ABSTRACT

Host-guest inclusion complexes between 2,6-dimethyl-β-Cyclodextrin (DIMEB) and enantiomers of ibuprofen (R/S-IBP) were simulated using the molecular docking, semi-empirical PM3 and ONIOM2 (B3LYP/6-31g(d,p): PM3) methods. The modelling results showed that the most stable geometries of two R and S-IBP/DIMEB complexes were similar. It also showed that the binding energy of (R)-IBP/DIMEB and (S)-IBP/DIMEB complexes calculated by PM3 were -53.770 and -57.278 kJ/mol, while those calculated by ONIOM2 method referred to -52.917 and -59.053 kJ/mol similarly. In addition, thermodynamic parameters obtained to follow the trend of a binding energy value. Furthermore, the modelling indicated that (S)-IBP/DIMEB inclusion complex was more stable than (R)-IBP/DIMEB. DIMEB inclusion complex with S-enantiomer was stronger than Ibuprofen R-enantiomer. The theoretical results were in agreement with the experimental data.

Keywords: inclusion complex, ibuprofen, dimethyl-β-cyclodextrin, PM3, ONIOM2.

INTRODUCTION

Ibuprofen [2(4-isobutylphenyl) propionic acid (Fig. 1)] is commercially introduced as non-steroidal anti-inflammatory drug (NSAID), a prostaglandin and a thromboxane inhibitor. Ibuprofen is optically an active compound. It exists as S- and R-enantiomer. The commercial product is a racemic mixture. However, each enantiomer exhibits different pharmacodynamics, pharmacokinetic and toxicological properties [1]. If it is compared with racemic form, S-ibuprofen has better clinical efficiency, less variability from therapeutic effects and toxicity, while R-enantiomer structure does not indicate a pharmacological action. Moreover, it triggers a chiral inversion of human body caused by toxicity resulted by a hybrid triglycerides formation [2]. Its enantiomer can cause gastrointestinal toxicity, water sodium retention, kidney perfusion, increase the allergic reactions and other side effect [3]. The experimental separation of racemic Ibuprofen is done by GC [4, 5], HPLC [6, 7] and CE [8] method. GC is very exciting in respect to develop the cyclodextrin as a stationary phase.

Dimethyl β-Cyclodextrin (2,6-dimethyl-β-Cyclodextrin, DIMEB) is a derivate of β-Cyclodextrin.

Fig. 1. Ibuprofen chemical structure.
Cyclodextrin is widely used due to its ability to create inclusion complex with various spatial molecules [9 - 11]. Main use of cyclodextrin is not only used in the field of pharmacy, cosmetics, food, and agrochemical industry, but also in analytical chemistry application, especially in chiral compounds separation [4-8]. DIMEB is used as chiral stationary phase to separate racemic ibuprofen during application of GC method [5]. Molecular modeling can be used to explain the limitation of the complex inclusion between stationary phase and analyte. It can be used to predict a required stationary phase for separation of racemic ibuprofen accuracy.

Nowadays, various theories are used to model host-guest inclusion complex. The last theories are between a certain guest molecule and cyclodextrin host molecule. Among those theories, molecular mechanics [12 - 13], molecular dynamics [14 - 16], semiempirical methods (such as AM1, PM3) [17 - 25], hybrid ONIOM method [26 - 29] have been widely used to model the inclusion complex between a guest molecule and cyclodextrin (and its derivative) host molecule. The most frequently used is the hybrid ONIOM method developed by Morokuma et al. [26-28] has an excellent accuracy as well as lower computational cost compared with ab initio and DFT methods. Moreover, hybrid ONIOM method found efficient and reliable in investigating the host-guest interaction between the guest molecule and cyclodextrin host molecule and its derivatives [27].

In this research, the interaction of the inclusion complex of R/S-ibuprofen with dimethyl-β-cyclodextrin was studied by PM3 and ONIOM2 (B3LYP/6-31g(d,p):PM3) method implemented with Gaussian 09 program. The purposes of the research were to find the reason why and how chiral recognition of R/S-ibuprofen occurred by dimethyl-β-cyclodextrin, to investigate the main driving force that leads to the inclusion of complex formation, to explain and obtain better understanding of the results reported by Cretu et al. Studying the chiral recognition mechanism of R/S-ibuprofen by dimethyl-β-cyclodextrin, the energy of interaction between R/S-ibuprofen and β-cyclodextrin was initially determined by using PM3 method. Furthermore, ONIOM2 (B3LYP/6-31g(d): PM3) method was applied to show a different interaction energy between R-ibuprofen and dimethyl-β-cyclodextrin as well as between S-ibuprofen and dimethyl-β-cyclodextrin.

