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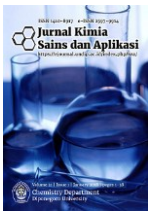

Validation of Semiempirical Calculation Methods for the Development of 1,2,3-Triazole-based Compounds

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Abstract

Compounds based on 1,2,3-triazole have been widely utilized as anticancer agents. There are hydrogen bonds in compounds that can interact with a target biomolecule to form new compounds or derivative compounds that have useful biological activities. The 1,2,3-triazole compound has proven biological activities, including analgesic, antimicrobial, antiviral, anti-inflammatory, and antifungal properties. Molecular modeling for the development of 1,2,3-triazole compounds can be performed using a computational chemistry approach. One of the calculation methods used in molecular modeling is semiempirical calculations. The semiempirical method consists of 12 methods. This research was conducted to select 1 of 12 methods for the 1,2,3-triazole compound. First, the research procedure was to optimize the 1,2,3-triazole compound. Second, calculated the NMR spectrum. Third, calculated the physical properties, such as bond length and bond angles, and then calculated the Predicted Residual Sum of Squares (PRESS) value. The research results showed that the INDO semiempirical method had the smallest (lowest) PRESS value, namely 1.679. The INDO semiempirical method was the most suitable method for calculating 1,2,3-triazole compounds.

1. Introduction

Two carbon atoms and three nitrogen atoms make up the five-membered ring of the 1,2,3-triazole molecule [1]. A simple aromatic heterocycle is 1,2,3-triazole. Compared to other organic molecules with three neighboring nitrogen atoms, this structure is extremely stable. Nevertheless, the nitrogen molecule (N_2) is lost during flash vacuum pyrolysis at 500°C, resulting in the formation of a three-membered aziridine ring. Ring chain tautomerism makes some 1,2,3-triazole compounds relatively easy to split. The Dimroth rearrangement is one example of this [2]. As a bioisostere in medicinal chemicals, 1,2,3-triazole has been used in research as a building block for more complicated chemical compounds, including pharmaceutical medications, such as tazobactam and mubritinib [3].

Numerous molecules of both biological and industrial relevance contain the heterocyclic ring of 1,2,3-triazole [4]. Although reductive cleavage is possible, the 1,2,3-triazole ring is extremely stable and is typically not broken by oxidation or hydrolysis. The presence of two pyridine-type nitrogen atoms in the ring reduces the ease of quaternization and necessitates strong conditions. 1,2,3-triazole compounds experience electrophilic substitution at carbon or nitrogen, just like other heterocycles. Alkyl halides, dimethyl sulfate, and diazomethane readily alkylate them at the nitrogen. Triazolium salts are also formed by quaternizing 1,2,3-triazole under forcing conditions. 1,2,3-triazole compounds with water to produce triazolium anions and hydronium ions [5].

Compounds based on 1,2,3-triazole have been widely synthesized and used as anti-cancer drugs [6]. The

compound contains hydrogen bonds, allowing it to interact with biomolecular targets and form new compounds or derivatives with useful biological activity. Triazole rings have been widely used in therapeutic applications due to their biological activities, including analgesic, antimicrobial, antiviral, anticancer, anti-inflammatory, and antifungal effects [7, 8].

Molecular modeling for the development of 1,2,3-triazole can be carried out using a computational chemistry approach. The calculation method used in molecular modeling is semiempirical [9]. The semiempirical method has succeeded in synthesizing anti-cancer drugs from Kalanon derivatives through Quantitative Structure-Activity Relationship (QSAR) analysis [10]. The semiempirical calculation method is a method that uses the concept of quantum mechanics [11].

In the HyperChem program, there are 12 types of semiempirical calculation methods. The twelve methods are Extended Hückel, Complete Neglect of Differential Overlap (CNDO), Intermediate Neglect of Differential Overlap (INDO), Modified Intermediate Neglect of Differential Overlap 3 (MINDO/3), Modified Neglect of Diatomic Overlap (MNDO), Modified Neglect of Diatomic Overlap d (MNDO/d), Austin Model 1 (AM1), Recife Model 1 (RM1), Parameterized Model 3 (PM3), Zerner's Intermediate Neglect of Differential Overlap-1 (ZINDO/1), Zerner's Intermediate Neglect of Differential Overlap-S (ZINDO/S) and Typed Neglect of Differential Overlap (TNDO).

