Susceptibility of Sesbagrandiflorain B against Chlorination: A DFT Study

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Abstract. Sesbagrandiflorain B is a novel aryl benzofuran derivative isolated from Sesbania grandiflora. Due to its novelty, there is almost no study on the reactivity and properties on this compound. In this study, we perform calculation to determine the reactivity of sesbagrandiflorain B against chlorination reaction based on fukui indices and energy calculation of reactant, intermediate, and product structures. The properties of the system are calculated using DFT B3LYP/6-311++g(d), and to simulate the effect of solvent we employ polarizable continuum model (PCM) on GAMESS-US 2018 package software. From the structure of sesbagrandiflorain B, there are five possible positions that susceptible to chlorination. The energy of reaction in those positions are significantly different from each other with energy of the intermediate formations are 446.48 kJ, 428.06 kJ, 428.63 kJ, 364.08 kJ, and 388.86 kJ, indicating that the selectivity of sesbagrandiflorain B against chlorination reaction. The intermediate formation of sesbagrandiflorain B chlorination that is simulated without solvent tend to be endothermic while the implementation of PCM to the system significantly reduce the intermediate energy, suggesting that the solvent promote the reaction to be thermodynamically driven. For some position, the solvent also stabilizes the product of chlorination reaction.

Keywords: benzofuran, sesbania grandiflora, chlorination, sesbagrandiflorain

1. Introduction
Heterocyclic compounds have important roles in discover and synthesis novel molecules which possess physiological and pharmacological activity. One of heterocyclic compound that widely used is benzofuran. Benzofuran derivatives are very useful for developing new potential therapeutic agents. It is the important intermediate on synthesis a lot of new and useful heterocyclic compound that is difficult to obtain without involving benzofuran as intermediate [1]. It also has a good bioactivity such as antihyperglycemic, analgesic, antiparasitic, antimicrobial, antitumor, and kinase inhibitor. Substituted benzofuran also applied in fluorescence sensor, oxidant, bleaching agent, and so on [2].

Many benzofuran derivatives compound isolated from natural products. Recently, the isolation of novel benzofuran derivatives compound, 6-methoxy-2-(2’,3’-dihydroxy-5’-methoxyphenyl)-1-benzofuran-3-carbaldehyde (sesbagrandiflorain A) and 6-hydroxy-2-(2’,3’-dihydroxy-5’-methoxyphenyl)-1-benzofuran-3-carbaldehyde (sesbagrandiflorain B) from the stem bark of Sesbania grandiflora has been reported [3]. Antibacterial activity and cytotoxicity of EtOAc extract of the stem bark of S. grandiflora including sesbagrandiflorain A and B were also conducted [4]. S. grandiflora is a flowering plant that is native to tropical Asia. Different parts of this plant have been used as herbal medicines to treat anemia, bronchitis, fever, and tumors [5-7]. Earlier studies on the leaves, seeds, and roots of S. grandiflora showed the presence of various secondary metabolites, e.g., α-5-methyl-5-
pentacosanol, galactomannan, and flavonoids, some of which exhibited antituberculosis activity against Mycobacterium tuberculosis H37Rv [8-11].

Based on the structure and the abundance of S. grandiflora, sesbagrandiflorain A and B is expected to be a beneficial compound and potential starting material of various benzofuran derivatives compound that is hard to be synthesized from another starting material. However, the study of sesbagrandiflorain’s chemical reactivity is very rarely conducted. Chemical reactivity of sesbagrandiflorain can be studied theoretically through computational calculation. Density Functional Theory (DFT) is widely used and effective to obtain various information of a molecule [12]. Recently, we have reported theoretical study of chemical reactivity descriptor, such as ionization energy, electron affinity, hardness and electronegativity of sesbagrandiflorain A [13]. Another descriptor is Fukui indices, that predicts the susceptibility of molecule against electrophilic, nucleophilic and radical reactants [14].

