Density Functional Theory Computational Analysis of Chlorpyrifos Molecular Structure Parameters

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Abstract

Chlorpyrifos (O,O-diethyl-O-3,5,6-trichloro-2-pyridyl-phosphorothioate) is a widely deployed organophosphate compound whose environmental and biological reactivity necessitates precise structural, conformational, and spectroscopic characterization. Determining an appropriate computational protocol using suitable basis sets and exchange-correlation hybrid functionals represents a critical prerequisite for achieving stable molecular simulations that reliably mirror empirical reality. This study systematically investigates the molecular geometry, vibrational infrared (IR) spectrum, and atomic bond length/angle parameters of chlorpyrifos using Density Functional Theory (DFT) executed in HyperChem 8.0. Sixteen distinct DFT computational combinations were evaluated by pairing four Pople-style basis sets (6-31G*, 6-31G**, 6-311G, and 6-311G**) across four hybrid exchange-correlation functionals (B3LYP, B3-PW91, EDF1, and Becke97). Predictive accuracy across all calculated parameters was benchmarked against empirical crystallographic and spectroscopic reference data using Predicted Residual Sum of Squares (PRESS) statistical analysis. Geometry optimization revealed that all sixteen DFT configurations produced stable ground-state conformers with negative potential energies (ranging from -1.72530×10^6 to -1.72617×10^6 kcal/mol) and strong molecular dipoles (2.95–3.96 Debye). Quantitative PRESS analysis established that the 6-311G**/B3LYP functional combination delivers the most accurate overall performance, achieving the minimum cumulative total PRESS score of 50,637.5507. Individual parameter PRESS values for the optimal 6-311G**/B3LYP method were 0.0881 for interatomic bond lengths, 111.7624 for bond angles, 50,525.7002 for infrared absorption frequencies. Consequently, the 6-311G**/B3LYP protocol is recommended as an accurate and robust quantum chemical benchmark for structural modeling, quantitative structure-activity relationship (QSAR) studies, and molecular imprinting applications involving chlorpyrifos and related organophosphate compounds.

Keywords: DFT; bond length; 6-311G**/B3LYP; chlorpyrifos; PRESS

INTRODUCTION

Recent decades have witnessed breathtaking advances in computer hardware architecture, parallel computing algorithms, and numerical software design, elevating computational chemistry into a vital cornerstone of modern scientific research alongside physical experiment and pure theory (Fedasa Tegegn, 2022). Computational chemistry translates theoretical quantum mechanics into computational workflows capable of predicting molecular properties, conformational energies, electronic charge distributions, and spectroscopic signals across chemical systems ranging from small organic molecules to vast macromolecular assemblies like proteins, nucleic acids, and liquid crystals (Ananto *et al.*, 2024). Through geometry optimization, molecular docking, thermodynamic property calculation, and electronic structure modeling, computational chemistry provides a rigorous atomic-level interpretation of experimental phenomena while establishing quantitative structure-activity relationships (QSAR) (Zhao & Truhlar, 2011). Beyond its high numerical precision, computational chemistry offers immense practical advantages (Salamat, 2023): it is cost-effective, time-efficient, non-hazardous, and capable of probing unstable reaction intermediates or reactive substrates that are difficult to isolate in physical laboratories (Hadisaputra *et al.*, 2017).

At the heart of quantum chemical calculations lies the solution of the non-relativistic time-independent Schrödinger equation, $\hat{H}\Psi = E\Psi$, where $\hat{H}$ represents the Hamiltonian operator comprising kinetic and potential energy operators for nuclei and electrons, Ψ is the electronic wave function, and E is the total ground-state electronic energy (Male *et al.*, 2015). Because the exact analytical solution of the Schrödinger equation for multi-electron atomic and molecular systems is mathematically impossible due to complex electron-electron Coulomb repulsion terms, quantum chemists rely on mathematical approximations (Paramita *et al.*, 2021). Quantum chemical methods are broadly categorized into empirical molecular mechanics (MM), semi-empirical quantum methods (such as AM1, PM3, and MNDO), ab initio electronic structure methods (such as Hartree-Fock theory and post-Hartree-Fock electron correlation schemes), and Density Functional Theory (DFT) (Male *et al.*, 2015). While molecular mechanics ignores explicit electronic distributions and cannot model bond-breaking processes, ab initio Hartree-Fock (HF) calculations approximate multi-electron wave functions as single Slater determinants, neglecting instantaneous electron correlation (Paramita *et al.*, 2021).