The Extended Hückel (EH) method is a semiempirical method in computational chemistry developed by Roald Hoffmann in 1963. This method predicts the electronic structure and chemical properties of molecules. The advantages of this method are faster compared to the ab initio method. Second, it can predict the electronic structure and chemical properties with sufficient accuracy. It can be used for large and complex molecules and is easy to use compared to other methods, for the third and fourth, respectively. The limitations of this method include its reduced accuracy in predicting chemical properties, inability to account for relativistic effects, and limited suitability for molecules with highly complex bonds, as well as its inability to predict spectroscopic properties with high accuracy [12].

In computational chemistry, a semiempirical technique called ZINDO/S (Zerner's Intermediate Neglect of Differential Overlap/Spectral) is used to forecast the spectroscopic characteristics of molecules, including their fluorescence and UV-Vis spectra. Michael Zerner and his group created the ZINDO/S technique in 1970. The fundamental idea is that the integral of atomic orbitals can be calculated using the INDO (Intermediate Neglect of Differential Overlap) approximation, also known as INDO/Spectral. The structure of molecular electronics can be calculated using the Self-Consistent Field (SCF) method, and excitation energies and spectroscopic spectra can be calculated using perturbation techniques. The advantages of this method include faster computing compared to the ab initio method, the ability to predict spectroscopic properties with sufficient accuracy, its applicability to large and complex molecules, and its simplicity, making it easier to compare with other methods. Limitations are that it is less accurate for predicting particular chemical properties, and less suitable for molecules with very complex bonds [13]. Validation is a step to select an appropriate calculation method. The parameters for validation are the structure data and the ^{1}H NMR spectrum of the experiment [9]. This research aims to validate the semiempirical calculation method to develop the 1,2,3-triazole-based compound [14].

2. Experimental

2.1. Instrument and Materials

This study was conducted at the Physical Chemistry Laboratory of Jenderal Soedirman University, Department of Chemistry, Faculty of Mathematics and Natural Sciences. The computational work was performed on a personal computer equipped with an Intel® Core™ i5-6500 processor (3.20 GHz), 8 GB of RAM, and a 64-bit Windows 10 operating system. HyperChem version 8.0 software was used for the calculations [15]. The theoretical study employed 1,2,3-triazole as the model compound [16].

2.2. Modeling of 1,2,3-Triazole Compounds

The first step of this study involved modeling the 1,2,3-triazole compound using HyperChem software. The compound was constructed in three-dimensional (3D) form, after which an appropriate calculation method was selected based on the parameters of the 1,2,3-triazole model [14].

2.3. Geometry Optimization

The 1,2,3-triazole compound was modeled in three-dimensional (3D) form, followed by geometry optimization calculations using various semiempirical methods. The methods evaluated included Extended Hückel (EH), CNDO, INDO, MINDO/3, MNDO/d, MNDO, AM1, RM1, PM3, ZINDO/1, ZINDO/S, and TNDO, which were applied alternately [14]. This step served as an initial screening of semiempirical methods; methods that failed to achieve geometry optimization were excluded from further consideration.

2.4. ^{1}H Nuclear Magnetic Resonance (NMR) Spectrum Analysis

After geometry optimization, the ^{1}H NMR spectrum was calculated by selecting all hydrogen atoms present in the compound. Hydrogen atom selection was performed using the *Select* menu in the HyperChem software workspace. The ^{1}H NMR calculation was then carried out with the spectrometer frequency set to 300 MHz and the reference shielding value set to 25.3 [14].

2.5. Physical Properties of the Compounds

The physical properties of the 1,2,3-triazole compound evaluated in this study included bond lengths (in ångströms) and bond angles (in degrees). These data were obtained using HyperChem software [15].

2.6. The Calculation of Predicted Residual of Sum Squares (PRESS)

To determine the optimal calculation method for the 1,2,3-triazole molecule, data from the NMR spectra, bond lengths, and bond angles obtained using each method were compiled in Microsoft Excel and evaluated using the Predicted Residual Sum of Squares (PRESS) method. As defined in Equation (1), the PRESS value is calculated as the sum of the squared differences between experimentally observed values and the corresponding predicted results [14]. PRESS is calculated in total for each set of bond length, bond angles, and NMR spectrum.

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

3. Results and Discussion

Compounds based on 1,2,3-triazoles are widely used as antiviral and anticancer agents. For example, 2-C-(oxymethyl)-2,3:5,6-di-*O*-isopropylidene-*D*-mannofuranose bis-*O*-[(1-decyl-1H-1,2,3-triazol-4-yl)methyl] has been reported to exhibit anticancer activity, while compounds such as 2-{4-[(1-benzoylbenzimidazol-2-ylthio)methyl]-1H-1,2,3-triazol-1-yl}-*N*-nitrophenylacetamide show antiviral properties. In addition to their anticancer and antiviral activities [17], 1,2,3-triazole derivatives have also been reported as antimicrobial and antioxidant agents [18]. Computational analysis begins with the selection of semiempirical methods. The molecular model of the 1,2,3-triazole compound was constructed and visualized using the HyperChem software interface [19].

