon radical is generated at C4 [22]. This free radical at C4 has been suggested as an important substance in antimalarial activity [23]. The study of molecular docking between artemisinin and its receptor, heme, conducted by Tonmunphean *et al.* also indicated that heme iron preferentially interacts with O1 rather than O2 [24]. This phenomenon

leads to the importance of geometry parameters C3O13 and O1O2C3, which were selected to be associated with the suggested mechanism in this model.

Table 4 presents the geometrical parameters selected by PCA, the methods, the basis sets, and the variations in the geometrical parameters with respect to the experimental data (Δ and $\Delta\%$). The semiempirical and Hartree-Fock methods do not exhibit a good agreement between the theoretical and experimental values for the bond angles and torsion angles, particularly for the angles formed by atoms O13C12C12a and O2C3O13C12, respectively.

The semiempirical methods (AM1, PM3, and ZINDO) present deviations of $\Delta = 0.990^\circ$ ($\Delta\% = 0.864$), $\Delta = -0.700^\circ$ ($\Delta\% = -0.611$), and $\Delta = 1.230^\circ$ ($\Delta\% = 1.074$), respectively, in relation to the angle O13C12C12a. For angle O2C3O13C12, deviations of $\Delta = -6.070^\circ$ ($\Delta\% = -16.861$), $\Delta = -16.700^\circ$ ($\Delta\% = -46.388$), and $\Delta = -0.370^\circ$ ($\Delta\% = -1.027$) were observed. For the Hartree-Fock methods (HF/6-31G, HF/6-31G*, HF/6-31G**, HF/3-21G, HF/3-21G*, HF/3-21G**, and HF/6-311G), the angle formed by atoms O13C12C12a have deviations of $\Delta = 2.220^\circ$ ($\Delta\% = 1.938$), $\Delta = 5.800^\circ$ ($\Delta\% = 5.065$) and $\Delta = 2.200^\circ$ ($\Delta\% = 1.921$), $\Delta = 2.420^\circ$ ($\Delta\% = 2.113$), $\Delta = 2.420^\circ$ ($\Delta\% = 2.113$), $\Delta = 2.470^\circ$ ($\Delta\% = 2.157$), and $\Delta = 2.140^\circ$ ($\Delta\% = 1.868$), respectively. For the angle O2C3O13C12, deviations of $\Delta = 2.610^\circ$ ($\Delta\% = 7.250$), $\Delta = 4.966^\circ$ ($\Delta\% = 13.794$), $\Delta = 4.900^\circ$ ($\Delta\% = 13.611$), $\Delta = 3.700^\circ$ ($\Delta\% = 10.277$), $\Delta = 3.640^\circ$ ($\Delta\% = 10.111$), $\Delta = 3.820^\circ$ ($\Delta\% = 10.611$), and $\Delta = 2.990^\circ$ ($\Delta\% = 8.305$) were obtained. For the DFT/B3LYP method, the four levels (6-31G, 6-31G*, 6-31G**, and 3-21G) exhibited excellent results for the bond angle O1O2C3, with deviations of $\Delta = -0.800^\circ$ ($\Delta\% = -0.740$) for DFT/B3LYP 6-31G, $\Delta = -0.180^\circ$ ($\Delta\% = -0.166$) for DFT/B3LYP 6-31G*, $\Delta = 0.180^\circ$ ($\Delta\% = -0.166$) for DFT/B3LYP 6-31G**, and $\Delta = 2.510^\circ$ ($\Delta\% = 2.321$) for DFT/B3LYP 3-21G, as shown in **Table 4**.

As also shown in **Table 4**, by accounting for the features of the basis sets B3LYP/6-31G* and B3LYP/6-31G**, excellent results were obtained in relation to the bond length C3O13 and bond angle O1O2C3, which exhibited good agreement with the experimental values reported in the literature. Thus, for the 6-31G* and 6-31G** bases, these parameters are close to the crystallographic experimental data in the region of the endoperoxide ring of artemisinin.