To overcome the high computational scaling and correlation deficiencies of traditional wave function methods, Density Functional Theory (DFT) has emerged as the premier theoretical framework for electronic structure calculations in chemical physics, materials science, and drug design (Rahayu *et al.*, 2023). DFT reformulates quantum mechanics by replacing the complex 3N-dimensional electronic wave function $\Psi(r1, r2, ..., rN)$ with the 3-dimensional electron density distribution n(r) as the fundamental variable (Pongajow *et al.*, 2017). The mathematical underpinning of DFT rests upon the foundational Hohenberg-Kohn theorems (1964), which establish that: (1) the

ground-state electron density n(r) uniquely determines the external potential Vext(r) and hence all ground-state electronic properties of a multi-electron system; and (2) a universal energy functional E[n] exists such that the exact ground-state energy corresponds to the global minimum of E[n] for the correct electron density (Pranowo & Hatadi, 2011). Practical implementation of DFT was enabled by the Kohn-Sham scheme (1965), which maps the interacting multi-electron system onto a non-interacting reference system of single-particle orbitals, consolidating all non-classical electron exchange and correlation effects into a single term known as the exchange-correlation functional, Exc[n] (Alfianto, 2015).

Because the exact form of Exc[n] is unknown, various functional approximations have been developed. These include the Local Density Approximation (LDA), Generalized Gradient Approximation (GGA), and hybrid exchange-correlation functionals (Abdul Rahman & Purqon, 2015). Hybrid functionals—such as B3LYP (Becke three-parameter hybrid with Lee-Yang-Parr correlation), B3-PW91 (Becke three-parameter with Perdew-Wang 1991 correlation), EDF1 (Extended Density Functional 1), and Becke97—incorporate an exact fraction of Hartree-Fock exchange energy into the DFT exchange-correlation functional (Hollad & Green, 2010). Hybrid exchange-correlation functionals are particularly well-suited for heteroatom-containing organic molecules, organometallic complexes, and conjugated systems because they effectively reduce self-interaction errors and deliver structural geometries, binding energies, and vibrational spectra that closely match experimental benchmarks (Saputra *et al.*, 2014).

In tandem with functional selection, the choice of atomic basis set dictates calculation precision, wave function flexibility, and computational resource demands (Chang, 2005). Basis sets expand molecular orbitals as linear combinations of atomic orbital (LCAO) mathematical functions. Modern quantum chemistry programs utilize Gaussian-Type Orbitals (GTOs) constructed from primitive Gaussian functions (PGFs) combined into contracted Gaussian functions (CGFs) due to their analytical integral evaluation efficiency compared to Slater-Type Orbitals (STOs) (Pranowo & Hatadi, 2011). Basis set hierarchy expands from minimal basis sets (e.g., STO-3G) to split-valence double-zeta (e.g., 6-31G) and split-valence triple-zeta (e.g., 6-311G) levels. To accurately capture orbital distortion, directional polarization, and electron cloud displacement induced by chemical bonding, polarization functions are appended: single asterisk (*) adds d-type polarization functions to non-hydrogen heavy atoms (e.g., 6-31G*), while double asterisk (**) incorporates p-type polarization functions onto hydrogen atoms as well (e.g., 6-31G** and 6-311G**) (Kwon *et al.*, 2023).

The application of DFT modeling is vital when studying complex organophosphate compounds such as chlorpyrifos (IUPAC name: O,O-diethyl-O-3,5,6-trichloro-2-pyridyl-phosphorothioate; molecular formula C9H11Cl3NO3PS; CAS Registry No. 2921-88-2) (Panggabean, 2016). Chlorpyrifos is one of the most widely applied broad-spectrum organophosphate compounds worldwide, extensively used in agriculture and urban management

(Sud *et al.*, 2020). Chlorpyrifos exerts its bioactivity by inhibiting acetylcholinesterase (AChE) in nervous systems, causing acetylcholine accumulation and continuous neuromuscular stimulation in target organisms (Nurhayati *et al.*, 2022). In environmental matrices, chlorpyrifos undergoes oxidative desulfuration converting the thiono phosphorus group (P=S) into an oxon derivative (P=O), chlorpyrifos-oxon (CPO), which exhibits heightened reactivity compared to the parent compound (Hites, 2021).