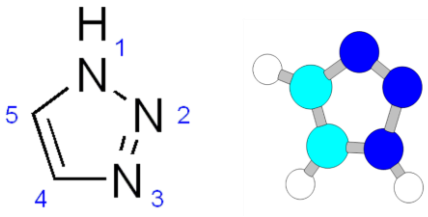

Figure 1. 1,2,3-triazole compound; where hydrogen atoms are shown as white spheres, carbon atoms as light blue spheres, and nitrogen atoms as dark blue spheres

Table 1. Geometry optimization results of the 1,2,3-triazole compound obtained using various semiempirical calculation methods in HyperChem software

No.	Calculation method	Total energy (kcal/mol)
1.	PM3	-769.95
2.	CNDO	-2512.46
3.	MNDO	-787.31
4.	MINDO/3	-835.21
5.	MNDO/d	-787.31
6.	INDO	-2298.98
7.	RM1	-848.18
8.	AM1	-750.82
9.	TNDO	-2813.53
10.	ZINDO/1	-2345.97
11.	ZINDO/S	-
12.	EH	-

Not all semiempirical calculation methods were able to successfully optimize the geometry of the 1,2,3-triazole compound. Among the twelve semiempirical methods evaluated, the EH and ZINDO/S methods failed to achieve geometry optimization for 1,2,3-triazole. The geometry optimization results obtained using the remaining semiempirical methods are summarized in Table 1.

There are several technical differences among the semiempirical methods implemented in HyperChem. One key distinction lies in how electron–electron interactions are treated, while another important difference concerns the parameterization schemes employed by each method. As shown in Table 1, the TNDO method yielded the lowest total energy (-2813.53 kcal/mol), whereas the highest energy was obtained using the AM1 method (-750.82 kcal/mol). The EH and ZINDO/S methods failed to achieve geometry optimization. The EH method is less suitable for molecules with complex bonding, while the ZINDO/S method has limitations in accurately predicting certain chemical properties and is also less appropriate for molecules with complex bond structures. Consequently, ten semiempirical methods were selected as candidates for further analysis.

The group developed the NDO methods, which are divided into CNDO and INDO, based on the techniques used to collect parameters. They selected parameters primarily based on theory. Their goal was to provide them with values as close as possible to those that might be achieved using the same basis set in an exact Hartree-Fock computation. To replicate experimental quantities, MINDO/3, MNDO, and AM1 were selected based on various factors, including formation temperatures and sample molecule geometries. Compared to the CNDO and INDO approaches, the methodologies produced outcomes that were more in line with experimentation [9].

When using the MNDO/d technique with main group elements, d orbitals were crucial. The neglect of diatomic differential overlap (NDDO) approximation served as the foundation for the PM3 technique, a reparameterization of the AM1 method. When Coulomb and exchange integrals are calculated, NDDO keeps all one-center differential overlap terms. The parameter values are the primary difference between PM3 and AM1. The parameters for PM3 were obtained by comparing a wider range of computational and experimental molecular properties. In general, PM3 has fewer repulsive non-bonded interactions than AM1. The PM3 method is parameterized for several main group elements and geometries and is predominantly applied to organic compounds, producing results that are more consistent with experimental data than those obtained using CNDO and INDO methods.

A modified version of the intermediate neglect of differential overlap (INDO) served as the foundation for the ZINDO/1 approach. For the first row transition metals only, Zerner's first INDO/1 employed Slater orbital exponents with a distance dependence. However, for every element that was available, HyperChem employed constant orbital exponents. When combined with the

singly excited CI method, ZINDO/S is an INDO method parameterized to replicate UV-Visible spectroscopic transitions [15].

Numerous thermodynamic and kinetic features of chemical processes are investigated using data from semiempirical computations. Chemical phenomena are clearly related to the energies and geometries of molecules. Although they are less well-defined, other metrics, such as atomic charges and frontier orbitals, yield insightful qualitative findings. The net outcome of electronic kinetic energies and interactions between all of the system's electrons and atomic cores is the total energy in a molecular orbital calculation. According to the Born-Oppenheimer approximation, this is the potential energy for nuclear motion [9].

