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Study of Stability and Reactivity of Cyclopolic Acid Compounds and Their Derivatives Using Semi-empirical Methods AM1 and PM3

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ABSTRACT

The semiempirical method is a method that can be selected in computational chemistry. This method can be used to study the stability and reactivity of cyclopolic acid compounds and their derivatives. This method is simple method in optimizing a compound in calculating the parameters possessed by the atom. Cyclopolic acid is an organic compound that can be found in corn and beans. Analysis using two methods on HyperChem Professional application are AM1 and PM3. Analysis Result shows that the total energy and gradient of each compound do not have significant differences in calculations. As in the structure of 2-formyl-3-(hydroxymethyl)-6-methoxy-5-methylterephthalic acid has a total energy of -80608.1868567 (kcal/mol) and a gradient of 0.0898817 (kcal/mol/Ang) with the AM1 method and total energy of -74935.9180118 (kcal/mol) and a gradient of 0.0874369 (kcal/mol/Ang) with the PM3 method. The stable structure is in the structure of the 2-formyl-3-(hydroxymethyl)-6-methoxy-5-methylterephthalic acid based on the calculation of the total energy and gradient. Meanwhile, according to the calculation of the difference between LUMO-HOMO, it has different results. Where according to the calculation of the energy difference between LUMO-HOMO, the most stable compound structure is the structure of 2-formyl-3-(hydroxymethyl)-4-isocyano-6-metoxy-5-methylbenzoic acid but is not reactive. Likewise, the 2-formyl-4-hidroxy-3-(hydroxymethyl)-6-methoxy-5-methylbenzoic acid, 2-formyl-3-(hydroxymethyl)-6-methoxy-5-methyl-4-(oxo-λ6-methyl)benzoic acid and 2-formyl-3-(hydroxymethyl)-6-methoxy-5-methylterephthalic acid are reactive but unstable compound structure.

Keywords: semiempirical methods, cyclopolic acid, stability, reactivity

ABSTRAK

Studi stabilitas dan reaktifitas senyawa asam siklopolat dan turunannya dengan metode semiempirik (AM1 dan PM3) merupakan suatu metode yang dapat dipilih di kimia komputasi. Metode ini merupakan metode sederhana dalam mengoptimasi suatu senyawa dalam menghitung parameter-parameter yang dimiliki oleh atom. Asam siklopolat merupakan senyawa organik yang dapat dijumpai pada tanaman jagung dan kacang-kacangan. Dari hasil analisis menggunakan perangkat lunak (software) yakni aplikasi HyperChem Profesional dengan meggunakan dua metode yakni metode AM1 dan PM3 dengan melihat energi total dan gradient dari masing-masing senyawa diperoleh data yang tidak terlalu memiliki perbedaan perhitungan yang signifikan atau bahkan dapat dikatakan hampir sama perhitungannya. Seperti pada struktur senyawa asam siklopolat yang ke-3 memiliki energi total -80608.1868567 (kcal/mol) dan gradient 0.0898817 (kcal/mol/Ang) dengan metode AM1 dan energi total -74935.9180118 (kcal/mol) dan gradient 0.0874369 (kcal/mol/Ang) dengan metode PM3. Struktur yang stabil ialah pada struktur senyawa asam siklopolat yang ke-3 berdasarkan perhitungan energi total dan

gradient. Sedangkan menurut perhitungan selisih LUMO-HOMO memiliki hasil yang berbeda. Dimana menurut perhitungan selisih energi LUMO-HOMO struktur senyawa yang paling stabil ialah struktur senyawa asam siklopolat yang ke-4 akan tetapi tidak reaktif. Begitupun sebaliknya struktur senyawa asam siklopolat yang ke 1,2 dan 3 merupakan struktur senyawa yang reaktif namun tidak stabil.

Kata kunci: metode semiempirik, asam siklopolat, stabilitas, reaktifitas

INTRODUCTION

Computational chemistry is a branch of chemistry that uses computer programs to calculate the parameters of an atom. The parameter which is always involved in the calculation is the electrons that are owned by the atom. The most widely used fields of computational chemistry are DFT (Oliveira, Seifert, Heine, & Duarte, 2009) and semiempirical (Lipkowitz & Boyd, 1990). Semiempirical can be used to study the total energy and energy of an atom of HOMO and LUMO. There are several methods commonly used, namely the AM1 and PM3 methods. This method is widely chosen because the parameters that are calculated are only the valence electrons of the atoms so the analysis time is relatively short (Asmara et al., 2015).