HCA was used to explore and more appropriately group the methods and basis sets according to their similarities. A dendrogram was obtained with autoscaled processing based on the Euclidean distance and incremental method, as shown in **Figure 4**. This figure illustrates the grouping of the three classes: semiempirical (AM1, PM3, and ZINDO), Hartree-Fock (HF/6-31G,

HF/6-31G*, HF/6-31G**, HF/3-21G, HF/3-21G*, HF/3-21G**, and HF/6-311G), and DFT (B3LYP/6-31G, B3LYP/6-31G*, B3LYP/6-31G**, and B3LYP/3-21G). The semiempirical method has long branches, indicating a low similarity with the experimental data. However, the Hartree-Fock method exhibits similarity between the basis sets, indicated by short branches, for the HF/3-21G**, HF/3-21G*, and HF/3-21G bases. Cardoso *et al.* [25] studied artemisinin and some of its derivatives with activity against D-6 strains of *Plasmodium falciparum* using the HF/3-21G method. To verify the reliability of the geometry obtained, Cardoso *et al.* compared the structural parameters of the artemisinin trioxane ring with theoretical and experimental values from the literature. Ferreira *et al.* [26] also studied artemisinin and 18 derivatives with antimalarial activity against W-2 strains of *Plasmodium falciparum* through quantum chemistry and multivariate analysis. The geometry optimization of structures was realized using the Hartree-Fock method and the 3-21G** basis set.

The DFT/B3LYP method exhibits high similarity between the basis sets, particularly for the B3LYP/6-31G* and B3LYP/6-31G** basis sets, as indicated by the short branches between them, shown in **Figure 4**.

The results of the theoretical methods and experimental data exhibited a distribution similar to that obtained with PCA. Thus, HCA confirmed the results achieved by PCA.

3.3. Statistical Analysis of Parameters

In this step, regression models with high values of r (%), R_A^2 (%), Q^2 , and F (a statistic assessing the overall significance) and low values of MAE, CMAE, SEE, PRESS, and S_{PRESS} were selected.

The most relevant statistical parameters are given in **Table 5**. When comparing the semiempirical methods, the best values were found for ZINDO ($r = 99.7039\%$, $R_A^2 = 99.3496\%$, $Q^2 = 99.3909$, $F = 1681.28$, SEE = 5.3983, MAE = 4.335, CMAE = 4.0998, PRESS = 305,773, and $S_{\text{PRESS}} = 1.7486$). Among the basis sets for the Hartree-Fock method, the best values were observed for HF/6-31G ($r = 99.9609\%$, $R_A^2 = 99.9142\%$, $Q^2 = 99.9118\%$, $F = 12811.33$, SEE = 1.9641, MAE = 1.491, CMAE = 1.4715, PRESS = 44.286, $S_{\text{PRESS}} = 0.6654$), HF/6-311G ($r = 99.9606\%$, $R_A^2 = 99.9134\%$, $Q^2 = 99.9124\%$, $F = 12705.14$, SEE = 1.9733, MAE = 1.492, CMAE = 1.4626, PRESS = 43.985, $S_{\text{PRESS}} = 0.6632$), and HF/3-21G* ($r = 99.9532\%$, $R_A^2 = 99.8970\%$, $Q^2 = 99.9063\%$, $F = 10679.82$, SEE = 2.1638, MAE = 1.647, CMAE = 1.6311, PRESS = 47.017, $S_{\text{PRESS}} = 0.6856$).

The DFT method using B3LYP, with the valence-separate basis sets B3LYP/6-31G, B3LYP/6-31G*, and B3LYP/6-31G**, achieved the best results among all of the methods and basis sets studied herein (semiempirical

Table 4. Geometrical parameters selected by PCA, the methods, the basis sets, and the variation in geometrical parameters with respect to the experimental data (Δ and $\Delta\%$).