A molecule's stable shape has a low total energy. Different stable or metastable conformations and isomers of a molecule are described by geometries at various energy minima (local minima + the global minimum). Geometries that correlate to energy minima are typically obtained by geometry optimizations using NDO techniques. The binding energy of the electrons is reported by the HyperChem status line, although the heat of formation is also provided by all SCF methods.

Fitting to experimentally determined temperatures (enthalpies) of formation for a set of molecules at 298 K allows for the parameterization of MINDO/3, MNDO, AM1, and PM3. For these methods, the heat of formation is obtained by subtracting the electronic binding energy from the atomic heats of formation and is reported in the calculation log file. In practice, the heat of formation is the parameter most commonly discussed, as it is more informative than the binding energy.

Stewart's review provides the following information for various molecular structures, including hydrocarbons, strained ring complexes, compounds with heteroatoms, radicals, and ions. AM1 predicts heats of formation within a few kilocalories per mole for most organic compounds; however, even advanced semiempirical methods can fail for certain systems, particularly halogen-rich inorganic molecules such as perchloryl fluoride [9].

Table 2. ^{1}H NMR spectrum data for the 1,2,3-triazole compound with HyperChem software

Method	^{1}H NMR peak (σ, ppm)
Experiment	7.8
CNDO	7.814
MNDO	7.708
MINDO3	7.780
MNDO/d	7.708
INDO	7.870
RM1	7.695
AM1	7.884
TNDO	7.359
ZINDO/1	7.688
PM3	7.804

^{1}H NMR experiment spectrum data of the 1,2,3-triazole compound was 7.8 ppm (Table 2). Data on the physical properties of structures, such as bond lengths and angles, play an important role in geometry optimization. For 1,2,3-triazole, experimentally available structural data include the N–N and N=N bond lengths, and the N–N=N bond angle. The reported bond lengths are 1.352 Å for N–N and 1.312 Å for N=N, while the N–N=N bond angle is 106.7° [16]. Experimental data and calculation data for the optimization of the 1,2,3-triazole compound are seen in Table 3.

Semiempirical calculation methods that cannot calculate up to the optimization geometry are the EH, MINDO/3, and ZINDO/S methods. The EH method is more suitable for large and complex systems. The MINDO/3 method is a semi-empirical method in computational chemistry developed by Dewar and friends in 1975. This method predicts the electronic structure and chemical properties of molecules. MINDO/3 semiempirical molecular orbital methods were used to compute atomic charges and geometries of certain structures, including substituted singlet and triplet carbenes and the associated diazomethanes. These findings show that MINDO/3 can predict the inherent substituent effects in singlet carbenes when compared to experimental data [20].

The PRESS explores how far and close it is to the experimental data. The closer it is to experimental data, in other words, the smaller the PRESS value, the more the semiempirical method was elected [21]. A type of cross-validation used in regression analysis, the PRESS in statistics provides a summary assessment of how well a model fits a sample of observations that were not used to estimate the model. After totaling the PRESS data, the lowest value is selected.

Table 3. Experimental data and bond length data calculations, bond angle for 1,2,3-triazole compound with HyperChem

Method	N-N bond length (Å)	N=N bond length (Å)	N-N=N bond angle (°)
CNDO	1.31203	1.27242	108.651
INDO	1.31635	1.27826	107.993
MINDO/3	1.29269	1.23101	108.864
MNDO	1.34083	1.26881	109.276
MNDO/d	1.34083	1.26882	109.276
AM1	1.34452	1.27307	109.776
RH1	1.40314	1.30277	108.039
PM3	1.35586	1.28111	108.187
ZINDO/1	1.31811	1.27811	108.546
TNDO	1.30815	1.26001	108.951
Experiment	1.35200	1.31200	106.700

Table 4. ^{1}H NMR spectrum, PRESS data, N-N bond length, N=N bond length, and N-N=N bond angle for the 1,2,3-triazole compound with HyperChem software

Method	Amount/PRESS
CNDO	3.809
INDO	1.679
MINDO/3	4.693
MNDO	6.646
MNDO/d	6.646
AM1	9.470
RM1	1.807
PM3	2.212
ZINDO/1	3.423
TNDO	5.266

Table 4 was a PRESS calculation that was closest to the experimental data. For each semiempirical method, the deviations from the experimental data were squared and summed to obtain the PRESS value. The INDO method yielded the lowest PRESS value (1.679), indicating the best agreement with the experimental data, whereas the AM1 method produced the highest PRESS value (9.470). Based on these results, the INDO semiempirical method was selected for subsequent calculations of the 1,2,3-triazole compound [9].

