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Selection of semi-empirical calculation methods for insecticide development

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ABSTRACT

Background: Insecticides are substances used to control, repel, or eradicate troublesome organisms, particularly insect-based plant pests. The discovery of new insecticide compounds fuels the ongoing development of insecticides. The integration of computational chemistry into the development of insecticidal chemicals was beneficial.

Objective: This study aims to identify the most suitable method among 12 available semiempirical calculation methods in the Hyperchem application.

Methods: The selection process involved comparing experimental data of the infra-red spectrum of chlorpyrifos with corresponding calculation data.

Results: The largest Predicted Residual of Sum Squares (PRESS) value was observed in the INDO method of 55466.3856. Conversely, the smallest PRESS value was observed in the AM1, measuring 3242.6549. The AM1 semiempirical method yields the smallest value.

Conclusion: The results indicated that the calculation method chosen was the AM1 semiempirical method.

Introduction

Insecticides play a significant role in increasing agricultural production, particularly in controlling plant pests. However, insecticides also possess toxic properties. In Indonesia, most insecticides utilized belong to the organophosphate group, with chlorpyrifos being one example [1]. Chlorpyrifos is a highly toxic compound with an LC_{50} value of 0.024 g/L in fish [2]. This value is used to determine the toxicity of insecticides in a given concentration and its potential to cause the death of test animals [3,4]. Due to the various functional groups present, the use of insecticide combinations offers a variety of reaction mechanisms [5].

In the 1950s, the development of computer technology started molecular modeling. Techniques invented by artificial intelligence (AI) developing computational scientists have been mainly applied to drug design in recent years. These methods are called de novo or rational drug design [6]. The general method is used to identify the active functional group and enter the desired functional group to interact with other functional groups. This method also studies toxicological and anti-inflammatory effects [7]. Some researchers studied a compound, namely chlorpyrifos.

Chlorpyrifos is a white solid with a sharp odor. If chlorpyrifos enters the body waters, it will kill aquatic biotas such as fish and shrimp. This chlorpyrifos insecticide is non-systemic and works when it comes in contact with the skin, is ingested, and is inhaled [8]. Its molecular formula is $C_9H_{11}Cl_3NO_3PS$, with a molecular weight of 350.59 g/mol. Chlorpyrifos has a melting point of 42 °C and a specific gravity of 1.4 g/cm^3. It belongs to the organothiophosphate group, as illustrated in Figure 1.

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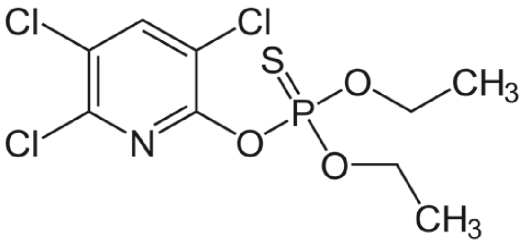

Figure 1. Chlorpyrifos: an example of the organo-thiophosphate compound

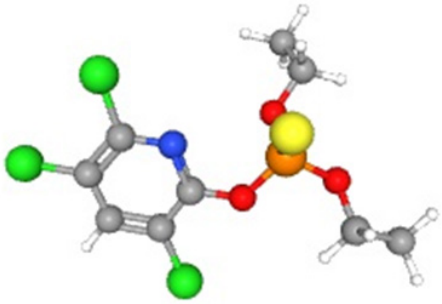

Figure 2. Geometry optimization of chlorpyrifos compound through semiempirical methods

The present study employed a semi-empirical calculation method, which was carried out using the Hyperchem software. There are 12 different semi-empirical methods available for calculation [9], and the method selected for chlorpyrifos calculation was based on experimental infrared (IR) spectra data [10,11]. Semi-empirical methods utilize the principles of quantum mechanics [12], and the available methods in the software include Extended Huckel, Complete Neglect of Differential Overlap (CNDO), Intermediate Neglect of Differential Overlap (INDO), Modified Intermediate Neglect of Differential Overlap 3 (MINDO3), Modified Neglect of Diatomic Overlap (MNDO), Modified Neglect of Diatomic Overlap d (MNDOd), Austin Model 1 (AM1), Recife Model 1 (RM1), Parameterized Model 3 (PM3), Zero Intermediate Neglect of Differential Overlap-1 (ZINDO-1), Zero Intermediate Neglect of Differential Overlap-S (ZINDO-S), and Typed Neglect of Differential Overlap (TNDO) (HyperCube, 2007). The choice of the method was determined by comparing the results with the experimental IR spectra [11]. This study aims to select one method of 12 semi-empirical calculation methods available in the Hyperchem application.