**EXPERIMENTAL**

All calculations were transferred by using Gaussian 09 program. The starting geometries of (R/S)-ibuprofen were taken from the HIC-UP server. Dimethyl-β-cyclodextrin was constructed using Avogadro from crystallographic parameter of β- cyclodextrin. It was also taken from HIC-UP. H-atoms of hydroxyl groups in C2 and C6 of β-cyclodextrin were replaced with methyl groups. Both of them were fully optimized by the PM3 method. The PM3-optimized structures of (R/S)-ibuprofen and dimethyl-β-cyclodextrin were used for molecular docking calculations that were carried out with by Lamarckian Genetic Algorithm (LGA) of the automated docking program Autodock 4.2. Dimethyl-β-cyclodextrin was used as the host, meanwhile (R/S)-ibuprofen acted as a guest. The lowest energy of the host-guest inclusion complex conformation gained from the molecular docking was selected for a further optimization using PM3 method aimed to obtain binding energy and thermodynamic parameters value at PM3 level.

The calculated values of the binding energy and thermodynamic parameters were further optimized using ONIOM2 (B3LYP/6-31g(d):PM3) method, whereas dimethyl-β-cyclodextrin was treated at low layer calculation using PM3 method, meanwhile R/S-ibuprofen molecule was dealt with a high layer calculation using DFT method with B3LYP exchange-correlation functional and 6-31g(d,p) basis set. The binding energy (BE) was defined by equation:

\[
BE = E(cur\text{host} - cur\text{guest})^{\text{opt}} - \\
-[E(\text{host})^{\text{opt}} + E(\text{guest})^{\text{opt}}]
\]

where \(E(cur\text{host} - cur\text{guest})^{\text{opt}}\), \(E(\text{host})^{\text{opt}}\) and \(E(\text{guest})^{\text{opt}}\) represented the total energy of the optimized structure resulting from the calculation from inclusion complex of R/S-ibuprofen with dimethyl-β-cyclodextrin, whereas dimethyl-β-cyclodextrin molecule as a free host and R/S-ibuprofen as a free guest respectively.

**RESULTS AND DISCUSSION**

Inclusion complex between R/S-ibuprofen and dimethyl-β-cyclodextrin using host:guest ratio of 1:1 is model based on the ground of the experimental research.
reported by Crupi [39]. The results of a molecular modelling by both methods were shown in Fig. 2. It was evident that either R-enantiomer or S-enantiomer entered the DIMEB cavity through the wider side. This was valid for both methods. In addition, the conformation of ibuprofen leads into significant changes during the formation of inclusion complex. Both R/S-ibuprofen enantiomers showed a specific formation throughout building the most stable inclusion complex with DIMEB. The changes of molecular geometries of R/S-ibuprofen obtained using ONIOM2 method were illustrated in Table 1.

The distance between the C1 and C3 atom, C1-C13 atom, C3 and C12 atom, C2 and C11 atom, C4 and C10 atom are used to describe the molecular size of R/S-ibuprofen. The bond angle of O2-C1-O1, C13-C11-C10, C1-C2-C3 and the dihedral angle of O1-C1-C2-C4, C3-C2-C4-C9, and C7-C10-C11-C13 are used to describe the shape of the molecule of R/S-ibuprofen. Those geometry changes in ibuprofen enantiomer structures indicate that both of enantiomer molecules tend to be flexible when entering the cavity of DIMEB in the inclusion complex formation process.

The thermodynamic parameters, such as the enthalpy change (ΔH), the entropy change (ΔS) and the Gibbs free energy change (ΔG) had been obtained by both methods were summarized in Table 2 for the two complexes. A statistical thermodynamic calculation is performed at 1 atm and 298.15 K using the parametric model PM3 and ONIOM2.