Parameters	Semiempirical									
	AM1	Δ_{AM1}	$\Delta/\%$	PM3	Δ_{PM3}	$\Delta/\%$	ZINDO	Δ_{ZINDO}	$\Delta/\%$	Exp
Bond length/Å										
C3O13	1.427	0.018	1.245	1.428	0.017	1.176	1.396	0.049	3.391	1.445
Bond angle/°										
O1O2C3	112.530	-4.430	-4.098	110.340	-2.240	-2.072	114.310	-6.210	-5.744	108.100
O13C12C12a	113.510	0.990	0.864	115.200	-0.700	-0.611	113.270	1.230	1.074	114.500
Torsion angle/°										
O2C3O13C12	42.070	-6.070	-16.861	52.700	-16.700	-46.388	36.370	-0.370	-1.027	36.000
<i>ab initio</i> /Hartree-Fock/HF										
Parameters	6-31G	Δ_{6-31G}	$\Delta/\%$	6-31G*	Δ_{6-31G^*}	$\Delta/\%$	6-31G**	$\Delta_{6-31G^{**}}$	$\Delta/\%$	Exp
Bond length/Å										
C3O13	1.435	0.010	0.692	1.388	0.057	3.944	1.408	0.037	2.560	1.436
Bond angle/°										
O1O2C3	108.800	-0.700	-0.647	106.100	2.000	1.850	109.460	-1.360	-1.258	107.100
O13C12C12a	112.280	2.220	1.938	108.700	5.800	5.065	112.300	2.200	1.921	112.080
Torsion angle/°										
O2C3O13C12	33.390	2.610	7.250	31.034	4.966	13.794	31.100	4.900	13.611	32.300
<i>ab initio</i> /Hartree-Fock/HF										
Parameters	3-21G*	Δ_{3-21G^*}	$\Delta/\%$	3-21G**	$\Delta_{3-21G^{**}}$	$\Delta/\%$	6-311G	Δ_{6-311G}	$\Delta/\%$	Exp
Bond length/Å										
C3O13	1.435	0.010	0.692	1.435	0.010	0.692	1.434	0.011	0.761	1.445
Bond angle/°										
O1O2C3	107.080	1.020	0.943	107.060	1.040	0.943	109.210	-1.110	-1.026	108.100
O13C12C12a	112.080	2.420	2.113	112.030	2.470	2.157	112.360	2.140	1.868	114.500
Torsion angle/°										
O2C3O13C12	32.360	3.640	10.111	32.180	3.820	10.611	33.010	2.990	8.305	36.000
DFT/B3LYP										
Parameters	6-31G	Δ_{6-31G}	$\Delta/\%$	6-31G*	Δ_{6-31G^*}	$\Delta/\%$	6-31G**	$\Delta_{6-31G^{**}}$	$\Delta/\%$	Exp
Bond length/Å										
C3O13	1.473	-0.028	-1.937	1.441	0.004	0.276	1.441	0.004	0.276	1.473
Bond angle/°										
O1O2C3	107.300	-0.800	-0.740	108.280	-0.180	-0.166	108.280	-0.180	-0.166	105.590
O13C12C12a	113.640	-0.860	-0.751	113.250	1.250	1.091	113.240	1.260	1.100	113.300
Torsion angle/°										
O2C3O13C12	34.970	1.030	2.861	32.800	3.200	8.888	32.780	3.220	8.944	33.750

Δ = theoretical – experimental; $\Delta\%$ = $\Delta \times 100/\text{experimental}$.