Methods

Equipment

This study was theoretical research conducted on a computer with the following specifications: Intel(R) Core (TM) i5-6500 CPU @ 3.20GHz, 8.00 GB RAM, Windows 10 64-bit operating system, x64 processor, and Hyperchem 8.0 Program. The research used the molecular model of chlorpyrifos and selected the semi-empirical method based on the infrared spectrum (IR) obtained from previous studies [4].

Molecular modeling of chlorpyrifos

After the chlorpyrifos molecule reached stable energy, the infrared spectrum was calculated using the Hyperchem Program. The calculation was performed by selecting the Compute menu and the vibrational spectrum in the available options.

Geometry optimization

The chlorpyrifos molecule was drawn into a three-dimensional (3D) shape, and the geometry optimization calculation was performed. The methods used for the calculation were the Extended Huckel method, AM1, CNDO, INDO, MINDO3, MNDO/d, MNDO, PM3, RM1, TNDO, ZINDO/1, and ZINDO/S, and the geometry optimization was set with parameters of RMS gradient = 0.01 kcal/(Å.mol), algorithm = Polak-Ribiere, molecular charge = 0 and spin multiplicity = 1.

Infrared spectrum analysis

The infrared spectrum was calculated using the Hyperchem Program by selecting the Compute menu and the vibrational spectrum from the available options.

Method selection and analysis

The data were obtained from the IR spectrum calculation method for each method used. The best calculation method was determined by the Predicted Residual of Sum Squares (PRESS) method, where the smallest value was chosen as the result.

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

Results

A molecular of chlorpyrifos was generated, then the model was transformed into a three-dimensional (3D) image and subjected to geometry optimization (Table 1). Subsequent to this, we calculate the infrared spectrum of the optimized geometry. To accomplish this, various calculation methods were employed to determine the infrared spectrum. The outcome of these

Table 1. Geometry optimization of chlorpyrifos compound through semiempirical methods

Semiempirical Method	Energy (kcal/mol)
Extended Huckle	Not available
CNDO	-128624.2295725
INDO	-126935.8539243
MINDO3	Not available
MNDO	-90619.6154333
MNDOd	-83020.9839350
AM1	-90312.6379481
RM1	-90247.9739025
PM3	-81589.0217856
ZINDO-1	-119190.3506318
ZINDO-S	Not available
TNDO	-128577.4162867

calculations are presented in Figure 2 and summarized in Table 1.

Experimental infrared spectrum data, sourced from previous studies (referred to as experimental data in Table 1) [4], were used for comparison. The calculation results of the infrared spectrum, obtained using the Hyperchem version 8 program, are outlined in Table 2 [9]. The comparison between the calculated and experimental data for the chlorpyrifos infrared spectrum is provided in Table 3.

Identifying the best semi-empirical calculation method was based on the criterion of achieving the lowest Predicted Residual of Sum Squares (PRESS) value [11]. The final results of this calculation are provided in Table 4.

Discussion

The initial step involves modeling the chlorpyrifos molecule and optimizing its geometry, as depicted in Figure 1. Subsequently, the next stage encompasses calculating the infrared spectrum. After obtaining the infrared spectrum value, a comparison was drawn between these values and the closest experimental data [11].

The three-dimensional structure of the chlorpyrifos compound consists of various atoms: carbon (gray circles), hydrogen (white circles), chlorine (green circles), nitrogen (blue circles), oxygen (red circles), phosphorus (orange circles), and sulfur (yellow circles) (Figure 2).

Table 2. Experimental data of infrared spectrum and wave number

No	Spectrum of chlorpyrifos experiment	Wave number (cm^{-1})
1	Spectrum 1	767.58
2	Spectrum 2	829.78
3	Spectrum 3	1486.06
4	Spectrum 4	1588.96
5	Spectrum 5	1658.33

Table 1 shows that among these semi-empirical calculation methods, the CNDO approach yields the lowest energy value of -128624.2295725 kcal/mol. Conversely, the MNDO semi-empirical calculation method has the highest value of -90619.6154333 kcal/mol. Notably, there semi-empirical calculation methods are incapable of conducting molecular modeling for chlorpyrifos compounds [12]. These methods are Extended Huckle, MINDO3, and ZINDO-S.