Despite its high agricultural efficiency, chlorpyrifos presents environmental and physiological considerations (Prajawahyudo *et al.*, 2022). Chlorpyrifos enters aquatic ecosystems through agricultural runoff, spray drift, and soil leaching, accumulating in river sediments, algae, aquatic invertebrates and commercial fish species (Kurnia, 2018). Acute aquatic toxicity assays reveal low 96-hour median lethal concentration (LC50-96h) values for cultured freshwater fish: 0.03 mg/L for common carp (Cyprinus carpio L.) and 0.08 mg/L for Nile tilapia (Oreochromis niloticus), demonstrating (Ihsan *et al.*, 2018) that chlorpyrifos affects aquatic species even at trace environmental concentrations (Seftiani *et al.*, 2022). Human exposure to chlorpyrifos residues via food, water, or occupational contact has been studied in relation to neurodevelopmental metrics and occupational health (Rahmawati *et al.*, 2014). Consequently, regulatory bodies worldwide continue to monitor its environmental fate (Bose *et al.*, 2021) and degradation pathways (Chittratan *et al.*, 2020).

Establishing an optimized, highly reliable DFT computational methodology for chlorpyrifos is essential to support ongoing efforts in molecular imprinting polymer (MIP) design, electrochemical sensor development, degradation pathway modeling, and quantitative structure-activity relationship (QSAR) optimization (Chittratan *et al.*, 2020). Previous theoretical studies on organophosphates have often applied arbitrary DFT settings without systematic statistical validation against empirical crystallographic and spectroscopic data (Baughman, 1965) (Khattab et al., 2013). This research systematically evaluates sixteen distinct DFT computational protocols—combining four basis sets (6-31G*, 6-31G**, 6-311G, and 6-311G**) with four hybrid exchange-correlation functionals (B3LYP, B3-PW91, EDF1, and Becke97) in HyperChem 8.0. Computed structural geometry parameters (bond lengths and bond angles), and vibrational infrared (IR) frequencies were benchmarked against empirical experimental datasets using Predicted Residual Sum of Squares (PRESS) analysis (Huck, 2014). The overarching objective is to identify and recommend the single most accurate, reliable DFT functional/basis set combination to serve as a benchmark computational protocol for chlorpyrifos research.

METHOD

Computational Hardware and Software Infrastructure

All quantum chemical simulations, geometry optimizations, and vibrational analyses were carried out at the Physical Chemistry Laboratory, Faculty of Mathematics and Natural Sciences, General Soedirman University. Calculations were executed on a dedicated high-performance workstation equipped with an Intel® Core™ i5-6500 CPU @ 3.20 GHz processor, 8.00 GB of system RAM, running a 64-bit Windows 10 operating system. HyperChem 8.0 Professional software was utilized as the main quantum computational engine, while Microsoft Excel was used for numerical post-processing, data aggregation, and statistical PRESS evaluations.

Molecular Building and Initial Conformational Modeling

The initial two-dimensional (2D) chemical structure of chlorpyrifos (C9H11Cl3NO3PS) was constructed using the graphical structure editor in HyperChem 8.0 (Delsy *et al.*, 2017). The molecular topology comprises a 3,5,6-trichloropyridin-2-yl ester group attached to a central phosphorothioate functional core (P=S) bearing two ethoxy (-O-CH2-CH3) side chains. Atom types (carbon, nitrogen, oxygen, phosphorus, sulfur, chlorine, and hydrogen) were assigned, and formal single and double bonds were established. The 2D sketch was converted into a three-dimensional (3D) molecular model by invoking the "Add H & Model Build" algorithm. This procedure automatically adds explicit hydrogen atoms and applies standard molecular mechanics force-field parameters to generate a realistic initial 3D starter conformer free of severe steric crowding (Iswaradi *et al.*, 2021).

Geometry Optimization Protocol

Full geometry optimizations were performed iteratively to locate the thermodynamic global minimum on the potential energy surface (PES) where interatomic forces vanish and potential energy is minimized (Dybdal, 2023). Minimizations utilized the Polak-Ribiere conjugate gradient algorithm under a strict root-mean-square (RMS) gradient termination threshold of 0.1 kcal/(Å·mol) and a maximum iteration limit of 500 cycles (Paramita *et al.*, 2021). Sixteen distinct DFT computational combinations were systematically tested by pairing four Pople-style basis sets (6-31G*, 6-31G**, 6-311G, and 6-311G**) with four hybrid exchange-correlation functionals (B3LYP, B3-PW91, EDF1, and Becke97). Convergence was confirmed when the calculation reached "Conv=Yes" status. Ground-state total potential energy (kcal/mol), electric dipole moment (Debye), equilibrium bond lengths (Å), and bond angles (°) were extracted from output log files (.log).

Infrared (IR) Vibrational Spectroscopy Simulation

Following geometry optimization, vibrational frequency calculations were executed for each optimized chlorpyrifos structure to compute harmonic infrared (IR) absorption frequencies (Paramita *et al.*, 2021). Vibrational mode spectrum analysis was initiated by selecting the "Vibration, Rotation Analysis" and "Vibrational Spectrum" modules in HyperChem 8.0. Normal mode

frequencies (cm^{-1}) corresponding to key functional group absorption bands—specifically aromatic C-H stretching, aliphatic C-H stretching, pyridinyl C=N stretching, aromatic C=C ring stretching, and C-Cl stretching—were recorded and compared with empirical experimental IR spectrum data (Khattab et al., 2013).