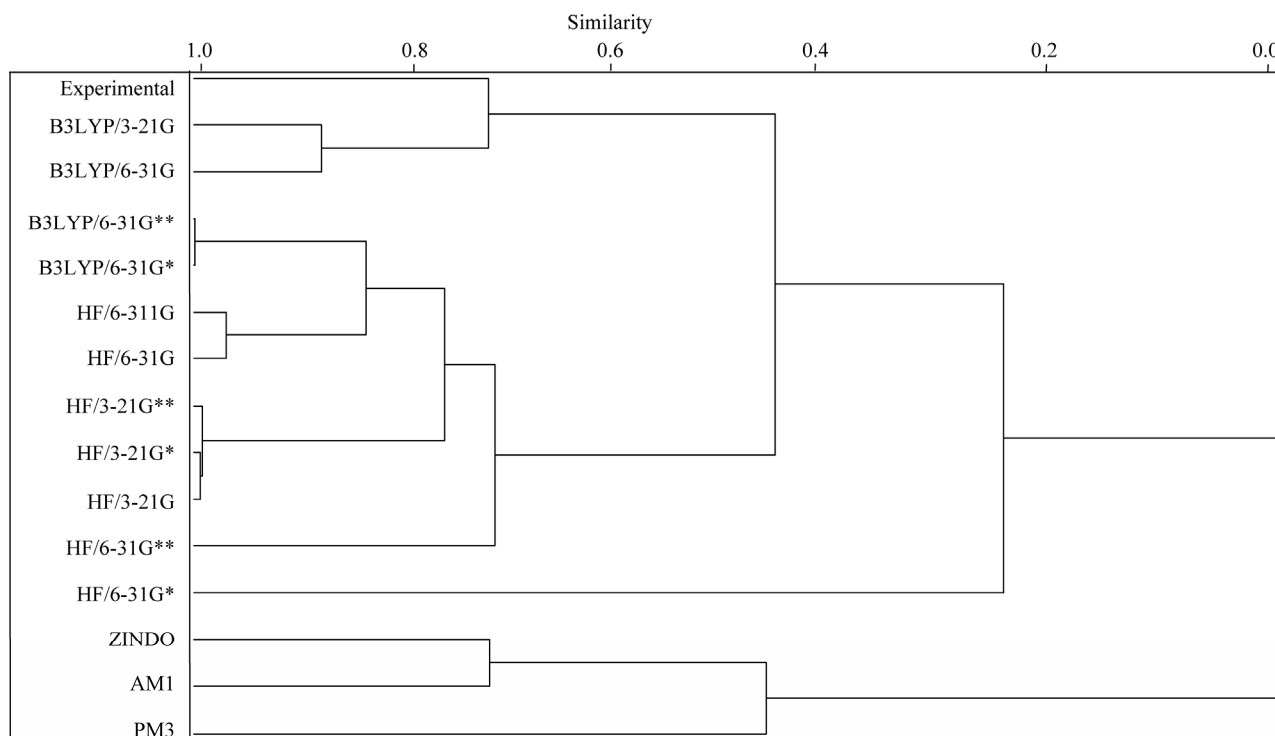


Figure 4. Dendrogram for five methods, seven basis sets, and one factor related to the experimental geometrical parameters of the 1,2,13-trioxane ring.

and Hartree-Fock), as shown in **Table 5**. However, these minimum bases (6-31G and 3-21G) have several deficiencies; thus, a polarization function was included to improve upon these bases (*i.e.*, p orbitals represented by *). These orbitals follow restricted functions that are centered at the nuclei. However, it was found that the atomic orbitals become distorted or polarized when a molecule is formed. For this reason, one must consider the possibility of a non-uniform displacement of electric charges outside of the atomic nucleus, *i.e.*, polarization. Thus, it is possible to obtain a better description of the charges and deformations of atomic orbitals within a molecule. A mode of polarization can be considered by introducing functions for which the values of l (quantum number of the orbital angular momentum) are larger than those of the fundamental state of a given atom. For these types, the basis set names denote the polarization functions. Thus, 6-31G* refers to basis set 6-31G with a polarization function for heavy atoms (*i.e.*, atoms other than hydrogen), and 6-31G** refers to the inclusion of a polarization function for hydrogen and helium atoms [27].

When basis sets with polarization functions are used in calculations involving anions, good results are not obtained due to the electronic cloud of anionic systems, which tend to expand. Thus, appropriate diffuse functions must be added because they allow for a greater orbital occupancy in the region of space. Diffuse functions are important in the calculations of transition metals be-

cause metal atoms have “ d ” orbitals, which tend to diffuse. It then becomes necessary to include diffuse functions in the basis function associated with the configuration of a neutral metal atom to obtain a better description of the metal complex. The 6-31G** basis is particularly useful in the case of hydrogen bonds [27-30].

Pereira *et al.* (2008) studied four structures of artemisinin by reductive decomposition A, B1, B2, and B3 with 13 species (QHS, 1/2, 3, 4, 5, 5a, 6, 7, 18, 18a, 19, 20, and 21), and the structures of the studied species were analyzed in terms of geometrical parameters, Löwdin bond orders, atomic partial charges, spin densities, electronic energies, free energies, and entropy. These studies were carried out at the B3LYP/6-31G** level [31].