The foundational CNDO method simplifies calculations by considering only s and p orbitals, represented through linear combinations of the Slater function [13]. Conversely, the integral MNDO method lacks parameterization but approximates calculations using the classical multipole technique [14]. Extended Huckle, MINDO3, and ZINDO-S aim to increase the applicability of theories such as INDO, rendering them more versatile [12].

Experimental data for the infrared spectrum was obtained from previous research, herein referred to as experimental data [4]. This data is presented as spectrum values and wave numbers, as listed in Table 2.

The research data involves computed infrared spectrum results using the Hyperchem version 8 program (Table 3). Notably, three semi-empirical methods did not produce an infrared spectrum, suggesting these methods cannot be optimized in geometry.

Table 3 shows the proximity between experimental and calculated values. The lowest value of the Predicted Residual of Sum Squares (PRESS) is the value of the selected semi-empirical calculation method [11]. This analysis leads to Table 4.

The calculation in Table 4, the INDO semi-empirical method yields the largest PRESS value of 55466.3856.

Table 3. Data calculation and experimental data of chlorpyrifos infrared spectrum

Methods	Infrared Spectrum (cm^{-1})				
	Spectrum 1	**Spectrum 2**	**Spectrum 3**	**Spectrum 4**	**Spektrum 5**
Extended Huckel	Not available	Not available	Not available	Not available	Not available
CNDO	608.54	900.52	1445.60	1542.61	1636.08
INDO	534.56	846.76	1461.26	1577.78	1646.51
MINDO 3	Not available	Not available	Not available	Not available	Not available
MNDO	760.79	852.05	1454.34	1537.80	1685.03
MNDO d	757.56	820.31	1481.19	1521.07	1652.35
AM1	774.55	803.97	1479.83	1539.29	1663.02
RH1	741.28	845.18	1455.19	1478.58	1646.88
PM3	785.89	826.23	1497.84	1559.78	1719.61
ZINDO-1	796.47	874.38	1457.41	1675.65	1768.51
ZINDO-S	Not available	Not available	Not available	Not available	Not available
TNDO	726.78	871.57	1409.38	1506.54	1637.43
Experiment	767.58	829.78	1486.06	1588.96	1658.33

Table 4. Predicted residual of sum squares (PRESS) data for all semiempirical calculation methods

Method	$(y_1 - y_1')^2$	$(y_2 - y_2')^2$	$(y_3 - y_3')^2$	$(y_4 - y_4')^2$	$(y_5 - y_5')^2$	The number of PRESS
(EH - Eks)	Not available	Not available	Not available	Not available	Not available	Not available
(CNDO - Eks)	25293.7216	5004.1476	1637.0116	2148.3225	495.0625	34578.2658
(INDO - Eks)	54298.3204	288.3204	615.04	124.9924	139.7124	55466.3856
(MINDO 3 - Eks)	Not available	Not available	Not available	Not available	Not available	Not available
(MNDO - Eks)	46.1041	495.9529	1006.1584	2617.3456	712.89	4878.451
(MNDO d - Eks)	100.4004	89.6809	23.7169	4609.0521	35.7604	4858.6107
(AM1 - Eks)	***48.5809***	***666.1561***	***38.8129***	***2467.1089***	***21.9961***	***3242.6549***
(RH1 - Eks)	691.69	237.16	952.9569	12183.7444	131.1025	14196.6538
(PM3 - Eks)	335.2561	12.6025	138.7684	851.4724	3755.2384	5093.3378
(ZINDO-1 - Eks)	834.6321	1989.16	820.8225	7515.1561	12139.6324	23299.4031
(ZINDO-S - Eks)	Not available	Not available	Not available	Not available	Not available	Not available
(TNDO - Eks)	1664.64	1746.4041	5879.8224	6793.0564	436.81	16520.7329

Conversely, similar to the empirical method, the AM1 approach exhibits the lowest PRESS value of 3242.6549 [11]. Based on these outcomes, it can be concluded that the AM1 semi-empirical method is the most suitable for insecticide development.

Conclusions

The AM1 semi-empirical calculation method was the calculation method chosen and suitable for use in the development of insecticidal compounds.

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Author contributions

PI designed this study; EVY and ES contributed to data collection; PI and HE made the first script; PIs contribute to data analysis, and all authors contributed to the interpretation of the data and approved the final version of the manuscript.

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