Electrophilic substitution plays the important roles in reaction mechanism of many bioactive molecule syntheses. One of the important electrophilic substitution is chlorination reaction. The presence of chlorine plays the pivotal roles in a large number of natural products. It has been found that the introduction of a chlorine atom into one or more specific positions of a biologically active molecule may improve the intrinsic biological activity [15,16]. The application of chlorine in medicinal chemistry is one of the fastest growing hot areas in chemistry as its fascinating and instructive role of halogens distribution in the field of drug development. Interestingly, among four halogens, chlorine is the one which is more frequently found in drugs than others, even fluorine [17,18]. In this study, we perform Fukui indices calculation of sesbagrandiflorain B. Furthermore, susceptibility of sesbagrandiflorain B against electrophilic reagents is studied through chlorination reaction. Hopefully it can provide information to develop sesbagrandiflorain into other useful compounds.

2. Experimental Setup

All of computational calculation were conducted on high performance computer of ITB and public server XSEDE [19,20]. Quantum mechanics calculation was performed using GAMESS-US 2018 package software [21].

2.1. Geometry Optimization and Single Point Calculation

Geometry optimization were conducted to obtain the combination of bonds length, bonds angle and dihedral angle of the molecular structure which has the lowest energy [12]. Geometry optimization is performed on stable structures (products and reactants) as well as intermediate structures using Hartree-Fock (HF) method with basis set of 6-31G. The HF method was chosen due to its quite accurate results of structure prediction, but shorter calculation time compared with higher level methods. All of geometry optimization were conducted without solvent and with solvent, using Polarizable Continuum Model (PCM) solvent. PCM is one of methods that represent the solvated molecule model based on quantum mechanical calculation [22]. The solute, that influenced by interacting solvent, was treated by quantum mechanics, while the solvent was modeled as unlimited polarizable continuum [23]. In this experiment, we simulated the calculation without solvent, PCM water and PCM ethanol.

Higher level methods were needed to calculate the energy of molecule since the energy that obtained from HF calculation is quite overestimate [24]. In this experiment, single point energy calculation is performed using various levels of theory and basis set, such as B3LYP/6-31G, B3LYP/6-31++G, B3LYP/6-311++g, B3LYP/6-311++g(d) and M06/6-31G. Those result were used to determine the electronic population distribution in the sesbagrandiflorain molecule. Furthermore, electronic population distribution was used to calculate Fukui Indices, that determine the susceptibility of molecule against electrophilic, nucleophilic and radical attack [14].

2.2. Fukui Indices

Local reactivity of molecule can be predicted from Fukui Indices based on electronic population [25]. In this experiment, we utilized Lowdin population that obtained from single point calculation to calculate Fukui Indices, based on equation (1), (2) and (3).
\[ f_{k}^+ = qk(N+1) - qk(N) \quad (1) \]

\[ f_{k}^- = qk(N) - qk(N-1) \quad (2) \]

\[ f_{k}^0 = \frac{qk(N+1) - qk(N-1)}{2} \quad (3) \]

Which \( qk \) is Lowdin population, \( N \) is the number of neutral molecules and \( f_{k}^+, f_{k}^- \), and \( f_{k}^0 \) correspond to Fukui Indices that in a good agreement with the reactivity towards nucleophilic, electrophilic and radical attack, respectively. In this study, we perform the \( f_{k}^- \) to determine the reactivity towards electrophilic, especially chlorine species that is involved in chlorination reaction.

2.3. Chlorination Reaction Energy
In this research, we performed chlorination reaction energy calculation on several possible position based on Fukui indices results. Chlorination reaction energy was calculated from the differences between product and reactant energy. Intermediate structure of each possible mechanism also calculated. All of the structures mentioned were optimized using HF/6-31g and single point energy calculation was calculated using B3LYP/6-311++g(d). The results in various solvents were then compared.

3. Results and Discussion

3.1. Geometry Optimization and Single Point Calculation
The result of geometry optimization without solvent shows that benzofuran moiety of sesbagrandiflorain is planar, while the aryl moiety that connected to sesbagrandiflorain B has different plane with benzofuran (Figure 1). There is no significant difference between structure of sesbagrandiflorain B that optimized with or without various solvent. This structure was then used as input for single point calculation to determine the susceptibility electrophilic attacks.