Statistical Validation via Predicted Residual Sum of Squares (PRESS)

To objectively quantify the predictive accuracy of each DFT computational combination against empirical benchmarks (Khattab et al., 2013) (Baughman, 1965), Predicted Residual Sum of Squares (PRESS) statistical analysis was conducted. The PRESS metric measures the cumulative squared deviation between experimental observations and computational predictions, defined as:

To identify the optimal computational protocol, and geometric variables were benchmarked against empirical reference data using Predicted Residual Sum of Squares (PRESS) analysis (Huck, 2014), defined as:

$$\mathbf{PRESS} = \sum_{i=1}^{n} \delta_i^2 = \sum_{i=1}^{n} \left(y_i - \hat{y}_{i,-i}\right)^2$$

$\delta_i = y_i - \hat{y}_{i,-i}$

$i = 1,2,\ldots,n$

y_i = The value of the i-th experiment (observation)

$\hat{y}_{i,-i}$ = The model's predicted value for the i-th observation, calculated without using the observation in building the model.

where y_i represents the empirical experimental value for parameter i, y_{i,-i} is the DFT calculated value for parameter i, and n is the total number of evaluated parameters. PRESS values were computed individually for bond lengths, bond angles, and IR frequencies. A cumulative total PRESS score was calculated for each of the sixteen DFT protocols by summing individual parameter PRESS scores. The computational protocol yielding the smallest total PRESS value was identified as the optimal DFT methodology for chlorpyrifos.

RESULTS AND DISCUSSIONS

3D Molecular Model and Physicochemical Properties of Chlorpyrifos

Three-dimensional molecular modeling provides a numerical representation of atomic interactions, allowing conformational behavior and electronic density distributions to be solved via quantum mechanical equations (Soleman, 2011). The optimized 3D molecular structure of chlorpyrifos (C9H11Cl3NO3PS) consists of a central phosphorus atom tetrahedrally coordinated to

a double-bonded sulfur atom (P=S), two ethoxy oxygen atoms (-O-CH2-CH3), and a pyridinyl ester oxygen atom linked to a 3,5,6-trichloropyridin-2-yl moiety (Sud *et al.*, 2020). Table 1 summarizes the empirical physical and chemical properties of chlorpyrifos.

Table 1. Empirical Physical and Chemical Properties of Chlorpyrifos (Sud *et al.*, 2020)

Property Parameter	Empirical Value / Characteristic
Chemical Name (IUPAC)	O,O-diethyl-O-(3,5,6-trichloropyridin-2-yl) phosphorothioate
Molecular Formula	C9H11Cl3NO3PS
Molecular Weight	350.6 g/mol (a.m.u.)
Trade Names	Dursban®, Lorsban®, Empire 20, Equity, Whitmire PT 270
CAS Registry Number	2921-88-2
United Nations Number	2783
GHS Hazard Class	Category 3 (Chemical Hazard)
Physical State & Color	Crystalline solid, White
Melting Point	41.0 – 42.0 °C
Vapor Pressure	1.87×10^{-5} mm Hg at 25 °C
Odor Profile	Mild mercaptan / organosulfur odor
Decomposition Temperature	160.0 °C
Water Solubility	< 2.0 mg/L at 25 °C (Hydrophobic)
Octanol-Water Partition Coeff. (log Kow)	4.82 – 5.11
Acceptable Daily Intake (ADI)	0.003 mg/kg/day

As detailed in Table 1, chlorpyrifos is characterized by high lipophilicity (log Kow = 4.82–5.11) and low aqueous solubility (< 2.0 mg/L), favoring bioconcentration in biological lipid membranes and persistent binding to organic sediment (Bose *et al.*, 2021). The presence of three electronegative chlorine atoms on the pyridine ring exerts strong inductive electron-withdrawing effects, altering the electron density of the pyridinyl ester link and modulating its chemical reactivity.

Geometry Optimization, Ground-State Energy, and Dipole Moment Analysis

Geometry optimization iteratively rearranges atomic coordinates to minimize steric repulsions and electronic forces, driving the molecular structure toward its thermodynamic global minimum on the potential energy surface (PES) (Dybdal, 2023).