Computational chemistry is often applied to predict the stability and reactivity of a compound. Natural compounds are often studied in computational chemistry such as myristine (Chandra, Asmuruf, & Siallagan, 2020), quinoline (Dhuha, Aswad, & Haeria, 2014), mangiferin (Dewi & Sanjaya, 2018), and indole-based natural compounds (Setiadji, Ivansyah, & Pribadi, 2015). Another compound that has the potential to be studied is cyclopolic or cyclopiazonic acid. Cyclopiazonic acid or abbreviated as CPA, refers to α-CPA. CPA was isolated from the culture extract as the main toxic metabolite of Penicillium cyclopium Westling (strain CSIR 1082) or under the original name Penicillium griseofulvum Dierckx, during routine toxicity screening of microfungi. P. cyclopium was isolated from peanuts which caused acute toxicosis in ducks and mice (Birkinshaw, Raistrick, Ross, & Stickings, 1952).

CPA is an indole tetramic and a lipophilic monobasic acid that have structural similarities to lysergic acid (Duncanson, Grove, & Zealley, 1953). CPA has metal chelating capabilities. This suggests that the previously isolated flavodoxin (sodium cyclopiazonate) is a metal chelating complex of CPA (Johnson.S, 2020).

The potential toxic risk of CPA to humans and animals was initially thought to be low because it was less potent than other secondary toxicigenic metabolites of microfungi (e.g. aflatoxins and sterigmatocystins). As a result, the CPA did not attract the attention of the scientific community. Scientific interest in CPA has increased since 1977, suggesting that the yields are productive and that the important food and feed contaminant Aspergillus flavus can produce CPA. Gradually, CPA research has focused on the occurrence of CPA and aflatoxins in the food and feed chain (Haeria, 2014). It is necessary to research related to the reactivity of this compound that has toxic activity.

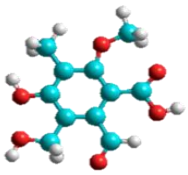
The ergot-like alkaloid cyclopiazonic acid (α-cyclopiazonic acid, α-CPA) is a hydrindanetramic acid indole mycotoxin produced by many species of fungi in the Ascomycete genera Penicillium and Aspergillus. α-CPA was first isolated from the liquid culture of Westling's Penicillium cyclopium in 1968, the main toxic compounds of these microorganisms (Roncal, 2016).

In quantum chemistry, the discovery of the AM1 method is very useful. Many calculation procedures have not been thorough, although they can be used in terms of simple molecules, for example, the molecular orbital self-consistent field (MOSCF) method takes a long time to calculate. The AM1 approach is sufficiently compatible to be used as a relatively simple thought for the desired calculation (Azizah et al., 2013). This method is often used to select suitable monomers and their reactivity in the synthesis of the particular polymer.

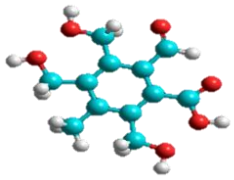
For this reason, we are interested in conducting research using the same method to determine the stability and reactivity of cyclopolate compounds and their derivatives. How to compare the stability of cylopolic acid compounds and their derivatives when using two different methods. How to compare the reactivity of cylopolic acid compounds and their derivatives when using two different methods.

METHODOLOGY

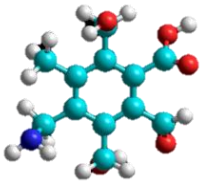
This study uses data on four structures of cyclopolic acid compounds and their derivatives as shown in Figure 1.



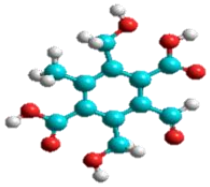
a) 2-formyl-4-hidroxy-3-(hydroxymethyl)-6-methoxy-5-methylbenzoic acid



b). 2-formyl-3-(hydroxymethyl)-6-methoxy-5-methyl-4-(oxo-λ^6-methyl)benzoic acid



c). 2-formyl-3-(hydroxymethyl)-6-methoxy-5-methylterephthalic acid



d). 2-formyl-3-(hydroxymethyl)-4-isocyano-6-metoxy-5-methylbenzoic acid

Figure 1. Cyclopolate acid compounds and their derivatives

Materials and equipment

This research uses a computer device with an Intel® Celeron® Processor N3350 HD Graphics, 500 GB HDD, 2 GB DDR3 L Memory RAM, and uses Hyperchem Professional® software.