Barbosa *et al.* (2011) performed molecular modeling and chemometric studies involving artemisinin and 28 derivatives exhibiting anticancer activity against human hepatocellular carcinoma HepG2. The calculations of the studied compounds were performed at the B3LYP/6-31G** level [32].

Carvalho *et al.* (2011) used the B3LYP/6-31G** method to study artemisinin and 31 analogues with antileishmanicidal activity against *Leishmania donovani*. The authors proposed a set of 13 artemisinins, seven of which are less active and six of which have not been tested; of these six, one is expected to be more active against *L. donovani* [33].

The statistical analysis revealed good correlations ($r >$

Table 5. Calculated correlation and fitting parameters for different methods and basis sets.

Method and basis set		<i>a</i>	<i>b</i>	<i>r</i> /%	R_A^2 /%	MAE ^b	CMAE ^c	<i>F</i>	SEE	PRESS	S_{PRESS}	Q^2 /%
Semiempirical	°/AM1	0.3527 (±2.2869)	0.9975 (±0.0269)	99.6375	99.2040	3.817	3.8668	1372.07	6.0341	364.982	1.9104	99.2729
	°/PM3	1.7477 (±3.9789)	0.9815 (±0.0468)	98.8797	97.5491	6.807	6.6778	438.82	10.4985	1125.718	3.3551	97.7576
	°/ZINDO	1.4298 (±2.0459)	0.9879 (±0.0240)	99.7039	99.3496	4.335	4.0998	1681.28	5.3983	305.773	1.7486	99.3909
Hartree-Fock/HF	°/6-31G	0.8997 (±0.7444)	0.9922 (±0.0087)	99.9609	99.9142	1.491	1.4715	12811.33	1.9641	44.286	0.6654	99.9118
	°/6-31G*	0.2600 (±1.1455)	0.9890 (±0.0134)	99.9071	99.7957	2.352	2.1988	5375.55	3.0225	98.767	0.9938	99.8033
	°/6-31G**	0.3649 (±0.8369)	0.9969 (±0.0098)	99.9511	99.8925	1.701	1.6137	10231.47	2.2083	49.7003	0.7049	99.9010
	°/3-21G	0.1135 (±0.8242)	0.9980 (±0.0097)	99.9527	99.8960	1.643	1.6281	10572.08	2.1748	47.494	0.6891	99.9054
	°/3-21G*	0.1156 (±0.8200)	0.9980 (±0.0096)	99.9532	99.8970	1.647	1.6311	10679.82	2.1638	47.017	0.6856	99.9063
	°/3-21G**	0.1206 (±0.8601)	0.9979 (±0.0101)	99.9485	99.8868	1.720	1.7042	9707.47	2.2694	51.715	0.7191	99.8970
	°/6-311G	0.8464 (±0.7478)	0.9927 (±0.0088)	99.9606	99.9134	1.492	1.4626	12705.14	1.9733	43.985	0.6632	99.9124
DFT/B3LYP	°/6-31G	0.4455 (±0.3781)	0.9960 (±0.0044)	99.9900	99.9780	0.824	0.8457	50025.59	0.9977	11.367	0.3371	99.9774
	°/6-31G*	0.2160 (±0.5843)	0.9981 (±0.0068)	99.9762	99.9477	1.036	1.0427	21041.00	1.5417	24.099	0.4909	99.9520
	°/6-31G**	-0.0257 (±0.5282)	0.9993 (±0.0062)	99.9806	99.9574	0.870	0.8856	25814.64	1.3936	19.485	0.4414	99.9612
	°/3-21G	-0.4588 (±0.9309)	1.0025 (±0.0109)	99.9402	99.8686	2.044	1.9031	8363.10	2.4562	61.878	0.7866	99.8767
	°/3-21G*	-0.3886 (±0.9058)	1.0020 (±0.0106)	99.9433	99.8754	1.999	1.8794	8824.32	2.3901	58.246	0.7631	99.8840
	°/3-21G**	-0.3994 (±0.9435)	1.0021 (±0.0111)	99.9385	99.8649	2.069	1.9459	8134.51	2.4895	63.162	0.7947	99.8742

Notes: ^aLinear fitting parameters refer to $\delta_{\text{calcd}}(^{\circ}) = a + b\delta_{\text{exptl}}$ for $n = 12$; ^bMean average error: $\text{MAE} = \sum_n |\delta_{\text{calcd}} - \delta_{\text{exptl}}|/n$; ^cCorrected mean average error: $\text{CMAE} = \sum_n |\delta_{\text{corr}} - \delta_{\text{exptl}}|/n$ (see text); Where $\delta_{\text{corr}} = (\delta_{\text{calcd}} - a)/b$ to correct for systematic errors.