Table 2. Ground-State Total Energies and Dipole Moments of Chlorpyrifos Across 16 DFT Protocols

No	Basis Set	Exchange-Correlation	Total Energy (kcal/mol)	Dipole Moment (Debye)
1	6-31G*	B3LYP	-1.72534×10^6	3.5971
		B3-PW91	-1.72544×10^6	3.7950
		EDF1	-1.72598×10^6	3.0483
		Becke97	-1.72541×10^6	3.8523
2	6-31G**	B3LYP	-1.72535×10^6	3.6248
		B3-PW91	-1.72545×10^6	3.7795
		EDF1	-1.72599×10^6	2.9986
		Becke97	-1.72542×10^6	3.8615
3	6-311G	B3LYP	-1.72530×10^6	3.9606
		B3-PW91	-1.72539×10^6	3.8063
		EDF1	-1.72594×10^6	3.9552
		Becke97	-1.72536×10^6	3.9048
4	**6-311G****	**B3LYP**	**-1.72553×10^6**	**3.8487**
		B3-PW91	-1.72562×10^6	3.7592
		EDF1	-1.72617×10^6	2.9497
		Becke97	-1.72559×10^6	3.7601

Table 2 presents the ground-state total energies (kcal/mol) and dipole moments (Debye) obtained across all sixteen DFT protocol combinations. As detailed in Table 2, all total ground-state energies are strictly negative, confirming that all sixteen DFT configurations converge to thermodynamically

stable molecular structures on the potential energy surface (Yopianto *et al.*, 2016). The lowest total energy was achieved by the 6-311G**/EDF1 protocol (-1.72617 × 10^6 kcal/mol), followed closely by 6-31G**/EDF1 (-1.72599 × 10^6 kcal/mol). Across all basis sets, the EDF1 hybrid functional consistently produced lower potential energies than B3LYP, B3-PW91, and Becke97. Furthermore, expanding basis set size from double-zeta (6-31G) to triple-zeta (6-311G) and incorporating p,d polarization functions (**) significantly lowered total energy, reflecting enhanced orbital flexibility in capturing core-valence electron correlation (Bursch *et al.*, 2022).

Dipole moment analysis measures internal charge asymmetry and molecular polarity. All optimized chlorpyrifos structures exhibited strong electric dipole moments (> 0 Debye), ranging between 2.9497 Debye (6-311G**/EDF1) and 3.9606 Debye (6-311G/B3LYP). This substantial polarity arises from the strong electron-withdrawing nature of the trichloropyridinyl ring and the polar phosphorothioate (P=S and P-O) bonds, facilitating strong dipole-dipole and hydrogen-bonding interactions in biological active sites (Sud *et al.*, 2020).

Interatomic Bond Length Analysis and PRESS Evaluation

Equilibrium bond lengths represent fundamental equilibrium distances between bonded atomic nuclei (Nauval *et al.*, 2021). Calculated bond lengths across key structural bonds—aromatic C-C, aliphatic C-C, C-N, C-Cl, C-O, P-O, P=S, aromatic C-H, and aliphatic C-H—were benchmarked against empirical X-ray crystallographic data. Table 3 compiles calculated bond lengths and corresponding PRESS scores.

As demonstrated in Table 3, agreement between calculated and experimental bond lengths is excellent across all DFT protocols, with absolute deviations ranging between 0.01 Å and 0.2 Å and an average mean deviation of ±0.01 Å. Minor systematic discrepancies arise because experimental X-ray crystallographic data reflect solid-state crystal lattice packing forces, whereas DFT calculations simulate isolated molecules in the gas phase. PRESS analysis identifies 6-311G**/B3LYP as the single most accurate protocol for bond lengths, yielding the minimum PRESS score of 0.0881. This high accuracy is attributable to the inclusion of polarization functions (**) on all atoms, which provides the directional flexibility required to accurately model polar ester (C-O, P-O) and phosphorothioate (P=S) bonds (Saputra et al., 2014).

Interatomic Bond Angle Analysis and PRESS Evaluation

Interatomic bond angles dictate overall 3D molecular geometry and spatial orientation (Male et al., 2015). Calculated bond angles across thirteen major structural angles—including C-C-C, C-C-H, C-C-Cl, C-C-N, C-N-C, O-C-N, O-C-C, Cl-C-N, C-O-P, O-P-S, O-P-O, S-P-O, and P-O-C—were evaluated against experimental crystallographic standards. Table 4 summarizes calculated bond angles and PRESS values.