![Figure 1](image_url)

**Figure 1.** (a) Molecular structure of sesbagrandiflorain A and (b) optimized structure of sesbagrandiflorain B
3.2. Fukui Indices
Fukui Indices was then calculated with various theory. The order of reactivity towards electrophilic attack can be seen in Table 1, 2 and 3, that demonstrate almost similar tendency when it simulated in non-solvated or solvated (PCM water and methanol) model. However, the molecule tends to undergo electrophilic attack on the water as its solvent, due to the higher Fukui Indices.

Table 1. Reactivity order of atoms in sesbagrandiflorain B molecule toward electrophilic attack (no solvent).

| No | HF/6-31g | B3LYP/6-31g | B3LYP/6-31++g | B3LYP/6-311++g | B3LYP/6-311++g(d) |
|----|----------|-------------|---------------|----------------|-------------------|
| 1  | O5       | O5          | O5            | O5             | O4                |
| 2  | C15      | C15         | C15           | C15            | C15               |
| 3  | C8       | O3          | O4            | O4             | C15               |
| 4  | O6       | O4          | O3            | O3             | C14               |
| 5  | O4       | C11         | C11           | C11            | C11               |

Table 2. Reactivity order of atoms in sesbagrandiflorain B molecule toward electrophilic attack (PCM Water).

| No | HF/6-31g | B3LYP/6-31g | B3LYP/6-31++g | B3LYP/6-311++g | B3LYP/6-311++g(d) |
|----|----------|-------------|---------------|----------------|-------------------|
| 1  | O5       | O5          | O5            | O5             | O4                |
| 2  | C15      | C15         | C15           | C15            | O5                |
| 3  | C8       | O3          | O4            | O4             | C15               |
| 4  | O6       | O4          | O3            | O3             | C14               |
| 5  | O4       | C11         | C11           | C11            | C11               |

Table 3. Reactivity order of atoms in sesbagrandiflorain B molecule toward electrophilic attack (PCM Ethanol).

| No | HF/6-31g | B3LYP/6-31g | B3LYP/6-31++g | B3LYP/6-311++g | B3LYP/6-311++g(d) |
|----|----------|-------------|---------------|----------------|-------------------|
| 1  | O5       | O5          | O5            | O5             | O4                |
| 2  | C15      | C15         | C15           | C15            | O5                |
| 3  | C8       | O3          | O4            | O4             | C15               |
| 4  | O6       | O4          | O3            | O3             | C14               |
| 5  | O4       | C11         | C11           | C11            | C11               |

Based on Table 1, 2, and 3, we can be clearly observed that some atoms in the sesbagrandiflorain molecules tend to be more reactive (higher \(f_k^-\)) in solvated condition rather than non-solvated, such as O1, C8 and C2. This is the finding that in order to carry out a reaction involving a certain electrophilic, a suitable solvent is necessarily needed. From the structure of sesbagrandiflorain B, it is known that there are five points that allow electrophilic substitution reaction to occur due to the substitutable proton availability (Figure 2), labelled as C1, C3, C4, C10 and C13 as well as written on Figure 1.
Figure 2. Five plausible of chlorination reaction take place

The order of $f_k^-$ for some atoms that plausible to undergo electrophilic attack that derived from calculation with various method and condition is served in Table 4. The order of reactivity is quite similar for the same system that calculated with various methods, but exhibit the different result regarding to the order of reactivity. It confirms that each solvent is affecting the regioselectivity.