Procedure

The structure of the cyclopolic acid compound and its derivatives was modeled using the Hyperchem Professional ® program with the semiempirical method (AM1 and PM3). The first step that needs to be done is to run the HyperChem program, input one of the cyclopolic acid

compounds or their derivatives and create it in a 3-dimensional (3D) structure, set up to select empirical methods (AM1 and PM3), geometry optimization with the method that has been selected with convergence limits. 0.1 kcal / Å with the Polak Ribiere algorithm, the output produced is a stable structure and its reactivity and the last step is to exit the HyperChem program (Paramita, Permata S., Vaulina Y.D., Nasrokhah, & Iswanto, 2020)

Descriptor Analysis

After the structure is optimized to find the most stable structure. Furthermore, descriptor analysis is carried out to calculate the reactivity and stability of the structure being modeled. The descriptor used to analyze the stability and reactivity of the structure is the value of HOMO, LUMO, electronegativity, chemical hardness, and the electrophilicity index. HOMO (Highest Occupied Molecular Orbital) is the highest energy molecular orbital that has electrons. LUMO (Lowest Unoccupied Molecular Orbital) is the lowest energy to place or excite an electron. Electronegativity is a chemical property that describes the ability of an atom (or more rarely a functional group) to attract an electron (or electron density) towards itself in a covalent bond. The formula is as follows:

$$\text{Electronegativity } (\chi) = \frac{E.HOMO+E.LUMO}{2} \quad (1)$$

Chemical hardness is the resistance of a material or metal to deformation that is compressive deformation or identification. The formula is as follows:

$$\text{Chemical hardness } (\eta) = \frac{E.LUMO+E.HOMO}{2} \quad (2)$$

The Electrophilicity Index is a parameter that measures the susceptibility of a chemical species to accept electrons. The higher the value of the electrophilicity for a chemical species, the better its electrophilicity properties. Electrophilicity is formulated as follows:

$$\text{Electrophilicity } (\omega) = \chi^2 / 2\,\eta \quad (3)$$

RESULTS AND DISCUSSION

Based on the results of the analysis using the AM1 and PM3 semi-empirical methods carried out with calculations using HyperChem Professional, two data can be analyzed, namely the calculation of total energy and gradient as well as the calculation of LUMO and HOMO energy.

Gradient and total energy calculations

The results of surface potential energy and gradient calculations based on calculations using HyperChem Professional can be seen in tables 1 and 2. The smallest energy of a compound structure can be assumed to be a stable structure (Rendrahadi, 2014). Likewise, a structure that has large energy has an unstable structure. Surface potential energy can reflect the stability and reactivity of a compound. Compounds that have large surface potential energy that is unstable and react easily. Stable compounds have a small total surface potential energy (Tuslinah & Indra, 2013). The result of the crunch using the semiempirical methods PM3 is the summation of kinetic energy and reject energy of atomic nucleus in the system (Ivansyah, 2020).

From the research conducted using the AM1 and PM3 semiempirical methods which can be seen in tables 1 and 2 above, they do not have many energy differences. By using these two

methods, namely AM1 and PM3, it can be seen that based on the total energy in the four structures of cyclopolic acid compounds and their derivatives which have the lowest total energy, are in the structure of the third compound in tables 1 and 2. Each of them has a total energy of -90948.4976859 (kcal/mol) with the AM1 method and the PM3 method of -84443.1866093 (kcal/mol). While the structure of other cyclopolic acid compounds using the AM1 method can be revealed in the structure of 2-formyl-4-hidroxy-3-(hydroxymethyl)-6-methoxy-5-methylbenzoic acid. cyclopolic acid compound having total energy of -80608.1868567 (kcal/mol), the 2nd compound -84192.2525649 (kcal/mol), and the structure of the 4th compound - 81936.1865432 (kcal/mol). Whereas using the PM3 method has the total energy for the structure of the 1st cyclopolic acid compound -74935.9180118 (kcal/mol), 2nd -78380.2396523 (kcal/mol), and the structure of the 4th cyclopolic acid compound -75739.5951076 (kcal/mol). This means that of the four cyclopolic acid compounds and their derivatives, the structure of the three cyclopolic acids has a stable structure among the other cyclopolic acid structures.