Both ZINDO/S and EH methods are unable to calculate dipole moments. The EH method is the simplest and fastest semiempirical approach available in HyperChem; however, it is also the least accurate. EH treats electron-electron interactions in a highly simplified manner, not explicitly accounting for them, but instead incorporating their effects implicitly through parameterization. ZINDO/S is an INDO-based method developed for molecular systems containing transition metals. It is specifically parameterized for the calculation of electronic excitation energies and UV–Vis spectra, whereas ZINDO/1 is primarily intended for molecular geometry calculations [15].

The University of Texas at Austin's Dewar group created the MINDO/3. In order to replicate experimental quantities, this group selected a variety of criteria, including sample molecule geometries. The MNDO, MNDO/d, AM1, and PM3 approaches are based on the NDDO approximation. They have an extra class of electron repulsion integrals in addition to the integrals used in the INDO methods. Specifically, these methods account for interactions between the overlap density of two orbitals centered on the same atom and the overlap density of two orbitals centered on another atom. This is an important step in figuring out how various atoms are affected by electron-electron interactions [9].

The TNDO approximation is a novel semi-empirical technique that requires extensive investigation before its parameterization can be fully established across a wide range of applications. TNDO is practically the same as INDO (TNDO/2) or CNDO (TNDO/1); however, the sole distinction is that the semi-empirical parameters depend on the type of atom rather than the atomic number. TNDO can be regarded as a hybrid between semiempirical quantum mechanics and molecular mechanics, as it employs AMBER atom types. Successful application of TNDO, therefore, requires extensive research to develop parameters for the various possible atom types and chemical environments. For instance, TNDO/2 has distinct values for C-C single bonds, double bonds, triple bonds, and aromatic bonds, in contrast to INDO, which has a single bonding parameter for all C-C bonds. Both the feature that is being predicted and certain chemical conditions influence the atom parameters.

In other words, the general TNDO scheme has distinct parameter sets for various qualities rather than a single generic set of parameters for every circumstance. As a result, one set of parameters is used to project chemical shifts in HyperNMR, which employs TNDO, while another set is used to predict spin-spin coupling. Only the TNDO semi-empirical approach has a mechanism for selecting and copying parameter sets that is linked to the menu item Select Parameter Set. The n-octanol–water partition coefficient (K_ow), also commonly denoted as P or expressed as log P, represents the distribution of a compound between n-octanol and water. For the 1,2,3-triazole compound, the calculated log P value is 0.07 (Table 5), indicating that the compound is essentially nonpolar [15].

The 1,2,3-triazole compound had a dipole moment of 4.138 debyes. Any system with a separation of charges will have a dipole moment. As a result, they can occur in both covalent and ionic bonds. The difference in electronegativity between two atoms that are chemically linked causes dipole moments. The polarity of a chemical bond between two atoms in a molecule is measured by a bond dipole moment. It is related to the concept of electric dipole moment, a measurement of the distance between positive and negative charges in a system. Another physical quantity is molecular weight. The 1,2,3-triazole compound had a molecular weight of 69.07 amu. Although the term "molecular weight" is formally equivalent to relative molecular mass, its usage varies in practice. When expressed in daltons (Da), molecular weight is numerically comparable to molar mass, but differs in units. For macromolecules, it is commonly reported as an average value in kilodaltons (kDa) [9].

Table 5. Theoretical variables of the 1,2,3-triazole compound with the semiempirical INDO method on HyperChem software

No.	Name of variable	Value
1	Log P	0.07
2	Dipole moment	4.138 debyes
3	Molecular weight	69.07 amu
4	Hydration energy	-17.19 kcal/mol
5	Volume	258.95 Å^3

Hydration energy, also known as hydration enthalpy, is the quantity of energy released when a molecule or ion is solvated in water and is a crucial parameter in quantitative solvation studies. Determination of hydration energy is one of the more challenging aspects of molecular property prediction because it reflects a balance between solute–solvent interactions and the intrinsic stability of the solute. For the 1,2,3-triazole molecule, the calculated hydration energy is -17.19 kcal mol^{-1}. Molecular volume describes the three-dimensional space occupied by a molecule and is commonly reported in cubic ångströms ($Å^3$) in computational studies. The calculated molecular volume of 1,2,3-triazole is 258.95 $Å^3$ [15].

4. Conclusion

Based on the comparative evaluation of semiempirical and quantum mechanical methods, the Intermediate Neglect of Differential Overlap (INDO) approach was selected as the most suitable method for modeling 1,2,3-triazole-based compounds. Molecular docking, quantitative structure-activity relationship analysis, and molecular modeling provide a reliable foundation for further development.

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