Based on the binding energy (ΔE) data, it was
indicated that the inclusion complex formed between S-ibuprofen and dimethyl-β-cyclodextrin was more stable than R-ibuprofen. Several conclusions could be drawn on the ground of ∆H, ∆G and ∆S values showed in Table 2: the formation of the inclusion complex contained S-ibuprofen and dimethyl-β-cyclodextrin is more exothermic than R-ibuprofen; even though the value of ∆G formation was positive, the formation of the inclusion complex between S-ibuprofen and dimethyl-β-cyclodextrin is more spontaneous than R-ibuprofen; formation of the inclusion complex between S-ibuprofen and dimethyl-β-cyclodextrin is more favored than R-ibuprofen with dimethyl-β-cyclodextrin because it had the more positive ∆S value. The results referred to ∆H and ∆S were obtained by computational modelling using quantum semiempiric PM3 and ONIOM2 method. It was

Table 1. A geometry structure parameter of R/S-ibuprofen after interacting with DIMEB.

<table>
<thead>
<tr>
<th>Distance Between atoms</th>
<th>Free IBP</th>
<th>DIMEB- R-IBP</th>
<th>DIMEB- S-IBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R-IBP</td>
<td>S-IBP</td>
<td></td>
</tr>
<tr>
<td>C1-C3</td>
<td>2.541</td>
<td>2.487</td>
<td>1.539</td>
</tr>
<tr>
<td>C1-C13</td>
<td>7.595</td>
<td>7.748</td>
<td>7.914</td>
</tr>
<tr>
<td>C3-C12</td>
<td>8.621</td>
<td>8.480</td>
<td>8.571</td>
</tr>
<tr>
<td>C4-C10</td>
<td>4.330</td>
<td>4.294</td>
<td>4.357</td>
</tr>
<tr>
<td>Angle(°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2-C1-O1</td>
<td>119.185</td>
<td>110.998</td>
<td>120.349</td>
</tr>
<tr>
<td>C13-C11-C10</td>
<td>111.448</td>
<td>110.998</td>
<td>111.655</td>
</tr>
<tr>
<td>C1-C2-C3</td>
<td>112.631</td>
<td>109.283</td>
<td>108.874</td>
</tr>
<tr>
<td>Dihedral(°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1-C1-C2-C4</td>
<td>-120.165</td>
<td>100.280</td>
<td>138.950</td>
</tr>
<tr>
<td>C3-C2-C4-C9</td>
<td>-63.491</td>
<td>32.136</td>
<td>-13.861</td>
</tr>
<tr>
<td>C7-C10-C11-C13</td>
<td>-61.178</td>
<td>-72.951</td>
<td>83.843</td>
</tr>
</tbody>
</table>

Table 2. Binding energy (∆E) and thermodynamic parameter value.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PM3</th>
<th>ONIOM2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R-IBP/DIMEB</td>
<td>S-IBP/DIMEB</td>
</tr>
<tr>
<td>∆E (kJ/mol)</td>
<td>-53.770</td>
<td>-57.278</td>
</tr>
<tr>
<td>∆H (kJ/mol)</td>
<td>-56.249</td>
<td>-59.756</td>
</tr>
<tr>
<td>∆G (kJ/mol)</td>
<td>33.669</td>
<td>30.146</td>
</tr>
<tr>
<td>∆S (kJ/mol.K)</td>
<td>-0.30174</td>
<td>-0.30169</td>
</tr>
</tbody>
</table>
found that the spontaneous formation of R/S-ibuprofen inclusion complex is enthalpy driven process because both ΔH and ΔS values are negative. The result of enthalpy/entropy compensation arises from the fact that the more tightly bonded complex (ΔH_S < ΔH_R) is more ordered (ΔS_S > ΔS_R). Since the entropy term increases with the temperature T, an isoenantioselective temperature exists [29].

CONCLUSIONS

Inclusion complex of ibuprofen enantiomers with dimethyl-β-cyclodextrin was modeled by using semi empirical PM3 and hybrid ONIOM2 methods. The last combination use was found successful for the calculation of the interaction energy difference and the thermodynamic parameters of inclusion complexes formation. The results showed that both methods gave a similar trend. S-ibuprofen/ dimethyl-β-cyclodextrin inclusion complex was found more stable than R-ibuprofen/ dimethyl-β-cyclodextrin inclusion complex. This computational modelling result was in accordance with experimental research reported by Cretu [5]. It showed that the R-enantiomer of ibuprofen would be eluted prior to S-ibuprofen due to the stronger inclusion complex of the S-enantiomer with dimethyl-β-cyclodextrin. It was also because the formation of this inclusion complex more exothermic and spontaneous than the formation by the R-entiomer of ibuprofen.

Acknowledgements

E.S. Nurhidayah acknowledges the Higher Education Ministry of Indonesia (DIKTI) government for financial support of the work in the framework of the BPPDN.

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