98% and $R_A^2 > 99\%$) for all models with respect to the angles observed in crystallographic data. **Figure 5** presents the predicted and residuals values that were constructed for the two best linear regression models using the DFT (B3LYP/6-31G* and B3LYP/6-31G**) method. The linear regression models for each basis set and method exhibited results that were similar to the experimental values (see **Figures 5(a)-(d)**).

In these figures, the residues are randomly distributed about the zero value of the line, and therefore, there is strong evidence supporting a lack of fit for these models. Currently, the linearity of a straight calibration line is often verified using a correlation coefficient (*r*) computer

program to perform regression. Unfortunately, there is a statistical test that can be applied to this coefficient to check linearity of straight line at a given confidence level [34].

In **Figure 5(c)**, the maximum and minimum residue values obtained for the B3LYP/6-31G* method are shown to be 1.9911 and -3.3488, respectively. As shown in **Figure 5(d)**, the maximum and minimum residue values for the B3LYP/6-31G** method were 1.9820 and -3.1718, respectively.

The statistical parameter results for the methods and basis sets exhibited a distribution similar to that obtained with HCA (see **Figure 4**). However, the results of the

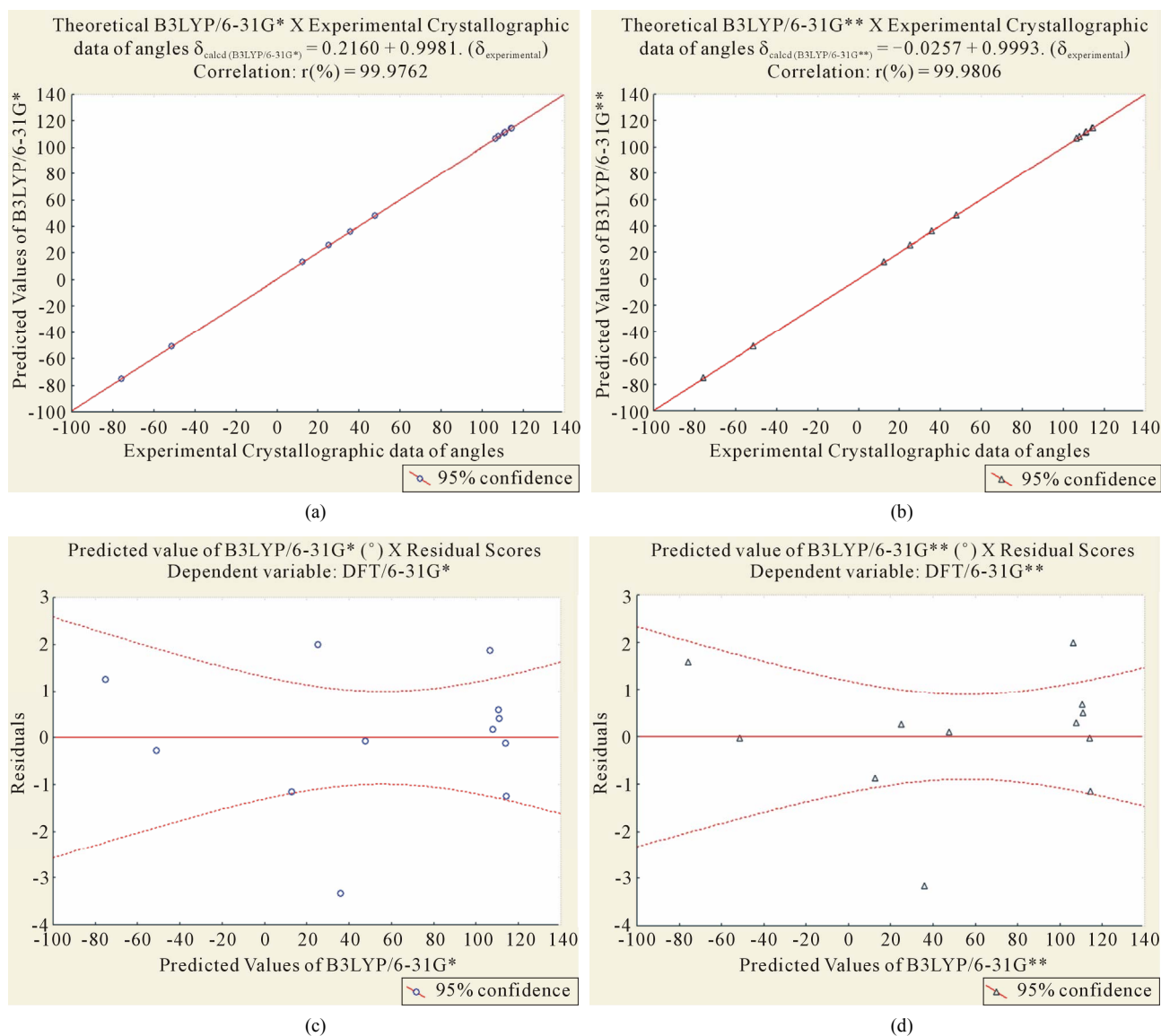


Figure 5. Correlation between the calculated and experimental angle data; predicted values for the DFT/B3LYP method and the 6-31G* and 6-31G** basis sets (a) and (b) and residual values (c) and (d).

DFT method for the B3LYP/6-31G** basis set exhibited the lowest values for MAE, CMAE, SEE, PRESS, and S_{PRESS} ; in comparison with B3LYP/6-31G*, the two sets have a variation of MAE = ± 0.166 , CMAE = ± 0.1571 , SEE = ± 0.1481 , PRESS = ± 4.614 , and S_{PRESS} = ± 0.0495 .

The molecular properties obtained depend on the method and basis set used, which represent a number of functions used in the expansion monoelctronics (orbital) and parameter characteristics that must be optimized. Therefore, it is of fundamental importance that these functions be carefully evaluated to obtain accurate results. Many studies have been performed to develop methods and basis sets that can provide more accurate results. In recent years, other sets have been employed in electronic structure calculations in addition to the methods and ba-