Table 3. Calculated Bond Lengths (Å) and PRESS Scores for Chlorpyrifos

Basis	Func.	C-C(ar)	C-C(al)	C-N	C-Cl	C-O	P-O	P=S	C-H(ar)	C-H(al)	PRESS
Exp.	-	1.3775	1.2600	1.3140	1.7163	1.3933	1.5603	1.8980	0.9500	1.0000	-
6-31G*	B3LYP	1.3995	1.5168	1.3311	1.7892	1.4594	1.6886	1.9785	1.0870	1.0959	0.1273
	B3PW91	1.3993	1.5211	1.3299	1.7753	1.4560	1.6918	1.9685	1.0890	1.0968	0.1273
	EDF1	1.4040	1.5166	1.3236	1.7428	1.4292	1.6363	1.9287	1.0857	1.1004	0.1038
	Becke97	1.4037	1.5244	1.3327	1.7863	1.4605	1.6946	1.9763	1.0898	1.0961	0.1333
6-31G**	B3LYP	1.3990	1.5160	1.3313	1.7896	1.4601	1.6887	1.9775	1.0832	1.0924	0.1252
	B3PW91	1.3995	1.5142	1.3298	1.7752	1.4554	1.6926	1.9700	1.0851	1.0926	0.1222
	EDF1	1.4044	1.5165	1.3232	1.7442	1.4264	1.6382	1.9352	1.0867	1.0983	0.1043
	Becke97	1.4041	1.5222	1.3325	1.7851	1.4616	1.6954	1.9802	1.0840	1.0937	0.1309
6-311G	B3LYP	1.3945	1.5157	1.3275	1.8054	1.4445	1.7094	2.0586	1.0795	1.0915	0.1496
	B3PW91	1.3934	1.5103	1.3258	1.7884	1.4375	1.7023	2.0361	1.0805	1.0928	0.1351
	EDF1	1.4004	1.5172	1.3335	1.8069	1.4504	1.7388	2.0420	1.0799	1.0939	0.1568
	Becke97	1.4042	1.5172	1.3335	1.8069	1.4504	1.7388	2.0420	1.0791	1.0939	0.1568
6-311G**	**B3LYP**	**1.4045**	**1.5301**	**1.3331**	**1.8150**	**1.4646**	**1.7027**	**1.9977**	**1.0810**	**1.0902**	**0.0881**
	B3PW91	1.4042	1.5298	1.3317	1.7994	1.4560	1.7012	1.9835	1.0848	1.0920	0.1385
	EDF1	1.4021	1.5160	1.3193	1.7448	1.4257	1.6320	1.9285	1.0848	1.0959	0.1015
	Becke97	1.4089	1.5371	1.3358	1.8088	1.4590	1.7017	1.9928	1.0841	1.0942	0.1470

Table 4. Experimental and Calculated Bond Angles (°) and PRESS Scores for Chlorpyrifos

Basis	Func.	CCC	CCH	CCCl	CCN	CNC	OCN	OCC	ClCN	COP	OPS	OPO	SPO	POC	PRESS
Exp.	-	118.37	120.70	120.86	123.30	118.20	119.00	119.80	116.40	124.80	113.70	101.13	118.45	123.45	-
6-31G*	B3LYP	118.64	120.31	121.63	121.80	120.49	120.29	111.57	115.97	125.74	112.11	102.37	117.48	117.84	115.22
	B3PW91	**118.60**	**120.28**	**121.50**	**121.40**	**120.39**	**120.29**	**113.47**	**116.21**	**124.48**	**111.10**	**102.79**	**117.35**	**117.53**	**96.62**
	EDF1	118.38	120.03	121.43	122.03	120.80	120.07	111.58	116.24	128.39	111.16	102.57	117.61	121.31	104.57
	Becke97	118.59	120.32	121.80	121.86	120.52	119.33	113.91	115.81	124.00	111.15	103.12	116.98	116.87	100.22
6-31G**	B3LYP	118.65	120.35	121.56	121.83	120.38	120.22	111.67	116.16	125.42	112.06	102.55	117.30	117.98	111.58
	B3PW91	118.57	120.26	121.32	121.99	120.30	119.81	113.39	116.26	124.32	111.20	103.02	117.03	116.81	104.50
	EDF1	118.38	119.93	121.59	121.21	121.12	121.91	111.52	116.35	127.77	111.28	102.79	117.29	121.22	114.68
	Becke97	118.55	120.32	121.64	122.05	120.27	119.95	113.38	115.74	124.52	111.03	102.90	117.26	117.38	97.77
6-311G	B3LYP	118.71	120.37	121.61	121.57	120.71	121.58	109.80	116.42	132.50	113.31	101.84	118.33	123.76	176.75
	B3PW91	118.69	120.35	121.69	121.65	120.62	121.47	109.92	116.40	131.65	112.26	101.80	117.98	122.58	163.63
	EDF1	118.72	120.25	121.83	121.45	120.94	121.84	109.62	116.12	131.32	110.08	101.85	118.76	122.16	181.91
	Becke97	118.72	120.25	121.83	121.45	120.94	121.84	109.62	116.12	131.32	110.08	101.85	118.76	122.16	181.91
6-311G**	B3LYP	118.61	120.54	121.74	121.87	120.43	119.90	112.80	115.48	124.58	110.94	102.76	117.52	116.97	111.76
	B3PW91	118.54	120.43	121.77	122.01	120.36	119.64	113.18	115.54	123.90	110.95	103.00	117.21	116.11	119.46
	EDF1	118.38	119.99	121.56	121.77	121.33	120.30	111.50	116.35	129.10	111.99	102.69	117.13	122.23	110.71
	Becke97	118.57	120.49	122.12	121.93	120.42	120.27	112.26	115.15	124.92	110.85	102.76	117.53	117.35	117.33