Table 1. The surface potential energy and gradient calculations of cyclopolic acid compounds and their derivatives by the AM1 method

Cyclopolic Acid Compounds and their derivatives	**Parameter**	
	Total energy	**Gradient**
2-formyl-4-hidroxy-3-(hydroxymethyl)-6-methoxy-5-methylbenzoic acid.	-80608.1868567 (kcal/mol)	0.0898817 (kcal/mol/Ang)
2-formyl-3-(hydroxymethyl)-6-methoxy-5-methyl-4-(oxo-λ^6-methyl)benzoic acid	-84192.2525649 (kcal/mol)	0.1158617 (kcal/mol/Ang)
2-formyl-3-(hydroxymethyl)-6-methoxy-5-methylterephthalic acid	-90948.4976859 (kcal/mol)	0.0843060 (kcal/mol/Ang)
2-formyl-3-(hydroxymethyl)-4-isocyano-6-metoxy-5-methylbenzoic acid.	-81936.1865432 (kcal/mol)	0.0987816 (kcal/mol/Ang)

Table 2. The surface potential energy and gradient calculations of cyclopolic acid compounds and their derivatives by the PM3 method.

Cyclopolic Acid Compounds and their derivatives	**Parameter**	
	Total energy	**Gradient**
2-formyl-4-hidroxy-3-(hydroxymethyl)-6-methoxy-5-methylbenzoic acid.	-74935.9180118 (kcal/mol)	0.0874369 (kcal/mol/Ang)
2-formyl-3-(hydroxymethyl)-6-methoxy-5-methyl-4-(oxo-λ^6-methyl)benzoic acid.	-78380.2396523 (kcal/mol)	0.0964766 (kcal/mol/Ang)
2-formyl-3-(hydroxymethyl)-6-methoxy-5-methylterephthalic acid	-84443.1866093 (kcal/mol)	0.0962096 (kcal/mol/Ang)
2-formyl-3-(hydroxymethyl)-4-isocyano-6-metoxy-5-methylbenzoic acid.	-75739.5951076 (kcal/mol)	0.0977099 (kcal/mol/Ang)

HOMO and LUMO

The calculation of the energy and energy difference of Lumo-Homo from the structure of the cyclopolic acid compound and its derivatives can be seen in tables 3 and 4. To determine the reactivity of a compound structure, we can calculate the energy difference between LUMO and HOMO. If the energy difference is much larger, the structure of a compound is less stable but the structure of the compound is reactive. On the other hand, the structure of a compound that has a smaller energy difference is reactive but less stable (Saputra, 2013).

Table 3. The structure of HOMO and LUMO along with the energy of cyclopolic acid compounds and their derivatives by the AM1 method.

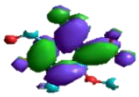
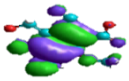
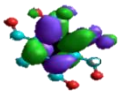
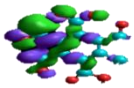
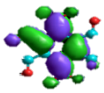
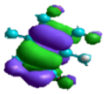
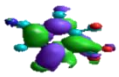
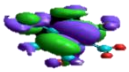
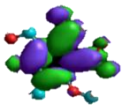
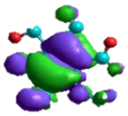
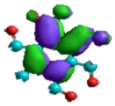
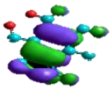
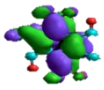
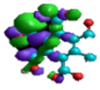
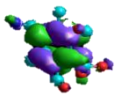
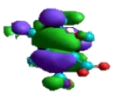
Cyclopolic Acid and its Derivatives	LUMO	HOMO
2-formyl-4-hidroxy-3-(hydroxymethyl)-6-methoxy-5-methylbenzoic acid.	 -0,9683546 eV	 -9,609875 eV
2-formyl-3-(hydroxymethyl)-6-methoxy-5-methyl-4-(oxo-λ^6-methyl)benzoic acid.	 -0,9104196 eV	 -9,888955 eV
2-formyl-3-(hydroxymethyl)-6-methoxy-5-methylterephthalic acid	 -1,44174 Ev	 -10,34779 eV
2-formyl-3-(hydroxymethyl)-4-isocyano-6-metoxy-5-methylbenzoic acid.	 -0,9425859 eV	 -10,13745 eV

Table 4. The structure of Homo and Lumo along with the energy of cyclopolic acid compounds and their derivatives by the PM3 method.