Table 4. Order of group reactivity toward electrophilic attack

| Methods         | No solvent | PCM water | PCM methanol |
|-----------------|------------|-----------|--------------|
| HF/6-31g        | C10>C13>C3>C1>C4 | C3>C13>C10>C4>C1 | C3>C13>C10>C4>C1 |
| B3LYP/6-31g     | C10>C3>C13>C4>C1 | C13>C4>C3>C1>C10 | C13>C4>C3>C1>C10 |
| B3LYP/6-311++g  | C10>C3>C13>C4>C1 | C13>C3>C4>C1>C1 | C13>C3>C4>C1>C10 |
| B3LYP/6-311++g(d) | C3>C10>C13>C1>C4 | C13>C3>C4>C1>C10 | C13>C3>C4>C1>C10 |

3.3. Chlorination Reaction Energy

Sesbagrandiflorain B molecules can undergo reactions that involve either an electrophilic or a nucleophilic attack. One plausible reaction is an electrophilic substitution reaction. In this research, we calculated the species involved in the chlorination reaction of the sesbagrandiflorain molecule, which is an electrophilic substitution reaction. Generally, the mechanism of electrophilic substitution of an aromatic compound occurs in two stages; attack by an electrophile to produce an intermediate cation and releasing a proton from the cation to restore aromatization [26]. The energy calculation was carried out on the reactant, intermediate and product in different condition (non-solvated and PCM water) to investigate the susceptibility of molecule towards chlorination reagent.

Chlorination reaction tends to occur exothermically [27]. We calculate the energy of reactant, intermediate and product to investigate the susceptibility of sesbagrandiflorain B towards chlorination reaction thermodynamically. The energy calculation of chlorination reaction in position 1-5 were shown in Figure 3-7. Total reaction that occur in all possible position is exothermic, both in the solvated model and non-solvent model. There is no significant different between the energy of total reaction. Interestingly, the intermediate formation reaction energy was significantly different. In the non-solvent model, stage 1 of the chlorination reaction was endothermic, while other was exothermic. It suggests that use of solvent stabilize the intermediate, thus making it easier for molecules to undergo reactions thermodynamically since the intermediate formation is rate determining step of chlorination reaction.
Figure 3. Energy diagram of the chlorination at position C1

Figure 4. Energy diagram of the chlorination at position C3

Figure 5. Energy diagram of the chlorination at position C4
There is a difference between the energy of the intermediate formation, especially at position C1, C3, C10 and C13, indicating that the selectivity of sesbagrandiflorain B against chlorination reaction. The lowest intermediate formation reaction energy of the system that calculated in non-solvent model is C3, indicating that this position is the most reactive moieties toward chlorination reaction (based on thermodynamic point of view), in line with the reactivity prediction from Fukui indices (Table 4). Fukui indices prediction also in a good agreement with the intermediate formation reaction energy of solvated model, demonstrate that the lowest energy of reaction is reached by the chlorination at position C13. It indicates that the most reactive moieties toward chlorination reaction in the solvated model is C13. The intermediate formation of chlorination reaction at position C10 is the lowest, but the product energy is not significantly different and the product is not stabilized thus chlorination reaction is not thermodynamically favourable at that position. The energy of chlorination reaction in PCM water have a tendency to be slightly lower than the reaction that modelled in PCM methanol. It confirms that water stabilize the intermediate and the product better than that of methanol. Thus, the reaction will be more favourable to occur in the more polar solvent.
4. Conclusion

The chlorination reaction of sesbagrandiflorain B is exothermic reaction, while the intermediate formation of some position is endothermic. The energy of reaction in those positions are significantly different from each other with energy of the intermediate formations are 446.48 kJ, 428.06 kJ, 428.63 kJ, 364.08 kJ, and 388.86 kJ based on non-solvent model; 6.64 kJ, 19.64 kJ, 21.73 kJ, -61.38 kJ, and -17.77 kJ for PCM water; 16.03 kJ, 29.23 kJ, 29.22 kJ, -53.53 kJ and -8.75 kJ for PCM methanol; indicating that the selectivity of sesbagrandiflorain B against chlorination reaction. The intermediate formation of sesbagrandiflorain B chlorination that is simulated without solvent tend to be endothermic while the implementation of PCM to the system significantly reduce the intermediate energy, suggesting that the solvent promote the reaction to be thermodynamically driven. For some position, the solvent also stabilizes the product of chlorination reaction.

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