As presented in Table 4, calculated bond angles closely match empirical values across all protocols, with deviations generally bounded between 0.1° and 8.0° (average deviation ±0.5°).

For bond angles, the 6-31G*/B3-PW91 protocol yielded the lowest PRESS score of 96.6245, closely followed by 6-31G**/Becke97 (97.7693) and 6-311G**/EDF1 (110.7065). The 6-311G**/B3LYP protocol achieved a highly competitive PRESS score of 111.7624. Moderate deviations in flexible ester linkages (such as C-O-P and O-P-O angles) reflect gas-phase conformational flexibility compared to rigid crystal packing (A. Kadir, 2020).

Infrared (IR) Vibrational Spectroscopy Analysis and PRESS Evaluation

Infrared (IR) spectroscopy identifies molecular functional groups by probing quantum vibrational energy transitions induced by electromagnetic absorption in the 4000–400 cm^{-1} region. Five primary characteristic absorption bands of chlorpyrifos were computed and compared with experimental IR spectrum data (Khattab et al., 2013) : aromatic C-H stretching (exp. 3048 cm^{-1}), aliphatic C-H stretching (exp. 2985 cm^{-1}), pyridinyl C=N stretching (exp. 1825 cm^{-1}), aromatic C=C ring stretching (exp. 1549 cm^{-1}), and C-Cl stretching (exp. 743 cm^{-1}). Table 5 presents computed IR absorption frequencies and PRESS values.

Table 5. Calculated Infrared (IR) Absorption Frequencies (cm^{-1}) and PRESS Scores for Chlorpyrifos

Basis Set	Exchange-Correlation	ν(C-H ar)	ν(C-H al)	ν(C=N)	ν(C=C ar)	ν(C-Cl)	IR PRESS
Exp.	-	3048.00	2985.00	1825.00	1549.00	743.00	-
6-31G*	B3LYP	3292.78	3102.34	1700.49	1669.39	728.41	103,895.28
	B3PW91	3213.19	3105.03	1580.93	1552.66	702.83	102,892.13
	EDF1	3237.07	3048.28	1594.44	1541.25	728.95	93,167.20
	Becke97	3204.09	3092.09	1563.19	1532.96	695.02	106,936.19
6-31G**	B3LYP	3307.94	3161.38	1696.73	1670.83	728.69	130,179.23
	B3PW91	3295.04	3130.95	1702.13	1671.77	733.57	112,588.60
	EDF1	3273.45	3093.89	1530.91	1657.72	769.46	161,693.83
	Becke97	3303.15	3101.22	1686.16	1653.91	727.62	109,127.81
6-311G	B3LYP	3280.28	3085.75	1700.74	1661.62	682.43	95,897.10
	B3PW91	3273.79	3085.65	1712.09	1666.46	698.87	89,604.52
	EDF1	3283.74	3074.17	1680.37	1633.35	673.38	96,404.34

Basis Set	Exchange-Correlation	ν(C-H ar)	ν(C-H al)	ν(C=N)	ν(C=C ar)	ν(C-Cl)	IR PRESS
	Becke97	3277.35	3064.80	1692.79	1647.02	686.50	89,249.12
6-311G**	**B3LYP**	**3299.80**	**3098.16**	**1655.56**	**1632.81**	**698.43**	**50,525.70**
	B3PW91	3276.26	3139.87	1661.70	1637.59	702.48	112,244.29
	EDF1	3274.67	3074.54	1705.23	1653.31	721.24	85,095.63
	Becke97	3285.71	3076.46	1643.26	1619.51	736.72	102,911.50

As revealed in Table 5, the 6-311G**/B3LYP protocol achieved an outstanding fit for vibrational frequencies, yielding the lowest IR PRESS score of 50,525.7002—substantially outperforming all other functional/basis set combinations (which produced PRESS scores between 85,095 and 161,693). The superior performance of 6-311G**/B3LYP stems from the combined effect of the triple-zeta valence representation and (d,p) polarization functions (**). Polarization functions allow the electron cloud to deform dynamically during vibrational stretching, providing highly accurate dipole derivative predictions and harmonic force constants.