sis sets described previously [30]. Generally, the inclusion of polarization functions in the molecular basis allows for a greater probability of better results for many chemical properties of interest, such as the dissociation energy and dipole moment. In practice, the inclusion of polarization functions with d and f symmetry for small s and p basis sets has been shown to be unsatisfactory; thus, polarization functions should only be added to saturated basis sets.

These results confirm the relevance of theoretical data used to calculate the angles of crystallographic data for this compound (artemisinin) for the method and basis set DFT/B3LYP 6-31G**. HCA confirmed the results obtained by statistical analysis. Therefore, we conclude that the DFT method combined with the B3LYP/6-31G**

basis set can be used for the calculation of molecular properties and for the molecular modeling of artemisinin and its derivatives with biological activity based on the mechanism of action in the region of the endoperoxide ring (1,2,13-trioxane).

4. Conclusions

The statistical analysis techniques of PCA and HCA were vital in enabling the classification of methods and basis sets into three separate groups. The geometrical parameters that were found to be the most important in the classification of methods and basis sets were related to the trioxane ring: C3O13, O1O2C3, O13C12C12a, and O2C3O13C12. The HCA results were similar to those obtained with PCA.

The DFT/B3LYP method with valence-separate basis set 6-31G** exhibited the best results and high predictive ability compared to the methods and basis sets studied herein (semiempirical, Hartree-Fock, and DFT). This method is suitable for molecular modeling studies of artemisinin and for determining the conformation of its derivatives along with their biological activity and mechanism of action in the region of the endoperoxide ring. The DFT/B3LYP 6-31G** method can be used for future calculations of molecular properties, which represent a means of obtaining chemical information contained in the molecular structure of a compound for chemical, pharmacological, and toxicological studies on quantitative structure-activity and structure-property relationships.

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