Cyclopolic Acid Compounds and their derivatives	LUMO	HOMO
2-formyl-4-hidroxy-3-(hydroxymethyl)-6-methoxy-5-methylbenzoic acid.	 -0,9104196 eV	 -9,589423 eV
2-formyl-3-(hydroxymethyl)-6-methoxy-5-methyl-4-(oxo-λ^6-methyl)benzoic acid	 -0,8829568 eV	 -9,80397 eV
2-formyl-3-(hydroxymethyl)-6-methoxy-5-methylterephthalic acid	 -1,364283 eV	 -10,05228 eV
2-formyl-3-(hydroxymethyl)-4-isocyano-6-metoxy-5-methylbenzoic acid.	 -0,6305259 eV	 -10,08898 eV

The difference in HOMO LUMO energy can reflect the stability and reactivity of a compound. Compounds that have a small homo LUMO energy difference mean that electrons in the compound are more easily excited to higher energy levels. If electrons are easily excited then the compound has a large reactiveness. If a compound has a large HOMO LUMO energy difference then the electrons in the compound are difficult to excite. Compounds that have electrons difficult to excite will have high stability (Tuslinah & Indra, 2013).

From the results obtained using the AM1 and PM3 methods, there is a difference between the LUMO and HOMO calculations as seen in tables 3 and 4 above. It can be explained that the structure of cyclopolic acid compounds 1-3 has a smaller difference in the LUMO-HOMO calculation than the structure of the 4th cyclopolic acid compound. This means that the structure of the 1-3 cyclopolic acid compound is reactive compared to the 4th cyclopolic acid structure. However, the structure of the 4th cyclopolic acid compound has good reactivity than the structure of the 1,2 and 3 cyclopolic acid compounds.

Table 5. Total energy (E), energy (E_{LUMO}-E_{HOMO}), chemical hardness (η), electronegativity (χ), and electrophilicity (ω) of cyclopolic acid compounds and their derivatives by the AM1 method.

Cyclopolic acid compounds and their derivatives	E (kcal/mol)	E_{LUMO} (eV)	E_{HOMO} (eV)	(χ,eV)	(η,eV)	(ω,eV)
2-formyl-4-hidroxy-3-(hydroxymethyl)-6-methoxy-5-methylbenzoic acid.	-80608.186	-0,968	-9,609	-5,2885	4,3205	60,41837
2-formyl-3-(hydroxymethyl)-6-methoxy-5-methyl-4-(oxo-λ^6-methyl)benzoic acid	-84192.252	-0,910	-9,888	-5,399	4,489	65,42538
2-formyl-3-(hydroxymethyl)-6-methoxy-5-methylterephthalic acid	-90948.497	-1,441	-10,347	-5,894	4,453	77,34691
2-formyl-3-(hydroxymethyl)-4-isocyano-6-metoxy-5-methylbenzoic acid.	-81936.186	-0,942	-10,137	-5,5395	4,5975	70,53958

Table 6. Total energy (E), energy (E_{LUMO}-E_{HOMO}), chemical hardness (η), electronegativity (χ), and electrophilicity (ω) of cyclopolic acid compounds and their derivatives by the PM3 method.

Cyclopolic acid compounds and their derivatives	E (kcal/mol)	E_{LUMO} (eV)	E_{HOMO} (eV)	χ (eV)	η (eV)	ω (eV)
2-formyl-4-hidroxy-3-(hydroxymethyl)-6-methoxy-5-methylbenzoic acid.	-74935.918	-0,910	-9,589	-5,2495	4,3395	-59,79234
2-formyl-3-(hydroxymethyl)-6-methoxy-5-methyl-4-(oxo-λ^6-methyl)benzoic acid	-78380.239	-0,882	-9,803	-5,3425	4,4605	-63,65647
2-formyl-3-(hydroxymethyl)-6-methoxy-5-methylterephthalic acid	-84443.186	-1,364	-10,052	-5,708	4,344	-70,76650
2-formyl-3-(hydroxymethyl)-4-isocyano-6-metoxy-5-methylbenzoic acid.	-75739.595	-0,630	-10,088	-5,359	4,729	-67,90579

CONCLUSION

From the data obtained after optimizing the cyclopolic acid compound and its derivatives using the HyperChem Professional application based on the AM1 and PM3 method, it can be concluded that each compound has almost the same total energy calculation. This is also similar to the gradient of each compound which also has little or no difference in numbers. The same thing happened in the calculation of Lumo-Homo energy. The stable structure is in the structure of the 3rd cyclopolic acid compound based on the calculation of the total energy and gradient. Meanwhile, according to the calculation of the Lumo-Homo difference has different results. Where according to the calculation of the energy difference between Lumo-Homo, the structure of the most stable compound is the structure of the 4th but not reactive cyclopolic acid compound. Likewise, the structure of cyclopolic acid compounds which are 1, 2, and 3 is a reactive but unstable compound structure.

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