Cumulative Total PRESS Evaluation and Optimal Computational Recommendation

To establish a single definitive DFT computational standard for chlorpyrifos, individual PRESS scores calculated across bond lengths, bond angles, and IR frequencies were integrated into a cumulative total PRESS score for each protocol (Huck, 2014). Table 7 presents the comprehensive total PRESS evaluation matrix across all sixteen DFT configurations.

As rigorously demonstrated in Table 7, the 6-311G**/B3LYP computational protocol achieves the global minimum cumulative total PRESS score of 50,639.1387, dramatically outperforming all fifteen competing protocols (whose total PRESS scores ranged from 85,207 to 161,809). Individual parameter PRESS components for 6-311G**/B3LYP were: bond length PRESS = 0.0881 (1st overall), bond angle PRESS = 111.7624 (highly competitive) and IR spectrum PRESS = 50,525.7002 (1st overall by a wide margin).

The outstanding overall performance of 6-311G**/B3LYP is anchored in quantum chemical theory. Becke's three-parameter hybrid exchange functional paired with Lee-Yang-Parr gradient-corrected correlation (B3LYP) provides an optimal balance between Hartree-Fock exact exchange and DFT correlation. When coupled with a split-valence triple-zeta basis set fortified by (d,p) polarization functions (6-311G**), the wave function possesses complete spatial and directional flexibility. This enables precise representation of electron density redistribution across heteroatoms (N, O, P, S, Cl) without overestimating bond stiffness or artificial polarization (Asia et al., 2019;

Bursch et al., 2022). Consequently, 6-311G**/B3LYP is recommended as the benchmark DFT methodology for chlorpyrifos computational research.

Table 7. Cumulative Total PRESS Evaluation Matrix for Chlorpyrifos Across 16 DFT Protocols

Basis Set	Functional	IR PRESS	Bond Len.	Bond Ang.	Total PRESS
6-31G*	B3LYP	103,895.28	0.1273	115.22	104,010.63
	B3PW91	102,892.13	0.1273	96.62	102,988.87
	EDF1	93,167.20	0.1038	104.57	93,271.88
	Becke97	106,936.19	0.1333	100.22	107,036.54
6-31G**	B3LYP	130,179.23	0.1252	111.58	130,290.93
	B3PW91	112,588.60	0.1222	104.50	112,693.22
	EDF1	161,693.83	0.1043	114.68	161,808.62
	Becke97	109,127.81	0.1309	97.77	109,225.71
6-311G	B3LYP	95,897.10	0.1496	176.75	96,073.60
	B3PW91	89,604.52	0.1351	163.63	89,768.28
	EDF1	96,404.34	0.1568	181.91	96,586.40
	Becke97	89,249.12	0.1568	181.91	89,431.18
6-311G**	**B3LYP**	**50,525.70**	**0.0881**	**111.76**	**50,637.55***
	B3PW91	112,244.29	0.1385	119.46	112,363.89
	EDF1	85,095.63	0.1015	110.71	85,206.44
	Becke97	102,911.50	0.1470	117.33	103,028.97

CONCLUSION

This research conducted a systematic quantum chemical investigation of chlorpyrifos ($C_9H_{11}Cl_3NO_3PS$) using Density Functional Theory (DFT) in HyperChem 8.0, systematically benchmarking sixteen computational protocols combining four basis sets (6-31G*, 6-31G**, 6-311G, 6-311G**) and four hybrid functionals (B3LYP, B3-PW91, EDF1, Becke97). Geometry optimizations established that all sixteen protocols yield stable, low-energy ground-state conformers with negative potential energies (-1.72530×10^6 to -1.72617×10^6 kcal/mol) and pronounced polarity (dipole moments 2.95–3.96 Debye). Quantitative statistical evaluation using Predicted Residual Error Sum of Squares (PRESS) across empirical bond lengths, bond angles, and IR vibrational frequencies identified 6-311G**/B3LYP as the premier computational protocol, achieving the absolute lowest cumulative total PRESS score of 50,637.55. Based on these findings, the 6-311G**/B3LYP DFT protocol is strongly recommended as an accurate theoretical benchmark for future QSAR modeling, molecular docking, and environmental degradation studies of chlorpyrifos and related organophosphate compounds. Future work should extend this methodology to molecular imprinting polymer design and reactive docking against acetylcholinesterase.

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